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Lucijanić, Marko; Marelić, Daniela; Stojić, Josip; Marković, Ivan; Sedlić, Filip; Kralj, Ivan; Ručević, Davor; Bušić, Nikša; Javor, Patrik; Lucijanić, Tomo; ...

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RESEARCH PAPER

Predictors of prolonged hospitalization of COVID-19 patients

Marko Lucijanic[1,2] · Daniela Marelic[2] · Josip Stojic[3] · Ivan Markovic[4] · Filip Sedlic[2,5] · Ivan Kralj[6] · Davor Rucevic[7] · Niksa Busic[8] · Patrik Javor[9] · Tomo Lucijanic[10,11] · Josko Mitrovic[2,12] · Ivica Luksic[2,11,13]

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Key summary points

Aim To investigate predictors of prolonged hospitalization of COVID-19 patients.

Findings Multivariate analysis recognized higher severity of COVID-19 symptoms, worse functional status, referral from other institutions, certain indications for admission (neurologic, surgical and social), certain chronic comorbidities (obesity, chronic liver disease, hematological malignancy, transplanted organ), and complications that arise during hospital stay (venous thromboembolism, bacterial sepsis and Clostridioides difficile infection) as independent predictors of prolonged hospitalization.

Message Development of specific measures aimed at improvement of functional status and prevention of complications might reduce the length of hospitalization.

Abstract

Purpose Despite the importance of hospital bed network during the pandemic, there are scarce data available regarding factors predictive of prolonged length of hospitalization of COVID-19 patients.

Methods We retrospectively analyzed a total of 5959 consecutive hospitalized COVID-19 patients in period 3/2020–6/2021 from a single tertiary-level institution. Prolonged hospitalization was defined as hospital stay > 21 days to account for mandatory isolation period in immunocompromised patients.

Results Median length of hospital stay was 10 days. A total of 799 (13.4%) patients required prolonged hospitalization. Factors that remained independently associated with prolonged hospitalization in multivariate analysis were severe or critical COVID-19 and worse functional status at the time of hospital admission, referral from other institutions, acute neurological, acute surgical and social indications for admission vs admission indication of COVID-19 pneumonia, obesity, chronic liver disease, hematological malignancy, transplanted organ, occurrence of venous thromboembolism, occurrence of bacterial sepsis and occurrence of Clostridioides difficile infection during hospitalization. Patients requiring prolonged hospitalization experienced higher post-hospital discharge mortality (HR = 2.87, $P < 0.001$).

✉ Marko Lucijanic
markolucijanic@yahoo.com

1 Hematology Department, University Hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb, Croatia

2 School of Medicine, University of Zagreb, Zagreb, Croatia

3 Department of Gastroenterology, Hepatology and Clinical Nutrition, University Hospital Dubrava, Zagreb, Croatia

4 Special Hospital for Pulmonary Diseases, Zagreb, Croatia

5 Department of Oncology, Division of Pathophysiology and Experimental Oncology, University Hospital Center Zagreb, Zagreb, Croatia

6 Internal Medicine Department, General Hospital Sisak, Sisak, Croatia

7 Intensive Care Unit Department, University Hospital Dubrava, Zagreb, Croatia

8 Cardiology Department, University Hospital Dubrava, Zagreb, Croatia

9 Faculty of Medicine, University of Rijeka, Rijeka, Croatia

10 Endocrinology Department, University Hospital Dubrava, Zagreb, Croatia

11 Primary Respiratory and Intensive Care Center, University Hospital Dubrava, Zagreb, Croatia

12 Clinical Immunology, Allergology and Rheumatology Department, University Hospital Dubrava, Zagreb, Croatia

13 Maxillofacial Surgery Department, University Hospital Dubrava, Zagreb, Croatia

Conclusions Not only severity of COVID-19 clinical presentation but also worse functional status, referral from other hospitals, certain indications for admission, certain chronic comorbidities, and complications that arise during hospital stay independently reflect on the need of prolonged hospitalization. Development of specific measures aimed at improvement of functional status and prevention of complications might reduce the length of hospitalization.

