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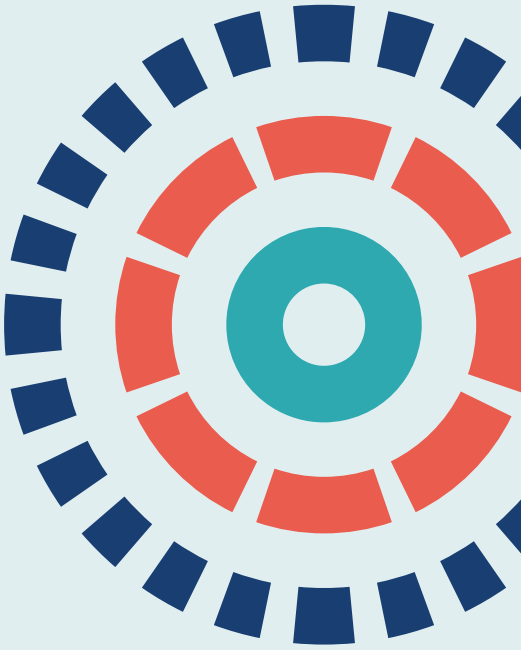

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[1]Clinical Trials Unit, Intensive Care National Audit & Research Centre, London, UK
[2]Intensive Care Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK
[3]School of Immunology & Microbial Sciences, Kings College London, London, UK
[4]Population Health Sciences, University of Bristol, Bristol, UK
[5]Department of Renal Medicine, North Bristol NHS Trust, Bristol, UK
[6]Department of Clinical and Experimental Medicine, Faculty of Health Sciences, University of Surrey, Guildford, UK
[7]Department of Critical Care, University College London Hospitals NHS Foundation Trust, London, UK
[8]Bloomsbury Institute for Intensive Care Medicine, Division of Medicine, University College London, London, UK
[9]Department of Critical Care, Guy's and St Thomas' NHS Foundation Trust, London, UK
[10]Intensive Care Unit, University Hospital Centre Zagreb, Zagreb, Croatia
[11]Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK
[12]Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK
[13]Diabetes UK, London, UK
[14]Department of Cardiothoracic Surgery, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK
[15]Department of Anaesthesia and Intensive Care, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK
[16]Warwick Medical School, University of Warwick, Coventry, UK
[17]Department of Anaesthesia and Intensive Care Medicine, Royal United Hospital Bath NHS Trust, Bath, UK
[18]Critical Care Unit, Southmead Hospital, North Bristol NHS Trust, Bristol, UK

*Corresponding author

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Abstract

Improving risk prediction model quality in the critically ill: data linkage study

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[1]Clinical Trials Unit, Intensive Care National Audit & Research Centre, London, UK
[2]Intensive Care Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK
[3]School of Immunology & Microbial Sciences, Kings College London, London, UK
[4]Population Health Sciences, University of Bristol, Bristol, UK
[5]Department of Renal Medicine, North Bristol NHS Trust, Bristol, UK
[6]Department of Clinical and Experimental Medicine, Faculty of Health Sciences, University of Surrey, Guildford, UK
[7]Department of Critical Care, University College London Hospitals NHS Foundation Trust, London, UK
[8]Bloomsbury Institute for Intensive Care Medicine, Division of Medicine, University College London, London, UK
[9]Department of Critical Care, Guy's and St Thomas' NHS Foundation Trust, London, UK
[10]Intensive Care Unit, University Hospital Centre Zagreb, Zagreb, Croatia
[11]Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK
[12]Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK
[13]Diabetes UK, London, UK
[14]Department of Cardiothoracic Surgery, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK
[15]Department of Anaesthesia and Intensive Care, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK
[16]Warwick Medical School, University of Warwick, Coventry, UK
[17]Department of Anaesthesia and Intensive Care Medicine, Royal United Hospital Bath NHS Trust, Bath, UK
[18]Critical Care Unit, Southmead Hospital, North Bristol NHS Trust, Bristol, UK

*Corresponding author david.harrison@icnarc.org

Background: A previous National Institute for Health and Care Research study [Harrison DA, Ferrando-Vivas P, Shahin J, Rowan KM. Ensuring comparisons of health-care providers are fair: development and validation of risk prediction models for critically ill patients. *Health Serv Deliv Res* 2015;**3**(41)] identified the need for more research to understand risk factors and consequences of critical care and subsequent outcomes.

Objectives: First, to improve risk models for adult general critical care by developing models for mortality at fixed time points and time-to-event outcomes, end-stage renal disease, type 2 diabetes, health-care utilisation and costs. Second, to improve risk models for cardiothoracic critical care by

enhancing risk factor data and developing models for longer-term mortality. Third, to improve risk models for in-hospital cardiac arrest by enhancing risk factor data and developing models for longer-term mortality and critical care utilisation.

Design: Risk modelling study linking existing data.

Setting: NHS adult critical care units and acute hospitals in England.

Participants: Patients admitted to an adult critical care unit or experiencing an in-hospital cardiac arrest.

Interventions: None.

Main outcome measures: Mortality at hospital discharge, 30 days, 90 days and 1 year following critical care unit admission; mortality at 1 year following discharge from acute hospital; new diagnosis of end-stage renal disease or type 2 diabetes; hospital resource use and costs; return of spontaneous circulation sustained for > 20 minutes; survival to hospital discharge and 1 year; and length of stay in critical care following in-hospital cardiac arrest.

Data sources: Case Mix Programme, National Cardiac Arrest Audit, UK Renal Registry, National Diabetes Audit, National Adult Cardiac Surgery Audit, Hospital Episode Statistics and Office for National Statistics.

Results: Data were linked for 965,576 critical care admissions between 1 April 2009 and 31 March 2016, and 83,939 in-hospital cardiac arrests between 1 April 2011 and 31 March 2016. For admissions to adult critical care units, models for 30-day mortality had similar predictors and performance to those for hospital mortality and did not reduce heterogeneity. Models for longer-term outcomes reflected increasing importance of chronic over acute predictors. New models for end-stage renal disease and diabetes will allow benchmarking of critical care units against these important outcomes and identification of patients requiring enhanced follow-up. The strongest predictors of health-care costs were prior hospitalisation, prior dependency and chronic conditions. Adding pre- and intra-operative risk factors to models for cardiothoracic critical care gave little improvement in performance. Adding comorbidities to models for in-hospital cardiac arrest provided modest improvements but were of greater importance for longer-term outcomes.

Limitations: Delays in obtaining linked data resulted in the data used being 5 years old at the point of publication: models will already require recalibration.

Conclusions: Data linkage provided enhancements to the risk models underpinning national clinical audits in the form of additional predictors and novel outcomes measures. The new models developed in this report may assist in providing objective estimates of potential outcomes to patients and their families.

Future work: (1) Develop and test care pathways for recovery following critical illness targeted at those with the greatest need; (2) explore other relevant data sources for longer-term outcomes; (3) widen data linkage for resource use and costs to primary care, outpatient and emergency department data.

Study registration: This study is registered as NCT02454257.

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Report Supplementary Material 1 Risk modelling for quality improvement in the critically ill: making best use of available data

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/EQAB4594).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AHA	American Heart Association
aHR	adjusted hazard ratio
AIC	Akaike information criterion
AKI	acute kidney injury
APACHE	Acute Physiology And Chronic Health Evaluation
APC	admitted patient care
BIC	Bayesian information criterion
BMI	body mass index
cHR	cause-specific hazard ratio
CI	confidence interval
CIF	cumulative incidence function
CKD	chronic kidney disease
CMP	Case Mix Programme
CPR	cardiopulmonary resuscitation
DHSC	Department of Health and Social Care
ESRD	end-stage renal disease
GCS	Glasgow coma scale
GLM	generalised linear model
HbA_{1c}	glycated haemoglobin
HES	Hospital Episode Statistics
HQIP	Healthcare Quality Improvement Partnership
HRG	health-care resource group
ICD-10	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision
ICNARC	Intensive Care National Audit & Research Centre
IGARD	Independent Group Advising on the Release of Data
IQR	interquartile range
MI	myocardial infarction
NACSA	National Adult Cardiac Surgery Audit
NCAA	National Cardiac Arrest Audit
NDA	National Diabetes Audit
NICOR	National Institute for Cardiovascular Outcomes Research
NIHR	National Institute for Health and Care Research
NRI	net reclassification improvement
ONS	Office for National Statistics
RCS	Royal College of Surgeons
ROSC	return of spontaneous circulation
RRT	renal replacement therapy
SD	standard deviation
SE	standard error
sHR	subdistribution hazard ratio
SMR	standardised mortality ratio
SOFA	Sequential Organ Failure Assessment
UKRR	UK Renal Registry

Plain English summary

Large amounts of information (data) are collected about patients using NHS services, but we do not make the best possible use of these data to improve patient care. Data are held by different organisations in different databases. Joining up these databases (data linkage) can give us a more complete picture of what happened to a patient.

The Intensive Care National Audit & Research Centre is an independent charity that runs national clinical audits to monitor and improve care for critically ill patients. These audits use statistical models that take information about the patient know before, or soon after, the start of their illness to make a prediction of their likely outcome. In this research study, we used data linkage to improve these models and ensure that the audits provide useful information back to hospitals to support quality improvement. However, it took over 4 years to link the databases.

By linking with death certificate information, we were able to predict how many patients die by 30 days, 90 days and 1 year after their critical illness. By linking with routine hospital data, we were able to take better account of how sick patients were before they became critically ill and look at how many days they spent in hospital in the year after their critical illness and the costs of these hospital stays. By linking with two other national clinical audits, we were able to develop new models to predict important problems of kidney failure and diabetes that some patients experience after critical care. By linking with another national clinical audit, we were able to get a more complete picture of how sick patients having heart surgery were before they were admitted to an intensive care unit, helping us to improve our models to make fairer comparisons for these patients.

Scientific summary

Background

A previous National Institute for Health and Care Research study identified the opportunity to make better use of routinely collected data (both administrative data from death registrations and routine hospital returns and high-quality clinical data from national clinical audits) to better understand the risk factors for, and consequences of, critical illness. Data linkage with routinely collected data sources can provide enhanced information on risk factors and allow exploration of additional outcome measures, leading to improvements in the risk models used to underpin national clinical audits.

Objectives

1. To improve risk models for adult general critical care by (1a) developing risk models for mortality at fixed time points and time-to-event outcomes, developing risk models for longer-term chronic health outcomes of (1b) end-stage renal disease (ESRD) and (1c) type 2 diabetes, and (1d) developing risk models for subsequent health-care utilisation and costs.
2. To improve risk models for cardiothoracic critical care by (2a) enhancing risk factor data and (2b) developing risk models for longer-term mortality.
3. To improve risk models for in-hospital cardiac arrest by (3a) enhancing risk factor data, (3b) developing risk models for longer-term mortality and (3c) developing risk models for subsequent critical care utilisation.
4. Immediate translation of the improved risk models into practice through (4a) adoption into routine comparative outcome reporting for the national clinical audits, and (4b) communication of research output to providers, managers, commissioners, policy-makers and academics in critical care.

Methods and results

Data sources and data linkage

The primary sources of data for this project were the Case Mix Programme (CMP) national clinical audit of adult critical care and the National Cardiac Arrest Audit (NCAA) of in-hospital cardiac arrests. These were linked with data collected for the UK Renal Registry (UKRR), National Diabetes Audit (NDA), National Adult Cardiac Surgery Audit (NACSA), Hospital Episode Statistics (HES) and Office for National Statistics (ONS) death registrations.

The following records were extracted: for CMP, all patients admitted to a participating critical care unit in England between 1 April 2009 and 31 March 2016; for NCAA, all patients experiencing an in-hospital cardiac arrest in a participating hospital in England between 1 April 2011 and 31 March 2016; for UKRR, all patients who started renal replacement therapy (RRT) prior to 31 December 2016 and were alive on 1 April 2009; for NDA, all registrations in audit years 2008–9 to 2015–16; for NACSA, all patients undergoing cardiac surgery between 1 April 2009 and 31 March 2016; for HES, all finished consultant episodes ending between 1 April 2004 and 31 March 2016; for ONS, all deaths registered from 1 April 2009 to 31 March 2016.

NHS Digital, acting as a trusted third party, undertook a bespoke data linkage between the HES/ONS data set and the five national clinical audits. The CMP and NCAA were treated as index data sets. The approvals and data linkage processes were extremely protracted, taking over 4 years from submitting the first data access request to receiving the final linked data set.

Between 1 April 2009 and 31 March 2016, there were 1,007,149 eligible admissions to 248 adult critical care units participating in the CMP. Of these, 965,576 (95.9%) admissions had identifiable links with HES. Between 1 October 2011 and 31 March 2016, there were 89,030 eligible resuscitation team visits following 2222 calls for cardiac arrests reported by 202 hospitals participating in NCAA. Of these, 83,939 (94.3%) had identifiable links with HES.

Mortality after hospital discharge among critically ill patients in England

Patients were included in this analysis if they were discharged alive from hospital between 1 April 2009 and 15 March 2010 following an episode of critical care; the final follow-up date was 15 March 2015. The outcome was time to death following discharge from acute hospital, established by data linkage with death registrations.

Of 50,869 patients discharged alive from hospital, 17,489 (34.4%) died during follow-up. Mortality at 30 days, 90 days, 1 year and 5 years was 2.1%, 4.7%, 11.8% and 32.3%, respectively. Five-year mortality for the age- and sex-matched general population was 10%. Pre-existing risk factors such as age, comorbidities, and functional status had the greatest influence on longer-term outcomes. Acute severity, organ support and length of stay in critical care had comparatively small effects.

Risk models for mortality following admission to adult critical care

Risk prediction models were developed for mortality at 30 days, 90 days and 1 year following admission to critical care, and at 1 year following hospital discharge.

The models for 30-day and 90-day mortality included 119,509 patients admitted to a participating critical care unit between 1 January 2014 and 31 December 2014. The starting point for model development was the previous risk prediction model for acute hospital mortality. All risk factors remained important in predicting 30-day mortality. The final model showed excellent discrimination (c index 0.90) in both internal and external validation. Differences in benchmarking between acute hospital mortality and 30-day mortality were modest and there was little evidence that using a fixed time point reduced heterogeneity. When refitted to 90-day mortality, the relative importance of severe conditions such as metastatic disease and severe liver disease increased.

The model for 1-year mortality following admission included 127,855 patients admitted between 1 January 2013 and 31 December 2013. All risk factors for acute hospital mortality remained important in predicting 1-year mortality. Fewer acute conditions were retained and there were more cancer-related conditions. Most additional comorbidities available via data linkage with HES were important in predicting 1-year mortality; however, the strongest effects remained for the severe conditions already collected in the CMP.

The model for 1-year mortality following hospital discharge included 100,450 patients discharged alive from hospital between 1 January 2013 and 31 December 2013. The effects of comorbidities were largely similar when the model for 1-year mortality was refitted to hospital survivors.

Risk models for development of end-stage renal disease following critical care

Patients were included in this analysis if they were discharged alive from hospital between 1 April 2009 and 31 March 2016 following a critical care episode, excluding those with pre-existing ESRD. The outcome was new receipt of RRT for ESRD following hospital discharge, identified by linkage with UKRR. Death from any cause before ESRD was treated as a competing risk. Cause-specific hazard ratios were estimated using Cox proportional cause-specific regression models, and subdistribution hazard ratios and cumulative incidence functions were estimated using Fine-Gray regression models.

A total of 598,603 patients were included in the analysis. Median follow-up time was 2.7 years and 2831 (0.47%) patients subsequently received RRT for ESRD (1.52 per 1000 person-years follow-up). The strongest predictors were prior hospital admissions involving chronic kidney disease [adjusted

hazard ratio (aHR) 4.11] or acute kidney injury (aHR 1.73) in the preceding 5 years, admission following nephrectomy (aHR 1.92), creatinine during the first 24 hours of critical care (aHR 7.4 for 120 vs. 60 μmol l^{-1}), and duration of renal support (aHR 1.13 per day).

Risk models for development of type 2 diabetes following critical care

Patients were included in this analysis if they were discharged alive from hospital between 1 April 2009 and 31 March 2016 following a critical care episode, excluding those with pre-existing diabetes (type 1 or type 2). The outcome was a new registration for type 2 diabetes, based on the date of diagnosis recorded in the NDA. Death from any cause before a diagnosis of type 2 diabetes was treated as a competing risk. Cause-specific hazard ratios (cHRs), subdistribution hazard ratios (sHRs) and cumulative incidence functions were estimated as for the analysis of ESRD.

A total of 497,967 patients were included in the analysis. Median follow-up time was 2.8 years, and 12,808 (2.6%) patients were subsequently diagnosed with type 2 diabetes (7.8 per 1000 person-years follow-up). The strongest predictors were blood glucose during the first 24 hours of critical care (aHR 3.0 for 12 vs. 8 mmol l^{-1}), pancreatic surgery (aHR 2.83), severe liver disease (aHR 1.60), body mass index (aHR 2.5 for 35 vs. 25 kg/m^2) and Asian (aHR 2.13) and black (aHR 1.43) ethnicities.

Hospital resource use and costs post-critical care

Patients were included in this analysis if they were discharged alive from hospital between 1 April 2013 and 31 December 2014 following a critical care episode. Resource use was measured as the number of days in acute hospital until 1 year following discharge. Total cost was calculated by summing the costs for subsequent hospitalisation and for subsequent critical care admissions, based on health-care resource groups and the Department of Health and Social Care-admitted patient care tariff. A two-part regression model was used to model predictors of costs: a logistic model for any cost versus no cost and a generalised linear model with a gamma distribution and a log link function for the mean cost, conditional on non-zero cost.

A total of 207,805 patients were included in the analysis. The mean health-care cost during the first year after index hospital discharge was £3734. The distribution of total cost was highly skewed with a large mass at zero. A total of 97,593 patients (47%) had a non-zero health-care cost with a mean cost of £7951 (median £4566, interquartile range £2288–9587); 14,293 (6.9%) patients were admitted to critical care during the first year after index hospital discharge, with a mean cost of £9466 (median £4142, interquartile range £2761–9436). Predictors subsequent health-care cost were: previous hospitalisation, critical care length of stay, age, body mass index, illness severity, mechanical ventilation, dependency prior to admission, source of admission, cardiopulmonary resuscitation, deprivation, severe conditions in the past medical history and comorbidities identified by data linkage with HES.

Risk models for adult cardiothoracic care

Patients were included in this analysis if they were admitted to a cardiothoracic critical care unit between 1 April 2009 and 31 March 2015 within 20 days following cardiac surgery, identified by data linkage with NACSA. Risk models were developed for two outcomes: acute hospital mortality and 1-year mortality.

A total of 27,687 patients admitted to seven cardiothoracic critical care units were included in the analysis: 1072 (3.9%) died during the hospitalisation and 1918 (6.9%) died during the 1-year follow-up. The starting point for model development was the previous risk prediction model for acute hospital mortality. In addition to predictors from the previous model, the following factors from NACSA and HES were found to be important: diabetes, atrial fibrillation/flutter, dyspnoea status pre-surgery, history of pulmonary disease, history of neurological dysfunction, extracardiac arteriopathy, operative urgency, cumulative bypass time, severe cardiovascular disease and congestive heart failure. The final model had excellent discrimination (c index 0.89–0.91); however, we found little impact on benchmarking compared with a generic model. Additional predictors in the model for 1-year mortality were renal

function/dialysis, left ventricular ejection fraction, number of previous myocardial infarctions and major aortic procedure.

Risk models for in-hospital cardiac arrest

Prediction models were developed for return of spontaneous circulation (ROSC) sustained for > 20 minutes (ROSC > 20 minutes), hospital survival, 1-year survival and total length of stay in critical care (based on data linkage with CMP).

The risk models for ROSC > 20 minutes, hospital survival and 1-year survival included 26,748 patients experiencing an in-hospital cardiac arrest in one of 172 hospitals between 1 January 2013 and 31 December 2014. The models were validated on 7073 patients experiencing an in-hospital cardiac arrest between 1 January 2015 and 30 June 2015. In the development data set, 12,566 (47.0%) patients achieved ROSC > 20 minutes, 5349 (20.0%) survived to hospital discharge and 4,454 (16.6%) survived to 1 year. The starting point for model development was previous prediction models for ROSC > 20 minutes and hospital survival. All factors from the previous models remained important and the following addition comorbidities, identified from HES, were added: for all three models, congestive cardiac failure, malignancy and metastatic solid tumour; for ROSC > 20 minutes, peripheral vascular disease, diabetes mellitus and chronic renal disease; for hospital survival, peripheral vascular disease, liver disease and hemiplegia or paraplegia; and for 1-year survival, liver disease and chronic renal disease.

A total of 4841 patients were included in the analysis of length of stay in critical care. The mean total critical care unit length of stay was 8 days for hospital survivors and 4 days for non-survivors, with mean costs of approximately £13,000 and £7,000, respectively. For survivors, the following factors were significant in determining total critical care unit length of stay: age, severe conditions in the past medical history, location of arrest, presenting rhythm, reason for admission to critical care by body system, number of advanced organs supports received, Intensive Care National Audit & Research Centre (ICNARC) physiology score, and interactions between severe conditions in the medical history and ICNARC physiology score. For non-survivors, only the following variables significantly influenced the total critical care unit length of stay: age, number of advanced organs supports received; ICNARC physiology score, and interactions between number of advanced organs supports and ICNARC physiology score.

Conclusions

We have successfully linked CMP and NCAA with five other data sources, providing enhancements in risk models for these audits in the form of additional predictors and novel outcome measures. The greatest barriers to maximising the full potential of data linkage were the inordinate amount of time obtaining and maintaining approvals for the use of multiple data sources from multiple data controllers.

Implications for health care

These results have potentially important implications for the future benchmarking of critical care units through the CMP and NCAA. Having demonstrated feasibility of these linkages, ICNARC should investigate cost-effective approaches to routinely link data to support ongoing reporting from the audits. Although comorbidities were found to improve predictions, they had a greater influence on longer-term than shorter-term outcomes. Given the time-lags involved in linking data, we propose that initial quarterly reporting for the audits continue to use directly collected data and that data linkage is undertaken annually to provide enhanced annual reporting including 1-year outcomes.

At the bedside, the new models may assist in providing objective estimates of potential outcomes to patients and their families. A better understanding of factors predictive of worse longer-term outcomes may help to identify those patients requiring greater support in their recovery following critical illness.

Recommendations for research

- Multidisciplinary research should develop and test care pathways for recovery following critical illness using risk models to target those with the greatest need.
- Further relevant data sources for longer-term outcomes following critical illness should be explored, for example stroke.
- Data linkage for resource use and costs following critical illness should be widened to include primary care, outpatient and emergency department data.

Study registration

This study is registered as NCT02454257.

Funding

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Chapter 1 Introduction

In her Annual Report of the Chief Medical Officer 2011, Professor Dame Sally Davies identified the importance and potential 'to do much more, particularly through the linkage of existing data' (Contains information licensed under the Non-Commercial Government Licence v3.0).[1] Ten years on from this report, much of this potential has yet to be realised.

Adult critical care has a long history of risk prediction and benchmarking outcomes.[2] In the UK, the Intensive Care National Audit & Research Centre (ICNARC) co-ordinates national clinical audits benchmarking outcomes from adult critical care and in-hospital cardiac arrest.[3,4] Risk prediction models for adult critical care have been developed and improved over many years, combining information on the patient's functional status (age, comorbidities, dependency) with their acute severity of illness (reason for admission, physiological measurements) to predict the risk of death in acute hospital.[5] Based on large, representative data sets, these models achieve discrimination (c index or area under the receiver operating characteristic curve) exceeding 0.9. Models for in-hospital cardiac arrest are more limited in terms of the availability of data for patients on the ward compared with the detailed physiological measurements recorded in critical care, and consequently have discrimination in the order of 0.8. The models are used to generate regular reports to critical care units and hospitals participating in the audits comparing observed outcomes against the outcomes predicted by the risk model.

A previous National Institute for Health and Care Research (NIHR) study identified a number of important and essential new directions to better understand the epidemiology of, risk factors for and consequences of critical illness in the areas of adult general critical care, cardiothoracic critical care and in-hospital cardiac arrest.[6] A key theme across all these areas was the opportunity to make better use of routinely collected data (both administrative data from death registrations and routine hospital data returns and high-quality clinical data from national clinical audits) to improve the risk models used to underpin the national clinical audits. Data linkage with other routinely collected data sources has the potential to provide enhanced information on risk factors from, at or prior to the episode of critical illness. This may be particularly useful in settings such as in-hospital cardiac arrest where the available data around the point of arrest are more limited, or for subgroups of critically ill patients where specific information not of relevance to all critical care admissions may be available. In addition, data linkage can allow exploration of alternative and additional outcome measures. Current risk prediction models for critical care and in-hospital cardiac arrest are focused on mortality at hospital discharge.[7,8] Alternative and additional outcome measures include assessing mortality at fixed time points rather than at hospital discharge, including longer-term mortality, but also going beyond mortality to explore important chronic health outcomes, resource use and costs.

Aim and objectives

The aim of the current study was to better understand the epidemiology of, risk factors for and consequences of critical illness leading to improvements in the risk models used to underpin national clinical audits for adult general critical care, cardiothoracic critical care and in-hospital cardiac arrest using data linkage with other routinely collected data sources.

Specific objectives were as follows:

1. To improve risk models for adult general critical care by (1a) developing risk models for mortality at fixed time points and time-to-event outcomes, developing risk models for longer-term chronic health outcomes of (1b) end-stage renal disease (ESRD) and (1c) type 2 diabetes, and (1d) developing risk models for subsequent health-care utilisation and costs.

2. To improve risk models for cardiothoracic critical care by (2a) enhancing risk factor data, and (2b) developing risk models for longer-term mortality.
3. To improve risk models for in-hospital cardiac arrest by (3a) enhancing risk factor data, (3b) developing risk models for longer-term mortality and (3c) developing risk models for subsequent critical care utilisation.
4. Immediate translation of the improved risk models into practice through (4a) adoption into routine comparative outcome reporting for the national clinical audits; and (4b) communication of research output to providers, managers, commissioners, policy-makers and academics in critical care.

Chapter 2 describes the data sources and the process of data linkage and data management. *Chapter 3* reports the methods that were generic across all streams of work. *Chapter 4* reports the long-term (5-year) outcomes for patients discharged alive from hospital following an episode of critical illness. *Chapter 5* reports the development and validation of models for mortality at fixed time points and time-to-event outcomes in adult critical care (objective 1a). *Chapter 6* reports the development and validation of models for development of ESRD following critical care (objective 1b). *Chapter 7* reports the development and validation of models for the development of diabetes following critical care (objective 1c). *Chapter 8* reports the development and validation of models for subsequent health-care utilisation and costs following critical care (objective 1d). *Chapter 9* reports the development and validation of new models for adult cardiothoracic critical care (objective 2). *Chapter 10* reports the development and validation of new models for in-hospital cardiac arrest (objective 3). Finally, *Chapter 11* draws conclusions from the project as a whole, including implications for health care (objective 4), and makes recommendations for further research in this field.

Chapter 2 Data linkage and data management

Data sources

The primary sources of data for this project were the Case Mix Programme (CMP) national clinical audit of adult intensive care and the National Cardiac Arrest Audit (NCAA) of in-hospital cardiac arrests. To provide additional information on past medical history and long-term outcomes, data from the CMP and NCAA were linked with data collected for the UK Renal Registry (UKRR), National Diabetes Audit (NDA), National Adult Cardiac Surgery Audit (NACSA), Hospital Episode Statistics (HES) and Office for National Statistics (ONS) death registrations.

The Case Mix Programme

The CMP is the national clinical audit for adult critical care with a remit for England, Wales and Northern Ireland. The CMP has been established for 20 years and the resulting high-quality clinical database (of > 2 million critical care admissions) has underpinned evaluations of policy and practice in critical care.[9] The CMP has 100% participation of adult, general critical care units delivering Level 3 or combined Level 2/3 care (intensive care units and combined intensive care/high-dependency units); over the time period of this study, participation of these units increased from 90% to approaching 100%. Participation of other critical care units, such as specialist units (e.g. neurocritical care units and cardiothoracic critical care units) and stand-alone Level 2 (high dependency) units is lower. Data on consecutive admissions to each participating critical care unit are recorded prospectively and abstracted from the medical records by trained data collectors according to precise rules and definitions. The data collected include demographics, past medical history, physiological and diagnostic data from the first 24 hours following admission to the critical care unit, outcome and activity data. The data undergo extensive validation checks, both within local software systems and centrally on submission to ICNARC, before being pooled into the CMP database. Details of data collection and validation have been reported previously, and the CMP database has been independently assessed and scored highly by the Directory of Clinical Databases (DoCDat) against their 10 domains (describing elements of coverage and accuracy).[3]

The National Cardiac Arrest Audit

The NCAA was established in 2009 as a joint venture between ICNARC and the Resuscitation Council (London, UK). The NCAA is the national clinical audit of patients aged > 28 days in acute hospitals in the UK who receive cardiopulmonary resuscitation (CPR) and are attended by the hospital-based resuscitation team (or equivalent) in response to a 2222 call (2222 is the emergency telephone number used to summon a resuscitation team in UK hospitals). CPR is defined in NCAA as the receipt of chest compressions and/or defibrillation. Standardised data are collected at the time of the cardiac arrest and from the medical records according to precise rules and definitions. Staff members at participating hospitals enter data onto a dedicated secure online data entry system. Data are validated, both at the point of entry and centrally, for completeness, logicality and consistency. Details of data collection and validation have been reported previously.[4]

The UK Renal Registry

The UKRR (https://renal.org/about-us/who-we-are/uk-renal-registry; accessed 28 October 2022) was established by the Renal Association (now the UK Kidney Association; Bristol, UK) and provides a focus for the collection and analysis of standardised data relating to the incidence, clinical management and outcome of end-stage renal disease. The Registry has been in operation since 1995, with 100% coverage of adult renal units in England and Wales since 2007.

The National Diabetes Audit

The NDA (https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-diabetes-audit; accessed 28 October 2022) is the largest annual clinical audit in the world and is managed by NHS Digital working with Diabetes UK (London, UK) and the National Cardiovascular Intelligence Network, Public Health England. The National Diabetes Core audit, covering care processes, treatment targets, complications and mortality for people with diabetes in primary care and specialist services, is now in its ninth year. Over recent years, the audit has included > 80% of people diagnosed with diabetes in England and Wales.

The National Adult Cardiac Surgery Audit

The NACSA (www.nicor.org.uk/national-cardiac-audit-programme/adult-cardiac-surgery-adult-surgery-audit/; accessed 28 October 2022) collects consecutive operation data from all 35 NHS hospitals in the UK that carry out adult heart surgery. It has been running since 1977, making it the longest running of all UK national clinical audits. The audit is managed by the National Institute for Cardiovascular Outcomes Research (NICOR) at Barts Health NHS Trust, in association with the Society for Cardiothoracic Surgery.

Hospital Episode Statistics for England

The HES database is produced by NHS Digital using records provided by hospitals for the purpose of reimbursement of services funded through the NHS.[10] This study used the admitted patient care (APC) section of the HES database, which contains one record for each episode of care under one consultant during a hospital admission. The HES data set captures all publicly funded hospital activity, which is estimated to represent 98–99% of all hospital activity in England.[10] APC records include information about diagnoses and treatments received, alongside admission details (provider, dates, locations, etc.) and limited patient demographics.

Office for National Statistics death registrations

The ONS death registrations (mortality database) contains information abstracted from civil registrations of deaths registered in England and Wales. The database captures 100% of deaths registered in England and Wales but may not capture the deaths of English/Welsh residents occurring in other countries. Registration is delayed in cases of coroners' investigations. The database includes information about the date, cause and location of death. Although constructed by the ONS, the database is routinely linked to HES and available jointly through NHS Digital.

Selection of records

The following records were extracted from each data source:

- For the CMP, all patients admitted to a participating critical care unit in England between 1 April 2009 and 31 March 2016.
- For the NCAA, all patients experiencing an in-hospital cardiac arrest in a participating hospital in England between 1 April 2011 (the start of data collection to the current scope) and 31 March 2016.
- For the UKRR, all patients in the registry that started renal replacement therapy (RRT) prior to 31 December 2016 and were alive on 1 April 2009, with links to either CMP or NCAA.
- For the NDA, all registrations in audit years 2008–9 to 2015–16, with links to either CMP or NCAA.
- For the NACSA, all patients undergoing cardiac surgery between 1 April 2009 and 31 March 2016, with links to either CMP or NCAA.
- For HES, all finished consultant episodes ending between 1 April 2004 and 31 March 2016 (the earlier start date was selected to allow up to 5 years lookback for evaluation of comorbidities), with links to either CMP or NCAA.
- For ONS death registrations, all deaths registered from 1 April 2009 to 31 March 2016, with links to either CMP or the NCAA.

National data opt-outs were applied to HES and death registrations (and therefore to the subsequent linked study data sets). The prevalence of opt-out in England was approximately 2.7% at the time of data linkage.[11]

Data linkage

NHS Digital, acting as a trusted third party, undertook a bespoke data linkage between the routinely linked HES/ONS data set and the five national clinical audits. The CMP and NCAA were treated as index data sets, with any patient appearing in either of these being included in the final pseudonymised data set for analysis.

The data linkage process (*Figure 1*) worked as follows: each national clinical audit provider uploaded to NHS Digital's secure file sharing platform data sets consisting of the available identifiers for patients included in each national clinical audit, together with an anonymous local key permitting linkage back to locally held data for the audit. NHS Digital linked the data sets and returned to each provider a key consisting of the local identifier and a project-specific, common key for each patient linked to either the CMP or NCAA. Each national audit provider external to ICNARC then supplied direct to ICNARC a pseudonymised data set of the clinical fields required for the project together with the common key, only for those patients linked to the CMP or NCAA. Similarly, NHS Digital provided to ICNARC pseudonymised data extracts of HES and ONS data together with the common key only for patients identified in either the CMP or NCAA. ICNARC used the common key to combine the data extracts provided by the national audit providers and NHS Digital with pseudonymised data extracts from the CMP and NCAA to create the final linked project data set.

Prior to analysis, ICNARC pseudonymised the CMP and NCAA data extracts by replacing date of birth with age in years, replacing the date of admission to the critical care unit or date of in-hospital cardiac arrest with the month and year, replacing all other dates in the data set (including date of death) with the number of days relative to these index dates, replacing postcode with area-level deprivation measures; and replacing hospital/critical care unit names with pseudo-identifiers. Consequently, the final pseudonymised data set contains no patient-identifiable data.

Initial data linkage was planned to include data up to 31 March 2015 with a subsequent update to 31 March 2016. Owing to delays in the approvals process, only HES and ONS data were included in this two-stage process, with all other data sources linked once over the full time period.

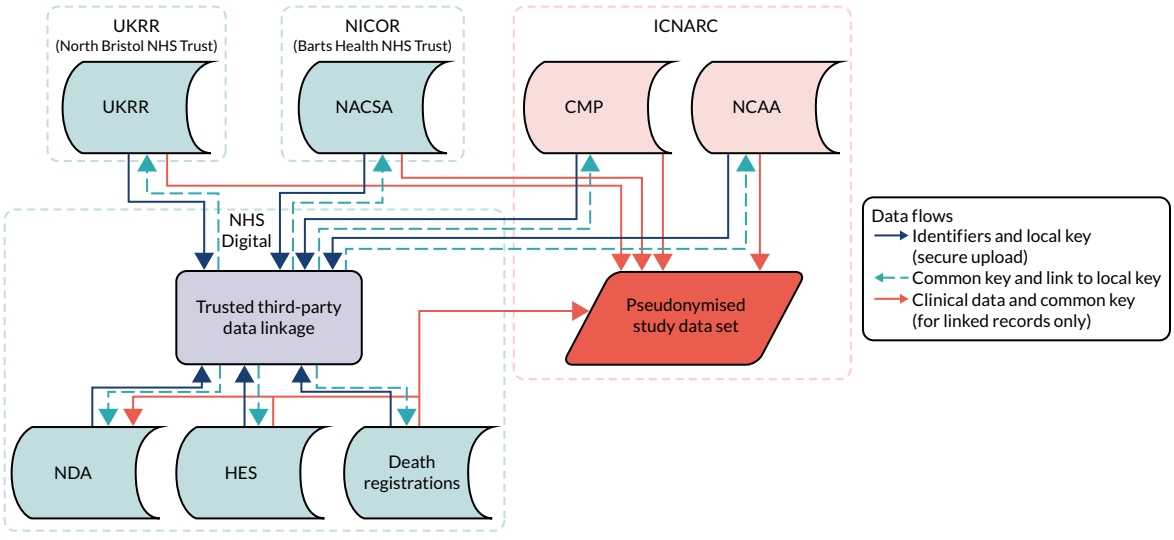

FIGURE 1 Study data flows.

The data for this study were handled under the same security arrangements as for patient-identifiable data from the CMP and NCAA. Data sets resulting from the linkage process were stored on ICNARC's secure servers. No identifiable information has been retained and only the staff involved in the study have access to the data sets.

Results

The approvals and data linkage processes were extremely protracted, taking over 4 years from submitting the first data access request to receiving the final linked data set (*Table 1*). Some of the specific causes of delays included the following:

- Rebranding of the Health and Social Care Information Centre as NHS Digital following the care.data controversy,[12] and a resulting pause in all data applications while internal processes were reviewed.
- Failure of NHS Digital to transfer required forms to ONS.
- Introduction of a new online application system at NHS Digital, with the ongoing applications transferred onto this system.
- Introduction of the European General Data Protection Regulation (GDPR)[13] and requirement to update fair processing information and privacy notices in line with this.
- Replacement of the Data Access Advisory Group at NHS Digital with the Independent Group Advising on the Release of Data (IGARD), operating to terms of reference that had not been made available to applicants.
- Use of an out-of-date application form by NICOR in preparing the submission for approval from the Healthcare Quality Improvement Partnership [(HQIP), data controller for NACSA].
- Change of data controller for the NDA from HQIP to NHS Digital.
- NHS Digital providing incorrect data sets back to the national clinical audit providers (containing the wrong audit's local keys), which took a further 4 months to be replaced with corrected versions.
- Change of host organisation for NICOR from University College London to Barts Health.
- Need to renew data-sharing agreements that had expired while waiting for data to be processed.

TABLE 1 Timeline of data applications and data linkage

Data source	Initial request for data access	Date of approval	Data uploaded to NHS Digital	File returned by NHS Digital to audit providers	Linked data received at ICNARC
HES/death registrations (initial)	September 2015	July 2016	September 2016[a]	N/A	November 2016
HES/death registrations (update)	March 2017	August 2017	February 2018[a]	N/A	January 2019[b]
NDA	December 2016	August 2017[c]	July2018[d]	January 2019[b]	April 2019
UKRR	January 2016	February 2016	February 2018	January 2019[b]	February 2019
NACSA	January 2016	December 2017	May 2018	January 2019[b]	November 2019

a Upload of CMP/NCAA identifiers.
b File with incorrect linkage keys returned in September 2018 and replaced with correct file in January 2019.
c During the application process, data controller for the NDA passed from HQIP to NHS Digital and approval was therefore included under the HES application.
d Internal transfer from NHS Digital National Clinical Audit team to Data Access Request Service team.

In addition to these specific causes, there were numerous unexplained delays waiting for processing to take place, for example a 9-month delay between submitting an application to NICOR for NACSA data and the application being submitted from NICOR to HQIP, and a 7-month delay between uploading data to NHS Digital and receiving a linkage file back.

The final linkage results were as follows:

- Between 1 April 2009 and 31 March 2016, there were 1,007,149 eligible admissions to 248 adult critical care units participating in the CMP. Of these, 965,576 (95.9%) admissions had identifiable links with HES.
- Between 1 April 2011 and 31 March 2016, there were 89,030 eligible resuscitation team visits following 2222 calls for cardiac arrest reported by 202 hospitals participating in NCAA. Of these, 83,939 (94.3%) had identifiable links with HES.

Chapter 3 Methods

Study design

This was a risk modelling study linking existing data from multiple sources.

Sample size

The selection of sites was based on those participating in the CMP and NCAA.

The coverage of the CMP is extremely high, with 256 critical care units participating during the time period covered, including 97% of NHS adult general critical care units in England and Wales. We linked data for the period 1 April 2009 to 31 March 2015, enabling exploration of trends and fit of models over time, although only data from the last 2 years were used to fit the final models as our previous research has established that the fit of risk models deteriorates over time.[14] This was anticipated to give a total sample size of over 850,000 admissions (700,000 critical care unit survivors) for exploring trends and fit over time with 330,000 admissions (280,000 critical care unit survivors) for model fitting. As the CMP is an ongoing programme, additional data accrued while the study was ongoing. At 1 year into the study, an additional 170,000 admissions (150,000 critical care unit survivors) were anticipated to be available and the linkage was updated, providing data for external validation.

Of the 27 specialist cardiothoracic critical care units providing Level 3 (intensive) care, eight were participating in the CMP at the outset of the project. From 1 April 2009 to 31 March 2015 the anticipated sample size was approximately 34,000 admissions to these units (3000 deaths) for objective 2. The updated data linkage was anticipated to include an additional 2300 admissions (200 deaths) for external validation.

The coverage of NCAA is increasing over time and at the outset of the project stood at 181 hospitals, including over 75% of acute hospitals in England and Wales. From 1 April 2011 to 31 March 2015 we anticipated a sample size of approximately 56,000 in-hospital cardiac arrests (10,000 survivors) for objective 3. The updated data linkage was anticipated to include an additional 16,000 in-hospital cardiac arrests (3000 survivors) for external validation.

Setting/context

This study was set in adult critical care units, cardiothoracic critical care units and acute hospitals in England.

Data sources and linkage

Data sources and the data linkage process were described in *Chapter 2*.

Study population

The study population comprised five cohorts: CMP admission cohort, CMP hospital survivor cohort, CMP cardiothoracic critical care cohort, NCAA in-hospital cardiac arrest cohort and NCAA critical care admission cohort. These cohorts are described below.

Case Mix Programme cohorts

For the CMP admission cohort, we selected patients admitted to NHS adult critical care units in England participating in the CMP with identifiable linkage with HES and death registrations. False linkage and errors in linkage with HES and death registrations were excluded. The linked cohort includes patients admitted to participating critical care units between 1 April 2009 and 31 March 2015. The final follow-up date for death registrations was 15 March 2015. For patients with multiple hospital episodes that included critical care unit admissions, we considered the index hospital admission to be the first hospital admission during the analysis period. Re-admissions to critical care and transfers between critical care units during the index hospital admission were excluded.

For the CMP hospital survivor cohort, we selected from the CMP admission cohort those patients who survived to discharge from acute hospital (i.e. the end of the index hospital admission).

For the CMP cardiothoracic critical care cohort, we selected from the CMP admission cohort those patients who were admitted to a cardiothoracic critical care unit participating in the CMP.

National Cardiac Arrest Audit cohorts

For NCAA, data are collected for all individuals (excluding neonates) receiving chest compressions and/or defibrillation and attended by a hospital-based resuscitation team (or equivalent) in response to a 2222 call (2222 is the telephone number used to summon a resuscitation team in UK NHS hospitals). For the NCAA in-hospital cardiac arrest cohort, we selected validated team visits from hospitals in England participating in NCAA with valid linkage with HES and death registrations between 1 October 2009 and 31 March 2015. False linkage and errors in linkage with HES and death registrations were excluded. The final follow-up date for death registrations was 15 March 2015. For patients with multiple hospital episodes that included an in-hospital cardiac arrest, we considered the index hospital admission to be the first hospital admission during the analysis period. Individual team visit records meeting the following criteria were excluded from the cohort: arrests that occurred pre hospital (but were subsequently attended by a hospital-based resuscitation team – usually in the emergency department – and therefore met the scope of NCAA); second and subsequent visits to the same patient during the same hospital stay; and patients for whom it was identified, after commencing resuscitation, that a 'do not attempt cardiopulmonary resuscitation' decision was already documented in the patient's notes.

For the NCAA critical care admission cohort, we selected from the NCAA in-hospital cardiac arrest cohort those patients with valid linkage with CMP, for whom a critical care unit admission occurred after the first in-hospital cardiac arrest recorded in NCAA and during the index hospital admission.

Outcomes

Mortality at discharge from acute hospital

Outcome defined as mortality at discharge from acute hospital (acute hospital mortality), as used for the current risk models. Patients transferred to another acute hospital were followed up until final discharge.

Mortality at 30 days, 90 days and 1 year and survival time

Outcome was defined as mortality at 30 days, 90 days and 1 year following critical care unit admission and time from critical care unit admission or discharge alive to death using the date of death obtained by data linkage with death registrations. In addition, 1-year post-discharge mortality was defined as mortality at 1 year following discharge from acute hospital for patients who survived the index hospitalisation.

Hospital resource use and costs post-critical care

Outcome was defined as number of days in acute hospital, either during the original hospital episode (as identified from CMP data) or during subsequent hospital episodes (as identified through data linkage with HES) and total hospitalisation costs calculated from NHS reference costs.[15]

New diagnosis of end-stage renal disease post-critical care

Outcome was defined as new receipt of RRT for ESRD, based on the date of diagnosis recorded in the UKRR database, after the date of discharge from hospital.

New diagnosis of diabetes post-critical care

Outcome was defined as a new registration for type 2 diabetes, based on the date of diagnosis recorded in the NDA database, after the date of discharge from hospital.

Return of spontaneous circulation > 20 minutes (National Cardiac Arrest Audit)

Outcome was defined as return of spontaneous circulation (ROSC) sustained for > 20 minutes.

Hospital survival (National Cardiac Arrest Audit)

Outcome was defined as survival to discharge from the hospital in which the in-hospital cardiac arrest occurred. Patients transferred to another acute hospital are counted as hospital survivors.

Variables

The main body of the risk predictions models for each objective of the present project was the CMP/NCAA predictors previously included in published risk models.[7,8,16]

New pre- and intra-operative risk factors obtained by data linkage with the NACSA and risk factors obtained by data linkage with HES such as the Charlson Comorbidity Index derived from *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10),[17] diagnostic codes were assessed for inclusion in the new risk models for each outcome.

Further details relating to the variables considered in each modelling process are explained in *Appendix 1* and/or in their corresponding chapter.

Comorbidities

There are two measures to derive comorbidities: severe conditions in the past medical history – defined according to the Acute Physiology And Chronic Health Evaluation (APACHE) II method[18] (*Table 2*) – and comorbidities based on Armitage and van der Meulen's 2010 Royal College of Surgeons (RCS) Charlson

TABLE 2 Severe conditions in the past medical defined according to APACHE II

Condition	Definition
Very severe cardiovascular disease	Fatigue, claudication, dyspnoea or angina at rest (New York Heart Association Functional Class IV)
Severe respiratory disease	Permanent shortness of breath with light activity due to pulmonary disease, or a requirement for home ventilation
Severe liver disease	Biopsy-proven cirrhosis, portal hypertension or hepatic encephalopathy
ESRD	Ongoing requirement for renal replacement therapy for irreversible renal disease
Metastatic disease	Distant metastases documented by surgery, imaging or biopsy
Haematological malignancy	Acute or chronic myelogenous leukaemia, acute or chronic lymphocytic leukaemia, multiple myeloma or lymphoma
Immunocompromise	AIDS (HIV positive and AIDS-defining illness), congenital immunohumoral or cellular immune deficiency state, chemotherapy, radiotherapy or daily high-dose steroid treatment (≥ 0.3 mg kg^{-1} prednisolone or equivalent)

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

Score[17] (*Table 3*). Severe conditions in the past medical history are recorded in the CMP. Conditions must have been evident in the 6 months prior to admission to the critical care unit and documented in the patient's notes at or prior to admission. RCS Charlson comorbidities were identified from linked HES records by relevant ICD-10 codes (see *Table 3*) in any of the first seven diagnosis fields of the index hospital admission or of any episode that finished during the year preceding the index hospital admission.

To allow the use of both severe and lower levels of comorbidity in the same model, and reduce duplication of these measures, we combined the nine APACHE II comorbidities and 13 of the RCS Charlson comorbidities to produce 19 comorbid categories (*Table 4*). Acquired immune deficiency syndrome (AIDS) and human immunodeficiency virus (HIV) were not included because these diagnosis codes were supressed in the HES extract, and CMP data indicate it was a rare diagnosis in this patient group.

Sepsis

The CMP database can be used to identify patients who had sepsis at admission to the unit or who developed sepsis during the first 24 hours in the unit based on their reason for admission to critical care and physiology measured during the first 24 hours following admission. It cannot be used to identify patients who developed sepsis after the first 24 hours following admission to the unit.

Based on the current international consensus definitions,[20] sepsis-3 is defined as infection plus new organ dysfunction, defined as an increase in a Sequential Organ Failure Assessment (SOFA) score of ≥ 2 or points. In the CMP, this is operationalised as evidence of infection from the primary or secondary reason for admission to the critical care unit plus organ dysfunction, defined as a SOFA score of ≥ 2 points in any one organ system or a SOFA score of ≥ 1 points in two or more organ systems, based on physiological data from the first 24 hours following admission.[21] Full details of the organ dysfunction definitions are summarised in *Appendix 1*, *Table 37*.

TABLE 3 Royal College of Surgeons Charlson comorbidities indicating ICD-10 codes for 14 disease categories

RCS Charlson comorbidities	ICD-10 codes
Previous MI	I21,[a] I22,[a] I23,[a] I252
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Peripheral vascular disease	I70–I73, I770, I771, K551, K558, K559, R02, Z958, Z959
Cerebrovascular disease	G45, G46, I60–I69
Dementia	A810, F00–F03, G30, G31
Chronic pulmonary disease	I26, I27, J40-J45, J46,[a] J47, J60–J67, J684, J701, J703
Rheumatological disease	M05, M06, M09, M120, M315, M32–M36
Liver disease	B18, I85, I864, I982, K70, K71, K721, K729, K76, R162, Z944
Diabetes mellitus	E10–E14
Hemiplegia or paraplegia	G114, G81–G83
Chronic renal disease	I12, I13, N01, N03, N05, N07, N08, N171,[a] N172,[a] N18, N19,[a] N25, Z49, Z940, Z992
Malignancy	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C80–C85, C88, C90–C97
Metastatic solid tumour	C77–C79
AIDS/HIV	B20–B24

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; MI, myocardial infarction.
Reproduced with permission from Armitage JN.[19]
a These ICD-10 codes were not included as comorbidities if identified from the index hospitalisation.

TABLE 4 Combining Severe conditions in the past medical history (APACHE II) and RCS Charlson comorbidities

Body system	Comorbidities
Cardiovascular	Previous MI (excluding very severe cardiovascular disease)
	Congestive cardiac failure (excluding very severe cardiovascular disease)
	Peripheral vascular disease
	Very severe cardiovascular disease
Neurological	Cerebrovascular disease
	Dementia
	Hemiplegia or paraplegia
Respiratory	Chronic pulmonary disease (excluding severe respiratory disease)
	Severe respiratory disease
Liver	Liver disease (excl. severe liver disease)
	Severe liver disease
Renal	Chronic renal disease (excluding end-stage renal failure)
	ESRD
Malignancy	Any malignancy (excluding haematological malignancy and metastatic disease)
	Haematological malignancy
	Metastatic disease (including metastatic solid tumour)
Other	Immunocompromise
	Diabetes mellitus
	Rheumatological disease

MI, myocardial infarction.

Statistics and data analysis

Handling of missing data

The percentage of physiological predictors with missing values in the CMP data set ranged from 0.6% for highest heart rate to 13.9% for blood lactate. In a previous work[6] exploring the impact of missing data on developing ICNARC risk prediction models using CMP data, no differences in the inference were found and coefficient estimates appeared to be insensitive to the missing data and the various models used to deal with them. The study[6] concluded that under the CMP, missingness scenario benefits of using multiple imputation in developing the risk prediction model are likely to be minimal. Therefore, for objective 1 (risk models for adult critical care using the full CMP cohorts) we decided that the model building and analysis process would be done with non-imputed (complete-case) data and a parallel analysis would be done at the same time on the multiply imputed data set to test the consistency of the results.

For analysis relating to objective 2 (risk models for cardiothoracic critical care) and objective 3 (risk models for in-hospital cardiac arrest), missing data were imputed to address potential bias and loss of precision in these smaller data sets. Fully conditional specification was used as the multiple imputation method.[22] All the candidate predictors (with or without missing values) and the outcome, as well as auxiliary variables related to missingness, were entered into the imputation model.[23,24] When required, simple or zero-skewness log transformation for non-normality was applied. Unless the rate of missing information is unusually high, there tends to be little or no practical benefit to using more than 10 imputations and so, in the following analysis, 10 repeat imputations were performed.

Patient characteristics

Demographic, clinical and other characteristics of the patients included in the development and validation data sets for the risk prediction models for each objective were summarised. Categorical variables were summarised by frequencies and percentages. Percentages were calculated according to the number of patients for whom data were available. Continuous variables were summarised by mean and standard deviation (SD), as well as median and interquartile range (IQR).

Analysis of outcome measures

Methods for model development were based on those used for the development of risk models for acute hospital mortality in the previous NIHR study.[6] Binary outcomes were modelled with logistic regression models.

Models for longer-term chronic health outcomes analyses had to account for competing events, in particular when some patients die before being observed at the stage of interest. Death should be considered as a competing event because it precludes the observation of the stage of interest. To account for both the time-to-onset and competition with death, cause-specific Cox proportional hazards models[25] and Fine/Gray models[26] were considered.

It is well recognised that the statistical analysis of health-care resource use and cost data poses a number of difficulties. First, we reviewed the literature on methods and models in the field of calculating and predicting health-care resource use and costs, their ability to address with the usually statistical issues that is, skewness, excess zeros, multimodality and heavy right tails, as well as specific challenges of the project such as competing risk and censoring. Before a decision was made, we met with health economics experts to discuss the above issues. Finally, a generalised linear model with a gamma distribution and a log-link function was agreed as the most reasonable approach.[27]

An analysis plan was finalised with input from the Clinical Advisory Group for each objective prior to modelling.

In all, the following approaches for model development were applied depending on the outcome and objectives of the analysis:

- To model mortality/survival at fixed time points (hospital discharge, 30 days, 90 days, 1 year, ROSC > 20 minutes): logistic regression (including, if appropriate, random effects of critical care unit/hospital).
- To model time-to-event outcomes: standard survival regression methods such as Kaplan–Meier survival curves and Cox regression.
- To model chronic health outcomes with a competing risk of death: cause-specific Cox proportional hazards models and Fine/Gray models.
- To model critical care/hospital resource use and costs: generalised linear model with a gamma distribution and a log-link function.

Functional form

In the previous project,[6] the functional form of physiological predictors and the optimal approach to deal with these were explored. We decided to use restricted cubic splines because they showed the flexibility of fractional polynomials but with better behaviour in the tails, they captured the most prominent features of the relationship between predictors and outcomes, and the fit was more plausible than the previous categorical approach.

So, after having rejected the hypothesis of linearity, the following approaches for modelling continuous predictors were applied.

The predictor–outcome relationship was explored by expanding the variable into multiple terms and testing pooled and individual non-linearity. Spline fits could be sensitive to the number of knots so, to avoid overfitting, spurious dips and inflexion points, as well as unrealistic features of the curve, three, four or five knots were considered. Knot positions were selected according to the recommendations of Harrell.[28] Right restricted cubic splines (i.e. with the linearity restriction applied only at the right-hand end of the curve) were used when appropriate (e.g. for variables that were bounded by zero) to allow more flexibility.

To judge the plausibility and accuracy of the fitted curves, we plotted observed log-odds against the alternative modelling approaches and used a running line smoother as a reference. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were calculated to compare the fit of the strategies for modelling continuous variables, taking three-knot restricted cubic splines as reference, to assess if the increased complexity of the model resulting from including more knots was worthwhile.

The best functional form for each predictor was selected based on fitting, plausibility, accuracy and prior knowledge about the predictor.

We finally explored collapsing extreme points to determine if the shape of the curves could be affected by outlying values. Additional analyses using imputed data were done in parallel to provide reassurance about the results.

Approach to model development

For each newly developed or revised risk prediction model, we adopted the following general approach to model development:

1. Potential predictors were identified and patterns of missing data within the potential predictors were explored, with particular attention to the completeness and accuracy of data linkage between the databases. Approaches to handling the missing data were compared, based on the best performing approaches from previous work.
2. The most appropriate functional form for each potential predictor was explored, taking into consideration the use of continuous non-linear models (e.g. restricted cubic splines or right-restricted cubic splines) for continuous predictors and appropriate categorisation and structure of categorical predictors.
3. A main effects model was fitted through a process of deleting terms, re-fitting and verifying, using Wald and/or likelihood ratio tests to remove non-significant predictors, and the BIC as the basis to determine which predictors make an important contribution to the fit of the model.
4. The functional form and significance of each predictor included in the main effects model were then re-examined to confirm if any changes were required based on adjustment for other important predictors.
5. Finally, interactions between the predictors were introduced based on clinical input to identify and prioritise the potentially important interactions to consider and avoid over fitting, with interactions retained if they have a positive effect on the BIC.

The starting point for revised risk models was the previously developed risk model for each outcome. The addition of new predictors was considered and then the effect of those predictors previously included in the existing models was re-assessed to determine whether or not they still made an important contribution to the model (see point 3 above).

For developing risk models for mortality/survival at fixed time points and time-to-event outcomes (objectives 1a, 2b, 3b), the starting point for each new risk model was the risk model for survival to hospital discharge developed in the previous objective (2a and 3a) and the existing model for adult general critical care. In each case, this risk model was refitted to the new outcome, risk factors that

were previously considered but were found not to be important predictors for hospital survival were reassessed by adding them to the model and, finally, the effect of those risk factors previously included in the risk model was reassessed to determine whether or not they still made an important contribution to the model (see above). It was anticipated that predictors representing age, chronic ill health and functional status would have a greater impact on longer-term outcomes than on hospital survival, whereas predictors relating to the acute illness would have less impact.

As the important risk factors and their relationships with the outcome may be very different from those considered previously, the new risk models for critical care resource use and for longer-term chronic health outcomes were developed, de novo, using the methods previously described.

Assessing the predictive performance

Throughout the study, risk prediction models were validated for their discrimination, calibration and overall fit. The panel of measures described here was used to give an overall assessment of model performance.

The discrimination of the model was estimated by the c index (equivalent to the area under the receiver operating characteristic curve)[29] and accuracy was assessed by Brier's score (mean squared error between outcome and prediction).[30] We assessed calibration graphically with predicted probability on the x-axis and the observed outcomes on the y-axis in 10 equal-sized risk groups (calibration plot) and by Cox's calibration regression (linear recalibration of the predicted log odds).[31] The standardised mortality ratio (SMR) with 95% confidence interval (CI) was calculated to observe the difference between actual and expected mortality by dividing the observed number of deaths by the number of deaths predicted by the model. Because of the size of the data sets to be used, we did not assess the calibration of the model with the Hosmer–Lemeshow c-statistic because this may have led to misleading conclusions.[32]

Internal and external validation

Each newly developed or revised risk prediction model was validated using the above measures both within the development sample and in independent validation data.

When a prognostic model is based on a very large sample size and relevant variables are included in the final model, optimism is small and so, the apparent estimates of model performance (c index and Brier's score in the development data) are attractive because of their stability.[33] However, to assess optimistic performance within the development data, the percentage of over-fitting was estimated by refitting the model in 100 bootstrap replications of the data set and evaluating the resulting model in the original development data to calculate the optimism-corrected statistics.[34,35]

When existing risk prediction models were modified, the performance of the revised model was compared with the existing model using reclassification techniques.[36] The improvement in reclassification was quantified as the net reclassification improvement (NRI). NRI is an index that attempts to quantify how well a new model reclassifies subjects – either appropriately or inappropriately – as compared with an existing model. We calculated the NRI both using pre-defined categories of risk and also as a continuous measure (i.e. the proportion with any improvement in predicted risk compared against the proportion with any worsening in predicted risk).

In addition, the risk models developed were compared, when relevant, against existing risk models (e.g. the $ICNARC_{H-2015}$ model[7]).

Time-to-event analysis

Statistical methods relevant to model time-to-event outcomes are described in the corresponding chapters.

Patient and public involvement

Patient representatives on the ICNARC Board of Trustees and the NCAA Steering Group contributed to the original study proposal. Three independent patient and public members were included in the Study Steering Committee overseeing the study (see *Acknowledgements*). Patient and public representatives across all these groups consistently highlighted the importance of long-term outcomes and improving recovery pathways following critical care. The patient and public members of the Study Steering Committee also provided assurance that the approaches to handling patient data and maintaining confidentiality were robust and acceptable to the general public.

Chapter 4 Mortality after hospital discharge among critically ill patients in England

Introduction

To date, the main outcome for national clinical audits, including the CMP and NCAA, has been mortality at acute hospital discharge. However, recovery from critical illness can be a slow process, with studies reporting substantial ongoing burden of mortality several years after discharge from hospital.[37,38] Therefore, understanding the consequences of critical illness has become a focus of international interest, as evidenced by the topic of a recent round table conference.[39] In the present project, data linkage with death registrations has permitted follow-up of longer-term mortality, enabling us to better understand the time course of recovery from critical illness and which risk factors have an impact on longer-term mortality.

The aim of this chapter is to describe the long-term (5-year) survival for patients discharged alive from hospital following admission to an adult, general critical care unit overall, compared with age- and sex-matched general population by patient subgroups

Methods

Study cohort

The cohort for this chapter was the CMP hospital survivor cohort (see *Chapter 3*).

Inclusion and exclusion criteria

From the CMP hospital survivor cohort, patients were selected if they were discharged from acute hospital (from their index hospital admission) between 1 April 2009 and 15 March 2010 – allowing 5 years of follow-up for all patients to the final follow-up date for death registrations of 15 March 2015.

Outcome measure

The outcome measure was time to death following discharge from acute hospital. The outcome was defined as death (from any cause) within 5 years of discharge from hospital and number of days from hospital discharge to death, established by data linkage with death registrations. Patients not reported to have died were censored at 15 March 2015.

