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Infection as a predictor of mortality in decompensated liver cirrhosis: exploring the relationship to severity of liver failure

Running head: Infections in decompensated cirrhosis

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Abstract

Background. Infections are common in patients with liver cirrhosis (LC) and increase mortality. We explored the relationship between infection and liver dysfunction in their effects on mortality.

Methods. Single-center data on decompensated LC patients hospitalized between March 2014 and December 2017 (index period) were reviewed until death, liver transplantation or December 31 2018. Infections were classified as community-acquired (CAi) or hospital/health-care associated (HCAi). Child-Pugh, Model for the end-stage liver disease (MELD) and chronic liver failure-organ failure (CLiF-OF) scores indicated liver (dys)function.

Results. We enrolled 155 patients (85% alcoholic liver disease), 65 without infection at 1st hospitalization, 48 with CAi and 42 with HCAi. Multidrug resistant agents were confirmed in 2/48 (4.2%) CAi and 10/42 (23.8%) HCAi patients. At 1st hospitalization, infection was independently associated with worse liver dysfunction and *vice-versa*, and with higher 30-day mortality (OR=2.73, 95%CI 1.07-6.94). The association was reduced with adjustment for MELD/CLiF-OF scores, but mediation analysis detected an indirect (via liver dysfunction) association. Twenty-eight patients were repeatedly hospitalized, 11 with new HCAi. HCAi was independently associated with twice higher risk of medium-term mortality and added additional risk to any level of liver dysfunction, considering all or patients who survived the first 30 days. In those repeatedly hospitalized, HCAi appeared independently associated with a higher probability of infection and higher MELD scores at subsequent hospitalizations.

Conclusion. Infection (particularly HCAi) adds mortality risk to any level of liver dysfunction in decompensated LC patients. Mechanisms of long(er)-term effects (in acute episode survivors) seemingly include enhanced deterioration of liver function.

Key words: liver cirrhosis; liver function; infection; mortality

Introduction

Patients with liver cirrhosis are at an increased risk of infections due to a number of contributing factors like liver dysfunction and associated immune dysfunction, porto-systemic shunting, malnutrition, increased bacterial translocation from the gastro-intestinal tract and, likely, genetically determined disposition [1]. Prevalence of infection and of particular infectious causative agents vary worldwide, but increased prevalence of multidrug resistant bacteria (to up to 38%) has been reported in Europe over the past decade, particularly in the healthcare settings (hospital and healthcare-associated infections) [2, 3]. In patients with cirrhosis, infection greatly increases mortality: in this setting, 30-day mortality is around 30% and additional 30% of the patients die within a 12-month period. Consequently, infection in cirrhosis has been proposed as a distinct stage in the natural history of the disease with a dismal prognosis [4]. Accordingly, bacterial and/or fungal infections are considered among the most important triggers of acute-on-chronic liver failure (ACLF), a syndrome characterised by high mortality due to failure of extrahepatic organs in the presence of cirrhosis [5]. It is seen in around 1/3 of the hospitalized patients with liver cirrhosis and infection [2]. However, the relationship between liver cirrhosis and infection is complex and should not be considered unidirectional [6] – it has not been completely resolved whether infected patients die due to subsequently worsened liver function or whether they get the infection during the process of dying due to deteriorating liver function and consequently increased susceptibility to infection. In a single study addressing this issue factors independently associated with increased mortality were infection, higher MELD score, longer intensive treatment unit stay and older age [7]. One-year mortality remained higher even in patients who recovered from the initial infective episode suggesting a prolonged and irreversible negative impact of infection on survival in patients with cirrhosis [7]. In the present analysis we aimed to evaluate infection as a predictor of 30-day

and medium-term mortality specifically in patients with decompensated liver cirrhosis and to explore its relationship with the severity of liver failure.

Methods

Study outline

We retrospectively reviewed medical records of patients with decompensated liver cirrhosis hospitalized at least once at a single center between March 1 2014 and December 31 2017 (index period). Decompensated cirrhosis (jaundice, hepatic encephalopathy, ascites or bleeding varices) was diagnosed either during the index period or at a previous occasion. The analysis was to include consecutive patients except those with co-existing hepatocellular carcinoma outside the Milan criteria, human immunodeficiency virus infection, solid organ or hematological malignancy, patients with advanced chronic heart failure [8] and those who died within 72 hours (e.g., severely hemodynamically instable, resuscitated on admission, multi-organ failure). Records were tracked until death, liver transplantation, loss of contact or December 31 2018; patients repeatedly hospitalized during the index period could have "switched" the infection status, i.e., from "no infection" to "infection". Potential confounders were also re-recorded at such occasions (Fig. 1A). The analysis was approved by the Institutional Ethics Committee.