Keywords COVID-19 · SARS-CoV-2 · Prolonged hospitalization · Comorbidities

Introduction

Coronavirus disease 2019 (COVID-19) is an acute viral disease caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although majority of affected patients present with only mild respiratory symptoms, some patients may develop systemic inflammatory response to SARS-CoV-2 infection with severe life-threatening symptoms and multiorgan failure. Prior to wide-spread availability of vaccination, up to 15–20% affected patients developed acute respiratory insufficiency requiring oxygen supplementation and consequent hospitalization [1]. Thus, COVID-19 imposes significant challenges on healthcare systems due to its ability to overwhelm available infrastructure with high number of acutely ill and potentially unstable patients. Despite evident benefits of vaccination regarding reduced number of patients presenting with severe or critical form of the disease and improved outcomes of patients with breakthrough infections [2], vaccine hesitancy, inappropriate immune response to vaccination and waning effects of vaccination still remain substantial problems for controlling the pandemic [3–5].

Despite importance of hospital bed network during the pandemic, there are scarce data on factors affecting the length of hospital stay of COVID-19 patients available at the moment [6, 7]. In this study we aim to comprehensively investigate factors associated with prolonged hospitalization by evaluating large tertiary-center registry.

Methods

We have retrospectively analyzed data on 5959 concomitantly hospitalized COVID-19 patients hospitalized in the University hospital Dubrava, Zagreb, Croatia, in period from 3/2020 to 6/2021. During the study period hospital was completely repurposed to serve as a tertiary-level institution and regional referral center for most severe COVID-19 patients and for patients that required emergent medical care and were concomitantly SARS-CoV-2 positive. All patients tested positive for SARS-CoV-2, either on polymerase chain reaction (PCR) test, or on antigen test in the presence of compatible clinical symptoms. Patients were treated according to the contemporary guidelines and majority of them received oxygen supplementation, corticosteroids and LMWH thromboprophylaxis [8]. Demographic, laboratory and clinical data were obtained by evaluation of written and electronical medical documentation and are a part of the hospital registry project, "Registry of hospitalized COVID-19 patients in University Hospital Dubrava Respiratory center" (ClinicalTrials.gov identifier: NCT05151094). Demographic, laboratory and clinical parameters were evaluated at the time of hospital admission, whereas the clinical course of the disease was analyzed during hospitalization (mechanical ventilation, venous and arterial thrombotic events, major bleeding, bacterial sepsis, Clostridioides difficile (C. difficile) infection). Mortality was evaluated during hospitalization and after hospital discharge. COVID-19 severity was categorized as mild, moderate, severe and critical according to the World health organization (WHO) classification [9]. Intensity of COVID-19 symptoms was graded using the modified early warning score (MEWS) score [10]. The Eastern cooperative oncology group (ECOG) scale [11] was used to determine functional status of patients at the time of hospital admission. Comorbidities were evaluated as particular entities and were summarized using the Charlson comorbidity index (CCI) [12].

We defined prolonged hospitalization as duration of hospital stay > 21 day encompassing three-week period. We chose this approach to account for prescribed mandatory isolation period that variated individually for specific patients and lasted longest for 20 days in specific patient subgroups during the pandemic (immunocompromised patients).

The study was approved by the University Hospital Dubrava Review Board (Nm: 2022/2709–09).

Statistical methods

Normality of distribution of numerical variables was tested using the Kolmogorov–Smirnov test. Neither of numerical variables had normal distribution. They were presented as median and interquartile range (IQR) and were compared regarding prolonged hospitalization status using the Mann Whitney *U* test. Categorical variables were presented as frequencies and percentages and were compared regarding prolonged hospitalization status using the chi squared test. Post-hospital discharge survival analysis was based on the Kaplan–Meier method and was performed using the Cox–Mantel version of the log rank test [13, 14]. Multivariate predictors of prolonged hospitalization were assessed using the logistic regression. During the model building, all

univariately associated variables, age and sex were considered via backwards approach (inclusion criteria $P < 0.05$, exclusion criteria $P > 0.1$) [15]. P values < 0.05 were considered as statistically significant. All analyses were performed using the MedCalc statistical software version 20.014 (MedCalc Software Ltd, Ostend, Belgium; 2022).

Results

Overview of patients' characteristics and length of hospitalization

Among total of 5959 evaluated COVID-19 patients, there were 2613 (43.8%) female and 3346 (56.2%) male patients. Median age was 72 years, IQR (62–81). Median CCI was 4 points, IQR (3–6). Median ECOG score was 3 points, IQR (1–4).

