Research article

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Low haemoglobin level predicts early hospital readmission in patients with cirrhosis and acute decompensation

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Background & Aims: Patients with decompensated cirrhosis present frequent hospitalisations with a relevant clinical and socio-economic impact. This study aims to characterise unscheduled readmissions up to 1-year follow-up and identify predictors of 30-day readmission after an index hospitalisation for acute decompensation (AD).
Methods: We performed a secondary analysis of a prospectively collected cohort of patients admitted for AD. Laboratory and clinical data at admission and at discharge were collected. Timing and causes of unscheduled readmissions and mortality were recorded up to 1 year.
Results: A total of 329 patients with AD were included in the analysis. Acute-on-chronic liver failure was diagnosed in 19% of patients at admission or developed in an additional 9% of patients during the index hospitalisation. During the 1-year follow-up, 182 patients (55%) were rehospitalised and 98 (30%) more than once. The most frequent causes of readmission were hepatic encephalopathy (36%), ascites (22%), and infection (21%). Cumulative incidence of readmission was 20% at 30 days, 39% at 90 days, and 63% at 1 year. Fifty-four patients were readmitted for emergent liver-related causes within 30 days. Early readmission was associated with a higher 1-year mortality (47 *vs.* 32%, $p = 0.037$). Multivariable Cox regression analysis showed that haemoglobin (Hb) ≤8.7 g/dl (hazard ratio 2.63 [95% CI 1.38–5.02], $p = 0.003$) and model for end-stage liver disease-sodium score (MELD-Na) >16 at discharge (hazard ratio 2.23 [95% CI 1.27–3.93], $p = 0.005$), were independent predictors of early readmission. In patients with MELD-Na >16 at discharge, the presence of Hb ≤8.7 g/dl doubles the risk of early rehospitalisation (44% *vs.* 22%, $p = 0.02$).
Conclusion: Besides MELD-Na, a low Hb level (Hb ≤8.7 g/dl) at discharge emerged as a new risk factor for early readmission, contributing to identification of patients who require closer surveillance after discharge.
Impact and Implications: Patients with decompensated cirrhosis face frequent hospitalisations. In the present study, type and causes of readmissions were analysed during 1-year follow-up in patients discharged after the index hospitalisation for an acute decompensation of the disease. Early (30-day) liver-related readmission was associated with higher 1-year mortality. The model for end-stage liver disease-sodium score and low haemoglobin at discharge were identified as independent risk factors for early readmissions. Haemoglobin emerged as a new easy-to-use parameter associated with early readmission warranting further investigation.

Keywords: Early readmission; Hospitalisation; Haemoglobin; Anaemia; Systemic inflammation; MELD score; Liver cirrhosis.
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Introduction

Decompensated cirrhosis is associated with high morbidity and mortality and is characterised by a wide variety of acute complications resulting in frequent emergent hospitalisations.[1,2]

For patients surviving their hospitalisation, there is a high risk of readmission in the period after discharge as a result of the development of a new complication or suboptimal management during the index hospitalisation. Readmission rates after an unscheduled hospitalisation are reported from 20% to 37% at 30 days and up to 53% at 90 days,[2–7] which are higher than those reported in the general population in the United States[8] and entail a heavy socio-economic burden.[9,10] In Europe, a recent large French retrospective study showed that the annual cost of

hospitalisations in patients with decompensated liver cirrhosis is around 25,000 euro.[11] Hospitalisation caused by cirrhosis was 30% more expensive in Italy than that caused by heart failure or chronic obstructive pulmonary disease.[12]

Discharging patients with decompensated cirrhosis can be a complex decision-making process and effective strategies to decrease readmission are needed. Therefore, the identification of risk factors for early readmission can contribute to a better timing of discharge and to the inclusion of patients in programmes of closer surveillance after discharge, which have been shown able to improve outcomes.[13,14]

Several independent risk factors for hospital readmission have been so far identified, being mostly related to the severity of the disease, such as prognostic scores (*i.e.* Child-Pugh, model for end-stage liver disease [MELD]) and to the presence of complications, such as ascites or hepatic encephalopathy (HE).[2,3,15] Other proposed risk factors not related to cirrhosis are represented by demographic factors (*i.e.* male sex and young age) or comorbidities (*i.e.* diabetes and high Charlson Comorbidity Index).[2,5,15–17]

Thus, the aim of this study was to characterise, in a cohort of decompensated cirrhotic patients with prospectively collected data, the rehospitalisations up to 1 year and the risk factors for early (30-day) liver-related readmissions after an index hospitalisation as a result of acute decompensation (AD), some of whom were complicated by acute-on-chronic liver failure (ACLF).[18]

Patients and methods

Study design and population

We performed a secondary analysis of prospectively collected data in consecutive patients with cirrhosis admitted to the regular wards of the IRCCS Azienda Ospedaliera-Universitaria di Bologna, Bologna, Italy[19] from January 2014 to March 2016. The aim of the core study was to investigate the prognostic role of bacterial and fungal infections in patients with cirrhosis.[19] The study protocol was approved by the local institutional review boards. Written informed consent was obtained from patients or from legal surrogates before enrolment, according to the 1975 Declaration of Helsinki.