Infection

Diagnosis of infection was based on the same criteria as recently published in a large UK cohort of patients with cirrhosis [7]. In brief, in the absence of a positive culture (e.g., urine, sputum, ascites, pleural effusion, stool, bile, blood), diagnosis was based on consistent presence of general (e.g., fever or hypothermia, neutrophilic leukocytosis) and/or localized clinical (e.g., abdominal pain, vomiting, diarrhea, dysuria, cough, purulent sputum, dyspnea, cellulitis), physical, imaging and laboratory findings (e.g., pulmonary infiltration, ascites or pleural effusion with neutrophils $\geq 250/mm^3$, pyuria). Infections were classified as "hospital", "healthcare-associated" and "community acquired" using the criteria validated for pneumonia [9] and used also in patients with liver cirrhosis [10]:

hospital infection – infection occurring after more than 48 hours since admission; healthcare-associated infection (HCA) – infection occurring within 48 hours since admission in patients with any of the following (i) attended a hospital or a hemodialysis clinic or received intravenous chemotherapy within 30 days before the index infection, (ii) were hospitalized for at least 2 days or had undergone surgery within 6 months before the index infection, (iii) reside in a nursing home/long-term care facility; community acquired (CA) infection – present at admission or occurring within 48 hours since admission, not meeting the criteria for HCA. Since the current cohort was limited in size and considering the closely related etiology, pathophysiology and outcomes [9, 10] of hospital and HCA infections, these two types of infections were considered a single category – HCA (as opposed to CA infections).

Liver failure

All patients were evaluated for the Child-Pugh score [11], Model for the end-stage liver disease (MELD) score [12] and European Foundation for the study of chronic liver failure – organ failure score (CLiF-OF) [13]. Ascites was evaluated using abdominal ultrasound or computed tomography. Presence of esophageal/gastric varices was assessed endoscopically and grading was by the modified Westaby/Cales classification as endorsed by the British Society of Gastroenterology [14, 15]. Encephalopathy was graded using the West Haven criteria [16].

Patient follow-up

Patients were followed-up through medical records or a direct contact until death or censoring: liver transplantation, December 31 2018 or loss to follow-up (e.g., moving to another center). Patients with no infection or with a CA infection at the 1st hospitalization during the index period who subsequently (>30 days after the 1st hospitalization) developed an infection or a more ominous form (i.e., HCA) were censored at that point and “switched” to a new infection status.

Data analysis

We intended (Fig. 1A) to evaluate independent associations specifically: (i) between infection and organ failure scores of interest - MELD (indicates hepatic and renal function [12]) or CLiF-OF (indicates additionally pulmonary function and hemodynamic status [13]); (ii) between infection at/during 1st hospitalization and 30-day mortality; and (iii) between infection and overall medium-term mortality. For the assessment of (i) infection – MELD/CLiF-OF relationship, the main analysis was cross-sectional (data at 1st hospitalization), hence "bi-directional", with MELD or CLiF-OF scores and presence of infection treated as either dependent or independent variables (general linear models for MELD/CLiF-OF as dependent variables, generalized for presence of infection). Child-Pugh class (patients were class B or C in a 1:2 ratio) was considered an independent variable: MELD and CLiF-OF scores largely overlapped between class B and class C patients (MELD range 6-31, 90th percentile 24.8 if class B vs. range 6-40, 90th percentile 31.5 if class C; CLiF-OF range 6-12, 90th percentile 8.8 if class B vs. range 6-13, 90th percentile 10 if class C), hence by adjusting for the Child-Pugh class independent association between infection and a broader organ failure status, potentially more relevant regarding mortality, could be evaluated. Other adjustments were included based on univariate associations with the outcomes or biological plausibility regarding mortality. Ancillary analysis was based on limited longitudinal data in patients with repeated hospitalizations during the index period and was also "bi-directional", with either MELD score (linear mixed models) or presence of infection (general estimating equations) as a dependent variable. For the assessment of (ii) relationship between infection and 30-day mortality (generalized linear models), adjustments were based on the same rationale as in (i) with additional alternative introduction of MELD and CLiF-OF scores. Data indicated complex relationships between infection, MELD or CLiF-OF scores and the outcome, hence exploratory mediation analysis (enables decomposition of total effects [17]) was performed to separate direct and possible indirect (mediated) associations. Further exploratory models investigated interactions between the infection status and organ failure

indicators in their effects on 30-day mortality. In the assessment of (iii) relationship between infection and overall medium-term mortality (proportional hazard regression models), changed infection status (at repeated hospitalizations) and re-recorded subject characteristics were treated as time-varying covariates. Adjustment for Child-Pugh class was based on the same rationale as in (i) and further adjustments were based on biological plausibility, with additional alternative introduction of MELD and CLiF-OF scores. Exploratory analyses evaluated interactions and potential indirect associations. We used SAS 9.4 for Windows software (SAS Inc., Cary, NC) and SAS macro "mediation" for mediation analysis [17].

