The Burden of Hyperbilirubinemia in Critically Ill Patients with Hematological Malignancies: Post-hoc Analysis of a Prospective Multicenter Multinational Study

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Abstract

Background

The evidence on the clinical significance of hyperbilirubinemia (HB) in critically ill patients with hematological malignancies is scarce. We therefore studied its burden in a 2010-2011 Franco-Belgian multicenter prospective study designed to evaluate the prognosis of these patients.

Patients and methods

The cohort comprised 893 patients from 17 centers, 61% men, with a median (interquartile range) age of 60 (49 – 70) years, and preferentially with underlying non-Hodgkin lymphoma (32%) or acute myeloid leukemia (27%). HB was defined as a total serum bilirubin ≥ 33 µmol/L at intensive care unit (ICU) admission. Our main goal was to evaluate the relationship between HB and outcome of critically ill hematological patients. Causes and management of HB in the ICU were analyzed as secondary end points.

Results

HB concerned 185 (21%) patients. Cyclosporine and antimicrobial treatments, ascites and cirrhosis, acute kidney injury, neutropenia, and myeloma (adjusted odd ratio [aOR] 0.38, p=0.006) were risk factors. Hospital mortality was 56.3% and 36.3% in patients with and without HB, respectively (p<0.0001 with the log-rank test). Adjusted for severity of illness, the adjusted odds ratio (95% confidence interval) of HB for in-hospital mortality was 1.86 (1.28, 2.72). HB was overlooked by the ICU team for 92 (53%) patients. Overwise, liver workups for HB led to treatment modifications in 32 (40%) patients, including chemotherapy for cancer progression that was associated with reduced mortality with an adjusted odds ratio of 0.23, (p=0.02).

Conclusion

HB is associated with outcome of critically ill hematological adult patients and should be systematically explored and treated.

Introduction

Liver abnormalities are common in critically ill patients with hematological malignancies and is reported after hematopoietic stem cell transplantation (HSCT) (1,2), targeted therapies, immunoconjugate antibodies and immunotherapies (3–5). Causes are frequently multifactorial, including drug-induced liver injury (DILI) (6–8), transfusional iron overload (9), infections (10), sepsis (11), prolonged parenteral nutrition (12), underlying hepatic disease (13) and cancer-related complications such as tumoral infiltration (14), hepatic graft-versus-host disease (GvHD) after allogenic HSCT (allo-HSCT) (15), sinusoidal obstruction syndrome (SOS) (16,17), tumor lysis syndrome (18) and haemophagocytic syndrome (19).

Diagnosis of liver injury in critically ill hematological patients is challenging as clinical, biological and radiological findings are, in general, nonspecific, and because of the absence of systematic guidelines, including on the use of liver biopsies. Total serum bilirubin level, a biomarker of liver function, has been incorporated in several organ dysfunction scores (20,21) to grade liver injury in intensive care patients. Hyperbilirubinemia (HB), defined as an increased total serum bilirubin level ≥ 68 µmol/L, has been associated with a doubled risk of mortality in a large cohort allo-HSCT patients (22,23). In pediatric patients, a total serum bilirubin ≥ 33 µmol/L one month after allo-HSCT has been associated with higher non-relapse mortality (24). HB seems more associated with mortality than hepatocellular injury, defined as elevated aminotransferase levels without HB in hematological patients (25).

Overall, the level of evidence, including incidence, risks, causes and management, on HB is scarce in critically ill hematological patients. In order to decipher its burden, we analyzed a large prospective multicenter sample of critically ill hematological patients and report on the management of HB by caring physicians.

Patients And Methods

Study population

We performed a post hoc analysis of a Franco-Belgian multicenter prospective study assessing the prognosis of patients with hematological malignancies admitted in 17 ICU between January 2010 and May 2011 (26). Among the 1011 patients enrolled in the original study, only patients with total serum bilirubin measurement at admission were included. Two groups were created according to liver SOFA score (21) at ICU admission: one with HB defined as a liver SOFA score >1 (total bilirubinemia ≥ 33 µmol/L) and one without HB defined as a liver SOFA score ≤ 1 (total bilirubinemia < 33 µmol/L) (24). The appropriate ethics committees approved the study (26) and all patients or relatives were informed and consented to participate in the study.

Data collected in the prospective cohort

All patients had a diagnosis of initial/relapsed hematological malignancy within 5 years before ICU admission. The performans status (27) and the Charlson comorbidity index (28) were determined at ICU admission. History of mild, moderate or severe liver diseases was defined by a hepatic Charlson comorbidity index ≥ 1 (severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis or cirrhosis without portal hypertension). Underlying malignancies, disease status at ICU admission, radiotherapy and chemotherapy received in the last month and HSCT were recorded. In allo-HSCT patients, the type of donor, type and intensity of conditioning regimen and GvHD prophylaxis and treatment were collected. Chemotherapy, systemic corticosteroids, hematopoietic growth factors and immunosuppressive drugs prescribed by the hematologist in charge of each patient and administered during ICU stay were recorded. Neutropenia was defined as a neutrophil count of less than 0.5 G/L and presence of haemophagocytosis features on myelogram was informed. Data from clinical examination at ICU admission were reported

such as digestive, neurological, cutaneous, renal and hematological symptoms. Organ dysfunctions, presence of sepsis and life sustaining therapies at ICU admission and during the ICU stay were also recorded.