Detailed information on inclusion and exclusion criteria were reported elsewhere.[19] Briefly, all consecutive patients with cirrhosis were screened for enrolment at admission. Inclusion criteria were as follows: (a) cirrhosis diagnosed by a composite of clinical signs, laboratory tests, endoscopy, and imaging; (b) unscheduled hospital admission because of an episode of AD;[18] (c) age >18 years. Additional inclusion criteria for this analysis were the availability of clinical and biochemical data at hospital discharge. Exclusion criteria were: (i) admission for a scheduled procedure; (ii) hepatocellular carcinoma (HCC) beyond the Milan criteria;[20] (iii) extrahepatic malignancy; (iv) previous liver transplantation (LT). The follow-up period for patients included in the analysis starts from admission to index hospitalisation up to 1 year or death or LT. For the purpose of the study, only unscheduled readmissions occurring during follow-up after discharge from the index hospitalisation were considered. Scheduled liver or non-liver related readmissions were not included in the analysis. Early readmissions were defined as those occurring within 30 days from discharge.

Data collection

The following data were collected at the time of hospital admission: demographic characteristics, aetiology of cirrhosis, laboratory and clinical data including the presence of HCC and/or other comorbidities assessed by the Charlson Comorbidity Index.[21] Laboratory data and prognostic scores were also collected at discharge. Based on the collected data, the MELD,[22] MELD-sodium (MELD-Na),[23] Child-Turcotte-Pugh,[24] and CLIF-C acute decompensation (CLIF-C AD)[25] scores were calculated.

During the index hospitalisation, patients were assessed daily for the occurrence of bacterial infections and nosocomial ACLF (nACLF). Finally, date regarding timing of rehospitalisation with the leading cause, LT, and death were collected up to 1 year.

Definitions

AD and ACLF were diagnosed according to the criteria of the EASL-CLIF.[18] With AD we refer to patients with cirrhosis admitted to the hospital as a result of acute development of large ascites, hepatic encephalopathy, gastrointestinal (GI) haemorrhage, bacterial infection, or any combination of these. With ACLF, we refer to a distinct syndrome which is observed among patients admitted to the hospital for AD characterised by single or multiple organ failures and high 28-day mortality (>15% at 28 days).

Bacterial infections were diagnosed according to international[26–28] and local guidelines. Nosocomial infections were considered if infection signs and/or symptoms started more than 48 h after hospital admission. nACLF was defined as any occurrence of ACLF after 48 h from hospital admission. Readmission was defined as 'liver-related' when it occurred for ascites decompensation, HE, GI bleeding, bacterial infections, jaundice, or renal failure complicated or not by ACLF.

Statistical analysis

For all continuous parameters the normality of distribution and homogeneity of variance were evaluated by the Kolmogorov-Smirnov and Levene tests, then variables were reported as mean and standard deviation or median and IQR as appropriate. Accordingly, comparisons between groups were performed using the Student *t* test or Mann–Whitney *U* test when appropriate. Categorical parameters were reported as frequency and percentage and compared using the X^2 square or Fisher exact test. The cumulative incidence of early and total readmissions during follow-up was estimated according to the Kaplan–Meier Method and compared using the log rank test. The cumulative incidence of death was estimated considering LT as a competing event, cumulative incidence curves were compared using Gray's test. Survival time to readmission, death, or LT was calculated from discharge from index hospitalisation.

A multivariable Cox regression analysis with stepwise backward selection method was performed to identify predictors of early readmission. For each predictor the hazard ratio (HR) and the 95% CI were reported. The internal validity of this model was evaluated by using bootstrap resampling in which 1,000 replications were generated by sampling with replacement from the original dataset. A multivariable competing risk regression analysis with stepwise backward elimination according to the Fine and Gray method was also performed as sensitivity analysis. In this model, death, non-liver related readmission, and LT not preceded by admission for AD were considered as competing events.

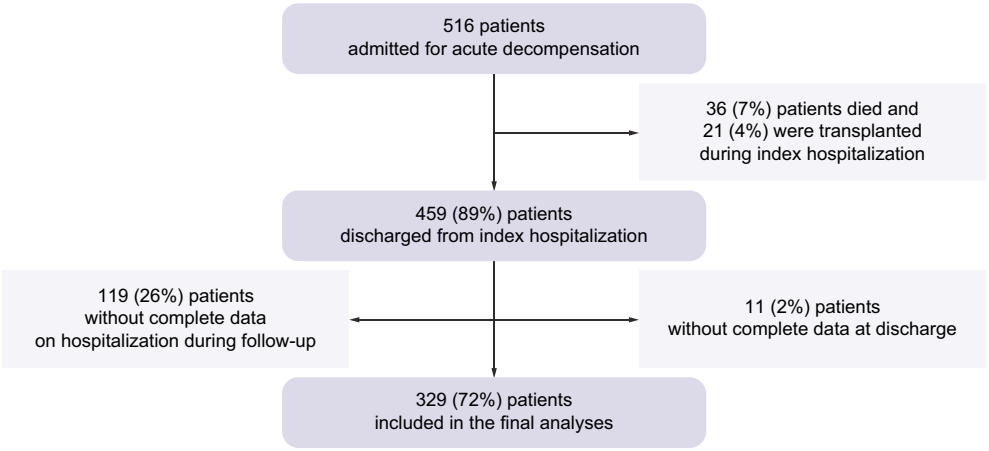

Fig. 1. Flow chart of the study.