Results

Patients

A total of 155 patients (85% with alcoholic liver disease) were included in the present analysis, 65 free of infection at the 1st hospitalization, 48 diagnosed with CA and 42 with HCA infection (Fig. 1A). Twenty-eight patients were repeatedly hospitalized during the index period, 11 of whom "changed" the infection status: 10 of those without infection and one of those with CA infection at the 1st hospitalization subsequently developed HCA infection (Fig. 1A). The 65 patients free of infection at 1st hospitalization provided a total of 974 patient-months of observation till the end of follow-up or development of HCA (censoring) and 26 (40.0%) died (Fig. 1B). Those with CA infection at 1st hospitalization provided a total of 747 patient-months of observation (till end of follow-up or development of HCA) and 54.2% died (Fig. 1B), while those with HCA at 1st or any subsequent hospitalization provided 599 post-HCA patient-months of observation and 79.2% died (Fig. 1B).

At the 1st hospitalization during the index period, patients across the infection categories were of comparable age with somewhat higher proportion of those with previous hospitalizations for decompensated cirrhosis among those with HCA infection vs. other subsets (Table 1). Men by far prevailed in all subsets and comparable numbers of patients were included by year of the index period (Table 1). More severe encephalopathy appeared more common among patients with infection (particularly HCA) than in those without it (Table 1). Patients with infection were more commonly classified as Child-Pugh class C and had numerically higher MELD and CLiF-OF scores than the patients without infection (Table 1). At least one positive culture specimen was found in 76.2% patients with HCA vs. 45.8% in patients with CA infection. Overall, 29/54 positive cultures (53.0%) were Gram positive strains. At least one multidrug resistant agent was found in 23.8% HCA and in 4.2% CA infection patients (Table 1). Overall, 199 hospitalization episodes were observed during the index period, 82 with no signs of infection and 117 with verified infections (51 CA

infection episodes and 66 HCA infection episodes) (Supplemental Digital Content 1, Fig. S1 shows break-down of hospitalizations in respect to the infectious status). A total of 43 infection sites were identified in CA infection episodes [55.8% urinary tract, 16.3% pneumonia, 13.9% spontaneous bacterial peritonitis (SBP)], and a total of 67 in HCA infection episodes (67.2% urinary tract, 25.4% SBP and 7.5% pneumonia) (Supplemental Digital Content 1, Table S1A summarizes data on infection sites). Most common individual agents were *E. coli* in CA infection episodes and *Enterococcus faecalis* in HCA infections (Supplemental Digital Content 1, Table S1B summarizes data on infectious agents).

Relationship between infection and liver failure

Based on cross-sectional data at 1st hospitalization, infection was independently associated with a higher CLiF-OF score and higher MELD score (Table 2A). In reverse, higher CLiF-OF and MELD scores were each independently associated with higher odds of (concurrent) infection (Table 2B). Ancillary analysis of 28 patients with repeated hospitalizations investigated the relationship between the actual and subsequent infection status and MELD scores. All 28 patients were hospitalized twice, 12 were hospitalized 3 times, 3 were hospitalized 4 times and one was hospitalized 5 times during the index period (Supplemental Digital Content 2, Fig. S2 shows transition status regarding infections at repeated hospitalizations and respective individual MELD scores). Data suggested that higher MELD score at a given hospitalization ("actual score", a dependent variable) was associated with a history of an infection at (any of) the previous hospitalizations, and with a higher MELD score at the previous hospitalization, with a significant interaction (Supplemental Digital Content 2, Table S2A summarizes the multivariate analysis): a) the effect of (previous) infection was seen in patients with lower preceding MELD scores, but not in those with higher MELD scores; b) the effect of the previous MELD score was greater in patients

with no previous infection than in those with a previous infection. In a reverse analysis (Supplemental Digital Content 2, Table S2B summarizes the multivariate analysis) higher odds of infection at a given hospitalization ("actual infection") were associated with a history of previous infection and higher actual but not previous (at the preceding hospitalization) MELD score.