Data collection

Medical hospital records of patients with HB at ICU admission were selected and reviewed by an expert panel including an intensivist (MB), a hematologist (CS) and hepatologists (CM and VM). The five following questions were assessed: (1) was HB at ICU admission mentioned by the attending physician in the medical records? (2) was a diagnostic strategy carried out to explore HB, including a liver biopsy? (3) which cause of HB was suspected by the attending physician or confirmed by hepatic histology when liver biopsy was performed just before ICU admission or during ICU stay? (4) which specific treatments were initiated? (5) which cause of HB was considered *a posteriori* by the expert panel? Etiologic diagnoses of HB were established by the expert panel according to pre-established definitions of GvHD (15), SOS (17), haemophagocytic syndrome (19), hypoxic hepatitis (29), sepsis (11),viral hepatitis (30), liver fungal infections (10), drug induced liver injury (31).

Statistical analysis

Results were reported as median and interquartile ranges or counts and proportions (%). Qualitative variables were compared using the chi-square test or Fisher's exact test as appropriate and continuous variables using the Mann-Whitney test. Multivariate analyses were performed using logistic regressions. Variables yielding P-values < 0.20 in the univariate analyses or considered clinically relevant were entered in backward stepwise logistic regression models. Survival curves were constructed according to the Kaplan-Meier method and compared with the log-rank test. P-values <0.05 were considered statistically significant. Statistical analyses were done using SPSS software (version 20).

Results

Characteristics of patients

Among the 1011 patients included in the TRIALOH study (26), 118 (11.7%) were excluded because total serum bilirubin level was not measured at ICU admission (Figure 1). Among the 893 remaining patients, 185 (20.7%) patients had HB, defined as a total bilirubinemia ≥ 33 µmol/L at admission, which corresponds to a SOFA score > 1.

Characteristics of the cohort by HB are presented in Table 1. Median (interquartile range) age was 60 (49 – 70) years and there was a majority (61%) of men. Less than 5% of patients had a history of liver diseases. Non-Hodgkin lymphoma was the most frequent underlying hematological malignancy (31.5%), followed by acute myeloid leukemia (27.1%) and myeloma (11.9%). There were 133 (14.7%) allo-HSCT patients, including 6.8% with a previous myeloablative conditioning regimen. About two-third of patients (64.9%) had been treated with antibiotics before ICU transfer. Acute respiratory failure concerned almost

two-third (62.4%) of patients at ICU admission, followed by cardiovascular failure (43.1%), acute kidney injury (31%) and acute liver failure (8.8%). A total of 497 (55.7%) patients had at least two organ failures at ICU admission. Digestive, hematological (such as lymphadenopathy, mucositis, hepatomegaly, splenomegaly, purpura, and intraoral hemorrhage) and/or neurological symptoms were found on clinical examination in one-quarter of patients. Renal symptoms (such as decreased urine output, anuria, hematuria, and pyuria) were present in one-third of patients (32.2%). Nearly one-third of patients (30.8%) were neutropenic, sepsis was diagnosed for 578 (64.7%) patients, and a high majority of patient received antimicrobial therapy at ICU admission and during ICU stay. About 10% of patients were receiving chemotherapy at ICU admission. Few patients had positive Cytomegalovirus (CMV) or Herpes simplex virus (HSV) nucleic acid testing (NAT). Haemophagocytosis features were described on myelograms in 16 patients (1.8%). Half of patients required invasive mechanical ventilation and/or vasoactive drugs during ICU stay, and one-third needed renal replacement therapy.

Table 1. Characteristics of patients

	All (n=893)	With HB (n=185)	Without HB (n=708)	*p*
Age (years), median [IQR]	60 [49-70]	56 [47-54]	61 [49-70]	<0.0001
Male sex, n (%)	545 (61.0)	121 (65.4)	424 (59.9)	0.171
Performans status >1, n (%)	470 (52.6)	93 (50.3)	377 (53.2)	0.47
Charlson comorbidity index, median [IQR]	4 [3-6]	4 [2-5]	4 [3-6]	0.005
Hepatic Charlson comorbidity index ≥1, n (%)	41 (4.6)	15 (8.1)	26 (3.7)	0.01
SOFA score at admission, median [IQR]	6 [3-9]	8 [6-13]	5 [3-8]	<0.0001
SOFA score without bilirubin level at admission, median [IQR]	5 [3-8]	6 [4-10]	5 [3-8]	<0.0001
Underlying malignancy, n (%)				
Acute myeloid leukemia	242 (27.1)	56 (30.3)	186 (26.3)	0.276
Acute lymphocytis leukemia	64 (7.2)	13 (7.0)	51 (7.2)	0.934
Non-hodgkin lymphoma	281 (31.5)	60 (32.4)	221 (31.2)	0.751
Hodgkin lymphoma	23 (2.6)	5 (2.7)	18 (2.5)	0.902
Myeloma	106 (11.9)	11 (5.9)	95 (13.4)	0.005
Chronic lymphocytic leukemia	70 (7.8)	8 (4.3)	65 (8.8)	0.046
Chronic myeloid leukemia	16 (1.8)	1 (0.5)	15 (2.1)	0.15
Myelodysplastic syndrome	32 (3.6)	10 (5.4)	22 (3.1)	0.134
Other	59 (6.6)	21 (11.4)	38 (5.4)	0.004
Disease status at ICU admission, n (%)				0.69
No remission/progression	340 (38.1)	63 (34.1)	277 (39.1)	
Complete remission	148 (16.6)	36 (19.5)	112 (15.8)	
Partial remission	62 (6.9)	13 (7.0)	49 (6.9)	
Newly diagnosed malignancy	214 (24.0)	46 (24.9)	168 (23.7)	