Statistical analysis

Kaplan–Meier survival curves were generated to describe mortality after hospital discharge among critical care admissions. Estimated cumulative mortality from 30 days to 5 years is reported both overall and for patient subgroups identified from the primary reason for admission to the critical care unit (pneumonia, bowel tumour, traumatic brain injury, cardiac surgery). The survival curve for critical care survivors was compared with that for the age- and sex-matched general population.

Results

Of the 789,149 CMP admissions with identifiable linkage with HES and death registrations in England between 1 April 2009 and 31 March 2015 (see *Chapter 2*), there were a total of 50,869 first admissions to adult general critical care units discharged alive from acute hospital between 1 April 2009 and 15 March 2010.

During the follow-up period after hospital discharge, there were 17,489 (34.4%) deaths among critical care hospital survivors. A comparison with the age- and sex-matched general population showed excess mortality among critical care survivors. The overall 5-year survival rate was 67.6% (95% CI 67.2% to 68.0%) compared with a predicted survival rate of 90% based on the general population; this corresponds to more than a three-fold increase in 5-year mortality among critical care survivors (*Figure 2*).

Mortality rates at 30 days, 90 days and 1 year were 2.1%, 4.7% and 11.8%, respectively. Approximately one-quarter of the deaths within 5 years occurred within the first 6 months following hospital discharge. This pattern of higher death rates over the earlier follow-up time was consistent across all patient subgroups considered, and particularly relevant for patients with severe conditions in their medical history (*Table 5*).

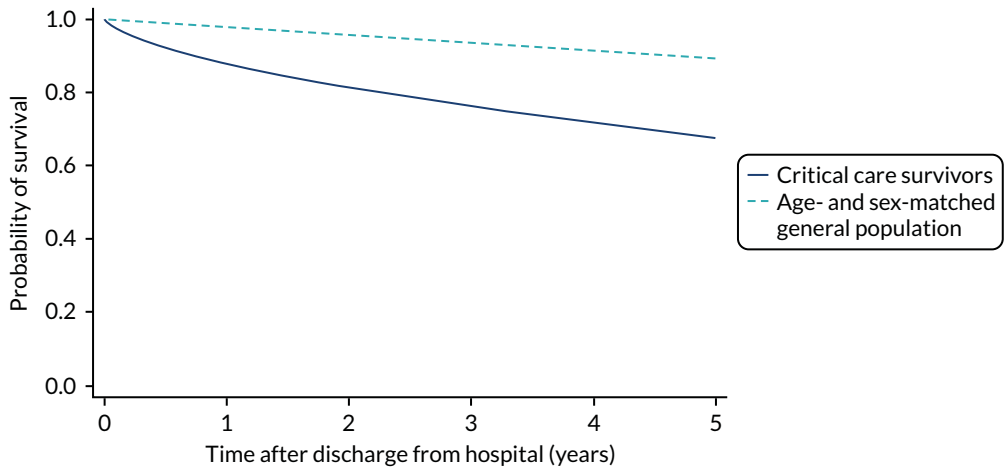

FIGURE 2 Kaplan–Meier survival curve for critical care survivors compared with the age- and sex-matched general population.

TABLE 5 Cumulative mortality after hospital discharge among critical care survivors – overall and by demographics and comorbidities

	Mortality (%)				
Characteristics	**30 days**	**90 days**	**1 year**	**5 years**	**Overall[a]**
Overall	2.1	4.7	11.8	32.3	34.4
Age (years)					
< 30	0.6	1.1	2.6	6.0	6.3
30–39	0.8	1.7	5.1	11.9	12.3
40–49	1.4	3.0	7.4	19.1	19.9
50–59	1.9	4.0	11.0	27.5	29.0
60–69	2.0	4.8	12.6	35.1	37.2
70–79	2.7	6.2	15.6	43.7	46.7
≥ 80	4.5	9.4	20.7	59.5	63.6

TABLE 5 Cumulative mortality after hospital discharge among critical care survivors – overall and by demographics and comorbidities (*continued*)

Characteristics	Mortality (%)				
	30 days	90 days	1 year	5 years	Overall[a]
Sex					
Male	2.3	4.9	12.6	33.8	35.8
Female	1.9	4.4	11.0	30.6	32.6
Deprivation					
1 (least)	2.3	5.3	12.2	32.6	34.6
2	2.1	4.8	12.0	33.3	35.6
3	2.2	4.8	12.2	32.8	35.0
4	2.2	4.6	11.6	32.5	34.2
5 (most)	2.1	4.5	11.7	31.7	33.5
Severe conditions in medical history					
Severe liver disease					
No	2.1	4.7	11.8	32.2	34.3
Yes	4.7	9.1	18.6	43.8	45.8
Haematological malignancy					
No	2.1	4.6	11.7	32.1	34.1
Yes	5.4	15.4	35.8	62.6	64.3
Metastatic disease					
No	2.0	4.4	11.3	31.4	33.5
Yes	7.9	15.6	36.5	71.7	72.9
Severe respiratory disease					
No	2.0	4.6	11.7	31.8	33.8
Yes	4.9	10.3	24.2	59.7	62.4
End-stage renal disease					
No	2.1	4.6	11.7	32.1	34.1
Yes	6.3	10.9	24.7	56.9	59.8
Very severe cardiovascular disease					
No	2.1	4.8	11.8	32.1	34.1
Yes	4.2	8.3	21.5	55.6	59.3
Prior dependency					
Able to live without assistance	1.6	3.7	9.9	27.8	29.6
Some (minor/major) assistance	4.4	9.1	20.6	52.6	55.5
Total assistance	6.6	10.7	18.4	42.6	44.5

a Death at any time during follow-up (individual patients were followed up to death or censored between 5 and 6 years following hospital discharge).

Five-year mortality among those aged 70–80 years was 43.7% compared with 6.0% among younger (< 30 years) survivors of critical illness. This pattern of increasing mortality with increasing age was consistent across all time points assessed (see *Table 5*).

Among admissions with any of the severe comorbidities (APACHE II definition), patients with metastatic disease and haematological malignancy showed the worst prognosis. One-year mortality for metastatic disease was 36.5% (95% CI 33.8% to 39.2%) increasing to 71.7% (95% CI 69.2% to 74.3%) at 5 years after hospital discharge and an increase from 35.8% (95% CI 32.1% to 39.2%) to 62.4% (95% CI 58.7% to 66.5%) for haematological malignancy. All comorbidities survival curves displayed an increased early mortality (at 30/90 days) after discharge but a more gradual decrease during the rest of the period (see *Report Supplementary Material 1*, Figure S1). Metastatic disease and haematological malignancy showed a steeper gradient during the first year than the other groups, which indicated a higher risk for these patients during this period. Univariable associations with 5-year survival for severe comorbidities were all significant ($p < 0.001$ by log-rank test).

Five-year mortality increased with acute illness severity, as assessed by the ICNARC Physiology Score (*Table 6*).[40] The gradient was steeper when considering the APACHE II score, which also incorporates age and comorbidities.[18] There was little association between long-term mortality and the length of

TABLE 6 Cumulative mortality after hospital discharge among critical care survivors – by acute admission characteristics

	Mortality (%)				
Characteristics	**30 days**	**90 days**	**1 year**	**5 years**	**Overall[a]**
Admission type					
Medical	2.7	5.5	12.3	31.1	32.9
Elective surgery	1.1	3.1	11.2	34.9	37.3
Emergency surgery	2.4	5.2	11.6	31.4	33.3
CPR within 24 hours prior to admission					
No CPR	2.1	4.7	11.9	32.3	34.4
Community CPR	3.0	4.7	8.3	25.8	28.1
In-hospital CPR	3.9	6.8	14.6	38.6	41.4
ICNARC physiology score (quintiles)					
< 10	1.1	2.5	7.9	25.4	27.0
10–13	1.4	3.9	10.7	30.8	32.9
14–17	2.5	5.2	13.7	34.9	37.0
18–24	3.1	6.8	15.3	38.4	40.5
> 24	4.1	7.7	15.8	39.5	42.1
APACHE II score (quintiles)					
< 11	0.9	2.0	5.7	17.6	18.7
11–13	1.3	3.4	10.0	30.1	32.3
14–16	2.1	5.0	13.0	36.5	39.1
17–21	3.3	6.9	16.6	42.9	45.4
> 21	4.9	9.8	21.8	50.2	52.5

a Death at any time during follow-up (individual patients were followed up to death or censored between 5 and 6 years following hospital discharge).

stay in critical care or organ supports received, although a longer hospital stay was associated with increased mortality (*Table 7*).

Table 8 shows the mortality for specific patient subgroups. Close to 90% of hospital survivors following traumatic brain injury survived for 5 years, but only half of patients with a bowel tumour diagnosis survived for a similar period.

TABLE 7 Cumulative mortality after hospital discharge among critical care survivors, by length of stay and organ support

	Mortality (%)				
Characteristics	**30 days**	**90 days**	**1 year**	**5 years**	**Overall[a]**
Total critical care unit length of stay in hours (quintiles)					
< 22	1.7	3.8	9.6	27.1	29.0
22–41	1.4	3.4	10.1	29.8	31.8
42–71	1.9	4.7	12.4	33.9	35.9
72–152	2.6	5.4	13.8	36.1	38.3
> 152	3.0	6.3	13.5	35.0	40.0
Hospital length of stay in days (quintiles)					
< 6	1.1	2.1	5.4	16.8	18.7
6–9	1.0	2.4	8.2	26.0	28.0
10–15	1.8	3.9	11.0	32.6	34.6
16–29	2.4	5.8	14.2	38.4	40.9
> 29	3.9	8.4	18.7	44.4	46.6
Receipt of advanced respiratory support					
No	2.1	4.8	12.5	34.5	36.6
Yes	2.2	4.6	10.9	29.2	31.1
Duration of advanced respiratory support (quintiles)[b]					
1–2	1.9	4.1	10.3	27.6	29.5
3–7	2.5	5.5	12.3	31.6	33.3
8–14	2.7	5.2	10.4	29.4	31.2
+ 14	2.3	5.2	12.2	33.8	36.2
Receipt of advanced cardiovascular support					
No	2.0	4.4	11.5	31.8	33.7
Yes	3.0	6.1	13.8	35,2	37.5
Receipt of renal support					
No	2.0	4.4	11.4	31.6	33.6
Yes	4.5	8.9	18.3	43.4	45.4
Receipt of neurological support					
No	2.1	4.7	12.1	33.1	35.1
Yes	2.2	4.5	10.1	25.0	26.5

a Death at any time during follow-up (individual patients were followed up to death or censored between 5 and 6 years following hospital discharge).
b Only in admissions with advance respiratory support.

TABLE 8 Cumulative mortality after hospital discharge among critical care survivors for specific patient subgroups

	Mortality (%)				
Patient subgroups	30 days	90 days	1 year	5 years	Overall[a]
Pneumonia	3.0	6.1	13.6	36.0	38.0
Bowel tumour	3.6	9.0	21.6	49.6	51.7
Traumatic brain injury	1.8	2.6	4.1	10.8	11.6
Cardiac surgery	1.2	3.0	7.8	28.9	31.9

a Death at any time during follow-up (individual patients were followed up to death or censored between 5 and 6 years following hospital discharge).

Discussion

Reporting long-term mortality following critical care is essential for a better understanding of the consequences of critical illness, helping to inform clinicians, policy-makers and health service planners. In the present chapter, data linkage with death registrations has enabled us to describe the time course of recovery from critical illness and which risk factors have an impact on longer-term mortality.

We have confirmed that there is an excess mortality among critical care survivors. Of patients discharged alive from acute hospital following an episode of critical care in 2009/10, almost one-third died during the subsequent 5 years compared with 10% of the age- and sex-matched general population. Pre-existing risk factors such as age, comorbidities and functional status had the greatest influence on longer-term outcome. Admissions with oncology conditions in the medical history had the worst prognosis. Acute severity, organ support and length of stay in critical care had comparatively small effects.

We found that the 1-year and 5-year mortality in critical care survivors discharged alive from hospital were 11.8% and 32.3%, respectively. These results are remarkably similar to those reported by Lone *et al.*[38] in a multicentre study of critical care units in Scotland, which reported mortality of 10.9% and 32.3% at these time points, and also to a large multicentre study from Ontario, Canada, which reported mortality of 11.1% and 29.0%, respectively.[37]

Chapter 5 Risk models for mortality following admission to adult critical care

Introduction

Acute hospital mortality has predominantly been selected as the main outcome for national clinical audits. This is partly because of its convenience to record and collect, as follow-up of patients beyond acute hospital discharge has not been practicable. However, some research[41] suggests that time-based outcomes, for example, mortality at 30 or 90 days following admission or duration of survival, would be less prone to bias arising from variation in provision of community health and social care services, which may affect the timing at which patients are discharged from acute hospital. Furthermore, exploring longer-term end points, such as 1 year, would also enable us to better understand the time course of recovery from critical illness and which risk factors have an impact on longer-term mortality.[42] Data linkage with death registrations has permitted us to follow up patients admitted to critical care units for both short- and longer-term mortality.

In addition, the risk prediction models developed for adult general critical care were limited to the available predictors within the CMP data set, which, in turn, are limited by what it is feasible to expect providers to routinely collect for the purpose of national clinical audit. Data linkage with HES has expanded the available predictors, permitting us to evaluate the impact of a wider number of comorbidities than are recorded in the CMP, which may be expected to have greater prognostic importance for determining 1-year mortality.

This chapter reports on the development and validation of risk prediction models for patients admitted to adult critical care units, evaluating mortality at fixed time points (30 days, 90 days and 1 year). We focus the present chapter on mortality at 30 days and 1 year, with results for 90 days used to compare and consolidate the 30-day findings.

Methods

Methods common to all objectives and analyses were describe in *Chapter 3*. Details relating to the study cohorts, inclusion and exclusion criteria and outcomes can be found in the same chapter.

Outcomes and candidate predictors

Risk prediction models were developed for three outcomes: mortality at 30 days, 90 days and 1 year following admission to the critical care unit. Patients were followed up to each end point from the first critical care unit admission during the index hospital admission. This starting point was selected for a benchmarking purpose.[43] A second 1-year follow-up time point from hospital discharge for hospital survivors was also established with the aim to compare the role of comorbidities among hospital survivors.

The starting point for the risk prediction models in the present chapter was the set of physiological and non-physiological predictors from the CMP previously included in the existing model to predict mortality at discharge from acute hospital.[7] Severe conditions in the medical history that were previously considered but were found not to be important predictors for acute hospital mortality were reassessed for short-term outcomes. The full list of candidate predictors from the CMP is presented in *Appendix 1*, *Table 38*.

It was anticipated that chronic ill health has had a greater impact on longer term outcomes than on mortality at 30 days or at discharge from acute hospital. Combinations of severe conditions in the past medical history (APACHE II) and RCS Charlson comorbidities, as described in *Chapter 3*, were therefore included in the 1-year analyses.

Development of a risk model for 30-day mortality

The steps to developing a risk model for 30-day mortality, starting from the predictors in the model for acute hospital mortality, were as outlined in *Chapter 3*.

Reasons for admission to critical care are recorded in the CMP using the ICNARC Coding Method: a five-tiered (type – surgical or non-surgical/body system/anatomical site/physiological or pathological process/condition) coding system specifically developed for this purpose.[44] Currently, coefficients for the ICNARC model are applied at three levels of the hierarchical code—either at tier 5, the individual condition, or at tier 4, the process, or at process/the body system combination. The following steps were followed in updating the primary reason for admission categories:

- As starting point, the current process and process/system categories were retained.
- The set of categories was refined by adding specific conditions.
- Process/system categories were split into individual conditions that had sufficient sample size (number of events ≥ 20).
- Each individual condition was retained as a new category if it was significant as a stand-alone variable in the model after adjusting for process/system (likelihood ratio tests, $p < 0.001$) and made an important contribution to the fit of the model (based on the presence of a strong effect on the BIC).

Finally, interactions between the categories and physiology were introduced based on clinical input to identify and prioritise the potentially important interactions to consider and avoid overfitting, with interactions retained if their likelihood ratio test p-value was < 0.001 and had a positive effect on the BIC.

Use of 30-day mortality for benchmarking

Existing risk prediction models for critical care, including the ICNARC model, have been based on an outcome of mortality at hospital discharge. These models have been used for national clinical audits, including the CMP and NCAA, to underpin fair comparisons among health-care providers. Research from the Netherlands[42] has suggested that comparison of risk-adjusted mortality across critical care units using mortality at 30 or 90 days, rather than at hospital discharge, results in less heterogeneity.

To assess the effect of using 30-day mortality for benchmarking instead of acute hospital mortality, the final model for 30-day mortality was used to predict acute hospital mortality in the development data set. We used second-level customisation: acute hospital mortality was set as the outcome and the predictors were the variables included in the final model for 30-day mortality. The performance of this customised model (discrimination, calibration and accuracy) was used to assess whether or not the 30-day model could be used to predict mortality at acute hospital discharge.

As the SMR is used on benchmarking to evaluate the performance of a critical care unit we explored the effect of using 30-day versus in-hospital mortality on the SMR and the impact of the location of critical care units on a funnel plot of SMR against sample size.[45] Upper two and three SD control limits were used to identify higher-than-expected mortality and lower two and three SD control limits were used to identify lower-than-expected mortality.

Development of a risk model for 90-day mortality

The same approach used to customise the model to predict acute hospital mortality was applied when extending mortality prediction from 30 days to 90 days. A second-level customisation of the final 30-day mortality model was used to predict mortality at 90 days following admission to critical care.

Development of a risk model for mortality at 1 year following critical care admission

The risk model for mortality at 1 year following critical care admission was developed using the methods outlined in *Chapter 3* using, as a starting point, the previous model for acute hospital mortality and considering the additional comorbidity variables in the development.

Development of a risk model for mortality at 1 year following hospital discharge

The risk model for mortality at 1 year following hospital discharge was developed using the methods outlined in *Chapter 3* using, as a starting point, the previous model for mortality at 1 year following critical care admission.

Results

Mortality at 30 days

Between 1 January 2014 and 31 December 2014, there were 153,494 first admissions to 235 adult critical care units in England participating in the CMP with identifiable linkage with HES and death registrations, of which 123,719 (80.6%) had complete data for all candidate physiological predictors (see below). Patients who were dead, were in line for palliative care or had all active treatment withdrawn immediately on admission and patients with missing values in non-physiological predictors were excluded. In total, 119,509 patients were included in the development data set. As described in *Chapter 3*, missing values were not imputed in the primary analyses for adult critical care.

Of the 119,509 patients, 22,579 (18.9%) died during the 30-day follow-up. Of these, 16,129 (13.5%) died during the critical care admission. The median critical care unit length of stay was 57 hours (IQR 26–122 hours) for 30-day survivors and 68 hours (IQR 28–151 hours) for 30-day non-survivors. The median hospital length of stay was 14 days (IQR 7–29 days) for 30-day survivors and 7 days (IQR 3–15 days) for 30-day non-survivors.

The characteristics of the included patients are described in *Table 9*. The median age was 66 years (IQR 52–75 years) and most of the admissions were able to live without assistance in daily activities (76.4%).

The most common severe condition in the medical history was immunocompromise (7.3%). Regarding RCS Charlson comorbidities, chronic pulmonary disease (13.2%), diabetes mellitus (13%) and malignancy (10.7%) were the most prevalent.

Model development

Functional form and significance of CMP physiological and non-physiological predictors previously included in the existing model for adult general critical were reassessed. Consistency with both optimal functional form and global significance of the predictors was found after fitting a model considering all physiological and non-physiological predictors from the current ICNARC model (*Table 10*).

In line with the previous project,[6] we decided to use restricted cubic splines to model continuous candidates because these showed the flexibility of fractional polynomials but with better behaviour in the tails and captured the most prominent features of the relationship between predictors and outcomes, and because the fit was more plausible than a categorical approach.[6] For body mass index (BMI), a simplification using three knots was enough to accommodate the non-linear behaviour and had better AIC and BIC than four knots.

TABLE 9 Characteristics and outcomes of the development data set for the risk model for mortality at 30 days following critical care admission

Characteristic	Value
Number of admissions	119,509
Demographics	
Age (years)	
Mean (SD)	62 (17.1)
Median (IQR)	66 (52–75)
Sex, male, *n* (%)	67,398 (56.4)
Ethnicity, *n* (%)	
White	107,146 (89.7)
Mixed	603 (0.5)
Asian	4563 (3.8)
Black	2620 (2.2)
Other	4577 (3.8)
Reason for admission by body system, *n* (%)	
Respiratory	23,072 (19.3)
Cardiovascular	23,531 (19.7)
Gastrointestinal	31,288 (26.2)
Neurological (including eyes)	15,463 (12.9)
Genito-urinary	11,870 (9.9)
Endocrine, metabolic, thermoregulation and poisoning	7089 (5.9)
Haematological/immunological	1179 (1.0)
Musculoskeletal	4902 (4.1)
Dermatological	1087 (0.9)
Quintile of deprivation, *n* (%)	
1 (least deprived)	20,109 (16.9)
2	21,633 (18.2)
3	23,300 (19.6)
4	25,162 (21.2)
5 (most deprived)	28,657 (24.1)
Patient-related factors	
CPR within 24 hours prior to admission, *n* (%)	
No CPR	112,714 (94.3)
Community CPR	3608 (3.0)
In-hospital CPR	3187 (2.7)
Prior dependency, *n* (%)	
Able to live without assistance in daily activities	90,894 (76.4)
Some (minor/major) assistance with daily activities	27,153 (22.8)
Total assistance with all daily activities	884 (0.7)

TABLE 9 Characteristics and outcomes of the development data set for the risk model for mortality at 30 days following critical care admission (*continued*)

Characteristic	Value
Location prior to critical care admission, *n* (%)	
ED or not in hospital: unplanned	27,317 (22.9)
ED or not in hospital: planned	843 (0.7)
Theatre, elective/scheduled: planned	29,888 (25.0)
Theatre, elective/scheduled – unplanned	4129 (3.5)
Theatre, emergency/urgent	21,426 (17.9)
Ward or intermediate care area	29,553 (24.7)
Other critical care unit – repatriation	585 (0.5)
Other critical care unit – planned/unplanned transfer	4750 (4.0)
Other acute hospital	1018 (0.9)
Medical history	
Severe conditions in medical history (APACHE II), *n* (%)	
Very severe cardiovascular disease	2342 (2.0)
Severe respiratory disease	2756 (2.3)
Severe liver disease	3312 (2.8)
ESRD	1928 (1.6)
Metastatic disease	6001 (5.0)
Haematological malignancy	2327 (1.9)
Immunocompromise	8721 (7.3)
RCS Charlson comorbidities, *n* (%)	
Previous MI	5922 (5.0)
Congestive cardiac failure	6369 (5.3)
Peripheral vascular disease	6200 (5.2)
Cerebrovascular disease	3580 (3.0)
Dementia	1090 (0.9)
Chronic pulmonary disease	15,754 (13.2)
Rheumatological disease	2498 (2.1)
Liver disease	2458 (2.1)
Diabetes mellitus	15,592 (13.0)
Hemiplegia or paraplegia	931 (0.8)
Chronic renal disease	6246 (5.2)
Malignancy	12,789 (10.7)
Severity scores from the first 24 hours following critical care admission	
ICNARC physiology score	
Mean (SD)	17 (9.0)
Median (IQR)	15 (10–22)

continued

TABLE 9 Characteristics and outcomes of the development data set for the risk model for mortality at 30 days following critical care admission (*continued*)

Characteristic	Value
APACHE II score	
Mean (SD)	16 (6.8)
Median (IQR)	15 (11–20)
Physiology from the first 24 hours following critical care admission	
Highest heart rate (min^{-1}), mean (SD)	104 (23)
Lowest systolic blood pressure (mmHg), mean (SD)	95 (19)
Highest temperature (°C), mean (SD)	37.6 (0.9)
Lowest respiratory rate (min^{-1}), mean (SD)	12.8 (4.1)
Urine output (ml), mean (SD)	1861 (1435)
PaO_2/FiO_2 (kPa), mean (SD)	34.2 (15.6)
Lowest pH, mean (SD)	7.31 (0.11)
$PaCO_2$ (kPa), mean (SD)	5.9 (1.9)
Highest blood lactate (mmol l^{-1}), mean (SD)	2.7 (2.7)
Highest urea (mmol l^{-1}), mean (SD)	9.9 (9.1)
Highest creatinine (μmol l^{-1}), mean (SD)	134 (149)
Highest serum sodium (mmol l^{-1}), mean (SD)	139 (5)
Lowest white blood cell count (× 10^9 l^{-1}), mean (SD)	12.2 (8.8)
Neutrophil count (× 10^9 l^{-1}), mean (SD)	10.0 (6.2)
Lowest platelet count (× 10^9 l^{-1}), mean (SD)	210 (109)
Sepsis, *n* (%)	35,138 (29.4)
Organ dysfunction, *n* (%)	103,921 (87.0)
Organ support during critical care stay	
Receipt of advanced respiratory support, *n* (%)	55,405 (46.4)
Duration of advanced respiratory support (calendar dates), median (IQR)	2 (2–6)
Receipt of basic or advanced cardiovascular support, *n* (%)	28,975 (24.2)
Duration of basic or advanced cardiovascular support (calendar days), median (IQR)	2 (1–4)
Receipt of renal support, *n* (%)	12,523 (10.5)
Duration of renal support (calendar days), median (IQR)	3 (2–6)
Outcomes	
Critical care unit mortality, *n* (%)	16,129 (13.5)
Acute hospital mortality, *n* (%)	23,976 (20.1)
30-day mortality, *n* (%)	22,579 (18.9)
Critical care unit length of stay (hours), mean (SD)	119 (194)
For 30-day survivors	120 (207)
For 30-day non-survivors	113 (123)

TABLE 9 Characteristics and outcomes of the development data set for the risk model for mortality at 30 days following critical care admission (*continued*)

Characteristic	Value
Critical care unit length of stay (hours), median (IQR)	61 (26–128)
For 30-day survivors	58 (26–122)
For 30-day non-survivors	69 (28–151)
Acute hospital length of stay (days), mean (SD)	22 (33)
For 30-day survivors	24 (34)
For 30-day non-survivors	11 (28)
Acute hospital length of stay (days), median (IQR)	12 (6–25)
For 30-day survivors	14 (7–29)
For 30-day non-survivors	7 (3–15)

MI, myocardial infarction.

TABLE 10 Model performance in the development cohort

Model	df	LL	BIC	C index (95% CI)	Brier's score
Main model[a]	110	−36784.79	74867	0.888 (0.886 to 0.890)	0.095
Main model + new predictors	115	−36641.15	74638	0.889 (0.887 to 0.891)	0.095
Main model + new predictors + reason for admission	184	−35210.77	72584	0.898 (0.896 to 0.901)	0.091
Final model	226	−35028.98	72711	0.900 (0.897 to 0.902)	0.091

LL, log-likelihood.
a Physiological and non-physiological predictors from the CMP previously included in the existing model to predict mortality at discharge from acute hospital.

Severe conditions in the medical history were added into the model, but the only conditions finally retained were very severe cardiovascular disease, severe respiratory disease and immunocompromise, because of their significant effect and contribution to the model.

After adjusting for current and new potential predictors, deprivation was not retained in the main term model owing to the lower contribution to the model fit.

The new categories of primary reason for admission are shown in *Table 11*. Conditions were selected after the modelling process described above. A total of 57 process/system combinations and 13 individual conditions from the ICNARC Coding Method form the new reason for admission categories. These accounted for 94.5% and 5.5% of admissions, respectively. Fifteen significant primary reasons for admission/physiology interactions were retained in the model.

Interactions included in the previous model between severe liver disease with physiology, CPR with physiology, ventilation with physiology and physiology with physiology were re-assessed. Only the interactions between severe liver disease and temperature and between ventilation and heart rate were not significant after adjusting for the main term model plus the new primary reason categories and interactions. They were finally dropped.

TABLE 11 Final categories of reason for admission included in the model

Reason of admission categorical variable	Frequency	Percentage
Combinations of process and system		
Accidental intoxication or poisoning (endocrine)	398	0.33
Acidaemia (endocrine)	336	0.28
Burns or hyperthermia (dermatological)	115	0.10
Collapse (respiratory)	501	0.42
Coma or encephalopathy (neurological)	991	0.83
Congenital or acquired deformity or abnormality		
Cardiovascular	556	0.47
Cardiovascular, endocrine, gastrointestinal, genitourinary or haematological/immunological	1549	1.30
Musculoskeletal	1175	0.98
Neurological	654	0.55
Respiratory	763	0.64
Degeneration		
Cardiovascular	2442	2.04
Neurological	39	0.03
Diabetes mellitus (endocrine)	1790	1.50
Dissection or aneurysm (cardiovascular)	3633	3.04
Failure		
Cardiovascular	1138	0.95
Genitourinary	4616	3.86
Haemolysis or thrombocytopaenia	93	0.08
Haemorrhage		
Cardiovascular	141	0.12
Gastrointestinal	2374	1.99
Genitourinary	660	0.55
Neurological	1709	1.43
Respiratory	151	0.13
Hyperkalaemia (endocrine)	284	0.24
Hypokalaemia (endocrine)	103	0.09
Hyponatraemia (endocrine)	266	0.22
Hypoplasia or dysplasia (haematological/immunological)	121	0.10
Hypothermia (endocrine)	83	0.07
Infection		
Cardiovascular	451	0.38
Dermatological, gastrointestinal, haematological/immunological, musculoskeletal or neurological	6438	5.39
Genitourinary	1878	1.57
Respiratory	6133	5.13

TABLE 11 Final categories of reason for admission included in the model (*continued*)

Reason of admission categorical variable	Frequency	Percentage
Inflammation		
Cardiovascular, dermatological, genitourinary, musculoskeletal, respiratory	2863	2.40
Gastrointestinal	10,189	8.53
Neurological	177	0.15
Non-traumatic aneurysm, dissection, perforation or rupture (cardiovascular)	2677	2.24
Obstruction		
Cardiovascular	7948	6.65
Gastrointestinal	4288	3.59
Genitourinary	606	0.51
Respiratory	1255	1.05
Oedema, inflammation, fibrosis or inhalation (respiratory)	104	0.09
Seizures (neurological)	2388	2.00
Self-harm or self-poisoning (endocrine)	2950	2.47
Shock and hypotension (cardiovascular)	2003	1.68
Transplant or related (cardiovascular, endocrine, genitourinary, haematological/immunological, respiratory)	297	0.25
Transplant or related (gastrointestinal)	523	0.44
Trauma		
Neurological	391	0.33
Perforation or rupture (cardiovascular)	334	0.28
Perforation or rupture (dermatological, genitourinary, musculoskeletal, respiratory)	3348	2.80
Perforation or rupture (gastrointestinal)	5666	4.74
Perforation or rupture (neurological)	2014	1.69
Tumour or malignancy		
Cardiovascular, dermatological, endocrine, gastrointestinal, musculoskeletal, respiratory	12,089	10.12
Genitourinary	4065	3.40
Haematological/immunological	414	0.35
Neurological	2117	1.77
Vascular		
Cardiovascular; genitourinary	138	0.12
Gastrointestinal	891	0.75
Neurological	1579	1.32
Specific conditions		
Acute alcoholic hepatitis	185	0.15
Alcoholic cirrhosis	325	0.27
Anoxic or ischaemic coma or encephalopathy	1037	0.87
Asthma attack in new or known asthmatic	1147	0.96
Fungal or yeast pneumonia	148	0.12

continued

TABLE 11 Final categories of reason for admission included in the model (*continued*)

Reason of admission categorical variable	Frequency	Percentage
Hanging or strangulation	153	0.13
Intracerebral haemorrhage	1178	0.99
Multiple rib fractures	276	0.23
Non-traumatic subdural haemorrhage	390	0.33
Pulmonary fibrosis or fibrosing alveolitis	182	0.15
Secondary hepatic tumour	895	0.75
Secondary hydrocephalus	137	0.11
Thrombo-occlusive disease of brain	561	0.47

Following the development process, the significance and importance of the predictors in the final model are shown in *Appendix 2*, *Table 41*. Full coefficients for the final model are presented in *Appendix 3*, *Table 45*. The distribution of predicted acute hospital mortality from the new model is shown in *Figure 3*. The final model showed good performance (c index 0.900 and Brier's score 0.091) and, internally, calibration of the model was satisfactory (*Figure 4*). Overfitting was of limited relevance because of the very large data set and, as expected, model optimism was negligible (0.49% estimated overfitting).

The estimates for the model parameters obtained using data from the multiply imputed data set were similar to values estimated from the development data set and, therefore, the bias that could arise from using only the available information was considered to be very small.

Model validation

The performance in the validation data set of 134,750 admissions from 31 March 2015 to 31 March 2016 is presented in *Table 12* and *Figure 5*. Discrimination and accuracy were excellent: a c index of 0.90 (95% CI 0.89 to 0.91) and Brier's score of 0.088. The calibration of the model was satisfactory, with a calibration slope of 0.998 and a calibration intercept of 0.013. The observed and mean predicted mortality were 17.8.% and 17.6%, respectively, for a SMR (observed divided by predicted mortality) of 1.01 (95% CI 1.00 to 1.02), which indicated a good calibration in the main.

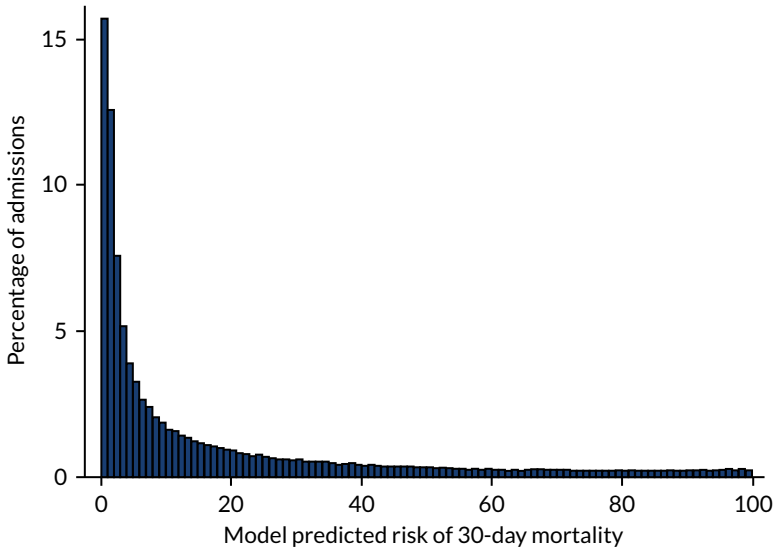

FIGURE 3 Distribution of predicted risk from the final risk model for mortality at 30 days following critical care admission in the development data set.

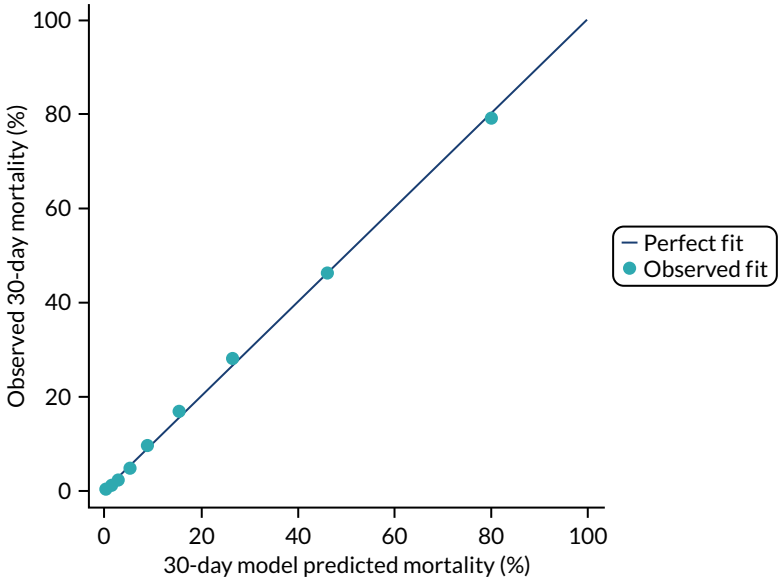

FIGURE 4 Calibration of the final risk model for mortality at 30 days following critical care admission in the development data set.

TABLE 12 Overall predictive performance of the final risk model for mortality at 30 days and customised risk model for mortality at 90 days following critical care admission in the external validation data set

Model	c index (95% CI)	Brier's score	Predicted mortality (%)	Observed mortality (%)	SMR (95% CI)
Final risk model for mortality at 30 days	0.900 (0.897 to 0.912)	0.088	17.69	17.82	1.01 (1.00 to 1.02)
Final customised risk model for mortality at 90 days	0.883 (0.880 to 0.884)	0.105	21.47	21.53	1.00 (0.99 to 1.01)

Use of 30-day mortality for benchmarking

The performance in the development data set for the customised model for predicting acute hospital mortality was excellent: a c index of 0.899 (95% CI 0.897 to 0.901) and Brier's score of 0.095. The calibration of the model was satisfactory (*Figure 6*). This indicated that the model performs well when applied for prediction of acute hospital mortality.

The effect of benchmarking by using mortality at 30 days after critical care admission instead of acute hospital mortality was assessed in the 232 included critical care units. There was strong agreement between SMRs calculated on 30-day mortality and acute hospital mortality (Supplementary material, Figure S2). Funnels plots of SMR for individual critical care units (*Figure 7*) show that 21 units (9%) moved across the 2SD (dashed funnel line) and 3SD (solid funnel line) boundaries when the outcome was changed to 30-day mortality. *Table 13* summarises the comparison of SMR position between acute hospital mortality and 30-day mortality. When changing from acute hospital mortality to 30-day mortality, 12 units moved to less extreme positions in the funnel (one from below 3SD to inside the funnel, six from below 2SD to inside the funnel and five from above 2SD to inside the funnel) and nine units moved to more extreme positions in the funnel (one from below 2SD to below 3SD, five from inside the funnel to below 2SD, one from inside the funnel to above 2SD and two from above 2SD to above 3SD). This suggests that there was little difference in heterogeneity across critical care units when assessed with 30-day mortality rather than acute hospital mortality.

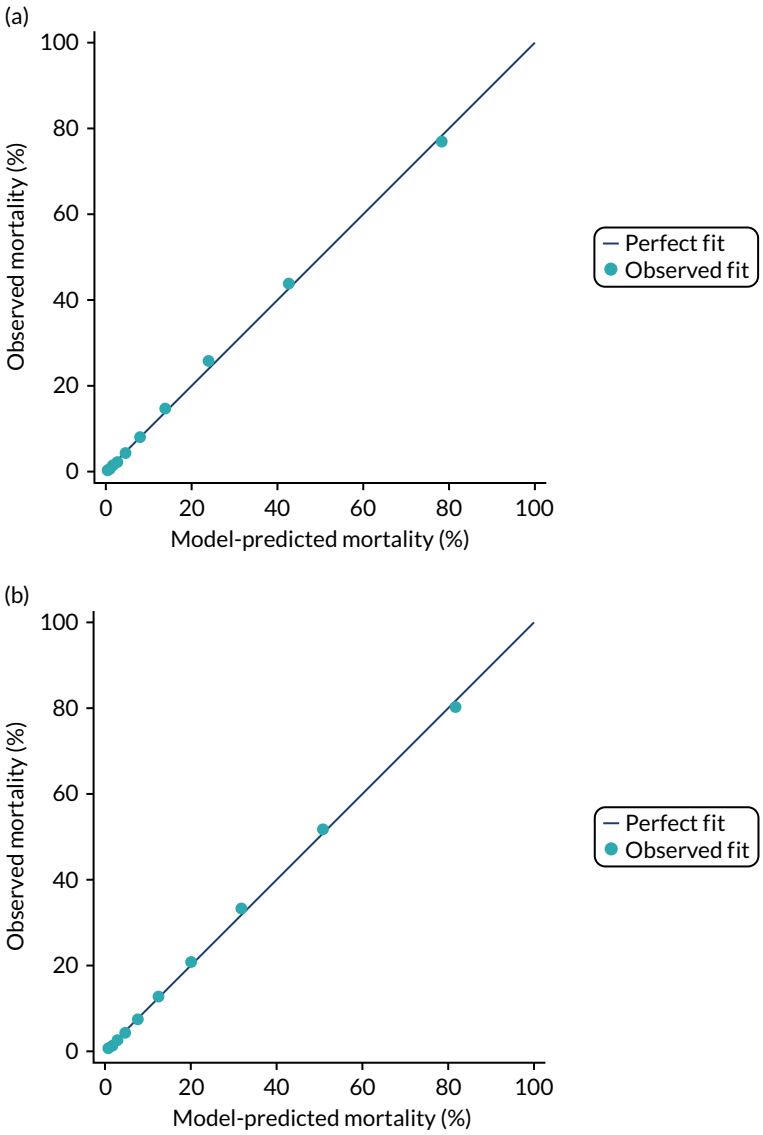

FIGURE 5 Calibration of (a) the final risk model for mortality at 30 days following critical care admission and (b) the customised risk model for mortality at 90 days following critical care admission in the external validation data set.

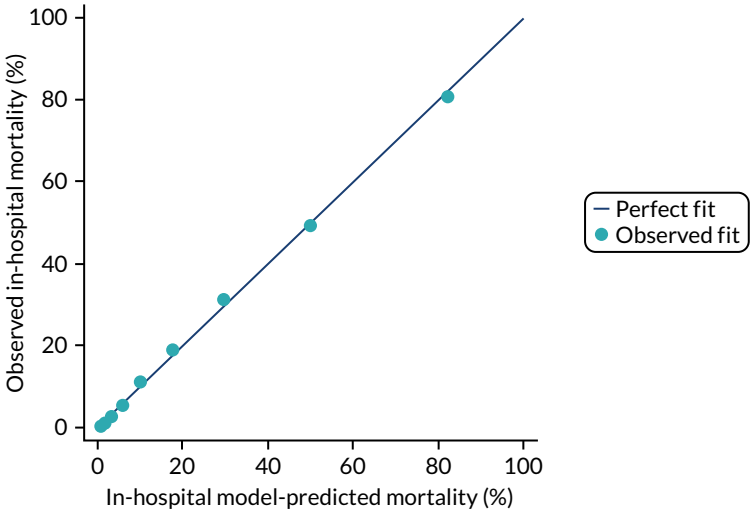

FIGURE 6 Calibration of the customised risk model for acute hospital mortality in the development data set.

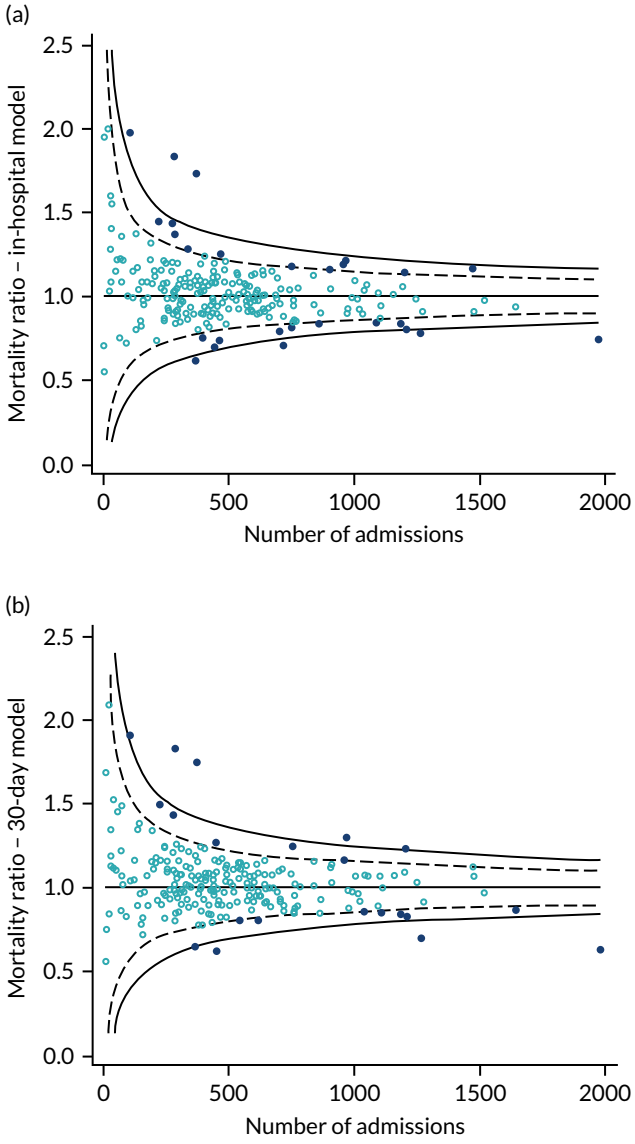

FIGURE 7 Funnel plots of SMR for (a) acute hospital mortality and (b) 30-day mortality.

TABLE 13 Comparison of SMR positions in the funnel plots based on acute hospital mortality versus 30-day mortality

	30-day mortality					
Acute hospital mortality	**Below 3SD**	**Below 2SD**	**Inside funnel**	**Above 2SD**	**Above 3SD**	**Total**
Below 3SD	3	0	1	0	0	4
Below 2SD	1	2	6	0	0	9
Inside funnel	0	5	199	1	0	205
Above 2SD	0	0	5	4	2	11
Above 3SD	0	0	0	0	3	3
Total	4	7	211	5	5	232

Shaded cells signify no change in position within the funnel plots.

Mortality at 90 days

The performance of the customised model for 90-day mortality was good, presenting a c index of 0.883 (95% CI 0.881 to 0. 885) and a Brier's score of 0.1077. Variables' significance and importance were consistent with the results for 30-day mortality. Age, sedated/paralysed/Glasgow coma scale (GCS) and source of admission/urgency of surgery were the strongest predictors. However, severe conditions in the medical history (such as metastatic disease and severe liver disease) and BMI had a more relevant role in the model (see *Appendix 2*, *Table 41*). The model showed good discrimination in the validation data set, a c index of 0.883 (95% CI 0.880 to 0.884) a Brier's score of 0.1045 and a SMR of 1.00 (95% CI 0.99 to 1.01), which indicated good calibration (see *Table 12* and *Figure 5*). The final coefficients are shown in *Appendix 3*, *Table 46*.

Mortality at 1 year following critical care admission

Between January 2013 and December 2013, there were 144,720 first admissions to 235 adult critical care units in England participating in the CMP with identifiable linkage with HES and death registrations. After the exclusions, a total of 127,855 were included in the development data set.

In total, 38,191 (29.9%) patients died during the one-year follow-up. Of these, 18,038 (14.1%) died during the critical care admission.

Baseline severe and chronic conditions of the included patients and associated 1-year mortality are described in *Table 14*. The most common severe condition in the medical history was immunocompromise (6%) and the highest 1-year mortality was associated with haematological malignancy (62%). Regarding RCS Charlson comorbidities, chronic pulmonary disease (14%), any malignancy (13%) and diabetes mellitus (12%) were the most prevalent. Dementia (48%), metastatic solid tumour (48%) and chronic renal disease (44%) were associated with the highest 1-year mortality. *Figure 8* shows the Kaplan–Meier survival curve for 1-year survival after critical care admission.

Model development

Functional form and significance of CMP physiological and non-physiological predictors previously included in the existing model for acute hospital mortality were reassessed. Consistency with global significance of the existing predictors was found after fitting a model considering all physiological and non-physiological variables from the current ICNARC model. The functional form of the continuous physiological predictors was reassessed for the 1-year mortality outcome. In all cases, predictors showed significant non-linearity ($p < 0.001$). The optimal functional form selected to model the continuous physiological predictors was four knots for heart rate, systolic blood pressure and creatinine. For temperature, urine output, PaO_2/FiO_2, urea, white blood cell count, potassium, glucose, blood lactate, platelet count, neutrophil count and urine output extending to five knots was needed. For arterial pH, a simplification using three knots was enough to accommodate the non-linear behaviour. Finally, respiratory rate and $PaCO_2$ were modelled using right-restricted cubic splines. This was necessary to capture the initial decrease in mortality and 'spoon' behaviour. This approach had a better fit than five knots and was more plausible than four.

Age and BMI were modelled as continuous, non-linear relationships using restricted cubic splines with five knots.

Following the development of the main model, severe conditions in the past medical history (APACHE II) and RCS Charlson comorbidities were added into the model. As key predictors for long-term mortality, the significance and importance of the comorbidities are shown in *Appendix 2*, *Table 42*. All APACHE II severe conditions and most RCS Charlson comorbidities were retained because of their significant effect and contribution to the model, except previous myocardial infarction (MI), dementia, hemiplegia or paraplegia, diabetes mellitus and rheumatological disease. The incorporation of APACHE II and RCS Charlson comorbidities, in particular metastatic disease and severe liver disease, in the risk prediction model produced better fit (*Table 15*). The comorbidities with the greatest magnitude of association were metastatic disease, severe liver disease and hematological malignancy (*Table 16*).

TABLE 14 Prevalence and 1-year mortality associated with comorbidities in the development data set and among hospital survivors in the development data set

Comorbidities	Development data set ($n = 126,447$), %		Hospital survivors ($n = 100,450$), %	
	Prevalence	One-year mortality following critical care admission	Prevalence	One-year mortality following hospital discharge
Severe conditions in the past medical history (APACHE II)				
Very severe cardiovascular disease	2	50	1	20
Severe respiratory disease	2	53	2	24
Severe liver disease	2	54	2	20
End-stage renal failure	2	44	1	24
Haematological malignancy	2	62	3	41
Metastatic disease	3	55	1	32
Immunocompromise	6	45	6	28
RCS Charlson comorbidities				
Previous MI	3	36	3	18
Congestive cardiac failure	6	43	5	21
Peripheral vascular disease	5	34	5	17
Cerebrovascular disease	3	37	3	18
Dementia	1	48	1	27
Hemiplegia or paraplegia	1	37	1	18
Chronic pulmonary disease	14	36	13	17
Liver disease	3	43	3	20
Chronic renal disease	6	44	6	23
Any malignancy	13	36	14	24
Metastatic solid tumour	3	48	3	36
Diabetes mellitus	12	35	12	17
Rheumatological disease	2	37	2	17
Overall		30		12

MI, myocardial infarction.

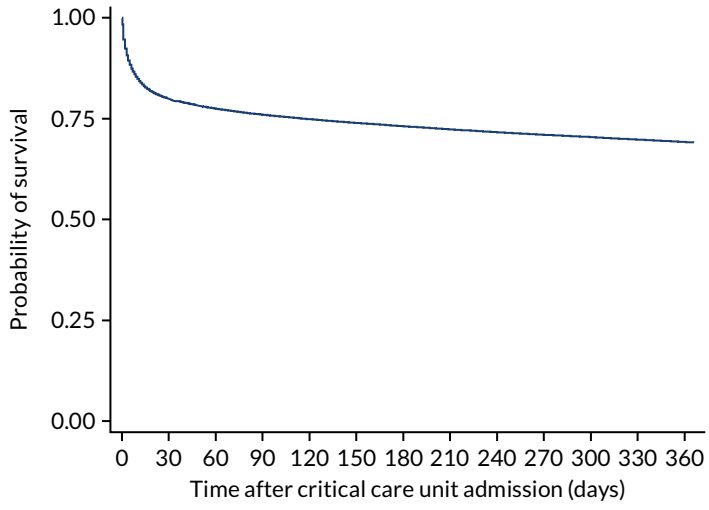

FIGURE 8 Kaplan–Meier survival curve for 1 year following critical care admission.

TABLE 15 Model performance for predicting mortality at 1 year following critical care admission and for predicting mortality at 1 year following hospital discharge in the development cohort

Model	df	LL	BIC	c index (95% CI)	Brier's score
One year following critical care admission					
Main model[a]	81	−45347.44	91637	0.825 (0.822 to 0.828)	0.149
Main model + comorbidities	100	−43853.09	88867	0.839 (0.836 to 0.842)	0.144
Main model + comorbidities + reason for admission	167	−42429.44	86790	0.851 (0.848 to 0.854)	0.139
Main model + comorbidities + reason for admission + interactions	292	−41992.53	84571	0.854 (0.851 to 0.856)	0.138
One year following hospital discharge					
Main model[b]	81	−26226.97	53376	0.721 (0.716 to 0.726)	0.102
Main model + comorbidities	100	−24908.08	50952	0.766 (0.761 to 0.771)	0.097

a Physiological and non-physiological predictors from the CMP previously included in the existing model to predict mortality at discharge from acute hospital.
b Final risk model for mortality at one year following critical care admission excluding comorbidities.

TABLE 16 Odds ratios for comorbidities in the risk model for mortality at 1 year following critical care admission and in the risk model for mortality at 1 year following hospital discharge

Comorbidity	OR (95% CI) for 1-year mortality following critical care admission	OR (95% CI) for 1-year mortality following hospital discharge
Previous MI	1.12 (1.00 to 1.23)	1.14 (1.00 to 1.28)
Congestive cardiac failure	1.28 (1.19 to 1.38)	1.40 (1.27 to 1.54)
Peripheral vascular disease	1.19 (1.10 to 1.28)	1.23 (1.12 to 1.35)
Very severe cardiovascular disease	1.30 (1.15 to 1.46)	1.17 (0.98 to 1.37)
Cerebrovascular disease	1.16 (1.05 to 1.28)	1.17 (1.00 to 1.33)
Dementia	1.13 (0.97 to 1.32)	1.37 (1.13 to 1.65)
Hemiplegia or paraplegia	1.07 (0.88 to 1.28)	1.22 (0.95 to 1.55)
Chronic pulmonary disease	1.13 (1.07 to 1.19)	1.21 (1.13 to 1.29)
Severe respiratory disease/home ventilation	1.73 (1.55 to 1.92)	1.62 (1.40 to 1.87)
Liver disease	1.46 (1.31 to 1.63)	1.44 (1.24 to 1.66)
Severe liver disease	2.39 (2.16 to 2.63)	1.87 (1.61 to 2.17)
Chronic renal disease	1.25 (1.15 to 1.34)	1.29 (1.17 to 1.42)
End-stage renal failure	1.73 (1.55 to 1.92)	1.56 (1.30 to 1.87)
Any malignancy	1.60 (1.51 to 1.69)	1.89 (1.76 to 2.02)
Haematological malignancy	2.15 (1.89 to 2.42)	2.11 (1.79 to 2.47)
Metastatic disease	4.04 (3.74 to 4.36)	4.46 (4.10 to 4.85)
Immunocompromise	1.47 (1.36 to 1.57)	1.58 (1.45 to 1.71)
Diabetes mellitus	1.03 (0.97 to 1.08)	1.17 (1.09 to 1.25)
Rheumatological disease	1.01 (0.90 to 1.12)	1.01 (0.87 to 1.16)

OR, odds ratio.

After adjusting for comorbidities, deprivation was not retained in the main term model because of a low contribution to the model fit.

A total of 56 process/system combinations and 18 individual conditions from the ICNARC Coding Method (*Table 17*) were selected after the modelling process described above. Comparing with the ICNARC acute hospital mortality and the 30-days primary reason for admission categories, the selected individual conditions were less acute and more cancer-related. Significant interactions with physiology ($n = 24$) were incorporated to the model.

Interactions included in the previous model between severe liver disease with physiology, CPR with physiology, ventilation with physiology and physiology with physiology appeared to be less important for 1-year mortality and only the interactions between CPR and temperature and between ventilation and respiratory rate, PaO_2/FiO_2 and $PaCO_2$ were included after adjusting for the main term model plus the new primary reason categories and interactions.

The final model showed good performance (c index of 0.855 and Brier's score of 0.118) and internally, calibration of the model was satisfactory (*Figure 9*). Overfitting was of limited relevance because of the very large data set and, as expected, model optimism was negligible (0.77% estimated overfitting). Full coefficients for the final model are presented in *Appendix 3, Table 47*.

TABLE 17 Comparison of individual reasons for admission included in the risk models for acute hospital mortality and 1-year mortality

Acute hospital mortality	One-year mortality
Toxic or drug-induced coma or encephalopathy	Toxic or drug-induced coma or encephalopathy
Lower limb artery stenosis or occlusion	Lower limb artery stenosis or occlusion
Anaphylaxis	Anaphylaxis
Leaking large bowel anastomosis	Leaking large bowel anastomosis
Acute alcoholic hepatitis/alcoholic cirrhosis	Acute alcoholic hepatitis/alcoholic cirrhosis
Thrombo-occlusive disease of brain	Thrombo-occlusive disease of brain
Secondary hydrocephalus	Secondary hydrocephalus
Pulmonary fibrosis or fibrosing alveoli	Pulmonary fibrosis or fibrosing alveolitis
Asthma attack in new or known asthmatic	Asthma attack in new or known asthmatic
Hanging or strangulation	Hanging or strangulation
Anoxic or ischaemic coma or encephalopathy	Anoxic or ischaemic coma or encephalopathy
Entero-enteric or entero-cutaneous fistula	CABG for chronic angina
Fractured ribs	Pancreatic or pancreato-duodenal tumour
Fungal or yeast pneumonia	Secondary hepatic tumour
Haemolysis or thrombocytopaenia	Small bowel tumour
Intracerebral haemorrhage	Malignant large bowel tumour
	Large bowel tumour
	Carotid or vertebral artery stenosis or occlusion

Shaded cells signify reasons for admission that were included in the risk model for 1-year mortality and not in the risk model for acute hospital mortality.

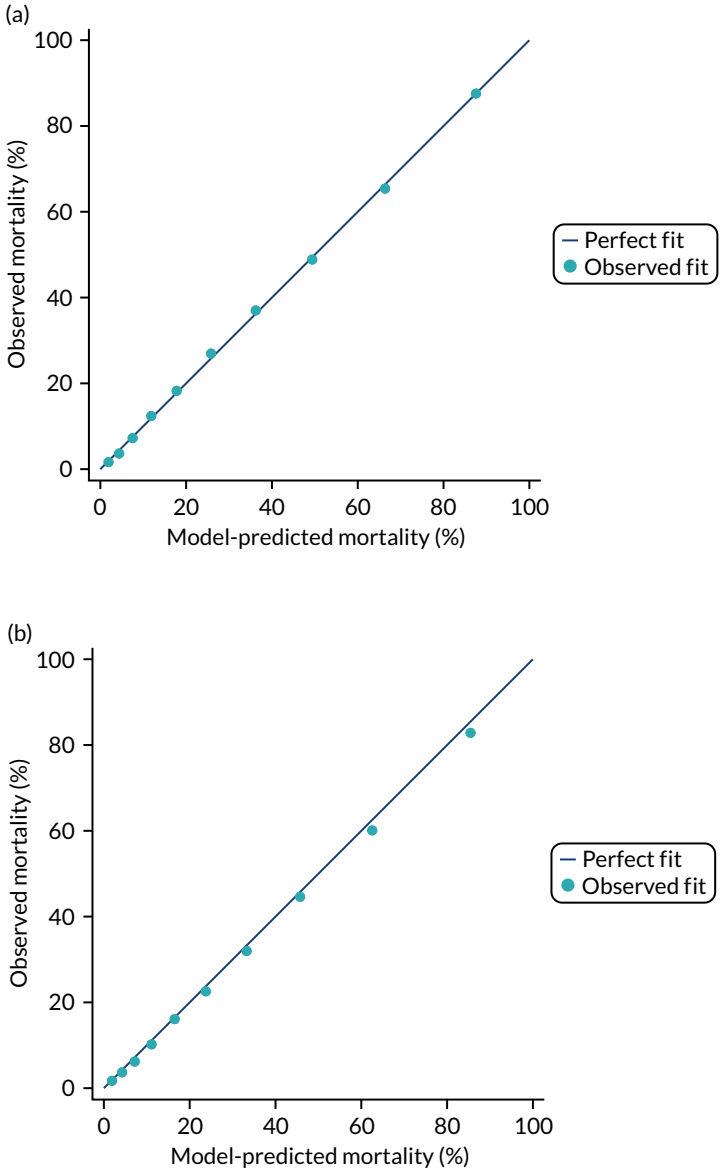

FIGURE 9 Calibration of the final risk model for mortality at one year following critical care admission in (a) the development data set and (b) the validation data set.

Model validation

A total of 126,447 admissions from 31 March 2015 to 31 March 2016 were selected for the validation data set. The same eligibility and exclusion criteria were applied as for the development data set. Discrimination and accuracy were good with a c index of 0.848 (95% CI 0.846 to 0.851) and a Brier's score of 0.1348. The calibration of the model was satisfactory, with a calibration slope of 0.983 and a calibration intercept of –0. 097 and supported visually by calibration plots (see *Figure 9*). The observed and mean predicted mortality were 28.0% and 29.1%, respectively, for a SMR of 0.96 (95% CI 0.95 to 0.97), which indicated a satisfactory calibration.

Mortality at 1 year following hospital discharge

A total of 100,450 admissions discharged alive from hospital between January 2013 and December 2013 were selected for the hospital survival cohort. With the aim of evaluating if the effect of comorbidities is different among hospital survivors, their significance and contribution were retested in a model considering 1-year survival from hospital discharge as outcome and adjusting by the variables resulting in the previous main term model.

Comorbidities were present among hospital survivors in similar proportions to the critical care admission cohort (see *Table 14*). In general, comorbidity remained in importance as predictors of 1-year mortality (see *Appendix 2*, *Table 42*) and showed a similar effect (see *Table 16*), with dementia and diabetes mellitus arising as significant and important predictors. On the other hand, and liver disease and haematological malignancy became less important predictors of 1-year mortality for hospital survivors. Very severe cardiovascular disease and cerebrovascular disease were not significant after adjusting for main terms.

The c index of the main terms model without and with comorbidities were 0.721 (95% CI 0.716 to 0.726) and 0.766 (95% CI 0.761 to 0.771), respectively. The addition of comorbidities showed a greater improvement of the performance of the model (see *Table 15*) in the hospital survivor cohort, although the performance was better when predicting 1-year mortality in the critical care admission cohort.

Discussion

We have developed risk models for mortality at 30 days, 90 days and 1 year following critical care admission and at 1 year following hospital discharge. When comparing the model for 30-day mortality with the previous model for acute hospital mortality, all risk factors for acute hospital mortality remained important in predicting 30-day mortality. Differences in benchmarking between acute hospital mortality and 30-day mortality were modest and there was little evidence that using a fixed time point reduced heterogeneity. When the model for 30-day mortality was refitted to 90-day mortality, all risk factors remained important, although the relative importance of severe conditions such as metastatic disease and severe liver disease increased.