Infection and 30-day mortality after the 1st hospitalization

Thirty-day mortality was 10.8% in patients without infection, 22.9% in patients with CA and 31.0% in patients with HCA infection (Table 1). Considering the limited sample size and the fact that only one death more in CA patients and one less in HCA patients would have resulted in closely similar 30-day mortality in these two subsets (i.e., 12/48 or 25% vs. 12/42 or 28.6%), all patients with infection were considered as a single group in this analysis. When not accounting for the CLiF OR or MELD scores, infection was independently associated with 2.73-times higher odds of 30-day mortality than no infection, and the effect of Child-Pugh class C (vs. B, or A in one patient) was similar (Table 3). When CLiF-OF score was entered into the model, the strength of association between infection and mortality and between Child-Pugh class and mortality was greatly reduced and higher CLiF-OF was the only variable independently associated with higher 30-day mortality (Table 3). The same was observed when MELD score was entered into the model instead of CLiF-OF (Table 3). These facts, together with associations depicted in Table 2 suggested CLiF-OF/MELD scores as possible links between infection and 30-day mortality. Analysis (limited by the cross-sectional nature of data) that assumed infection as a predictor, CLiF-OF or MELD scores as mediators and 30-day mortality as an outcome indicated an indirect association between infection and higher 30-day mortality mediated via CLiF OR or MELD scores (Fig. 2). In a "reverse" mediation analysis in which CLiF-OF or MELD scores were considered predictors and infection was a mediator, higher CLiF-OF or MELD scores were associated with higher 30-day mortality apparently exclusively directly, with no relevant indirect effect that would be mediated *via* infection (Supplemental Digital Content 3, Table S3 summarizes total, direct and indirect effects from the

analysis). Tests of interactions indicated consistent effects of infection on 30-day mortality regardless of the level of liver failure, however considering the limited sample size, all estimates were rather imprecise (wide confidence intervals) (Supplemental Digital Content 4, Table S4 summarizes multivariate models testing interactions). Overall, infection apparently conveyed a considerable additional risk of 30-day mortality to each level of the liver failure, regardless of whether expressed as Child-Pugh class (B or C), CLiF-OF or MELD scores (e.g., low, medium or high).

Infection and overall medium-term mortality

HCA infection, but apparently not CA infection (within the current limited sample), was independently associated with 2.0 to 2.5-times higher risk of death irrespective of whether CLiF-OF or MELD scores were accounted for. Older age, anemia and CLiF-OF/MELD scores were also independently associated with a higher instantaneous risk of death (Table 4). Tests of interactions indicated consistent effects of infection regardless of the level of liver failure, however considering the limited sample size, all estimates were rather imprecise (wide confidence intervals) (Supplemental Digital Content 5, Table S5A summarizes multivariate models testing interactions). Overall, data suggested that infection, primarily HCA infection, consistently conveyed considerable additional risk of death to each level of the liver failure, regardless of whether expressed as Child-Pugh class (B or C), CLiF-OF or MELD scores (e.g., low, medium or high) (Supplemental Digital Content 5, Table S5B summarizes estimated probabilities of survival at 12 months by infection status-by-liver status). Analysis including only subjects who survived beyond day 30 after the 1st hospitalization during the index period yielded practically identical results (Supplemental Digital Content 6, Table S6 summarizes multivariate models). When outcome was defined as time to death *or* infection, HCA infections were associated with close to twice higher risk vs. no infection (HR=1.88, 95%CI 1.15-3.08), but the associations was greatly reduced when accounting for CLiF-OF (HR=1.36, 95% CI 1.04-1.28) or the MELD scores (HR=1.54, 95%CI 0.92-2.58) (Supplemental Digital Content 7, Table S7A summarizes the multivariate models). Mediation analysis revealed

independent indirect (via CLiF-OF or MELD) association between HCA infection and the risk of (a new episode of) infection or death (Supplemental Digital Content 7, Table S7B provides total, direct and indirect effects). When CLiF-OF or MELD were considered predictors and HCA infection a mediator, higher values of either score were exclusively directly associated with a higher risk of (a new episode of) infection or death, i.e., there was no indirect association that would be mediated through their association with infection (Supplemental Digital Content 7, Table S7C provides total, direct and indirect effects).