For the purpose of the analysis continuous parameters were categorised according to the Youden Index computed by receiver operating characteristics (ROC) curve analysis. All tests were two-sided and values of p <0.05 were considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 27, IBM Corp., Armonk, NY, USA), STATA (StataCorp LLC, College Station, TX, USA) version 17 and the cmprsk package on R statistical software (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

Results

Study population

A total of 516 patients with cirrhosis admitted for AD were included. Fifty-seven patients died or underwent LT during the index hospitalisation. Of the remaining 459 patients, 130 (28%) patients were excluded because clinical and biochemical data at discharge and information on their hospitalisations during follow-up were not available. Thus, 329 (72%) patients were included in the final analysis (Fig. 1). Baseline anthropometric data, aetiology of cirrhosis, and clinical complications were comparable between patients included and those excluded from the final analysis (Table S1). Moreover, the 1-year cumulative incidence of death (considering LT as a competing event) was similar between the two groups (34% [95% CI 29–40%] *vs.* 38 [95% CI 30–47%]; p = 0.422).

Baseline characteristics of patients and index hospitalisation

Baseline demographic, biochemical, and clinical data of patients are reported in Table S2. Overall, the median age of the patients was 63 years with a predominance of males. The more frequent

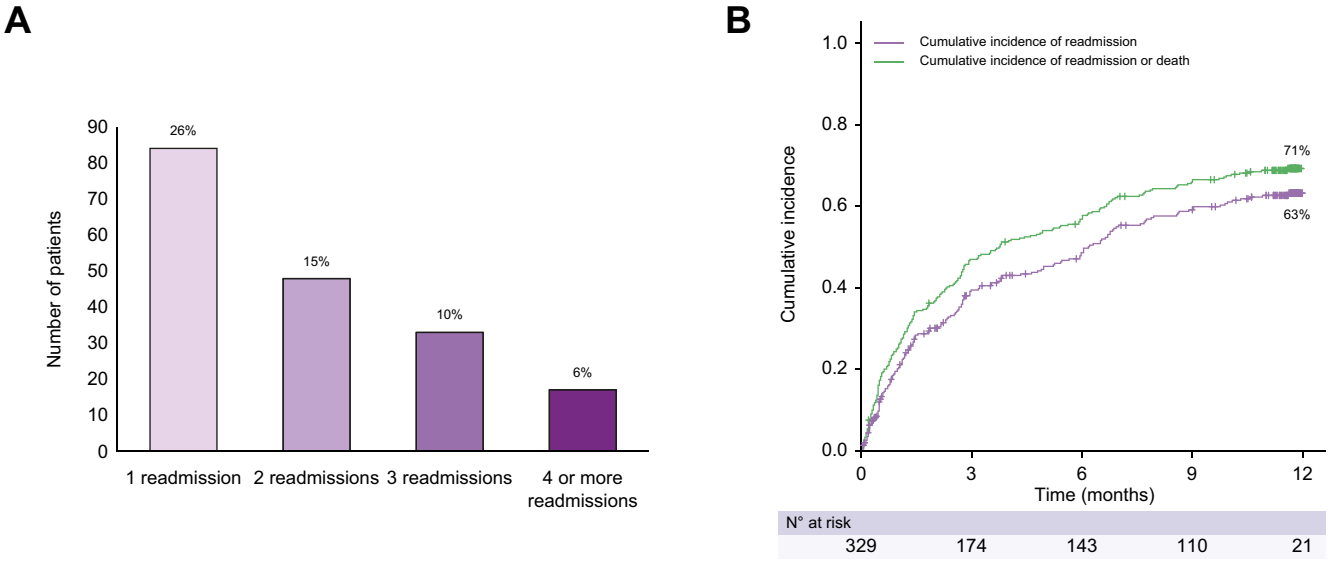

Fig. 2. Number of readmissions and cumulative incidence of readmissions during the follow-up period. (A) Number of patients with one, two, three, or four or more readmissions during the follow-up period. (B) Kaplan-Meier estimate of the cumulative incidence of all cause readmissions during follow-up (purple line, death and transplant considered as censoring events) and cumulative incidence of all cause readmission or death (green line, transplant considered as censoring event).