Severity of COVID-19 on admission was mild in 560 (9.4%), moderate in 286 (4.8%), severe in 4202 (70.5%) and critical in 911 (15.3%) patients. Leading cause of hospital admission was COVID-19 pneumonia in 4299 (72.1%), other acute medical condition in 675 (11.3%), acute surgical condition in 508 (8.5%), acute neurological condition in 228 (3.8%), febrility without pneumonia in 140 (2.3%) and social and other reasons in 109 (1.8%) patients. Most patients came from their homes due to worsening of clinical condition (2899 (48.6%)), whereas 2490 (41.8%) were referred from other hospitals and 570 (9.6%) patients came from nursing homes.

Median length of hospitalization was 10 days, IQR (6–16). Majority of patients were hospitalized for less than 7 days (2103 (35.3%)) or 8–14 days (2158 (36.2%)), whereas hospitalization for 15–21 days was required in 899 (15.1%) and for > 21 days in 799 (13.4%) patients. Likelihood of death during hospitalization showed statistically significant trend of decrease with longer duration of hospitalization ($P < 0.001$) as shown in Fig. 1A. In other words, the fatal outcome determined the length of hospitalization more pronounced in patients hospitalized for a short time, while other factors increasingly influenced the prolonged course of treatment.

Factors associated with prolonged hospitalization

Associations of prolonged hospitalization (> 21 days) with demographic parameters and reasons for hospital admission are shown in Supplementary Table S1, patients' comorbidities in Supplementary Table S2, laboratory parameters in Supplementary Table S3 and COVID-19 severity and clinical course during hospitalization in Supplementary Table S4.

In unadjusted analyses, prolonged hospitalization was significantly associated with origin of referral (referral from other institutions favoring prolonged hospitalization), leading cause of hospital admission (non-COVID-19 pneumonia related causes favoring prolonged hospitalization), higher comorbidity burden as assessed by CCI, presence of obesity, peripheral artery disease, gastroesophageal reflux/ulcer disease, chronic liver disease, liver cirrhosis, previous myocardial infarction, hematologic malignancy, prior organ transplantation, lower hemoglobin, higher red blood cell distribution width, lower absolute lymphocyte count, higher D-dimers, higher alkaline phosphatase and lower serum albumin levels, more severe COVID-19 presentation at the time of hospital admission, shorter duration of COVID-19 symptoms at the time of hospital admission, worse ECOG functional status on admission, presence of pneumonia and

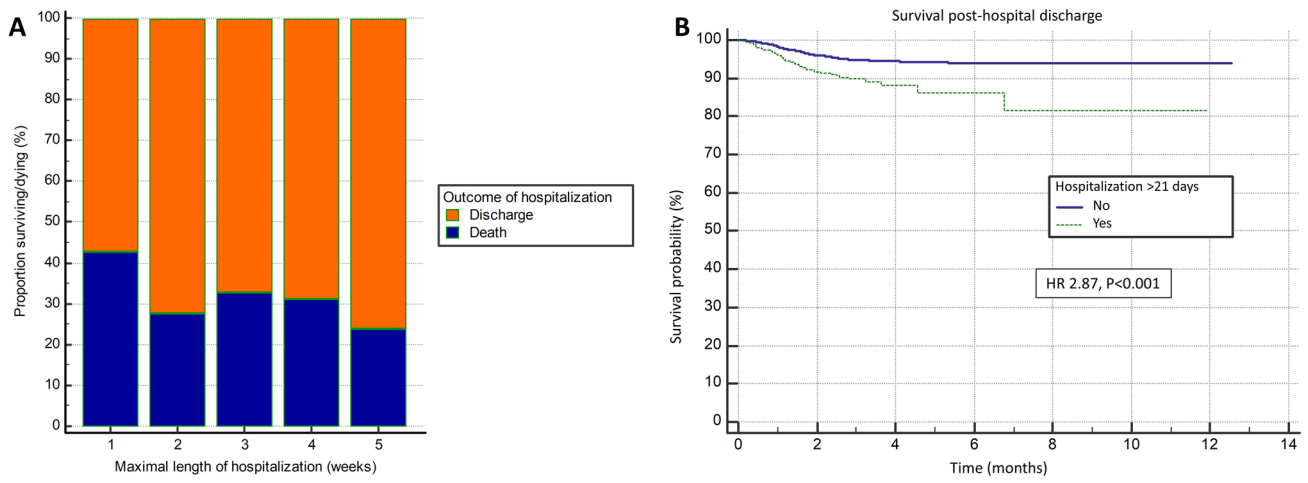

Fig. 1 **A** In-hospital mortality stratified according to the length of hospitalization. **B** Post-hospital discharge mortality stratified according to the length of hospital stay

