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Hepatic dysfunction impairs prognosis in critically ill patients with hematological malignancies: a post-hoc analysis of a prospective multicenter multinational dataset.

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List of abbreviations

HD: Hepatic dysfunction

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

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

Abstract

Purpose

Hyperbilirubinemia is frequent in patients with hematological malignancies admitted to the intensive care unit (ICU). Literature about hepatic dysfunction (HD) in this context is scarce.

Methods

We investigated the prognostic impact of HD analyzing a prospective multicenter cohort of 893 critically ill hematology patients. Two groups were defined: patients with HD (total bilirubin ≥ 33 µmol/L at ICU admission) and patients without HD.

Results

Twenty one percent of patients were found to have HD at ICU admission. Cyclosporine, antimicrobials before ICU admission, abdominal symptoms, ascites, history of liver disease, neutropenia, increased serum creatinine and myeloma were independently associated with HD. Etiology remained undetermined in 73% of patients. Hospital mortality was 56.3% and 36.3% respectively in patients with and without HD ($p<0.0001$). Prognostic factors independently associated with hospital mortality in HD group were, performance status >1 (OR=2.07 , 95% CI=1.49-2.87, $p<0.0001$), invasive mechanical ventilation (OR=3.92, 95% CI=2.69-5.71, $p<0.0001$), renal replacement therapy (OR=1.74, 95% CI=1.22-2.47, $p=0.002$), vasoactive drug (OR= 1.81, 95% CI=1.21-2.71, $p=0.004$) and SOFA score without bilirubin level at ICU admission (OR=1.09, 95% CI=1.04-1.14, $p<0.0001$).

Conclusions

HD is common, underestimated, infrequently investigated, and is associated with impaired outcome in critically ill hematology patients. HD should be considered upon ICU admission and managed as other organ dysfunctions.

1. Introduction

Alterations of liver biomarkers are common in critically ill patients with hematological malignancies. Therapies are frequently associated with hepatotoxicity such as hematopoietic stem cell transplantation (HSCT) procedure [1,2], chemotherapy, targeted therapies, immuno-conjugate antibodies and immunotherapies [3–5]. Causes of hepatic dysfunctions are often multifactorial, including drug-induced liver injury (DILI) [6–8], post-transfusional iron overload [9], infections [10], sepsis [11], prolonged parenteral nutrition [12], underlying hepatic disease [13], cancer-related liver 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].

Diagnostic of liver injury etiology in critically ill hematological patients is difficult as clinical, biological and radiological findings are frequently non specific. There are no systematic guidelines for the diagnostic approach of hepatic failure and the role of liver biopsy in this context is under-evaluated. Total serum bilirubin level, a biomarker of liver dysfunction, is part of several organ dysfunction scores [20,21] to assess liver injury severity in intensive care unit (ICU) patients. Hyperbilirubinemia, defined as an increased total serum bilirubin level ≥ 68 µmol/L, has been associated with a higher mortality in a large cohort of 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]. Hyperbilirubinemia appears to be a better biomarker of hepatic dysfunction (HD), impacting outcome, than hepatocellular injury, defined by elevated aminotransferases, in hematological patients [25].

Hematological patients are increasingly admitted to the ICU. Hyperbilirubinemia is a daily concern for intensivists, but frequently under investigated. Available data on incidence, risk factors, causes, management and outcome of HD in critically ill hematology patients are very scarce. In order to investigate the prognostic impact of hepatic dysfunction as primary objective, we analyzed a large prospective multicenter cohort of critically ill patients with hematological malignancies admitted to the ICU. The secondary objectives were to report the incidence of HD, to identify factors associated with HD and to describe management and causes of HD in critically ill hematology patients.

2. Methods

2.1. 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, patients with total serum bilirubin assessment available at admission were included. Two groups were defined according to liver SOFA score [21] at ICU admission: patients with HD defined as a liver SOFA score >1 (total bilirubinemia ≥ 33 μmol/L) and patients without HD 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.