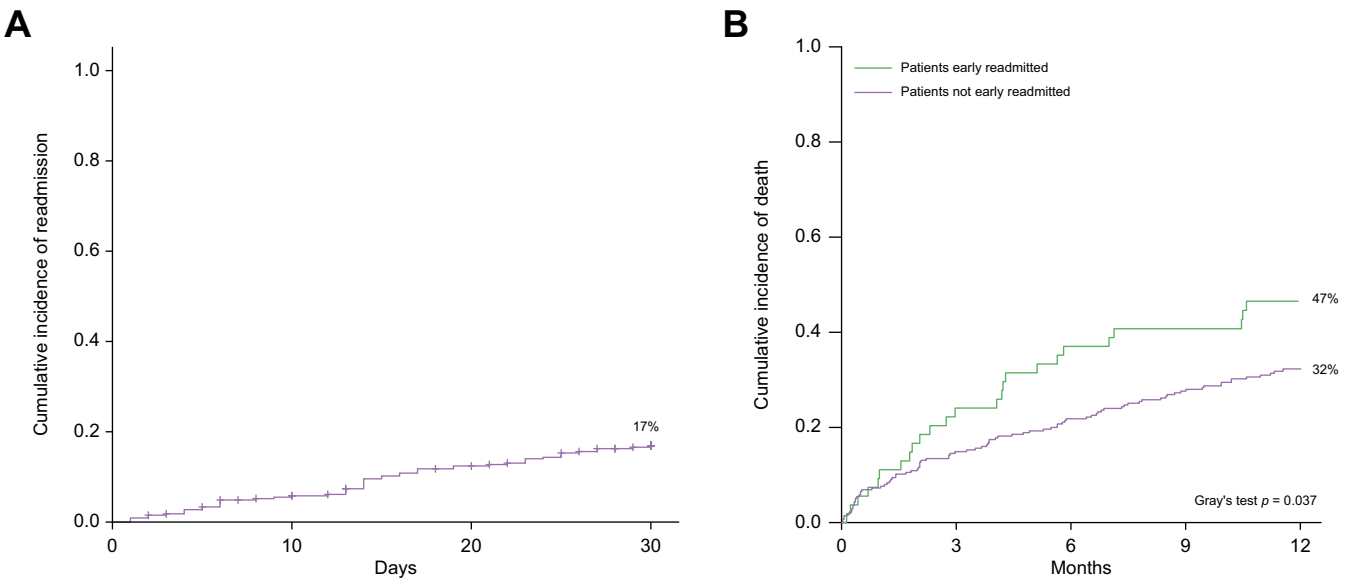

Fig. 3. Cumulative incidence of liver-related early readmissions and cumulative incidence of death during the follow-up period. (A) Thirty-day cumulative incidence of liver-related early readmissions. (B) Cumulative incidence function of mortality considering liver transplantation as a competing event in patients readmitted within 30 days (early readmission) for liver-related causes as compared with those not early readmitted. The cumulative incidence was compared using Gray's test.

complications of cirrhosis at admission were ascites (57%), renal dysfunction (18%), and grade III/IV HE (17%). Twenty-two percent of patients had bacterial infection at admission, and an additional 11% developed nosocomial infection during the index hospitalisation. Moreover, 19% of subjects had ACLF at admission and a further 9% developed nACLF during the hospital stay. Finally, 29 (9%) of patients had refractory ascites.

About 50% of patients were in class B Child-Pugh, while the median MELD score was 15. The number of patients with HCC was 69 (21%). Finally, the median length of the index hospitalisation was 11 days (7–19 days) (Table S2).

Readmissions

During the follow-up period, 369 hospitalisations were recorded in 182 patients. Eighty-four patients (25%) were readmitted once, and 98 patients (30%) were readmitted more than once. Namely, 48 patients were readmitted twice, 33 patients three times, and 17 patients four or more times (Fig. 2A). The more frequent causes of readmissions were HE (26%), ascites (16%), and bacterial infections (15%). In 101 cases (27%), readmission was not related to liver disease. The main causes for non-liver related readmissions were cardiological and vascular diseases (6%), traumatic injuries (6%), GI illness excluding complications related to portal hypertension (6%), neurological disorders excluding HE (3%), pulmonary diseases excluding infections (2%), metabolic and endocrinological diseases (2%), and urinary disorders excluding infections (2%).

Cumulative incidence of any-cause of first readmission was 20% (95% CI: 16–25%) at 30 days, 39% (95% CI: 34–45%) at 90 days, and 63% (95% CI: 57–68%) at the end of follow-up (Fig. 2B). Cumulative incidence of any-cause of first readmission or death was 25% (95% CI: 21–30%) at 30 days, 47% (95% CI: 42–53%) at 90 days, and 71% (95% CI: 64–73%) at the end of follow-up (Fig. 2B). The median time between discharge from the index hospitalisation and first readmission was 56 days (9–159 days).

Of the 63 readmissions occurring within 30 days, 54 were liver-related with a cumulative incidence of 17% (95% CI: 13–21%) (Fig. 3A). No differences were detected in the frequency of causes responsible for readmissions occurring within or after 30 days except for GI bleeding which was more frequent in late readmissions (Table 1).

Table 1. Causes of first readmission occurring within or after 30 days from discharge of index hospitalisation.

	Within 30 days (n = 63)	After 30 days (n = 119)	
	n (%)	n (%)	*p* value
Liver-related	54 (84)	90 (76)	0.128
Ascites	11 (17)	23 (19)	0.843
Bacterial infection	15 (24)	22 (18)	0.441
Hepatic encephalopathy grade III/IV	17 (27)	19 (16)	0.082
Other liver-related	11 (17)	26 (22)	0.564
Renal dysfunction	6 (10)	6 (5)	0.346
Jaundice	3 (5)	3 (3)	0.418
Gastrointestinal bleeding	2 (3)	17 (14)	0.021
Not liver-related causes	9 (14)	29 (24)	0.128

Data are reported as absolute frequency and percentage (%), comparisons were made using the X^2 test.