When comparing the model for 1-year mortality with the previous model for acute hospital mortality,[7] all risk factors for acute hospital mortality remained important in predicting 1-year mortality. Age had a non-linear effect in the model, the importance of BMI increased and all severe comorbidities were important. Individual conditions included as primary reasons for admission to critical care included fewer acute conditions and more cancer-related conditions. When considering additional comorbidities available via data linkage with HES, most of these were important in predicting 1-year mortality; however, the strongest effects remained for the severe conditions already collected in the CMP.

The effects of comorbidities were largely similar when the model for 1-year mortality was refitted to hospital survivors. Dementia and diabetes mellitus became important in the model for 1-year mortality following hospital discharge, and very severe cardiovascular disease and cerebrovascular disease were not important.

Chapter 6 Risk models for development of end-stage renal disease following critical care

Introduction

The occurrence of acute kidney injury (AKI) (formerly known as acute renal failure) is common among critically ill patients; is associated with high mortality;[46–49] and has been linked with subsequent chronic kidney disease (CKD), ESRD and high health-care costs.[50,51] In this chapter, we use the data linkage between the CMP and the UKRR to evaluate this relationship and to develop risk models to predict the development of ESRD among survivors of critical illness.

Methods

Methods common to all objectives and analyses were described in *Chapter 3*.

Study cohort

We selected NHS adult critical care units in England participating in the CMP with identifiable linkage with HES and death registrations. False linkage and errors in linkage with HES and death registrations were excluded. The linked cohort included patients discharged from hospital between 1 April 2009 and 31 March 2016 following a critical care admission. The final follow-up date was 31 December 2016 (based on the latest available data from the UKRR at the time of linkage). For patients with multiple hospital episodes that included critical care admissions, we considered the index admission to be the first hospital admission during the analysis period. Re-admissions to critical care and transfers during the index admission were excluded.

Inclusion and exclusion criteria

Patients included in the model were all those discharged alive from acute hospital following a critical care unit admission. Patients were excluded if they had pre-existing ESRD, identified by:

- linkage with the UKRR indicating a date of diagnosis of ESRD prior to the date of discharge from hospital of the index admission
- ICD-10 codes indicating ESRD (I120, I129, N186, Z49, Z940, Z992) in any diagnosis field from linked HES records from a hospital episode either prior to or during the index admission
- recording of an ongoing requirement for RRT for irreversible ESRD in the CMP.

Outcome

The main outcome was new receipt of RRT for ESRD, based on the date of diagnosis recorded in the UKRR database, after the date of discharge from hospital. The competing risk was death from any cause before ESRD, identified via linkage with death registrations. Deaths after ESRD were not considered.

Candidate variables

As the important risk factors and their relationships with the outcome may be very different from those considered for other outcome measures, risk models for ESRD were developed de novo, using the same methods as previously applied to develop the original risk models for acute hospital mortality in adult critical care. Potentially important candidate predictors were chosen based on expert clinical opinion and availability in the linked data sources. RCS Charlson comorbidities were identified as described in *Chapter 3*,

except for CKD and AKI, for which the lookback period was extended to 5 years. A description of the candidate predictors is given in *Appendix 1*, *Table 38*.

Statistical analyses

For the description of cohort characteristics, assessment of optimal functional form and selection of covariables, we followed the same methodology as described in *Chapter 3*.

The incidence rate was calculated as the number of new cases of ESRD divided by the follow-up time and expressed as the number of events per 1000 person-years. Because outcomes of death and ESRD have an important competing effect, analysis of the predictors of ESRD needs to consider the risk of dying before ESRD. In the competing risk context, two different approaches to regression modelling exist: the Cox proportional cause-specific regression model and the Fine-Gray regression model. The former models the dependence of the cause-specific hazard function on covariates and the latter models the dependence of the cumulative incidence function (CIF) on predictors. Both methods were considered pertinent in the present study as we aimed to explore the role of acute and chronic risk factors on development of ESRD following a critical care admission. For the cause-specific model, the explained variation (R^2) was determined. The proportional hazard assumption was tested by visual inspection of Schoenfeld residual plots and log-log plots.

Results

Of 628,562 patients discharged alive from acute hospital between 1 April 2009 and 31 March 2016, 29,959 were excluded owing to pre-existing ESRD, leaving a cohort of 598,603 patients included in the analysis (*Figure 10*).

The median duration of follow-up was 2.7 years (IQR 1.4–4.6 years) and 2831 (0.47%) patients developed ESRD during follow-up (incidence rate 1.52 per 1000 person-years; 95% CI 1.46 to 1.58). The CIF for ESRD is shown in *Figure 11*. A total of 194,691 (32.5%) patients died without developing ESRD.

Patient characteristics

Characteristics of the overall cohort, as well as divided by outcome, are detailed in *Table 18*. Compared with the overall cohort, patients who developed ESRD were similar in age (mean 60 years), with a higher proportion of males (62% vs. 55%) and of non-white ethnicities (16% vs. 7%). More than 30% suffered from CKD in either the current hospital admission or an admission during the previous 5 years (compared with 3.6% for the overall cohort) and 6% (vs. < 1%) had previous hospital admissions involving AKI. The most prevalent non-renal chronic condition in patients who developed ESRD was diabetes (24% vs. 10%). Patients who developed ESRD had higher creatinine levels during the first 24 hours following admission to critical care (mean 530 vs. 111 µmol l^{-1}) and urea (mean 27 vs. 8 µmol l^{-1}) and lower urine output (mean 1354 vs. 2013 ml) and more than half had received renal support during the critical care unit stay (51% vs 5%).

Predictors of end-stage renal disease

Table 19 shows the cHR after the modelling process. Although pregnancy was not associated with development of ESRD, it was kept for confounding. An increasing heart rate, respiratory rate, arterial pH, white blood cell count, $PaCO_2$ and urine output during the first 24 hours of critical care were all linearly associated with a decrease in the risk of developing ESRD. On the other hand, increasing systolic blood pressure was significantly associated with an increased risk of ESRD. Non-linear associations were observed between the risk of ESRD and the following factors: age, sodium, creatinine, urea and blood lactate. These factors were modelled by restricted cubic splines. *Figure 12* shows the adjusted cause-specific graphs associated with these non-linear relationships to facilitate the presentation and interpretation. There was a huge increase in the risk of ESRD when

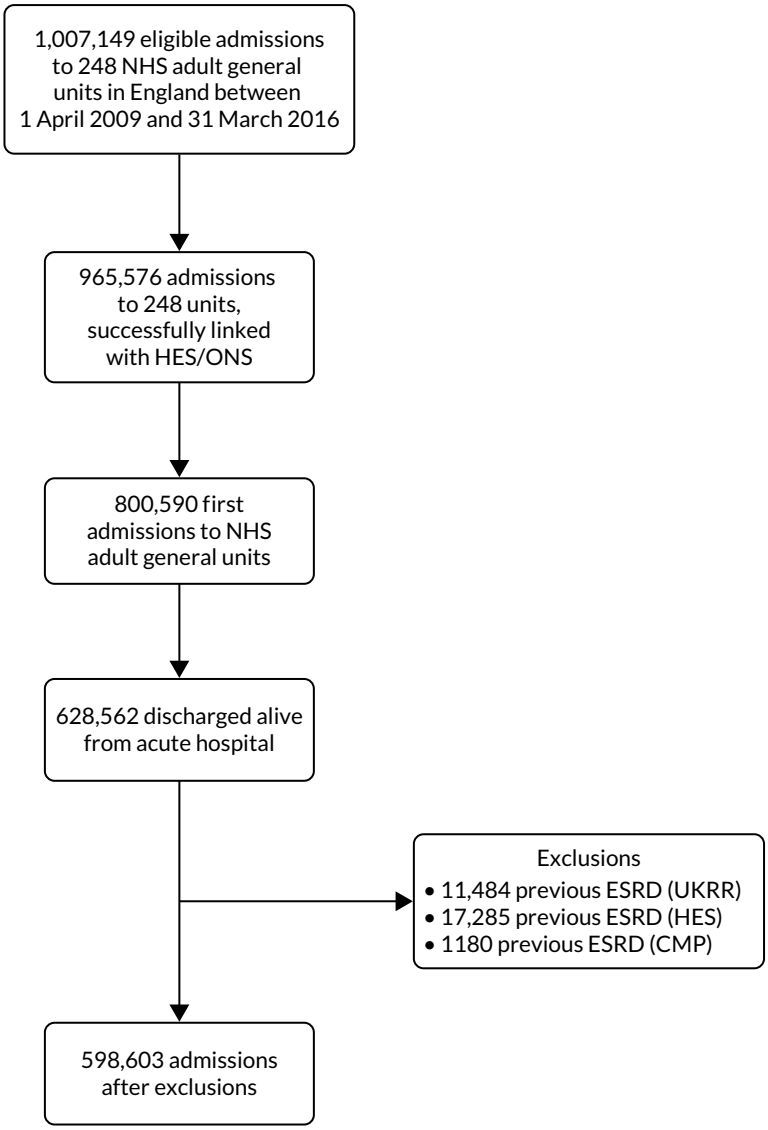

FIGURE 10 Flow-diagram for cohort identification.

FIGURE 11 Cumulative incidence of ESRD.

TABLE 18 Characteristics of the overall cohort, those who developed ESRD during follow-up and those who died during follow-up without developing ESRD

Characteristics	Cohort	ESRD	Death before ESRD
Number of patients (%)	598,603	2831 (0.47)	194,691 (32.5)
Demographics			
Age (years)			
Mean (SD)	60 (18.4)	60 (15.8)	69 (14.2)
Median (IQR)	63 (48–74)	62 (49–72)	71 (61–79)
Gender, males (%)	331,723 (55.4)	1767 (62.4)	112,020 (57.5)
Ethnicity, *n* (%)			
White	538,570 (90.0)	2293 (81.0)	181,016 (93.0)
Mixed	3275 (0.5)	18 (0.6)	607 (0.3)
Asian	20,212 (3.4)	228 (8.1)	4363 (2.2)
Black	12,733 (2.1)	150 (5.3)	2619 (1.3)
Other	7261 (1.2)	58 (2.0)	1484 (0.8)
Not stated	16,117 (2.7)	84 (3.0)	4450 (2.3)
Deprivation, *n* (%)			
1 (least deprived)	100,451 (17.4)	421 (15.4)	33,661 (17.8)
2	108,384 (18.8)	451 (16.5)	36,041 (19.1)
3	115,576 (20.0)	565 (20.6)	38,282 (20.3)
4	119,632 (20.7)	599 (21.9)	38,668 (20.5)
5 (most deprived)	132,893 (23.0)	703 (25.7)	42,355 (22.4)
Medical history			
Kidney disease, *n* (%)			
CKD (5-year lookback)	21,336 (3.6)	869 (30.7)	10,918 (5.6)
Previous AKI (5-year lookback)	4601 (0.8)	177 (6.3)	2528 (1.3)
RCS Charlson comorbidities, *n* (%)			
MI	14,827 (2.5)	79 (2.8)	6141 (3.2)
Congestive cardiac failure	22,958 (3.8)	205 (7.2)	11,397 (5.9)
Peripheral vascular disease	26,010 (4.3)	206 (7.3)	11,428 (5.9)
Cerebrovascular disease	18,229 (3.0)	83 (2.9)	7816 (4.0)
Dementia	4485 (0.7)	18 (0.6)	3043 (1.6)
Chronic pulmonary disease	67,705 (11.3)	291 (10.3)	29,573 (15.2)
Rheumatological disease	10,381 (1.7)	70 (2.5)	4708 (2.4)
Liver disease	10,577 (1.8)	67 (2.4)	4940 (2.5)
Diabetes mellitus	60,655 (10.1)	682 (24.1)	26,516 (13.6)
Hemiplegia or paraplegia	4291 (0.7)	18 (0.6)	1992 (1.0)
Malignancy	72,218 (12.1)	226 (8.0)	37,032 (19.0)
APACHE II severe conditions in medical history, *n* (%)			
Severe liver disease	9866 (1.6)	53 (1.9)	4623 (2.4)
Metastatic disease	28,033 (4.7)	51 (1.8)	19,756 (10.1)

TABLE 18 Characteristics of the overall cohort, those who developed ESRD during follow-up and those who died during follow-up without developing ESRD (*continued*)

Characteristics	Cohort	ESRD	Death before ESRD
Haematological malignancy	7441 (1.2)	54 (1.9)	4361 (2.2)
Severe respiratory disease/home ventilation	9510 (1.6)	39 (1.4)	5859 (3.0)
Immunocompromise	36,134 (6.0)	143 (5.1)	20,316 (10.4)
Very severe cardiovascular disease	7650 (1.3)	51 (1.8)	3824 (2.0)
Prior dependency, *n* (%)			
Able to live without assistance in daily activities	488,965 (82.2)	2237 (79.4)	138,913 (71.7)
Some (minor/major) assistance with daily activities	101,612 (17.1)	569 (20.2)	52,975 (27.3)
Total assistance with all daily activities	4064 (0.7)	12 (0.4)	1822 (0.9)
Patient-related factors			
CPR within 24 hours prior to admission, *n* (%)			
No CPR	581,304 (97.1)	2764 (97.6)	189,346 (97.3)
Community CPR	8795 (1.5)	13 (0.5)	2044 (1.0)
In-hospital CPR	8497 (1.4)	54 (1.9)	3298 (1.7)
Location prior to critical care admission, *n* (%)			
ED or not in hospital, unplanned	127,237 (21.3)	778 (27.5)	34,131 (17.5)
ED or not in hospital, planned	4781 (0.8)	15 (0.5)	964 (0.5)
Theatre, elective/scheduled, planned	185,172 (30.9)	449 (15.9)	60,665 (31.2)
Theatre, elective/scheduled, unplanned	30,160 (5.0)	75 (2.6)	10,267 (5.3)
Theatre, emergency/urgent	113,051 (18.9)	257 (9.1)	37,061 (19.0)
Ward or intermediate care area	121,646 (20.3)	1121 (39.6)	46,013 (23.6)
Other critical care unit, repatriation	1318 (0.2)	9 (0.3)	464 (0.2)
Other critical care unit, planned/unplanned transfer	10,161 (1.7)	93 (3.3)	3566 (1.8)
Other acute hospital	5077 (0.8)	34 (1.2)	1560 (0.8)
Primary reason for admission by body system, *n* (%)			
Respiratory	100,767 (16.8)	387 (13.7)	37,074 (19.0)
Cardiovascular	109,457 (18.3)	422 (14.9)	31,509 (16.2)
Gastrointestinal	163,816 (27.4)	335 (11.8)	61,917 (31.8)
Neurological (including eyes)	80,999 (13.5)	124 (4.4)	21,555 (11.1)
Genito-urinary	56,793 (9.5)	1195 (42.2)	20,396 (10.5)
Endocrine, Metabolic, Thermoregulation and Poisoning	43,029 (7.2)	243 (8.6)	7918 (4.1)
Haematological/Immunological	4598 (0.8)	32 (1.1)	1842 (0.9)
Musculoskeletal	32,554 (5.4)	69 (2.4)	10,615 (5.5)
Dermatological	6327 (1.1)	24 (0.8)	1809 (0.9)
Psychiatric	248 (0.0)	0 (0.0)	52 (0.0)
Sepsis, *n* (%)	141,405 (23.6)	658 (23.2)	50,746 (26.1)

continued

TABLE 18 Characteristics of the overall cohort, those who developed ESRD during follow-up and those who died during follow-up without developing ESRD (*continued*)

Characteristics	Cohort	ESRD	Death before ESRD
Severity scores from the first 24 hours in the critical care unit			
APACHE II score, mean (SD)	13 (5.7)	19 (6.3)	16 (5.6)
APACHE II score, median (IQR)	13 (10–17)	19 (15–23)	15 (12–19)
ICNARC physiology score, mean (SD)	14 (7.1)	20 (7.4)	15 (7.1)
ICNARC physiology score, median (IQR)	12 (9–18)	19 (14–24)	14 (10–19)
Physiology during the first 24 hours in the critical care unit			
Highest heart rate (min^{-1}), mean (SD)	101 (22)	102 (22)	101 (22)
Lowest systolic blood pressure (mmHg), mean (SD)	98 (18)	108 (25)	97 (19)
Highest temperature (°C), mean (SD)	37.6 (0.9)	37.5 (0.9)	37.6 (0.9)
Lowest respiratory rate (min^{-1}), mean (SD)	12.4 (4.3)	12.8 (3.6)	12.5 (3.9)
Urine output (ml), mean (SD)	2012 (1660)	1353 (1347)	1796 (1268)
PaO_2/FiO_2 (kPa), mean (SD)	36.4 (15.8)	36.1 (16.5)	35.3 (15.4)
Lowest arterial pH, mean (SD)	7.33 (0.09)	7.27 (0.12)	7.33 (0.09)
$PaCO_2$ (kPa), mean (SD)	5.9 (1.7)	5.1 (1.8)	5.9 (1.9)
Highest blood lactate (mmol l^{-1}), mean (SD)	2.3 (1.9)	2.2 (2.3)	2.3 (1.9)
Highest urea (µmol l^{-1}), mean (SD)	8.4 (8.0)	26.9 (18.1)	9.8 (8.8)
Highest creatinine (µmol l^{-1}), mean (SD)	111 (122)	530 (476)	121 (131)
Highest sodium (mmol l^{-1}), mean (SD)	139 (5)	138 (5)	139 (5)
Lowest white blood cell count ($\times 10^9$ l^{-1}), mean (SD)	11.5 (7.5)	11.3 (6.0)	11.5 (9.0)
Neutrophil count ($\times 10^9$ l^{-1}), mean (SD)	9.5 (5.5)	9.4 (5.5)	9.5 (5.7)
Lowest platelet count ($\times 10^9$ l^{-1}), mean (SD)	212 (105)	206 (112)	215 (111)
Mechanical ventilation, *n* (%)	230,968 (38.6)	861 (30.4)	65,895 (33.8)
Organ dysfunction, *n* (%)	477,861 (79.8)	2512 (88.7)	162,871 (83.7)
Length of stay			
Critical care unit length of stay (hours), mean (SD)	100 (173)	139 (2038)	109 (188)
Critical care unit length of stay (hours), median (IQR)	47 (23–102)	75 (38–158)	52 (25–116)
Acute hospital length of stay (days), mean (SD)	22 (29.9)	29 (33.1)	27 (32.9)
Acute hospital length of stay (days), median (IQR)	12 (7–25)	19 (10–36)	16 (9–32)
Organ support during critical care stay			
Receipt of advanced respiratory support, *n* (%)	230,968 (38.6)	861 (30.4)	65,895 (33.8)
Duration of advanced respiratory support (days), median (IQR)	2 (1–5)	3 (2–7)	2 (2–6)
Receipt of advanced cardiovascular support, *n* (%)	103,500 (17.3)	493 (17.4)	32,665 (16.8)
Duration of advanced cardiovascular support (days), median (IQR)	2 (1–3)	2 (1–4)	2 (1–3)
Receipt of renal support, *n* (%)	28,963 (4.8)	1436 (50.7)	10,855 (5.6)
Duration of renal support (days), median (IQR)	4 (2–7)	3 (2–6)	3 (2–6)

TABLE 19 Cause-specific hazard ratio and sHR with 95% CIs for ESRD after hospital discharge following critical care, and cHR for the competing risk of mortality

Predictor	cHR (95% CI)	sHR (95% CI)	cHR[a] (95% CI)
Age (years) – RCS (33,63,81)			
age_1	0.99 (0.98 to 1.00)	0.99 (0.98 to 0.99)	1.03 (1.03 to 1.04)
age_2	0.98 (0.97 to 0.98)	0.97 (0.96 to 0.98)	1.00 (1.00 to 1.00)
Male sex	0.76 (0.70 to 0.83)	0.78 (0.71 to 0.85)	1.21 (1.20 to 1.22)
Ethnicity			
White	ref	ref	ref
Mixed	1.67 (1.00 to 2.78)	1.67 (1.02 to 2.70)	0.91 (0.83 to 0.99)
Asian	1.85 (1.59 to 2.16)	1.94 (1.60 to 2.35)	0.84 (0.81 to 0.86)
Black	1.62 (1.34 to 1.96)	1.65 (1.33 to 2.03)	0.90 (0.87 to 0.95)
Other/not stated	2.14 (1.63 to 2.81)	2.16 (1.65 to 2.84)	0.89 (0.84 to 0.95)
Pregnant/recently pregnant	0.63 (0.40 to 1.00)	0.68 (0.42 to 1.07)	0.13 (0.11 to 0.16)
Severe liver disease	0.81 (0.60 to 1.10)	0.70 (0.51 to 0.95)	2.00 (1.94 to 2.07)
Metastatic disease	0.65 (0.48 to 0.88)	0.41 (0.30 to 0.57)	3.42 (3.36 to 3.48)
Peripheral vascular disease	1.29 (1.09 to 1.53)	1.25 (1.05 to 1.48)	1.26 (1.24 to 1.29)
Diabetes	1.35 (1.22 to 1.49)	1.30 (1.16 to 1.45)	1.28 (1.26 to 1.30)
CKD (5-year lookback)	4.11 (3.72 to 4.54)	3.58 (3.18 to 4.03)	1.45 (1.26 to 1.29)
AKI (5-year lookback)	1.73 (1.45 to 2.05)	1.64 (1.36 to 1.98)	1.36 (1.31 to 1.42)
Surgical status			
Non-surgical	ref	ref	ref
Elective surgery	1.25 (1.08 to 1.43)	1.36 (1.16 to 1.60)	0.80 (0.79 to 0.81)
Emergency surgery	0.98 (0.84 to 1.43)	1.04 (0.88 to 1.21)	0.88 (0.87 to 0.89)
Sepsis	0.86 (0.77 to 0.95)	0.89 (0.79 to 0.99)	1.00 (0.99 to 1.00)
Trauma	0.78 (0.63 to 0.96)	0.81 (0.65 to 0.99)	0.83 (0.81 to 0.85)
Nephrectomy	1.92 (1.50 to 2.46)	1.91 (1.49 to 2.44)	1.13 (1.08 to 1.17)
Vascular surgery	1.23 (1.01 to 1.50)	1.29 (1.05 to 1.53)	0.78 (0.76 to 0.79)
Mechanical ventilation[b]	1.29 (1.14 to 1.45)	1.29 (1.14 to 1.46)	0.86 (0.84 to 0.86)
Highest heart rate[b] (per 10 min^{-1} increase)	0.97 (0.95 to 0.99)	0.97 (0.95 to 0.99)	1.03 (1.02 to 1.03)
Lowest respiratory rate[b] (per 5 min^{-1} increase)	0.93 (0.88 to 0.99)	0.94 (0.88 to 0.99)	1.02 (1.01 to 1.02)
Lowest systolic blood pressure[b] (per 1 mmHg increase)	1.02 (1.01 to 1.02)	1.02 (1.01 to 1.02)	0.99 (0.99 to 0.99)
Urine output[b] (per 500 ml increase)	0.89 (0.87 to 0.90)	0.89 (0.88 to 0.91)	0.97 (0.96 to 0.97)
Lowest arterial pH[b] (per 1 increase)	0.52 (0.35 to 0.79)	0.45 (0.29 to 0.69)	1.83 (1.83 to 2.14)
$PaCO_2$[b] (per 1 kPa increase)	0.91 (0.89 to 0.94)	0.91 (0.88 to 0.94)	1.05 (1.04 to 1.05)
Highest blood lactate[b] (mmol l^{-1}) – RCS (0.9,1.8,4.2)			
bl_1	0.72 (0.66 to 0.78)	0.72 (0.66 to 0.79)	0.97 (0.96 to 0.98)
bl_2	1.41 (1.25 to 1.59)	1.40 (1.24 to 1.59)	1.05 (1.03 to 1.06)

continued

TABLE 19 Cause-specific hazard ratio and sHR with 95% CIs for ESRD after hospital discharge following critical care, and cHR for the competing risk of mortality (*continued*)

Predictor	cHR (95% CI)	sHR (95% CI)	cHR[a] (95% CI)
Highest sodium[b] (mmol l^{-1}) – RCS (134,139,144)			
na_1	1.04 (1.02 to 1.05)	1.04 (1.02 to 1.05)	0.98 (0.97 to 0.98)
na_2	0.95 (0.93 to 0.97)	0.95 (0.94 to 0.97)	1.02 (1.01 to 1.02)
Highest creatinine[b] (μmol l^{-1}) – RCS (44,69,96,271)			
cr_1	0.96 (0.94 to 0.98)	0.97 (0.94 to 0.98)	0.98 (0.98 to 0.98)
cr_2	3.49 (2.72 to 4.48)	3.33 (2.72 to 4.48)	1.25 (1.23 to 1.26)
cr_3	0.07 (0.04 to 0.12)	0.08 (0.04 to 0.12)	0.65 (0.63 to 0.66)
Highest urea[b] (mmol l^{-1}) – RCS (3.2,6.1,14.9)			
ur_1	1.16 (1.07 to 1.24)	1.15 (1.06 to 1.25)	1.06 (1.05 to 1.07)
ur_2	0.83 (0.75 to 0.92)	0.84 (0.75 to 0.93)	0.92 (0.75 to 0.92)
Lowest white blood cell count[b] (per 10×10^9 l^{-1} increase)	0.90 (0.84 to 0.96)	0.90 (0.84 to 0.96)	1.03 (1.03 to 1.04)
Duration of advanced respiratory support (calendar days)	0.97 (0.96 to 0.99)	0.98 (0.96 to 0.99)	0.99 (0.99 to 0.99)
Duration of basic/advanced cardiovascular support (calendar days)	0.94 (0.91 to 0.96)	0.95 (0.92 to 0.97)	0.97 (0.97 to 0.97)
Duration of renal support (calendar days)	1.13 (1.09 to 1.12)	1.11 (1.09 to 1.13)	0.99 (0.98 to 0.99)
Critical care unit length of stay (per day)	0.97 (0.96 to 0.99)	0.97 (0.96 to 0.99)	1.00 (1.00 to 1.00)
Hospital length of stay after discharge from critical care (per 10 days)	0.92 (0.91 to 0.96)	0.92 (0.91 to 0.96)	1.05 (1.05 to 1.05)

a Cause-specific mortality model.
b During the first 24 hours following admission to critical care.
RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

creatinine (measured during the first 24 hours of critical care) increased over a range from 100 to 200 μmol l^{-1}. Patients with CKD [adjusted hazard ratio (aHR) 4.11], AKI (aHR 1.73), peripheral vascular disease (aHR 1.29) and diabetes (aHR 1.35) were more likely to receive RRT for ESRD than those without these conditions. Mechanical ventilation (aHR 1.29), vascular surgery (aHR 1.23) and nephrectomy (aHR 1.92) were also associated with an increased risk of ESRD. However, some severe conditions in the medical history [severe liver disease (aHR 0.81) and metastatic disease (aHR 0.65)] were associated with a lower likelihood of RRT for ESRD. The effects of the rest of the variables in the model are presented in *Table 19*. CPR prior to admission, cardiac surgery, severe cardiovascular disease, MI and congestive cardiac failure were not considered significant after adjusting for the rest of the variables in the model. No significant interactions were demonstrated.

Harrell's c-statistic for the model was 0.94, with an explained variation (R^2) of 0.985 (95% CI 0.982 to 0.987, based on 100 bootstrap samples). Most of the prognostic information was carried by duration of renal support, surgical status, CKD and highest creatinine, because the R^2 decreased considerably on dropping those variables (see *Report Supplementary Material 1*, Table S1).

Predictors of cumulative incidence of end-stage renal disease

Results of the competing risk analysis using the Fine–Gray approach were consistent with the cause-specific Cox results. Significant predictors of cumulative incidence of ESRD and the corresponding

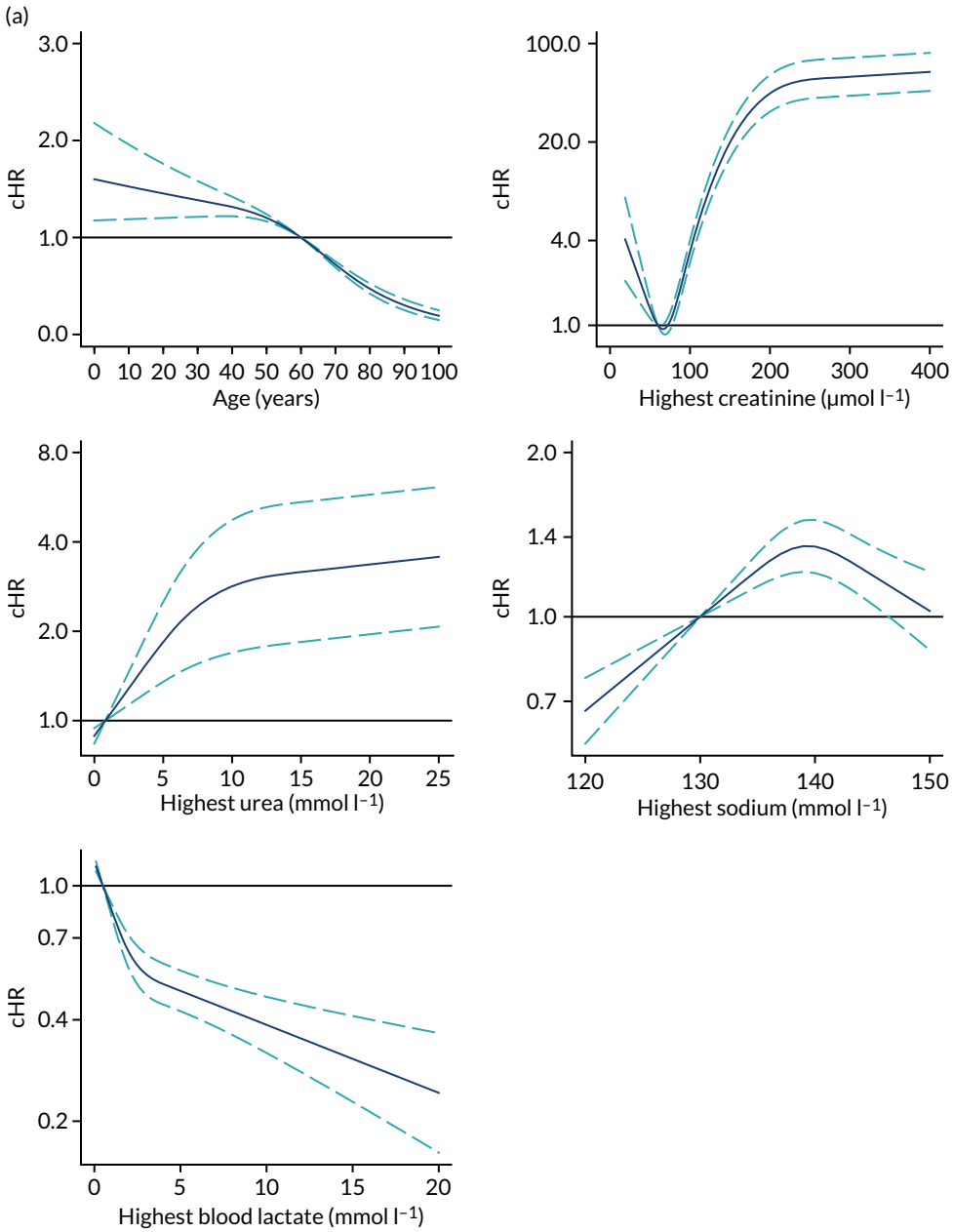

FIGURE 12 Cause-specific hazard ratio for (a) ESRD and (b) mortality before ESRD after hospital discharge following critical care for continuous predictors included in the model as non-linear using restricted cubic splines.[a] a, Physiological parameters assessed during the first 24 hours following admission to critical care. (*continued*)

adjusted sHR are presented in *Table 19*. *Figure 13* provides a graphical interpretation of the non-linear association between continuous factors and the cumulative incidence (absolute risk over time) of the development of ESRD. Cumulative incidence of ESRD increases with increasing age and urea, particularly in admissions with elevated creatinine. On the other hand, admissions with higher blood lactate had a lower risk of RRT for ESRD (adjusted for other variables in the model). The presence of severe liver disease (sHR 0.70) and metastatic disease (sHR 0.41) were significantly associated with a lower risk of RRT for ESRD. CKD (sHR 3.58) was associated with a substantial increase in the cumulative incidence of ESRD (*Figure 14*). Previous AKI (sHR 1.64), diabetes (sHR 1.30) and peripheral vascular disease (sHR 1.25) were also all associated with a higher risk of ESRD.

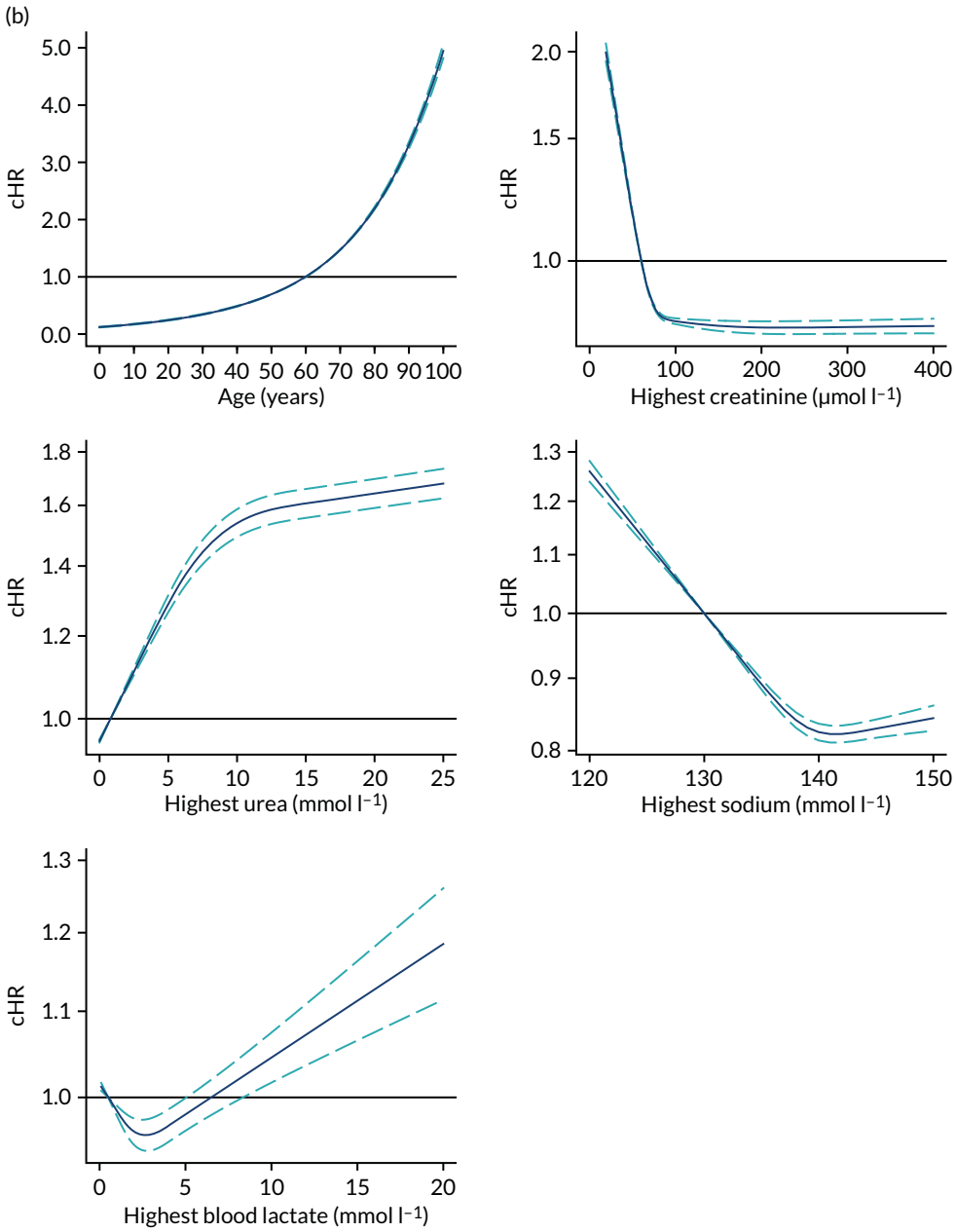

FIGURE 12 Cause-specific hazard ratio for (a) ESRD and (b) mortality before ESRD after hospital discharge following critical care for continuous predictors included in the model as non-linear using restricted cubic splines.[a] a, Physiological parameters assessed during the first 24 hours following admission to critical care.

Predictors of pre-end-stage renal disease mortality

Cause-specific hazard ratios for the competing risk of mortality are presented in *Table 19* and *Figure 12*. Notably, severe liver disease (cHR 2.00) and metastatic disease (cHR 3.42) elevated the risk of dying without first developing ESRD.

Discussion

We have successfully linked data between the CMP and UKRR to establish the incidence of RRT for ESRD following an episode of critical illness. Overall, the rate of RRT for ESRD was low (approximately 0.5% over a median of 2.7 years' follow-up) but a number of factors were predictive of higher rates,

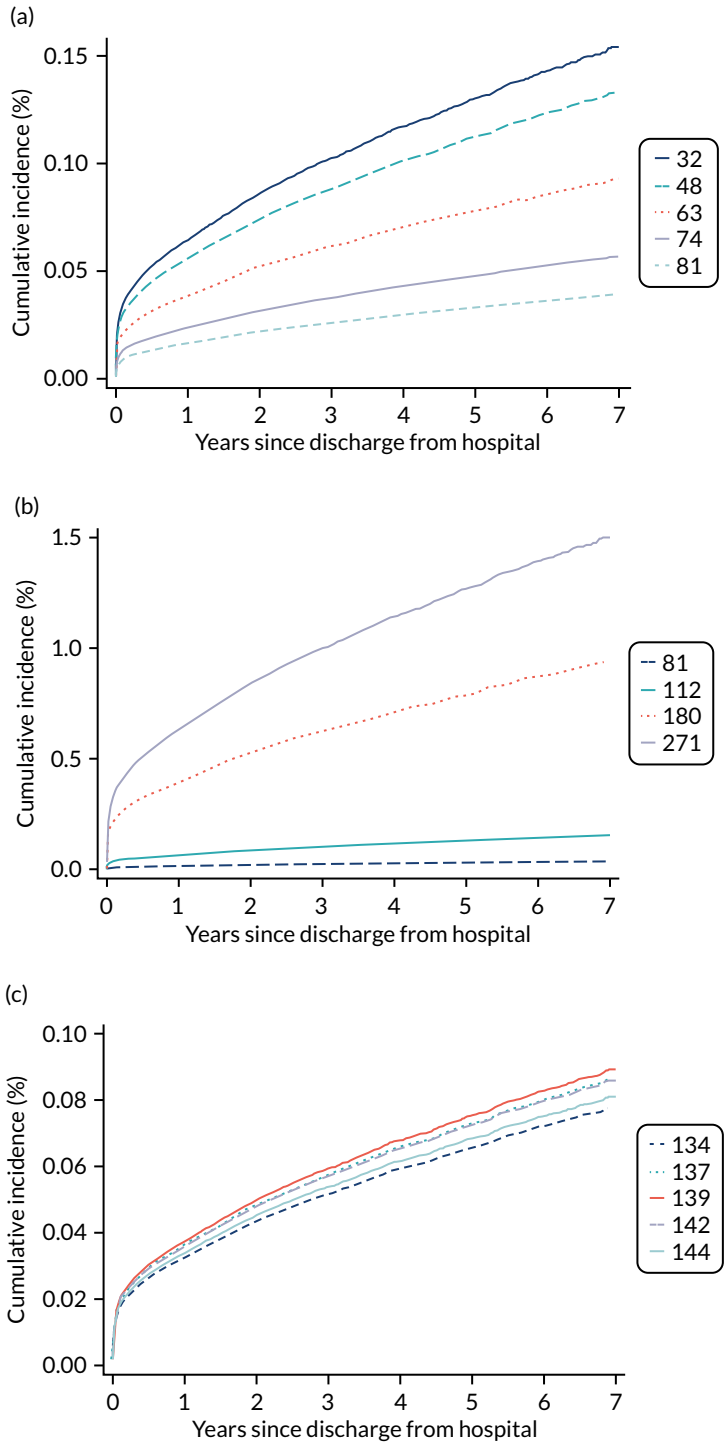

FIGURE 13 Cumulative incidence of ESRD in the 7 years after hospital discharge following critical care according to predictors included in the Fine–Gray competing risks model. (a) Age; (b) highest creatinine; (c) highest sodium; (d) highest urea; (e) highest blood lactate.[a] a, Physiological parameters assessed during the first 24 hours following admission to critical care. (*continued*)

most notably CKD, previous hospital episodes with AKI, admission following nephrectomy, creatinine measured during the critical care stay, and duration of renal support.

In the present study, we deliberately focused on the specific outcome of developing ESRD, with the aim of determining the risk factors that are associated with this outcome following a critical care admission. However, the competing risk of death before developing ESRD was considered applying two

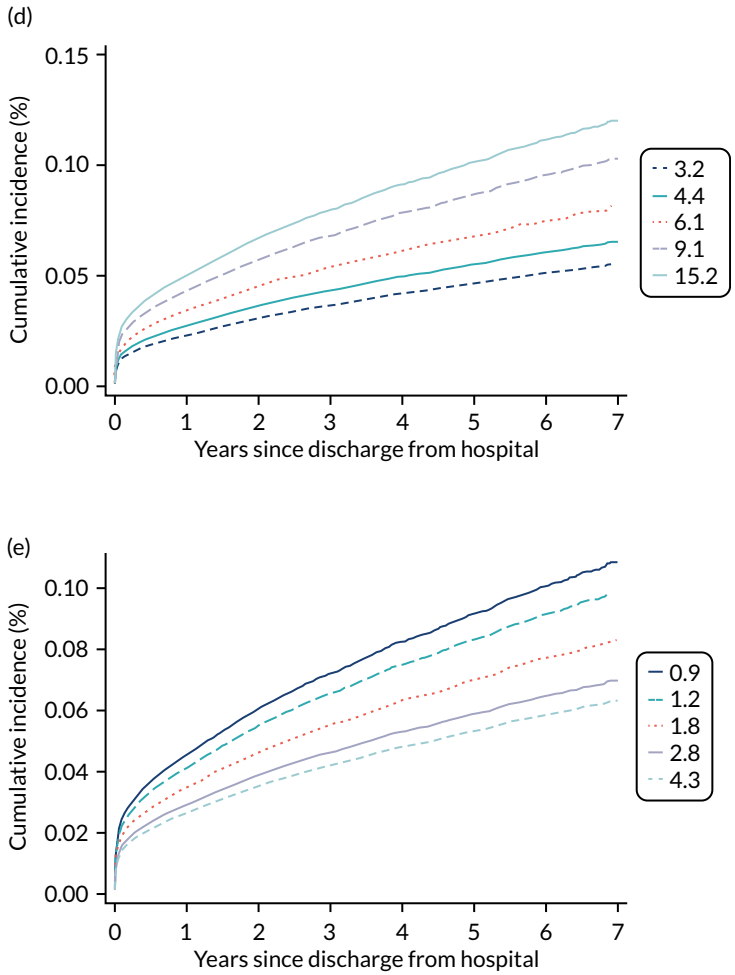

FIGURE 13 Cumulative incidence of ESRD in the 7 years after hospital discharge following critical care according to predictors included in the Fine–Gray competing risks model. (a) Age; (b) highest creatinine; (c) highest sodium; (d) highest urea; (e) highest blood lactate.[a] a, Physiological parameters assessed during the first 24 hours following admission to critical care.

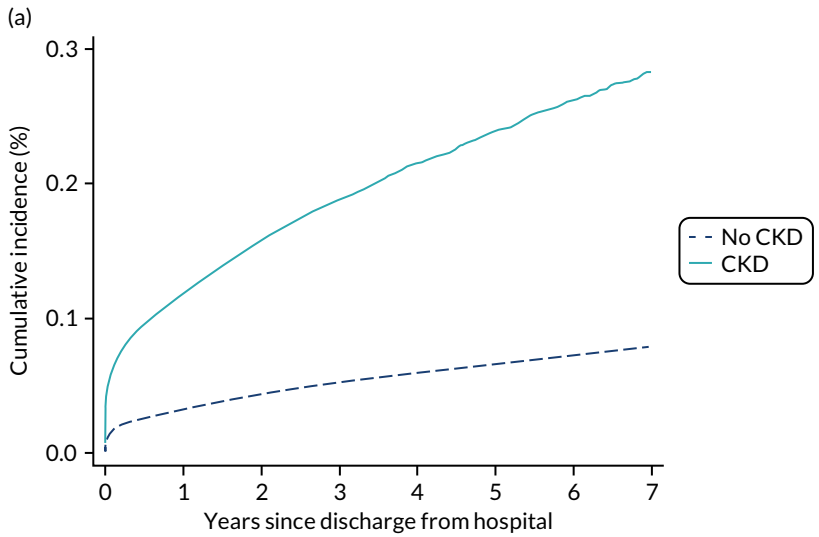

FIGURE 14 Cumulative incidence of ESRD in the 7 years after hospital discharge following critical care according to predictors included in the Fine–Gray competing risks model (comorbidities). (a) CKD; (b) AKI; (c) PVD; (d) diabetes; (e) severe liver disease; (f) metastatic. PVD, peripheral vascular disease. (*continued*)

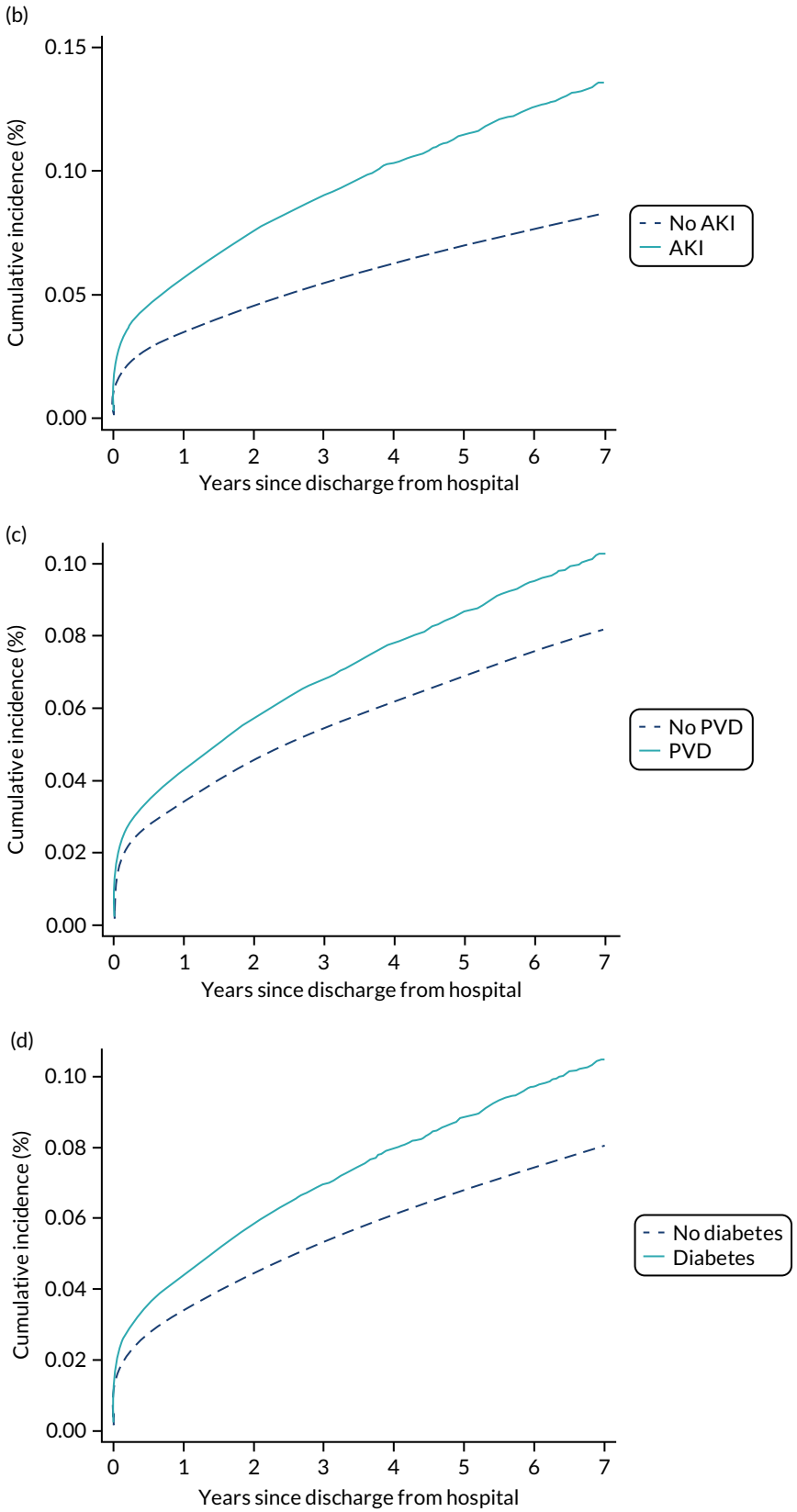

FIGURE 14 Cumulative incidence of ESRD in the 7 years after hospital discharge following critical care according to predictors included in the Fine–Gray competing risks model (comorbidities). (a) CKD; (b) AKI; (c) PVD; (d) diabetes; (e) severe liver disease; (f) metastatic. PVD, peripheral vascular disease. (*continued*)

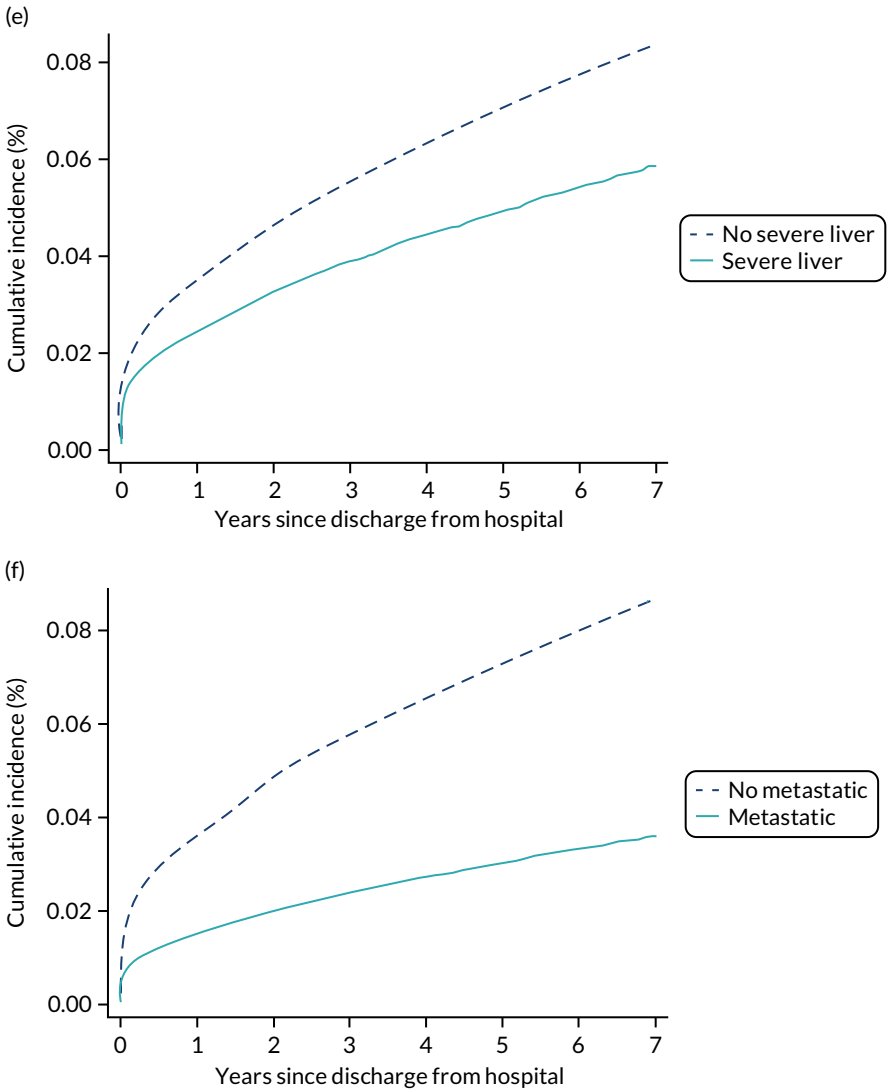

FIGURE 14 Cumulative incidence of ESRD in the 7 years after hospital discharge following critical care according to predictors included in the Fine–Gray competing risks model (comorbidities). (a) CKD; (b) AKI; (c) PVD; (d) diabetes; (e) severe liver disease; (f) metastatic. PVD, peripheral vascular disease.

different approaches: the proportional cause-specific hazards method and the subdistribution hazards approach proposed by Fine and Gray. The two approaches focus on different aspects of analysis and complement each other. The cause-specific Cox model may be preferred for answering aetiological research questions or when the interpretation of the hazard ratio has a special interest. On the other hand, there is currently consensus that for prognostic studies, a formal competing-risk (Fine–Gray) model that looks at the cumulative incidence of an ESRD while also taking into consideration death before ESRD is the most appropriate method to use.[52] Regression models based on the CIF explore the association between predictors and the absolute risk and therefore are essential for medical decision-making and prognosis research questions. However, a complete understanding of effects of prognostic factors on a competing risk end point requires modelling both cause-specific hazards and cumulative incidences.[53] Although the cHR directly measures the association of a covariate on the event of interest as the competing event only contributes passively by removing individuals from the risk set, the sHR is a measure of association that takes into consideration the potential relationship between the covariate with both the event of interest and the competing event. Consequently, the effect of a covariate on the cause-specific hazard for an event can be different from its effect on the corresponding CIF. For most of the covariates in our study, the cause-specific and the cumulative incidence analyses were consistent with each other, and we could interpret the covariate effect on the

cumulative incidence of ESRD as a direct effect and not as an indirect effect of the competing risk of death before ESRD. However, special attention should be paid to metastatic disease and severe liver disease. In both cases, we may speculate that patients with these conditions are less likely to receive RRT for ESRD, which may explain the association with a lower risk of RRT for ESRD. Metastatic disease in the medical history presents a strong cHR for mortality (3.42) and, as expected, the sHR for ESRD is lower than the corresponding cHR (0.41 vs. 0.65).[54] This difference suggests that despite the direct effect between metastatic disease and development of ESRD (cHR 0.65), mortality contributes to a lower sHR for ESRD because those with metastatic disease had a higher cause-specific hazard rate for death. In the case of severe liver disease, the 95% CI for the cHR (0.60 to 1.10) suggests no association. However, the cHR for mortality (2.0) drives a sHR for ESRD of < 1 because of the differential modification of the risk sets. Therefore, patients with liver disease will be less likely to have ESRD because of the association of liver disease with the competing event, death before ESRD. These examples demonstrate that both approaches for dealing with competing risk data may yield different results, which is explained by the different composition of the risk sets. These findings are in agreement with previous studies.[55,56] However, as mentioned before, the cHR and the sHR do not have the same interpretation.

A major strength of the present work is the large cohort of admissions to critical care and long follow-up period. This study has some limitations. Unfortunately, information about baseline renal function is not recorded in any of the linked data sources, and consequently its influence in developing ESRD is not studied here. It was possible to only model the outcome of ESRD treated by RRT, as no routine data sources capture kidney failure not treated with RRT. HES and CMP identified substantial numbers of patients with pre-existing ESRD that were not identified from UKRR, suggesting that using UKRR registrations as the outcome measure is likely to under-represent the total burden of ESRD in this patient group. In addition, we explored only the association between AKI, as identified from diagnostic coding during previous hospitalisations, but this did not permit us to explore the risk of ESRD in patients with different stages of AKI. We also did not determine the association between recurrence, duration and aetiology of AKI and ESRD. Furthermore, procedure codes from HES were not available for the complete study period, and therefore it was not possible to identify cardiac surgery, vascular surgery and nephrectomy from the HES data. As an alternative, we were able to identify these using the information recorded in the CMP.

These results are in line with increasing evidence showing that the burden of severe AKI extends beyond hospitalisation and includes an increased risk of death and chronic dialysis dependency.[51,57–62] This analysis is, to our knowledge, the largest study to date with data from the UK and is immediately relevant to the NHS. Long-term follow up after AKI is recommended[63,64] but there is still debate and controversy as to what constitutes optimal aftercare.[65] Identifying those who are at highest risk of serious long-term complications is essential.

Chapter 7 Risk models for development of type 2 diabetes following critical care

Introduction

The occurrence of hyperglycaemia is common among critically ill patients, regardless of diabetes status, and is associated with acute severity of illness and outcomes. Critical illness-related hyperglycaemia has previously been linked with subsequent development of type 2 diabetes in small cohorts.[66,67] Data linkage between the CMP, HES, NDA and death registrations has permitted us to explore this in a much larger cohort and establish whether peak blood glucose in the first 24 hours of admission to the critical care unit and other risk factors are associated with the likelihood of developing type 2 diabetes in survivors of critical illness.

Methods

Methods common to all objectives and analyses were described in *Chapter 3*.

Study cohort

The cohort for this chapter is the CMP hospital survivor cohort (see *Chapter 3*) of patients discharged from hospital between 1 April 2009 and 31 March 2016 following a critical care episode. The final follow-up date was 31 March 2017 (based on the latest available data from the NDA at the time of linkage).

Exclusion criteria

Patients were excluded if they had pre-existing diabetes (type 1 or type 2), identified by:

1. linkage with the NDA indicating a date of diagnosis prior to or during the critical care episode
2. *ICD-10* codes indicating diabetes in any diagnosis field from linked HES records prior to or during the critical care episode
3. a primary or secondary reason for admission to the critical care unit in the CMP associated with diabetes.

Outcome

The main outcome was incidence of type 2 diabetes. As the actual timing of the development of diabetes is unknown, we used as a surrogate measure a new registration for type 2 diabetes, based on the date of diagnosis recorded in the NDA database, after the date of discharge from hospital. The competing risk was death from any cause before type 2 diabetes, identified via linkage with death registrations. Deaths after a diagnosis of type 2 diabetes were not considered. The association between glucose and mortality was also explored as a secondary outcome.

Candidate variables

Potentially important candidate predictors and controlling variables were chosen based on expert clinical opinion and availability in the linked data sources. A description of the candidate predictors is given in *Appendix 1*, *Table 38*. The primary aim was to evaluate the association between serum glucose levels in the first 24 hours after admission and subsequent risk of type 2 diabetes.

Statistical analyses

For the description of cohort characteristics, assessment of optimal functional form and selection of covariables, we followed same methodology as described in *Chapter 3*.

The incidence rate was calculated as the number of cases of new-onset type 2 diabetes divided by the follow-up time and expressed as the number of events per 1000 person-years. The hazard ratios and cumulative mortality function were assessed by Cox (cause-specific hazard) and Fine–Gray (subdistribution hazard) methods; both approaches were described in *Chapter 6*. For the cause-specific model, the explained variation (R^2) was determined. The proportional hazard assumption was tested by visual inspection of Schoenfeld residual plots and log-log plots.

Results

After exclusions, a total of 497,967 patients admitted to 248 NHS adult, general critical care units in England participating in the CMP and discharged alive from hospital between 1 April 2009 and 31 March 2016 were included in the analysis (*Figure 15*).

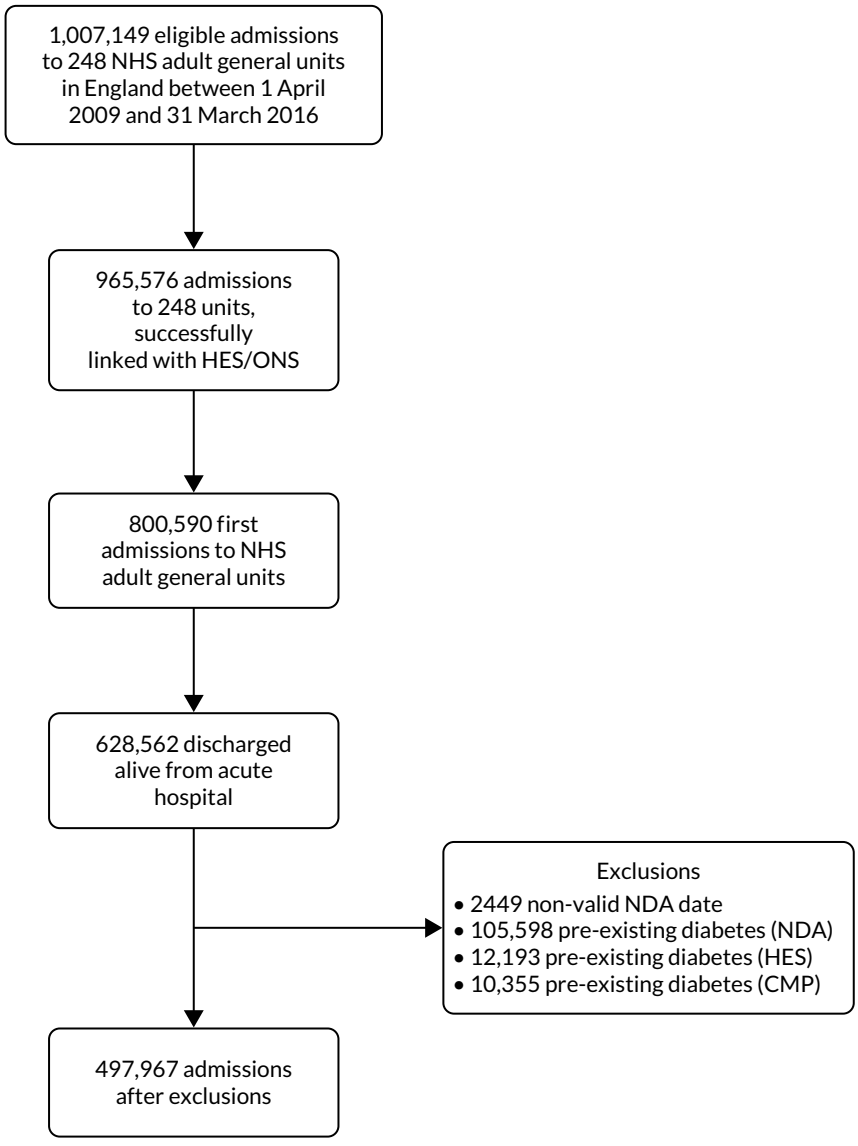

FIGURE 15 Flow-diagram for cohort identification.