presence of bilateral pneumonia ($P < 0.05$ for all analyses). Prolonged hospitalization was also significantly associated with requirement for mechanical ventilation, occurrence of venous thromboembolic events, major bleeding, bacterial sepsis and C. difficile infection during hospital stay ($P < 0.05$ for all analyses). There were no significant associations of prolonged hospitalization with age, sex, other chronic metabolic comorbidities or laboratory parameters at the time of hospital admission.

The multivariate logistic regression model assessing independent predictors of prolonged hospitalization chosen among univariately significantly associated parameters is shown in Table 1. Factors that remained independently associated with prolonged hospitalization were severe or critical COVID-19 (OR = 1.95, $P = 0.006$) and worse functional status at the time of hospital admission (OR = 1.12, $P = 0.015$), referral from other institutions (OR = 1.34, $P = 0.012$), acute neurological (OR = 2.57, $P = 0.036$), acute surgical (OR = 2.63, $P = 0.006$) and social indications for admission vs indication of COVID-19 pneumonia (OR = 2.38, $P < 0.001$), obesity (OR = 1.28, $P = 0.040$), chronic liver disease (OR = 1.81, $P = 0.029$), hematological malignancy (OR = 2.89, $P < 0.001$), transplanted organ (OR = 2.27, $P = 0.047$), occurrence of venous thromboembolism (OR = 3.08, $P < 0.001$), occurrence of bacterial sepsis (OR 3.97, $P < 0.001$) and occurrence of C. difficile infection during hospitalization (OR = 6.69, $P < 0.001$).

Long-term significance of prolonged hospitalization

Patients requiring prolonged hospitalization were statistically significantly more likely to experience higher post-hospital discharge mortality in comparison to shorter hospitalized patients (HR 2.87, 95% CI (1.86–4.39); $P < 0.001$) as shown in Fig. 1B.

Discussion

To the best of our knowledge, our study based on a large dataset of mostly severe or critical COVID-19 patients, who are mostly older persons and with high comorbidity burden, is the first to comprehensively investigate factors associated with prolonged hospitalization. As our data reveal, not only severity of COVID-19 symptoms at the time of presentation but also worse functional status, referral from other hospitals, certain indications for admission, certain chronic comorbidities, and complications that arise during hospital stay reflect on the need of prolonged hospitalization. Prolonged hospitalization may also be a negative indicator of patient outcome following their discharge from the hospital.

There are several points we would like to emphasize. Majority of hospitalized patient ended their hospitalizations during two weeks from hospital admission. Death as an important factor for duration of hospital stay in severe and critical COVID-19 patients dominantly affects early period of hospitalization, whereas other factors become increasingly more important during prolonged course of treatment. We deliberately chose to analyze prolonged hospital stay > 21 days to avoid both administrative reasons for prolonged hospitalization (mandatory isolation period among immunocompromised patients), as well as to ameliorate bias associated with factors prognostic of worse survival. In our opinion this is the optimal way to analyze this issue. Observed associations likely translate into other cut-offs for duration of hospital stay.

Table 1 Multivariate logistic regression model assessing independent predictors of prolonged hospitalization of COVID-19 patients (> 21 days)

	Odds ratio	95% CI	*P* value
Referral from other institution	1.34	1.06–1.69	0.012*
Acute neurological indication for admission vs pneumonia	2.57	1.06–6.20	0.036*
Acute surgical indication for admission vs pneumonia	2.63	1.32–5.24	0.006*
Social indication for admission vs pneumonia	2.38	1.44–3.93	< 0.001*
Obesity (BMI > 30 kg/m^2)	1.28	1.01–1.62	0.040*
Chronic liver disease	1.81	1.06–3.10	0.029*
Hematological malignancy	2.89	1.71–4.88	< 0.001*
Transplanted organ	2.27	1.01–5.12	0.047*
Severe or critical COVID-19	1.95	1.20–3.15	0.006*
ECOG functional status	1.12	1.02–1.23	0.015*
Venous thromboembolism	3.08	2.19–4.34	< 0.001*
Bacterial sepsis	3.97	3.04–5.19	< 0.001*
C. difficile infection	6.69	4.50–9.96	< 0.001*