2.2. Data collected in the prospective cohort

All patients had a diagnosis of initial/relapsed hematological malignancy within 5 years before ICU admission. Performance status [27] and Charlson comorbidity index [28] were determined at ICU admission. History of mild, moderate or severe liver disease 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 malignancy, disease status at ICU admission, history of allogenic HSCT, radiotherapy and chemotherapy received in the month before ICU admission were collected. For allo-HSCT patients, the type of donor, type and intensity of conditioning regimen, GvHD prophylaxis and treatment were collected. Chemotherapy, systemic corticosteroids, hematopoietic growth factors and immunosuppressive agents recommended by the hematologists and administered during ICU stay were recorded. Neutropenia was defined as a neutrophil count lower than 0.5 G/L. Data from clinical examination at ICU admission were reported such as abdominal, neurological, cutaneous, renal and hematological symptoms. Organ dysfunctions, sepsis and life sustaining therapies at ICU admission and during ICU stay were also collected.

2.3. 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. Interactions and correlations between explanatory variables were carefully checked. 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. For each model, discrimination was tested by the C-statistic which was equivalent to receiver-operating characteristic area under the curve (AUC). Survival analysis were performed 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).

3. Results

3.1. Characteristics of patients

Among the 1011 patients included in the TRIALOH study [26], 118 (11.7%) were excluded because total serum bilirubin was not available at ICU admission. The 893 remaining patients were analyzed, including 185 (20.7%) patients presenting with HD, defined by bilirubinemia ≥ 33 µmol/L at ICU admission.

Characteristics of patients are presented in Table 1. Median age was 60 (49 – 70) years and there was a preponderance of males (61%). Less than 5% of patients had a history of liver disease. 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% who had received myeloablative conditioning regimen. About two-third of patients (64.9%) have received antibiotics before ICU admission. Main reason for ICU admission and organ failures at ICU admission are presented in Table 2. Acute respiratory failure (ARF) was the first reason for ICU admission (62.4%), followed by cardiovascular failure (43.1%), acute kidney injury (31%) and acute hepatic failure (8.8%). A total of 497 (55.7%) patients had at least two organ failures at ICU admission. Patients presented at ICU admission with abdominal symptoms in 24.3%, jaundice in 3.8%, abdominal pain in 13.8% and ascites in 3.2%. Thirty percent of patients were neutropenic. Median bilirubinemia was 57 µmol/L in patients with HD, with aspartate aminotransferase, alanine aminotransferase and Gamma glutamyltranspeptidase 2, 1.4 and 2.4 ULN respectively. Median prothrombin time was 57% in patients with HD, compared to 66% in patients without HD. Patients presenting with HD had an increased creatinine level (126 µmol/L) and lactates level (2.9 mmol/L) compared to patients without HD. Organ support

consisted of non-invasive mechanical ventilation (NIV), invasive mechanical ventilation (MV), vasopressors and renal replacement therapy (RRT) in 33.5%, 59.5%, 63.2%, 42.7% respectively in patients with HD and in 28.7%, 46.8%, 49.9% and 24.6% in patients without HD. The majority of patients (91.3%) received antimicrobial therapy at ICU admission and during ICU stay, with no difference in HD and no HD groups. Patients with HD were more frequently treated with antifungals (49.7%), hematopoietic growth factors (23.2%) and cyclosporine (7.6%).

3.2. HD etiologies

We reported etiologies of HD in these patients. The cause of HD had not been investigated in 70 % of patients. When the caring physician considered HD at ICU admission, a diagnosis was proposed in only 27% of patients. Diagnoses were specific infiltration (6.4%), drug toxicity (5.6%), hypoxic hepatitis (3.5%), haemophagocytic syndrome (2.3%) and infectious causes (1.7%). SOS and GVHD both represented 1.2% of patients. The other causes (5%) were thrombotic microangiopathy, AL amyloidosis, active right hepatic arterial bleeding, cirrhosis decompensation, neuroendocrine tumor with liver infiltration, left biliary dilatation without obstructive etiology and multiorgan failure.

3.3. Impact of HD on outcome

Hospital mortality was 40.5% in the cohort. ICU mortality and hospital mortality were 45.4% and 56.3% respectively in patients with HD and 24.7% and 36.3% in patients without HD. HD was associated with hospital mortality (odd ratio [OR]=2.26, 95% CI=1.62 – 3.14, p<0.0001). After adjustment for invasive MV, RRT and vasoactive drugs, HD remained an independent factor associated with hospital mortality (adjusted OR=1.86, 95% CI=1.28 – 2.72, p=0.001). Hospital cumulative survival curve was illustrated in figure 1 (p<0.0001).