Unknown	129 (14.4)	27 (14.6)	102 (14.4)	
Chemotherapy in the last 1 month, n (%)				
Antracyclin	379 (42.4)	91 (49.2)	288 (40.7)	0.037
Aracytin	266 (29.8)	74 (40.0)	192 (27.1)	0.001
Cyclophosphamide	308 (34.5)	62 (33.5)	246 (34.7)	0.945
Bortezomid	63 (7.1)	7 (8.8)	56 (7.9)	0.051
Busulfan	17 (1.9)	7 (3.8)	10 (1.4)	0.036
Thalidomide	44 (4.9)	4 (2.2)	40 (5.6)	0.051
Fludarabin	88 (9.9)	26 (14.1)	62 (8.8)	0.031
Radiotherapy, n (%)	62 (7.0)	19 (10.3)	43 (6.1)	0.048
Allo-HSCT, n (%)	131 (14.7)	45 (24.3)	86 (12.2)	<0.0001
Auto-HSCT, n (%)	133 (14.9)	28 (15.1)	105 (14.9)	0.935
Myeloablative conditioning regimen for allo-HSCT	61 (6.8)	18 (9.7)	43 (6.1)	0.079
Treatments before ICU admission, n (%)				
Systemic corticosteroids the month before	339 (38.1)	76 (41.1)	263 (37.4)	0.354
Cyclosporin the month before	73 (8.2)	32 (17.4)	41 (5.8)	<.0001
Mycophenolate Mofetil the month before	45 (5.0)	17 (8.2)	28 (4.0)	0.004
Antimicrobial therapy the 10 days before	579 (64.9)	139 (75.1)	440 (62.2)	0.001
Organ failure at ICU admission, n (%)				
Acute respiratory failure	556 (62.4)	117 (63.2)	439 (62.2)	0.791
Cardiovascular failure	384 (43.1)	84 (45.4)	300 (42.5)	0.473
Acute kidney injury	276 (31.0)	67 (36.2)	209 (29.6)	0.083
Acute hepatic failure	78 (8.8)	43 (23.2)	35 (5.0)	<.0001

Coagulopathy	181 (20.3)	52 (28.1)	129 (18.3)	0.003
Neurological failure	202 (22.6)	47 (25.4)	155 (21.9)	0.314
Multi-Organ failure	497 (55.7)	123 (66.5)	375 (52.9)	0.001
Clinical situations at ICU admission, n (%)				
Digestive symptoms	215 (24.3)	75 (40.5)	140 (20.0)	<0.0001
Jaundice	34 (3.8)	32 (17.3)	2 (0.3)	<0.0001
Diarrhea	91 (10.2)	23 (12.4)	68 (9.6)	0.258
Gastrointestinal bleeding	16 (1.8)	6 (3.2)	10 (1.4)	0.095
Abdominal pain	123 (13.8)	39 (21.1)	84 (11.9)	0.001
Occlusive syndrome	28 (3.1)	7 (3.8)	21 (3.0)	0.57
Ascites	29 (3.2)	17 (9.2)	12 (1.7)	<0.0001
Renal symptoms	285 (32.2)	71 (38.4)	214 (30.6)	0.045
Tumor lysis syndrome	87 (9.7)	21 (11.4)	66 (9.3)	0.407
Hematological symptoms	233 (26.3)	62 (33.5)	171 (24.4)	0.012
Hepatomegaly	89 (10.0)	27 (14.6)	62 (8.8)	0.018
Splenomegaly	78 (8.7)	22 (11.9)	56 (7.9)	0.088
Mucositis	36 (4.0)	13 (7.0)	23 (3.2)	0.02
Neurological symptoms	221 (24.9)	51 (27.6)	170 (24.2)	0.349
Neutropenia	262 (30.8)	76 (42.7)	186 (27.6)	<0.0001
Sepsis	578 (64.7)	119 (64.3)	459 (64.8)	0.898
Treatment received at ICU admission, n (%)				
Antimicrobial therapy	732 (82.0)	154 (83.2)	578 (81.6)	0.613
Cyclosporin	33 (3.7)	14 (7.6)	19 (2.7)	0.002
Chemotherapy	108 (12.1)	19 (10.3)	89 (12.6)	0.39