The median follow-up was 2.8 years (IQR 1.5 to 4.6 years) and 12,808 (2.6%) patients were subsequently diagnosed with type 2 diabetes after hospital discharge (incidence rate 7.8 per 1000 person-years; 95% CI 7.6 to 7.9). A total of 155,489 (31.2%) patients died without a diagnosis of type 2 diabetes.

Patient characteristics

Characteristics of the overall cohort, as well as divided by outcome, are detailed in *Table 20*. Compared with the overall cohort, patients with subsequent type 2 diabetes were slightly older (mean age 62 vs. 59 years), with a higher proportion of males (60% vs. 55%) and higher BMI (mean 30.7 vs. 26.7 kg/m^2). Five per cent of the patients who developed type 2 diabetes were Asian compared with only 3% in the overall cohort. There was also a much stronger deprivation gradient across those who developed type 2 diabetes (from 15% in the least deprived quintile to 26% in the most deprived quintile) compared with the overall cohort (18% to 22%). Severity scores were similar for patients who developed type 2 diabetes and the overall cohort, but there were differences in some individual physiological parameters. In particular, the patients who went on to develop type 2 diabetes had higher serum glucose levels (mean 10.2 vs 8.5 mmol l^{-1}) during the first 24 hours in the critical care unit.

TABLE 20 Characteristics of the overall cohort, those with a diagnosis of type 2 diabetes during follow-up and those who died during follow-up without a diagnosis of type 2 diabetes

Characteristics	Overall cohort	Diagnosis of type 2 diabetes	Death without a diagnosis of type 2 diabetes
Number of patients (%)	461,905	11,138 (2.4)	140,570 (30.4)
Demographics			
Age (years)			
Mean (SD)	59 (18.9)	62 (13.5)	69 (14.7)
Median (IQR)	62 (46, 74)	63 (53, 72)	71 (61, 80)
Sex, male (%)	253,452 (54.9)	6623 (59.5)	79,858 (56.8)
Body mass index (kg/m^2), mean (SD)	26.7 (6.2)	30.7 (7.6)	25.9 (5.7)
Ethnicity, *n* (%)			
White	417,848 (90.5)	9827 (88.2)	131,857 (93.8)
Mixed	2608 (0.6)	52 (0.5)	429 (0.3)
Asian	13,335 (2.9)	544 (4.9)	2277 (1.6)
Black	9752 (2.1)	307 (2.8)	1761 (1.3)
Other	5803 (1.3)	148 (1.3)	1052 (0.7)
Not stated	12,187 (2.6)	245 (2.2)	3077 (2.2)
Deprivation, *n* (%)			
1 (least deprived)	80,630 (18.1)	1632 (15.1)	25,630 (18.8)
2	85,285 (19.2)	1912 (17.7)	26,708 (19.6)
3	89,430 (20.1)	2080 (19.3)	27,866 (20.4)
4	90,513 (20.4)	2401 (22.3)	27,232 (20.0)
5 (most deprived)	98,689 (22.2)	2756 (25.6)	28,955 (21.2)

continued

TABLE 20 Characteristics of the overall cohort, those with a diagnosis of type 2 diabetes during follow-up and those who died during follow-up without a diagnosis of type 2 diabetes (*continued*)

Characteristics	Overall cohort	Diagnosis of type 2 diabetes	Death without a diagnosis of type 2 diabetes
Medical history			
RCS Charlson comorbidities, *n* (%)			
Previous MI	10,381 (2.2)	273 (2.5)	4185 (3.0)
Congestive cardiac failure	17,595 (3.8)	525 (4.7)	8392 (6.0)
Peripheral vascular disease	19,344 (4.2)	528 (4.7)	8069 (5.7)
Cerebrovascular disease	13,299 (2.9)	310 (2.8)	5425 (3.9)
Dementia	3277 (0.7)	38 (0.3)	2241 (1.6)
Chronic pulmonary disease	54,239 (11.7)	1546 (13.9)	23,632 (16.8)
Rheumatological disease	8270 (1.8)	194 (1.7)	3614 (2.6)
Liver disease	11,711 (2.5)	345 (3.1)	5348 (3.8)
Hemiplegia or paraplegia	3102 (0.7)	76 (0.7)	1365 (1.0)
Renal	16,724 (3.6)	370 (3.3)	8913 (6.3)
Malignancy	67,901 (14.7)	1152 (10.3)	36,360 (25.9)
APACHE II severe conditions in medical history, *n* (%)			
Very severe cardiovascular disease	5276 (1.1)	165 (1.5)	2477 (1.8)
Severe respiratory disease	6801 (1.5)	202 (1.8)	4082 (2.9)
Severe liver disease	7005 (1.5)	244 (2.2)	3094 (2.2)
ESRD	29,462 (6.4)	451 (4.0)	16,131 (11.5)
Metastatic disease	22,578 (4.9)	241 (2.2)	15,626 (11.1)
Haematological malignancy	6046 (1.3)	76 (0.7)	3500 (2.5)
Immunocompromise	4092 (0.9)	80 (0.7)	2045 (1.5)
Prior dependency, *n* (%)			
Able to live without assistance in daily activities	381,144 (83.1)	9277 (83.9)	100,854 (72.1)
Some (minor/major) assistance with daily activities	74,125 (16.2)	1745 (15.8)	37,590 (26.9)
Total assistance with all daily activities	3367 (0.7)	34 (0.3)	1397 (1.0)
Patient-related factors			
CPR within 24 hours prior to admission, *n* (%)			
No CPR	448,443 (97.1)	10,778 (96.8)	136,911 (97.4)
Community CPR	7307 (1.6)	183 (1.6)	1507 (1.1)
In-hospital CPR	6150 (1.3)	177 (1.6)	2151 (1.5)
Location prior to critical care admission, *n* (%)			
ED or not in hospital, unplanned	96,396 (20.9)	1936 (17.4)	23,649 (16.8)
ED or not in hospital, planned	4022 (0.9)	79 (0.7)	734 (0.5)
Theatre, elective/scheduled, planned	144,225 (31.2)	3725 (33.4)	44,938 (32.0)
Theatre, elective/scheduled, unplanned	22,675 (4.9)	644 (5.8)	7166 (5.1)
Theatre, emergency/urgent	90,603 (19.6)	1939 (17.4)	27,745 (19.7)

TABLE 20 Characteristics of the overall cohort, those with a diagnosis of type 2 diabetes during follow-up and those who died during follow-up without a diagnosis of type 2 diabetes (*continued*)

Characteristics	Overall cohort	Diagnosis of type 2 diabetes	Death without a diagnosis of type 2 diabetes
Ward or intermediate care area	91,196 (19.7)	2461 (22.1)	32,315 (23.0)
Other critical care unit, repatriation	1024 (0.2)	17 (0.2)	336 (0.2)
Other critical care unit, planned/unplanned transfer	7672 (1.7)	256 (2.3)	2494 (1.8)
Other acute hospital	4092 (0.9)	81 (0.7)	1193 (0.8)
Primary reason for admission by body system, *n* (%)			
Respiratory	78,585 (17.0)	2092 (18.8)	26,854 (19.1)
Cardiovascular	83,804 (18.1)	2595 (23.3)	22,079 (15.7)
Gastrointestinal	126,581 (27.4)	3180 (28.6)	44,996 (32.0)
Neurological (including eyes)	66,969 (14.5)	1119 (10.0)	16,262 (11.6)
Genito-urinary	43,865 (9.5)	946 (8.5)	15,298 (10.9)
Endocrine, metabolic, thermoregulation and poisoning	27,680 (6.0)	473 (4.2)	4500 (3.2)
Haematological/immunological	3601 (0.8)	57 (0.5)	1356 (1.0)
Musculoskeletal	25,863 (5.6)	538 (4.8)	8013 (5.7)
Dermatological	4728 (1.0)	133 (1.2)	1173 (0.8)
Psychiatric	220 (0.0)	5 (0.0)	38 (0.0)
Severity scores from the first 24 hours in the critical care unit			
APACHE II score, mean (SD)	13 (5.7)	13 (5.6)	16 (5.6)
APACHE II score, median (IQR)	13 (9–17)	13 (10–17)	15 (12–19)
ICNARC physiology score, mean (SD)	14 (7.0)	14 (7.4)	15 (7.1)
ICNARC physiology score, median (IQR)	12 (8–17)	13 (9–18)	14 (10–19)
Physiology during the first 24 hours in the critical care unit			
Highest glucose (mmol l^{-1}), mean (SD)	8.5 (2.8)	10.2 (3.8)	8.5 (2.8)
Highest heart rate (min^{-1}), mean (SD)	101 (22)	102 (21)	101 (22)
Lowest systolic blood pressure (mmHg), mean (SD)	97.9 (18.4)	99.6 (18.9)	97.0 (18.8)
Highest temperature (°C), mean (SD)	37.6 (0.9)	37.7 (0.9)	37.6 (0.9)
Lowest respiratory rate (min^{-1}), mean (SD)	12.3 (4.4)	12.5 (3.8)	12.4 (3.8)
Urine output (ml), mean (SD)	1991 (1737)	2023 (1262)	1746 (1269)
PaO_2/FiO_2 (kPa), mean (SD)	36.7 (15.9)	31.9 (14.1)	35.7 (15.5)
$PaCO_2$ (kPa), mean (SD)	5.9 (1.7)	6.3 (1.9)	5.9 (1.8)
Lowest arterial pH, mean (SD)	7.33 (0.09)	7.32 (0.09)	7.33 (0.09)
Highest blood lactate (mmol l^{-1}), mean (SD)	2.3 (1.8)	2.6 (1.9)	2.2 (1.8)
Highest urea (μmol l^{-1}), mean (SD)	8.1 (7.9)	8.7 (7.8)	9.8 (9.1)
Highest creatinine (μmol l^{-1}), mean (SD)	111 (134)	119 (123)	128 (158)
Highest sodium (mmol l^{-1}), mean (SD)	139 (4)	139 (4)	139 (5)
Lowest white blood cell count (× 10^9 l^{-1}), mean (SD)	11.4 (7.4)	11.9 (6.6)	11.4 (9.3)

continued

TABLE 20 Characteristics of the overall cohort, those with a diagnosis of type 2 diabetes during follow-up and those who died during follow-up without a diagnosis of type 2 diabetes (*continued*)

Characteristics	Overall cohort	Diagnosis of type 2 diabetes	Death without a diagnosis of type 2 diabetes
Neutrophil count (× 10^9 l^{-1}), mean (SD)	9.4 (5.4)	9.7 (5.2)	9.4 (5.8)
Lowest platelet count (× 10^9 l^{-1}), mean (SD)	210 (104)	211 (102)	214 (111)
Mechanical ventilation, *n* (%)	167,419 (36.2)	4267 (38.3)	43,454 (30.9)
Sepsis, *n* (%)	107,315 (23.2)	2863 (25.7)	35,904 (25.5)
Organ dysfunction, *n* (%)	364,663 (78.9)	8873 (79.7)	116,751 (83.1)
Length of stay			
Critical care unit length of stay (hours), mean (SD)	99 (173)	111 (190)	108 (186)
Critical care unit length of stay (hours), median (IQR)	46 (23–100)	49 (23–114)	51 (24–114)
Acute hospital length of stay (days), mean (SD)	21 (30)	21 (29)	27 (33)
Acute hospital length of stay (days), median (IQR)	12 (7–24)	12 (7–24)	16 (9–32)
Organ support during critical care stay			
Receipt of advanced respiratory support, *n* (%)	180,520 (39.1)	4563 (41.0)	47,065 (33.5)
Duration of advanced respiratory support (calendar days), median (IQR)	2 (1–5)	2 (1–6)	2 (2–6)
Receipt of advanced cardiovascular support, *n* (%)	78,550 (17.0)	2265 (20.3)	22,853 (16.3)
Duration of advanced cardiovascular support (calendar days), median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
Receipt of renal support, *n* (%)	22,176 (4.8)	656 (5.9)	8768 (6.2)
Duration of renal support (calendar days), median (IQR)	4 (2–7)	4 (2–7)	3 (2–6)

The *n* values do not sum to the total numbers because of varying amounts of missing data for each variable.

Predictors of subsequent type 2 diabetes

After exploring non-linearity and their best functional form had been determined, continuous predictors of age, BMI, highest glucose, systolic blood pressure, lowest haemoglobin and lowest white blood cell count were entered into a multivariable model along with the rest of potential factors detailed in *Appendix 1*, *Table 38*. Variables significant at $p < 0.05$ were retained and non-linearity was reassessed. *Table 21* shows the cHR and sHR after the modelling process. Non-linear associations were observed between the risk of subsequent type 2 diabetes and age, BMI, glucose and white blood cell count, and these variables were modelled using restricted cubic splines. *Figure 16* shows the adjusted cause-specific graphs associated with these non-linear relationships compared with reference values. There was a positive non-linear relationship between highest glucose and subsequent type 2 diabetes, with a marked increase between 8 and 12 mmol l^{-1}. Risk of diagnosis of type 2 diabetes increased steeply with increasing BMI up to around 35 kg/m^2, after which the increase was more gradual. Male patients (cHR 1.23), increasing systolic blood pressure, patients with severe liver disease (cHR 1.60), chronic pulmonary disease (cHR 1.20) and notably patients who had received pancreatic surgery (cHR 2.83) were also associated with an increased risk of type 2 diabetes. In addition, Asian (cHR 2.13) and black (cHR 1.43) patients were more likely to develop diabetes type 2 diabetes than white patients. On the other hand, receiving mechanical ventilation (cHR 0.86) and immunocompromise (cHR 0.73) were associated with a decreased risk of subsequent type 2 diabetes.

TABLE 21 Cause-specific hazard ratio and sHR with 95% CIs for a diagnosis of type 2 diabetes after hospital discharge following critical care

	cHR (95% CI)	sHR (95% CI)
Age (years) – RCS (23,48,62,72,85)		
age_1	1.08 (1.07 to 1.09)	1.08 (1.07 to 1.09)
age_2	0.89 (0.87 to 0.91)	0.89 (0.87 to 0.91)
age_3	1.34 (1.17 to 1.52)	1.37 (1.20 to 1.56)
age_4	0.69 (0.51 to 0.92)	0.62 (0.46 to 0.83)
Male sex	1.23 (1.18 to 1.29)	1.20 (1.15 to 1.26)
Ethnicity		
White	Ref	Ref
Mixed	1.14 (0.85 to 1.51)	1.13 (0.84 to 1.51)
Asian	2.13 (1.94 to 2.35)	2.17 (1.97 to 2.39)
Black	1.43 (1.26 to 1.62)	1.44 (1.27 to 1.63)
Other	1.34 (1.12 to 1.59)	0.91 (0.79 to 1.06)
Pregnant/recently pregnant	0.51 (0.37 to 0.71)	0.52 (0.38 to 0.72)
Deprivation		
1 (least deprived)	Ref	Ref
2	1.08 (1.00 to 1.16)	1.07 (1.00 to 1.15)
3	1.10 (1.02 to 1.18)	1.09 (1.01 to 1.16)
4	1.27 (1.18 to 1.36)	1.24 (1.16 to 1.33)
5 (most deprived)	1.37 (1.28 to 1.46)	1.31 (1.23 to 1.41)
Body mass index (kg/m^2) – RCS (19,23,26,29,38)		
bmi_1	1.15 (1.10 to 1.20)	1.18 (1.13 to 1.23)
bmi_2	0.59 (0.43 to 0.82)	0.54 (0.39 to 0.75)
bmi_3	14.49 (4.22 to 49.57)	18.57 (5.31 to 64.93)
bmi_4	0.24 (0.00 to 0.91)	0.02 (0.00 to 0.07)
Immunocompromise	0.73 (0.66 to 0.81)	0.57 (0.51 to 0.63)
Severe liver disease	1.60 (1.39 to 1.83)	1.36 (1.19 to 1.55)
Chronic pulmonary disease	1.20 (1.13 to 1.27)	1.10 (1.03 to 1.17)
Previous MI	1.19 (1.05 to 1.36)	1.09 (0.95 to 1.24)
Pancreatic surgery	2.83 (2.48 to 3.23)	2.35 (2.05 to 2.68)
Sepsis	1.15 (1.10 to 1.21)	1.15 (1.09 to 1.21)
Surgical status		
Elective surgery	Ref	Ref
Non-surgical	1.25 (1.18 to 1.31)	1.17 (1.11 to 1.23)
Emergency surgery	1.12 (1.06 to 1.20)	1.10 (1.03 to 1.16)
Highest glucose ($mmol\ l^{-1}$) – RCS (5.2,6.9,8.1,9.6,13.0)		
$gluco_1$	1.09 (1.07 to 1.18)	1.09 (1.01 to 1.19)
$gluco_2$	0.67 (0.35 to 1.27)	0.62 (0.32 to 1.22)
$gluco_3$	88.61 (9.40 to 834)	110.61 (10.73 to 1140)
$gluco_4$	0.0002 (0.000 to 0.002)	0.0001 (0.000 to 0.002)

continued

TABLE 21 Cause-specific hazard ratio and sHR with 95% CIs for a diagnosis of type 2 diabetes after hospital discharge following critical care (*continued*)

	cHR (95% CI)	sHR (95% CI)
Lowest systolic blood pressure (per 10 mmHg increase)	1.05 (1.04 to 1.06)	1.05 (1.04 to 1.06)
Lowest white blood cell count (10×10^9 l^{-1}) – RCS (5.6,10.4,17.9)		
$lwbc_1$	1.02 (1.01 to 1.03)	1.02 (1.01 to 1.04)
$lwbc_2$	0.97 (0.96 to 0.98)	0.97 (0.96 to 0.98)
Mechanical ventilation	0.86 (0.83 to 0.91)	0.91 (0.87 to 0.96)
Critical care unit length of stay (per 5 day increase)	1.01 (1.00 to 1.03)	1.01 (1.00 to 1.01)

RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

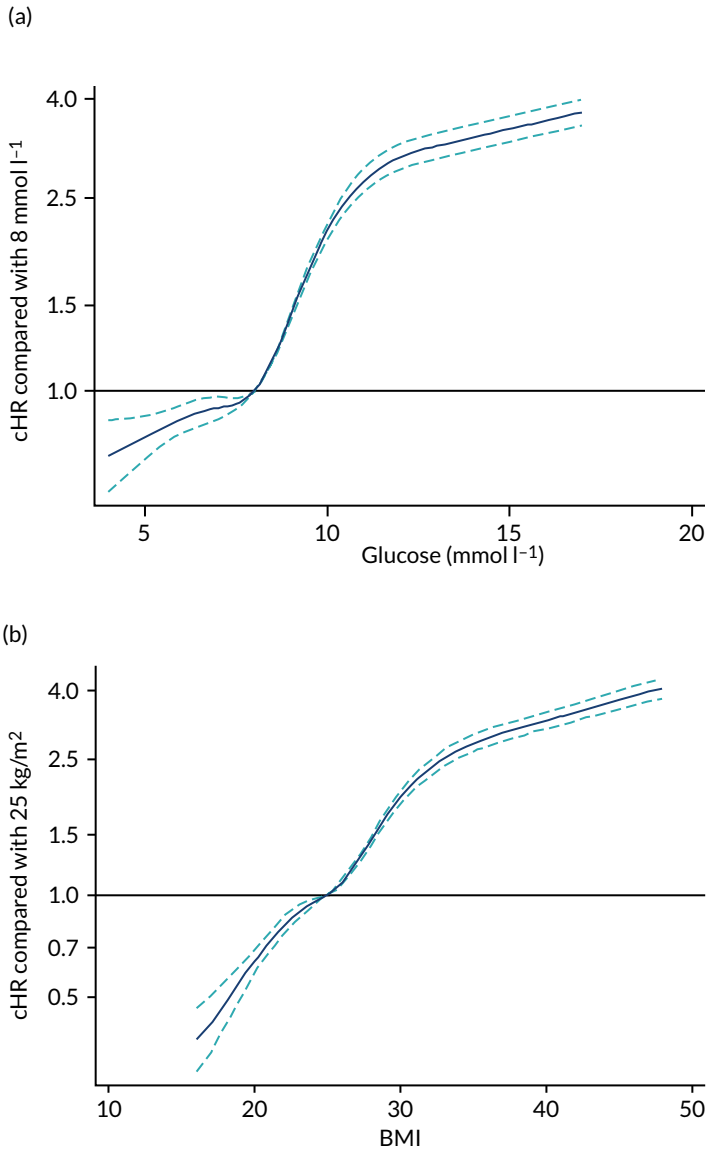

FIGURE 16 Cause-specific hazard ratio for subsequent type 2 diabetes after hospital discharge following critical care for continuous predictors included in the model as non-linear using restricted cubic splines. (a) Glucose; (b) BMI; (c) age; (d) lowest white blood cell count. (*continued*)

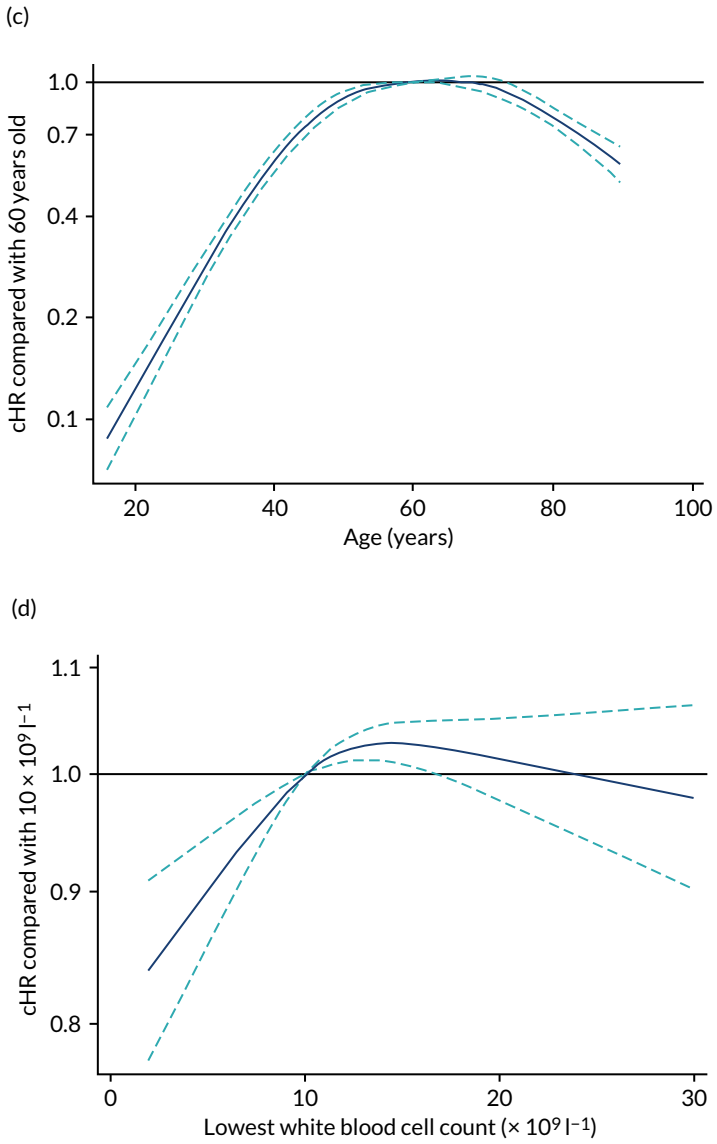

FIGURE 16 Cause-specific hazard ratio for subsequent type 2 diabetes after hospital discharge following critical care for continuous predictors included in the model as non-linear using restricted cubic splines. (a) Glucose; (b) BMI; (c) age; (d) lowest white blood cell count.

Harrell's c-statistic for the model was 0.77, with an explained variation (R^2) of 0.420 (95% CI 0.407 to 0.435, based on 100 bootstrap samples). Most of the prognostic information was carried by highest glucose and BMI.

Glucose and mortality

Highest glucose had a complex non-linear association with mortality (*Figure 17*). Compared with a value of 7 mmol l^{-1}, there was an increase in likely mortality associated with low values of glucose; above this value, the risk of mortality increased steeply up to 9 mmol l^{-1}, after which the increase was more gradual.

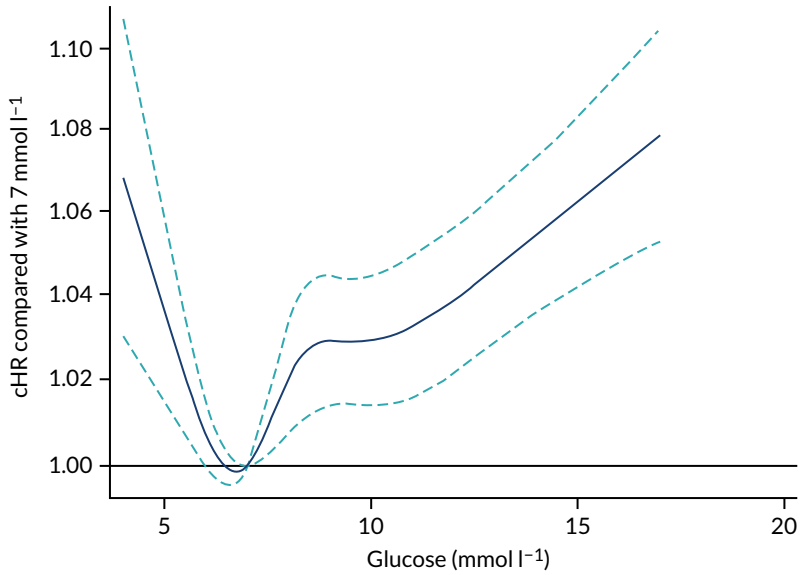

FIGURE 17 Cause-specific hazard ratio for mortality after hospital discharge following critical care for highest glucose in the first 24 hours

Predictors of cumulative incidence of subsequent type 2 diabetes

Results of the competing risk analysis using the Fine–Gray approach were in line with the cause-specific Cox results (see *Table 21*). When we plotted the cumulative incidence, that is, the probability of a subsequent diagnosis of type 2 diabetes, adjusted to the mean of the rest of the variables, we observed how the cumulative incidence increased with increasing BMI, and particularly in admissions with elevated glucose (*Figure 18*). We found the 3-year absolute risk of diagnosis of type 2 diabetes to be > 4% in patients with a glucose level of 11 mmol l^{-1} compared with a risk of 2% for a level of 9 mmol l^{-1}, and < 1% for a patient with a level of 7 mmol l^{-1}. In addition, pancreatic surgery notably increased the cumulative incidence (*Figure 19*), with a 3-year absolute risk of type 2 diabetes diagnosis above 3% compared with a risk of 1% for patients who did not undergo pancreatic surgery. Non-white ethnicities showed an increased cumulative incidence, with the 3-year absolute risk of type 2 diabetes being > 3% for Asian patients and > 2% for black patients compared with 1.2% for patients of white ethnicity. Other categorical factors had a smaller impact (*Figure 20*).

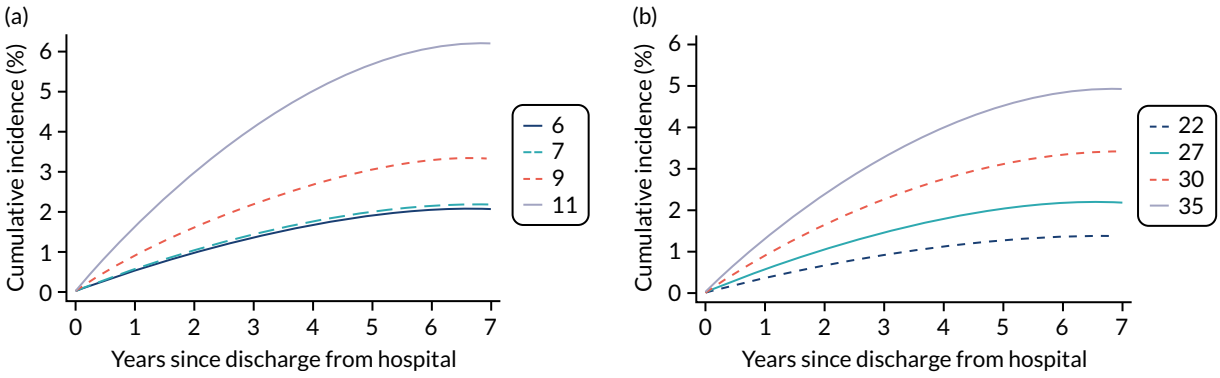

FIGURE 18 Cumulative incidence of type 2 diabetes in the 7 years after hospital discharge following critical care according to continuous patient factors included in the model. (a) Glucose; (b) BMI; (c) age; (d) lowest white blood cell count; (e) lowest systolic blood pressure. (*continued*)

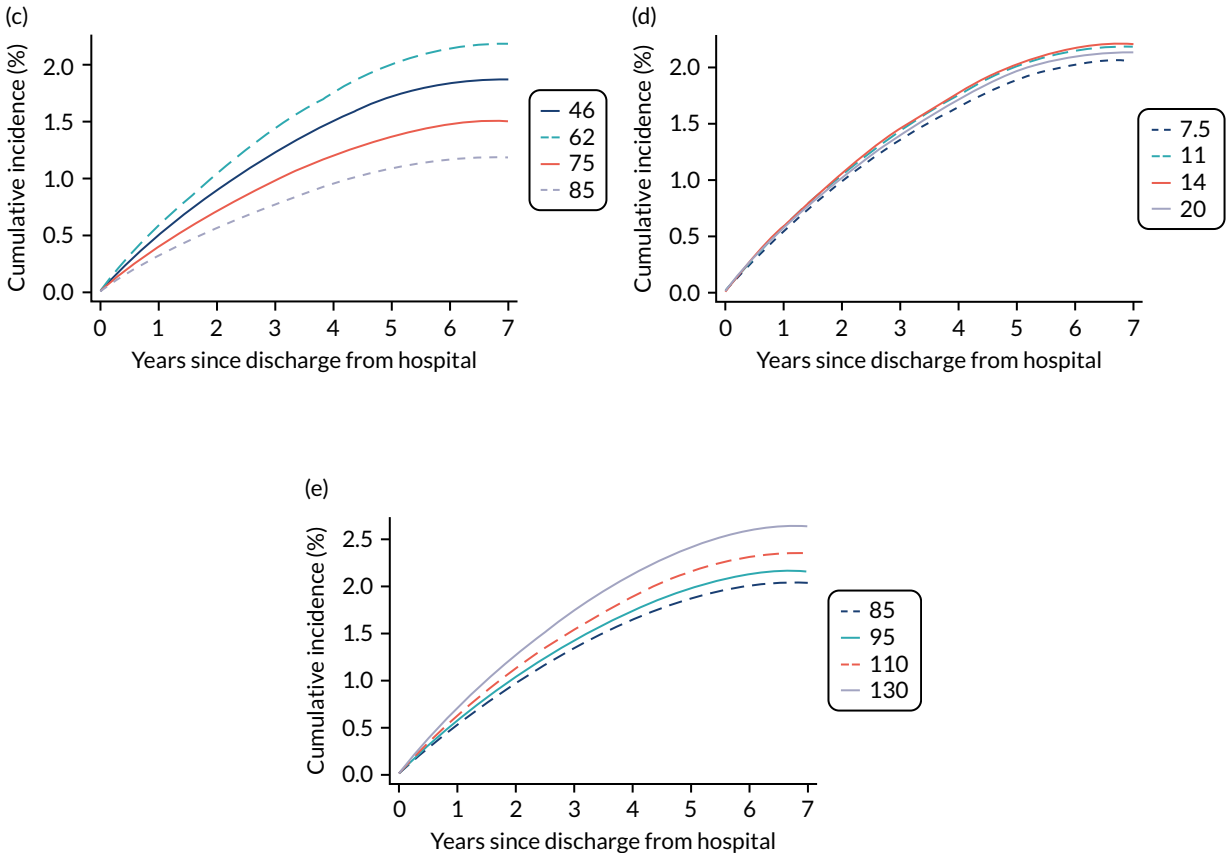

FIGURE 18 Cumulative incidence of type 2 diabetes in the 7 years after hospital discharge following critical care according to continuous patient factors included in the model. (a) Glucose; (b) BMI; (c) age; (d) lowest white blood cell count; (e) lowest systolic blood pressure.

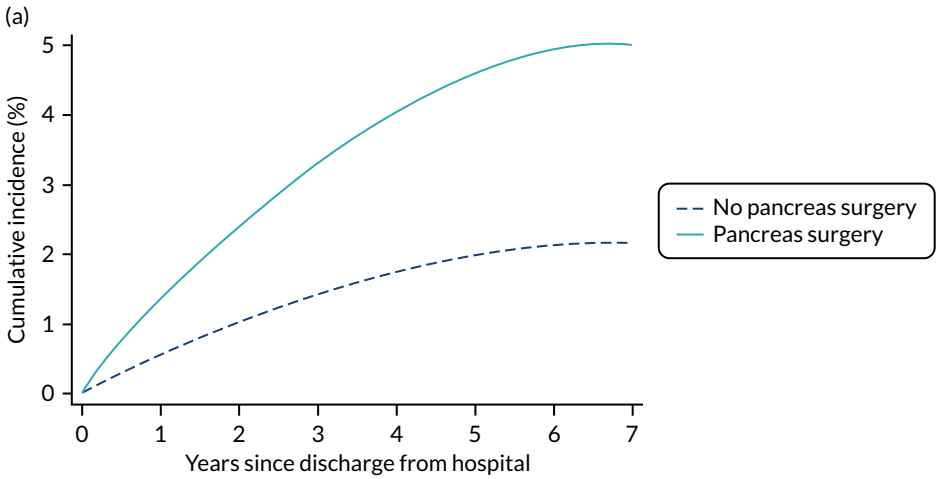

FIGURE 19 Cumulative incidence of type 2 diabetes in the 7 years after hospital discharge following critical care according to categorical patient factors included in the model. (a) Pancreatic surgery; (b) severe liver disease; (c) ethnicity; (d) deprivation. (*continued*)

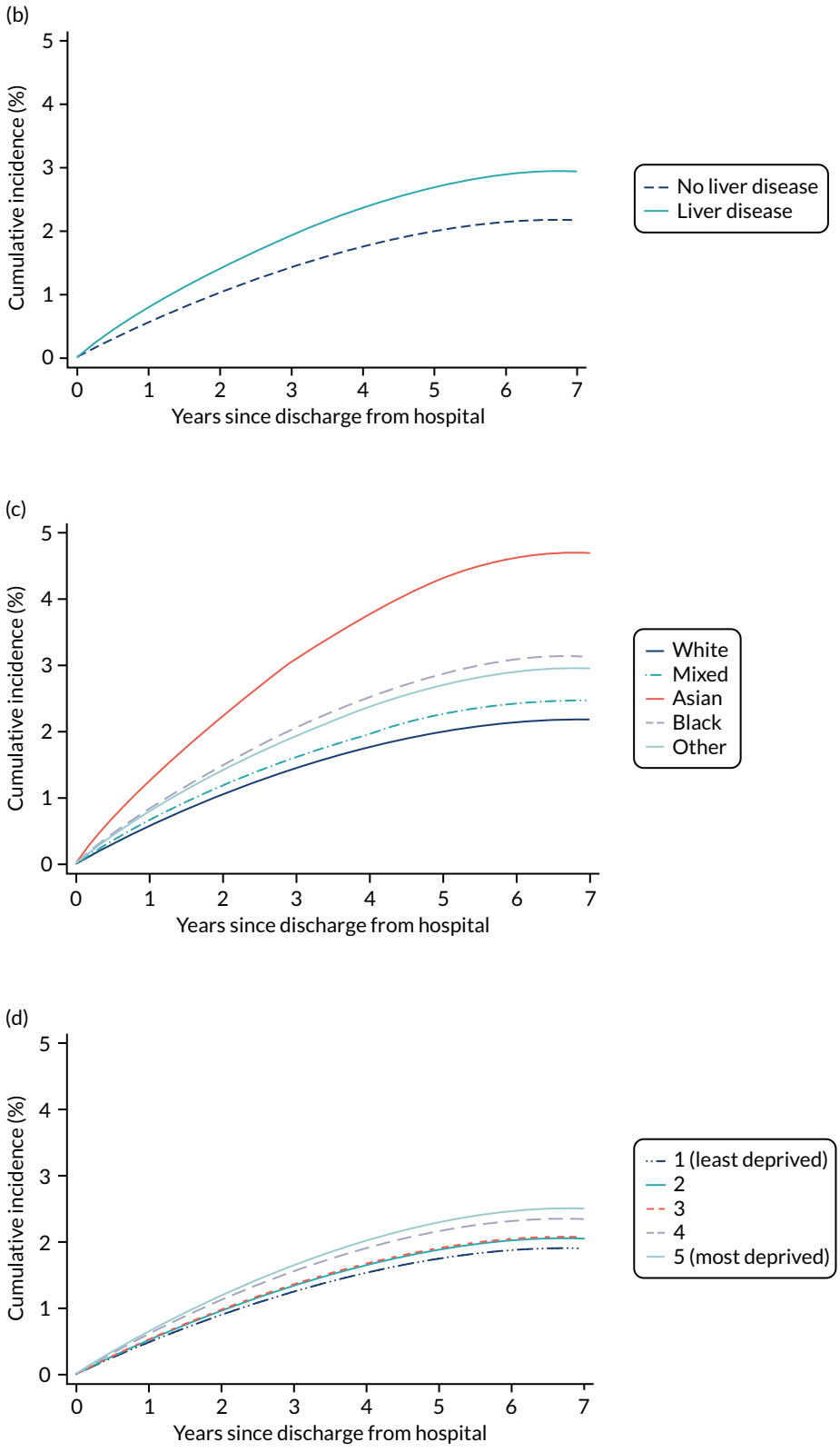

FIGURE 19 Cumulative incidence of type 2 diabetes in the 7 years after hospital discharge following critical care according to categorical patient factors included in the model. (a) Pancreatic surgery; (b) severe liver disease; (c) ethnicity; (d) deprivation.

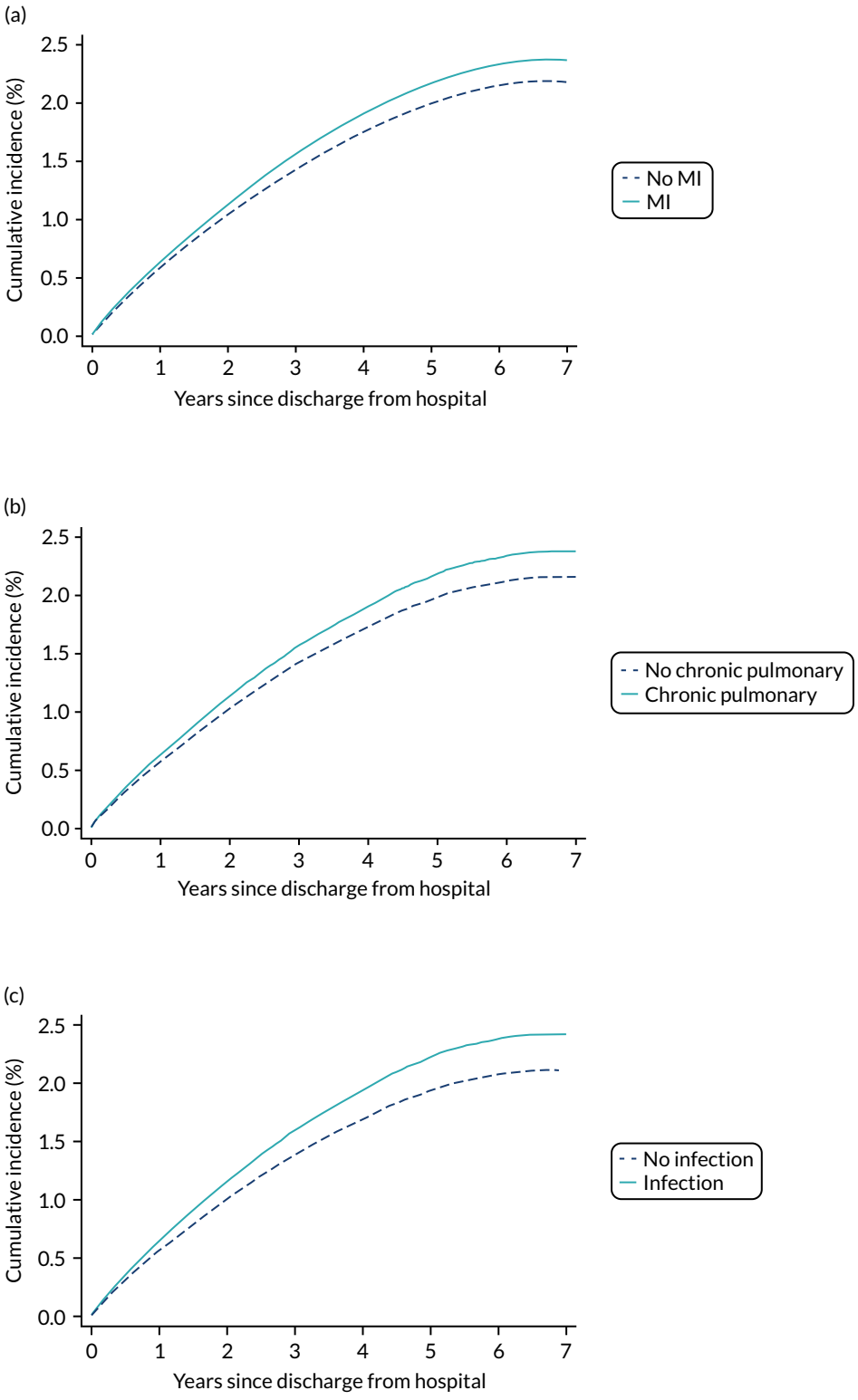

FIGURE 20 Cumulative incidence of type 2 diabetes in the 7 years after hospital discharge following critical care according to categorical patient factors included in the model (continued). (a) Previous MI; (b) chronic pulmonary disease; (c) sepsis; (d) surgical status; (e) mechanical ventilation; (f) immunocompromise. (*continued*)

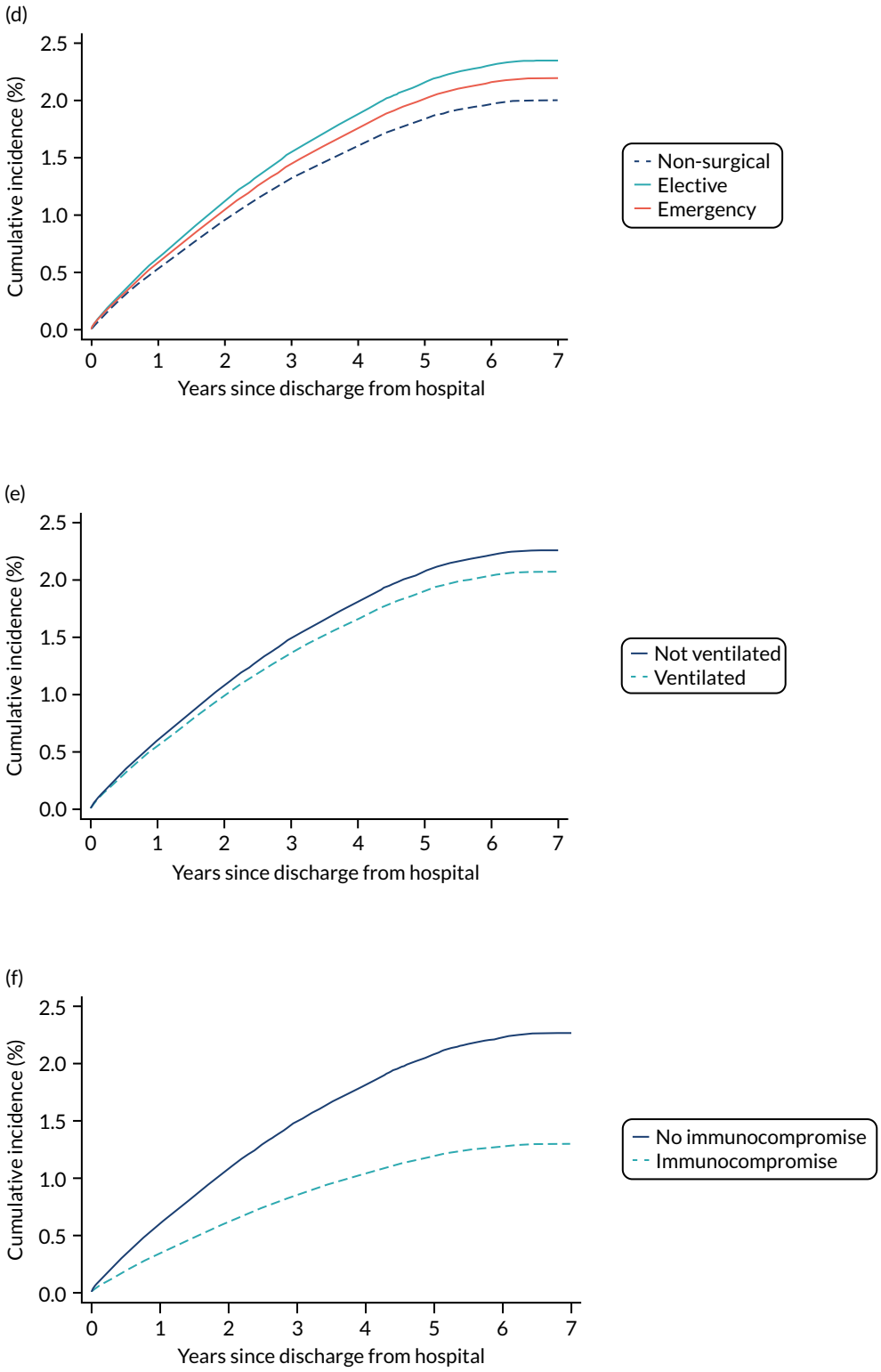

FIGURE 20 Cumulative incidence of type 2 diabetes in the 7 years after hospital discharge following critical care according to categorical patient factors included in the model (continued). (a) Previous MI; (b) chronic pulmonary disease; (c) sepsis; (d) surgical status; (e) mechanical ventilation; (f) immunocompromise.

Discussion

We have identified demographic and clinical factors significantly associated with the risk of a subsequent diagnosis of type 2 diabetes in survivors of critical illness and described their association with the outcome. Our results show a strong association of blood glucose during the first 24 hours of critical care with incidence of subsequent type 2 diabetes, which is consistent with previous findings.[66,67] In addition, patients undergoing pancreatic surgery and those with severe liver disease had an increased risk for developing type 2 diabetes. One of the main findings of our study is that BMI is independently non-linearly associated with the risk of developing type 2 diabetes. This is an interesting finding as previous studies have not had available data on BMI. Asian and black ethnicity were also associated with an increased risk when compared with white patients. Mechanical ventilation was associated with a lower risk for diagnosis of type 2 diabetes as well as lower mortality. This could suggest that the sicker patients who received mechanical ventilation likely died during the hospitalisation. Those ventilated patients who survived hospitalisation were a selected group destined to have better outcomes.

The main strengths of the study were the large, representative, high-quality clinical data set and the rigour of variable collection, with coverage of almost 100% of adult general critical care units in England during the study period. There were, however, some limitations. Coverage of the NDA was considerably lower than for the CMP, varying from 56.4% to 88.4% (assessed relative to the Quality and Outcomes Framework)[68] across the years included. The low coverage (particularly in the 2013–14 and 2014–15 years) will have been mitigated to some degree by the use of multiple years' data, as patients first registered in the 2015–16 audit year (with 83.4% coverage) will include patients with a diagnosis date during the years with lower coverage. This will, however, likely result in an underestimation of the incidence of new diagnoses. In addition, new registrations based on the date of diagnosis recorded in the NDA database was used as a surrogate marker for incidence of diabetes, and the true incidence of diabetes might be higher than reported in this study. However, this approach has been used in previous studies and considered to be a valid surrogate.[69] As glycated haemoglobin (HbA_{1c}) is not routinely measured on admission to critical care and not recorded in the CMP, the proportion of patients who had pre-existing but unrecognised type 2 diabetes is unknown. Previous epidemiological studies[70] report the prevalence of unknown diabetes to be between 5% and 10% of patients admitted to critical care. The absence of HbA_{1c} from the CMP data set may also have contributed to the worse discrimination of the model for type 2 diabetes than that for ESRD reported in the previous chapter.

These findings suggest that prevention programmes and follow-up after hospital discharge might need to be considered in patients with critical illness and elevated glucose, particularly among patients from ethnic minorities and those with a higher BMI.

Chapter 8 Hospital resource use and costs post critical care

Introduction

Survivors of critical care experience significant morbidity with substantial resultant health-care resource use and costs.[71] Although the ageing of the population together with improvements in critical care will fuel an increase in critical care survivors, there has been limited research on the ongoing costs of illness and the use of health-care resources among survivors of critical care.[71] Data linkage with HES has enabled us to estimate the cost of subsequent hospitalisations and explore their association with severity and/or duration of critical illness and other risk factors.

Methods

Data and resource use

The patients included in the prediction model were those discharged alive from hospital between January 2013 and December 2014. The resource use was measured as the number of days in acute hospital care during subsequent hospital episodes (as identified through data linkage with HES) from the hospital discharge until 1-year follow-up or death within that period. For hospitalisations in which the patient was admitted and discharged on the same day, the number of days in hospital was 0. For those subsequent hospitalisations in which the patient was discharged more than 1-year after index discharge, only the days in hospital occurring during the study period were considered. Total subsequent cost was calculated by summing the cost for subsequent hospitalisations and the cost for subsequent critical care admissions. The cost for each subsequent hospitalisation was measured as the cost of the full hospital spell.

The cost of the full hospital spell was valued using the Department of Health and Social Care's (DHSC) APC tariff. Information from the HES episodes files were used in the cost for hospitalisation calculation. The dominant health-care resource group (HRG) was identified from HES data [Secondary Uses Service (SUS)-generated core spell HRG]. When the HES field was not available, the HRG attributed to the admission episode was used. The bed-day cost for each HRG was assigned using the DHSC APC tariff.[72] Total spell length of stay was identified from the spell's discharge information (spell duration) in the final episode of the spell. When the patient was discharged more than 1 year after the index discharge, only the days in hospital occurring during study period were considered. Days in critical care were removed from the overall spell duration as critical care has a different tariff. Each HRG was matched to their corresponding trim point for determining long versus short stays for each spell. We used patient classification and the admission method from the HES data set to identify day case and elective inpatient stay. Those HRGs with a locally determined cost were identified and they were not included in this calculation. We assumed that the reference costs for the same period were proxies for the tariff for non-attached HRGs. Hence, these were cross-matched from the HRG4 to the HRG4+ currency design and valued using spell-level NHS reference costs.[15] Finally, missing or unlinked HRGs were valued using the average by type of admission of all HRGs.

Statistical analysis

Days in hospital and cost were reported as described in *Chapter 3*.

To assess the predictors of costs during the year after the index hospital discharge, a two-part regression model was used. Health-care costs usually have distributions that are skewed with a large

mass at zero. In modelling such outcomes, a two-part model has become a best-practice approach, improving the fit of the model and allowing for better understanding of results.[73] A logistic regression was first used to assess the predictors of having health-care cost (at least one hospital and/or critical care admission) during the year following index hospital discharge. Then, conditional on having any health-care cost, a generalised linear model (GLM) with a gamma distribution and a log-link function was selected to determine the predictors of 1-year cost after index hospital discharge. We checked the log link against several other functional form alternatives. In addition, a modified 'Park Test'[74] was used to test the distribution family. Non-linearity, inclusion of variables and interactions were assessed using methods described in *Chapter 3*. As recommended,[75] we applied the general practice that any variable that is in either the first part or the second part model will be in both. No variables are included in one part but excluded from the other. In addition, final selected variables were tested for jointly significant in both parts of the two-part model. Predicted values and marginal effects were then calculated accounting for the full model.

Results

Between 1 January 2013 and 31 December 2014, a total of 207,805 first adult critical care admissions were discharge alive from hospital in England. Of those, 25,317 (12.2%) individuals died within 1 year following hospital discharge.

Baseline characteristics

The baseline characteristics of the included patients are described in *Table 22*. The median age was 64 years (IQR 49–75 years) and more than a half of patients were male. Most of the patients were able to live without assistance in daily activities (79.4%). The median critical care length of stay of the cohort was 48 hours (IQR 23–103 hours) and the median hospital length of stay was 12 days (IQR 7–25 days).

Subsequent hospital/critical care admission during the first year and estimated health-care cost

Results are summarised in *Table 23*. The rate of subsequent hospitalisations for the first year was 1.06 hospitalisations per patient. The mean health-care cost during the first year after index hospital discharge was £3734, with over half of costs having a value of zero. The distribution of total cost was highly skewed with a large mass at zero (*Figure 21*). A total of 97,593 patients (47%) had a subsequent health-care cost (hospitalisation/critical care admission) with a mean cost of £7952 (median £4566,

TABLE 22 Patient characteristics at index critical care admission

Characteristic	Value
Number patients discharged alive from hospital	207,805 (100.0)
Demographics	
Age (years), mean (SD)	61 (17.7)
Age (years), median (IQR)	64 (49–75)
Sex, males (%)	115,122 (55.4)
Ethnicity, *n* (%)	
White	186,625 (89.8)
Mixed	1173 (0.6)
Asian	7611 (3.7)
Black	4819 (2.3)
Other	7577 (3.6)

TABLE 22 Patient characteristics at index critical care admission (*continued*)

Characteristic	Value
Reason for admission to critical care by body system, *n* (%)	
Respiratory	34,420 (16.6)
Cardiovascular	39,067 (18.8)
Gastrointestinal	55,951 (26.9)
Neurological (including eyes)	26,477 (12.7)
Genito-urinary	21,781 (10.5)
Endocrine, Metabolic, Thermoregulation and Poisoning	14,932 (7.2)
Haematological/Immunological	1546 (0.7)
Musculoskeletal	11,424 (5.5)
Dermatological	2141 (1.0)
Psychiatric	64 (0.0)
Quintile of deprivation, *n* (%)	
1 (least deprived)	34,296 (17.2)
2	37,072 (18.5)
3	39,588 (19.8)
4	42,000 (21.0)
5 (most deprived)	47,013 (23.5)
Patient-related factors	
CPR within 24 hours prior to admission, *n* (%)	
No CPR	201,806 (97.1)
Community CPR	3056 (1.5)
In-hospital CPR	2943 (1.4)
Prior dependency, *n* (%)	
Able to live without assistance in daily activities	165,226 (79.9)
Some (minor/major) assistance with daily activities	40,121 (19.4)
Total assistance with all daily activities	1349 (0.7)
Location prior to critical care admission, *n* (%)	
ED or not in hospital, unplanned	44,437 (21.4)
ED or not in hospital, planned	1464 (0.7)
Theatre, elective/scheduled, planned	65,102 (31.3)
Theatre, elective/scheduled, unplanned	9847 (4.7)
Theatre, emergency/urgent	38,796 (18.7)
Ward or intermediate care area	42,769 (20.6)
Other critical care unit, repatriation	487 (0.2)
Other critical care unit, planned/unplanned transfer	3285 (1.6)
Other acute hospital	1618 (0.8)

continued

TABLE 22 Patient characteristics at index critical care admission (*continued*)

Characteristic	Value
Medical history	
Severe conditions in medical history (APACHE II), *n* (%)	
Very severe cardiovascular disease	2792 (1.3)
Severe respiratory disease	3343 (1.6)
Severe liver disease	3616 (1.7)
ESRD	3019 (1.5)
Metastatic disease	9633 (4.6)
Haematological malignancy	2666 (1.3)
Immunocompromise	12,923 (6.2)
RCS Charlson comorbidities, *n* (%)	
Previous MI	8002 (3.9)
Congestive cardiac failure	10,025 (4.8)
Peripheral vascular disease	10,282 (4.9)
Cerebrovascular disease	6279 (3.0)
Dementia	1848 (0.9)
Chronic pulmonary disease	26,495 (12.7)
Rheumatological disease	4136 (2.0)
Liver disease	3958 (1.9)
Diabetes mellitus	25,453 (12.2)
Hemiplegia or paraplegia	1671 (0.8)
Chronic renal disease	9579 (4.6)
Malignancy	23,863 (11.5)
Severity scores from the first 24 hours following critical care admission	
ICNARC physiology score, mean (SD)	14 (7.1)
ICNARC physiology score, median (IQR)	13 (9–18)
APACHE II score, mean (SD)	14 (5.8)
APACHE II score, median (IQR)	13 (10–17)
Physiology from the first 24 hours following critical care admission	
Highest heart rate (min^{-1}), mean (SD)	100 (22)
Lowest systolic blood pressure (mmHg), mean (SD)	98 (19)
Highest temperature (°C), mean (SD)	37.6 (0.9)
Lowest respiratory rate (min^{-1}), mean (SD)	12.4 (3.6)
Urine output (ml), mean (SD)	1975 (1347)
PaO_2/FiO_2, mean (SD)	36.5 (15.4)
Lowest arterial pH, mean (SD)	7.33 (0.09)
Associated $PaCO_2$, mean (SD)	5.9 (1.7)
Highest blood lactate, mean (SD)	2.3 (1.9)

TABLE 22 Patient characteristics at index critical care admission (*continued*)

Characteristic	Value
Highest urea, mean (SD)	8.8 (8.5)
Highest creatinine, mean (SD)	123 (149)
Highest serum sodium, mean (SD)	138 (5)
Lowest white blood cell count, mean (SD)	11.6 (7.3)
Associated neutrophil count, mean (SD)	9.6 (5.4)
Lowest platelet count, mean (SD)	212 (103)
Sepsis, *n* (%)	48,850 (23.5)
Organ dysfunction, *n* (%)	166,293 (80.0)
Organ support during critical care stay	
Receipt of advanced respiratory support, *n* (%)	76,699 (36.9)
Duration of advanced respiratory support (calendar days), median (IQR)	2 (1–5)
Receipt of basic or advanced cardiovascular support, *n* (%)	35,751 (17.2)
Duration of basic/advanced cardiovascular support (calendar days), median (IQR)	2 (1–3)
Receipt of renal support, *n* (%)	12,464 (6.0)
Duration of renal support (calendar days), median (IQR)	3 (2–6)
Length of stay	
Critical care unit length of stay (hours), mean (SD)	99 (170.2)
Critical care unit length of stay (hours), median (IQR)	48 (23–103)
Acute hospital length of stay (days), mean (SD)	21 (31)
Acute hospital length of stay (days), median (IQR)	12 (7–25)

The *n* values do not sum to the total numbers because of varying amounts of missing data for each variable.

TABLE 23 Summary of outcomes

Outcome	Value
Total health-care cost (£), mean (SD)	3734 (8171)
At least one hospitalisation/critical care admission, *n* (%)	97,593 (46.9)
Total health-care cost[a] (£), mean (SD)	7952 (11,176)
Total health-care cost[a] (£), median (IQR)	4566 (2288–9587)
At least one hospitalisation, *n* (%)	97,229 (46.8)
Total APC cost[a] (£), mean (SD)	6589 (7165)
Total APC cost[a] (£), median (IQR)	4204 (2207–8482)
At least one critical care admission, *n* (%)	14,293 (6.8)
Total critical care cost[a] (£), mean (SD)	9465 (17,123)
Total critical care cost[a] (£), median (IQR)	4142 (2761–9436)

a For those with non-zero cost.

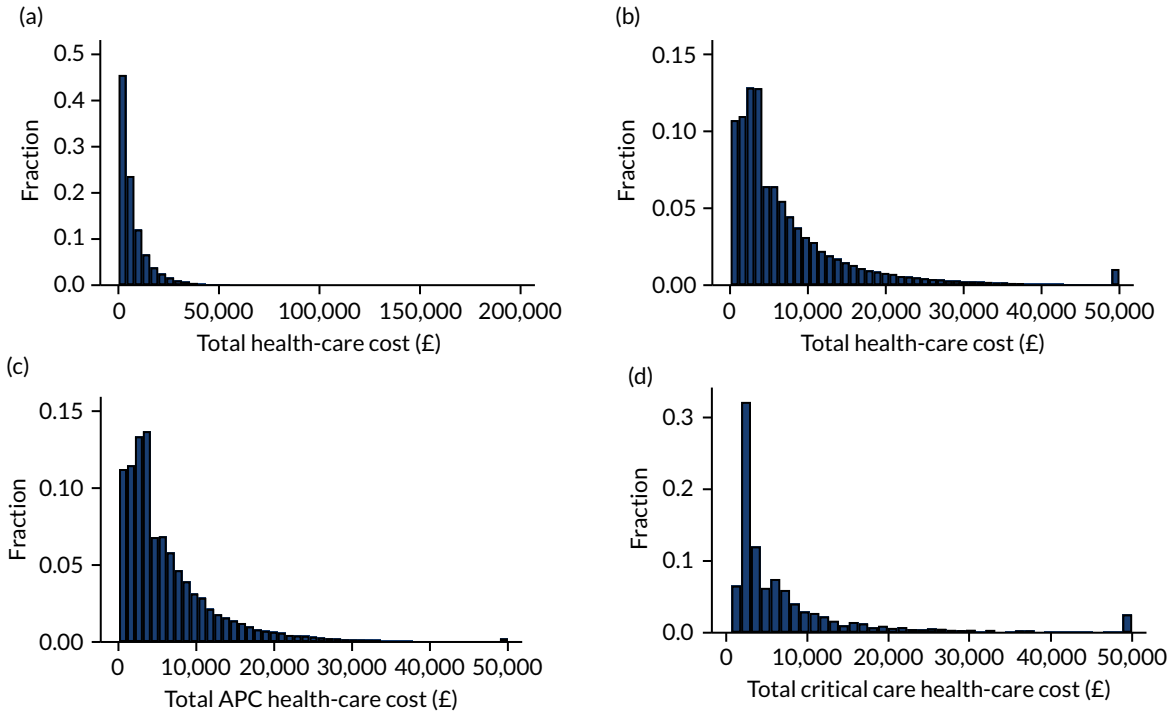

FIGURE 21 Distribution of total health-care cost: full distribution including zeros, the histogram of just positive values and split by APC and critical care cost. (a) Total health-care cost; (b) total health-care cost if > £0; (c) total APC health care cost if > £0; (d) total critical care health-care cost, if > £0.