3.4. Prognostic factors of hospital mortality in patients with HD

Univariate analyses of factors associated with hospital mortality according to HD are presented in supplemental table 1. Prognostic factors independently associated with hospital mortality in multivariate analysis in patients with HD at ICU admission are presented in Table 3. Identified risk factors for hospital mortality were performance status >1 (OR=2.07 , 95% CI=1.49-2.87, p<0.0001), invasive MV during ICU stay (OR=3.92, 95% CI=2.69-5.71, p<0.0001), RRT during ICU stay (OR=1.74, 95% CI=1.22-2.47, p=0.002), vasoactive drug during ICU stay (OR= 1.81, 95% CI=1.21-2.71, p=0.004) and SOFA score without bilirubin level at ICU admission (OR=1.09, 95% CI=1.04-1.14, p<0.0001). The AUC value of the logistic regression model was 0.801.

3.5. Risk factors for HD in critically ill hematology patients

Factors independently associated with HD in critically ill patients with hematological malignancies admitted to the ICU are presented in Table 4. Multivariate analysis identified as

risk factors for HD: cyclosporine treatment (OR=3.36, 95% CI=1.93-5.85, p<0.001), antimicrobials treatment before ICU admission (OR=1.58, 95% CI=1.04-2.4, p=0.03), abdominal symptoms (OR=2.18, 95% CI=1.46-3.26, p<0.001), ascites (OR=2.56, 95% CI=1.06-6.2, p=0.04), history of liver disease defined by a hepatic Charlson comorbidity index ≥ 1 (OR=2.23, 95% CI=1.06-4.7, p=0.02), neutropenia (OR=1.46, 95% CI=1-2.14, p=0.049) and increased serum creatinine (OR=1.0, 95% CI=1-1, p=0.02). Myeloma had a protective effect on HD (OR=0.38, 95% CI=0.19-0.76, p=0.006). The AUC value of the logistic regression model was 0.719. Among the 29 patients with ascites at ICU admission, 24 (83%) of them had not a history of liver disease (p<0.0001).

4. Discussion

In this large multicentric cohort of critically ill patients with hematological malignancy at ICU admission, 21% of patients presented with HD defined as a total serum bilirubin level ≥ 33 µmol/L. HD strongly impacted outcome as it was associated with an increased mortality.

This is the first study exploring the impact of HD in critically ill hematology patients. We identified as risk factors of mortality in patients with at ICU admission patients characteristics such as performance status and other organ dysfunctions at ICU admission, represented by the SOFA score without bilirubin level, and during ICU stay, requiring invasive MV, vasoactive drugs and RRT. Our results are in line with those previously reported in critically ill patients in the ICU, emphasizing the crucial role of the number of organ dysfunctions at the time of ICU admission on outcome, and the remaining poor prognostic associated with MV, vasoactive drugs and RRT in these patients [26,29]. This suggests that hyperbilirubinemia ≥ 33 µmol/L in hematology patients should draw the physician's attention, similarly to a need for oxygen or low urine output.

We identified as risk factors of HD patients with a history of hepatic failure, patients with abnormal clinical examination at ICU admission presenting with abdominal symptoms and ascites, neutropenia, antimicrobial treatments before ICU admission, acute kidney injury (AKI) with increased creatinine, and patients treated with cyclosporine. In hematology patients, HD and AKI seem to share similar risk factors such as sepsis, antimicrobials and cyclosporine nephrotoxicity and tumor lysis syndrome [30]. Ascites can be explained in these patients by SOS [17], engraftment syndrome in allo-HSCT patients [31], capillary leak syndrome [32] which can also be causes of AKI. Ascites, sepsis, neutropenia and cyclosporine were associated with the poor prognosis of allo-HSCT patients in the ICU, especially with active GVHD [31,32].