Systemic corticosteroids	173 (19.4)	36 (19.5)	137 (19.4)	0.98
Stress dose corticosteroids	159 (17.8)	36 (19.5)	132 (17.4)	0.514
Life sustaining therapies at ICU admission, n(%)				
Invasive mechanical ventilation	261 (29.2)	60 (32.4)	201 (28.4)	0.282
Noninvasive mechanical ventilation	149 (16.4)	40 (21.6)	109 (15.4)	0.043
Vasoactive drugs	297 (33.3)	72 (98.9)	225 (31.8)	0.068
Renal replacement therapy	106 (11.9)	29 (15.7)	77 (10.9)	0.072
Laboratory testing at ICU admission				
Total Bilirubinemia, µmol/L	14 [8-26]	57 [42-100]	12 [8-18]	<0.0001
Aspartate aminotransferase, x ULN	1 [1-2]	2 [1-3.9]	1 [1-1]	<0.0001
Alanine aminotransferase, x ULN	1 [1-1.7]	1.4 [1-2.9]	1 [1-1.4]	<0.0001
Gamma glutamyltranspeptidase, x ULN	1.5 [1-3.5]	2.4 [1-5.4]	1.4 [1-3]	<0.0001
Alkaline phosphatase, x ULN	1 [1-1]	1 [1-2.3]	1 [1-1]	<0.0001
Prothrombin Time, %	64 [51-77]	57 [44-73]	66 [53-79]	<0.0001
Platelets, G/L	62 [30-147]	39 [18-72]	71 [32-157]	<0.0001
Serum creatinine, µmol/L	102 [69-170]	126 [80-206]	98 [67-156]	<0.0001
Hemoglobin, g/dL	9.1 [8-10.6]	8.7 [7.9-10.2]	9.2 [8-10.6]	0.062
Leucocytes, G/L	5.5 [0.8-15.3]	2.3 [0.3-12.3]	6.0 [11-17]	<0.0001
Bicarbonate concentration, mmol/L	22 [18-25]	21 [17-25]	22 [18-25]	0.038
Lactate, mmol/L	2.1 [1.2-4.2]	2.9 [1.6-5.9]	2.0 [1.2-4.1]	0.001
Positive CMV NAT	46 (5.2)	19 (10.3)	27 (3.8)	<0.0001
Positive HSV NAT	30 (3.4)	13 (7.0)	17 (2.4)	0.002

Life-Sustaining therapies during ICU stay, n (%)				
Noninvasive mechanical ventilation	265 (29.7)	62 (33.5)	203 (28.7)	0.199
Invasive mechanical ventilation	441 (49.4)	110 (59.5)	331 (46.8)	0.002
Vasoactive drugs	470 (52.6)	117 (63.2)	353 (49.9)	0.001
Renal replacement therapy	253 (28.4)	79 (42.7)	174 (24.6)	<0.0001
Treatment received during ICU stay, n (%)				
Antibiotic treatment	815 (91.3)	173 (93.5)	642 (90.7)	0.224
Antifungal treatment	357 (40.0)	92 (49.7)	265 (37.4)	0.002
Antiviral treatment	385 (43.1)	88 (47.6)	297 (41.9)	0.169
Stress dose corticosteroids	550 (61.6)	119 (64.3)	431 (60.9)	0.391
Hematopoietic growth factors	155 (17.4)	43 (23.2)	112 (15.8)	0.018
Nosocomial infection during ICU stay, n (%)	152 (17.0)	48 (25.9)	104 (14.7)	<0.0001

Note: HB was defined as total serum bilirubin level ≥ 33 μmol/L. (ICU: Intensive care unit; HB: hyperbilirubinemia; SOFA score: Sepsis-related Organ Failure Assessment score; Allo-HSCT: allogenic hematopoietic stem cell transplantation; Auto-HSCT: autologous hematopoietic stem cell transplantation; CMV: Cytomegalovirus; HSV: Herpes simplex virus; NAT: Nucleic acid testing; UNL: upper limit of normality)

HB and outcome

ICU mortality and hospital mortality were (n=84) 45.4% and (n=103) 56.3% and (n=175) 24.7% and (n=254) 36.3% for patients with and without HB. HB was associated with hospital mortality (odd ratio [OR]=2.26, 95% CI=1.62 – 3.14, p<0.0001 and Figure 2). After adjustment for invasive mechanical ventilation (MV), renal replacement therapy (RRT) and vasoactive drugs, HB remained an independent factor associated with hospital mortality (adjusted OR=1.86, 95% CI=1.28 – 2.72, p=0.001). Median ICU and hospital lengths of stay were not different for patients with and without HB. Independent risk factors for hospital mortality among HB patients were hepatic Charlson comorbidity index ≥ 1 (OR=11.67, 95% CI=1.37-99.72, p=0.025), performance status >1 (OR=2.14, 95% CI=1.04-4.41, p=0.040), acute respiratory

failure (ARF) at before ICU admission (OR=2.23, 95% CI=1.03-4.82, p=0.042), mechanical ventilation (MV) during ICU stay (OR=4.84, 95% CI=2.24-10.46, p<0.0001), RRT during ICU stay (OR=2.34, 95% CI=1.08-5.07, p=0.031), and chemotherapy initiated at ICU admission (OR=0.23, 95% CI=0.06-0.79, p=0.020). The univariate analyses are presented in additional table 1.