Table 2. Demographic, biochemical, and clinical characteristics at baseline and discharge from index hospitalisation and events during the index hospitalisation in patients readmitted for liver-related causes within 30 days or not readmitted within 30 days.

	Readmitted within 30 days (n = 54)	Not readmitted within 30 days (n = 275)	*p* value
Anthropometric data			
Age (years)	60 ± 15	63 ± 14	0.134
Male sex (n, %)	38 (70)	166 (60)	0.220
Aetiology of cirrhosis			
Viral (n, %)	19 (35)	114 (41)	0.449
Alcohol (n, %)	10 (19)	51 (19)	1.000
NASH (n, %)	2 (4)	21 (8)	0.393
Mixed (n, %)	13 (24)	49 (18)	0.340
Other (n, %)	10 (19)	40 (15)	0.533
Clinical and biochemical and haemodynamic data at admission			
Ascites (n, %)	35 (65)	151 (55)	0.230
Encephalopathy III/IV grade (n, %)	13 (24)	42 (15)	0.115
Renal dysfunction (n, %)	11 (20)	48 (17)	0.567
Gastrointestinal bleeding (n, %)	3 (6)	21 (8)	0.778
Bacterial infection at admission (n, %)	11 (20)	62 (23)	0.858
ACLF at admission (n, %)	14 (26)	47 (17)	0.129
Active alcohol consumption (n, %)	9 (17)	61 (22)	0.468
Hb (g/dl)	10.4 ± 1.5	10.7 ± 2.07	0.281
WBC (10^9/L)	5.64 (3.78–8.16)	5.2 (3.6–8.2)	0.471
CRP (mg/dl)	1.23 (0.35–2.66)	1.12 (0.38–3.17)	0.743
Platelets (10^9/L)	84 (55–124)	92 (59–143)	0.324
Sodium (mmol/L)	136 (132–139)	137 (134–140)	0.015
Bilirubin (mg/dl)	2.96 (1.37–5.82)	2.0 (1.1–3.5)	0.013
Creatinine (mg/dl)	0.92 (0.79–1.36)	0.95 (0.75–1.27)	0.463
Albumin (mg/dl)	3.08 ± 0.57	3.24 ± 0.61	0.089
INR	1.46 (1.33–1.58)	1.34 (1.23–1.56)	0.058
MAP (mmHg)	85 (76–93)	85 (79–93)	0.526
Heart rate (beats/min)	74 (66–85)	77 (68–86)	0.488
Prognostic scores at admission			
Child-Pugh score	9 (7–10)	8 (7–9)	0.088
Child-Pugh class			
Class A (n, %)	9 (17)	68 (25)	0.223
Class B (n, %)	28 (52)	139 (51)	0.883
Class C (n, %)	17 (32)	68 (25)	0.310
MELD	16 (11–21)	15 (10–19)	0.097
MELD-Na	20 (15–23)	17 (13–21)	0.008
CLIF-C AD	53 ± 9	51 ± 9	0.226
Comorbidities			
Charlson comorbidity index	6.00 (4.55–8.15)	6.10 (4.95–7.30)	0.825
HCC (n, %)	11 (20)	58 (21)	1.000
Diabetes (n, %)	26 (48)	91 (33)	0.043
Events occurring during index hospitalisation			
Hospital–related infection (n, %)	8 (15)	29 (11)	0.351
ACLF during hospital–stay (n, %)	10 (19)	21 (8)	0.020
Blood transfusion (n, %)	19 (35)	78 (29)	0.203
Length of index hospitalisation (days)	14 (8–21)	10 (7–18)	0.010
Clinical, biochemical and haemodynamic data at discharge from index admission			
Hb (g/dl)	9.9 (8.9–10.8)	10.3 (9.5–11.6)	0.010
WBC (10^9/L)	4.9 (3.5–6.9)	4.72 (3.39–6.55)	0.739
CRP (mg/dl)	0.91 (0.39–1.65)	0.86 (0.33–1.79)	0.519
Platelets (10^9/L)	74 (55–110)	92 (58–145)	0.108
Sodium (mmol/L)	137 (135–139)	139 (136–141)	0.014
Bilirubin (mg/dl)	3.2 (1.4–5.7)	1.8 (0.9–3.4)	0.003
Creatinine (mg/dl)	1.02 (0.80–1.25)	0.93 (0.71–1.27)	0.171
Albumin (mg/dl)	3.40 (3.30–3.90)	3.50 (3.10–3.90)	0.349
INR	1.42 (1.26–1.64)	1.35 (1.21–1.54)	0.096
MAP (mmHg)	83 (78–90)	83 (77–93)	0.606
HR (bpm)	70 (64–80)	70 (60–80)	0.548
MELD	16 (12–20)	14 (10–18)	0.018
MELD-Na	18 (12–21)	15 (11–19)	0.011
CLIF-C AD	50 ± 8	49 ± 9	0.298

Data are reported by mean and standard deviation, median and interquartile range or absolute frequency and percentage (%) as appropriate. Comparisons between groups were performed by means of Student's *t* test, Mann–Whitney *U* test or the X^2 test when appropriate. ACLF, acute-on-chronic liver failure; CLIF-C AD, CLIF consortium acute decompensation score; CRP, C-reactive protein; Hb, haemoglobin; HCC, hepatocellular carcinoma; HR, heart rate; INR, international normalised ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; RBCs, red blood cells; WBCs, white blood cells.