We found that hepatic impairment was strikingly under-investigated, as 70% of patients did not have any diagnostic workup, and 73% of causes remained undetermined. It highlights the difficulty in clinical practice to explore properly HD in these patients. There is, to date, no robust literature on the underlying causes of HD in critically ill hematology patients. HD is also frequently ignored in immunocompetent critically ill patients, although it is closely associated with outcome [33,34]. Furthermore, HD in critically ill hematology patients may not only increase their critical-illness severity, but also preclude the initiation of proper hematology treatments, while the liver transplant window is closed compared to non-hematology patients. Our findings support the idea that HD should be actively investigated as other organ failures, in order to identify etiology and treat it. Echocardiography, bacterial, virology and fungal workups, liver ultrasonography, CT-scan, and bone marrow aspirate should be performed immediately at bedside of HD patients. There are no guidelines supporting a systematic diagnostic approach, including the role of liver biopsies in these patients and empirical therapeutic approach. The indication for liver biopsy could complete the biological and radiological workup when cause of HD remains unknown and have to be

evaluated case by case. Data supported the faisability and safety of transjugular liver biopsy [35,36], which was associated with improved management in allo-HSHC patients [37].

We acknowledge some limitations of our study. It is limited by its heterogeneity, including underlying malignancies, cancer treatments and disease status at admission. The absence of exhaustive diagnostic work-up, which reflects daily reality, did not allow us to draw conclusions about etiologies and therapeutic management of hyperbilirubinemia in these patients. Moreover, there are no consensual ICU admission criteria for hematology patients. Admission differs according to center's experience, hematologists involvement and case-volume effect [38]. Therefore the timing between HD onset and ICU admission may differ widely between patients.

Nevertheless, our results suggest that HD in critically ill hematology patients should be considered as a real organ dysfunction, impacting outcome. Early recognition of HD should be the first step, as oxygen requirement is the first step for early ARF diagnosis [39]. Future studies are needed, to pave the way for recommendations on optimal systematic diagnostic strategy and therapeutic approach of HD in hematology patients.

5. Conclusions

HD is common, underestimated, infrequently investigated, and is associated with impaired outcome in critically ill hematology admitted to the ICU. HD 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 HD pathogenesis 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.

Declaration of competing interest

None.

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References

[1] McDonald GB. Hepatobiliary Complications of Hematopoietic Cell Transplantation, 40 Years On. Hepatology 2010;51:1450–60. https://doi.org/10.1002/hep.23533.

[2] Tuncer HH. Gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. World J Gastroenterol 2012;18:1851. https://doi.org/10.3748/wjg.v18.i16.1851.

[3] on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group, Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5. https://doi.org/10.1186/s40425-017-0300-z.

[4] Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol 2016;27:559–74. https://doi.org/10.1093/annonc/mdv623.

[5] Lambert J, Pautas C, Terré C, Raffoux E, Turlure P, Caillot D, et al. Gemtuzumab ozogamicin for *de novo* acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica 2019;104:113–9. https://doi.org/10.3324/haematol.2018.188888.

[6] McDonald GB, Slattery JT, Bouvier ME, Ren S, Batchelder AL, Kalhorn TF, et al. Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. Blood 2003;101:2043–8. https://doi.org/10.1182/blood-2002-06-1860.

[7] Patel B, Kirkwood AA, Dey A, Marks DI, McMillan AK, Menne TF, et al. Pegylated-asparaginase during induction therapy for adult acute lymphoblastic leukaemia: toxicity data from the UKALL14 trial. Leukemia 2017;31:58–64. https://doi.org/10.1038/leu.2016.219.

[8] Bath RK, Brar NK, Forouhar FA, Wu GY. A review of methotrexate-associated hepatotoxicity: Methotrexate hepatotoxicity. J Dig Dis 2014;15:517–24. https://doi.org/10.1111/1751-2980.12184.