Discussion

The ominous nature of infection in patients with liver cirrhosis (LC) has been well established: immediate and medium-term mortality is considerably higher in LC patients with a comorbid infection than in those without it. This particularly holds for hospital or healthcare-associated (HCA) infections with the increasing prevalence of multidrug-resistant (MDR) bacteria and fungi as the causative agents commonly resulting in acute failure of extrahepatic organs [1-5]. Clearly, infection may be viewed as a final "common pathway" of multiple debilitating mechanisms inherent to the progressive nature of LC that facilitates (imminent) poor outcomes, but it could also be a factor contributing to the progression of liver failure as the main driver of high mortality [6]. A recent retrospective analysis of a large UK cohort of LC patients (excluded were, as in the present analysis, patients who died shortly after admission) indicated bacterial infection as an independent predictor of medium-term mortality (independent of the degree of liver failure illustrated by the MELD score) that consistently conveyed an additional risk of death to stages of liver failure categorized as MELD score <15 or ≥15 [7]. The present analysis aimed to explore the relationship between the severity of liver failure and infection considering their effects on the early/medium-term mortality specifically in patients with decompensated LC. We used closely similar inclusion/exclusion criteria and definition of infection as the published study [7], but a limited sample size prompted us to consider hospital and HCA infections jointly (as "HCA", as opposed to community-acquired infection), and the role of multidrug resistant infections could not be meaningfully evaluated. For the same reason, most estimates, particularly those pertaining to potential interactions, were rather imprecise. The cohort included patients with rather compromised liver function (high average MELD score and prevalence of patients with Child-Pugh class C) and LC almost exclusively due to alcoholic liver disease (85%), with many patients having uninterrupted alcohol abuse before the 1st hospitalization during the index period and with generally questionable subsequent abstinence. There was also uncertainty about the history of possible relevant infections before the 1st hospitalization. However,

history of previous hospitalizations, i.e., before the index period, was not associated with any of the outcomes in the present analyses, i.e., presence of infection at the 1st hospitalization, MELD score, CLiF-OF score or subsequent mortality (not shown). A combination of a moderately-sized single center sample and the predominant morbidity limits generalizability of the present observations and/or comparisons with data on patients with other LC etiology or different severity of liver dysfunction at the start of observation. Present data demonstrate that in these patients (decompensated alcoholic LC) HCA infection is associated with around twice higher medium-term mortality (as compared to no infection) independently of the level of liver dysfunction and that it conveys additional mortality risk to any level of liver failure. The effect was consistent considering all patients or only those who survived the first 30 days post 1st admission supporting the view that HCA infection has long(er) term detrimental effects on the course of LC, as suggested also by others for a cohort with somewhat different (co)morbidity [7]. In these analyses, no clear effect of CA infection was obvious. In the analysis of 30-day mortality, we considered all infections (CA or HCA) jointly. The decision was guided by the limited size of the patient subsets and the fact the number of events was actually closely similar in the two subsets (CA and HCA). However, the raw proportion of deaths in patients with CA infection (22.9%) was twice higher than in patients without infection (10.8%) (Table 1). This suggests that CA infection might have a different impact on developments in LC patients: it might promote short-term poor outcomes, but without (in survivors) long(er)-term consequences (unlike HCA infection). Infection (HCA and CA considered jointly) was independently associated with higher 30-day mortality after the 1st hospitalization. Mediation analysis suggested that the "disappearance" of this association when accounting for the organ failure scores was only apparent, since the link between infection and mortality was "through" its association with higher MELD or CLiF-OF scores. The same was observed for the relationship between HCA, MELD or CLiF-OF scores and time to death *or* (a new episode of) infection. While the cross-sectional nature of the data (presence of infection, CLiF-OF and MELD scores at the 1st hospitalization) prevents

conclusions on causal relationships, this phenomenon of mediated associations (or effects) should be considered in such complex interrelationships. When infection was viewed as a predictor and CLiF-OF or MELD scores as mediators, an indirect link (via mediator) between infection and the outcome was detected. When CLiF-OF or MELD scores were viewed as predictors and infection as a mediator, the association between predictor(s) and the outcomes was only direct. While clearly in line with the conclusion that infection and worse liver function "go together", our data support the views (i) that a detrimental short-term effect of infection might not be straightforwardly obvious in patients with advanced liver dysfunction and (ii) that infection, and particularly HCA infection, might facilitate subsequent (in survivors) deterioration of liver/other organs function as a main driver of subsequent medium-term mortality. The effector "mechanism" might include increased susceptibility to a subsequent infection (with an imminent fatal outcome). Such views are supported also by the ancillary analysis of longitudinal data on 28 patients with repeated hospitalizations.

In conclusion, despite the limitations inherent to a moderately-sized single-center sample, the present data on a cohort of patients with decompensated LC predominantly due to alcoholic liver disease and with advanced liver dysfunction, suggest infection, and particularly hospital/HCA infection, as an independent predictor of 30-day and medium-term mortality conveying additional risk to any level of liver dysfunction. Data also suggest that hospital/HCA infection, if not resulting in an immediate lethal outcome, has a long(er)-term facilitating effect on progression of liver dysfunction as a main determinant of mortality in these patients: a hypothesis that should be evaluated in adequately designed prospective studies.