Table 3. Cox regression analysis of factors associated with early unplanned readmission (liver-related).

Parameter	Hazard ratio (95% CI)	*p* value
MELD-Na >16 at discharge	2.234 (1.268–3.934)	0.005
Hb ≤8.7 g/dl at discharge	2.629 (1.379–5.017)	0.003

Unscheduled non-liver related readmission and death without admission to the hospital were considered censoring events. Data are reported as hazard ratio and 95% confidence interval (CI). Hb, haemoglobin; MELD-Na, model for end-stage liver disease-sodium.

Patient outcomes

Overall, during the entire post-discharge follow-up, 113 patients died and 28 received a liver graft. In particular, in the first 30 days after discharge, 26 patients died and four underwent LT. The cumulative incidence of death considering transplantation as a competing risk event was significantly higher in patients who experienced at least one liver-related readmission within 30 days as compared with that of the remaining patients (47% [95% CI: 33–59%] *vs.* 32% [95% CI: 27–38%]; $p = 0.037$) (Fig. 3B).

Clinical characteristics of patients readmitted or not within 30 days

Patients who were readmitted within 30 days for liver-related causes did not differ from those who did not have early readmissions in terms of demographic data, aetiology of cirrhosis, and clinical features at admission of the index hospitalisation, except for type 2 diabetes which was more frequent in the former group.

Among baseline biochemical parameters, patients with early readmissions presented lower serum sodium and higher bilirubin levels at admission. As a result, the MELD-Na score at admission was significantly higher (Table 2).

Patients rehospitalised within 30 days more frequently developed ACLF during the index hospitalisation, whereas no differences were recorded in the incidence of nosocomial bacterial infections and number of blood transfusions. Moreover, the length of the index hospitalisation was significantly higher in patients with early readmission (Table 2).

Finally, among the biochemical data recorded at discharge, patients with early readmission were characterised by lower haemoglobin (Hb) and serum sodium and higher bilirubin levels. Overall, the severity of cirrhosis at discharge was higher in patients who were rehospitalised within 30 days, as assessed by the MELD and MELD-Na scores (Table 2).

Risk factors for liver-related readmission within 30 days

We performed a multivariable Cox regression analysis to identify the independent predictors of early readmission. The parameters significantly associated with early readmission at univariate analysis (Table 2) included in the initial model were the presence of diabetes, length of the index hospitalisation, nACLF, MELD-Na, and Hb level at discharge. Diabetes and nACLF were considered dichotomous variables, whereas length of hospital stay, MELD-Na, and Hb level at discharge were categorised according to their best cut-off as determined using ROC curve analysis. As reported in Table 3, MELD-Na >16 (HR 2.234 [95% CI: 1.268–3.934], $p = 0.005$) and Hb ≤8.7 g/dl (HR 2.629 [95% CI: 1.379–5.017], $p = 0.003$) at discharge were identified as independent predictors of early liver-related readmission. The internal validity of the Cox regression model was also evaluated by using bootstrap resampling in which 1,000 replications were generated by sampling with replacement from the original dataset. This model confirmed MELD-Na >16 (HR 2.23 [95% CI 1.25–3.99], $p = 0.007$) and Hb ≤8.75 g/dl (HR 2.63 [95% CI 1.32–5.24], $p = 0.006$) as independent predictors of hospital readmission.

As a further sensitivity analysis, we also performed a multivariable competing risk regression model, considering death, LT not preceded by admission for AD, and non-liver related readmission as competing events (Table S3). This model confirms MELD-Na >16 (sHR 2.25 [95% CI: 1.27–3.99], $p = 0.005$) and Hb ≤ 8.7 g/dl (sHR 2.38 [95% CI: 1.22–4.64], $p = 0.011$) as independent predictors, and identified the presence of diabetes (sHR 1.74 [95% CI: 1.02–2.99], $p = 0.044$) as an additional risk factor for early readmission.