[9] Majhail NS, Lazarus HM, Burns LJ. Iron overload in hematopoietic cell transplantation. Bone Marrow Transplant 2008;41:997–1003. https://doi.org/10.1038/bmt.2008.99.
[10] Fiore M, Cascella M, Bimonte S, Maraolo AE, Gentile I, Schiavone V, et al. Liver fungal infections: an overview of the etiology and epidemiology in patients affected or not affected by oncohematologic malignancies. Infect Drug Resist 2018;11:177–86. https://doi.org/10.2147/IDR.S152473.
[11] Jenniskens M, Langouche L, Vanwijngaerden Y-M, Mesotten D, Van den Berghe G. Cholestatic liver (dys)function during sepsis and other critical illnesses. Intensive Care Med 2016;42:16–27. https://doi.org/10.1007/s00134-015-4054-0.
[12] Naini BV, Lassman CR. Total parenteral nutrition therapy and liver injury: a histopathologic study with clinical correlation. Hum Pathol 2012;43:826–33. https://doi.org/10.1016/j.humpath.2011.07.008.
[13] Povsic M, Wong OY, Perry R, Bottomley J. A Structured Literature Review of the Epidemiology and Disease Burden of Non-Alcoholic Steatohepatitis (NASH). Adv Ther 2019. https://doi.org/10.1007/s12325-019-00960-3.
[14] Walz-Mattmüller R, Horny H-P, Ruck P, Kaiserling E. Incidence and Pattern of Liver Involvement in Haematological Malignancies. Pathol - Res Pract 1998;194:781–9. https://doi.org/10.1016/S0344-0338(98)80068-X.
[15] on behalf of the EBMT (European Society for Blood and Marrow Transplantation) Transplant Complications Working Party and the "EBMT–NIH (National Institutes of Health)–CIBMTR (Center for International Blood and Marrow Transplant Research) GvHD Task Force," Schoemans HM, Lee SJ, Ferrara JL, Wolff D, Levine JE, et al. EBMT–NIH–CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant 2018;53:1401–15. https://doi.org/10.1038/s41409-018-0204-7.
[16] Corbacioglu S, Jabbour EJ, Mohty M. Risk Factors for Development of and Progression of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome. Biol Blood Marrow Transplant 2019. https://doi.org/10.1016/j.bbmt.2019.02.018.
[17] Roeker LE, Kim HT, Glotzbecker B, Nageshwar P, Nikiforow S, Koreth J, et al. Early Clinical Predictors of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome after Myeloablative Stem Cell Transplantation. Biol Blood Marrow Transplant 2019;25:137–44. https://doi.org/10.1016/j.bbmt.2018.07.039.
[18] Belay Y, Yirdaw K, Enawgaw B. Tumor Lysis Syndrome in Patients with Hematological Malignancies. J Oncol 2017;2017:1–9. https://doi.org/10.1155/2017/9684909.
[19] La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77. https://doi.org/10.1182/blood.2018894618.
[20] Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912–9. https://doi.org/10.1182/blood-2005-05-2004.
[21] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.
[22] Gooley TA, Rajvanshi P, Schoch HG, McDonald GB. Serum bilirubin levels and mortality after myeloablative allogeneic hematopoietic cell transplantation. Hepatol Baltim Md 2005;41:345–52. https://doi.org/10.1002/hep.20529.