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Table1 Subject characteristics at 1st hospitalization during the index period. Data are median (range) or count (percent).

	No infection	Infection	Community acquired	HCA infection
N	65	90	48	42
Age (years)	61 (32-82)	62 (32-87)	60.5 (32-87)	64 (45-83)
Prior hosp. for decomp. cirrh.	12 (18.5)	18 (20.0)	5 (10.4)	13 (31.0)
Men	50 (76.9)	69 (76.7)	37 (77.1)	32 (76.2)
Year - 2014	17 (26.2)	29 (32.2)	12 (25.0)	17 (40.4)
2015	16 (24.6)	19 (21.1)	11 (22.9)	8 (19.1)
2016	19 (29.2)	21 (23.3)	13 (27.1)	8 (19.1)
2017	13 (20.0)	21 (23.3)	12 (25.0)	9 (21.4)
Alcoholic liver disease	56 (86.2)	77 (85.6)	40 (83.3)	37 (88.1)
Viral hepatitis	6 (9.2)	6 (6.7)	4 (8.3)	2 (4.8)
Any other cause	3 (4.6)	7 (7.7)	4 (8.3)	3 (7.1)
Tensascites/bleed admission	37 (56.9)	31 (34.4)	21 (43.8)	10 (23.8)
Encephalop./icterus admission	24 (36.9)	47 (52.2)	20 (41.7)	27 (64.3)
Ascites	55 (84.6)	74 (82.2)	38 (79.2)	36 (85.7)
Varices - None	18 (27.7)	36 (40.0)	20 (41.7)	16 (38.1)
Grade I	19 (29.2)	22 (24.4)	10 (20.8)	12 (28.6)
Grade II	17 (26.2)	22 (24.4)	11 (22.9)	11 (26.2)
Grade III	11 (16.9)	10 (11.1)	7 (14.6)	3 (7.1)
Encephalopathy - No	44 (67.7)	52 (57.8)	35 (75.9)	17 (40.5)
Grade I	7 (10.8)	6 (6.7)	2 (4.2)	4 (9.5)
Grade II	6 (9.2)	16 (17.8)	4 (8.3)	12 (28.6)
Grade III	8 (12.3)	16 (17.8)	7 (14.6)	9 (21.4)
Child-Pugh class - A	1 (1.5)	0	0	0
B	26 (40.0)	24 (26.7)	15 (31.3)	9 (21.4)
C	38 (58.5)	66 (73.3)	33 (68.7)	33 (78.6)
MELD score	18 (6-32)	22 (6-40)	22 (6-40)	21.5 (7-40)
CLiF Organ failure score	7 (6-10)	8 (6-13)	8 (6-13)	8.5 (6-12)
Serum bilirubin (μmol/L)	61 (9.9-708)	82 (6.2-891)	85 (62-500)	73.3 (9.6-891)
Serum creatinine (μmol/L)	85 (41-256)	95 (40-616)	92 (53-616)	108 (40-483)
International normalized ratio	1.48 (1.0-3.20)	1.57 (1.0-3.96)	1.56 (1.0-3.96)	1.61 (1.0-3.36)
Serum albumin (g/L)	28 (18-39)	25 (15-62)	25 (15-62)	25 (17-39)
Sodium (mmol/L)	137 (113-145)	135 (117-152)	135 (118-144)	134 (117-152)
ICU (none mech. ventilated)	6 (9.2)	9 (10.0)	4 (8.3)	5 (11.9)
Leukocytes (x 10^9/L)	6.8 (1.5-26.9)	7.7 (2.1-35)	8.2 (2.2-35.0)	6.7 (2.1-17.8)
Platelets (x 10^9/L)	99 (21-256)	110 (23-327)	110 (23-280)	110 (23-327)
C-reactive protein (mg/L)	12.0 (0.4-73.3)	25.9 (0.9-310)	39.0 (1.4-310)	21.2 (0.9-134)
Hemoglobin (g/L)	112 (34-152)	113 (50-166)	115 (50-158)	111 (68-166)
Anemic[1]	52 (80.0)	77 (85.6)	43 (89.6)	34 (81.0)
Using proton pump inhibitors	29 (44.6)	48 (53.3)	22 (45.8)	26 (61.9)
Using propranolol	34 (52.3)	44 (48.9)	19 (39.6)	25 (59.5)
Any positive culture	---	54 (60.0)	22 (45.8)	32 (76.2)
Any multidrug resistant agent	---	12 (13.3)	2 (4.2)	10 (23.8)
Empirical antibiotic "on target"	---	23 (25.6)	10 (20.8)	13 (31.0)
30-day mortality	7 (10.8)	24 (26.7)	11 (22.9)	13 (31.0)