IQR £2288–9587). When we split by source of cost, both hospitalisation and critical care costs had a large proportion of zeros and a declining distribution of positive costs (see *Figure 21*). For the 97,229 (47%) individuals with a subsequent APC cost, the mean cost was £6589 (median £4204, IQR £2207–8482). A total of 14,293 (6.9%) patients were admitted to critical care during the first year after index hospital discharge, with a mean cost of £9465 (median £4142, IQR £2761–9436).

Factors associated with non-zero health-care cost during the first year

After testing for linearity, the continuous variables age, BMI and ICNARC physiology score were modelling using restricted cubic splines. The specification test supported the use of the log-link and the gamma distribution. Results of the two-part model are presented in *Appendix 3*, *Table 48*. The predictors of whether the patient would have any subsequent health-care costs were previous hospitalisation, critical care length of stay, age, BMI, illness severity, mechanical ventilation, dependency prior to admission, source of admission, CPR and deprivation. Regarding severe conditions in the medical history, severe liver disease, metastatic disease, haematological malignancy, severe respiratory disease and ESRD were also found to be significant predictors. The model indicated that people with the following comorbidities were also more likely to have non-zero health-care costs in the year following hospital discharge: previous MI, congestive cardiac failure, peripheral vascular disease, dementia, chronic pulmonary disease, rheumatological disease, liver disease, diabetes mellitus, hemiplegia or paraplegia, chronic renal disease and any malignancy.

Factors associated with health-care cost during the first year, conditional on having non-zero cost

Conditional on hospital/critical care admission, the GLM identified similar predictors for health-care cost as those for non-zero cost, apart from CPR, previous MI and dementia. Patients who had previous hospitalisations and patients who required total assistance with daily activities had increased costs during the first year. In general, having severe conditions in the medical history or chronic conditions were found to incur significantly higher costs during the first year, but this declined with age.

Table 24 shows the combined marginal effects from both parts of the model. The predicted mean total cost was £3725 per person in the year following index hospital discharge, which is close to the observed mean of £3708. Previous hospitalisation was associated with an increase in health-care costs of £999. Patients with some or total assistance with daily activities also had higher costs. The results show that all severe or chronic conditions are associated with greater costs. To better understand the effect of the continuous variables and interactions, we plotted the marginal effect of the continuous predictors on the health-care costs (*Figures 22–24*).

TABLE 24 Predicted and marginal effects of health-care costs during the first year after hospital discharge in critical care admissions

Category	Predicted mean (£)	95% CI
Predicted total health-care cost (£ per patient)	3725	3687 to 3763
Marginal effects		
Critical care unit length of stay (per day increase)	49.9	43.6 to 56.1
Previous hospitalisation	999.0	912.7 to 1085.3
Mechanical ventilation	−582.3	−666.6 to −497.9
Dependency		
Some assistance with daily activities	821.6	728.0 to 915.1
Total assistance with daily activities	2643.3	2001.7 to 3284.8
Quintile of deprivation		
2	−51.2	−165 to 62.6
3	−27.5	−139.2 to 84.3
4	201.9	85.4 to 318.6
5 (most deprived)	201.9	95.1 to 325.9
Location prior to admission		
ED or not in hospital (planned admission)	−143.3	−622.1 to 335.6
Other acute hospital (not critical care)	117.0	−293.8 to 527.8
Other critical care unit (repatriation)	301.1	−453.6 to 1055.8
Other critical care unit (planned or unplanned transfer)	283.3	−36.4 to 603.1
Theatre (unplanned admission following elective or scheduled surgery)	−244.7	−418.2 to −71.2
Theatre (planned admission following elective or scheduled surgery)	−876.8	−984.5 to −769.0
Theatre (admission following emergency or urgent surgery)	36.8	−80.1 to 153.7
Ward or intermediate care area	571.4	452.1 to 690.8
CPR		
In-hospital CPR	686.3	305.3 to 1067.3
No CPR	747.3	468.6 to 1025.9

continued

TABLE 24 Predicted and marginal effects of health-care costs during the first year after hospital discharge in critical care admissions (*continued*)

Category	Predicted mean (£)	95% CI
Severe conditions in medical history (APACHE II)		
Severe respiratory disease	1516.5	1117.5 to 1915.5
Severe liver disease	2427.0	1981.3 to 2872.8
ESRD	3532.8	3101.4 to 3964.2
Metastatic disease	821.1	608.7 to 1033.4
Haematological malignancy	2587.4	2154.8 to 3019.9
Immunocompromise	516.8	358.4 to 675.3
RCS Charlson comorbidities		
Previous MI	378.2	211.3 to 545.2
Congestive cardiac failure	554.3	388.1 to 720.4
Peripheral vascular disease	904.7	741.4 to 1068.0
Dementia	364.1	51.6 to 676.5
Rheumatological disease	706.0	457.6 to 954.3
Hemiplegia or paraplegia	1869.4	1405.8 to 2333.1
Chronic renal disease	1292.3	1110.6 to 1474.0
Chronic pulmonary disease	798.5	684.8 to 912.2
Liver disease	1216.0	936.9 to 1495.0
Diabetes mellitus	1059.8	932.1 to 1187.4
Any malignancy	680.5	526.9 to 834.2

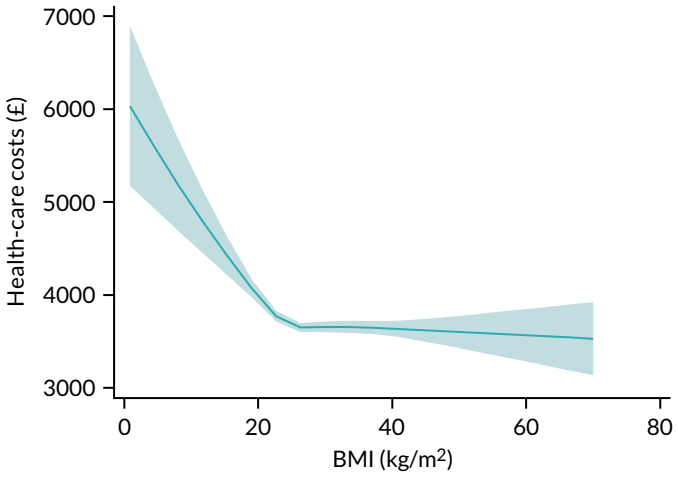

FIGURE 22 Marginal plot of the effect of BMI on total health-care costs.

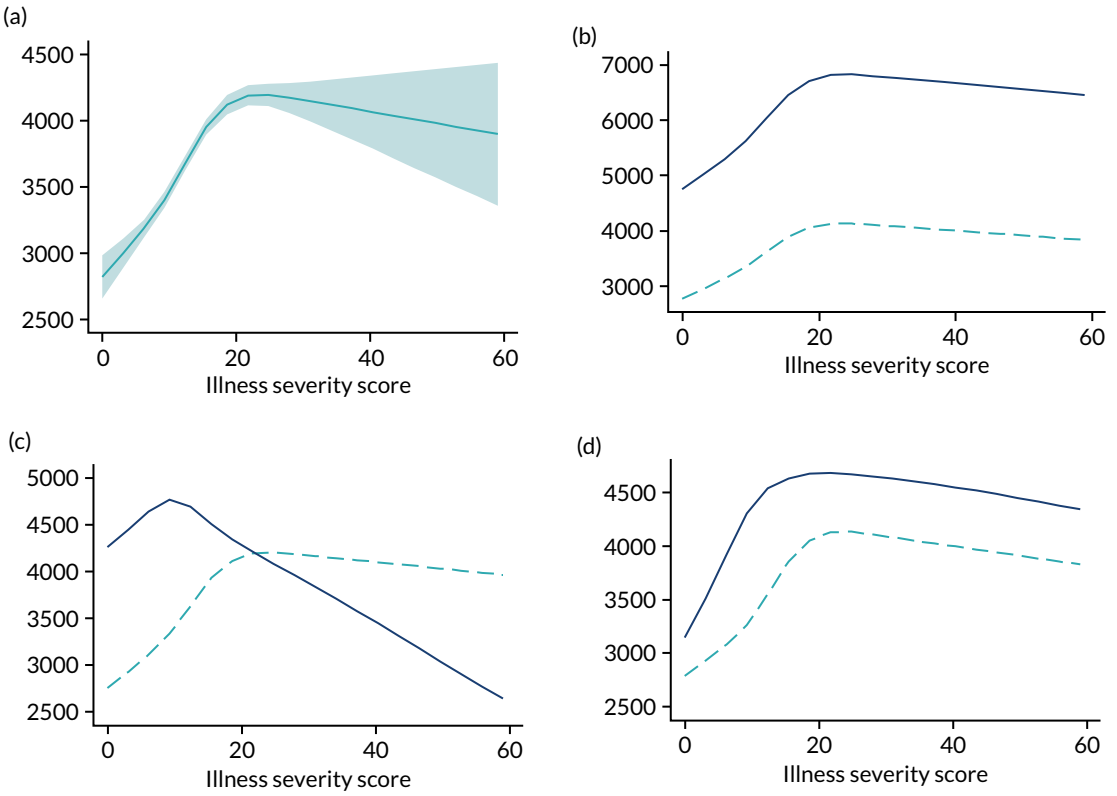

FIGURE 23 Marginal plot of the effect of ICNARC physiology score and interactions with comorbidities on total health-care cost. (a) Overall marginal effect; (b) severe liver disease in medical history; (c) metastatic disease; (d) chronic pulmonary disease. Solid line: presence of comorbidity. Dashed line signifies absence of comorbidity.

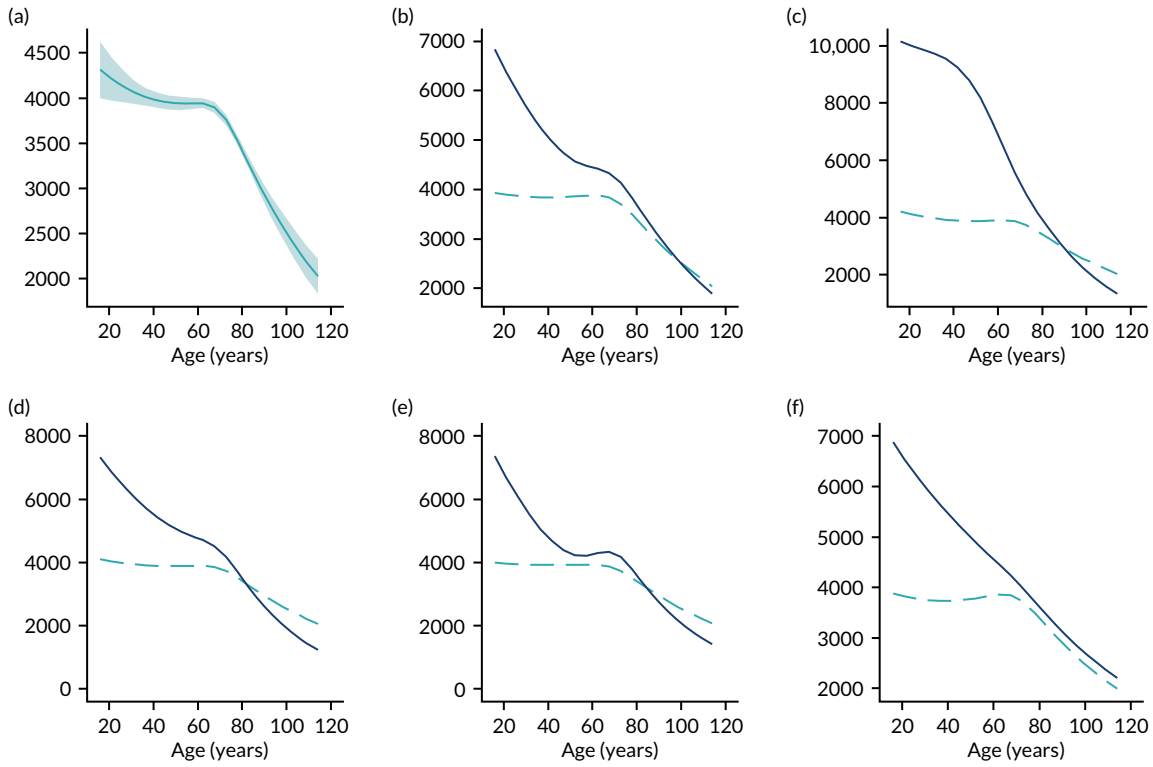

FIGURE 24 Marginal plot of the effect of age and interactions with comorbidities on total health-care cost (solid line: presence of comorbidity). (a) Overall marginal effect; (b) any malignancy; (c) haematological malignancy; (d) metastatic disease; (e) immunocompromise; (f) chronic pulmonary disease; (g) end-stage renal failure; (h) diabetes mellitus; (i) severe respiratory disease; (j) liver disease. Dashed line signifies absence of comorbidity. (*continued*)

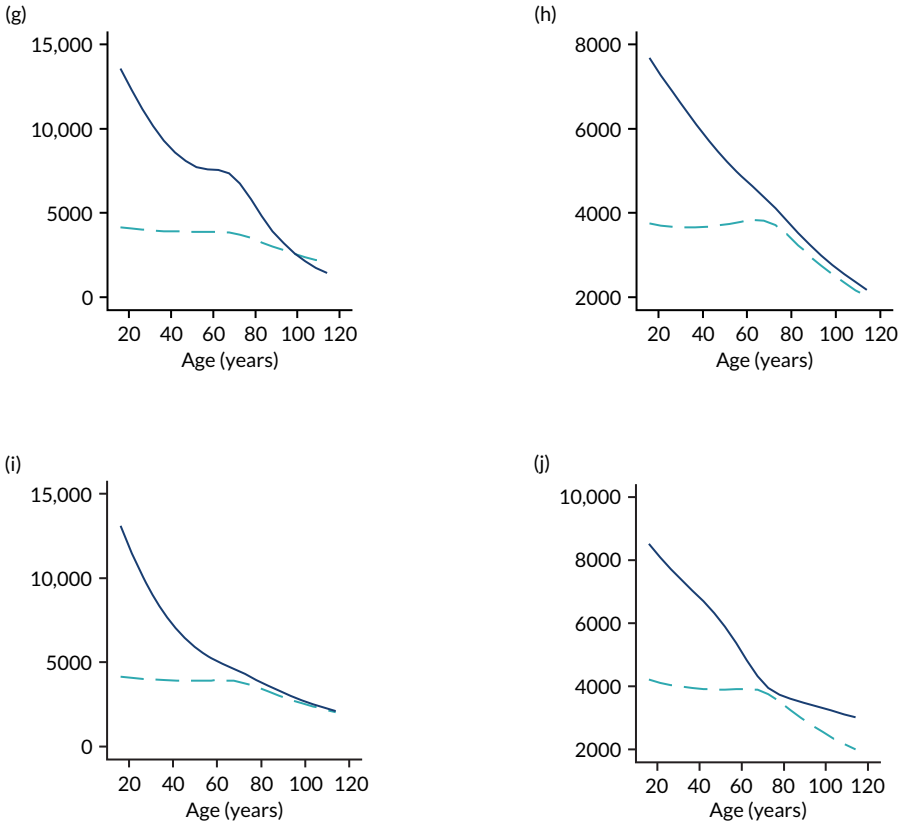

FIGURE 24 Marginal plot of the effect of age and interactions with comorbidities on total health-care cost (solid line: presence of comorbidity). (a) Overall marginal effect; (b) any malignancy; (c) haematological malignancy; (d) metastatic disease; (e) immunocompromise; (f) chronic pulmonary disease; (g) end-stage renal failure; (h) diabetes mellitus; (i) severe respiratory disease; (j) liver disease. Dashed line signifies absence of comorbidity.

Discussion

This chapter describes a process and its results for estimating health-care costs after critical illness using the DHSC APC tariff and data linkage with HES. Two-part models are an attractive approach to address the peculiar distribution of health-care costs; they also provide insight into the utilisation process. Modelling the outcomes with a two-part model allows for a separate investigation of the effect of covariates on having health-care costs during the first year after hospital discharge and on the value of those costs (if any), while providing cost predictions that account for both parts of the model.

Increasingly, patients admitted to critical care survive to hospital discharge, many with ongoing medical needs and substantial resultant costs. We found that over 47% of hospital survivors following critical care required at least one hospital/critical care admission during the first year after hospital discharge, with a mean health-care cost of £7951 per patient, and 6.9% were re-admitted to critical care during the first year after hospital discharge.

Patients who were in better health condition prior to admission to critical care accrued significantly lower health-care costs than those with poorer health. Our two-part model shows that previous hospitalisations, dependency and comorbidities are all strong and independent predictors of resource use and increased costs. The results are consistent with previous studies. Lone *et al.*,[38] in a population-based study in Scotland, found that factors present before admission to critical care were much stronger predictors of hospital resource use than those associated with the acute illness and a Dutch study[76] of critical care survivors concluded that healthcare costs are greatly influenced by the chronic

conditions of critically ill patients.[7] However, our study shows that the prevalence of higher health-care costs in patients with previous comorbidities than in those with no comorbidities is more pronounced in younger patients.

Most factors had effects in the expected direction. Exceptions to this included ventilation in the first 24 hours of critical care and patients with metastatic disease. This effect could be explained by an increased post-discharge mortality in those patients and a corresponding reduction in hospital/critical care length of stay.

Recent literature incorporates proximity to death in health-care expenditure models, especially in elderly or end-of-life populations and mostly focuses on age-related health-care expenditure growth.[77–80] However, this approach has been criticised for potential endogeneity problems.[81,82] Recent research[81] shows that the role played by proximity-to-death variables can be explained by available measures of morbidity and suggests that proximity to death is itself a 'red herring' that acts as a proxy for morbidity. In addition, proximity-to-death or related variables are less useful for forward planning or forecasting health-care expenditure, because a person's future time to death is unknown. Our work focused on determinants prior to critical illness such as previous hospitalisations, severity and/or duration of critical illness, underlying levels of dependency, and combinations of severe conditions in the medical history (APACHE II) and RCS Charlson comorbidities, which are themselves detailed measures of morbidity.

This analysis did have limitations. Primary among these was that we were only able to assess secondary care costs (hospital and critical care admissions). These patients would also have had substantial primary care, outpatient and emergency care costs, which could not be assessed with the data sources linked for this project. Wider data linkage may enable a fuller picture of the subsequent costs of critical illness to be obtained. Second, although we considered previous hospitalizations as a surrogate of resource use prior to the critical illness, we did not directly contrast the health-care costs during the period before critical care admission. Consequently, we cannot conclude whether the critical illness episode resulted in a higher level of health-care use or identify different trajectories of health-care use. This must be left to a future extension of the present chapter.

Chapter 9 Risk models for adult cardiothoracic critical care

Introduction

Cardiothoracic critical care presents some particular challenges for risk modelling, with a relatively low-risk population in comparison with other critical care subspecialties. Patients may present with considerable physiological derangement due to the effects on their body of undergoing cardiac surgery, but this is not associated with the same increase in risk that would be anticipated in other critical care settings. For this reason, critical care unit admissions following cardiac surgery have been excluded from many previous critical care risk models. In a previous research study, we developed and validated a novel risk model for cardiothoracic critical care.[16] The resulting model, based on 17,000 admissions to cardiothoracic critical care units, had excellent discrimination (c index 0.90).

For cardiothoracic critical care, our previous work[16] has focused on the data items available in the CMP. The data set is designed to implement risk models for adult general critical care. Aside from patient demographics, these are almost exclusively post-operative risk factors. However, the majority of admissions to cardiothoracic critical care units are admitted following cardiac surgery and many pre- and intra-operative risk factors may also influence outcome for these patients.[83] The NACSA collects pre-operative risk factors and intra-operative process measures that provide potentially important additional risk factor information to enhance our risk predictions among the cohort of patients admitted to cardiothoracic critical care units following cardiac surgery and to explore how risks change along the patient journey.

Linkage to death registrations also enables us to extend our risk models for cardiothoracic critical care to predict longer-term mortality. Finally, data linkage with HES enables us to improve the resulting risk prediction models by incorporating additional comorbidity information.

Methods

Study cohort

For the development data set, we selected NHS cardiothoracic critical care units in England participating in the CMP, with identifiable linkage with HES and death registrations between 1 April 2009 and 31 March 2015. The validation data set consisted of admissions to cardiothoracic critical care units between 1 April 2015 and 31 March 2016.

Inclusion and exclusion criteria

Patients included in the model were all admissions following cardiothoracic surgery identified from data linkage with NACSA, excluding any with a date of admissions preceding the NACSA procedure date or not in the first 20 days after surgery. Patients aged < 16 years, re-admissions to the critical care unit and patients transferred from another critical care unit were excluded.

Outcome

Risk models were developed for two outcomes: acute hospital mortality and 1-year mortality. Acute hospital mortality was defined as death before final discharge from acute hospital and included deaths after direct transfer to another acute hospital from the hospital housing the critical care unit. One-year mortality was obtained by data linkage with death registrations.

Candidate predictors

Candidate predictors were chosen based on the previously developed risk prediction model for acute hospital mortality among admissions to cardiothoracic critical care units,[16] pre- and intra-operative risk factors obtained by data linkage with NACSA, and APACHE II and RCS Charlson comorbidities (see *Appendix 1*, *Table 39*). Severe conditions in the past medical history (APACHE II) and RCS Charlson comorbidities were identified and defined as described in *Chapter 3*.

Statistical analyses

Methods common to all objectives and analyses were described in *Chapter 3*.

The starting point for the new risk model was the previously developed risk prediction model for acute hospital mortality among admissions to cardiothoracic critical care units using CMP data only. New pre- and intra-operative risk factors obtained by data linkage with NACSA (see *Appendix 1*, *Table 39*) and comorbidities from HES were assessed for inclusion in the new risk models. The effect of those predictors previously included in the risk model were reassessed to determine whether they still made an important contribution to the model (see *Chapter 3*). Predictors that were non-significant at a cut-off *p*-value of 0.05 were discarded. The model was refitted and the remaining predictors were retested. The process continued until all the predictors in the model were significant.

For developing a risk model for longer-term mortality (1 year), the resulting risk model was refitted to the new outcome, and predictors that were previously considered but were found not to be important predictors for hospital survival were reassessed by incorporating them to the model. A selection process was run as described above.

Net reclassification improvement was determined to further evaluate the resulting expanded models (see *Chapter 3*).

In addition, the risk models developed were compared against the best existing generic risk model for adult critical care in the UK, based on the most appropriate calibration for the time period (the $ICNARC_{H-2015}$ model[7]). The potential impact on benchmarking was explored by plotting each critical care unit's observed mortality against 95% and 99.8% reference ranges based on the expected mortality from each model.[84]

Results

Development of risk model for acute hospital mortality

Between 1 April 2009 and 31 March 2016, there were 40,516 admissions to seven cardiothoracic critical care units in England participating in the CMP with identifiable linkage with HES and death registrations. Of these, 31,415 (78%) were successfully linked with NACSA. After excluding admissions not following cardiac surgery, a total of 27,687 eligible admissions to seven cardiothoracic critical care units formed the development data set (*Figure 25*).

A total of 1072 (3.9%) admissions to cardiothoracic units died during the hospitalisation. Of these, 693 (2.5%) died during the critical care unit admission. The median hospital length of stay of the cohort was 10 days (IQR 7–16 days), with a median critical care unit length of stay 26 hours (IQR 21–68 hours). Cohort characteristics are shown in *Table 25*.

During our evaluation, the following variables were considered redundant or inoperative because of either high proportions of missing values or small sample sizes in the category of interest and were not included in the analysis: ventricular assist device used (pre operative), aortic valve procedure, mitral

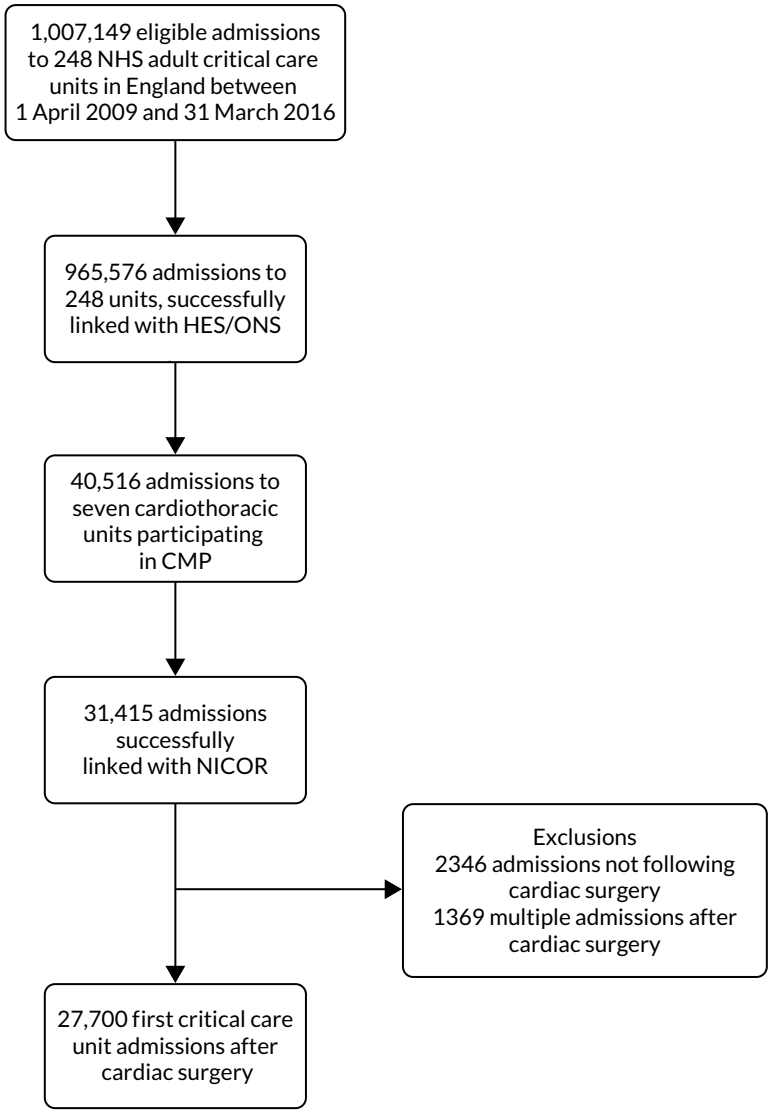

FIGURE 25 Flow diagram.

TABLE 25 Characteristics of the development and validation cohorts

Characteristic	Development cohort	Validation cohort
Number of patients	27,700	8692
Demographics		
Age (years), mean (SD)	67 (11.3)	67 (11.8)
Age (years), median (IQR)	69 (61–76)	69 (60–76)
Sex, males (%)	19,923 (71.9)	6245 (71.8)
Ethnicity, *n* (%)		
White	25,848 (93.3)	8019 (92.3)
Mixed	98 (0.4)	19 (0.2)
Asian	928 (3.4)	266 (3.1)
Black	108 (0.4)	66 (0.8)
Other	718 (2.6)	322 (3.7)

continued

TABLE 25 Characteristics of the development and validation cohorts (*continued*)

Characteristic	Development cohort	Validation cohort
Quintile of deprivation, *n* (%)		
1 (least deprived)	6208 (23.2)	1777 (21.3)
2	5745 (21.5)	1954 (23.4)
3	5464 (20.5)	1783 (21.4)
4	4686 (17.5)	1431 (17.2)
5 (most deprived)	4606 (17.2)	1398 (16.8)
Prior dependency, *n* (%)		
Able to live without assistance in daily activities	22,798 (82.8)	8076 (93.1)
Some (minor/major) assistance with daily activities	4745 (17.2)	584 (6.7)
Total assistance with all daily activities	5 (0.0)	17 (0.2)
Medical history		
Severe conditions in the medical history (APACHE II), *n* (%)		
Very severe cardiovascular disease	1453 (5.2)	228 (2.6)
Severe respiratory disease	131 (0.5)	26 (0.3)
Severe liver disease	24 (0.1)	7 (0.1)
ESRD	139 (0.5)	56 (0.6)
Metastatic disease	93 (0.3)	20 (0.2)
Haematological malignancy	81 (0.3)	16 (0.2)
Immunocompromise	186 (0.7)	42 (0.5)
Comorbidities evident in previous year (RCS Charlson and additional specific ICD-10 codes), *n* (%)		
Previous MI	1914 (6.9)	1118 (12.9)
Acute MI	4769 (17.2)	1437 (16.5)
Congestive cardiac failure	4567 (16.5)	1570 (18.1)
Congestive heart failure	1223 (4.4)	396 (4.6)
Arrhythmia	41 (0.1)	13 (0.1)
Peripheral vascular disease	2901 (10.5)	890 (10.2)
Cerebrovascular disease	819 (3.0)	265 (3.0)
Cerebrovascular accident	99 (0.4)	37 (0.4)
Chronic pulmonary disease	3897 (14.1)	1219 (14.0)
Diabetes mellitus	5174 (18.7)	1690 (19.4)
Chronic renal disease	1588 (5.7)	448 (5.2)
Acute renal disease	154 (0.6)	36 (0.4)
Hemiplegia or paraplegia	94 (0.3)	34 (0.4)
Malignancy	626 (2.3)	220 (2.5)
Metastatic disease	54 (0.2)	15 (0.2)
Pre- and intra-operative factors (NACSA)		
Previous heart operations, *n* (%)	1153 (5.8)	409 (7.5)
Left ventricular ejection fraction, *n* (%)		
Good (> 50%)	19,758 (71.6)	6242 (72.1)
Fair (30–50%)	6242 (22.6)	1968 (22.7)
Poor (< 30%)	1600 (5.8)	449 (5.2)

TABLE 25 Characteristics of the development and validation cohorts (*continued*)

Characteristic	Development cohort	Validation cohort
Angina status pre surgery, *n* (%)		
No angina	9268 (33.5)	3172 (36.5)
No limitation of physical activity	3569 (12.9)	759 (8.7)
Slight limitation of ordinary activity	7409 (26.8)	2246 (25.8)
Marked limitation of ordinary physical activity	4982 (18.0)	1569 (18.1)
Symptoms at rest or minimal activity	2464 (8.9)	945 (10.9)
Dyspnoea status pre surgery, *n* (%)		
No limitation of physical activity	6663 (24.1)	2083 (24.0)
Slight limitation of ordinary physical activity	12,260 (44.4)	3827 (44.0)
Marked limitation of ordinary physical activity	7312 (26.5)	2300 (26.5)
Symptoms at rest or minimal activity	1389 (5.0)	480 (5.5)
Number of previous MIs, *n* (%)		
None	18,356 (66.3)	5895 (67.9)
One	7716 (27.9)	2371 (27.3)
Two or more	1612 (5.8)	422 (4.9)
Interval between surgery and last MI, *n* (%)		
No previous MI	18,167 (66.4)	5846 (68.2)
< 6 hours	67 (0.2)	13 (0.2)
6–24 hours	134 (0.5)	37 (0.4)
1–30 days	4120 (15.0)	1439 (16.8)
31–90 days	919 (3.4)	223 (2.6)
> 90 days	3973 (14.5)	1016 (11.8)
Previous PCI, *n* (%)		
No previous PCI	24,698 (89.2)	7659 (88.3)
PCI < 24 hours before surgery	113 (0.4)	20 (0.2)
PCI > 24 hours before surgery; same admission	221 (0.8)	94 (1.1)
PCI > 24 hours before surgery; previous admission	2663 (9.6)	904 (10.4)
Diabetes management, *n* (%)		
No diabetes	21,398 (77.4)	6643 (76.4)
Diet	1062 (3.8)	305 (3.5)
Oral therapy	3629 (13.1)	1203 (13.8)
Insulin	1572 (5.7)	539 (6.2)
Cigarette smoking history, *n* (%)		
Never smoked	11,125 (40.3)	3580 (41.2)
Ex-smoker	13,657 (49.4)	4181 (48.1)
Current smoker	2854 (10.3)	927 (10.7)
History of hypertension, *n* (%)		
No hypertension	8542 (31.0)	2695 (31.2)
Treated or blood pressure > 140/90 on more than one occasion prior to admission	19,013 (69.0)	5933 (68.8)

continued

TABLE 25 Characteristics of the development and validation cohorts (*continued*)

Characteristic	Development cohort	Validation cohort
Renal function/dialysis, *n* (%)		
None	22,977 (98.5)	8559 (98.5)
Dialysis for acute renal failure: onset within 6 weeks of cardiac surgery	52 (0.2)	28 (0.3)
Dialysis for chronic renal failure: onset more than 6 weeks prior to cardiac surgery	172 (0.7)	76 (0.9)
No dialysis but pre-operative acute renal failure (anuria or oliguria < 10 ml/hour)	135 (0.6)	29 (0.3)
History of pulmonary disease, *n* (%)		
No chronic pulmonary disease	23,556 (85.1)	7389 (85.0)
COAD/emphysema or asthma	4133 (14.9)	1300 (15.0)
History of neurological dysfunction, *n* (%)	765 (2.8)	250 (2.9)
Extracardiac arteriopathy, *n* (%)	3004 (10.8)	996 (11.5)
Pre-operative heart rhythm, *n* (%)		
Sinus rhythm	23,549 (85.1)	7441 (85.7)
Atrial fibrillation/flutter	3465 (12.5)	1041 (12.0)
Complete heart block/pacing	451 (1.6)	154 (1.8)
Ventricular fibrillation or ventricular tachycardia	105 (0.4)	17 (0.2)
Other abnormal rhythm	108 (0.4)	32 (0.4)
Intravenous nitrates or any heparin, *n* (%)	1464 (5.3)	460 (5.3)
Cardiogenic shock (pre-operation), *n* (%)	338 (1.2)	92 (1.1)
Operative urgency, *n* (%)		
Elective	18,524 (66.9)	5544 (63.8)
Urgent	8157 (29.4)	2838 (32.7)
Emergency	905 (3.3)	290 (3.3)
Salvage	112 (0.4)	20 (0.2)
Intravenous inotropes prior to anaesthesia, *n* (%)	313 (1.1)	70 (0.8)
CABG, *n* (%)	17,768 (65.2)	5417 (62.7)
Valve procedure, *n* (%)	12,991 (48.1)	4216 (49.4)
Major aortic procedure, *n* (%)	2009 (7.4)	716 (8.4)
Other cardiac procedures, *n* (%)	1926 (9.0)	693 (8.6)
Cardiopulmonary bypass, *n* (%)	24,713 (89.4)	7881 (90.7)
Intra-aortic balloon pump used (pre operative), *n* (%)	472 (2.4)	146 (2.1)
Severity scores from first 24 hours following admission to critical care		
APACHE II score, mean (SD)	13.0 (4.3)	12.8 (4.2)
APACHE II score, median (IQR)	13 (10–16)	13 (10–15)
ICNARC physiology score, mean (SD)	13.0 (5.6)	13.5 (5.4)
ICNARC physiology score, median (IQR)	12 (10–16)	12 (10–16)
Physiology from first 24 hours following admission to critical care		
Highest heart rate (min^{-1}), mean (SD)	94.9 (14.2)	94.1 (14.5)
Lowest systolic blood pressure (mmHg), mean (SD)	90.0 (14.1)	89.3 (14.3)

TABLE 25 Characteristics of the development and validation cohorts (*continued*)

Characteristic	Development cohort	Validation cohort
Highest temperature (°C), mean (SD)	37.1 (0.8)	37.0 (0.7)
Lowest respiratory rate (min^{-1}), mean (SD)	10.4 (2.5)	10.4 (2.3)
PaO_2/FiO_2 (kPa), mean (SD)	32.3 (12.5)	33.0 (12.4)
Lowest arterial pH, mean (SD)	7.30 (0.06)	7.30 (0.05)
Highest urea (μmol l^{-1}), mean (SD)	7.2 (5.4)	6.8 (3.9)
Highest creatinine (μmol l^{-1}), mean (SD)	101 (55)	99 (53)
Highest sodium (mmol l^{-1}), mean (SD)	140 (4)	141 (4)
Lowest white blood cell count ($\times 10^9$ l^{-1}), mean (SD)	11.0 (4.5)	11.2 (4.1)
Urine output (ml), mean (SD)	2333 (1058)	2300 (1049)
$PaCO_2$ (kPa), mean (SD)	6.1 (1.0)	6.2 (1.0)
Highest blood lactate (mmol l^{-1}), mean (SD)	3.0 (2.2)	3.0 (2.0)
Lowest platelet count ($\times 10^9$ l^{-1}), mean (SD)	157 (61)	161 (61)
Neutrophil count ($\times 10^9$ l^{-1}), mean (SD)	9.2 (3.5)	9.4 (3.4)
Sepsis, *n* (%)	480 (1.7)	178 (2.0)
Organ dysfunction, *n* (%)	25,983 (93.8)	8130 (93.5)
Organ support during critical care		
Advanced respiratory support, *n* (%)	27,437 (99.1)	8568 (98.6)
Duration of advanced respiratory support (calendar days), median (IQR)	1 (1–2)	1 (1–2)
Basic/advanced cardiovascular support, *n* (%)	20,414 (73.7)	6484 (74.6)
Duration of basic/advanced cardiovascular support (calendar days), median (IQR)	2 (2–3)	2 (2–3)
Renal support, *n* (%)	1612 (5.8)	386 (4.4)
Duration of renal support (calendar days), median (IQR)	4 (2–6)	4 (2–7)
Outcomes		
Critical care unit length of stay (hours), mean (SD)	67 (126)	68 (123)
Critical care unit length of stay (hours), median (IQR)	26 (21–68)	28 (21–70)
Acute hospital length of stay (days), mean (SD)	15 (17)	14 (15)
Acute hospital length of stay (days), median (IQR)	10 (7–16)	9 (7–15)
Critical care unit mortality, *n* (%)	693 (2.5)	159 (1.8)
Acute hospital mortality, *n* (%)	1072 (3.9)	273 (3.1)
One-year mortality, *n* (%)	1918 (6.9)	523 (6.0)

CABG, coronary artery bypass graft; COAD, chronic obstructive airway disease; PCI, percutaneous coronary intervention. The *n* values do not sum to the total numbers because of varying amounts of missing data for each variable.

valve procedure, tricuspid valve procedure, pulmonary valve procedure, intra-aortic balloon pump used (intra operative), impeller device used (intra operative), ventricular assist device used (intra operative), other support device used (intra operative), aortic pathology – root segment, aortic pathology – ascending segment, aortic pathology – arch segment, aortic pathology – descending aorta segment, aortic pathology – abdominal segment, systolic pulmonary artery pressure (PA systolic), total number of distal coronary anastomoses and number of valves replaced/repaired.

A multivariable model with the factors included in the previous risk prediction model for acute hospital mortality among admissions to cardiothoracic critical care units was refitted, excluding location and cardiac surgery. The significance and functional forms for the remaining predictors were retested. The completeness for those variables was 98.2% and consequently data were not imputed. All predictors were significant, and their functional forms were consistent with the previous findings. Sex was then including and the c index and Brier's score for the main model were 0.873 and 0.0280, respectively. Comorbidities, pre-operative and factors from NACSA that were significant ($p < 0.1$) in univariable analyses were introduced into the main model and a final model was developed as described above.

The following factors from NACSA were found to be associated with acute hospital mortality on multivariable analysis: diabetes (categorised as no diabetes vs. diabetes controlled by diet/oral therapy/insulin), atrial fibrillation/flutter, dyspnoea status pre surgery (categorised as no limitation or slight limitation of ordinary physical activity vs. marked limitation of ordinary physical activity vs. symptoms at rest or minimal activity), history of pulmonary disease, history of neurological dysfunction; extracardiac arteriopathy, operative urgency (categorised as elective vs. urgent vs. emergency vs. salvage), and cumulative bypass time. Of the comorbidities and pre-existing conditions, only severe respiratory disease, severe cardiovascular disease and congestive heart failure were significant predictors of acute hospital mortality.

The first expanded model, incorporating factors from NACSA, performed moderately better than the baseline parsimonious model (*Table 26*). The second expanded model with severe conditions and pre-existing congestive heart failure resulted in minimal change to c index and Brier's score, with a c index of 0.892 and Brier's score of 0.0273 for the final model. *Appendix 2*, *Table 43*, summarises the significance and importance of the predictors in the final model. Full coefficients for the final model are presented in *Appendix 3*, *Table 49*. After comparing the reclassification of the two models using risk categories defined by thresholds of 0%, 2%, 5%, 10%, 20% and 50% (*Tables 27* and *28*), a total of 5766 (21%) admissions were reclassified and 3088 of those (54%) were placed in more appropriate categories. The total NRI for the expanded model was 7.0% (standard error 2.0%, $p < 0.0005$). The distribution of predicted acute hospital mortality from the new model is shown in *Figure 26*.

Validation of risk model of acute hospital mortality

The performance of the risk model for acute hospital mortality in the validation data set of 8692 admissions from April 2015 to March 2016 was excellent: a c index of 0.907 (95% CI 0.888 to 0.926) and Brier's score of 0.022. The calibration of the model was acceptable (*Figure 27*; see *Report Supplementary Material 1*, Figure S3), with a calibration slope of 1.06 and a calibration intercept of −0.083.

TABLE 26 Performance of the model for acute hospital mortality with incremental addition of predictors

Model	df	LL	BIC	c index (95% CI)	Brier's score
Main model	22	−3047.47	6329	0.872 (0.859 to 0.883)	0.0282
Main model + sex	23	−3031.00	6306	0.873 (0.859 to 0.884)	0.0280
Main model + sex + NACSA factors	34	−2914.19	6185	0.890 (0.878 to 0.899)	0.0273
Main model + sex + NACSA factors + comorbidities	37	−2900.63	6189	0.892 (0.880 to 0.901)	0.0273

BIC, Bayesian information criterion; LL, log-likelihood.

TABLE 27 Reclassification table for the new model compared with the previous model for cardiothoracic critical care units

	Risk category (expanded model incorporating additional predictors) (%)					
Risk category (parsimonious model)	**0–1.99**	**2–4.99**	**5–9.99**	**10–19.99**	**20–49.99**	**50–100**
Survivors, %						
0–1.99	16,930	1342	83	5		
2–4.99	1605	2412	570	90	6	
5–9.99	100	595	684	220	35	
10–19.99	25	72	255	327	112	4
20–49.99	2	7	25	129	291	37
50–100			1	5	36	74
Non-survivors, %						
0–1.99	98	38	2			
2–4.99	33	73	35	7	2	
5–9.99		27	53	40	9	1
10–19.99	1	7	33	66	53	3
20–49.99		1	2	42	135	41
50–100					27	174

Dark blue indicates no reclassification; light blue indicates improved classification; orange indicates worsened classification.

TABLE 28 Net reclassification improvement for the new model compared with the previous model for cardiothoracic critical care units

Change in classification	Survivors	Non-survivors
Down, *n* (%)	2857 (10.9)	174 (17.33)
No change, *n* (%)	20,718 (79.4)	599 (59.6)
Up, *n* (%)	2504 (9.6)	231 (23.0)
Net improvement[a] (SE)	+ 1.3% (0.2%)	+ 5.6% (2.0%)

SE, standard error.
a Net improvement defined as the proportion reclassified down minus the proportion reclassified up for survivors and the proportion reclassified up minus the proportion reclassified down for non-survivors.

Comparison with the Intensive Care National Audit and Research Centre$_{H\text{-}2015}$ model

We used the validation data set to compare the predictive accuracy of the developed cardiothoracic model with the ICNARC$_{H\text{-}2015}$ model, a general model that is currently used for benchmarking in the CMP for general and specialist units. Compared with the ICNARC$_{H\text{-}2015}$ model, the new model demonstrated small improvements in discrimination and accuracy (*Table 29*) but, overall, it presented a better calibration (*Figure 28*). Both the cardiothoracic and the ICNARC$_{H\text{-}2015}$ models tended to slightly overestimate mortality: observed mortality was 3.0% with predicted mortality of 3.5% and 4.1%, respectively, for SMRs of 0.85 (95% CI 0.75 to 0.96) and 0.73 (95% CI 0.65 to 0.83).

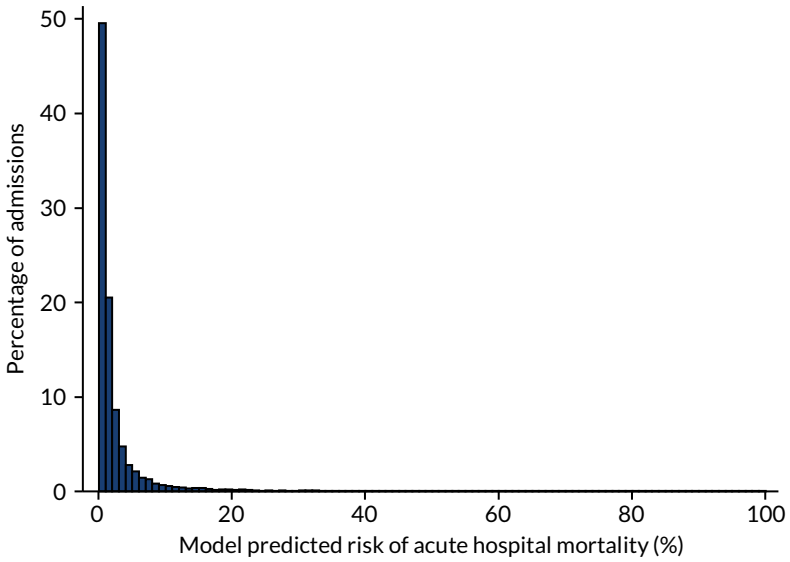

FIGURE 26 Distribution of predicted risk of acute hospital mortality.

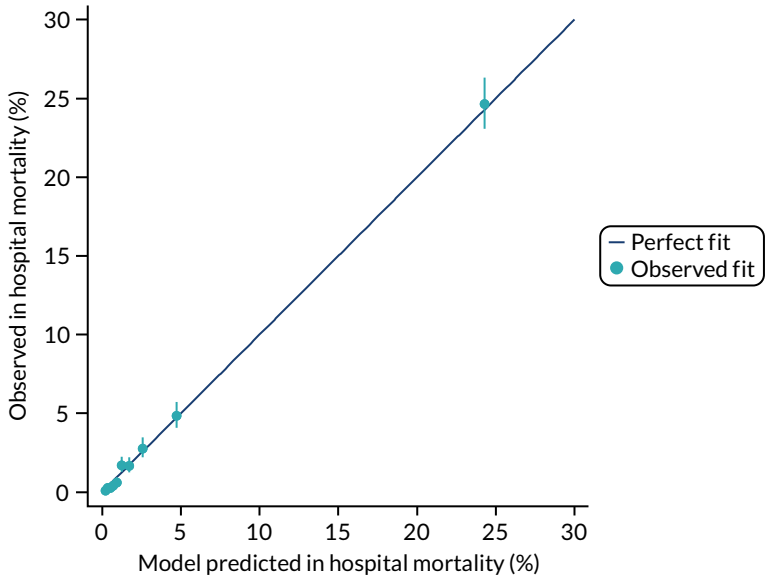

FIGURE 27 Calibration of the model for acute hospital mortality in the development cohort.

TABLE 29 External validation: overall predictive performance of the model for acute hospital mortality compared with the $ICNARC_{H\text{-}2015}$ model

Model	c index (95% CI)	Brier's score	Predicted mortality (%)	Observed mortality (%)	SMR (95% CI)
$ICNARC_{H\text{-}2015}$	0.8969 (0.8757 to 0.9181)	0.0225	4.1	3.0	0.73 (0.65 to 0.83)
New[a]	0.9073 (0.8881 to 0.9263)	0.0223	3.5	3.0	0.85 (0.75 to 0.96)

a Developed in this project.

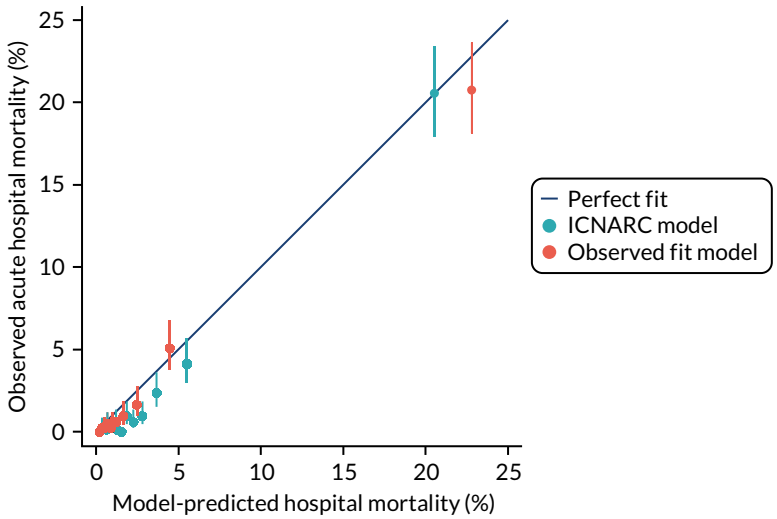

FIGURE 28 Calibration of the model for acute hospital mortality compared with the ICNARC$_{H\text{-}2015}$ model in the external validation cohort.

Figure 29 shows the observed value for each cardiothoracic critical care unit against 95% and 99.8% reference ranges for predicted mortality from the cardiothoracic and the ICNARC$_{H\text{-}2015}$ models to evaluate their impact on benchmarking. To compare the observed value with the expected value, we calculated predicted ranges based on the expected value and the number of eligible admissions for each cardiothoracic unit. Although the predicted range showed less variability for the cardiothoracic model, the number of critical care units that lie within the 95% reference range was similar for both models and only one cardiothoracic critical care unit showed some evidence that the acute hospital mortality was better than expected.

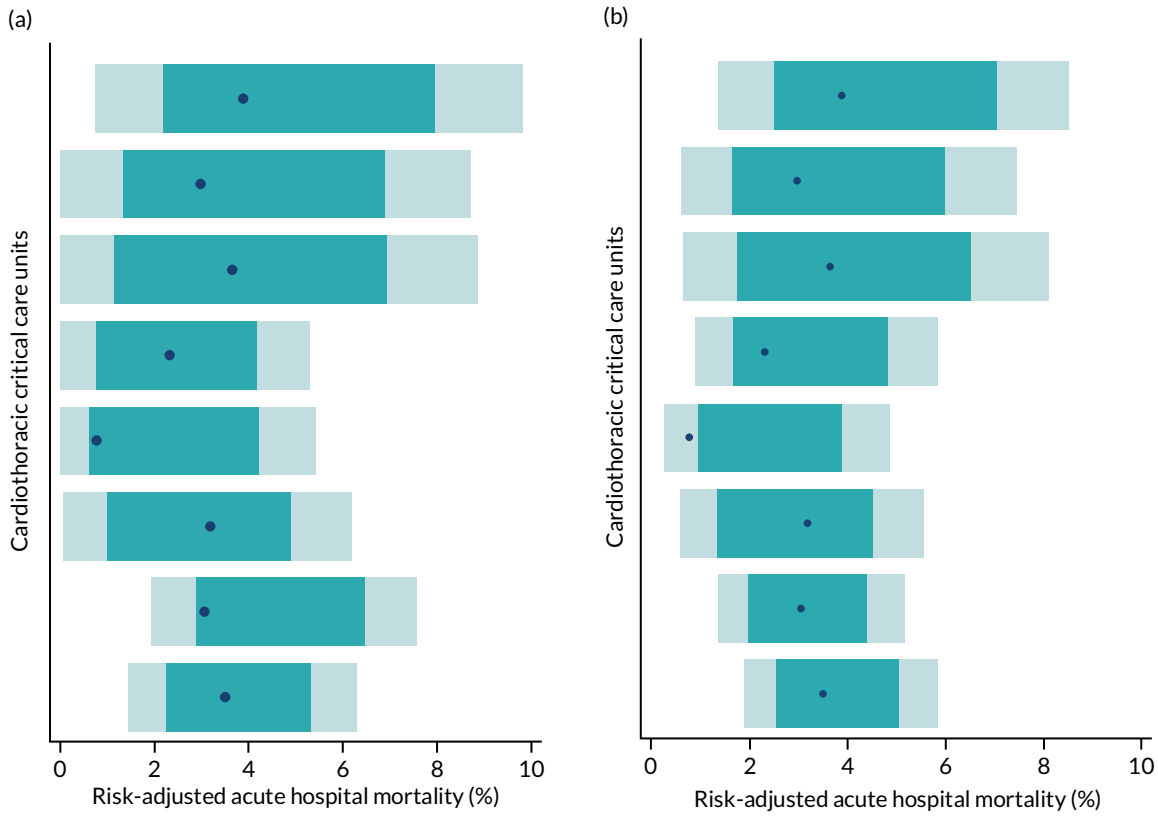

FIGURE 29 Observed acute hospital mortality vs. reference ranges for expected mortality for the seven cardiothoracic critical care units with (a) the ICNARC$_{H\text{-}2015}$ model and (b) the new model.

Development of risk model for 1-year mortality

For the development of the 1-year mortality model we used the same cohort that we used for the acute hospital mortality. Two admissions were excluded owing to missing date of death. The median follow-up was 5 years (IQR 3.9–6.4 years). In total, 1918 (6.92%) died during the 1-year follow-up, but most of the deaths were in the first month from admission. A Kaplan–Meier plot of time to death within 1 year is shown in *Figure 30*.

The risk model developed for in hospital mortality was refitted to the new outcome and all predictors were significantly associated. The model showed a good performance, with a c index of 0.824 (95% CI 0.814 to 0.834) and a Brier score of 0.0516. After the addition and reassessment of the predictors that were found not to be important predictors for acute hospital mortality, the following pre-operative factors from NACSA were included in the final model: renal function/dialysis [recategorised as none or dialysis for acute renal failure vs. dialysis for chronic renal failure vs. no dialysis but pre-operative acute renal failure (anuria or oliguria < 10 ml/hour)]; left ventricular ejection fraction, number of previous MIs and major aortic procedure. No additional pre-existing conditions were found to be important predictors. After accounting for these predictors, the discriminative ability of the model improved slightly with a c index of 0.827 (95% CI 0.816 to 0.837). The full model coefficients are presented in *Appendix 3*, *Table 49*.

Following the development process described above, the significance and importance of the predictors in the final model are shown in *Appendix 2*, *Table 43*. Age was one of the strongest predictors of 1-year mortality, followed by GCS, blood lactate and operative urgency. Compared with the short-term model (acute hospital mortality), pre-operative and pre-existing conditions had a more important role in the model performance, whereas physiological and laboratory variables were stronger predictors of acute hospital mortality.

Validation of risk model for 1-year mortality

The overall predictive performance of the 1-year model was well preserved in the validation data set compared with the development data set, with a c index of 0.815 (95% CI 0.794 to 0.835) and Brier's score of 0.0467, and presented a SMR of 0.97 (95% CI 0.89 to 1.06). The calibration in the validation cohort was satisfactory (*Figure 31*; see *Report Supplementary Material 1*, Figure S3).

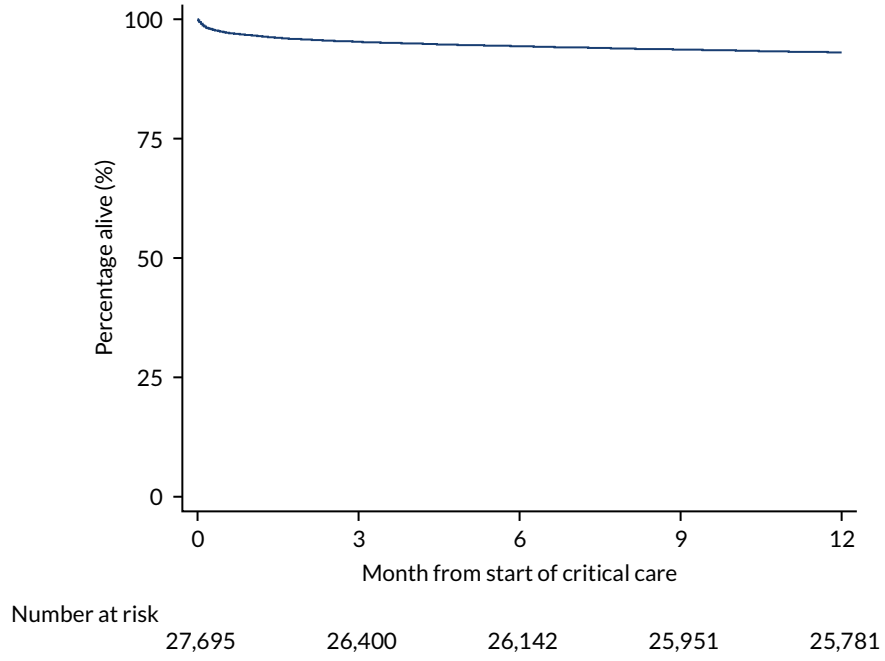

FIGURE 30 Kaplan–Meier plot of time to death within 1 year from admission to cardiothoracic unit.

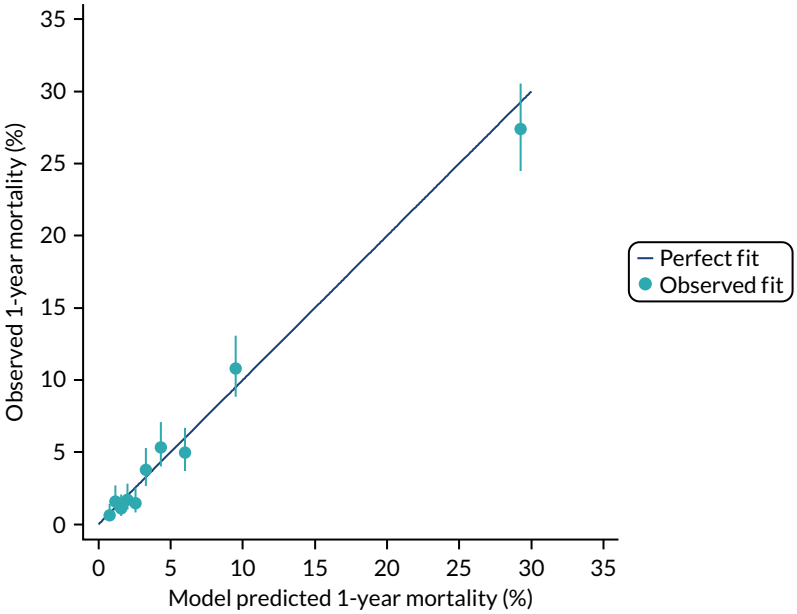

FIGURE 31 Calibration of the 1-year mortality model in the external validation cohort.

Discussion

Existing literature on predictors of mortality for post-cardiac surgery patients suggests that outcomes are best predicted by a combination of pre-operative, intra-operative and post-operative risk factors.[85,86] The purpose of this chapter was to develop and assess a specific risk model for admissions to cardiothoracic critical care following cardiac surgery using a combination of post-operative information such as clinical and physiological variables collected in the first 24 hours following admission to critical care, combined with pre- and intra-operative information and pre-existing conditions to improve risk prediction among this patient group. We have developed a risk prediction model with good discrimination (c index > 0.9) for predicting acute hospital mortality following cardiac surgery. This model validated well in subsequent data. Our results show that the incorporation of the following pre- and intra-operative variables from NACSA contributed to the model performance: diabetes, atrial fibrillation/flutter, dyspnoea status pre surgery, history of pulmonary disease, history of neurological dysfunction, extracardiac arteriopathy, operative urgency and cumulative bypass time. Also, we identified a set of pre-existing conditions that significantly predicted acute hospital mortality: severe respiratory disease, severe cardiovascular disease and congestive heart failure. However, they did not contribute substantively to the model's predictive performance.

Models specifically designed for cardiothoracic critical care units may be warranted given the differences in case mix of cardiothoracic critical care units from that of adult, general critical care units. Furthermore, there is potential that a single, general model may under- or over-estimate mortality in selected admission subpopulations or different unit types and so could show worse performance than a specifically designed or calibrated model. So, in addition, using the validation data set, we evaluated the developed model for cardiothoracic critical care units compared with the corresponding contemporary version of the ICNARC risk prediction model, which is currently used in benchmarking for both general and specialist critical care units in the CMP. The performance of both models was similar, although the cardiothoracic model demonstrated slightly better calibration. However, we found little impact on benchmarking when the specific cardiothoracic model was applied in place of the current general model.

In addition, we identified a set of pre- and intra-operative factors from NACSA that were shown to be determinants for longer-term survival of cardiac surgical patients after critical care admission. Apart from the factors included in the acute hospital mortality model, the updated risk model for 1-year mortality following critical care admission incorporated renal function/dialysis, left ventricular

ejection fraction, number of previous MIs and major aortic procedures. The adverse effect of diabetes and dialysis-dependent renal failure on cardiac-surgery mortality have been described previously,[87,88] but we have confirmed their importance for an extended outcome after critical care admission. Surprisingly, no additional pre-existing conditions were found to be important predictors. This finding was consistent with the acute hospital mortality analysis, in which pre- and intra-operative factors were found to play a more important role than pre-existing conditions after adjusting for age, sex and the core physiological variables. On the other hand, we showed that severe respiratory disease, severe cardiovascular disease and congestive heart failure were significantly associated with both short- and longer-term outcomes after critical care admission.

One of the limitations of the present work was that the models have not been directly compared with specific models for cardiac surgery, such as EuroSCORE II or the latest UK recalibration,[89] owing to the lack of some fields required for this comparison. However, such a comparison may not have been fair as our models incorporate post-surgery information and would therefore be expected to out-perform a purely pre-operative model when applied in this setting.

In conclusion, data linkage with NACSA greatly increased the available pre- and intra-operative data. However, clinical and physiological variables collected in the first 24 hours provided good prediction, and the improvements to predictive performance from a model incorporating pre- and intra-operative factors and pre-existing conditions were small.