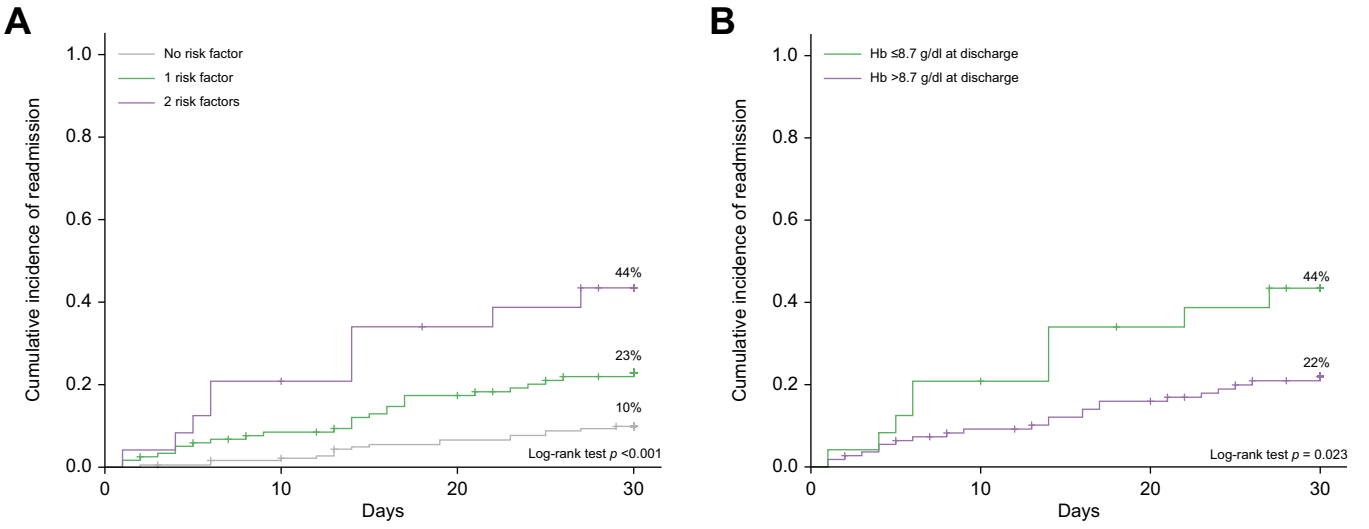

Fig. 4. Cumulative incidence of liver-related early readmissions according to the presence of the risk factors identified in the analyses. (A) Thirty-day cumulative incidence of liver-related early readmissions in patients presenting none, one, or two of the following independent risk factors: Hb ≤8.7 g/dl and MELD-Na >16 at discharge of the index hospitalisation. (B) Thirty-day cumulative incidence of liver-related early readmissions in patients with MELD-Na >16 presenting a Hb level of at least or lower than 8.7 g/dl at discharge. Comparisons were made using the log-rank test. Hb, haemoglobin; MELD-Na, model for end-stage liver disease-sodium.

Overall, a MELD-Na score >16 was found in 134 patients, whereas the number of patients with Hb ≤8.7 g/dl at discharge was 33 (10%). In the latter group, the main cause of anaemia was acute GI bleeding (three patients), iron deficiency (10 patients, six of whom had evidence of occult chronic GI bleeding), folate deficiency (two patients), and malnutrition in patients with chronic alcohol abuse (two patients). In the remaining 18 patients, the low Hb level was attributed to multifactorial factors (*i.e.* hypersplenism, hyporegenerative bone marrow, chronic inflammation). Interestingly, patients with Hb ≤8.7 g/dl presented higher levels of C-reactive protein (CRP) at discharge than those with Hb >8.7 g/dl (1.72 g/dl [IQR 0.47–2.95] *vs.* 0.79 g/dl [IQR 0.33–1.6], $p = 0.016$).

We then analysed the cumulative incidence of early readmission in patients presenting none, one, or two of these risk factors. As shown in Fig. 4A, the cumulative incidence of early readmission attributable to liver-related causes was 10% (95% CI: 6–13) in patients presenting no risk factors, 23% (95% CI: 16–32) in those with one risk factor and 44% (95% CI: 26–66) in those with two risk factors (p <0.001). Furthermore, we analysed the sub-population with MELD-Na >16 at discharge: in this subgroup of patients, the additional presence of Hb ≤8.7 g/dl at discharge doubled the cumulative incidence of 30-day readmission (44% [95% CI 26–66%] *vs.* 22% [95% CI: 15–31]: $p = 0.023$) (Fig. 4B).

Finally, the cumulative incidence of liver-related early readmission was similar in patients receiving blood transfusion or not during the index hospitalisation (20% [95% CI: 12–28%] *vs.* 15 [95% CI: 11–20%]; $p = 0.289$).

Discussion

Recurrent emergent hospitalisations represent a major clinical and socio-economic problem in patients with decompensated cirrhosis. The major findings of the present study can be summarised as follows: (1) the cumulative incidence of readmissions increases progressively over the year following discharge from an index hospitalisation as a result of AD, with a greater rate during the initial weeks; and (2) low Hb levels independently predict liver-related 30-day readmission.

The majority of available studies on readmissions have evaluated retrospective cohorts of patients and large national registries[5,16,29,30] or have limited the observation up to 90 days.[4,31] Based on the results of our study performed in a relatively large prospective cohort, a patient discharged after AD of cirrhosis carries about 50% chance of being rehospitalised at least once in the following year. Even more important, more than 50% of these patients had more than one readmission and almost 30% at least three over a year. This means that a relatively high number of patients with decompensated cirrhosis is at high risk of multiple readmissions, thus representing a heavy burden for healthcare systems.