[1]Hemoglobin <140 g/L in men or <120 g/L in women

CLiF –European Foundation for the study of Chronic Liver Failure; ICU – intensive care unit; MELD – Model for end-stage liver disease

Table 2 Association between infection at/during 1st hospitalization during the index period and co-incident CLiF-OF and MELD scores: summary of multivariate analysis[1]. Since data are cross-sectional, associations were assessed with infection as an independent and CLiF-OF or MELD scores as dependent variables (**A**), and in reverse, with probability of infection as a dependent variable (**B**).

A	**CLiF-OF score**		**MELD score**	
	β (95%CI)	P	β (95%CI)	P
Infection	0.99 (0.50, 1.48)	<0.001	3.81 (1.92, 5.70)	<0.001
Age	0.01 (-0.01, 0.03)	0.576	-0.02 (-0.11, 0.07)	0.611
Child-Pugh class C	1.13 (0.60, 1.66)	<0.001	6.40 (4.37, 8.44)	<0.001
Platelet count (by 50)	-0.04 (-0.23, 0.15)	0.670	-0.23 (-1.00, 0.45)	0.446
Hemoglobin	0.01 (0.00, 0.02)	0.085	0.02 (-0.02, 0.06)	0.266
B	**Model with CLiF-OF**		**Model with MELD**	
	OR (95%CI)	P	OR (95%CI)	P
CLiF-OF score	1.70 (1.28-2.26)	<0.001	---	---
MELD score	---	---	1.14 (1.06-1.22)	<0.001
Age	1.00 (0.97-1.04)	0.854	1.01 (0.98-1.04)	0.561
Child-Pugh class C	1.24 (0.55-2.77)	0.603	0.95 (0.40-2.25)	0.904
Platelet count (by 50)	1.35 (0.99-1.83)	0.053	1.35 (0.99-1.85)	0.054
Hemoglobin	0.99 (0.98-1.01)	0.455	1.00 (0.98-1.01)	0.649

[1]Independent variables were included based on the following: infection/organ failure scores – of primary interest; Child-Pugh class – see Data analysis; hemoglobin, platelet count – univariate association with organ failure scores or presence of infection, might reflect on subsequent mortality (indicating level of anemia or propensity to bleeding not captured by the organ failure scores); age – might reflect on subsequent mortality.

CLiF-OF –European Foundation for the study of Chronic Liver Failure Organ Failure score; MELD – Model for end-stage liver disease score

Table 3 Association between infection at/during 1st hospitalization during the index period and 30-day mortality: summary of multivariate analysis. Three models[1] were fitted to probability of 30-day mortality – one not accounting for CLiF-OF and MELD scores and one each accounting for each of the two organ failure scores.

	Without CLiF-OF/MELD		**Accounting for CLiF-OF**		**Accounting for MELD**	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Infection	2.73 (1.07-6.94)	0.035	1.52 (0.55-4.20)	0.424	1.84 (0.68-4.96)	0.226
Age	1.01 (0.97-1.05)	0.599	1.01 (0.97-1.05)	0.697	1.01 (0.97-1.06)	0.525
Child-Pugh class C	2.84 (1.04-9.18)	0.041	1.68 (0.52-5.37)	0.385	1.59 (0.59-5.10)	0.439
Platelet count	1.00 (0.99-1.01)	0.764	1.00 (0.99-1.01)	0.727	1.00 (0.99-1.01)	0.832
Hemoglobin	1.00 (0.98-1.02)	0.935	0.99 (0.97-1.01)	0.546	0.99 (0.98-1.01)	0.763
CLiF organ failure score	---	---	1.75 (1.31-2.32)	<0.001	---	---
MELD score	---	---	---	---	1.11 (1.03-1.19)	0.005

[1]Independent variables as in Table 2, based on similar rationale: infection, CLiF-OF or MELD scores – of primary interest regarding mortality; Child-Pugh class – see Data analysis; hemoglobin, platelet count – might be related to the organ failure scores/presence of infection; might reflect on mortality

CLiF-OF –European Foundation for the study of Chronic Liver Failure Organ Failure score; MELD – Model for end-stage liver disease score

Table 4 Association between infection (healthcare-associated, HCA, or community acquired) and the risk of death in patients with decompensated liver cirrhosis: summary of multivariate analysis. Three models[1] were fitted to time-to-death - one not accounting for CLiF-OF and MELD scores and one each accounting for each of the two liver failure scores.