CI confidence interval, *BMI* body mass index, *COVID-19* Coronavirus disease 2019, *ECOG* Eastern cooperative oncology group, *C.* Clostridioides

*Statistically significant at level $P < 0.05$

Age, sex and comorbidities, as well as severity of COVID-19 clinical presentation are known negative prognostic factors for survival during COVID-19 hospitalization [16]. On the opposite, factors associated with duration of hospital stay are less well understood and scarce clinical data exist on this issue. Factors like weaker muscle strength [17], higher acuity level of care [18] and use of specific drugs like remdesivir [19] are reported to be associated with longer COVID-19 hospitalization. Recent studies [6, 7] also addressed predictors associated with the length of stay of hospitalized COVID-19 patients but utilized a relatively short cutoff periods of > 3 and > 10 days which may not be completely comparable to the context of the current study, especially since death and administrative reasons may play important role during shorter periods. It should be noted that predictors of non-prompt recovery that were recognized in one of the aforementioned studies [7] were similar to predictors of prolonged hospitalization in our study including higher oxygen requirement, ICU admission, bacterial superinfections and shorter duration of symptoms at the time of hospital admission. As our data show, intensity of COVID-19 symptoms and functional impairment of patients are important predictors of hospitalization for > 21 days, especially if patients require mechanical ventilation support. Although adjusted OR for ECOG was of low magnitude, it represents obvious positive trend and increased risk of prolonged hospitalization of 12% with each point increase on ECOG scale. It is of particular interest that not the age or sex of patients per se, but comorbidity burden, particular comorbidities and the need to be hospitalized due to non-COVID-19 pneumonia related factors also significantly affect the need for prolonged hospital stay. This is especially true for chronic conditions that affect functional status of patients, require specific pharmacotherapies and more intensive nursing care like cardiovascular comorbidities, chronic liver disease and hematologic malignancies. Higher comorbidity burden and associated pharmacotherapy also predispose to complications like bacterial superinfections and bacterial sepsis, C. difficile infection, thromboembolic incidents and major bleeding, also reflecting on prolonged hospitalization. Raising awareness of independent predictors of prolonged hospital stay may help in development of specific measures targeted at modifiable factors. Examples could be improvement of functional status of patients by early mobilization, as well as prevention, early recognition and timely absolving of in-hospital complications.

Main limitations of our work are retrospective study design and single center experience. Study design limits conclusions about causality of observed associations. ECOG might be suboptimal measure of functional status in non-oncological patients. Information on important geriatric prognostic factors (i.e. cognition, nutrition, delirium, as well as standard comprehensive geriatric assessment and clinical frailty scale [20]) was not available in our study. These parameters have been shown to be more powerful in other settings than many of the variables significant in our study. Also, due to registry-level dataset, we had no access to information on the other potentially important predictors of prolonged hospitalization such as negativization of SARS-CoV-2 nasal swab [20] for a large proportion of analyzed patients, and we could not investigate them as predictors. Main strengths of our work are large real-life dataset of contemporary COVID-19 patients with mostly severe or critical clinical presentation upon admission, representative of tertiary-center experience.

In conclusion, we have determined a series of factors independently associated with prolonged hospitalization of COVID-19 patients, including severity of COVID-19 clinical presentation, worse functional status, referral from other hospitals, certain indications for admission, certain chronic comorbidities, and complications that arise during hospital stay. Development of specific measures aimed at improvement of functional status and prevention of complications might reduce the length of hospitalization.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41999-023-00787-w.

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Data availability Data is available from corresponding author on reasonable request.

Declarations

Conflict of interest All authors declare they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the University Hospital Dubrava Review Board (Nm: 2022/2709–09).

Informed consent Due to retrospective nature of the study informed consent was not required and was waived by the Review Board.

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