[23] Barba P, Martino R, Perez-Simón JA, Fernández-Avilés F, Piñana JL, Valcárcel D, et al. Incidence, characteristics and risk factors of marked hyperbilirubinemia after allogeneic hematopoietic cell transplantation with reduced-intensity conditioning. Bone Marrow Transplant 2012;47:1343–9. https://doi.org/10.1038/bmt.2012.25.
[24] Radhakrishnan K, Bishop J, Jin Z, Kothari K, Bhatia M, George D, et al. Risk factors associated with liver injury and impact of liver injury on transplantation-related mortality in pediatric recipients of allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant 2013;19:912–7. https://doi.org/10.1016/j.bbmt.2013.02.019.
[25] Thorvaldson L, Remberger M, Winiarski J, Omazic B, Fischler B, Sundin M. HLA, GVHD, and parenteral nutrition are risk factors for hepatic complications in pediatric HSCT. Pediatr Transplant 2016;20:96–104. https://doi.org/10.1111/petr.12623.
[26] Azoulay E, Mokart D, Pène F, Lambert J, Kouatchet A, Mayaux J, et al. Outcomes of Critically Ill Patients With Hematologic Malignancies: Prospective Multicenter Data From France and Belgium—A Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study. J Clin Oncol 2013;31:2810–8. https://doi.org/10.1200/JCO.2012.47.2365.
[27] Soares M, Salluh JIF, Carvalho MS, Darmon M, Rocco JR, Spector N. Prognosis of Critically Ill Patients With Cancer and Acute Renal Dysfunction. J Clin Oncol 2006;24:4003–10. https://doi.org/10.1200/JCO.2006.05.7869.
[28] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[29] Darmon M, Thiery G, Ciroldi M, de Miranda S, Galicier L, Raffoux E, et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy*: Crit Care Med 2005;33:2488–93. https://doi.org/10.1097/01.CCM.0000181728.13354.0A.
[30] Rosner MH, Perazella MA. Acute Kidney Injury in Patients with Cancer. N Engl J Med 2017;376:1770–81. https://doi.org/10.1056/NEJMra1613984.
[31] Spitzer TR. Engraftment syndrome: double-edged sword of hematopoietic cell transplants. Bone Marrow Transplant 2015;50:469–75. https://doi.org/10.1038/bmt.2014.296.
[32] Siddall E, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. Kidney Int 2017;92:37–46. https://doi.org/10.1016/j.kint.2016.11.029.
[33] Lescot T, Karvellas C, Beaussier M, Magder S. Acquired Liver Injury in the Intensive Care Unit: Anesthesiology 2012;117:898–904. https://doi.org/10.1097/ALN.0b013e318266c6df.
[34] Jenniskens M, Langouche L, Van den Berghe G. Cholestatic Alterations in the Critically Ill. Chest 2018;153:733–43. https://doi.org/10.1016/j.chest.2017.08.018.
[35] Kis B, Pamarthi V, Fan C-M, Rabkin D, Baum RA. Safety and Utility of Transjugular Liver Biopsy in Hematopoietic Stem Cell Transplant Recipients. J Vasc Interv Radiol 2013;24:85–9. https://doi.org/10.1016/j.jvir.2012.09.011.
[36] Ruggiu M, Bedossa P, Rautou PE, Bertheau P, Plessier A, Peffault de Latour R, et al. Utility and Safety of Liver Biopsy in Patients with Undetermined Liver Blood Test Anomalies after Allogeneic Hematopoietic Stem Cell Transplantation: A Monocentric Retrospective Cohort Study. Biol Blood Marrow Transplant 2018;24:2523–31. https://doi.org/10.1016/j.bbmt.2018.07.037.
[37] Shulman HM, Gooley T, Dudley MD, Kofler T, Feldman R, Dwyer D, et al. Utility of transvenous liver biopsies and wedged hepatic venous pressure measurements in sixty

marrow transplant recipients. Transplantation 1995;59:1015–22. https://doi.org/10.1097/00007890-199504150-00017.
[38] Zuber B, Tran T-C, Aegerter P, Grimaldi D, Charpentier J, Guidet B, et al. Impact of case volume on survival of septic shock in patients with malignancies*: Crit Care Med 2012;40:55–62. https://doi.org/10.1097/CCM.0b013e31822d74ba.
[39] Azoulay É, Schlemmer B. Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med 2006;32:808–22. https://doi.org/10.1007/s00134-006-0129-2.