Risk factors for HB in critically ill hematological patients at ICU admission

Patients with HB were younger than patients without HB; had more frequently hepatic comorbidities; had received more anthracyclins, aracytin, busulfan but not cyclophosphamide, thalidomide and fludarabine; had undergone more frequently allo-HSCT; were treated with cyclosporine, mycophenolate mofetil or antimicrobial therapy; presented with more organ failures and digestive clinical symptoms; had higher serum concentrations of hepatic enzymes, a longer prothrombin time, lower platelet and higher lactate levels; and required more life sustaining therapies during ICU stay. Factors independently associated with HB at ICU admission are presented in Table 2. The presence at ICU admission of cyclosporin treatment, antimicrobial therapy, digestive symptoms, ascites, history of liver diseases, neutropenia and increased serum creatinine level, were associated with an increased risk of HB. Myeloma and its treatments were not associated with a higher risk of HB.

Table 2. Factors independently associated with HB in critically ill hematological patients

	OR	95% CI	*p*
Cyclosporin the month before ICU admission	3.357	1.926-5.851	<0.0001
Antimicrobial treatment before ICU admission	1.578	1.038-2.401	0.033
Digestive symptoms at ICU admission	2.182	1.461-3.258	<0.0001
Hepatic Charlson comorbidity index ≥ 1	2.228	1.057-4.696	0.035
Ascites at ICU admission	2.562	1.059-6.196	0.037
Increased serum creatinine level at ICU admission	1.001	1.000-1.003	0.021
Neutropenia at ICU admission	1.465	1.001-2.144	0.049
Myeloma	0.378	0.188-0.761	0.006

Note: (HB: hyperbilirubinemia; ICU: Intensive Care Unit; CI: confidence interval). Hepatic Charlson comorbidity index was defined as cirrhosis +/- portal hypertension +/- variceal bleeding history.

Management of hematological patients with HB in the ICU

A total of 173 (93.5%) medical records of HB patients were reviewed. HB was overlooked by the caring physician in 92 (53%) patients. Otherwise, a liver workup was performed in 51 (63%) patients among 81

(47%) for whom HB at admission was reported in the medical record. The diagnostic strategies included one or more of the following tests: liver ultrasonography, abdominal CT scan, serology and hepatotropic viruses and/or herpes viruses NAT, liver biopsies, echocardiography, bone marrow aspirate or bone marrow biopsy, biological markers of hemolysis and haemophagocytic syndrome. Causes of HB were evoked by the caring physician for 48 (59%) patients (Table 3). Among these patients, 32 (40%) received a specific treatment for HB such as chemotherapy for 16 (19.8%) patients, discontinuation of cyclosporin for 4 (4.9%) patients, systemic corticosteroids for three (3.7%) patients with hemolysis and one (1.2%) patient with GvHD, introduction of dobutamine for three (3.7%) patients, antimicrobial treatment for three (3.7%) patients, anti-fibrinolytic for one (1.2%) patient with SOS, hepatic arterial embolization for one (1.2%) patient with active hepatic bleeding. Among patients with HB, liver biopsy was performed in nine (5.2%) patients just before ICU admission or during ICU stay. A liver biopsy was performed transcutaneously in five (2.9%) cases, post-mortem in two (1.2%) cases, intraoperatively in 1 (0.6%) case and with an unknown method in one (0.6%) case. Complications due to percutaneous liver biopsies occurred in two patients, including intrahepatic and intra-peritoneal hemorrhages, which led to hemorrhagic shock and death for one of them. No transjugular liver biopsy was performed during the study period. Hepatic histological findings, available for eight biopsies, were one CMV viral hepatitis, one blastic infiltration, one lymphoma infiltration, one neuroendocrine tumor with liver infiltration, one toxic or drug origin necrosis cell with steatosis, one thrombotic microangiopathy with haemophagocytis, one SOS with GvHD injury, and one extramedullary haematopoiesis. The expert panel reclassified *a posteriori* 65 (37.6 %) patients (Table 3), including 21 (12%) patients that could have had access to a specific treatment.

Table 3. Causes of HB at ICU admission in a cohort of 893 critically ill hematologic patients

	Caring physician n= 173	Reviewers* n=173
Specific infiltration, n (%)	11 (6.4)	18 (10.4)
Drug toxicity, n (%)	10 (5.8)	7 (4.0)
Hypoxic hepatitis, n (%)	6 (3.5)	12 (6.9)
Haemophagocytis syndrome, n (%)	4 (2.3)	9 (5.2)
Infectious hepatitis, n (%)	3 (1.7)	8 (4.6)
Haemolysis, n (%)	3 (1.7)	3 (1.7)
GvHD, n (%)	2 (1.2)	7 (4.0)
Sinusoidal obstruction syndrome, n (%)	2 (1.2)	3 (1.7)
Multi-organ failure, n (%)	1 (0)	5 (2.9)
Sepsis, n (%)	0 (0)	4 (2.3)
Other causes, n (%)	6 (3.5) §	4 (4.0) ¥
Undetermined, n (%)	33 (19)	93 (53.8)
No liver workup, n (%)	92 (53.2%)	-