	Without CLiF-OF/MELD		**Accounting for CLiF-OF**		**Accounting for MELD**	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
HCA infection vs. no infection	2.59 (1.59-4.31)	<0.001	1.93 (1.15-3.28)	0.013	2.01 (1.20-3.41)	0.008
Community acquired vs. no infection	1.35 (0.78-2.36)	0.280	1.14 (0.65-2.00)	0.653	1.01 (0.56-1.80)	0.981
Age (by 5 years)	1.13 (1.02-1.26)	0.023	1.13 (1.02-1.26)	0.025	1.16 (1.04-1.30)	0.007
Child-Pugh class C	1.34 (0.86-2.14)	0.199	0.92 (0.56-1.53)	0.743	0.88 (0.53-1.49)	0.636
Anemic	1.64 (0.93-3.13)	0.092	2.23 (1.22-4.40)	0.013	2.11 (1.17-4.14)	0.012
CLiF organ failure score	---	---	1.35 (1.18-1.53)	<0.001	---	---
MELD score	---	---	---	---	1.07 (1.04-1.11)	<0.001

[1]Several patients were re-hospitalized during the index period, some with a changed infection status: 10 subjects "crossed" from "no infection" (at 1st hospitalization) to "HCA infection" at one of the subsequent hospitalizations; 1 patient "crossed" from "community-acquired infection" to "HCA infection". All characteristics recorded at 1st hospitalization were recorded also at repeated hospitalizations, hence "infection status" and re-recorded covariates were considered as time-varying explanatory variables. Independent variables were included base on the following: infection /CLiF-OF or MELD scores – of primary interest; age, anemia – known to affect medium-term mortality in severely ill patients; Child-Pugh class – see Data analysis.

CLiF-OF –European Foundation for the study of Chronic Liver Failure Organ Failure score; MELD – Model for end-stage liver disease score

Figure legends

Figure 1. Study outline. **A**. Patient selection, follow-up and analysis. Patients with no infection or community-acquired infection at 1st hospitalization who were diagnosed with healthcare-associated infection (HCA) at some of the subsequent hospitalizations during the index period were censored at the time of HCA and "crossed" to the HCA infection (sub)cohort. **B**. Summary of survival data for the "no infection", "community acquired infection" and "HCA infection" (sub)cohorts. Dots represent censorings.

Figure 2. Summary of mediation analyses with infection as a predictor and 30-day mortality as an outcome, with different mediators: CLiF-OF score (upper panel) or MELD score (lower panel). All direct effects (predictor-to-mediator, predictor-to-outcome, mediator-to-outcome) are the same as in Table 2 and Table 3: mediation analysis enabled isolation of the indirect (*via* mediator variable) effect of infection on 30-day mortality. All estimates (coefficients or odds ratios, OR) are given with 95% confidence intervals. Covariate adjustment (for all direct and indirect associations) is the same as in Table 2 and Table 3. Since data on infection, CLiF-OF and MELD scores and covariates are cross-sectional, the "roles" of a predictor (infection) and a mediator (CLiF-OF or MELD scores) were assigned arbitrarily.

CLiF-OF –European Foundation for the study of Chronic Liver Failure Organ Failure score; MELD – Model for end-stage liver disease score

List of Supplemental Digital Content

1. Supplemental Digital Content 1.pdf. Fig. S1 – breakdown of hospitalization episodes by infection status; Table S1 – Data on infection locations and causative agents
2. Supplemental Digital Content 2.pdf. Fig S2 – transition through infection status at repeated hospitalizations; Table S2A –MELD score analysis; Table S2B –probability of infection analysis
3. Supplemental Digital Content 3.pdf. Table S3. "Reverse" mediation analysis of 30-day mortality
4. Supplemental Digital Content 4.pdf. TableS4. Tests of interaction between liver function scores and infection in their effect on 30-day mortality
5. Supplemental Digital Content 5.pdf. Table S5A Tests of interactions between liver function scores and infection in their effect on medium-term mortality. Table S5B Estimated adjusted predicted probabilities of survival at 12 months
6. Supplemental Digital Content 6.pdf. Table S6 Additional survival analysis in subjects who survived beyond day 30 after the 1st hospitalization
7. Supplemental Digital Content 7.pdf. Table S7A Multivariate analysis of time to death or (new) infection. Table S7B Mediation analysis of time to death or infection: HCA predictor. Table S7C Mediation analysis of time to death or infection: CLiF-OR or MELD score predictors.