Chapter 10 Risk models for in-hospital cardiac arrest

Introduction

We have previously developed and published prediction models[8] for ROSC > 20 minutes and survival to hospital discharge (hospital survival) following in-hospital cardiac arrest that underpin comparative reporting for NCAA. Simultaneously to our work developing risk models for NCAA,[8] a prediction model for hospital survival following in-hospital cardiac arrest was published from the American Heart Association (AHA) Get With the Guidelines–Resuscitation registry.[90] This identified largely similar risk factors to the NCAA risk models but included additional predictors not available in the NCAA data set, most notably pre-existing comorbidities. Data linkage with HES enables calculation of comorbidity indices from diagnoses and procedural codes recorded during the hospital episode, an approach that has been applied successfully in other clinical audits.[91] Combining this information with the existing risk factors enables us to determine the contribution of chronic health conditions to outcome from in-hospital cardiac arrest with a view to either routinely linking data in the future or establishing which comorbidity fields are important to collect directly within NCAA. Little is known about longer-term outcomes following in-hospital cardiac arrest and data linkage with death registrations enables us to extend our prediction models to explore the role of pre-existing conditions in determining 1-year survival.

Although many patients do not survive the initial resuscitation attempt, the treatment of those who do requires substantial resources, and many patients will be admitted to a critical care unit. Prediction models for cost and resource use have been primarily developed for calibration (getting the mean correct).[27] Less attention has been paid to the covariate effects. Data linkage between NCAA and the CMP allows us to better understand patterns of critical care resource use and organ support following successful resuscitation. Length of stay in the critical care unit has been used as a measure of critical care resource utilisation.[92] The aim of this analysis was to assess the impact of covariates on critical care resource utilisation to better understand the importance of patient characteristics in critical care resource utilisation following in-hospital cardiac arrest.

This chapter reports on the development and validation of prediction models for the following outcomes following in-hospital cardiac arrest: ROSC > 20 minutes and hospital survival, 1-year survival, and critical care utilisation.

Prediction models for survival outcomes

Methods

Methods common to all objectives and analyses were describe in *Chapter 3*. Details relating to the study cohorts and outcomes can be found in the same chapter.

Study cohort

The cohort for these models was the NCAA in-hospital cardiac arrest cohort (see *Chapter 3*).

Inclusion and exclusion criteria

For development of the prediction models, data were extracted from the NCAA in-hospital cardiac arrest cohort for all individuals with a 2222 call dated between 1 January 2013 and 31 December 2014. Second and subsequent team visits to the same patient were excluded. The following exclusion criteria

were applied to individual team visit records: patients whose last known status was still in hospital, patients missing either of the outcomes of ROSC > 20 minutes or hospital survival and patients with missing data for the candidate predictors.

For validation of the risk prediction models, data were extracted from the NCAA in-hospital cardiac arrest cohort for all individuals with a 2222 call dated between 1 January 2015 and 30 June 2015. The same eligibility and exclusion criteria were applied at the individual team visit level as for the development data set.

Outcomes and candidate predictors

Prediction models were developed for three outcomes: ROSC > 20 minutes, hospital survival and 1-year survival. Patients were followed up to discharge from the original acute hospital and any patients transferred to another acute hospital were reported as hospital survivors.

Previously developed prediction models[8] for ROSC > 20 minutes and hospital survival were the starting point. Predictors included in the previous model for ROSC > 20 minutes were age, sex, length of stay in hospital prior to arrest, reason for admission to/attendance at/visit to hospital, location of arrest, presenting/first documented rhythm, and interactions between location of arrest and presenting/first documented rhythm. Predictors included in the previous model for hospital survival model were age, length of stay in hospital prior to arrest, reason for admission to/attendance at/visit to hospital, location of arrest, presenting/first documented rhythm, and interactions between location of arrest and presenting/first documented rhythm. In both models, age was modelled as a continuous, non-linear relationship using restricted cubic splines with five knots. All other candidate predictors were modelled as categorical variables. Current predictors and new potential predictors (pre-existing comorbidities) are described in *Appendix 1*, *Table 40*.

Development and validation of prediction models for return of spontaneous circulation > 20 minutes and hospital survival

An initial model for each outcome including the current predictors was fitted using multilevel logistic regression. All variables in the current model were reassessed: each predictor was removed, and the reduced model was assessed for discrimination (c index), accuracy (Brier's score) and model fit (BIC).

All pre-existing comorbidities were added to the model. From this full model, comorbidities were selected for inclusion following the general approach to model development described in *Chapter 3*.

The resulting models were validated for discrimination, calibration and accuracy in the development data set and the validation data.

Development and validation of a prediction model for 1-year survival

It was anticipated that predictors representing age, chronic ill health and functional status would be stronger predictors of longer-term outcomes than of hospital survival. Using the prediction model for hospital survival as the starting point, a 1-year model was developed with the aim of determining the set of pre-existing comorbidities that could be determinants for longer-term survival following in-hospital cardiac arrest. The prediction model without comorbidities was refitted to the 1-year survival outcome, pre-existing comorbidities in the model and those that were previously considered but were found not to be important predictors for hospital survival were reassessed by adding them to the model. Finally, the effect of those predictors previously included in the prediction model were re-assessed to determine whether or not they still made an important contribution to the model.

Results

One hundred and eighty-one hospitals participated in NCAA between 1 January 2013 and 31 December 2014. During this time there was a total of 33,829 team visits following 2222 calls for cardiac arrest with identifiable linkage with HES and death registrations. After removing records that

were ineligible for inclusion in the prediction models, there were a total of 26,904 eligible patients and, of these, 26,748 (99.4%) patients from 172 hospitals were included in the modelling. The breakdown of the inclusion/exclusion process for the development data set is shown in *Figure 32*. Characteristics and outcomes of in-hospital cardiac arrest patients in the development and validation data sets are summarised in *Table 30*.

Development of prediction models for return of spontaneous circulation > 20 minutes and hospital survival

Age was significantly non-linear in both models ($p < 0.001$ for ROSC > 20 minutes, $p < 0.001$ for hospital survival) and was modelled as a continuous, non-linear relationship using restricted cubic splines with five knots. When the current predictors for each outcome were reassessed, all were retained in the model (see *Report Supplementary Material 1*, Table S2). The initial main model, including the current predictors and interaction between location of arrest and presenting rhythm, had a c index of 0.718 for ROSC > 20 minutes and 0.816 for hospital survival.

Royal College of Surgeons Charlson comorbidities and their associated outcomes are described in *Table 31*. All candidate predictors were entered into the full model, which was then simplified based on significance and contribution to the model fit. After adjusting for current and new potential predictors,

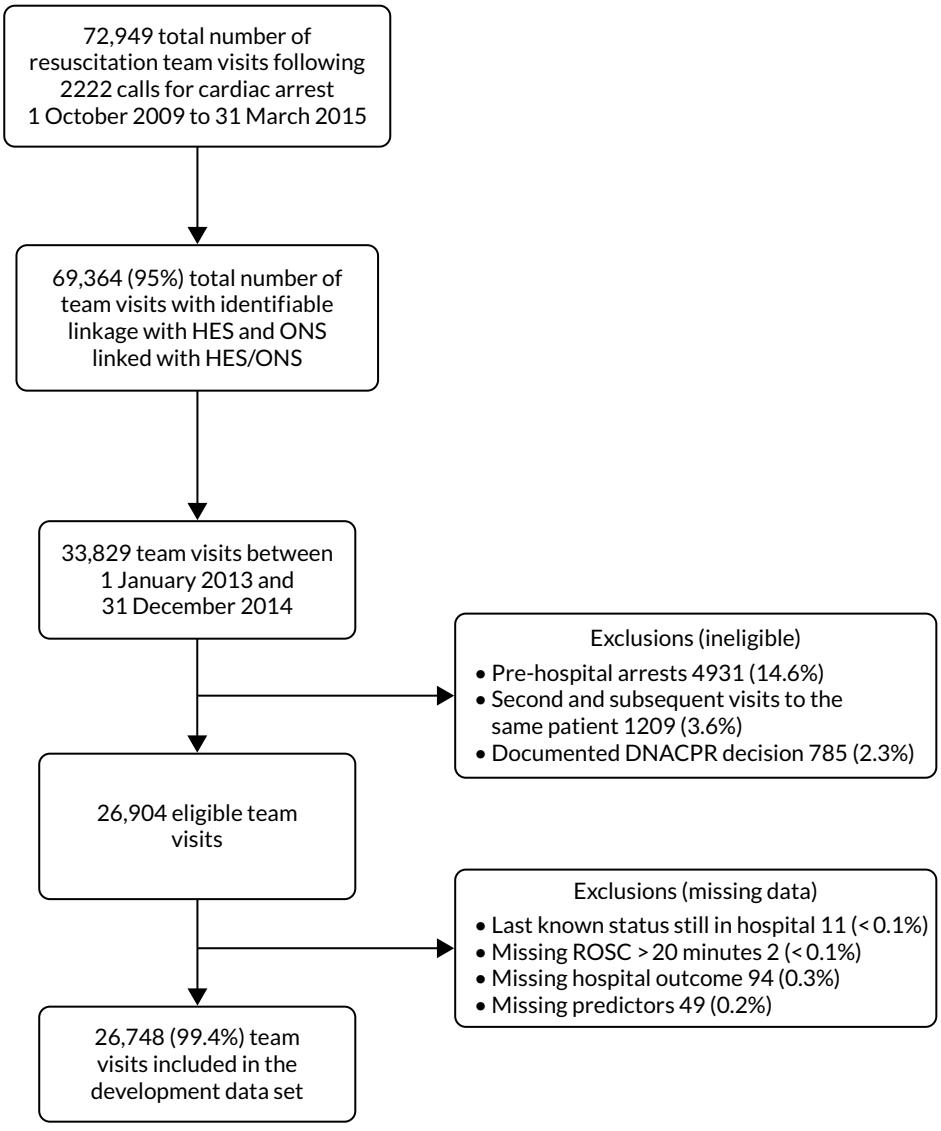

FIGURE 32 Flow diagram for cohort identification.

TABLE 30 Characteristics and outcomes of in-hospital cardiac arrest patients in the development and validation data sets

Characteristic	Development (*n* = 26,748)	Validation (*n* = 7073)
Age (years), mean (SD)	73 (16.4)	73 (16.2)
Sex male, *n* (%)	15,509 (58.0)	4173 (59.0)
Length of stay in hospital (days) prior to 2222 call, median (IQR)	2 (2–3)	2 (2–3)
Reason for admission to/attendance at/visit to hospital, *n* (%)		
Patient: medical	21,752 (81.3)	5955 (84.2)
Patient trauma	843 (3.2)	191 (2.7)
Patient: elective surgery	1678 (6.3)	354 (5.0)
Patient: emergency surgery	2103 (7.9)	451 (6.4)
Patient: obstetric	41 (0.2)	16 (0.2)
Outpatient	286 (1.1)	91 (1.3)
Staff or visitor	50 (0.2)	15 (0.2)
Location of arrest, *n* (%)		
Obstetrics ward	15,683 (58.6)	4255 (60.2)
Emergency department	2486 (9.3)	643 (9.1)
Emergency admissions unit	2161 (8.1)	587 (8.3)
Theatre and recovery	400 (1.5)	96 (1.4)
Cardiac catheter laboratory	876 (3.3)	260 (3.7)
Imaging department	352 (1.3)	96 (1.4)
Specialist treatment area	367 (1.4)	102 (1.4)
ICU or ICU/HDU; PICU	1344 (5.0)	237 (3.4)
HDU; PHDU	502 (1.9)	104 (1.5)
Coronary care unit	2329 (8.7)	636 (9.0)
Other intermediate care area	32 (0.1)	4 (0.1)
Clinic	111 (0.4)	28 (0.4)
Non-clinical area	109 (0.4)	25 (0.4)
Patient deteriorating (not yet arrested) at team arrival, *n* (%)	1412 (5.3)	377 (5.3)
Presenting/first documented rhythm, *n* (%)		
Ventricular fibrillation	2746 (10.3)	755 (10.7)
Ventricular tachycardia	1218 (4.6)	310 (4.4)
Shockable: unknown rhythm	128 (0.5)	45 (0.6)
Asystole	6160 (23.0)	1611 (22.8)
Pulseless electrical activity	13,908 (52.0)	3674 (51.9)
Bradycardia	206 (0.8)	56 (0.8)
Non-shockable: unknown rhythm	566 (2.1)	135 (1.9)
Unknown	1821 (6.8)	487 (6.9)
ROSC > 20 minutes, *n* (%)	12,566 (47.0)	3318 (46.9)
Hospital survival, *n* (%)	5349 (20.0)	1581 (22.4)

TABLE 31 Royal College of Surgeons Charlson comorbidities and outcomes in the development cohort and the validation cohort

	Development (*N* = 26,748)			Validation (*N* = 7073)		
Comorbidity	*n* (%)	ROSC > 20 min (%)	Hospital survival (%)	*n* (%)	ROSC > 20 min (%)	Hospital survival (%)
MI	1989 (7.4)	46.0	19.5	717 (10.1)	43.4	21.2
Congestive cardiac failure	3751 (14)	44.0	17.2	1088 (15.4)	47.3	18.8
Peripheral vascular disease	1726 (6.5)	44.4	16.8	454 (6.4)	48.0	21.1
Cerebrovascular disease	1247 (4.7)	44.2	16.5	295 (4.2)	48.8	21.7
Dementia	863 (3.2)	36.1	10.2	253 (3.6)	41.5	12.3
Chronic pulmonary disease	4576 (17.1)	44.1	16.3	1260 (17.8)	45.0	17.0
Rheumatological disease	707 (2.6)	44.3	18.1	207 (2.9)	40.6	15.9
Liver disease	708 (2.6)	51.5	16.5	171 (2.4)	42.7	12.3
Diabetes mellitus	4493 (16.8)	48.6	19.0	1248 (17.6)	46.3	19.5
Hemiplegia or paraplegia	265 (1.0)	43.4	11.7	50 (0.7)	52.0	28.0
Chronic renal disease	3242 (12.1)	46.9	16.4	934 (13.2)	45.6	17.1
Malignancy	2403 (9.0)	39.5	12.9	641 (9.1)	38.7	14.4
Metastatic solid tumour	738 (2.8)	33.6	8.3	193 (2.7)	32.6	12.4
Full cohort	26,748	47.0	20.0	7073	46.9	22.4

congestive cardiac failure, peripheral vascular disease, diabetes mellitus, chronic renal disease, malignancy and metastatic solid tumour were retained in the prediction model for ROSC > 20 minutes (see *Appendix 2*, *Table 44*). For hospital survival, congestive cardiac failure, peripheral vascular disease, liver disease, hemiplegia or paraplegia, malignancy and metastatic solid tumour were retained (see *Appendix 2*, *Table 44*).

The incorporation of comorbidities in the prediction models produced a small improvement in the performance for both outcomes (*Table 32*). When the performance of the models including

TABLE 32 Performance measures and validation of prediction models for ROSC > 20 minutes, hospital survival and 1-year survival

Model	df	LL	BIC	c index (95% CI)	Brier's score
ROSC > 20 minutes					
Full model	46	−16263	32995	0.718 (0.712 to 0.724)	0.212
Full model + comorbidities	52	−16209	32949	0.722 (0.716 to 0.727)	0.211
Validation (*n* = 7073)				0.718 (0.702 to 0.733)	0.212
Hospital survival					
Full model	45	−10268	20996	0.816 (0.809 to 0.821)	0.121
Full model + comorbidities	51	−10212	20945	0.818 (0.811 to 0.824)	0.120
Validation (*n* = 7073)				0.816 (0.799 to 0.833)	0.116
One-year survival					
Full model	45	−9035	18529	0.823 (0.817 to 0.830)	0.103
Full model + comorbidities	50	−8920	18349	0.829 (0.822 to 0.835)	0.102
Validation (*n* = 7073)				0.816 (0.799 to 0.833)	0.116

comorbidities was compared with the recalibrated current models (i.e. without comorbidities) using reclassification techniques (*Tables 33* and *34*), a total of 3507 (13.1%) patients were reclassified for ROSC > 20 minutes, with 1815 (51.8%) placed into more appropriate categories. The total NRI from including comorbidities was 0.0112 [standard error (SE) 0.0044; $p = 0.0116$]. When the reclassification for hospital survival was explored, 3646 (13.6%) were reclassified, with 1968 (54.0%) placed into more appropriate categories. The total NRI was 0.0189 (SE 0.0048; $p = 0.0001$).

Full coefficients for the final models for ROSC > 20 minutes and hospital survival are presented in *Appendix 3*, *Tables 50* and *51*.

Validation of prediction models for return of spontaneous circulation > 20 minutes and hospital survival

After exclusions, a total of 7073 patients experiencing an in-hospital cardiac arrest between 1 January 2015 and 30 June 2015 comprised the validation cohort. As for the development cohort, discrimination and accuracy were better for hospital survival (c index 0.82, Brier's score 0.116) than for ROSC > 20 minutes (c index 0.72, Brier's score 0.212). Calibration plots showed good calibration for the validation cohort (*Figure 33*; see *Report Supplementary Material 1*, Figure S4).

Development and validation of a prediction model for 1-year survival

A total of 4454 (16.7%) patients were alive after 1 year following an in-hospital cardiac arrest (*Figure 34*), 84% of 60-day survivors. All predictors, excluding pre-existing comorbidities, were reassessed for 1-year survival and were found to be significant (see *Report Supplementary Material 1*, Table S2). After their addition into the model, the following pre-existing comorbidities that were found significant for hospital survival significantly predicted 1-year survival following an in-hospital cardiac arrest: congestive cardiac failure, peripheral vascular disease, severe liver disease, malignancy and metastatic solid tumour. Chronic renal disease and dementia were also found to be significant predictors of 1-year survival, but hemiplegia or paraplegia was not (see *Appendix 2*, *Table 44*). Metastatic solid tumour, malignancy, congestive cardiac

TABLE 33 Reclassification table for ROSC > 20 minutes

	Risk category (new[b])					
Risk category (current[a])	**0–24.99%**	**25–39.99%**	**40–49.99%**	**50–69.99%**	**70–74.99%**	**75–100%**
Non-ROSC > 20min						
0–24.99%	3140	174				
25–39.99%	115	4012	483			
40–49.99%	2	438	2552	174		
50–69.99%		22	115	970	131	
70–74.99%			6	112	1229	42
75–100%				1	29	437
ROSC > 20min						
0–24.99%	738	65				
25–39.99%	44	2148	378			
40–49.99%		246	2077	212		
50–69.99%		11	128	1177	167	
70–74.99%			14	162	2616	153
75–100%					83	2200

Dark blue indicates no reclassification; light blue indicates improved classification; orange indicates worsened classification.
a Recalibrated current model (excluding comorbidities).
b New model (including comorbidities).

TABLE 34 Reclassification table for hospital survival

Risk category (current[a])	Risk category (new[b]) 0–1.99%	2–4.99%	5–9.99%	10–19.99%	20–49.99%	50–100%
Non-survivors						
0–1.99%	389	131				
2–4.99%	315	4025	477			
5–9.99%	15	534	5438	518		
10–19.99%		98	413	3855	262	
20–49.99%			22	252	3685	80
50–100%					71	821
Survivors						
0–1.99%	3					
2–4.99%	7	140	21			
5–9.99%		17	466	71		
10–19.99%		3	50	682	65	
20–49.99%			1	70	1832	91
50–100%					62	1766

Dark blue indicates no reclassification; light blue indicates improved classification; orange indicates worsened classification.
a Recalibrated current model (excluding comorbidities).
b New model (including comorbidities).

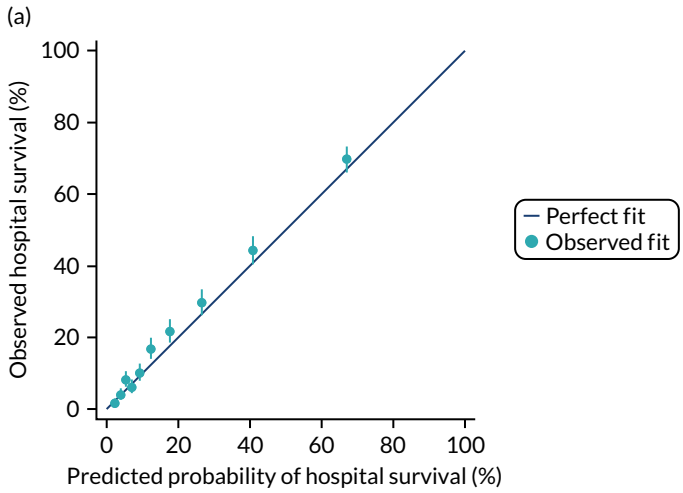

FIGURE 33 Calibration plot for ROSC > 20 minutes, hospital survival and for 1-year survival (validation set). (a) Hospital survival; (b) ROSC > 20 minutes; (c) 1-year survival. (*continued*)

failure, severe liver disease and chronic renal disease had a relevant role in predicting 1-year survival. The 1-year survival model coefficients are presented in *Appendix 3*, *Table 52*. The model c index after addition of comorbidities was 0.829 (95% CI 0.822 to 0.835). The model showed good discrimination in the validation cohort, with a c index of 0.816 (95% CI 0.799 to 0.833) and a Brier score of 0.116 (see *Table 32*), and acceptable calibration (see *Figure 33* and *Report Supplementary Material 1*, Figure S4).

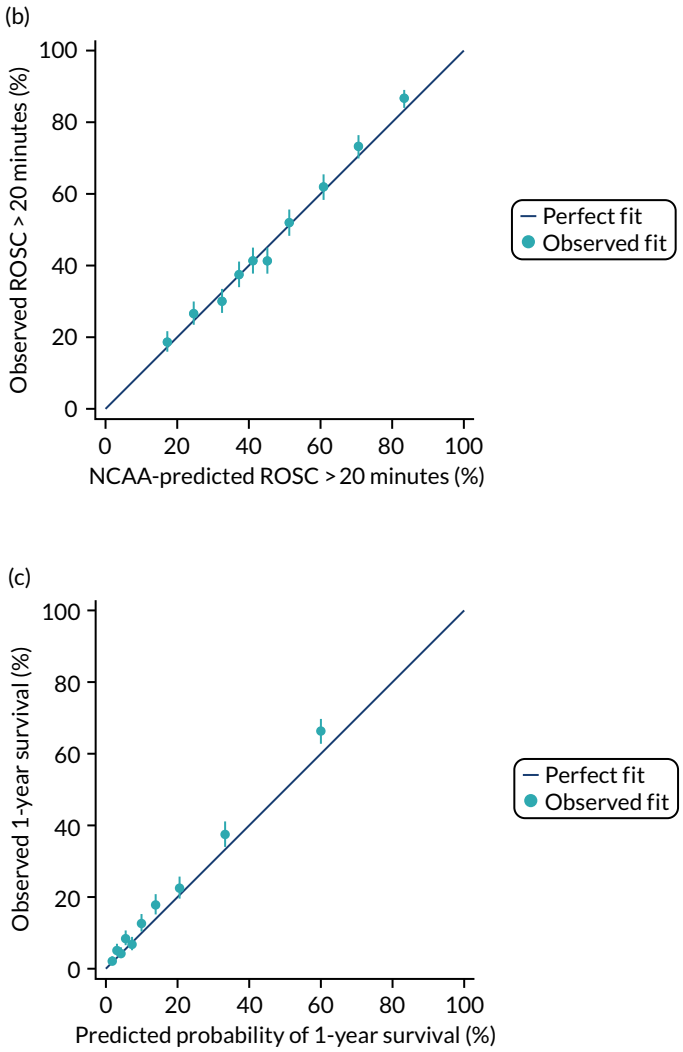

FIGURE 33 Calibration plot for ROSC > 20 minutes, hospital survival and for 1-year survival (validation set). (a) Hospital survival; (b) ROSC > 20 minutes; (c) 1-year survival.

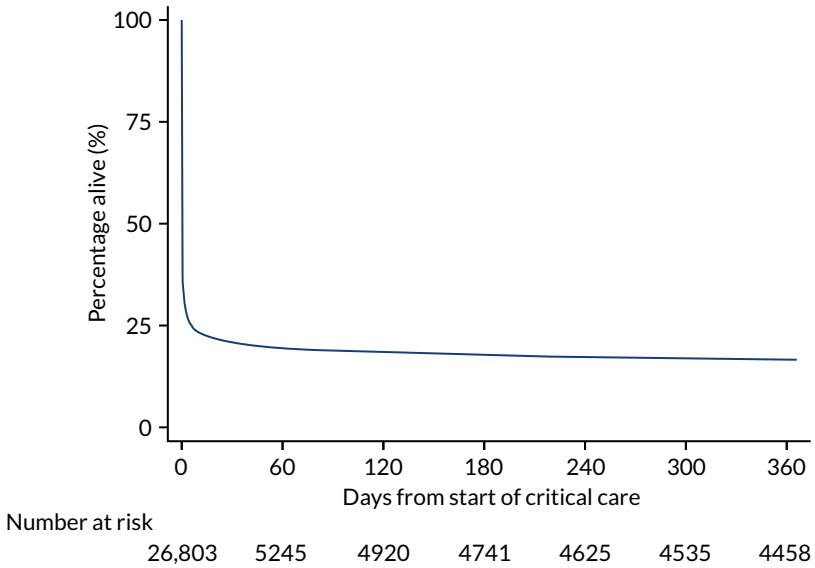

FIGURE 34 Kaplan–Meier survival estimate to 365 days following start cardiac arrest.

Modelling of critical care resource use following an in-hospital cardiac arrest

Methods

Methods common to all objectives and analyses were describe in *Chapter 3*. Details relating to the study cohorts and outcomes can be found in the same chapter.

Study cohort

The cohort for these models was the NCAA critical care admission cohort (see *Chapter 3*) of patients surviving the initial arrest with linked records in the CMP.

Inclusion and exclusion criteria

For development of the models, data were extracted from the NCAA critical care admission cohort for the full time period (1 April 2011 to 31 March 2015).

Outcomes and covariates

The outcome for modelling was defined as the total length of stay (in days and fractions of days) in a critical care unit (obtained through data linkage with the CMP) during the same hospital stay for the first team visit. Individuals with multiple hospital episodes were included multiple times in the analysis. Critical care unit length of stay was calculated using the time in minutes between the date and time of admission to critical care and the date and time of death or discharge from critical care and converted to days for analysis. For descriptive purposes, the critical care cost for each patient was calculated by assigning each critical care unit stay to a Healthcare Resource Group based on organ support data and costing each bed-day of care according to the national tariff for 2013.[93,94]

Covariates included in the model for critical care unit length of stay comprised all predictors from the original prediction models for ROSC > 20 minutes and hospital survival (see *Appendix 1*, *Table 40*) plus the following baseline covariates from CMP: severe conditions in medical history (any severe condition or specific conditions of severe cardiovascular disease, end-stage renal failure, severe liver disease or severe respiratory disease), source of admission to critical care (via the emergency department, theatre or recovery, ward, clinic or home), diagnostic category (based on the body system of the primary reason for admission to critical care), ICNARC Physiology Score, number of advanced organ supports received (0–4 from advanced respiratory support, advanced cardiovascular support, renal support and neurological support) and type of organ failures (cardiovascular, respiratory, renal, haematological, metabolic acidosis).

Handling of missing data

Although the number of missing data for physiology was moderate, from 1.6% for highest respiratory rate to 7.5% for highest urea, we used multiple imputation to address the potential bias and loss of precision that could result from a complete-case analysis (see *Chapter 3*). Patients missing all physiology were excluded.

Statistical modelling

Critical care unit length of stay had a highly right-skewed distribution (see *Report Supplementary Material 1*, Figure S5) with most patients staying < 7 days. To model this, a generalised linear model with a gamma distribution and a log-link function was selected on grounds that it could describe the distribution of the data.[27] As the distribution of length of stay and the association between predictors and length of stay differs between hospital survivors and non-survivors (see *Report Supplementary Material 1*, Figure S6), analyses were stratified by these two groups. Non-linearity of covariate effects was investigated by using restricted cubic splines and all first order interactions were explored. We used predictive margins to reflect the overall predicted mean critical care unit length of stay and the predicted means for each determinant accounting for the other characteristics in the model. Predicted values were generated with continuous covariates centred and categorical covariates held at the reference category.

Results

There were 64,871 validated team visits between 1 April 2011 and 31 March 2015. After removing cardiac arrest non-survivors, second and subsequent team visits to the same patient, patients < 16 years and arrests in critical care, 18,410 first team visits (patients) were considered for linkage. A total of 4864 were successfully linked with CMP, which corresponded to 5594 unique critical care unit admissions, including transfers and re-admissions. The outcome of total critical care unit length of stay during the same hospital stay was then calculated for each patient. Only the information from the first critical care unit admission was then kept in the analysis. After excluding 23 patients missing all physiology, a total of 4841 patients were entered into the analysis.

Characteristics and outcomes of survivors of in-hospital cardiac arrest admitted to critical care are summarised in *Table 35*, split by hospital survivors and non-survivors. A total of 1839 (38.0%) patients admitted to critical care following in-hospital cardiac arrest were alive at hospital discharge and 3002 (62.0%) were hospital non-survivors. The mean total critical care unit length of stay was 8 days for survivors and 4 days for non-survivors, with mean costs of approximately £13,000 and £7000, respectively.

Determinants of total critical care unit length of stay following in-hospital cardiac arrest in hospital survivors

Results of the multivariable analysis for total critical care unit length of stay following an in-hospital cardiac arrest in hospital survivors are presented in *Appendix 3*, *Table 53*. The following factors were significant in determining total critical care unit length of stay: location of arrest, presenting rhythm, reason for admission to critical care by body system, number of advanced organs supports received and severe conditions in the medical history. In addition, severity of illness, measured by the ICNARC Physiology Score, and age showed significantly non-linear associations with the total critical care unit length of stay. The interaction between severe conditions in the medical history and severity of illness also significantly influenced the total critical care unit length of stay following an in-hospital cardiac arrest.

The overall predicted mean for hospital survivors was 8.5 days (95% CI 8.0 to 9.2 days), being very similar to the observed mean. Taking into account the rest of the patients' characteristics in the model, the mean for a patient that had an arrest on the ward would be 10 days but if they were located in theatre the mean is 6 days (*Table 36*). Patients presenting following pulseless electrical activity or bradycardia are likely to have a longer critical care unit length of stay than those who present following shockable rhythms or asystole. *Figures 35* and *36* show the predicted values for age and for the ICNARC Physiology Score according to presence or absence of severe conditions in the medical history. We observe that for older patients the length of stay is shorter, and although the length of stay increases for sicker patients, the association is less strong for patients with severe conditions in their medical history.

Determinants of total critical care unit length of stay following an in-hospital cardiac arrest in hospital non-survivors

For non-survivors, only the following variables significantly influenced the total critical care unit length of stay following in-hospital cardiac arrest: number of advanced organ supports received, age and the ICNARC physiology score, both modelled using restricted cubic splines. The interaction between the ICNARC physiology score and number of advanced organ supports was significant, meaning that the effect of illness severity varied across the number of organs supported (see *Appendix 3*, *Table 54*).

The overall predicted mean total critical care unit length of stay for non-survivors was 4.5 days (95% CI 4.0 to 4.7 days). The association with age was similar to that for survivors but with a lower resource use (see *Figure 35*). Predicted total critical care unit length of stay decreased for sicker patients but decreased differently according to the number of organs supported (*Figure 37*).

TABLE 35 Characteristics of patients included in the models for critical care resource use

Characteristics	Hospital survivors	Hospital non-survivors
Number of patients (%)	1839 (38.0)	3002 (62.0)
Age (years), mean (SD)	64 (16)	69 (14)
Reason for attendance, *n* (%)		
Medical	1293 (70.3)	2451 (81.6)
Trauma	56 (3.0)	99 (3.3)
Elective/scheduled surgery	227 (12.3)	168 (5.6)
Emergency/urgent surgery	145 (7.9)	231 (7.7)
Obstetric	37 (2.0)	6 (0.2)
Outpatient	65 (3.5)	36 (1.2)
Staff/visitor	15 (0.8)	11 (0.4)
Prior hospital LOS, days, *n* (%)		
0	946 (51.4)	1073 (35.7)
1	331 (18.0)	528 (17.6)
2–7	361 (19.6)	925 (30.8)
8–30	179 (9.7)	434 (14.5)
> 30	22 (1.2)	42 (1.4)
Location of arrest, *n* (%)		
Ward or obstetrics area	773 (42)	1676 (55.8)
Emergency department	307 (16.7)	473 (15.8)
Emergency admissions unit	167 (9.1)	303 (10.1)
Theatre and recovery	170 (9.2)	75 (2.5)
Cardiac catheter laboratory	122 (6.6)	108 (3.6)
Imaging department	70 (3.8)	73 (2.4)
Specialist treatment area	49 (2.7)	63 (2.1)
Coronary care unit	126 (6.9)	199 (6.6)
Other intermediate care area	5 (0.3)	5 (0.2)
Clinic	24 (1.3)	9 (0.3)
Non-clinical area	24 (1.3)	17 (0.6)
Status at team arrival, *n* (%)		
Deteriorating, not yet arrested	129 (7.0)	217 (7.2)
Resuscitation ongoing	1488 (80.9)	2643 (88.1)
ROSC achieved	222 (12.1)	141 (4.7)
Presenting rhythm, *n* (%)		
Shockable: VF	383 (20.8)	318 (10.6)
Shockable: VT	131 (7.1)	113 (3.8)
Shockable: unknown rhythm	11 (0.6)	13 (0.4)
Non-shockable: asystole	178 (9.7)	422 (14.1)

continued

TABLE 35 Characteristics of patients included in the models for critical care resource use (*continued*)

Characteristics	Hospital survivors	Hospital non-survivors
Non-shockable: PEA	907 (49.3)	1875 (62.5)
Non-shockable: Bradycardia	13 (0.7)	13 (0.4)
Non-shockable: unknown rhythm	49 (2.7)	62 (2.1)
Unknown/never determined	167 (9.1)	182 (6.1)
Monitored area non-shockable arrest	263 (14.3)	230 (7.7)
Severe conditions in the past medical history, *n* (%)		
Severe cardiovascular disease	44 (2.4)	100 (3.3)
End-stage renal failure	104 (5.7)	122 (4.1)
Severe liver disease	38 (2.1)	111 (3.7)
Severe respiratory disease	37 (2.0)	127 (4.2)
Any severe condition in the past medical history	314 (17.1)	659 (22.0)
Reason for admission to critical care by body system, *n* (%)		
Cardiovascular	1040 (56.6)	1638 (54.6)
Respiratory	347 (18.9)	584 (19.5)
Gastrointestinal	120 (6.5)	254 (8.5)
Neurological (including eyes)	171 (9.3)	313 (10.4)
Genito-urinary	67 (3.6)	72 (2.4)
Endocrine, metabolic, thermoregulation and poisoning	67 (3.6)	90 (3.0)
Haematological/Immunological	2 (0.1)	19 (0.6)
Musculoskeletal	18 (1.0)	22 (0.7)
Dermatological	7 (0.4)	7 (0.2)
ICNARC physiology score, mean (SD)	22 (8)	32 (10)
Advanced organ supports received, *n* (%)		
Advanced respiratory support	1425 (77.5)	2777 (92.5)
Advanced cardiovascular support	1035 (56.3)	2129 (70.9)
Neurological support	389 (21.2)	961 (32.0)
Renal support	302 (16.4)	621 (20.7)
Number of advanced organ supports received, *n* (%)		
0	247 (13.4)	106 (3.5)
1	516 (28.1)	556 (18.5)
2	655 (35.6)	1218 (40.6)
3	359 (19.5)	964 (32.1)
4	62 (3.4)	151 (5.0)
Total critical care unit length of stay (days), mean (SD)	8 (12)	4 (9)
Total critical care unit length of stay (days), median (IQR)	4 (2–10)	3 (1–6)
Total critical care cost (£), mean (SD)	13,463 (20,309)	6934 (14,743)
Total critical care cost (£), median (IQR)	6291 (2761–16,567)	4142 (1573 to 9664)

LOS, length of stay; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 36 Predicted mean critical care unit length of stay (days) for hospital survivors by characteristics included in the model

	Predicted mean	95% CI
Overall predicted mean	8.5	8.0 to 9.2
Location of arrest		
Ward, obstetrics area, other intermediate care area, clinic or non-clinical area	10.4	9.3 to 11.3
ED or emergency admission unit	7.4	6.6 to 8.3
Theatre and recovery	5.9	4.7 to 7.0
Cardiac catheter lab or CCU	7.2	6.1 to 8.4
Imaging department or specialist treatment area	7.7	5.9 to 9.4
Reason for admission by body system		
Respiratory	11.3	9.7 to 12.8
Cardiovascular	7.5	6.9 to 8.17
Gastrointestinal	10.6	8.2 to 13.0
Neurological (including eyes)	8.5	6.8 to 10.1
Others	7.6	6.1 to 9.1
Number of advanced organs supports		
0	4.2	3.6 to 4.8
1	5.9	5.4 to 6.4
2	8.4	7.9 to 9.0
3	12.0	10.8 to 13.2
4	17.0	14.3 to 18.8
Presenting rhythm		
Shockable	6.9	6.2 to 7.6
Non-shockable	9.6	8.8 to 10.3

CCU, coronary care unit; ED, emergency department

Discussion

Data linkage with HES revealed that comorbidities identified from routine hospital data contribute to predicting outcomes following an in-hospital cardiac arrest. Different comorbidities were important for predicting ROSC > 20 minutes and hospital survival, and some comorbidities were associated with better outcomes rather than worse outcomes (particularly for ROSC > 20 minutes). However, the overall improvement in model performance from adding comorbidities to the existing models was small.

A recent systematic review of prognostic factors identified very few publications evaluating the role of comorbidities.[95] Our findings regarding comorbidities shared many commonalities with the previous work from the AHA *Get With The Guidelines – Resuscitation* registry.[90] The predictors in their full model for hospital survival included prior heart failure (odds ratio 0.94 compared with 0.87 for congestive cardiac failure in our model), hepatic insufficiency (odds ratio 0.52 compared with 0.72 for liver disease in our model) and metastatic or haematological malignancy (odds ratio 0.47 compared with 0.45 for metastatic solid tumour and 0.73 for any malignancy in our model). Additional comorbidity predictors in the *Get With The Guidelines – Resuscitation* model were hypotension (odds ratio 0.64), renal insufficiency (odds ratio 0.80) and diabetes mellitus (odds ratio 1.14), whereas our model included

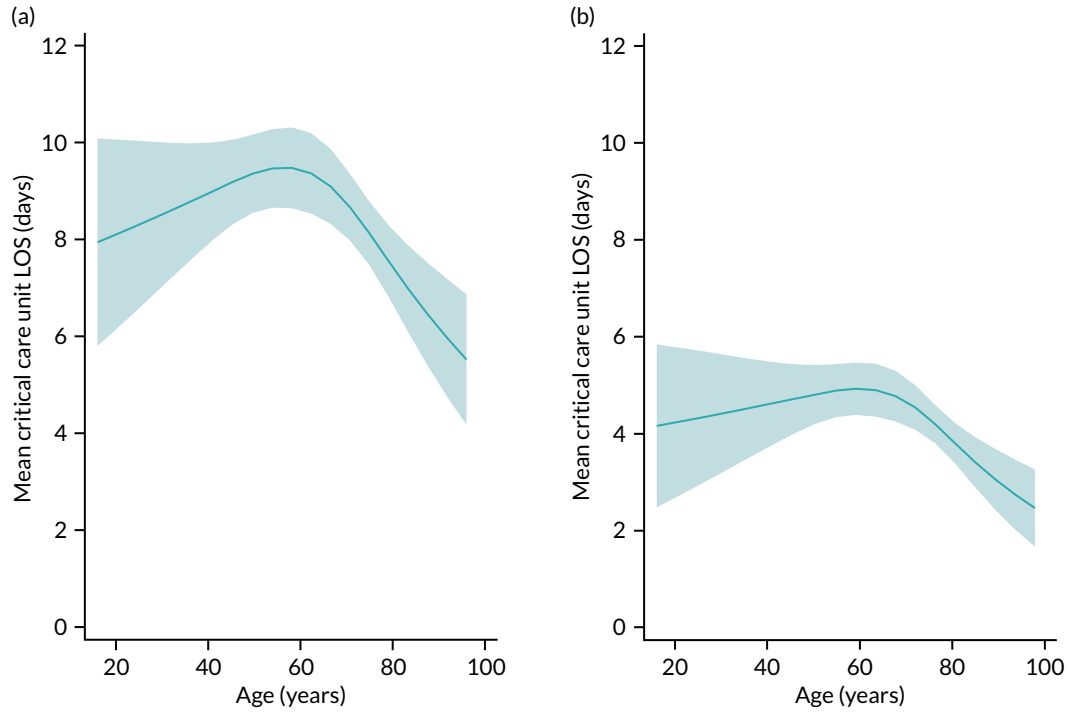

FIGURE 35 Predicted mean critical care unit length of stay for (a) hospital survivors and (b) hospital non-survivors by age. LOS, length of stay.

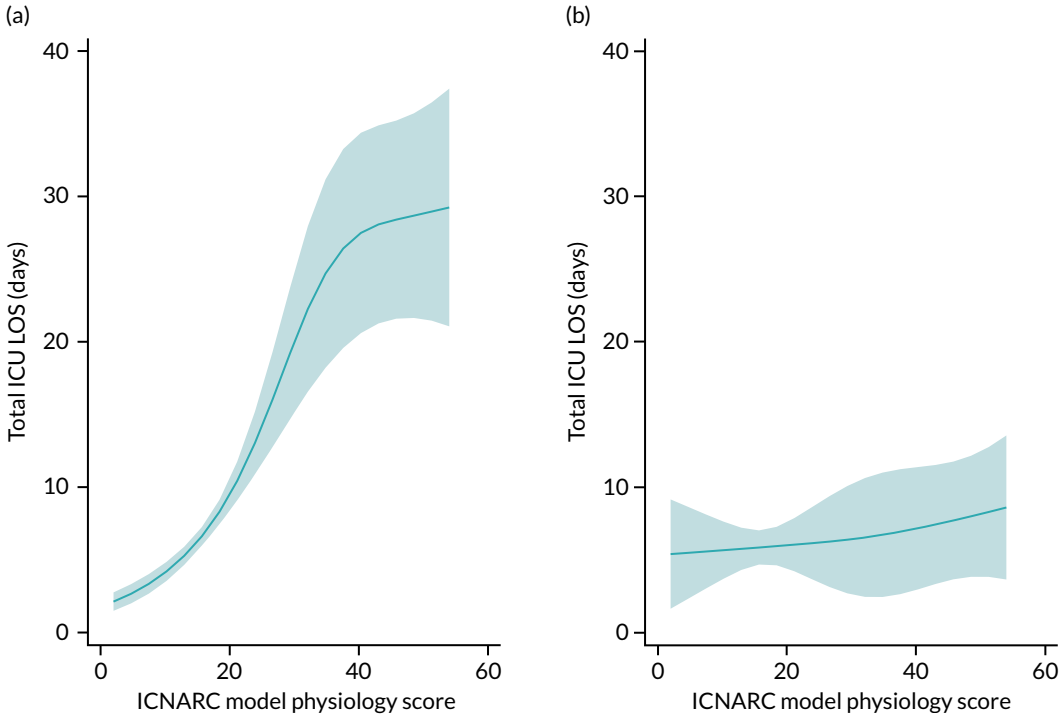

FIGURE 36 Predicted mean critical care unit length of stay for hospital survivors by severity of illness and severe conditions in the past medical history. (a) No previous comorbidities; (b) previous comorbidities. ICU, intensive care unit; LOS, length of stay.

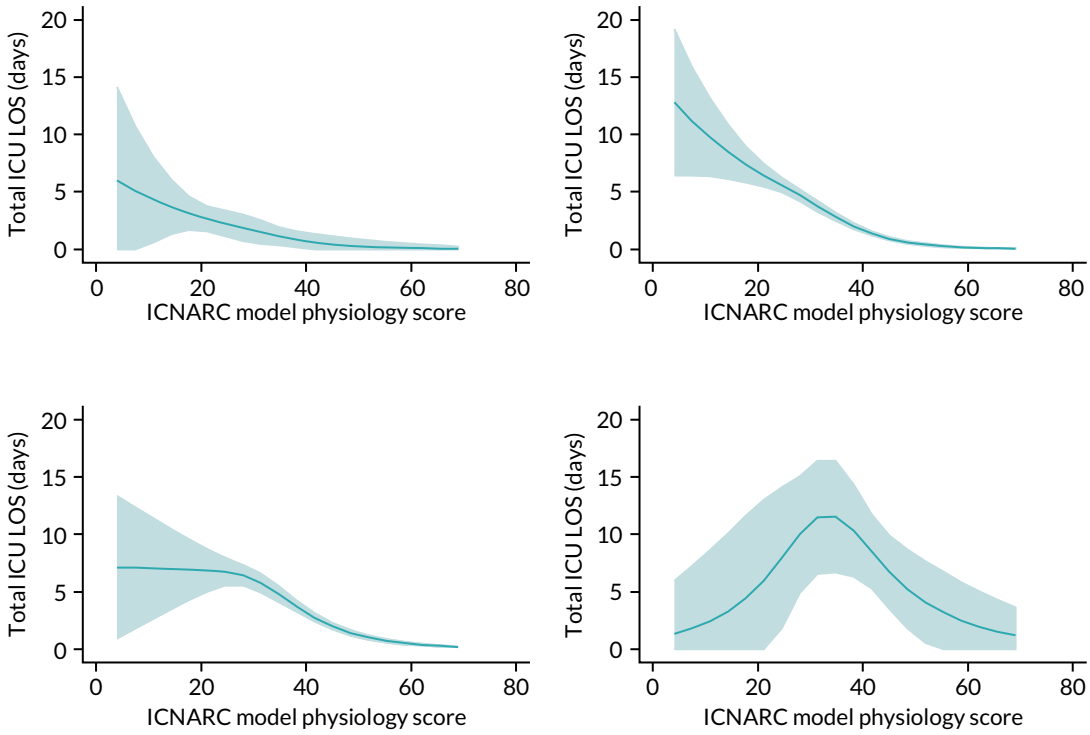

FIGURE 37 Predicted mean critical care unit length of stay for hospital survivors by severity of illness and number of advanced organ supports.

peripheral vascular disease (odds ratio 0.82) and hemiplegia or paraplegia (odds ratio 0.64). The finding that diabetes was predictive of improved survival is consistent with our model for ROSC > 20 minutes (odds ratio 1.15), and the coefficients for diabetes were positive in our model for hospital survival although it was not retained in the final model. The reason for the association between diabetes mellitus and a better outcome after an in-hospital cardiac arrest is not clear and contrasts with the findings following out-of-hospital cardiac arrest,[96] acute myocardial infarction[97] and another study of in-hospital cardiac arrest,[98] all of which showed diabetes mellitus to be associated with worse outcomes. In contrast, chronic renal disease was also predictive of improved ROSC > 20 minutes in our model (odds ratio 1.15) but was predictive of worse hospital survival in the *Get With The Guidelines – Resuscitation* model (odds ratio 0.80) and in other published models.[95] The precise reason for these differences between the NCAA and *Get With The Guidelines – Resuscitation* models are uncertain. The *Get With The Guidelines – Resuscitation* registry includes all in-hospital cardiac arrests including those occurring in critical care and perioperative settings, whereas NCAA includes only cardiac arrests attended by the hospital resuscitation team. In many UK hospitals cardiac arrests in closely monitored areas such as an intensive care unit are managed by the patient's own clinical team, and the hospital resuscitation team is not called. The patient population to derive the *Get With The Guidelines – Resuscitation* model is therefore different in terms of the patient population from which it is derived.

Data linkage with death registrations allowed us to extend these models to predict 1-year survival following an in-hospital cardiac arrest. Functional conditions such as severe liver disease and chronic renal disease, as well as dementia, were important determinants for 1-year survival. Age and pre-existing conditions, such as malignancy and metastatic solid tumour, had a greater impact on longer-term survival than on hospital survival.

A systematic review[99] of 1-year survival found huge variation in survival rates following an in-hospital cardiac arrest (95% prediction interval for a future study 5.6% to 28.8%, $I^2 = 100\%$). The review, however, pooled studies with very different inclusion criteria, for example those reporting on hospital survivors only and those on all in-hospital cardiac arrests, as well as studies restricted to particular

subpopulations such as patients undergoing cardiac surgery or those in critical care. When restricted to 18 studies in populations of general in-hospital cardiac arrest patients, survival to 1-year post arrest ranged from 3.5% to 25.4%. Our observed survival of 16.6% falls well within this range. On the other hand, the majority of 60-day survivors are still alive 1-year after admission to critical care. This indicates a better long-term prognosis than might be expected by clinicians. To our knowledge, this is the first study to explicitly evaluate predictors of 1-year survival in an in-hospital cardiac arrest cohort. However, a previous study[100] has investigated factors associated with 1-year survival without the need of in-home care, anoxic brain damage or nursing home admission.

Data linkage with the CMP allowed us to identify a set of patient characteristics significantly associated with the use of critical care following in-hospital cardiac arrest for hospital survivors and non-survivors. The following factors were significant in determining total critical care unit length of stay in survivors: age, location of arrest, presenting rhythm, reason for admission to critical care, number of advanced organ supports, severe conditions in the medical history, ICNARC physiology score, and the interaction between severe conditions in the medical history and ICNARC physiology score. For non-survivors, only age- and severity of illness-related variables (number of advanced organ supports and the ICNARC physiology score) significantly predicted the total critical care unit length of stay following an in-hospital cardiac arrest. None of the variables from NCAA had an important effect after adjusting for these CMP factors.

Our interest for this analysis was the identification of important determinants in the use of critical care following an in-hospital cardiac arrest. However, in comparatives studies,[101] a Gamma regression model has provided more accurate estimation of population mean. We therefore believe that our results provide useful insight into prediction models for likely resource use. In the context of prediction, it is important to note that our models for critical care unit length of stay were stratified by hospital survival, an event that would not be known at the point of prediction. Therefore, two predictions should be considered for each patient: the predicted length of stay conditional on survival and the predicted length of stay conditional on death. If a prediction of overall mean length of stay was required, these two predicted means would need to be weighted by predicted survival.

Chapter 11 Conclusions

Summary of findings

We have successfully linked CMP and NCAA with five other data sources, providing enhancements in risk models for these audits in the form of additional predictors and novel outcome measures.

When developing risk models for mortality following admission to adult critical care, predictors and performance were similar for a model based on 30-day mortality compared with the previous model for acute hospital mortality. Using 30-day mortality in place of acute hospital mortality did not reduce heterogeneity among providers. Models for longer-term outcomes reflected the increasing importance of chronic ill health and comorbidities over acute conditions. We have also developed, for the first time, models for predicting new onset chronic illness (ESRD and type 2 diabetes) following critical care. These offer not only the opportunity to benchmark critical care units on a wider panel of patient-centred longer-term outcomes other than mortality, but also the potential to identify patients at increased risk of these outcomes who may benefit from more intensive post-critical care follow-up. By comparison, the National Institute for Health and Care Excellence guideline on assessment and management of chronic kidney disease[102] recommends the use of the Kidney Failure Risk Equation[103] to guide decisions about referral to nephrology from primary care.

Almost half of acute hospital survivors following critical care accrued further acute hospital costs during the subsequent year following discharge. We therefore modelled this with a two-part model, first evaluating predictors of hospital re-admission and second modelling costs conditional on re-admission. The strongest predictors of health-care costs following critical care were prior hospitalisation, prior dependency and severe conditions in the medical history (particularly for younger patients).

We extended an existing model for predicting acute hospital mortality among patients admitted to cardiothoracic critical care units following cardiac surgery by incorporating additional pre- and intra-operative predictors. Although a number of these new predictors were identified as making an important contribution to the model, there was little improvement in overall performance. When the new model was compared with the generic $ICNARC_{H\text{-}2015}$ model currently used for benchmarking in these units, performance was similar. Using a generic model offers other advantages over a model specific to cardiac surgery, as the proportion of pure cardiac surgery admissions to cardiothoracic critical care units varies considerably among units, and we would therefore recommend ongoing use of the generic model.

We extended existing models for predicting ROSC > 20 minutes and hospital survival following an in-hospital cardiac arrest by incorporating additional comorbidities. Improvements to model performance were, however, small, and therefore the current models remain fit for purpose. As with the models for mortality following admission to adult critical care, comorbidities were of greater importance in models for longer-term outcomes following an in-hospital cardiac arrest. Different factors were found to be predictive of the critical care unit length of stay among survivors of an in-hospital cardiac arrest depending on hospital survival status. Among hospital survivors, many factors were predictive, including age, chronic health, arrest characteristics and acute severity of illness. Among hospital non-survivors, only age and acute severity of illness remained significant.

The greatest barrier to maximising the full potential of data linkage in this project was the inordinate amount of time required to obtain and maintain approvals for the use of multiple data sources from multiple data controllers. A consequence of this is that the data included in the modelling are already

5 years old at the point of publication, meaning that the models developed will already be in need of recalibration. Regrettably, this observation is neither new nor in any way unique to this project,[104–108] although we may be unique in the sheer number of different issues and delays faced in a single project. The COVID-19 pandemic has demonstrated that these barriers can be removed, or at least greatly reduced, when there is sufficient political will and public health imperative to do so. This has resulted in numerous data linkage projects that have helped to move forward our understanding of this novel threat.[109–113] An open letter to the UK Information Commissioner, Chief Medical Officers and data providers with 374 signatories (representing researchers involved in health and administrative data research) identified four ways in which administrative data research should not return to 'business as usual' following the pandemic:

- reduce costs of administrative data access to researchers through core government funding
- simplify approval processes for de-identified data access, in a way that is proportionate to the risk of re-identification
- reduce data release delays through increased capacity and more specialised data providers
- enable more efficient data use through remote systems that comply with data protection requirements.[114]

To help address these issues, Health Data Research UK is championing the use of trusted research environments (also known as data safe havens) to enable secure and trustworthy access to health data for research.[115] Health Data Research UK promote the 'five safes' model (safe people, safe projects, safe settings, safe data, safe outputs) to ensure a responsible approach to data security and privacy.

If these issues can successfully be addressed, then data linkage with administrative and routine clinical data sources continues to have the potential to benefit national clinical audits, as demonstrated in this project, but also in observational comparative effectiveness research[116] and data-enabled trials.[117]

Implications for health care

These results have potentially important implications for future benchmarking of critical care units through the CMP and NCAA. Having demonstrated the feasibility of these linkages, ICNARC should investigate cost-effective approaches to routinely link data to support ongoing reporting from the audits. Although there are potential practical benefits for benchmarking based on 30-day mortality rather than hospital mortality, for example the lack of missing data from patients with a long duration of hospital stay, the implications of these for timely reporting are likely to be outweighed by the time and cost associated with the data linkage process. Although comorbidities were found to improve predictions, they had a greater influence on longer-term than shorter-term outcomes. Given the time-lags involved in linking data, we propose that initial quarterly reporting for the audits continue to use directly collected data and that data linkage is undertaken annually to provide enhanced annual reporting including 1-year outcomes. Results of the models presented in this report should be reviewed to identify any key additional predictors to incorporate into direct data collection for the audits.

At the bedside, the new models developed in this report (particularly those relating to longer-term outcomes) may assist in providing objective estimates of potential outcomes to patients and their families. A better understanding of factors predictive of worse longer-term outcomes may help to identify those patients requiring greater support in their recovery following critical illness.

Recommendations for research

To maximise potential for use of linked data for research, it is essential that the research community and data providers come together to streamline approaches to data access. This necessity underpins the following recommendations with regard to further research using linked health-care data:

1. The availability of models developed in this project to predict patients with an increased risk of chronic health outcomes and greater subsequent health-care costs following an episode of critical illness provides the opportunity to target interventions earlier in the recovery phase for those at greater risk. We recommend multidisciplinary research to develop and test care pathways for recovery following critical illness targeted at those with the greatest need.
2. Data linkage with UKRR and NDA has confirmed the feasibility of using linked data to model longer-term outcomes following critical illness. We recommend that further relevant data sources should be explored, for example stroke.
3. Data linkage with HES admitted patient care records allowed us to consider the hospitalisation costs following critical illness. To better understand the resource use and costs following critical illness, we recommend widening data linkage to include primary care, outpatient and emergency department data.

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Investigators

Professor David A Harrison (Chief Investigator), Ms Paloma Ferrando-Vivas, Dr Fergus J Caskey, Dr Steve Harris, Dr Naomi Holman, Mr David Jenkins, Dr Stephen Webb, Professor Jerry P Nolan, Dr Jasmeet Soar and Professor Kathryn M Rowan.

Study steering committee

Professor David Cromwell (Independent Chair), Professor Gary Collins (Independent), Dr Gillian Fargher (Independent PPI), Ms Paloma Ferrando-Vivas (Investigator), Professor David A Harrison (Chief Investigator), Dr Nazir Lone (Independent), Mr Richard Mills (Independent), Mrs Cathy Taylor (Independent PPI) and Mr Ian Taylor (Independent PPI).

Contributions of authors

Paloma Ferrando-Vivas (https://orcid.org/0000-0002-2163-645X) (Statistician/Risk Modeller) conceived the study; contributed to the design of the study and the acquisition, analysis and interpretation of the data; and drafted and critically reviewed the manuscript.

Manu Shankar-Hari (https://orcid.org/0000-0002-5338-2538) (Professor in Critical Care Medicine and NIHR Clinician Scientist) contributed to the design of the study and the interpretation of the data, and critically reviewed the manuscript.

Karen Thomas (https://orcid.org/0000-0001-7548-4466) (Senior Statistician) contributed to the interpretation of the data and critically reviewed the manuscript.

James C Doidge (https://orcid.org/0000-0002-3674-3100) (Senior Statistician) contributed to the interpretation of the data and critically reviewed the manuscript.

Fergus J Caskey (https://orcid.org/0000-0002-5199-3925) (Consultant Senior Lecturer) conceived the study, contributed to the design of the study and the acquisition and interpretation of the data, and critically reviewed the manuscript.

Lui Forni (https://orcid.org/0000-0002-0617-5309) (Professor and Consultant Intensivist/Nephrologist) contributed to the design of the study and the interpretation of data and critically reviewed the manuscript.

Steve Harris (https://orcid.org/0000-0002-4982-1374) (Consultant in Critical Care & Perioperative Medicine and Honorary Associate Professor) conceived the study, contributed to the design of the study and the interpretation of the data, and critically reviewed the manuscript.

Marlies Ostermann (https://orcid.org/0000-0001-9500-9080) (Consultant in Nephrology and Critical Care) contributed to the design of the study and the interpretation of data and critically reviewed the manuscript.

Ivan Gornik (https://orcid.org/0000-0001-6146-1327) (Assistant Professor of Medicine) contributed to the design of the study and the interpretation of data and critically reviewed the manuscript.

Naomi Holman (https://orcid.org/0000-0002-7432-5786) (Research Assistant) conceived the study, contributed to the design of the study and the acquisition and interpretation of the data, and critically reviewed the manuscript.

Nazir Lone (https://orcid.org/0000-0003-2707-2779) (Senior Clinical Lecturer in Critical Care) contributed to the design of the study and the interpretation of data, and critically reviewed the manuscript.

Bob Young (https://orcid.org/0000-0002-1245-0100) (Clinical Lead, National Diabetes Audit) contributed to the design of the study and the interpretation of data, and critically reviewed the manuscript.

David Jenkins (https://orcid.org/0000-0003-3545-7580) (Consultant Cardiothoracic Surgeon) contributed to the design of the study and the interpretation of data, and critically reviewed the manuscript.

Stephen Webb (https://orcid.org/0000-0002-2413-7883) (Consultant in Intensive Care) conceived the study, contributed to the design of the study and the interpretation of the data, and critically reviewed the manuscript.

Jerry P Nolan (https://orcid.org/0000-0003-3141-3812) (Professor of Resuscitation Medicine and Consultant in Anaesthesia and Intensive Care Medicine) conceived the study, contributed to the design of the study and the interpretation of the data, and critically reviewed the manuscript.

Jasmeet Soar (https://orcid.org/0000-0001-5970-6073) (Consultant in Anaesthetics & Intensive Care Medicine) conceived the study, contributed to the design of the study and the interpretation of the data, and critically reviewed the manuscript.

Kathryn M Rowan (https://orcid.org/0000-0001-8217-5602) (Director and Honorary Professor) conceived the study, contributed to the design of the study and the interpretation of the data, and critically reviewed the manuscript.

David A Harrison (https://orcid.org/0000-0002-9002-9098) (Head Statistician and Honorary Professor) conceived and led the study; contributed to the design of the study and the acquisition, analysis and interpretation of the data; and drafted and critically reviewed the manuscript.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data or study materials may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data are vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 *Tables 37–40*: predictor definitions

TABLE 37 Definitions of organ dysfunction for Sepsis-3 as applied in the CMP

Organ dysfunction (points)	SOFA	Definition used in CMP
Cardiovascular		
1	MAP < 70 mmHg	MAP < 70 mmHg (calculated from lowest systolic blood pressure and paired diastolic blood pressure)
≥ 2	Administration of vasopressors	Advanced cardiovascular support (CCMDS)
Respiratory		
1	PaO_2/FiO_2 < 400 mmHg	PaO_2/FiO_2 < 400 mmHg (based on arterial blood gas with lowest PaO_2)
≥ 2	PaO_2/FiO_2 < 300 mmHg	PaO_2/FiO_2 < 300 mmHg
Renal		
1	Serum creatinine 1.2–1.9 mg dl^{-1} (110–170 µmol l^{-1})	Serum creatinine 1.2–1.9 mg dl^{-1} (110–170 µmol l^{-1})
≥ 2	Serum creatinine ≥ 2 mg dl^{-1} (≥ 171 µmol l^{-1}) or urine output < 500 ml	Serum creatinine ≥ 2 mg dl^{-1} (≥ 171 µmol l^{-1}) or urine output < 500 ml or renal support (CCMDS)
Haematological		
1	Platelet count < 150×10^9 l^{-1}	Platelet count < 150×10^9 l^{-1}
≥ 2	Platelet count < 100×10^9 l^{-1}	Platelet count < 100×10^9 l^{-1}
Neurological		
1	GCS 13–14	GCS 13–14
≥ 2	GCS ≤ 12	GCS ≤ 12 or sedated for entire of first 24 hours
Hepatic		
1	Serum bilirubin 1.2–1.9 mg dl^{-1} (20–32 µmol l^{-1})	Unable to assess
≥ 2	Serum bilirubin ≥ 2 mg dl^{-1} (≥ 33 µmol l^{-1})	Liver support (CCMDS)

CCMDS, critical care minimum data set; MAP, mean arterial pressure; SOFA, sequential organ failure assessment.