Note: (GvHD: Graft versus host disease). * A panel of experts composed of an intensivist, a hematologist and a hepatologist. § other causes were: n=1 thrombotic microangiopathy, n=1 AL amyloidosis, n=1 active right hepatic arterial bleeding, n=1 cirrhosis decompensation, n=1 neuroendocrine tumor with liver infiltration, n=1 left biliary dilatation without obstructive etiology; ¥ other causes were: n=1 thrombotic microangiopathy (histological finding), n=1 active right hepatic arterial bleeding, n=1 cirrhosis decompensation, n=1 neuroendocrine tumor with liver infiltration.

Discussion

In a large multicentric cohort, HB, defined as a total serum bilirubin level ≥ 33 µmol/L (twice the upper limit of normal range), concerned 21% of critically ill patients with hematological malignancy at ICU admission and was associated with outcome. The first underlying causes of HB were cancer progression, hypoxic hepatitis, cancer treatment toxicities, and sepsis. Liver workups for HB, including liver biopsies, led to high rates of treatment modifications, including cancer treatment, which was associated with reduced mortality. In spite of that, HB was overlooked by the intensive care teams in more than half of patients.

This is the largest study reporting on the burden of HB in critically ill hematological patients. Our findings demonstrate that HB is closely related to the prognosis hematological patients, as for other critical care

patients, including severely burned patients (32), patients with acute respiratory distress syndrome (ARDS) (33) and trauma (34). An identical serum bilirubin threshold, twice the upper limit of normal range, has been associated with an increased risk of mortality in patients with severe sepsis and septic shock (35).

There is, to date, no robust literature on the underlying causes of HB in critically ill hematological patients. In this series, almost one third of treatable liver diseases contributed to HB. In the rare subgroup of patients who underwent a throughout liver workup, cancer, cancer drug toxicities, heart failures and infections led frequently to therapeutic adjustments, including antimicrobial treatment modifications, chemotherapy initiations, cancer drug modifications, hemodynamic management, and defibrotide in patients with SOS.

We were surprised by the rather high number of patients in whom HB was overlooked in this cohort: total serum bilirubin was not measured in 12% of patients at ICU admission, was unrecognized in half of HB patients, and was poorly investigated (63%), diagnosed (59%) and treated (40%) when it was taken into account by the intensive care team. HB is also frequently ignored in other immunocompetent critically ill patients, although it is closely associated with outcome (36,37). Our findings support the idea that HB is not a satellite of the multi-organ failure syndrome and that it should be actively treated as other organ failures. Echocardiography, bacterial, virologic and fungal workups, liver ultrasonography, CT-scans, and bone marrow aspirate or biopsy should be performed immediately at bedside of HB patients. We acknowledge the absence of guideline to support empirical treatments or decide when to perform liver biopsies in hematological HB patients. The few numbers of liver biopsies performed in the cohort could have modified treatments. Percutaneous liver biopsy is contraindicated in the context of severe thrombopenia and was associated with mortality in this series. Transjugular liver biopsy is safe (38,39) and more than 20 years ago, Shulman at al. demonstrated that it significantly improved the management of allo-HSHC patients (40).

The presence at ICU admission of cyclosporin treatment, antimicrobial therapy, digestive symptoms, ascites, history of liver diseases, increased serum creatinine level, neutropenia were associated with HB. Cyclosporin treatment was strongly associated with HB, which confirmed the relationship between allo-HSCT and outcome of hematological patients (41). Other classical factors were neutropenia, favoring sepsis and requiring antimicrobial therapy. In hematological patients, HB and acute kidney injury (AKI) seem to share similar risk factors such as sepsis, antimicrobials and cyclosporin nephrotoxicity, tumor lysis syndrome (42), except chemotherapy which did not impact HB in our cohort. Ascites can be explained in these patients by SOS (17), engraftment syndrome in allo-HSCT patients (43), capillary leak syndrome (44) which can also be causes of AKI.

Our study is limited by its heterogeneity, including underlying malignancies, cancer treatments, disease status at admission, and by the high proportion of patients that did not undergo a complete liver workup, including liver biopsy. Its retrospective nature limited our conclusions because HB etiologies may vary widely between subgroups of patients. The absence of systematic NAT testing for hepatotropic viruses of

HB patients, including HEV (45), is an example, and underlines the importance to update management recommendations (30). There are currently no consensual ICU admission criteria for hematological patients. Admission differs according to center's experience, hematologist involvement in the ICU and case-volume effect (46), therefore the timing between HB onset and admission to the ICU varied between patients. Nevertheless, our results suggest that HB patients should be evaluated for ICU admission. Our results could pave the way for recommendations on HB in hematological patients. Early recognition of HB should be the first step, as for acute respiratory failure, which is easily and early diagnosed when oxygen begins to be necessary. Systematic diagnostic strategies for HB should be developed and validated in hematological patients, as for acute respiratory failure (47). It is well shown that an absence of etiological diagnosis impairs prognosis of patients with acute respiratory failure (48). It seems to be the same for HB.