Figure

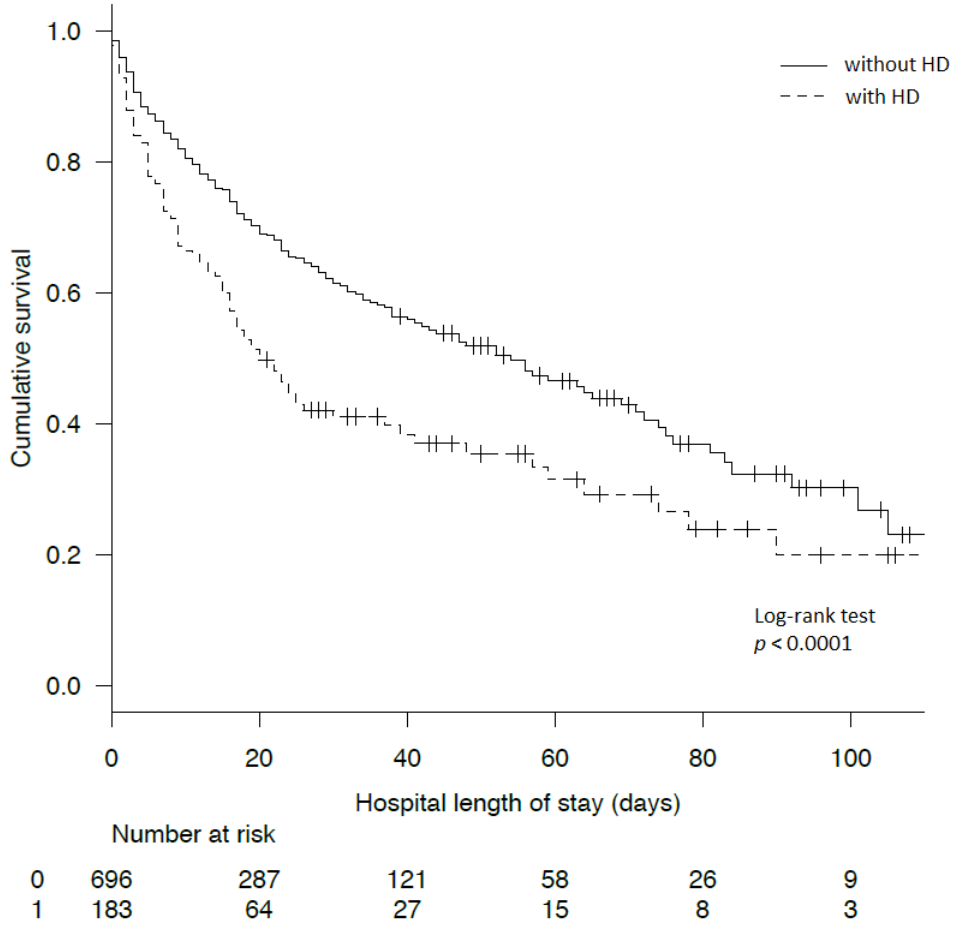

Fig 1. Hospital survival of critically ill hematology patients according to hepatic dysfunction (total serum bilirubin ≥ 33 µmol/L) at intensive care unit admission. *(HD: hepatic dysfunction)*

Tables

Table 1: Characteristics of patients.

	All patients (n=893)	With HD (n=185)	Without HD (n=708)	*p*
Age (years)	60 [49-70]	56 [47-54]	61 [49-70]	**<0.001**
Gender (male)	545 (61.0)	121 (65.4)	424 (59.9)	0.171
Performans status >1	470 (52.6)	93 (50.3)	377 (53.2)	0.47
Charlson comorbidity index	4 [3-6]	4 [2-5]	4 [3-6]	**0.005**
History of liver diseases	41 (4.6)	15 (8.1)	26 (3.7)	**0.01**
SOFA score at admission	6 [3-9]	8 [6-13]	5 [3-8]	**<0.001**
SOFA score without bilirubin level at admission	5 [3-8]	6 [4-10]	5 [3-8]	**<0.001**
Underlying hematological malignancy				
Acute myeloid leukemia	242 (27.1)	56 (30.3)	186 (26.3)	0.276
Acute lymphoblastic 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 lymphoid 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
Others	59 (6.6)	21 (11.4)	38 (5.4)	**0.004**
Disease status at ICU admission				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)	
Allo-HSCT patients	131 (14.7)	45 (24.3)	86 (12.2)	**<0.001**
Myeloablative conditioning regimen	61 (6.8)	18 (9.7)	43 (6.1)	0.079
Cyclosporine in the 30 days before ICU admission	73 (8.2)	32 (17.4)	41 (5.8)	**<0.001**
MMF in the 30 days before ICU admission	45 (5.0)	17 (8.2)	28 (4.0)	**0.004**
Auto-HSCT patients	133 (14.9)	28 (15.1)	105 (14.9)	0.935
Antimicrobial therapy in the 10 days before ICU admission	579 (64.9)	139 (75.1)	440 (62.2)	**0.001**

*HD: hepatic dysfunction, HSCT: allogenic stem cell transplantation, ICU: intensive care unit, MMF: mycophenolate mofetil, SOFA****: sequential organ failure assessment score.***

Table 2: Organ dysfunctions at ICU admission and treatments during ICU stay.