TABLE 38 Candidate predictors of risk models for adult general critical care: 30-day, 90-day and 1-year mortality, ESRD, diabetes and cost of subsequent hospitalisations

Candidate predictor	Definition	Categories	Risk model
Highest heart rate	Highest heart rate during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Lowest systolic blood pressure	Lowest systolic blood pressure during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Highest temperature	Highest central temperature during the first 24 hours following admission to the critical care unit. (If no central temperatures recorded, highest non-central temperature + 0.5 °C is substituted)	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Lowest respiratory rate	Lowest respiratory rate (either ventilated or non-ventilated) during the first 24 hours following admission to the critical care unit.	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
PaO_2/FiO_2	Ratio of PaO_2 to FiO_2 from the arterial blood gas with the lowest PaO_2 from blood sampled during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Lowest arterial pH	Lowest arterial pH from blood sampled during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
$PaCO_2$	$PaCO_2$ from the arterial blood gas with the lowest pH	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Highest blood lactate	Highest blood lactate during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD

TABLE 38 Candidate predictors of risk models for adult general critical care: 30-day, 90-day and 1-year mortality, ESRD, diabetes and cost of subsequent hospitalisations (*continued*)

Candidate predictor	Definition	Categories	Risk model
Urine output	Total urine output during the first 24 hours following admission to the critical care unit. (For admissions with a critical care unit length of stay < 24 hours, the total urine output over the entire stay is recorded and scaled to represent a 24-hour equivalent)	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Highest urea	Highest serum urea during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Highest creatinine	Highest serum creatinine during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Highest sodium	Highest serum sodium during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Lowest glucose	Lowest blood glucose during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Lowest haemoglobin	Lowest haemoglobin during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD Diabetes
Lowest white blood cell count	Lowest white blood cell count during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD Diabetes

continued

TABLE 38 Candidate predictors of risk models for adult general critical care: 30-day, 90-day and 1-year mortality, ESRD, diabetes and cost of subsequent hospitalisations (*continued*)

Candidate predictor	Definition	Categories	Risk model
Neutrophil count	Neutrophil count associated with the lowest white blood cell count during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Lowest platelet count	Lowest platelet count during the first 24 hours following admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Sedated/paralysed/GCS	Lowest total GCS during the first 24 hours following admission to the critical care unit. GCS must be assessed when the patient is determined to be free of the effects of sedation. (Separate categories included for patients either sedated or paralysed and sedated for the entire of the first 24 hours following admission)	15; 14; 7–13; 6; 5; 4; 3; sedated; paralysed and sedated	30-day mortality 90-day mortality 1-year mortality ESRD
Age	The age of the patient in whole years at admission to the critical care unit	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD Diabetes
Sex	The genotypical sex of the patient	Female; male	30-day mortality 90-day mortality 1-year mortality ESRD Diabetes
Body mass index	Calculated from the weight (either measured or estimated) and height (either measured or estimated) of the patient as weight in kilograms divided by height in metres squared	Continuous	30-day mortality 90-day mortality 1-year mortality ESRD
Deprivation	Quintiles of deprivation, assigned from the patient's usual residential postcode according to the Index of Multiple Deprivation 2010 for England, Welsh Index of Multiple Deprivation 2008 or Northern Ireland Multiple Deprivation Measure 2010	Quintile 1 (least deprived), 2, 3, 4 or 5 (most deprived)	30-day mortality 90-day mortality 1-year mortality ESRD Diabetes Resource use

TABLE 38 Candidate predictors of risk models for adult general critical care: 30-day, 90-day and 1-year mortality, ESRD, diabetes and cost of subsequent hospitalisations (*continued*)

Candidate predictor	Definition	Categories	Risk model
Severe conditions in the past medical history	Defined according to APACHE II.[9] Must have been evident in the 6 months prior to admission to the critical care unit and documented prior to or at admission to the unit	Seven binary variables (see *Chapter 3*)	30-day mortality 90-day mortality 1-year mortality ESRD (all conditions except ESRD) Diabetes (severe liver disease, metastatic disease, immunocompromise) Resource use
Dependency prior to admission	Dependency prior to admission to acute hospital, assessed as the best description for the dependency of the patient in the 2 weeks prior to admission to acute hospital and prior to the onset of the acute illness based on the level of assistance required with daily activities. (Daily activities include bathing, dressing, going to the toilet, moving in/out of bed/chair, continence and eating)	Able to live without assistance in daily activities, minor assistance with some daily activities, major assistance with majority of/all daily activities, total assistance with all daily activities	30-day mortality 90-day mortality 1-year mortality ESRD Diabetes Resource use
CPR prior to admission	CPR (internal or external cardiac massage) received within 24 hours prior to admission to the critical care unit, categorised as either in-hospital CPR (administered by an in-hospital resuscitation team or equivalent) or community CPR (not administered by an in-hospital resuscitation team or equivalent). When a patient received CPR both in the community and in hospital, this is recorded as community CPR	In-hospital CPR, community CPR, no CPR	30-day mortality 90-day mortality 1-year mortality ESRD Resource use
Source of admission/urgency of surgery/planned admission	The location of the patient immediately prior to admission to the critical care unit, combined with the urgency of surgery (for patients admitted direct from theatre) assigned according to the definitions of the National Confidential Enquiry into Patient Outcome and Death,[118] and whether admission to the critical care unit was planned or unplanned [For patients whose location immediately prior to admission was a transient location of clinic, imaging department, recovery (used as a temporary critical care area) or specialist treatment area, their last non-transient location is used]	Emergency department or not in hospital (unplanned admission), emergency department or not in hospital (planned admission), other acute hospital (not critical care); other critical care unit (repatriation), other critical care unit (planned or unplanned transfer), theatre (planned admission following elective or scheduled surgery), theatre (unplanned admission following elective or scheduled surgery), theatre (admission following emergency or urgent surgery), ward or intermediate care area	30-day mortality 90-day mortality 1-year mortality Resource use

continued

TABLE 38 Candidate predictors of risk models for adult general critical care: 30-day, 90-day and 1-year mortality, ESRD, diabetes and cost of subsequent hospitalisations (*continued*)

Candidate predictor	Definition	Categories	Risk model
Primary reason for admission	The primary reason for admission to the critical care unit, coded using the ICNARC coding method[22]	Five-tiered, hierarchical code	30-day mortality 90-day mortality 1-year mortality
Mechanical ventilation	Mechanical ventilation at any time during the first 24 hours following admission to the critical care unit, identified by recording of a ventilated respiratory rate	Yes/no	30-day mortality 90-day mortality 1-year mortality Diabetes Resource use
Ethnicity	Ethnicity of the patient	White, mixed, Asian, black, other, not stated	ESRD Diabetes
Pregnancy	Women identified as either currently pregnant or recently pregnant (within previous 42 days) at the time of admission to the critical care unit	Yes/no	ESRD Diabetes
RCS Charlson comorbidities	Defined by ICD-10 codes (see *Chapter 3*): 1-year look back	Yes/no	1-year mortality ESRD (previous MI, congestive cardiac failure, peripheral vascular disease, liver disease, diabetes and malignancy) Diabetes (previous MI, congestive cardiac failure, peripheral vascular disease, malignancy) Resource use
Chronic kidney disease	Defined by ICD-10 codes (see *Chapter 3*) excluding ESRD codes (I120, I129, N186, Z49, Z940, Z992): 5-year look back	Yes/no	ESRD
AKI	Defined by ICD-10 codes (N171, N172, N19): 5-year look back	Yes/no	ESRD
Surgical status	Surgical admissions were defined as those admitted directly to the critical care unit from theatre and recovery in the same hospital. The urgency of surgery was classified as either elective/scheduled or emergency/ urgent using the classification of the National Confidential Enquiry into Patient Outcome and Death	Elective surgery, emergency surgery, non-surgical	ESRD Diabetes
Lengths of stay	Total length of stay in days in critical care, acute hospital prior to critical care, acute hospital total, acute hospital following discharge from critical care	Continuous	ESRD Diabetes Resource use (total critical care length of stay)

TABLE 38 Candidate predictors of risk models for adult general critical care: 30-day, 90-day and 1-year mortality, ESRD, diabetes and cost of subsequent hospitalisations (*continued*)

Candidate predictor	Definition	Categories	Risk model
Sepsis	Defined based on primary reason for admission and physiology recorded during the first 24 hours of critical care (see *Chapter 3*)	Yes/no	ESRD Diabetes
Pancreatic surgery	Admissions following pancreatic surgery were identified if the following conditions were recorded as a surgical primary or secondary reason for admission to the critical care unit: traumatic pancreatitis or traumatic damage to pancreas, instrumental damage to pancreatic duct, pancreatic haemorrhage, pancreatic abscess or infected pseudocyst, infective pancreatitis, acute pancreatitis, chronic pancreatitis, not alcohol induced, alcohol-induced chronic pancreatitis, cytomegaloviral pancreatitis, mumps pancreatitis, pancreas or kidney/pancreas allograft, pancreatic fistula, pancreatic or pancreato-duodenal tumour, trauma-related pancreatic fistula, non-trauma-related pancreatic fistula and pancreatic pseudocyst	Yes/no	Diabetes
Acute myocardial infarction	Admissions following acute MI were identified if acute MI or coronary artery bypass graft for acute MI was recorded as the primary reason for admission	Yes/no	Diabetes
Stroke	Admissions following acute stroke were identified if thrombo-occlusive disease of brain was recorded as the primary reason for admission	Yes/no	Diabetes
Trauma	Admissions following trauma were identified if trauma or traumatic perforation or rupture were recorded at process level as a primary or secondary reason for admission	Yes/no	Diabetes
ICNARC model physiology score	ICNARC illness severity score	Continuous	Resource use
Previous hospitalisation	Hospitalisation before index hospitalisation (obtained through data linkage with the HES)	Yes/no	Resource use

TABLE 39 Candidate predictors of risk models for acute hospital mortality among admissions to cardiothoracic critical care units

Predictor	Approach to modelling
Existing predictors from previous model	
Age (years)	Continuous: RCS (37, 63, 74, 83)
Dependency prior to admission	Categorical (no assistance, some assistance, total assistance)
Lowest systolic blood pressure (mmHg)	Continuous: RCS (67, 85, 95, 112)
Lowest arterial pH	Continuous: RCS (7.16, 7.29, 7.33, 7.41)
Highest blood lactate (mmol l^{-1})	Continuous: linear
Highest creatinine (μmol l^{-1})	Continuous: RCS (51, 80, 106, 247)
Lowest white blood cell count (× 10^9 l^{-1})	Continuous: RCS (5.8, 9.2, 11.8, 17.8)
Lowest platelet count (× 10^9 l^{-1})	Continuous: RCS (73, 134, 183, 337)
Glasgow coma scale	Categorical (15, 9–14, 3–8, sedated)
Candidate predictors from NACSA	
Angina status pre surgery	Categorical (no angina, no limitation of physical activity, slight limitation of ordinary activity, marked limitation of ordinary physical activity, symptoms at rest or minimal activity)
Dyspnoea status pre surgery	Categorical (no limitation of physical activity, slight limitation of ordinary physical activity, marked limitation of ordinary physical activity, symptoms at rest or minimal activity)
Number of previous MIs	Continuous
Interval between surgery and last MI	Categorical (no previous MI, MI < 6 hours, MI 6–24 hours, MI 1–30 days, MI 31–90 days, MI > 90 days)
Left ventricular ejection fraction	Categorical (good, LVEF > 50%; fair, LVEF 30–50%; poor, LVEF < 30%)
Previous PCI	Categorical (no previous PCI; PCI < 24 hours before surgery, PCI > 24 hours before surgery, same admission, PCI > 24 hours before surgery, previous admission)
Diabetes management	Categorical (no diabetes, diet, oral therapy, insulin)
Cigarette smoking history	Categorical (never smoked, ex-smoker, current smoker)
History of hypertension	Categorical (no hypertension, treated or BP > 140/90 on more than one occasion prior to admission, unknown)
Actual creatinine at time of surgery	Continuous
Renal function/dialysis	Categorical (none; dialysis for acute renal failure: onset within 6 weeks of cardiac surgery; dialysis for chronic renal failure: onset > 6 weeks prior to cardiac surgery; no dialysis but pre-operative acute renal failure (anuria or oliguria < 10 ml/hour)
History of pulmonary disease	Categorical (no chronic pulmonary disease, COAD/emphysema, asthma)
History of neurological dysfunction	Binary (yes, no)
Extracardiac arteriopathy	Binary (yes, no)

TABLE 39 Candidate predictors of risk models for acute hospital mortality among admissions to cardiothoracic critical care units (*continued*)

Predictor	Approach to modelling
Pre-operative heart rhythm	Categorical (Sinus rhythm; Atrial fibrillation/flutter; Complete heart block/pacing; Ventricular fibrillation or ventricular tachycardia; Other abnormal rhythm)
PA systolic	Continuous (systolic pulmonary artery pressure in mm Hg recorded from echocardiographic, catheterisation data or Swan-Ganz catheter)
Intravenous nitrates or any heparin	Binary (yes, no)
Ventilated (Pre-Operation)	Binary (yes, no)
Cardiogenic shock (Pre-Operation)	Binary (yes, no)
Operative urgency	Categorical (elective; urgent; emergency; salvage)
Intravenous inotropes prior to anaesthesia	Binary (yes, no)
CABG	Binary (yes, no)
Valve procedure	Binary (yes, no)
Major aortic procedure	Binary (yes, no)
Other cardiac procedures	Binary (yes, no)
Total number of distal coronary anastomoses	Continuous
Number of valves replaced/repaired	Continuous
Aortic valve procedure	Categorical (replacement, repair, repair with ring, repair without ring, isolated commissurotomy, excision only; inspection)
Mitral valve procedure	Categorical (replacement, repair, repair with ring, repair without ring, isolated commissurotomy, excision only; inspection)
Tricuspid valve procedure	Categorical (replacement, repair, repair with ring, repair without ring, isolated commissurotomy, excision only; inspection)
Pulmonary valve procedure	Categorical (replacement, repair, repair with ring, repair without ring, isolated commissurotomy, excision only; inspection)
Number of aorta segments operated on	Continuous
Aortic pathology: root segment	Categorical (aneurysm, chronic dissection, acute dissection, trauma, penetrating atheromatous ulcer, pseudoaneurysm, intramural haematoma, normal, other)
Aortic pathology: ascending segment	Categorical (aneurysm, chronic dissection, acute dissection, trauma, penetrating atheromatous ulcer, pseudoaneurysm, intramural haematoma, normal, other)
Aortic pathology: arch segment	Categorical (aneurysm, chronic dissection, acute dissection, trauma, penetrating atheromatous ulcer, pseudoaneurysm, intramural haematoma, normal, other)
Aortic pathology: descending aorta segment	Categorical (aneurysm, chronic dissection, acute dissection, trauma, penetrating atheromatous ulcer, pseudoaneurysm, intramural haematoma, normal, other)

continued

TABLE 39 Candidate predictors of risk models for acute hospital mortality among admissions to cardiothoracic critical care units (*continued*)

Predictor	Approach to modelling
Aortic pathology: abdominal segment	Categorical (aneurysm, chronic dissection, acute dissection, trauma, penetrating atheromatous ulcer, pseudoaneurysm, intramural haematoma, normal, other)
Cardiopulmonary bypass	Binary (yes, no)
Intra-aortic balloon pump used (pre operative)	Binary (yes, no)
Impeller device used (pre operative)	Binary (yes, no)
Ventricular assist device used (pre operative)	Binary (yes, no)
Other support device used (pre operative)	Binary (yes, no)
Intra-aortic balloon pump used (intra operative)	Binary (yes, no)
Impeller device used (intra operative)	Binary (yes, no)
Ventricular assist device used (intra operative)	Binary (yes, no)
Other support device used (intraoperative)	Binary (yes, no)
Cumulative bypass time	Continuous (cumulative bypass time in minutes irrespective of the number of times on bypass)
Cumulative cross clamp time	Continuous (cumulative cross clamp time in minutes)
Total circulatory arrest time	Continuous (total circulatory arrest time in minutes)
Candidate predictors from CMP and HES	
Severe conditions in the medical history (APACHE II definitions): Respiratory disease; Cardiovascular disease	Binary (yes, no)
RCS Charlson comorbidities defined by ICD-10 codes (see *Chapter 3*) – 1 year look back: previous MI, congestive cardiac failure, peripheral vascular disease, diabetes; cerebrovascular disease, chronic pulmonary disease, hemiplegia or paraplegia, chronic renal disease and malignancy	Binary (yes, no)
Congestive heart failure (ICD-10 code I500)	Binary (yes, no)
Coronary artery disease (ICD-10 code I2510)	Binary (yes, no)
Arrhythmia (ICD-10 code I499)	Binary (yes, no)
Cerebrovascular accident (ICD-10 code I639)	Binary (yes, no)

BP, blood pressure; COAD, chronic obstructive airway disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

TABLE 40 Candidate predictors of risk models for in-hospital cardiac arrest models

Current predictors	Approach to modelling
Age	Restricted cubic splines with five knots
Sex	Categorical (male, female)
Length of stay in hospital prior to 2222 call	Categorical (0 days, 1 day, 2–7 days, ≥ 8 days)
Reason for admission to/attendance at/visit to hospital	Categorical (patient–medical, patient–trauma, patient–elective surgery, patient–emergency surgery, patient–obstetric, outpatient, staff or visitor)
Location of arrest	Categorical (emergency department; emergency admissions unit; ward, obstetric area, intermediate care area or other inpatient location; coronary care unit; critical care unit; imaging department or specialist treatment area; cardiac catheter laboratory; theatre and recovery)
Presenting/first documented rhythm	Categorical (ventricular fibrillation; ventricular tachycardia; shockable, unknown rhythm; asystole; pulseless electrical activity; bradycardia; non-shockable, unknown rhythm; unknown)
Interaction between location of arrest and presenting rhythm	Simplified categorisation for location of arrest (emergency department; emergency admissions unit, ward, obstetric area, intermediate care area or other inpatient location; coronary care unit or cardiac catheter lab; critical care unit; imaging department or specialist treatment area; theatre and recovery) and presenting rhythm (ventricular tachycardia, asystole, PEA, other non-shockable)
New potential predictors	
Pre-existing comorbidities	Defined using the RCS Charlson comorbidity index based on the presence of ICD-10 codes in prior hospitalisations with a 1-year look back (see *Chapter 3*). Thirteen binary (yes, no) variables: MI, congestive cardiac failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatological disease, liver disease, diabetes mellitus, hemiplegia or paraplegia, chronic renal disease, malignancy, metastatic solid tumour

PEA, pulseless electrical activity.

Appendix 2 Significance and importance of predictors in the risk models

TABLE 41 Significance and importance of predictors included in the final risk model for mortality at 30 days and customised risk model for mortality at 90 days following critical care admission

Predictor	Mortality at 30 days					Mortality at 90 days				
	p-value for non-linearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for non-linearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]
Physiological										
Highest heart rate	< 0.0001	< 0.0001	250.062	0.8988	0.0916	< 0.0001	< 0.0001	234.028	0.8823	0.1081
Lowest systolic blood pressure	0.0004	0.0012	42.787	0.8999	0.0913	0.0004	0.0012	18.351	0.8833	0.1078
Highest temperature	0.0025	0.0002	38.462	0.8999	0.0913	0.0027	0.0005	16.458	0.8832	0.1078
Lowest respiratory rate	0.0001	< 0.0001	186.982	0.8991	0.0916	0.0001	< 0.0001	147.176	0.8827	0.1080
PaO_2/FiO_2	< 0.0001	< 0.0001	370.549	0.8986	0.0918	< 0.0001	< 0.0001	253.337	0.8824	0.1082
Lowest arterial pH	< 0.0001	0.0001	38.777	0.8999	0.0913	< 0.0001	0.0001	11.439	0.8832	0.1078
$PaCO_2$	< 0.0001	< 0.0001	29.742	0.8997	0.0913	< 0.0001	< 0.0001	64.647	0.8831	0.1079
Highest blood lactate	< 0.0001	< 0.0001	29.866	0.8998	0.0913	0.0002	0.0008	18.343	0.8832	0.1078
Urine output	< 0.0001	< 0.0001	256.868	0.8990	0.0917	< 0.0001	< 0.0001	268.761	0.8825	0.1082
Highest urea	< 0.0001	< 0.0001	61.001	0.8995	0.0914	< 0.0001	< 0.0001	101.902	0.8828	0.1080
Highest creatinine	0.0001	< 0.0001	184.523	0.8991	0.0916	0.0001	< 0.0001	182.823	0.8825	0.1081
Highest sodium	< 0.0001	< 0.0001	248.721	0.8990	0.0916	< 0.0001	< 0.0001	268.567	0.8824	0.1081
Lowest white blood cell count	< 0.0001	< 0.0001	59.651	0.8996	0.0914	< 0.0001	< 0.0001	81.355	0.8829	0.1079
Lowest platelet count	< 0.0001	< 0.0001	177.737	0.8991	0.0916	< 0.0001	< 0.0001	234.962	0.8824	0.1081
BMI	< 0.0001	< 0.0001	138.239	0.8993	0.0915	< 0.0001	< 0.0001	260.538	0.8824	0.1081
Sedated/paralysed/GCS	–	< 0.0001	1070.664	0.8959	0.0928	–	< 0.0001	1097.521	0.8793	0.1094

Predictor	Mortality at 30 days					Mortality at 90 days				
	p-value for non-linearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for non-linearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]
Non-physiological										
Age	–	< 0.0001	2395.651	0.8915	0.0925	–	< 0.0001	2966.143	0.8730	0.1117
Very severe cardiovascular disease	–	< 0.0001	23.894	0.8999	0.0913	–	0.002	1.723	0.8833	0.1078
Severe respiratory disease	–	< 0.0001	20.536	0.8997	0.0913	–	< 0.0001	44.763	0.8831	0.1078
Severe liver disease	–	< 0.0001	133.173	0.8994	0.0915	–	< 0.0001	211.030	0.8825	0.1081
Metastatic disease	–	< 0.0001	252.370	0.8989	0.0916	–	< 0.0001	610.916	0.8810	0.1086
Haematological malignancy	–	< 0.0001	6.491	0.8998	0.0913	–	< 0.0001	56.260	0.8830	0.1079
Immunocompromise	–	< 0.0001	3.885	0.8998	0.0913	–	< 0.0001	47.963	0.8831	0.1078
Dependency prior to admission	–	< 0.0001	334.181	0.8986	0.0917	–	< 0.0001	550.623	0.8814	0.1085
CPR prior to admission	–	0.2475	45.560	0.8999	0.0912	–	0.6367	22.485	0.8833	0.1077
Source of admission/urgency of surgery	–	< 0.0001	943.299	0.8965	0.0925	–	< 0.0001	1075.626	0.8796	0.1093
Primary reason for admission	–	< 0.0001	410.259	0.8957	0.0928	–	< 0.0001	510.246	0.8788	0.1095
Ventilation	–	< 0.0001	17.782	0.8998	0.0913	–	< 0.0001	5.734	0.8832	0.1078
Interactions										
Arterial pH × $PaCO_2$	–	< 0.0001	13.037	0.8997	0.0913	–	< 0.0001	43.615	0.8830	0.1079
Arterial pH × blood lactate	–	< 0.0001	43.768	0.8998	0.0913	–	< 0.0001	26.304	0.8832	0.1078
Urine output × urea	–	< 0.0001	43.515	0.8998	0.0913	–	< 0.0001	14.948	0.8831	0.1078
CPR × temperature	–	0.0016	73.312	0.8999	0.0913	–	0.0002	43.391	0.8833	0.1078
CPR × systolic blood pressure	–	0.0042	75.677	0.8999	0.0913	–	0.0046	51.336	0.8833	0.1078
Dissection or aneurysm (cardiovascular) × lowest white blood cell count	–	0.0006	41.217	0.8999	0.0913	–	0.0026	17.991	0.8832	0.1078
Haemorrhage (neuro) × urine output	–	0.0008	25.852	0.8999	0.0913	–	< 0.0001	5.126	0.8832	0.1078
Haemorrhage (neuro) × blood lactate	–	0.0002	42.372	0.8999	0.0913	–	< 0.0001	1.534	0.8832	0.1078

continued

TABLE 41 Significance and importance of predictors included in the final risk model for mortality at 30 days and customised risk model for mortality at 90 days following critical care admission (*continued*)

Predictor	Mortality at 30 days					Mortality at 90 days				
	p-value for non-linearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for non-linearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]
Inflammation (gastrointestinal) × PaO_2/FiO_2	–	< 0.0001	38.753	0.8998	0.0913	–	0.0053	22.329	0.8832	0.1078
Obstruction (gastrointestinal) × urine output	–	0.0022	42.443	0.8999	0.0912	–	0.0007	16.439	0.8832	0.1078
Seizures (neurological) × sodium	–	0.0004	27.244	0.8998	0.0912	–	0.0004	4.121	0.8832	0.1078
Trauma, perforation or rupture (gastrointestinal) × arterial pH	–	< 0.0001	35.607	0.8999	0.0913	–	< 0.0001	9.588	0.8832	0.1078
Trauma, perforation or rupture (neurological) × sodium	–	< 0.0001	24.336	0.8999	0.0913	–	< 0.0001	0.854	0.8832	0.1078
Trauma, perforation or rupture (neurological) × urine output	–	< 0.0001	33.353	0.8999	0.0913	–	< 0.0001	0.8832	0.8832	0.1078
Vascular (neurological) × highest heart rate	–	< 0.0001	29.895	0.8998	0.0913	–	< 0.0001	2.945	0.8832	0.1078
Alcoholic hepatitis/cirrhosis × pH	–	0.0004	37.934	0.8999	0.0913	–	0.0324	25.247	0.8833	0.1077
Asthma attack in new or known asthmatic × urea	–	0.0006	42.046	0.8999	0.0912	–	0.0001	14.665	0.8832	0.1077
Intracerebral haemorrhage × urine output	–	< 0.0001	11.375	0.8998	0.0913	–	< 0.0001	19.098	0.8832	0.1078
Non-traumatic subdural haemorrhage × arterial pH		< 0.0001	37.952	0.8999	0.0913		0.0005	16.446	0.8832	0.1078
Thrombo-occlusive disease of brain × sodium	–	0.0004	28.881	0.8999	0.0913	–	0.0007	7.136	0.8832	0.1078
Ventilation × respiratory rate	–	< 0.0001	57.633	0.8999	0.0913	–	0.0006	36.849	0.8832	0.1078
Ventilation × PaO_2/FiO_2	–	< 0.0001	32.913	0.8998	0.0913	–	< 0.0001	7.190	0.8832	0.1078
Ventilation × $PaCO_2$	–	< 0.0001	5.369	0.8998	0.0913	–	< 0.0001	12.065	0.8832	0.1078

TABLE 42 Significance and importance of comorbidities in the risk model for mortality at 1 year following critical care admission and in the risk model for mortality at 1 year following hospital discharge

Predictor	1-year mortality following critical care admission				1 year following hospital discharge			
	p-value for Likelihood-ratio test	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for Likelihood-ratio test	Difference in BIC[a]	c index[a]	Brier's score[a]
Severe conditions in the medical history								
Very severe cardiovascular disease	< 0.0001	7.484	0.839	0.144	0.0691	−7.943	0.766	0.097
Severe respiratory disease	< 0.0001	92.862	0.838	0.144	< 0.0001	29.712	0.765	0.097
Severe liver disease	< 0.0001	279.302	0.837	0.144	< 0.0001	49.394	0.765	0.098
ESRD	0.0018	1.770	0.839	0.144	< 0.0001	11.267	0.765	0.097
Metastatic disease	< 0.0001	1239.326	0.833	0.146	< 0.0001	1109.389	0.750	0.099
Haematological malignancy	< 0.0001	139.259	0.838	0.144	< 0.0001	68.275	0.765	0.097
Immunocompromise	< 0.0001	102.778	0.838	0.144	< 0.0001	102.963	0.764	0.097
RCS Charlson comorbidities								
Previous MI	0.0296	−6.766	0.839	0.144	0.0491	−7.376	0.766	0.097
Congestive cardiac failure	< 0.0001	31.185	0.838	0.144	< 0.0001	36.655	0.765	0.097
Peripheral vascular disease	< 0.0001	9.509	0.839	0.144	< 0.0001	7.094	0.766	0.097
Cerebrovascular disease	0.0026	−2.435	0.839	0.144	0.0154	−5.370	0.766	0.097
Dementia	0.1124	−8.978	0.839	0.144	0.0015	−1.198	0.766	0.097
Chronic pulmonary disease	< 0.0001	11.947	0.839	0.144	< 0.0001	21.809	0.765	0.097
Rheumatological disease	0.8909	−11.479	0.839	0.144	0.9006	−11.231	0.766	0.097
Liver disease	< 0.0001	33.814	0.838	0.144	< 0.0001	12.167	0.765	0.097
Diabetes mellitus	0.2409	−10.123	0.839	0.144	< 0.0001	9.416	0.765	0.097
Hemiplegia or paraplegia	0.4769	−10.992	0.839	0.144	0.1153	−8.766	0.766	0.097
Chronic renal disease	< 0.0001	21.383	0.839	0.144	< 0.0001	15.289	0.765	0.097
Malignancy	< 0.0001	224.483	0.837	0.145	< 0.0001	316.247	0.758	0.097

TABLE 43 Significance and importance of predictors in the model for acute hospital mortality and 1-year mortality after admission to cardiothoracic critical care

Predictor	Acute hospital mortality					1-year mortality				
	p-value for nonlinearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for nonlinearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]
Previous model factors										
Age (years)	0.0004	< 0.0001	79.704	0.8821	0.0274	< 0.0001	< 0.0001	181.565	0.8111	0.0520
Lowest systolic blood pressure	< 0.0001	< 0.0001	33.378	0.8899	0.0275	0.0008	< 0.0001	12.397	0.8255	0.0517
Lowest arterial pH	< 0.0001	< 0.0001	26.766	0.8879	0.0274	< 0.0001	< 0.0001	23.772	0.8247	0.0517
Highest creatinine	< 0.0001	< 0.0001	78.280	0.8819	0.0274	0.0004	< 0.0001	25.157	0.8231	0.0516
Lowest white blood cell count	0.0039	0.0003	13.033	0.8917	0.0273	0.0286	0.0074	19.261	0.8266	0.0515
Lowest platelet count	< 0.0001	< 0.0001	11.792	0.8889	0.0274	< 0.0001	< 0.0001	24.073	0.8240	0.0517
Highest blood lactate	–	< 0.0001	102.872	0.8893	0.0279	–	< 0.0001	61.024	0.8264	0.0520
GCS	–	< 0.0001	131.644	0.8834	0.0277	–	< 0.0001	101.039	0.8211	0.0521
New factors										
Sex	–	< 0.0001	9.822	0.8916	0.0273	–	< 0.0001	10.156	0.8263	0.0515
Diabetes (no diabetes, diet/oral therapy/insulin)	–	0.001	1.149	0.8908	0.0272	–	< 0.0001	15.764	0.8260	0.0516
Atrial fibrillation/flutter	–	0.001	0.339	0.8912	0.0272	–	< 0.0001	24.953	0.8254	0.0516
Dyspnoea status pre-surgery (no limitation or slight limitation of ordinary physical activity, marked limitation of ordinary physical activity, symptoms at rest or minimal activity)	–	< 0.0001	3.267	0.8903	0.0273	–	< 0.0001	4.872	0.8256	0.0515
History of pulmonary disease	–	< 0.0001	18.711	0.8902	0.0273	–	< 0.0001	22.743	0.8254	0.0516
History of neurological dysfunction	–	0.005	2.830	0.8915	0.0273	–	0.011	4.104	0.8270	0.0515
Extracardiac arteriopathy	–	< 0.0001	1.419	0.8910	0.0272	–	< 0.0001	11.274	0.8258	0.0515

Predictor	Acute hospital mortality					1-year mortality				
	p-value for nonlinearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for nonlinearity	*p*-value for global effect	Difference in BIC[a]	c index[a]	Brier's score[a]
Operative urgency (elective, urgent, emergency, salvage)	–	< 0.0001	37.774	0.8872	0.0274	–	< 0.0001	40.605	0.8234	40.605
Cumulative bypass time	–	0.001	2.057	0.8918	0.0273	–	< 0.0001	7.967	0.8263	0.0515
Severe respiratory disease	–	0.005	3.576	0.8916	0.0272	–	0.004	2.690	0.8266	0.0515
Severe cardiovascular disease	–	0.002	0.947	0.8911	0.0272	–	< 0.0001	10.341	0.8254	0.0515
Congestive heart failure	–	0.009	3.700	0.8914	0.0272	–	< 0.0001	12.600	0.8261	0.0516
1-year new factors										
Renal function/dialysis	–	–	–	–	–	–	< 0.0001	5.798	0.8265	0.0515
LVEF	–	–	–	–	–	–	< 0.0001	0.424	0.8254	0.0515
Number of previous MIs	–	–	–	–	–	–	0.008	3.329	0.8271	0.0515
Major aortic procedure	–	–	–	–	–	–	0.007	3.001	0.8267	0.0515

LVEF, left ventricular ejection fraction.
a If variable is removed.

TABLE 44 Comorbidities significance and contribution to the model for ROSC > 20 minutes, to the model for hospital survival and to the 1-year survival model

Predictor	ROSC > 20 minutes				Hospital survival				1-year survival			
	p-value for likelihood-ratio test	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for likelihood-ratio test	Difference in BIC[a]	c index[a]	Brier's score[a]	*p*-value for likelihood-ratio test	Difference in BIC[a]	c index[a]	Brier's score[a]
MI	0.5016	−9.743	0.722	0.211	0.6982	−10.044	0.819	0.119	0.6122	−9.939	0.829	0.101
Congestive cardiac failure	< 0.0001	7.703	0.721	0.211	0.0066	−2.804	0.818	0.119	< 0.0001	11.692	0.828	0.102
Peripheral vascular disease	0.0026	−1.145	0.722	0.211	0.0039	−1.858	0.818	0.119	0.0478	−6.278	0.829	0.102
Cerebrovascular disease	0.8146	−10.139	0.722	0.211	0.3941	−9.468	0.818	0.119	0.9899	−10.196	0.829	0.101
Dementia	0.0332	−5.660	0.722	0.211	0.0619	−6.709	0.818	0.119	0.0265	−5.276	0.829	0.102
Chronic pulmonary disease	0.6941	−10.040	0.722	0.211	0.6860	−10.031	0.819	0.119	0.5037	−9.749	0.829	0.101
Rheumatological disease	0.6154	−9.942	0.722	0.211	0.3022	−9.130	0.818	0.119	0.8792	−10.173	0.829	0.101
Liver disease	0.0824	−7.177	0.722	0.211	0.0033	−1.539	0.819	0.119	< 0.0001	8.549	0.828	0.102
Diabetes mellitus	0.0003	2.958	0.722	0.212	0.0433	−6.111	0.818	0.119	0.5044	−9.751	0.829	0.101
Hemiplegia or paraplegia	0.9552	−10.191	0.722	0.211	0.0210	−4.869	0.818	0.119	0.0779	−7.089	0.829	0.102
Chronic renal disease	0.0011	0.389	0.722	0.211	0.5438	−9.826	0.819	0.119	< 0.0001	8.305	0.829	0.102
Malignancy	< 0.0001	6.718	0.722	0.211	< 0.0001	7.794	0.818	0.119	< 0.0001	23.211	0.828	0.102
Metastatic solid tumour	< 0.0001	5.389	0.722	0.211	< 0.0001	16.667	0.817	0.119	< 0.0001	37.563	0.828	0.102

a If predictor removed.

Appendix 3 Final model coefficients

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care

Predictor	Coefficient	95% CI
Age (years)	0.0372	0.036 to 0.039
Highest heart rate (min^{-1}): RCS (71,93,110,146)		
hr1	0.0002	−0.004 to 0.004
hr2	0.0350	0.019 to 0.050
hr3	−0.1053	−0.150 to −0.061
Lowest systolic blood pressure (mmHg): RCS (66,89,102,130)		
sbp1	−0.0226	−0.035 to -0.010
sbp2	0.0736	0.026 to 0.121
sbp3	−0.2476	−0.463 to −0.033
CPR × lowest systolic blood pressure		
In-hospital CPR × sbp1	−0.0020	−0.019 to 0.015
No CPR × sbp1	0.0021	−0.011 to 0.015
In-hospital CPR × sbp2	0.0110	−0.056 to 0.078
No CPR × sbp2	−0.0422	−0.091 to 0.006
In-hospital CPR × sbp3	−0.0801	−0.386 to 0.226
No CPR ×sbp3	0.1781	−0.042 to 0.398
Highest temperature (°C): RCS (36,37.2,38,39.2)		
temp1	−0.2494	−0.380 to −0.119
temp2	0.4294	−0.174 to 1.033
temp3	−0.8330	−3.444 to 1.779
CPR × temperature		
In-hospital CPR × temp1	−0.1356	−0.375 to 0.104
No CPR × temp1	−0.1425	−0.295 to 0.010
In-hospital CPR × temp2	−0.2133	−1.148 to 0.722
No CPR × temp2	−0.0551	−0.695 to 0.585
In-hospital CPR × temp3	1.4697	−2.403 to 5.343
No CPR × temp3	0.3069	−2.417 to 3.031
Lowest respiratory rate (min^{-1}): RRCS (10,12,13,20)		
rr1	−0.0695	−0.081 to −0.058
rr2	−0.0014	−0.016 to 0.013
rr3	0.0050	−0.020 to 0.030
rr4	−0.0038	−0.018 to 0.011
rr5	0.0003	0.000 to 0.001

continued

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Mechanical ventilation × respiratory rate		
Mechanical ventilation × rr1	0.0455	0.025 to 0.066
Mechanical ventilation × rr2	−0.0055	−0.024 to 0.013
Mechanical ventilation × rr3	0.0078	−0.024 to 0.040
Mechanical ventilation × rr4	−0.0027	−0.022 to 0.016
Mechanical ventilation × rr5	−0.0003	−0.001 to 0.000
PaO_2/FiO_2 (kPa): RCS (10,26,40,61)		
pf1	−0.0400	−0.049 to -0.031
pf2	0.0279	−0.002 to 0.058
pf3	−0.0151	−0.102 to 0.072
Mechanical ventilation × PaO_2/FiO_2		
Mechanical ventilation × pf1	0.0185	0.008 to 0.029
Mechanical ventilation × pf2	−0.0073	−0.046 to 0.032
Mechanical ventilation × pf3	−0.0227	−0.140 to 0.094
Lowest arterial pH: RCS (7.08,7.3,7.36,7.44)		
ph1	2.2280	0.240 to 4.216
ph2	−3.7155	−6.017 to −1.413
ph3	14.8746	−22.708 to 52.457
Highest urea (mmol l^{-1}): RCS (2.8,5.6,9.3,28.1)		
ur1	−0.0670	−0.119 to −0.015
ur2	1.7906	1.064 to 2.517
ur3	−3.3285	−4.641 to −2.016
Highest creatinine (mg dl^{-1}): RRCS (0.7,0.9,1.2,3)		
cr1	0.1524	0.132 to 0.173
cr2	3.5786	−7.778 to 14.935
cr3	−2.1249	−8.890 to 4.640
cr4	0.9874	−0.274 to 2.248
cr5	−0.0214	−0.034 to −0.009
Highest sodium (mmol l^{-1}): RCS (133,139,145)		
na1	−0.0543	−0.061 to -0.048
na2	0.0587	0.052 to 0.066
Lowest white blood cell count (× 10^9 l^{-1}): RCS (3.7,8.7,12.3,22.5)		
wbc1	−0.0544	−0.071 to −0.038
wbc2	0.3107	0.241 to 0.380
wbc3	−0.8773	−1.071 to −0.684
Urine output (ml): RCS (164,1215,2020,4255)		
up1	−0.0013	−0.001 to −0.001
up2	0.0026	0.002 to 0.003
up3	−0.0054	−0.007 to −0.003

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
$PaCO_2$ (kPa): RRCS (4.2,5.7,8)		
pc1	8.7347	6.758 to 10.712
pc2	−7.0267	−8.797 to −5.257
Mechanical ventilation × $PaCO_2$		
Mechanical ventilation × pc1	−0.1332	−0.196 to −0.071
Mechanical ventilation × pc2	0.0777	0.011 to 0.145
Highest blood lactate (mmol l^{-1}): RCS (0.7,1.5,2.5,8.2)		
bl1	−18.4582	−25.188 to −11.728
bl2	291.0167	184.419 to 397.615
bl3	−535.0153	−732.095 to −337.936
Lowest platelet count (× 10^9 l^{-1}): RCS (60,162,232,422)		
plc1	−0.0064	−0.007 to −0.006
plc2	0.0206	0.017 to 0.024
plc3	−0.0550	−0.066 to −0.044
BMI (kg/m^2): RCS (20.68,26.12,35.18)		
bmi1	−0.0528	−0.061 to −0.045
bmi2	0.0568	0.047 to 0.067
Sedated/paralysed/GCS (15)		
15	0	
14	0.1910	0.125 to 0.257
7–13	0.4143	0.353 to 0.476
Sedated	0.7665	0.703 to 0.829
6	0.8679	0.688 to 1.048
5 or paralysed and sedated	0.8237	0.695 to 0.953
4	1.3228	1.095 to 1.550
3	1.7984	1.679 to 1.917
Mechanical ventilation	1.2108	0.657 to 1.764
Source of admission/urgency of surgery		
ED or not in hospital, unplanned admission	0	
ED or not in hospital, planned admission	−0.0942	−0.295 to 0.107
Other acute hospital, not critical care	0.2087	0.032 to 0.386
Other critical care unit, repatriation	0.1204	−0.120 to 0.361
Other critical care unit, planned or unplanned transfer	0.0446	−0.049 to 0.139
Theatre, unplanned admission following elective or scheduled surgery	−0.7735	−0.932 to −0.615
Theatre, planned admission following elective or scheduled surgery	−1.2495	−1.357 to −1.142

continued

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Theatre, admission following emergency or urgent surgery	−0.3136	−0.387 to −0.241
Ward or intermediate care area	0.3238	0.271 to 0.377
CPR prior to admission		
Community CPR	0	
In-hospital CPR	4.5342	−4.192 to 13.261
No CPR	4.1969	−1.379 to 9.773
Dependency prior to admission		
No assistance with daily activities	0	
Some assistance with daily activities	0.4398	0.395 to 0.485
Total assistance with daily activities	0.5825	0.397 to 0.768
Severe liver disease	0.7380	0.628 to 0.848
Metastatic disease	0.9549	0.847 to 1.062
Haematological malignancy	0.4213	0.296 to 0.547
Severe respiratory disease/home ventilation	0.4062	0.301 to 0.511
Immunocompromise	0.2326	0.153 to 0.312
Very severe cardiovascular disease	0.2120	0.094 to 0.330
Arterial pH × $PaCO_2$		
ph1 × pc1	−1.2177	−1.492 to −0.944
ph1 × pc2	0.9847	0.741 to 1.229
ph2 × pc1	0.5001	0.177 to 0.823
ph3 × pc1	0.9259	−5.178 to 7.029
Arterial pH × blood lactate		
ph1 × bl1	2.5711	1.649 to 3.493
ph1 × bl2	−40.2105	−54.819 to −25.602
ph1 × bl3	73.9037	46.891 to 100.916
ph2 × bl1	−0.1771	−0.425 to 0.070
ph3 × bl1	5.6530	1.052 to 10.254
Urine output × urea		
up1 × ur1	0.0001	0.000 to 0.000
up1 × ur2	−0.0007	−0.001 to −0.000
up1 × ur3	0.0012	0.001 to 0.002
up2 × ur1	−0.0000	−0.000 to −0.000
up3 × ur1	0.0001	0.000 to 0.000
Primary reason for admission		
Congenital or acquired deformity or abnormality (cardiovascular)	0	
Acute alcoholic hepatitis	1.5041	0.998 to 2.010
Secondary hepatic tumour	−0.9741	−1.573 to −0.376

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Alcoholic cirrhosis	53.3508	−26.599 to 133.300
Intracerebral haemorrhage	2.0879	1.218 to 2.957
Thrombo-occlusive disease of brain	−25.4085	−38.885 to −11.932
Secondary hydrocephalus	1.5237	0.971 to 2.076
Non-traumatic subdural haemorrhage	−70.6247	−133.793 to −7.456
Accidental intoxication or poisoning (endocrine)	−0.7501	−1.305 to −0.196
Diabetes mellitus (endocrine)	−1.3006	−1.722 to −0.879
Dissection or aneurysm (cardiovascular)	−1.0128	−2.015 to −0.011
Haemolysis or thrombocytopaenia	0.0339	−0.620 to 0.688
Hyperkalaemia (endocrine)	−0.4174	−0.904 to 0.069
Acidaemia (endocrine)	−0.3027	−0.755 to 0.150
Hypokalaemia (endocrine)	−0.4409	−1.154 to 0.272
Hyponatraemia (endocrine)	−1.2861	−1.869 to −0.704
Hypoplasia or dysplasia (haematological/ immunological)	−0.2886	−0.855 to 0.278
Hypothermia (endocrine)	−0.6616	−1.362 to 0.039
Infection (dermatological, gastrointestinal, haematological/immunological, musculoskeletal, neurological)	−0.1243	−0.473 to 0.224
Inflammation (cardiovascular, dermatological, genitourinary, musculoskeletal, respiratory)	0.0043	−0.349 to 0.358
Obstruction (cardiovascular)	0.1781	−0.168 to 0.524
Oedema, inflammation, fibrosis or inhalation (respiratory)	0.2541	−0.378 to 0.886
Seizures (neurological)	−13.0836	−19.337 to −6.830
Self-harm or self-poisoning (endocrine)	−0.7964	−1.195 to −0.398
Shock and hypotension (cardiovascular)	−0.0228	−0.384 to 0.339
Transplant or related (cardiovascular, endocrine, genitourinary, haematological/immunological, respiratory)	−0.3441	−0.925 to 0.237
Trauma, perforation or rupture (dermatological, genitourinary, musculoskeletal, respiratory)	−0.0746	−0.437 to 0.287
Tumour or malignancy (cardiovascular, dermatological, endocrine, gastrointestinal, musculoskeletal, respiratory)	0.1583	−0.193 to 0.510
Burns or hyperthermia (dermatological)	0.5879	−0.105 to 1.281
Trauma (neurological)	−0.8295	−1.333 to −0.326
Non-traumatic aneurysm, dissection, perforation or rupture (cardiovascular)	−0.0271	−0.382 to 0.328
Collapse (respiratory)	−0.2954	−0.728 to 0.137
Coma or encephalopathy (neurological)	−0.1685	−0.559 to 0.222

continued

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Congenital or acquired deformity or abnormality (cardiovascular, endocrine, gastrointestinal, genitourinary, haematological/immunological)	−0.2133	−0.629 to 0.202
Failure (cardiovascular)	0.1727	−0.195 to 0.541
Failure (genitourinary)	−0.1717	−0.523 to 0.179
Haemorrhage (respiratory)	−0.1374	−0.762 to 0.487
Haemorrhage (cardiovascular)	0.0493	−0.578 to 0.676
Haemorrhage (gastrointestinal)	0.0670	−0.294 to 0.427
Haemorrhage (neurological)	0.2252	−1.092 to 1.543
Haemorrhage (genitourinary)	−0.9770	−1.675 to −0.279
Infection (respiratory)	−0.0473	−0.394 to 0.300
Infection (cardiovascular)	0.3124	−0.112 to 0.737
Infection (genitourinary)	−0.7277	−1.098 to −0.357
Inflammation (gastrointestinal)	0.6374	0.235 to 1.040
Inflammation (neurological)	−0.3360	−0.935 to 0.263
Obstruction (respiratory)	−0.1158	−0.494 to 0.262
Obstruction (gastrointestinal)	0.4427	−0.055 to 0.941
Obstruction (genitourinary)	−0.7185	−1.183 to −0.254
Transplant or related (gastrointestinal)	−2.1372	−2.870 to −1.404
Trauma, perforation or rupture (cardiovascular)	−0.4556	−0.966 to 0.055
Trauma, perforation or rupture (gastrointestinal)	32.4477	16.713 to 48.183
Trauma, perforation or rupture (neurological)	−1.4565	−8.721 to 5.808
Tumour or malignancy (neurological)	0.7262	0.333 to 1.120
Tumour or malignancy (genitourinary)	−0.2742	−0.675 to 0.126
Tumour or malignancy (haematological/immunological)	0.0903	−0.337 to 0.518
Vascular (gastrointestinal)	0.1237	−0.263 to 0.510
Vascular (neurological)	−5.4052	−9.893 to −0.917
Congenital or acquired deformity or abnormality (respiratory)	0.2974	−0.118 to 0.713
Congenital or acquired deformity or abnormality (musculoskeletal)	−0.7485	−1.307 to −0.190
Congenital or acquired deformity or abnormality (neurological)	−0.7022	−1.249 to −0.155
Degeneration (cardiovascular)	−0.4055	−0.827 to 0.016
Degeneration (neurological)	0.8871	0.050 to 1.724
Vascular (cardiovascular; genitourinary)	0.1870	−0.592 to 0.966
Pulmonary fibrosis or fibrosing alveolitis	1.7803	1.281 to 2.279
Asthma attack in new or known asthmatic	−2.4056	−4.909 to 0.098
Multiple rib fractures	−0.3466	−0.910 to 0.217

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Fungal or yeast pneumonia	1.1621	0.657 to 1.667
Hanging or strangulation	1.1366	0.590 to 1.683
Anoxic or ischaemic coma or encephalopathy	1.1334	0.757 to 1.510
Alcoholic hepatitis/cirrhosis × arterial pH		
ph1	−7.2666	−18.404 to 3.871
ph2	10.7613	−4.226 to 25.749
ph3	−189.2792	−356.488 to −22.070
Intracerebral haemorrhage × urine output		
up1	−0.0005	−0.001 to 0.000
up2	0.0027	−0.001 to 0.006
up3	−0.0066	−0.016 to 0.003
Thrombo-occlusive disease of brain × sodium		
na1	0.1971	0.099 to 0.295
na2	−0.1569	−0.243 to −0.071
Non-traumatic subdural haemorrhage × arterial pH		
ph1	10.2106	1.418 to 19.003
ph2	−24.8692	−37.023 to −12.715
ph3	286.1379	147.920 to 424.356
Dissection or aneurysm (cardiovascular) × lowest white blood cell count		
wbc1	0.1375	−0.004 to 0.279
wbc2	−0.4123	−0.988 to 0.163
wbc3	1.1460	−0.448 to 2.740
Seizures (neurological) × sodium		
na1	0.0925	0.046 to 0.138
na2	−0.0935	−0.145 to −0.042
Haemorrhage (neuro) × urine output		
up1	0.0004	−0.001 to 0.001
up2	−0.0001	−0.004 to 0.004
up3	−0.0001	−0.010 to 0.010
Haemorrhage (neuro) × blood lactate		
bl1	0.2468	−0.424 to 0.918
bl2	1.5342	−9.865 to 12.934
bl3	−4.1341	−25.493 to 17.225
Inflammation (gastrointestinal) × PaO_2/FiO_2		
pf1	−0.0274	−0.041 to −0.014
pf2	0.0751	0.014 to 0.136
pf3	−0.2018	−0.407 to 0.003

continued

TABLE 45 Coefficients for the risk model to predict mortality at 30 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Obstruction (gastrointestinal) × urine output		
up1	−0.0009	−0.001 to −0.000
up2	0.0048	0.002 to 0.008
up3	−0.0148	−0.023 to −0.006
Trauma, perforation or rupture (gastrointestinal) × arterial pH		
ph1	−4.5428	−6.742 to −2.344
ph2	4.8285	1.040 to 8.617
ph3	−23.6019	−79.114 to 31.911
Trauma, perforation or rupture (neurological) × sodium		
na1	0.0182	−0.035 to 0.071
na2	0.0290	−0.018 to 0.077
Trauma, perforation or rupture (neurological) × urine output		
up1	−0.0006	−0.002 to 0.000
up2	0.0027	−0.001 to 0.006
up3	−0.0065	−0.016 to 0.003
Vascular (neurological) × highest heart rate		
hr1	0.0646	0.010 to 0.119
hr2	−0.0792	−0.291 to 0.133
hr3	0.1404	−0.488 to 0.769
Asthma attack in new or known asthmatic × urea		
ur1	0.0901	−0.460 to 0.640
ur2	4.6763	−5.109 to 14.461
ur3	−10.8103	−29.632 to 8.012
Constant	2.0047	−13.203 to 17.213

RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care

Predictor	Coefficient	95% CI
Age (years)	0.0377	0.036 to 0.039
Highest heart rate (min^{-1}): RCS (71,93,110,146)		
hr1	0.0004	−0.003 to 0.004
hr2	0.0313	0.017 to 0.045
hr3	−0.0966	−0.137 to −0.056
Lowest systolic blood pressure (mmHg): RCS (66,89,102,130)		
sbp1	−0.0220	−0.034 to −0.010
sbp2	0.0698	0.023 to 0.117
sbp3	−0.2264	−0.440 to −0.013

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
CPR × lowest systolic blood pressure		
In-hospital CPR × sbp1	−0.0022	−0.019 to 0.015
No CPR × sbp1	0.0058	−0.007 to 0.018
In-hospital CPR × sbp2	0.0117	−0.055 to 0.079
No CPR × sbp2	−0.0495	−0.097 to −0.002
In-hospital CPR × sbp3	−0.0969	−0.400 to 0.206
No CPR × sbp3	0.1916	−0.026 to 0.409
Highest temperature (°C): RCS (36,37.2,38,39.2)		
temp1	−0.2421	−0.371 to −0.113
temp2	0.4892	−0.109 to 1.087
temp3	−1.1298	−3.719 to 1.460
CPR × temperature		
In-hospital CPR × temp1	−0.0925	−0.330 to 0.145
No CPR × temp1	−0.1002	−0.250 to 0.050
In-hospital CPR × temp2	−0.2787	−1.206 to 0.648
No CPR × temp2	−0.2141	−0.845 to 0.416
In-hospital CPR × temp3	1.7937	−2.056 to 5.643
No CPR × temp3	0.8380	−1.850 to 3.526
Lowest respiratory rate (min^{-1}): RRCS (10,12,13,20)		
rr1	−0.0625	−0.074 to −0.051
rr2	−0.0036	−0.017 to 0.009
rr3	0.0108	−0.011 to 0.033
rr4	−0.0075	−0.020 to 0.005
rr5	0.0004	0.000 to 0.001
Mechanical ventilation × respiratory rate		
Mechanical ventilation × rr1	0.0402	0.020 to 0.061
Mechanical ventilation × rr2	−0.0046	−0.021 to 0.012
Mechanical ventilation × rr3	0.0037	−0.025 to 0.033
Mechanical ventilation × rr4	0.0001	−0.017 to 0.017
Mechanical ventilation × rr5	−0.0004	−0.001 to −0.000
PaO_2/FiO_2 (kPa): RCS (10,26,40,61)		
pf1	−0.0367	−0.045 to −0.028
pf2	0.0446	0.017 to 0.072
pf3	−0.0764	−0.154 to 0.001
Mechanical ventilation × PaO_2/FiO_2		
Mechanical ventilation × pf1	0.0168	0.007 to 0.027
Mechanical ventilation × pf2	−0.0233	−0.059 to 0.013
Mechanical ventilation × pf3	0.0314	−0.076 to 0.139

continued

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Lowest arterial pH: RCS (7.08,7.3,7.36,7.44)		
ph1	3.6166	1.768 to 5.466
ph2	−4.1960	−6.352 to −2.040
ph3	28.1944	−6.496 to 62.885
Highest urea (mmol l^{-1}): RCS (2.8,5.6,9.3,28.1)		
ur1	−0.0420	−0.089 to 0.005
ur2	1.5152	0.849 to 2.181
ur3	−2.8502	−4.055 to −1.646
Highest creatinine (mg dl^{-1}): RRCS (0.7,0.9,1.2,3)		
cr1	0.1306	0.112 to 0.149
cr2	2.8473	−7.364 to 13.058
cr3	−2.2416	−8.330 to 3.847
cr4	1.1573	0.015 to 2.299
cr5	−0.0240	−0.035 to −0.013
Highest sodium (mmol l^{-1}): RCS (133,139,145)		
na1	−0.0512	−0.057 to −0.045
na2	0.0541	0.047 to 0.061
Lowest white blood cell count (× 10^9 l^{-1}): RCS (3.7,8.7,12.3,22.5)		
wbc1	−0.0556	−0.071 to −0.040
wbc2	0.2883	0.223 to 0.353
wbc3	−0.7974	−0.978 to −0.617
Urine output (ml): RCS (164,1215,2020,4255)		
up1	−0.0012	−0.001 to −0.001
up2	0.0023	0.002 to 0.003
up3	−0.0047	−0.006 to 0.003
$PaCO_2$ (kPa): RRCS (4.2,5.7,8)		
pc1	8.6540	6.796 to 10.512
pc2	−6.6736	−8.344 to −5.003
Mechanical ventilation × $PaCO_2$		
Mechanical ventilation × pc1	−0.1103	−0.170 to −0.051
Mechanical ventilation × pc2	0.0604	−0.003 to 0.124
Highest blood lactate (mmol l^{-1}): RCS (.7,1.5,2.5,8.2)		
bl1	−12.1647	−18.311 to −6.019
bl2	204.0701	106.168 to 301.972
bl3	−377.6584	−558.883 to −196.434
Lowest platelet count (× 10^9 l^{-1}): RCS (60,162,232,422)		
plc1	−0.0063	−0.007 to −0.006
plc2	0.0218	0.019 to 0.025
plc3	−0.0585	−0.068 to −0.049

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
BMI (kg/m^2): RCS (20.68,26.12,35.18)		
bmi1	−0.0592	−0.066 to −0.052
bmi2	0.0620	0.053 to 0.071
Sedated/paralysed/GCS (15)		
15	0	
14	0.2224	0.163 to 0.282
7–13	0.4270	0.371 to 0.483
Sedated	0.7300	0.671 to 0.789
6	0.8679	0.688 to 1.048
5 or paralysed and sedated	0.7914	0.667 to 0.916
4	1.1629	0.940 to 1.386
3	1.7144	1.598 to 1.831
Mechanical ventilation	1.1348	0.602 to 1.668
Source of admission/urgency of surgery		
ED or not in hospital (unplanned admission)	0	
ED or not in hospital (planned admission)	−0.1441	−0.337 to 0.048
Other acute hospital (not critical care)	0.1856	0.019 to 0.352
Other critical care unit (repatriation)	0.1397	−0.077 to 0.356
Other critical care unit (planned or unplanned transfer)	0.1135	0.027 to 0.200
Theatre (unplanned admission following elective or scheduled surgery)	−0.5455	−0.673 to −0.418
Theatre (planned admission following elective or scheduled surgery)	−1.1287	−1.220 to −1.037
Theatre (admission following emergency or urgent surgery)	−0.2553	−0.322 to −0.188
Ward or intermediate care area	0.3227	0.273 to 0.373
CPR prior to admission		
Community CPR	0	
In-hospital CPR	3.0502	−5.590 to 11.690
No CPR	2.5074	−2.955 to 7.970
Dependency prior to admission		
No assistance with daily activities	0	
Some assistance with daily activities	0.4896	0.448 to 0.531
Total assistance with daily activities	0.7598	0.588 to 0.931
Severe liver disease	0.8008	0.696 to 0.905
Metastatic disease	1.2427	1.147 to 1.338
Haematological malignancy	0.5031	0.384 to 0.622
Severe respiratory disease/home ventilation	0.3853	0.285 to 0.485
Immunocompromise	0.2865	0.214 to 0.359
Very severe cardiovascular disease	0.1798	0.069 to 0.291

continued

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Arterial pH × $PaCO_2$		
ph1 × pc1	−1.2098	−1.467 to −0.952
ph1 × pc2	0.9384	0.708 to 1.169
ph2 × pc1	0.6997	0.397 to 1.003
ph3 × pc1	−2.4420	−8.088 to 3.204
Arterial pH × blood lactate		
ph1 × bl1	1.6885	0.848 to 2.529
ph1 × bl2	−28.0452	−41.444 to −14.646
ph1 × bl3	51.8930	27.086 to 76.700
ph2 × bl1	−0.2602	−0.500 to −0.020
ph3 × bl1	7.2817	2.909 to 11.654
Urine output × urea		
up1 × ur1	0.0000	0.000 to 0.000
up1 × ur2	−0.0006	−0.001 to −0.000
up1 × ur3	0.0010	0.000 to 0.001
up2 × ur1	−0.0000	−0.000 to −0.000
up3 × ur1	0.0001	0.000 to 0.000
Primary reason for admission		
Congenital or acquired deformity or abnormality (cardiovascular)	0	–
Acute alcoholic hepatitis	1.3573	0.868 to 1.847
Secondary hepatic tumour	−1.0697	−1.562 to −0.577
Alcoholic cirrhosis	53.3078	−28.277 to 134.893
Intracerebral haemorrhage	1.9013	1.028 to 2.774
Thrombo-occlusive disease of brain	−22.3383	−34.611 to −10.065
Secondary hydrocephalus	1.3802	0.860 to 1.900
Non-traumatic subdural haemorrhage	−63.1698	−125.988 to −0.352
Accidental intoxication or poisoning (endocrine)	−0.8558	−1.369 to −0.343
Diabetes mellitus (endocrine)	−1.0476	−1.425 to −0.670
Dissection or aneurysm (cardiovascular)	−0.6190	−1.548 to 0.310
Haemolysis or thrombocytopaenia	−0.0992	−0.720 to 0.521
Hyperkalaemia (endocrine)	−0.1056	−0.544 to 0.333
Acidaemia (endocrine)	−0.3262	−0.750 to 0.098
Hypokalaemia (endocrine)	−0.3658	−0.998 to 0.267
Hyponatraemia (endocrine)	−1.1033	−1.605 to −0.601
Hypoplasia or dysplasia (haematological/immunological)	−0.2528	−0.792 to 0.286
Hypothermia (endocrine)	−0.3638	−1.004 to 0.276
Infection (dermatological, gastrointestinal, haematological/immunological, musculoskeletal, neurological)	−0.1026	−0.422 to 0.217