Conclusions

HB is common, underestimated, infrequently investigated, and is associated with outcome of critically ill hematological patients. HB should be considered upon ICU admission and managed as other organ dysfunctions. Collaborative and multidisciplinary clinical and research networks are crucial both to improve our understanding of HB pathogenesis and to develop diagnostic strategies and adapted therapeutic options, as well as prevention of liver injury. It implies an accurate severity assessment at ICU admission and a close collaboration between hematologists, intensivists and hepatologists. In this setting transjugular liver biopsy needs to be evaluated.

Abbreviations

HB: Hyperbilirubinemia

ICU: Intensive care unit

HSCT: Hematopoietic stem cell transplantation

Allo-HSCT: Allogenic hematopoietic stem cell transplantation

Auto-HSCT: Autologous hematopoietic stem cell transplantation

DILI: Drug-induced liver injury

SOS: Sinusoidal obstruction syndrome

GvHD: Graft-versus-host disease

SOFA score: Sepsis-related Organ Failure Assessment score

CMV: Cytomegalovirus

HSV: Herpes simplex virus

NAT: Nucleic acid testing

MV: Invasive mechanical ventilation

RRT: Renal replacement therapy

ARF: Acute respiratory failure

AKI: Acute kidney injury

UNL: Upper limit of normal range

ARDS: Acute respiratory distress syndrome

Declarations

Ethics approval and consent to participate: The study was approved by the appropriate ethics committees in France and Belgium. This statement is in “patients and methods” paragraph.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: MB, MD, DM and EA determined the study concept and design. AE, DM, MD, VL, FP, AK, AD, FV, MN, FB, CL, AR, APM, DB, RH, MJ acquired the prospective data. DM, MD and MB interpreted the data and performed the statistical analyses. MB, VM, CS and CM drafted the manuscript. All authors read and approved the final manuscript.