	All patients (n=893)	With HD (n=185)	Without HD (n=708)	*p*
Reason for ICU admission				
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)	**<0.001**
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 symptoms at ICU admission				
Abdominal symptoms	215 (24.3)	75 (40.5)	140 (20.0)	**<0.001**
Jaundice	34 (3.8)	32 (17.3)	2 (0.3)	**<0.001**
Abdominal pain	123 (13.8)	39 (21.1)	84 (11.9)	**0.001**
Ascites	29 (3.2)	17 (9.2)	12 (1.7)	**<0.001**
Sepsis	578 (64.7)	119 (64.3)	459 (64.8)	0.898
Biological characteristics at ICU admission				

Total Bilirubinemia (µmol/L)	14 [8-26]	57 [42-100]	12 [8-18]	**<0.001**
Aspartate aminotransferase (xULN)	1 [1-2]	2 [1-3.9]	1 [1-1]	**<0.001**
Alanine aminotransferase (xULN)	1 [1-1.7]	1.4 [1-2.9]	1 [1-1.4]	**<0.001**
Gamma glutamyltranspeptidase (xULN)	1.5 [1-3.5]	2.4 [1-5.4]	1.4 [1-3]	**<0.001**
Alkaline phosphatase (xULN)	1 [1-1]	1 [1-2.3]	1 [1-1]	**<0.001**
Prothrombin Time (%)	64 [51-77]	57 [44-73]	66 [53-79]	**<0.001**
Platelets (G/L)	62 [30-147]	39 [18-72]	71 [32-157]	**<0.001**
Serum creatinine (µmol/L)	102 [69-170]	126 [80-206]	98 [67-156]	**<0.001**
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]	**<0.001**
Neutropenia	262 (30.8)	76 (42.7)	186 (27.6)	**<0.001**
Lactates (mmol/L)	2.1 [1.2-4.2]	2.9 [1.6-5.9]	2.0 [1.2-4.1]	**0.001**
Life-sustaining therapies during ICU stay				
Non-invasive 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)	**<0.001**
Other treatments during ICU stay				

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
Hematopoietic growth factors	155 (17.4)	43 (23.2)	112 (15.8)	**0.018**
Chemotherapy	108 (12.1)	19 (10.3)	89 (12.6)	0.39
Corticosteroids	173 (19.4)	36 (19.5)	137 (19.4)	0.98
Cyclosporine	33 (3.7)	14 (7.6)	19 (2.7)	**0.02**

HD: hepatic dysfunction, ICU: intensive care unit, PCR: polymerase chain reaction, UNL: upper normality limit.

Table 3: Prognostic factors independently associated with hospital mortality in patients with hepatic dysfunction at intensive care unit admission.

	OR	95% CI	*p*
Charlson comorbidity index	1.06	0.99 -1.14	0.08
Performance status >1	2.07	1.49 – 2.87	<0.0001
Invasive MV during ICU stay	3.92	2.69 – 5.71	<0.0001
RRT during ICU stay	1.74	1.22 – 2.47	0.002
Vasoactive drugs during ICU stay	1.81	1.21 – 2.71	0.004
SOFA score without bilirubin level at admission	1.09	1.04 – 1.14	<0.0001

CI: confidence interval, HD: hepatic dysfunction, ICU: intensive care unit, OR: odds ratio, RRT: renal replacement therapy.

Table 4: Factors independently associated with hepatic dysfunction in critically ill patients with hematological malignancies admitted to the intensive care unit.

	OR	95% CI	*p*
Cyclosporine before ICU admission	3.36	1.93-5.85	<0.001
Antimicrobials before ICU admission	1.58	1.04-2.40	0.03
Abdominal symptoms at ICU admission	2.18	1.46-3.26	<0.001
History of liver disease	2.23	1.06-4.7	0.03
Ascites at ICU admission	2.56	1.06-6.2	0.04
Increased serum creatinine level at ICU admission	1.0	1.0-1.0	0.02
Neutropenia at ICU admission	1.46	1.0-2.14	0.049
Myeloma	0.38	0.19-0.76	0.006

CI: confidence interval, ICU: intensive care unit, OR: odds ratio.