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Inflammation (cardiovascular, dermatological, genitourinary, musculoskeletal, respiratory)	−0.0115	−0.337 to 0.314
Obstruction (cardiovascular)	0.1067	−0.211 to 0.425
Oedema, inflammation, fibrosis or inhalation (respiratory)	0.3037	−0.282 to 0.889
Seizures (neurological)	−12.8697	−18.110 to −7.629
Self-harm or self-poisoning (endocrine)	−0.7470	−1.110 to −0.384
Shock and hypotension (cardiovascular)	0.0123	−0.321 to 0.345
Transplant or related (cardiovascular, endocrine, genitourinary haematological/immunological, respiratory)	−0.0969	−0.603 to 0.409
Trauma, perforation or rupture (dermatological, genitourinary, musculoskeletal, respiratory)	−0.0071	−0.337 to 0.323
Tumour or malignancy (cardiovascular, dermatological, endocrine, gastrointestinal, musculoskeletal, respiratory)	0.2613	−0.059 to 0.581
Burns or hyperthermia (dermatological)	0.4322	−0.233 to 1.097
Trauma (neurological)	−0.5736	−1.024 to −0.123
Non-traumatic aneurysm, dissection, perforation or rupture (cardiovascular)	0.0084	−0.319 to 0.336
Collapse (respiratory)	−0.1862	−0.581 to 0.209
Coma or encephalopathy (neurological)	−0.0842	−0.443 to 0.274
Congenital or acquired deformity or abnormality (cardiovascular, endocrine, gastrointestinal; genitourinary; or haematological/immunological)	−0.3324	−0.709 to 0.044
Failure		
Cardiovascular	0.2470	−0.094 to 0.588
Genitourinary	−0.1292	−0.452 to 0.193
Haemorrhage		
Respiratory	−0.0365	−0.601 to 0.528
Cardiovascular	0.3360	−0.218 to 0.890
Gastrointestinal	0.1104	−0.221 to 0.441
Neurological	−0.6118	−1.886 to 0.662
Genitourinary	−1.1498	−1.796 to −0.504
Infection		
Respiratory	−0.0255	−0.344 to 0.293
Cardiovascular	0.5422	0.152 to 0.932
Genitourinary	−0.6214	−0.960 to −0.283
Inflammation		
Gastrointestinal	0.5584	0.182 to 0.934
Neurological	−0.1261	−0.649 to 0.397

continued

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Obstruction		
Respiratory	−0.0402	−0.387 to 0.307
Gastrointestinal	0.4012	−0.063 to 0.865
Genitourinary	−0.2088	−0.610 to 0.192
Transplant or related (gastrointestinal)	−2.0240	−2.634 to −1.414
Trauma, perforation or rupture		
Cardiovascular	−0.3750	−0.842 to 0.092
Gastrointestinal	37.0740	21.185 to 52.963
Neurological	−0.7006	−7.471 to 6.070
Tumour or malignancy		
Neurological	0.8926	0.544 to 1.242
Genitourinary	0.0381	−0.309 to 0.385
Haematological/immunological	0.1457	−0.255 to 0.547
Vascular		
Gastrointestinal	−0.0174	−0.375 to 0.340
Neurological	−4.6421	−8.294 to −0.990
Congenital or acquired deformity or abnormality		
Respiratory	0.3014	−0.080 to 0.683
Musculoskeletal	−0.6118	−1.066 to −0.158
Neurological	−0.4875	−0.952 to −0.023
Degeneration		
Cardiovascular	−0.1856	−0.554 to 0.183
Neurological	1.2478	0.469 to 2.026
Vascular (cardiovascular/genitourinary)	0.2510	−0.438 to 0.940
Pulmonary fibrosis or fibrosing alveolitis	1.9348	1.437 to 2.433
Asthma attack in new or known asthmatic	−1.8175	−3.884 to 0.249
Multiple rib fractures	−0.5563	−1.087 to −0.025
Fungal or yeast pneumonia	1.2060	0.721 to 1.691
Hanging or strangulation	1.0532	0.533 to 1.573
Anoxic or ischaemic coma or encephalopathy	1.0522	0.701 to 1.404
Alcoholic hepatitis/cirrhosis × arterial pH		
ph1	−7.2654	−18.629 to 4.098
ph2	8.9448	−6.144 to 24.034
ph3	−126.2808	−290.065 to 37.504
Intracerebral haemorrhage × urine output		
up1	−0.0005	−0.001 to 0.000
up2	0.0027	−0.001 to 0.006
up3	−0.0064	−0.016 to 0.003

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Thrombo-occlusive disease of brain × sodium		
na1	0.1737	0.084 to 0.263
na2	−0.1449	−0.225 to −0.065
Non-traumatic subdural haemorrhage × arterial pH		
ph1	9.1336	0.389 to 17.878
ph2	−22.4754	−34.487 to −10.464
ph3	258.9084	123.289 to 394.528
Dissection or aneurysm (cardiovascular) × lowest white blood cell count		
wbc1	0.0913	−0.040 to 0.223
wbc2	−0.3243	−0.861 to 0.212
wbc3	0.9967	−0.502 to 2.495
Seizures (neurological) × sodium		
na1	0.0919	0.053 to 0.130
na2	−0.0918	−0.136 to −0.048
Haemorrhage (neuro) × urine output		
up1	0.0005	−0.001 to 0.002
up2	−0.0009	−0.005 to 0.003
up3	0.0022	−0.008 to 0.012
Haemorrhage (neuro) × blood lactate		
bl1	0.6899	0.046 to 1.334
bl2	−4.3553	−15.336 to 6.626
bl3	6.5023	−14.081 to 27.085
Inflammation (gastrointestinal) × PaO_2/FiO_2		
pf1	−0.0213	−0.035 to −0.008
pf2	0.0610	0.004 to 0.118
pf3	−0.1670	−0.354 to 0.020
Obstruction (gastrointestinal) × urine output		
up1	−0.0009	−0.001 to −0.000
up2	0.0050	0.003 to 0.007
up3	−0.0146	−0.022 to −0.008
Trauma, perforation or rupture (gastrointestinal) × arterial pH		
ph1	−5.1914	−7.410 to −2.973
ph2	6.4971	2.903 to 10.092
ph3	−54.5498	−105.038 to −4.061
Trauma, perforation or rupture (neurological) × sodium		
na1	0.0117	−0.037 to 0.061
na2	0.0323	−0.012 to 0.077

continued

TABLE 46 Coefficients for the risk model to predict mortality at 90 days following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Trauma, perforation or rupture (neurological) × urine output		
up1	−0.0006	−0.002 to 0.000
up2	0.0030	−0.001 to 0.007
up3	−0.0074	−0.017 to 0.002
Vascular (neurological) × highest heart rate		
hr1	0.0536	0.009 to 0.099
hr2	−0.0610	−0.245 to 0.123
hr3	0.1049	−0.448 to 0.658
Asthma attack in new or known asthmatic × urea		
ur1	−0.0217	−0.486 to 0.442
ur2	6.5180	−2.004 to 15.040
ur3	−14.3583	−30.877 to 2.161
Constant	−8.5962	−22.840 to 5.647

RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care

Predictor	Coefficient	95% CI
Age (years): RCS (26,53,66,75,85)		
age1	0.0402	0.035 to 0.046
age2	−0.0162	−0.029 to −0.003
age3	0.1154	0.019 to 0.212
age4	−0.1381	−0.396 to 0.120
Highest heart rate (min^{-1}): RCS (72,92,110,143)		
hr1	0.0027	−0.001 to 0.006
hr2	0.0215	0.007 to 0.036
hr3	−0.0610	−0.098 to −0.024
Lowest systolic blood pressure (mmHg): RCS (70,89,101,130)		
sbp1	−0.0148	−0.018 to −0.012
sbp2	0.0305	0.018 to 0.043
sbp3	−0.0765	−0.121 to −0.032
Highest temperature (°C): RCS (36,37,37.6,38.1,39.2)		
temp1	−0.2375	−0.348 to −0.032
temp2	1.0934	−0.462 to 2.649
temp3	−4.3752	−15.621 to 6.871
temp4	7.2029	−15.989 to 30.395
CPR × temperature		
In-hospital CPR × temp1	−0.1748	−0.400 to 0.051
No CPR × temp1	−0.1905	−0.337 to −0.044
In-hospital CPR × temp2	−0.1153	−2.395 to 2.164

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
No CPR × temp2	0.0085	−1.615 to 1.632
In-hospital CPR × temp3	−0.6850	−16.135 to 14.765
No CPR × temp3	−0.4952	−11.999 to 11.009
In-hospital CPR × temp4	3.2344	−27.516 to 33.985
No CPR × temp4	0.4438	−23.106 to 23.994
Lowest respiratory rate (min^{-1}): RRCS (8, to 11,14,20)		
rr1	−0.0547	−0.066 to −0.043
rr2	−0.0068	−0.019 to 0.005
rr3	0.0040	−0.002 to 0.010
rr4	−0.0011	−0.003 to 0.001
rr5	0.0002	0.000 to 0.000
Mechanical ventilation × respiratory rate		
Mechanical ventilation × rr1	0.0360	0.014 to 0.058
Mechanical ventilation × rr2	0.0120	−0.003 to 0.027
Mechanical ventilation × rr3	−0.0090	−0.018 to 0.000
Mechanical ventilation × rr4	0.0038	0.001 to 0.007
Mechanical ventilation × rr5	−0.0006	−0.001 to 0.000
PaO_2/FiO_2 (kPa): RCS (11,24,34,44,60)		
pf1	−0.0327	−0.043 to −0.022
pf2	0.0702	0.011 to 0.130
pf3	−0.1565	−0.377 to 0.064
pf4	0.0855	−0.204 to 0.375
Mechanical ventilation × PaO_2/FiO_2		
Mechanical ventilation × pf1	−0.0070	−0.020 to 0.006
Mechanical ventilation × pf2	0.0679	−0.013 to 0.149
Mechanical ventilation × pf3	−0.2733	−0.586 to 0.039
Mechanical ventilation × pf4	0.3664	−0.069 to 0.802
Lowest arterial pH: RCS (7.15,7.33,7.41)		
ph1	−1.7813	−2.126 to −1.437
ph2	1.9573	1.631 to 2.284
Highest urea ($mmol\ l^{-1}$): RCS (2.8,4.8,6.9,10.7,26.7)		
ur1	0.0253	−0.019 to 0.070
ur2	0.7158	−0.930 to 2.361
ur3	−1.1823	−4.961 to 2.596
ur4	0.1892	−2.321 to 2.699
Highest creatinine ($mg\ dl^{-1}$): RCS (0.5,0.8,1.2,4.1)		
cr1	−0.5515	−0.766 to −0.337
cr2	13.6009	8.378 to 18.824
cr3	−24.4843	−33.797 to −15.172

continued

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Highest sodium (mmol l^{-1}): RCS (132,137,139,141,147)		
na1	−0.0315	−0.041 to −0.022
na2	−0.1065	−0.176 to −0.037
na3	1.3354	0.672 to 1.999
na4	−2.1229	−3.276 to −0.970
Lowest white blood cell count (× 10^9 l^{-1}): RCS (3.9,8,10.6,13.7,21.9)		
wbc1	−0.0229	−0.042 to −0.004
wbc2	0.0676	−0.100 to 0.235
wbc3	0.0945	−0.609 to 0.798
wbc4	−0.4690	−1.298 to 0.360
Urine output (ml): RCS (158,1020,1567,2300,4215)		
up1	−0.0009	−0.001 to −0.001
up2	0.0029	0.002 to 0.004
up3	−0.0072	−0.011 to −0.003
up4	0.0048	0.000 to 0.009
$PaCO_2$ (kPa): RRCS (3.7, 5.5, 6.1, 9.1)		
pc1	−0.0604	−0.092 to −0.029
pc2	0.0816	−0.050 to 0.213
pc3	−0.1446	−0.234 to −0.055
pc4	0.0728	0.028 to 0.117
pc4	−0.0012	−0.004 to 0.002
Mechanical ventilation × $PaCO_2$		
Mechanical ventilation × pc1	0.0357	0.002 to 0.069
Mechanical ventilation × pc2	0.1008	−0.166 to 0.368
Mechanical ventilation × pc3	0.0003	−0.142 to 0.142
Mechanical ventilation × pc4	−0.0340	−0.098 to 0.030
Mechanical ventilation × pc4	0.0035	0.000 to 0.007
Highest blood lactate (mmol l^{-1}): RCS (.8,1.3,1.9,2.9,7.1)		
bl1	0.2171	0.063 to 0.371
bl2	−7.9005	−14.312 to −1.490
bl3	17.6113	3.741 to 31.482
bl4	−11.7356	−20.697 to −2.774
Lowest platelet count (× 10^9 l^{-1}): RCS (62,144,193,248,398)		
plc1	−0.0063	−0.007 to −0.005
plc2	0.0230	0.015 to 0.032
plc3	−0.0376	−0.077 to 0.001
plc4	−0.0173	−0.067 to 0.032
BMI (kg/m^2): RCS (18.5,23.1,25.9,29.4,38.2)		
bmi1	−0.0734	−0.091 to −0.055
bmi2	0.1101	−0.035 to 0.255

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
bmi3	−0.1581	−0.789 to 0.473
bmi4	0.0222	−0.720 to 0.764
Sedated/paralysed/GCS (15)		
15	0	
14	0.1648	0.107 to 0.223
7–13	0.3286	0.272 to 0.385
Sedated	0.7157	0.534 to 0.898
6	0.5969	0.538 to 0.656
5 or paralysed and sedated	0.6487	0.522 to 0.775
4	0.9358	0.707 to 1.165
3	1.4348	1.309 to 1.561
Mechanical ventilation	1.0179	0.476 to 1.559
Source of admission/urgency of surgery		
ED or not in hospital (unplanned admission)	0	
ED or not in hospital (planned admission)	−0.1925	−0.433 to 0.048
Other acute hospital (not critical care)	0.1291	−0.050 to 0.308
Other critical care unit (repatriation)	0.2741	−0.023 to 0.571
Other critical care unit (planned or unplanned transfer)	0.1297	0.019 to 0.241
Theatre (unplanned admission following elective or scheduled surgery)	−0.4574	−0.572 to −0.343
Theatre (planned admission following elective or scheduled surgery)	−0.7712	−0.856 to −0.686
Theatre (admission following emergency or urgent surgery)	−0.1585	−0.226 to −0.091
Ward or intermediate care area	0.2743	0.224 to 0.325
CPR prior to admission		
Community CPR	0	
In-hospital CPR	6.0415	−2.032 to 14.115
No CPR	6.2556	0.997 to 11.514
Dependency prior to admission		
No assistance with daily activities	0	
Some assistance with daily activities	0.4080	0.366 to 0.450
Total assistance with daily activities	0.6734	0.485 to 0.862
Severe liver disease	1.0018	0.887 to 1.117
Metastatic disease	1.3364	1.255 to 1.418
Haematological malignancy	0.6660	0.541 to 0.791
Severe respiratory disease/home ventilation	0.5243	0.416 to 0.633
Immunocompromise	0.4022	0.331 to 0.474
End-stage renal failure	0.2855	0.138 to 0.433
Very severe cardiovascular disease	0.2767	0.154 to 0.399

continued

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Congestive cardiac failure	0.2893	0.213 to 0.365
Peripheral vascular disease	0.2573	0.177 to 0.337
Cerebrovascular disease	0.1884	0.091 to 0.286
Chronic pulmonary disease	0.1770	0.125 to 0.229
Liver disease	0.3927	0.280 to 0.505
Chronic renal disease	0.2335	0.157 to 0.310
Any malignancy	0.3475	0.283 to 0.411
Primary reason for admission		
Accidental intoxication, poisoning or medication event	0	–
Diabetes mellitus	−0.6676	−1.068 to −0.268
Dissection or aneurysm	16.9270	1.789 to 32.065
Failure	−1.9486	−10.729 to 6.832
Haemolysis or thrombocytopaenia	0.4483	−0.272 to 1.169
Haemorrhage	0.5971	0.092 to 1.102
Cardiovascular	−0.3180	−0.976 to 0.340
Gastrointestinal	0.5151	0.151 to 0.879
Neurological (including eyes)	−5.8257	−28.807 to 17.156
Genitourinary	−0.2582	−0.815 to 0.298
Hyperkalaemia	−0.0753	−0.559 to 0.408
Hypertension (cardiovascular) or over- or under-activity (cardiovascular/genitourinary)	0.1996	−0.163 to 0.562
Acidaemia	0.5458	0.083 to 1.008
Hypokalaemia	0.0024	−0.636 to 0.641
Hyponatraemia	−0.4733	−0.995 to 0.049
Hypoplasia or dysplasia	1.1075	0.441 to 1.774
Hypothermia	−0.1838	−0.756 to 0.389
Infection	0.3031	−0.066 to 0.672
Respiratory	1.0197	0.558 to 1.482
Cardiovascular	0.8110	0.381 to 1.241
Gastrointestinal	0.0700	−0.290 to 0.430
Neurological (including eyes)	−0.1316	−1.039 to 0.775
Genitourinary	−0.1171	−0.487 to 0.253
Inflammation	0.5741	0.116 to 1.032
Respiratory	0.5149	0.154 to 0.876
Gastrointestinal	0.5988	−0.034 to 1.231
Neurological (including eyes)	0.0965	−0.468 to 0.660
Obstruction	0.1350	−0.224 to 0.494
Respiratory	0.3482	−0.030 to 0.727
Cardiovascular	0.3609	0.005 to 0.716
Oedema, inflammation, fibrosis or inhalation	0.2641	−0.368 to 0.896
Seizures	−11.1015	−17.311 to −4.892

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Self-harm or self-poisoning	−0.2824	−0.662 to 0.098
Shock or hypotension	0.5697	0.200 to 0.940
Transplant (or related)	3.3775	0.823 to 5.932
Gastrointestinal	−1.6567	−2.201 to −1.113
Trauma, perforation or rupture	0.4698	0.048 to 0.891
Respiratory	0.0833	−0.335 to 0.502
Musculoskeletal	0.5132	0.146 to 0.880
Gastrointestinal	−1.7297	−3.217 to −0.243
Neurological (including eyes)	−1.7550	−3.437 to −0.073
Tumour or malignancy	0.9192	0.560 to 1.279
Gastrointestinal	3.0139	2.175 to 3.852
Neurological (including eyes)	3.6747	2.151 to 5.198
Vascular	0.2480	−0.380 to 0.876
Gastrointestinal	0.4165	0.031 to 0.802
Neurological (including eyes)	0.8837	0.435 to 1.332
Burns or hyperthermia	3.2998	−0.409 to 7.009
otherEndoc	−0.2853	−0.760 to 0.189
Collapse	0.4069	−0.018 to 0.832
Coma or encephalopathy	−0.8792	−4.851 to 3.093
Congenital or acquired deformity or abnormality	0.3360	−0.031 to 0.703
Musculoskeletal	−0.0871	−0.507 to 0.333
Neurological (including eyes)	0.2235	−0.229 to 0.676
Degeneration		
Musculoskeletal	2.0208	1.243 to 2.799
Neurological (including eyes)	−0.0133	−0.421 to 0.395
Cardiovascular	−14.1255	−24.495 to −3.756
CABG for chronic angina	0.9192	0.522 to 1.317
Lower limb artery stenosis or occlusion	−0.6020	−1.181 to −0.023
Anaphylaxis	1.7791	1.381 to 2.177
Pancreatic or pancreato-duodenal tumour	−0.1059	−0.532 to 0.320
Secondary hepatic tumour	1.4456	1.012 to 1.879
Small bowel tumour	−0.5314	−1.030 to −0.033
Leaking large bowel anastomosis	−0.4174	−1.871 to 1.037
Malignant large bowel tumour	1.4994	1.008 to 1.991
Alcoholic cirrhosis	0.4731	0.098 to 0.848
Large bowel tumour	0.1207	−0.322 to 0.564
Toxic or drug induced coma or encephalopathy	1.5003	1.098 to 1.902
Thrombo-occlusive disease of brain	1.8920	1.340 to 2.444
Secondary hydrocephalus	152.3005	32.230 to 272.371
Carotid or vertebral artery stenosis or occlusion	1.9850	1.445 to 2.525

continued

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Pulmonary fibrosis or fibrosing alveolitis	−1.0007	−1.475 to −0.526
Asthma attack in new or known asthmatic	1.2679	0.743 to 1.792
Hanging or strangulation	1.1365	0.746 to 1.527
Dissection or aneurysm × arterial pH		
ph1	−2.2849	−4.384 to −0.186
ph2	−0.1132	−2.470 to 2.243
Failure × temperature		
temp1	0.0878	−0.152 to 0.327
temp2	−1.0850	−2.512 to 0.342
temp3	5.0662	−3.501 to 13.634
temp4	−8.2784	−24.525 to 7.968
Failure × blood lactate		
bl1	−0.0659	−0.572 to 0.440
bl2	4.7589	−17.917 to 27.434
bl3	−9.3263	−59.077 to 40.424
bl4	4.4999	−28.325 to 37.325
Failure × $PaCO_2$		
pc1	0.0418	−0.043 to 0.127
pc2	−0.0309	−0.307 to 0.246
pc3	−0.0331	−0.256 to 0.190
pc4	0.0323	−0.086 to 0.151
pc4	−0.0056	−0.014 to 0.002
Haemorrhage: neurological (including eyes) × temperature		
temp1	0.1878	−0.439 to 0.815
temp2	−1.3921	−4.241 to 1.457
temp3	4.0789	−10.164 to 18.322
temp4	1.3577	−21.964 to 24.679
Haemorrhage: neurological (including eyes) × urine output		
up1	−0.0011	−0.002 to 0.000
up2	0.0120	0.003 to 0.021
up3	−0.0467	−0.079 to −0.014
up4	0.0489	0.017 to 0.081
Haemorrhage: neurological (including eyes) × blood lactate		
bl1	1.5292	0.677 to 2.381
bl2	−29.1072	−64.127 to 5.912
bl3	49.0447	−26.818 to 124.907
bl4	−17.3413	−66.669 to 31.987
Haemorrhage: neurological (including eyes) × $PaCO_2$		
pc1	0.0521	−0.080 to 0.184
pc2	0.2599	−2.426 to 2.945

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
pc3	−0.4601	−1.002 to 0.081
pc4	0.2745	0.067 to 0.482
pc4	−0.0196	−0.031 to −0.008
Infection: neurological (including eyes) × urine output		
up1	0.0007	−0.001 to 0.002
up2	−0.0092	−0.022 to 0.004
up3	0.0427	−0.008 to 0.093
up4	−0.0500	−0.103 to 0.003
Infection: respiratory × $PaCO_2$		
pc1	0.0525	0.020 to 0.085
pc2	−0.1969	−0.672 to 0.279
pc3	0.0903	−0.113 to 0.293
pc4	−0.0310	−0.118 to 0.056
pc4	−0.0027	−0.007 to 0.002
Inflammation: gastrointestinal × lowest platelet count		
plc1	0.0014	−0.004 to 0.007
plc2	0.0082	−0.042 to 0.058
plc3	−0.1248	−0.364 to 0.114
plc4	0.2390	−0.075 to 0.553
Seizures × sodium		
na1	0.0849	0.038 to 0.132
na2	−0.2056	−0.680 to 0.268
na3	−0.3675	−5.093 to 4.358
na4	2.4612	−5.868 to 10.791
Transplant (or related) × lowest white blood cell count		
wbc1	−0.6301	−1.125 to −0.135
wbc2	2.5151	−2.138 to 7.168
wbc3	−5.0071	−24.896 to 14.881
wbc4	0.9611	−22.733 to 24.655
Trauma, perforation or rupture: gastrointestinal × respiratory rate		
rr1	−0.0435	−0.106 to 0.019
rr2	0.0059	−0.021 to 0.033
rr3	0.0078	−0.011 to 0.027
rr4	−0.0082	−0.016 to −0.001
rr5	0.0014	0.000 to 0.002
Trauma, perforation or rupture: gastrointestinal × blood lactate		
bl1	0.7457	−0.085 to 1.577
bl2	−26.7689	−59.619 to 6.081
bl3	55.5694	−14.458 to 125.597
bl4	−32.7333	−76.836 to 11.370

continued

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Trauma, perforation or rupture: neurological (including eyes) × urine output		
up1	0.0012	0.000 to 0.003
up2	−0.0070	−0.018 to 0.004
up3	0.0229	−0.015 to 0.061
up4	−0.0192	−0.057 to 0.018
Trauma, perforation or rupture: neurological (including eyes) × blood lactate		
bl1	1.1179	−0.102 to 2.338
bl2	−30.5768	−79.059 to 17.906
bl3	64.0631	−39.581 to 167.707
bl4	−39.1497	−104.900 to 26.600
Tumour or malignancy: gastrointestinal × highest urea		
ur1	−0.4347	−0.631 to −0.238
ur2	10.0194	2.127 to 17.912
ur3	−19.1204	−37.844 to −0.396
ur4	8.8289	−4.280 to 21.938
Tumour or malignancy: neurological (including eyes) × heart rate		
hr1	−0.0180	−0.037 to 0.001
hr2	−0.0292	−0.125 to 0.066
hr3	0.1284	−0.148 to 0.404
Burns or hyperthermia × PaO_2/FiO_2		
pf1	−0.0428	−0.263 to 0.178
pf2	−0.4665	−1.844 to 0.911
pf3	1.0993	−4.512 to 6.710
pf4	0.3428	−8.083 to 8.769
Coma or encephalopathy × BMI		
bmi1	0.0325	−0.164 to 0.229
bmi2	1.6076	−0.137 to 3.352
bmi3	−9.1022	−17.144 to −1.060
bmi4	12.1000	2.109 to 22.091
CABG for chronic angina × lowest white blood cell count		
wbc1	2.2429	0.658 to 3.828
wbc2	−15.9445	−25.493 to −6.396
wbc3	64.1709	29.040 to 99.302
wbc4	−75.1789	−113.907 to −36.451
Malignant large bowel tumour × lowest platelet count		
plc1	0.0087	−0.004 to 0.022
plc2	−0.0711	−0.153 to 0.010
plc3	0.3219	−0.013 to 0.657
plc4	−0.3808	−0.770 to 0.009

TABLE 47 Coefficients for the risk model to predict mortality at 1 year following admission to critical care (*continued*)

Predictor	Coefficient	95% CI
Carotid or vertebral artery stenosis or occlusion × arterial pH		
ph1	−20.8485	−37.379 to −4.318
ph2	7.6999	−3.519 to 18.919
Constant	25.8772	21.050 to 30.704

RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

TABLE 48 Coefficients of the two-part model for modelling total health-care cost

Predictor	Coefficient (SE)	
	Health-care during 1 year after hospital discharge	If health care, total cost during 1 year after hospital discharge
Previous hospitalisation	0.426*** (0.012)	0.067*** (0.011)
Critical care unit length of stay (per day)	0.006*** (0.001)	0.011*** (0.001)
Age (spline base variables)		
age_1	0.008*** (0.001)	0.006*** (0.001)
age_2	−0.002** (0.002)	−0.000 (0.002)
age_3	0.011 (0.014)	−0.065*** (0.014)
BMI (spline base variables)		
bmi_1	−0.022*** (0.004)	−0.012*** (0.003)
bmi_2	0.082*** (0.019)	0.035** (0.016)
bmi_3	−1.99*** (0.050)	−0.077* (0.044)
Deprivation		
1 (least deprived)	0	0
2	0.027 (1.71)	−0.027 (1.90)
3	0.046*** (2.93)	−0.029* (2.10)
4	0.072*** (4.63)	0.020 (1.43)
5 (most deprived)	0.130*** (8.52)	−0.004 (0.31)
Dependency prior to admission		
No assistance with daily activities	0	0
Some assistance with daily activities	0.233*** (0.013)	0.098*** (0.010)
Total assistance with daily activities	0.572*** (0.062)	0.315*** (0.048)
ICNARC physiology score (spline base variables)		
$score_1$	0.018*** (0.004)	0.006 (0.004)
$score_2$	0.054** (0.021)	0.046** (0.020)
$score_3$	−0.179*** (0.050)	−0.132*** (0.048)
Source of admission/urgency of surgery		
ED or not in hospital (unplanned admission)	0	0
ED or not in hospital (planned admission)	−0.196*** (0.058)	0.070(0.059)

continued

TABLE 48 Coefficients of the two-part model for modelling total health-care cost (*continued*)

Predictor	Coefficient (SE)	
	Health-care during 1 year after hospital discharge	If health care, total cost during 1 year after hospital discharge
Other acute hospital (not critical care)	−0.028 (0.054)	0.056 (0.047)
Other critical care unit (repatriation)	−0.054 (0.096)	0.083 (0.080)
Other critical care unit (planned or unplanned transfer)	−0.014 (0.039)	0.060** (0.035)
Theatre (unplanned admission following elective or scheduled surgery)	−0.107*** (0.024)	−0.015 (0.021)
Theatre (planned admission following elective or scheduled surgery)	−0.345*** (0.015)	−0.084*** (0.014)
Theatre (admission following emergency or urgent surgery)	−0.004 (0.015)	0.013 (0.014)
Ward or intermediate care area	0.113*** (0.015)	0.087*** (0.013)
CPR prior to admission		
Community CPR	0	0
In-hospital CPR	0.368*** (0.055)	0.028 (0.053)
No CPR	0.329*** (0.040)	0.061 (0.042)
Severe conditions in the past medical history (APACHE II)		
Severe respiratory disease	0.829** (0.388)	1.283*** (0.307)
Severe liver disease	1.846*** (0.377)	0.604** (0.277)
End-stage renal disease	1.512*** (0.443)	1.000*** (0.272)
Metastatic disease	0.569** (0.349)	0.773*** (0.233)
Haematological malignancy	1.625*** (0.450)	0.499** (0.232)
Immunocompromise	0.763*** (0.218)	0.609*** (0.165)
RCS Charlson comorbidities		
Previous MI	0.156*** (0.025)	0.021 (0.018)
Congestive cardiac failure	0.144*** (0.023)	0.078*** (0.018)
Peripheral vascular disease	0.172*** (0.022)	0.144*** (0.016)
Dementia	0.163*** (0.051)	0.022 (0.032)
Chronic pulmonary disease	1.209*** (0.154)	0.181* (0.118)
Rheumatological disease	0.200*** (0.034)	0.092*** (0.025)
Liver disease	0.622* (0.338)	0.601*** (0.230)
Diabetes mellitus	1.75*** (0.162)	0.358*** (0.110)
Hemiplegia or paraplegia	0.485*** (0.057)	0.227*** (0.037)
Chronic renal disease	0.365*** (0.024)	0.149*** (0.016)
Any malignancy (excluding haematological malignancy and metastatic disease)	0.683** (0.255)	0.529*** (0.179)
Mechanical ventilation	−0.167*** (0.011)	−0.079*** (0.011)

TABLE 48 Coefficients of the two-part model for modelling total health-care cost (*continued*)

Predictor	Coefficient (SE)	
	Health-care during 1 year after hospital discharge	If health care, total cost during 1 year after hospital discharge
Interaction between age and severe respiratory disease		
age_1	−0.005 (0.010)	−0.023*** (0.008)
age_2	−0.008 (0.017)	0.013 (0.013)
age_3	0.048 (0.112)	−0.022 (0.080)
Interaction between age and severe liver disease		
age_1	−0.027*** (0.009)	−0.002 (0.007)
age_2	0.014 (0.017)	−0.018 (0.013)
age_3	−0.048 (0.131)	0.150 (0.094)
Interaction between age and ESRD		
age_1	−0.014 (0.011)	−0.014** (0.007)
age_2	0.013 (0.019)	0.016 (0.011)
age_3	−0.039 (0.130)	−0.134* (0.074)
Interaction between age and metastatic disease		
age_1	−0.003 (0.008)	−0.012** (0.005)
age_2	−0.015 (0.012)	0.011 (0.008)
age_3	0.016 (0.074)	−0.039 (0.047)
Interaction between age and haematological malignancy		
age_1	−0.020 (0.011)	0.002 (0.006)
age_2	0.012 (0.020)	−0.027** (0.012)
age_3	−0.127 (0.128)	0.178** (0.076)
Interaction between age and immunocompromise		
age_1	−0.013*** (0.005)	−0.013*** (0.004)
age_2	0.016* (0.010)	0.017*** (0.007)
age_3	−0.093* (0.064)	−0.094** (0.045)
Interaction between age and chronic pulmonary disease		
age_1	−0.016*** (0.003)	−0.004* (0.003)
age_2	0.005 (0.006)	−0.005 (0.005)
age_3	−0.018 (0.039)	0.053* (0.029)
Interaction between age and chronic renal disease		
age_1	0.003 (0.009)	−0.008 (0.006)
age_2	−0.038*** (0.016)	−0.005 (0.010)
age_3	0.255** (0.110)	0.070 (0.069)
Interaction between age and diabetes mellitus		
age_1	−0.029*** (0.004)	−0.003 (0.003)
age_2	0.019*** (0.007)	−0.006 (0.005)
age_3	−0.049 (0.041)	0.055* (0.029)

continued

TABLE 48 Coefficients of the two-part model for modelling total health-care cost (*continued*)

Predictor	Coefficient (SE)	
	Health-care during 1 year after hospital discharge	If health care, total cost during 1 year after hospital discharge
Interaction between age and any malignancy		
age_1	−0.007 (0.006)	−0.011*** (0.004)
age_2	0.005 (0.009)	0.009 (0.006)
age_3	−0.064 (0.049)	−0.013 (0.035)
Interaction between ICNARC physiology score and metastatic disease		
$score_1$	0.011 (0.017)	−0.009 (0.010)
$score_2$	−0.207** (0.096)	−0.049 (0.061)
$score_3$	0.466* (0.233)	0.150 (0.148)
Interaction between ICNARC physiology score and chronic pulmonary disease		
$score_1$	−0.002 (0.011)	0.025*** (0.008)
$score_2$	0.001 (0.058)	−0.166*** (0.045)
$score_3$	−0.017 (0.139)	0.391*** (0.107)
Constant	−1.130*** (0.101)	8.576*** (0.096)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

TABLE 49 Coefficients for the risk models to predict acute hospital mortality and 1-year mortality

Predictor	Coefficient for acute hospital mortality (95% CI)	Coefficient for 1-year mortality (95% CI)
Constant	19.0409 (5.2276 to 32.8542)	22.7658 (10.4998 to 35.081)
Age (years): RCS (37,63,74,83)		
age_1	−0.0084 (−0.0334 to 0.0165)	−0.0026 (−0.0228 to 0.0171)
age_2	0.0581 (0.0214 to 0.0949)	0.0463 (0.0183 to 0.0745)
age_3	−0.3178 (−0.6113 to −0.0242)	−0.1999 (−0.4187 to 0.0180)
Lowest systolic blood pressure (mmHg): RCS (67,85,95,112)		
sbp_1	−0.0344 (−0.0448 to −0.0241)	−0.01593 (−0.0248 to −0.0070)
sbp_2	0.0387 (0.0001 to 0.0773)	−0.0060 (−0.0357 to 0.0235)
sbp_3	−0.0587 (−0.2478 to 0.1304)	0.0963 (−0.0456 to 0.2387)
Lowest arterial pH: RCS (7.16,7.29,7.33,7.41)		
ph_1	−3.003 (−4.9167 to −1.090)	−3.5008 (−5.2058 to −1.7955)
ph_2	−4.7396 (−9.6991 to 0.2196)	−0.6731 (−4.6075 to 3.2181)
ph_3	121.2283 (66.9497 to 175.5069)	65.9343 (24.0232 to 109.1032)
Highest creatinine (μmol l^{-1}): RCS (51,80,106,247)		
cr_1	0.0060 (−0.0089 to 0.0211)	0.0005 (−0.0088 to 0.0102)
cr_2	0.0747 (−0.0693 to 0.2189)	0.0701 (−0.0275 to 0.1624)
cr_3	−0.1977 (−0.5138 to 0.1183)	−0.1718 (−0.3744 to 0.0450)

TABLE 49 Coefficients for the risk models to predict acute hospital mortality and 1-year mortality (*continued*)

Predictor	Coefficient for acute hospital mortality (95% CI)	Coefficient for 1-year mortality (95% CI)
Lowest white blood cell count (× 10^9 l^{-1}): RCS (5.8,9.2,11.8,17.8)		
wbc_1	−0.0460 (−0.1230 to 0.0311)	−0.0124 (−0.0738 to 0.0454)
wbc_2	0.0993 (−0.2264 to 0.4255)	−0.0159 (−0.2587 to 0.2351)
wbc_3	−0.1036 (−1.0347 to 0.8271)	0.1622 (−0.5521 to 0.8574)
Lowest platelet count (× 10^9 l^{-1}): RCS (73,134,183,337)		
pc_1	−0.0083 (−0.0121 to −0.0044)	−0.0098 (−0.0130 to −0.0067)
pc_2	0.0156 (−0.0095 to 0.0409)	0.0355 (0.0163 to 0.0546)
pc_3	−0.0182 (−0.0869 to 0.0504)	−0.0749 (−0.1267 to −0.0228)
Highest blood lactate (mmol l^{-1})	0.1339 (0.1088 to 0.1589)	0.0921 (0.0705 to 0.1136)
GCS		
15	0	0
9–14	0.5298 (0.2525 to 0.8071)	0.3022 (0.0915 to 0.5128)
3–8	1.5054 (0.9681 to 2.0425)	1.2111 (0.7318 to 1.6870)
Sedated	1.1835 (0.9681 to 1,3689)	0.8897 (0.7309 to 1.0441)
Male	0.3789 (0.2147 to 0.5431)	−0.2831 (−0.4078 to −0.1638)
Diabetes		
No diabetes	0	0
Diet/oral therapy/insulin	0.2948 (0.1255 to 0.4642)	0.3251 (0.2043 to 0.4511)
Preoperatory heart rhythm		
Sinus rhythm, complete heart block/pacing, ventricular fibrillation or ventricular tachycardia, other abnormal rhythm	0	0
Atrial fibrillation/flutter	0.2975 (0.1141 to 0.4805)	0.4164 (0.2835 to 0.5535)
Dyspnoea status pre surgery		
No limitation or slight limitation of ordinary physical activity	0	
Marked limitation of ordinary physical activity	0.2039 (0.0357 to 0.3721)	0.2161 (0.0918 to 0.3352)
Symptoms at rest or minimal activity	0.5878 (0.3505 to 0.8252)	0.4441 (0.2403 to 0.6251)
History of pulmonary disease	0.5020 (0.3238 to 0.6803)	0.3970 (0.2645 to 0.5298)
History of neurological dysfunction	0.4756 (0.1461 to 0.8052)	0.3333 (0.0698 to 0.5849)
Extracardiac arteriopathy	0.3470 (0.1520 to 0.5420)	0.3499 (0.2066 to 0.4961)
Operative urgency		
Elective	0	
Urgent	0.3561 (0.1884 to 0.5238)	0.3505 (0.2267 to 0.4715)
Emergency	0.9332 (0.6624 to 1.2040)	0.8001 (0.5514 to 1.0209)
Salvage	1.7730 (1.1748 to 2.3712)	1.3225 (0.7514 to 1.8664)
Cumulative bypass time (per minute)	0.0085 (0.0035 to 0.0135)	0.0071 (0.0036 to 0.0104)
Severe respiratory disease	0.8915 (0.2556 to 1.5274)	0.7726 (0.2426 to 1.2961)

continued

TABLE 49 Coefficients for the risk models to predict acute hospital mortality and 1-year mortality (*continued*)

Predictor	Coefficient for acute hospital mortality (95% CI)	Coefficient for 1-year mortality (95% CI)
Very severe cardiovascular disease	0.4161 (0.1561 to 0.6761)	0.4664 (0.2757 to 0.6655)
Congestive heart failure	0.3243 (0.0800 to 0.5686)	0.4613 (0.2786 to 0.6479)
Renal function/dialysis		
None or dialysis for acute renal failure: onset within 6 weeks of cardiac surgery	–	0
Dialysis for chronic renal failure: onset more than 6 weeks prior to cardiac surgery		0.4439 (0.149072 to 0.73891)
No dialysis but pre-operative acute renal failure (anuria or oliguria < 10 ml/hour)	–	0.3182 (0.1045002 to 0.53192)
Left ventricular ejection fraction		
Good (LVEF > 50%)	–	0
Fair (LVEF 30–50%)	–	0.2591 (0.1333 to 0.3807)
Poor (LVEF < 30%)	–	0.2855 (0.0944 to 0.4751)
Number of previous MIs	–	0.2676 (0.0752 to 0.4682)
Major aortic procedure	–	0.2625 (0.0725 to 0.4507)

RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

TABLE 50 Coefficients for the risk model to predict ROSC > 20 minutes following in-hospital cardiac arrest

Predictor	Patients, *N*	ROSC > 20 minutes, *n* (%)	Coefficient (95% CI)
Age: RCS (42,67,76,83,91)[a]			
age_1	–	–	−0.0065 (−0.0108 to −0.0022)
age_2	–	–	−0.0018 (−0.0148 to 0.0111)
age_3	–	–	−0.1002 (−0.2904 to 0.0899)
age_4	–	–	0.2704 (−0.2973 to 0.8381)
Sex			
Female	11,241	5215 (46.4)	0
Male	15,507	7349 (47.4)	−0.0728 (−0.1270 to -0.01871)
Prior length of stay (days)			
0	7150	3961 (55.4)	0
1	4647	2184 (47.0)	−0.1661 (−0.2582 to −0.0740)
2–7	8652	3705 (42.8)	−0.2534 (−0.3406 to −0.1661)
≥ 8	6299	2714 (43.1)	−0.2553 (−0.3491 to −0.1615)
Reason for attendance			
Patient: medical	21,750	9904 (45.5)	0
Patient: trauma	843	349 (41.4)	0.0890 (−0.0647 to 0.2428)
Patient: elective surgery	1678	1059 (63.1)	−0.0497 (−0.1524 to 0.0528)

TABLE 50 Coefficients for the risk model to predict ROSC > 20 minutes following in-hospital cardiac arrest (*continued*)

Predictor	Patients, *N*	ROSC > 20 minutes, *n* (%)	Coefficient (95% CI)
Patient: emergency surgery	2100	974 (46.4)	0.5358 (0.4169 to 0.6547)
Patient: obstetric	41	32 (78.0)	0.8754 (0.0934 to 1.6574)
Outpatient	286	214 (74.8)	0.3928 (0.0250 to 0.7606)
Staff or visitor	50	32 (64.0)	0.0543 (−0.5692 to 0.6780)
Location of arrest			
Emergency department	2486	1154 (46.4)	−0.1645 (−0.4105 to 0.0815)
Emergency admissions unit	2161	943 (43.6)	0.0786 (−0.0284 to 0.1856)
Ward, obstetric area, intermediate care area or other inpatient location	15,713	6273 (39.9)	0
Coronary care unit	2329	1449 (62.2)	0.6763 (0.4786 to 0.8740)
Critical care unit	1846	1222 (66.2)	0.3193 (0.0087 to 0.6301)
Imaging department or specialist treatment area	719	440 (61.2)	0.0684 (−0.3843 to 0.5212)
Cardiac catheter laboratory	874	632 (72.3)	0.0718 (−0.1219 to 0.2656)
Theatre and recovery	400	289 (72.3)	−0.8021 (−1.3882 to −0.2159)
Clinic or non-clinical area	220	162 (73.6)	0.6171 (0.2113 to 1.0228)
Presenting/first documented rhythm			
Ventricular fibrillation	2746	1987 (72.4)	0
Ventricular tachycardia	1218	999 (82.0)	0.5461 (0.37101 to 0.7213)
Shockable–unknown rhythm	128	69 (53.9)	−1.9549 (−2.0861 to −1.8236)
Asystole	6160	1788 (29.0)	−1.0562 (−1.1739 to −0.9384)
Pulseless electrical activity	13,908	6030 (43.4)	−0.0047 (−0.3832 to 0.3737)
Bradycardia	206	157 (76.2)	−0.0047 (−0.3832 to 0.3737)
Non-shockable–unknown rhythm	566	308 (54.4)	−0.5550 (−0.9474 to −0.1626)
Unknown	1816	1226 (67.5)	0.0614 (−0.3069 to 0.4298)
Interaction between asystole and location of arrest			
Emergency department	–	–	0.3187 (−0.0082 to 0.6456)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	1.141 (0.8601 to 1.4232)
Critical care unit	–	–	1.1163 (0.7441 to 1.4885)
Imaging department or specialist treatment area	–	–	0.9262 (0.3219 to 1.5306)
Theatre and recovery	–	–	3.2121 (2.3529 to 4.0713)
Interaction between PEA and location of arrest			
Emergency department	–	–	−0.0053 (−0.2655 to 0.2549)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	−0.5772 (−0.7981 to -0.3563)

continued

TABLE 50 Coefficients for the risk model to predict ROSC > 20 minutes following in-hospital cardiac arrest (*continued*)

Predictor	Patients, *N*	ROSC > 20 minutes, *n* (%)	Coefficient (95% CI)
Critical care unit	–	–	0.3153 (–0.0225 to 0.6532)
Imaging department or specialist treatment area	–	–	0.3245 (–0.1674 to 0.8165)
Theatre and recovery	–	–	1.6769 (1.0236 to 2.3301)
Interaction between other non-shockable/unknown rhythms and location of arrest			
Emergency department	–	–	–0.0481 (–0.4443 to 0.3480)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	–0.1078 (–0.5557 to 0.3400)
Critical care unit	–	–	0.2421 (–0.3315 to 0.8157)
Imaging department or specialist treatment area	–	–	0.9739 (0.2370 to 1.7109)
Theatre and recovery	–	–	0.9313 (–0.0340 to 1.8966)
Congestive cardiac failure			
No	22,997	10,912 (47.4)	0
Yes	3741	1652 (44.2)	–0.1851 (–0.2665 to –0.1036)
Peripheral vascular disease			
No	25,022	11,798 (47.2)	0
Yes	1726	766 (44.4)	–0.1757 (–0.2864 to –0.0651)
Diabetes mellitus			
No	22,255	10,382 (46.7)	0
Yes	4493	2182 (48.6)	0.1373 (0.0622 to 0.2124)
Chronic renal disease			
No	23,506	11,042 (47.0)	0
Yes	3242	1522 (46.9)	0.1429 (0.0554 to 0.2305)
Malignancy			
No	24,345	11,615 (47.7)	0
Yes	2403	949 (39.5)	–0.2221 (–0.3290 to –0.1151)
Metastatic solid tumour			
No	26,010	12,316 (47.4)	0
Yes	738	248 (33.6)	–0.3790 (–0.5695 to –0.1886)
Constant	–	–	1.4779 (1.2239 to 1.7320)
SD of random effect	–	–	0.2674 (0.2263 to 0.3160)
ICC	–	–	0.0213 (0.0153 to 0.0294)

CCU, coronary care unit; EAU, emergency admissions unit; PEA, pulseless electrical activity.

TABLE 51 Coefficients for the risk model to predict hospital survival following in-hospital cardiac arrest

Predictor	Patients	Hospital survival, *n* (%)	Coefficient (95% CI)
Age, RCS: (42,67,76,83,91)[a]			
age_1	–	–	−0.0214 (−0.0261 to −0.0167)
age_2	–	–	0.0027 (−0.0129 to 0.0185)
age_3	–	–	−0.2064 (−0.4562 to 0.0433)
age_4	–	–	0.6048 (−0.1853 to 1.3951)
Prior length of stay (days)			
0 days	7150	2151 (30.1)	0
1	4647	889 (19.1)	−0.2266 (−0.3425 to −0.1106)
2–7	8652	1381 (16.0)	−0.3695 (−0.4790 to −0.2601)
≥ 8	6299	926 (14.7)	−0.4948 (−0.6155 to −0.3742)
Reason for attendance			
Patient: medical	21,750	3952 (18.2)	0
Patient: trauma	843	112 (13.3)	0.0373 (−0.1905 to 0.2652)
Patient: elective surgery	1678	670 (39.9)	1.1162 (0.9836 to 1.2488)
Patient: emergency surgery	2100	386 (18.4)	−0.1205 (−0.2609 to 0.0198)
Patient: obstetric	41	25 (61.0)	1.0143 (0.3037 to 1.7249)
Outpatient	286	176 (61.5)	1.0864 (0.7220 to 1.4503)
Staff or visitor	50	26 (52.0)	0.8009 (0.1793 to 1.4224)
Location of arrest			
Emergency department	2486	528 (21.2)	0.1203 (−0.1194 to 0.3602)
Emergency admissions unit	2161	305 (14.1)	0.0394 (−0.1148 to 0.1936)
Ward, obstetric area, intermediate care area or other inpatient location	15,713	2043 (13.0)	0
Coronary care unit	2329	909 (39.0)	1.0237 (0.8495 to 1.1980)
Critical care unit	1846	526 (28.5)	−0.2528 (−0.5163 to 0.0107)
Imaging department or specialist treatment area	719	213 (29.6)	−0.0366 (−0.4609 to 0.3876)
Cardiac catheter laboratory	874	483 (55.3)	0.1219 (−0.0724 to 0.3162)
Theatre and recovery	400	213 (53.3)	−0.5005 (−1.1159 to 0.1147)
Clinic or non-clinical area	220	127 (57.7)	0.8422 (0.4335 to 1.2511)
Presenting/first documented rhythm			
Ventricular fibrillation	2746	1319 (48.0)	0
Ventricular tachycardia	1218	667 (54.8)	0.3145 (0.1646 to 0.4644)
Shockable–unknown rhythm	128	36 (28.1)	−0.3656 (−0.7882 to 0.0570)
Asystole	6160	617 (10.0)	−2.5342 (−2.7184 to −2.3501)
Pulseless electrical activity	13,908	1758 (12.6)	−1.6891 (−1.8199 to −1.5584)
Bradycardia	206	118 (57.3)	−0.0534 (−0.4171 to 0.3102)
Non-shockable–unknown rhythm	566	123 (21.7)	−0.7382 (−1.1337 to −0.3428)
Unknown	1816	709 (39.1)	0.2163 (−0.1353 to 0.5679)

continued

TABLE 51 Coefficients for the risk model to predict hospital survival following in-hospital cardiac arrest (*continued*)

Predictor	Patients	Hospital survival, *n* (%)	Coefficient (95% CI)
Interaction between asystole and location of arrest			
Emergency department	–	–	0.4315 (0.0199 to 0.8431)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	1.7054 (1.4115 to 1.9993)
Critical care unit	–	–	1.7546 (1.3781 to 2.1312)
Imaging department or specialist treatment area	–	–	1.5438 (0.8745 to 2.2130)
Theatre and recovery	–	–	3.3954 (2.578 to 4.2124)
Interaction between PEA and location of arrest			
Emergency department	–	–	−0.0341 (−0.3131 to 0.2449)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	−0.3391 (−0.5624 to −0.1156)
Critical care unit	–	–	0.7759 (0.4647 to 1.0872)
Imaging department or specialist treatment area	–	–	0.5762 (0.0835 to 1.0689)
Theatre and recovery	–	–	2.0426 (1.3633 to 2.7218)
Interaction between other non-shockable/unknown rhythms and location of arrest			
Emergency department	–	–	−0.4348 (−0.8374 to −0.0321)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	−0.3156 (−0.7197 to 0.0883)
Critical care unit	–	–	0.2443 (−0.2539 to 0.7427)
Imaging department or specialist treatment area	–	–	0.5452 (−0.0678 to 1.1583)
Theatre and recovery	–	–	0.7793 (−0.1729 to 1.731)
Congestive cardiac failure			
No	22,997	4702 (20.4)	0
Yes	3741	645 (17.2)	−0.1422 (−0.2492 to −0.0353)
Peripheral vascular disease			
No	25,022	5057 (20.2)	0
Yes	1726	290 (16.8)	−0.2035 (−0.3534 to −0.0537)
Liver disease			
No	26,041	5230 (20.1)	0
Yes	707	117 (16.5)	−0.3348 (−0.5629 to −0.1066)
Hemiplegia or paraplegia			
No	26,483	5316 (20.1)	0
Yes	265	31 (11.7)	−0.4379 (−0.8589 to −0.0169)
Malignancy			
No	24,345	5037 (20.7)	0
Yes	2403	310 (12.9)	−0.3215 (−0.4747 to −0.1683)

TABLE 51 Coefficients for the risk model to predict hospital survival following in-hospital cardiac arrest (*continued*)

Predictor	Patients	Hospital survival, *n* (%)	Coefficient (95% CI)
Metastatic solid tumour			
No	26,010	5286 (20.3)	0
Yes	738	61 (8.3)	−0.7962 (−1.1124 to −0.4801)
Constant	–	–	1.3090 (1.0394 to 1.5786)
SD of random effect	–	–	0.3156 (0.2627 to 0.3790)
ICC	–	–	0.0293 (0.0205 to 0.0418)

CCU, coronary care unit; EAU, emergency admissions unit; PEA, pulseless electrical activity.
RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

TABLE 52 Coefficients for the risk model to predict 1-year survival following in-hospital cardiac arrest

Predictor	Patients	1-year survival, *n* (%)	Coefficient (95% CI)
Age: RCS (42,67,76,83,91)			
age_1	–	–	−0.015 (−0.020 to −0.010)
age_2	–	–	−0.018 (−0.034 to −0.002)
age_3	–	–	−0.005 (−0.270 to 0.260)
age_4	–	–	0.111 (−0.740 to 0.963)
Prior length of stay (days)			
0	7150	1851 (25.8)	0
1	4647	759 (16.3)	−0.184 (−0.305 to −0.063)
2–7	8652	11,130 (13.0)	−0.367 (−0.482 to −0.253)
≥ 8	6299	714 (11.3)	−0.556 (−0.684 to −0.428)
Reason for attendance			
Patient: medical	21,750	3252 (14.9)	0
Patient: trauma	843	91 (10.8)	0.055 (−0.191 to 0.300)
Patient: elective surgery	1678	578 (34.4)	1.092 (0.955 to 1.229)
Patient: emergency surgery	2100	337 (16.0)	−0.092 (−0.239 to 0.056)
Patient: obstetric	41	25 (70.0)	1.157 (0.442 to 1.871)
Outpatient	286	147 (51.2)	0.989 (0.617 to 1.361)
Staff or visitor	50	24 (48.0)	0.847 (0.231 to 1.463)
Location of arrest			
Emergency department	2486	441 (17.9)	0.201 (−0.045 to 0.447)
Emergency admissions unit	2161	255 (11.8)	0.057 (−0.107 to 0.221)
Ward, obstetric area, intermediate care area or other inpatient location	15,713	1639 (10.4)	0
Coronary care unit	2329	761 (32.5)	0.950 (0.775 to 1.126)
Critical care unit	1846	435 (23.5)	−0.157 (−0.428 to 0.114)

continued

TABLE 52 Coefficients for the risk model to predict 1-year survival following in-hospital cardiac arrest (*continued*)

Predictor	Patients	1-year survival, *n* (%)	Coefficient (95% CI)
Imaging department or specialist treatment area	719	164 (22.8)	0.227 (–0.208 to 0.661)
Cardiac catheter laboratory	874	450 (51.3)	0.231 (0.038 to 0.425)
Theatre and recovery	400	202 (50.5)	–0.169 (–0.790 to 0.453)
Clinic or non-clinical area	200	107 (48.2)	0.713 (0.303 to 1.124)
Presenting/first documented rhythm			
Ventricular fibrillation	2746	1140 (41.4)	0
Ventricular tachycardia	1218	531 (43.2)	0.125 (–0.027 to 0.277)
Shockable–unknown rhythm	128	25 (19.5)	–0.581 (–1.054 to –0.108)
Asystole	6160	556 (9.0)	–2.211 (–2.400 to –2.021)
Pulseless electrical activity	13,908	1433 (10.3)	–1.585 (–1.725 to –1.445)
Bradycardia	206	103 (48.8)	0.027 (–0.339 to 0.393)
Non-shockable–unknown rhythm	566	98 (17.22)	–0.757 (–1.162 to –0.353)
Unknown	1816	568 (31.0)	0.115 (–0.237 to 0.468)
Interaction between asystole and location of arrest			
Emergency department	–	–	0.137 (–0.298 to 0.572)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	2.991 (2.170 to 3.811)
Critical care unit	–	–	0.743 (–0.002 to 1.488)
Imaging department or specialist treatment area	–	–	1.439 (1.048 to 1.829)
Theatre and recovery	–	–	1.554 (1.256 to 1.852)
Interaction between PEA and location of arrest			
Emergency department	–	–	–0.122 (–0.415 to 0.170)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	1.765 (1.079 to 2.452)
Critical care unit	–	–	0.071 (–0.454 to 0.595)
Imaging department or specialist treatment area	–	–	0.631 (0.306 to 0.957)
Theatre and recovery	–	–	–0.280 (–0.512 to –0.049)
Interaction between other non-shockable/unknown rhythms and location of arrest			
Emergency department	–	–	–0.636 (–1.060 to –0.212)
EAU, ward, obstetric area, intermediate care area or other inpatient location	–	–	0
CCU or cardiac catheter lab	–	–	0.511 (–0.426 to 1.448)
Critical care unit	–	–	0.297 (–0.320 to 0.914)
Imaging department or specialist treatment area	–	–	0.114 (–0.390 to 0.618)
Theatre and recovery	–	–	–0.536 (–0.950 to –0.122)

TABLE 52 Coefficients for the risk model to predict 1-year survival following in-hospital cardiac arrest (*continued*)

Predictor	Patients	1-year survival, *n* (%)	Coefficient (95% CI)
Liver disease			
No	26,041	4371 (16.7)	0
Yes	707	83 (11.7)	−0.538 (−0.794 to −0.282)
Congestive cardiac failure			
No	22,997	4008 (17.4)	0
Yes	3741	446 (11.9)	−0.338 (−0.460 to −0.216)
Renal disease			
No	23,506	4113 (17.5)	0
Yes	3242	341 (10.5)	−0.348 (−0.484 to −0.212)
Malignancy			
No	24,345	4251 (17.4)	0
Yes	2403	203 (8.4)	−0.537 (−0.712 to −0.363)
Metastatic solid tumour			
No	26,010	4,424 (17.0)	0
Yes	738	30 (4.07)	−1.215 (−1.629 to −0.802)
Constant	–	–	0.794 (0.5199 to 1.069)
SD of random effect	–	–	0.286 (0.030 to 0.353)
ICC	–	–	0.024 (0.005 to 0.036)

CCU, coronary care unit; EAU, emergency admissions unit; ICC, intracluster correlation; PEA, pulseless electrical activity.

TABLE 53 Coefficients for the model for critical care unit length of stay for hospital survivors following an in-hospital cardiac arrest

Predictor	Coefficient (95% CI)	*p*-value
Age: RCS (42,67,82)		
age_1	0.004 (−0.002 to 0.012)	0.0011
age_2	−0.012 (−0.021 to −0.004)	
Severe condition in the past medical history	1.080 (0.258 to 1.921)	0.010
Location of arrest		
Ward, obstetrics area, other intermediate care area, clinic or non-clinical area	ref	< 0.0001
ED or emergency admission unit	−0.329 (−0.471 to −0.188)	
Theatre and recovery	−0.562 (−0.774 to −0.355)	
Cardiac catheter lab or CCU	−0.351 (−0.534 to −0.169)	
Imaging department or Specialist treatment area	−0.293 (−0.534 to −0.053)	
Presenting rhythm		
Shockable	ref	< 0.0001
Non-shockable	0.331 (0.209 to 0.452)	

continued

TABLE 53 Coefficients for the model for critical care unit length of stay for hospital survivors following an in-hospital cardiac arrest (*continued*)

Predictor	Coefficient (95% CI)	*p*-value
Reason for admission to critical care by body system		
Respiratory	ref	< 0.0001
Cardiovascular	−0.404 (−0.563 to −0.245)	
Gastrointestinal	−0.064 (−0.327 to 0.198)	
Neurological (including eyes)	−0.288 (−0.521 to −0.057)	
Other	−0.398 (−0.635 to −0.162)	
ICNARC Physiology Score RCS(10,21,33)		
$score_1$	0.083 (0.064 to 0.102)	< 0.0001
$score_2$	−0.057 (−0.081 to −0.035)	
Interactions with severe conditions in the past medical history		
$score_1$	−0.077 (−0.127 to −0.027)	0.0012
$score_2$	0.062 (0.002 to 0.123)	
Number of advanced organ supports	0.352 (0.283 to 0.421)	< 0.0001

CCU, coronary care unit; ED, emergency department; RCS, restricted cubic spline. RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

TABLE 54 Coefficients for the model for critical care unit length of stay for hospital non-survivors following an in-hospital cardiac arrest

Predictor	Coefficient (95% CI)	*p*-value
Age: RCS (49,72,84)		
age_1	0.004 (−0.005 to 0.014)	0.0015
age_2	−0.014 (−0.026 to −0.004)	
Number of advanced organ supports		
0	ref	
1 or 2	0.728 (−1.041 to 2.495)	0.33
3	−0.006 (−1.963 to 1.954)	
4	−2.081 (−6.463 to 2.334)	
ICNARC Physiology Score: RCS (18,32,46)		
$score_1$	−0.047 (−0.126 to 0.031)	0.026
$score_2$	−0.040 (−0.206 to 0.126)	
Interactions with number of advanced organ supports		
1 or 2 organ supports $score_1$	0.007 (−0.074 to 0.089)	0.0011
3 organ supports $score_1$	0.045 (−0.041 to 0.132)	
4 organ supports $score_1$	0.136 (−0.024 to 0.297)	
1 or 2 organ supports $score_2$	−0.018 (−0.186 to 0.152)	
3 organ supports $score_2$	−0.029 (−0.199 to 0.141)	
4 organ supports $score_2$	−0.075 (−0.294 to 0.142)	

RCS (a,b,c) denotes restricted cubic spline with knots at positions a, b and c.

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