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Figures

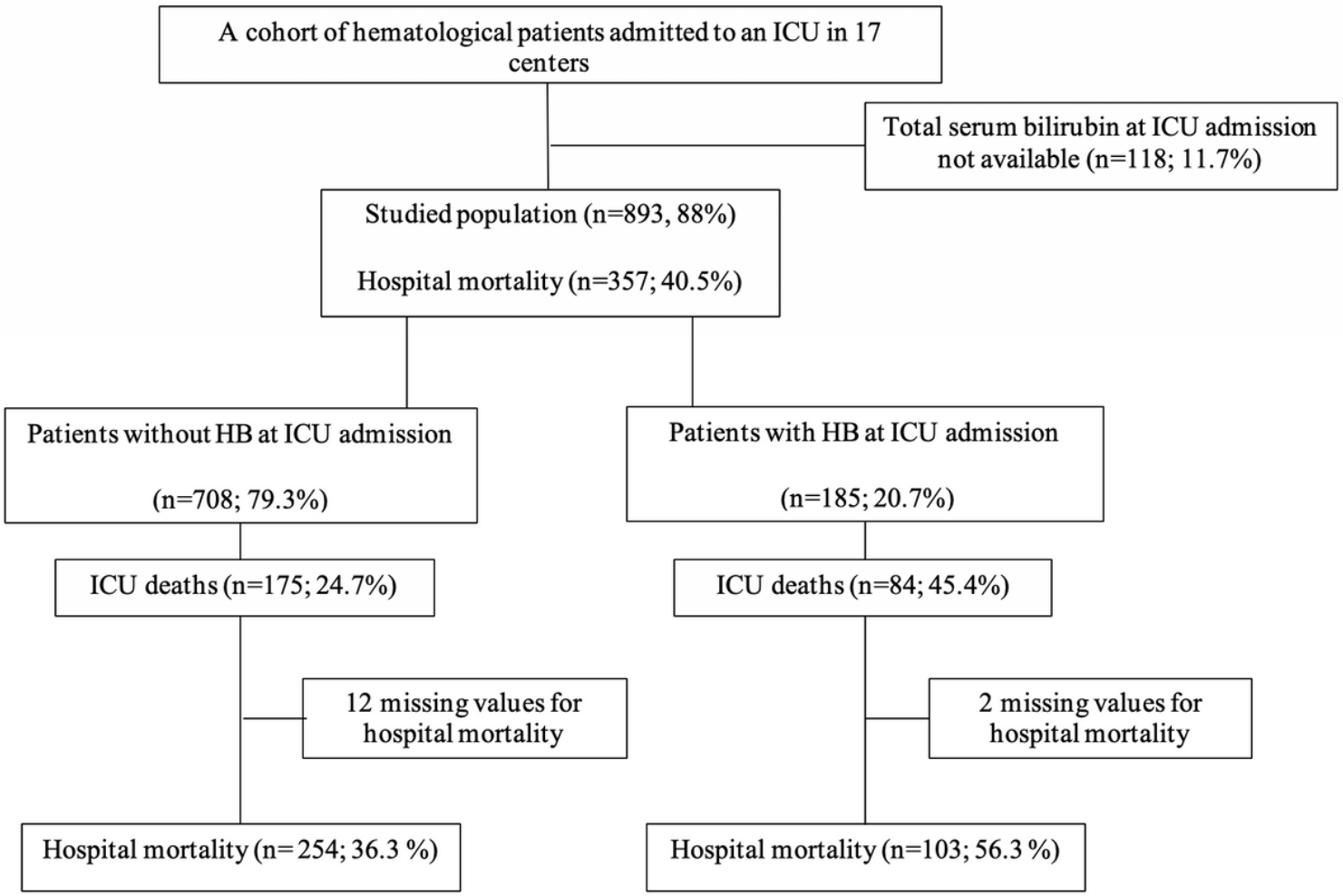

Figure 1

Flow chart of included patients. (ICU: Intensive care unit; HB: hyperbilirubinemia)

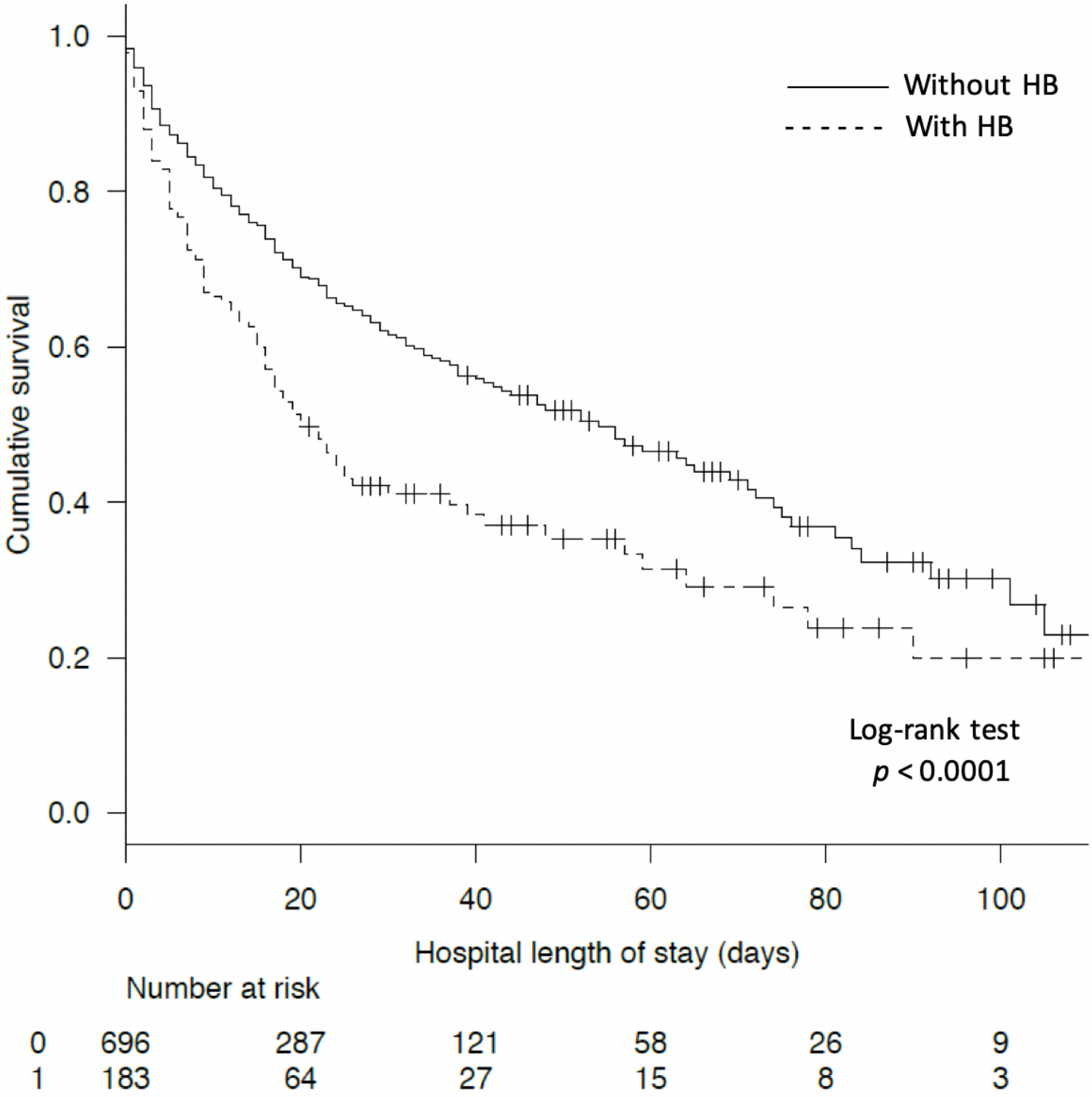

Figure 2

Hospital survival of critically ill hematological patients according to hyperbilirubinemia (total serum bilirubin ≥ 33 µmol/L) at ICU admission. (ICU: Intensive care unit; HB: hyperbilirubinemia)

Supplementary Files

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- AdditionalTable1.docx