Three out of four of all readmissions were because of liver-related causes with ascites and HE responsible for almost 60% of them. This implies that improving the management of these two complications will likely reduce the disease burden. In this regard, in addition to optimisation of drug therapy, early contacts with nurses or doctors after discharge, the education of patients and their caregivers, or telemedicine (*i.e.* smartphone apps) have shown encouraging results to reduce readmissions.[32–36] Implementation of long-term albumin administration in the outpatient setting may represent a further option, as it has been reported that this approach reduces HE, ascites, infections, and hospitalisation.[37,38]

In the present study, the rate of readmission within 30 days was close to 20%, which is comparable to or slightly lower than what was already reported.[2,5,29,30] Readmissions occurring within 30 days are relevant for several reasons. First, early rehospitalisation is associated with poorer survival,[15,29,39] as also confirmed by our study. Second, being rapidly readmitted is a psychological stressful event and leads to a rapid deterioration of the patient's quality of life. Third, early readmissions are considered an outcome indicator of in-hospital management of patients leading to reduced reimbursement to hospitals.[40]

Thus, many efforts have been made to identify parameters that can stratify patients at risk of early readmission. We found that the MELD-Na and Hb level at discharge independently predicted 30-day liver-related readmission. Although the association between the severity of cirrhosis and the risk of early readmission has been already reported,[2,15,31] the independent predicting role of the Hb level represents, to the best of our knowledge, a novel finding.

In our cohort, Hb levels ≤8.7 g/dl at discharge were associated with more than a double risk of early readmission. Thus, a simple inexpensive parameter available in all care settings can help to identify, among those with advanced cirrhosis (*i.e.* with MELD-Na >16), a sub-group of patients who have almost a 50% probability to be readmitted within 30 days and therefore should be included in a close surveillance outpatient programme.

Up to now, anaemia has been related to the severity of cirrhosis, as assessed by MELD and Child-Pugh scores,[41] and to the development of ACLF in outpatients[42] or in those admitted to the hospital for AD.[43] More recently, a retrospective study in almost 5,000 outpatients with advanced chronic liver disease found a significant association between anaemia and incidence of hepatic decompensation, hospitalisation, ACLF, and long-term overall survival.[44] Therefore, considering these data, we could hypothesise that a low Hb level can act as surrogate marker of disease severity and, among the multiple possible causes, the role of systemic inflammation that characterises advanced cirrhosis may be predominant, as also suggested by the higher level of CRP at discharge in patients with Hb ≤8.7 g/dl.

The last issue to discuss is whether our finding should prompt clinical interventions aimed at improving the circulating Hb level before discharge. Several considerations can be made. First, the cut-off we identified (8.7 g/dl) is a value for which current guidelines do not recommend red blood cell transfusion.[45,46] Second, the incidence of liver related early-readmission was similar in transfused and non-transfused patients and no difference was found in the number of blood transfusions received by early-readmitted or not early-readmitted patients during the index hospitalisation. Third, even in the presence of an apparent depletion, iron supplementation might not be appropriate in patients with AD and even less in the case of ACLF. Indeed, in these patients, who present a complex and still not fully clarified alteration of iron metabolism,[47] iron supplementation may increase the pool of circulating free iron driving an unwanted exacerbation of systemic inflammation.[48] Thus, studies are still needed before an indication to correct anaemia beyond the current recommendation can be proposed.

Some limitations of our study must be acknowledged. First, our study is a secondary analysis of a cohort of patients with prospectively collected data and the original study was not

designed to study anaemia and related parameters,[19] therefore a comprehensive characterisation of the aetiology of anaemia was not possible. Second, the number of patients enrolled is significantly lower compared with the large retrospective registry studies already published.[5,16,29,30] However, we believe that the prospective collection of the data in a relatively large cohort provides more robust and reliable information as compared with pure retrospective analysis. Finally, the number of discharged patients who could not be included in the analysis because of the lack of complete data on hospitalisation during follow-up was relatively high (28%). However, baseline characteristics and 1-year mortality of these patients were comparable to those included in the analysis, thus mitigating the risk of a selection bias.

In conclusion our study shows that multiple readmissions to hospital are frequent and distributed over a period of 1 year in patients with decompensated cirrhosis discharged after an index hospitalisation for AD. Furthermore, a low Hb level (≤8.7 g/dl) has been identified for the first time as an independent predictor of early liver-related readmission, contributing to identification of the sub-group of patients (about 10% of our entire cohort) who deserve closer surveillance by their inclusion in transitional care programmes with the objective of preventing rehospitalisations and saving healthcare resources.

Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; CLIF-C-AD, CLIF Consortium Acute Decompensation score; CRP, C-reactive protein; GI, gastrointestinal; Hb, haemoglobin; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, International Normalised Ratio; LT, liver transplantation; MAP, mean arterial pressure; MELD, model for end stage liver disease; Na, sodium; nACLF, nosocomial acute-on-chronic liver failure; NASH, non-alcoholic steatohepatitis; RBCs, red blood cells; WBCs, white blood cells.

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Conflicts of interest

All authors declare no conflicts of interest that are relevant to the content of this article.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design, interpretation of data, drafting of the manuscript: EP, MB, GZ, MD, PC. Collection of data: EP, GZ, MB, MT, GI, DP, FP, LV, CF. Analysis of data: EP, MB. Critical revision for important intellectual content: EP, MB, GZ, LV, CF, GB, MD, PC.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100698.

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Author names in bold designate shared co-first authorship.

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