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# Hémophagocytose hépatique et impact pronostique du HScore chez des patients d'oncohématologie

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Faculté des sciences  
médicales et paramédicales  
Aix-Marseille Université

**Hémophagocytose hépatique et impact pronostique du HScore chez des  
patients d'oncohématologie**

**T H E S E**

**Présentée et publiquement soutenue devant**

**LA FACULTÉ DES SCIENCES MEDICALES ET PARAMEDICALES  
DE MARSEILLE**

**Le 28 Septembre 2021**

**Par Monsieur Pierre-Nicolas BRIS**

**Né le 18 février 1994 à Poissy (78)**

Pour obtenir le grade de Docteur en Médecine

D.E.S. de MEDECINE INTENSIVE - REANIMATION NR

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# Hepatic hemophagocytosis and prognostic impact of HScore in oncohematology patients with hepatic dysfunction

## Résumé

### Introduction

La dysfonction hépatique chez le patient d'oncohématologie est fréquente, grave et de causes multiples. L'analyse anatomopathologique hépatique peut aider au diagnostic. L'atteinte hépatique au cours d'une lymphohistiocytose hémophagocytaire (LHH) est l'une des causes possibles.

Les objectifs étaient de caractériser les patients d'oncohématologie présentant une hémophagocytose hépatique (HH), d'étudier la présence d'une LHH en utilisant le HScore et de déterminer l'impact pronostique de cette HH.

### Matériel et méthode

Cette étude rétrospective monocentrique a inclus des patients d'oncohématologie pour lesquels une biopsie hépatique a été réalisée pour dysfonction hépatique entre 2016 et 2019. Nous avons comparé 2 groupes en fonction de la présence d'une HH sur l'histologie hépatique. Dans le groupe HH, nous avons comparé les patients avec ou sans diagnostic de LHH en utilisant le HScore avec un seuil de 169. La survie globale a été calculée en utilisant la méthode de Kaplan-Meier.

### Résultats

Parmi les cent seize biopsies, 65 retrouvaient de l'HH et 33 d'entre elles avaient un HScore supérieur à 169 faisant suspecter une LHH. Les principaux diagnostics histologiques associés à l'HH étaient la maladie du greffon contre l'hôte (55.4%), des signes d'infection hépatique (32.3%) et le syndrome d'obstruction sinusoidale (9.2%). La présence d'une HH était corrélée avec une élévation des enzymes hépatiques moins marquée (ASAT et ALAT à 66 et 74UI/L vs 166 et 198UI/L  $p < 0.001$ ), des cytopénies plus marquées, un score SOFA plus élevé (7 vs 5,  $p = 0.009$ ), et un HScore plus élevé (174 vs 119,  $p < 0.0001$ ). L'analyse du sous-groupe LHH, comparé au sous-groupe sans LHH, a montré une ferritinémie plus élevée (5728 vs 3038  $\mu\text{g/L}$ ,  $p = 0.005$ ), des cytopénies plus marquées, la présence plus fréquente d'une hémophagocytose médullaire (73.9% vs 27.3%,  $p = 0.005$ ), un score SOFA plus élevé (8 vs 5.5,  $p = 0.0029$ ) et un HScore plus élevé (200 vs 127,  $p < 0.0001$ ). L'HH était associée avec un pronostic plus sévère (survie à 1 an à 35% vs 58%  $p = 0.026$ ), aggravé par le diagnostic de LHH (survie à 1 an à 24% vs 50%  $p = 0.019$  si HH sans LHH)

### Conclusion

L'hémophagocytose hépatique aggrave le pronostic des patients d'oncohématologie. Le diagnostic précoce d'une LHH est nécessaire et le HScore apparaît être un bon outil diagnostique. De futurs travaux sont nécessaires afin de déterminer la stratégie diagnostique et thérapeutique optimale pour la dysfonction hépatique et la LHH en oncohématologie.

## **Abstract**

### **Purpose**

Acute liver dysfunction (ALD) is common and associated with an increased mortality in patients with hematological malignancies. Liver biopsy is useful for ALD diagnosis. Liver involvement of hemophagocytic lymphohistiocytosis (HLH) is one of the possible etiologies. The objectives were to characterize patients with ALD and hepatic hemophagocytosis (HH), to assess the impact of HLH diagnosis using HScore in patients with HH, and to assess the prognosis of HH on outcome in onco-hematology patients.

### **Methods**

We conducted a retrospective and monocentric study. We included patients with hematological malignancies who underwent liver biopsy between 2016 and 2019 for acute liver dysfunction. Two groups were compared according to the presence of hepatic hemophagocytosis on liver biopsy. In patients with hepatic hemophagocytosis, we analyzed patients according to HScore HLH criteria, with a defined threshold of 169. Overall survival was calculated using the Kaplan Meier method.

### **Results**

Hundred and sixteen biopsies were performed, 65 found HH. Among them, 33 had a HScore higher than 169, suggesting a HLH. Main histological diagnoses associated with HH were GVHD (55.4%), signs of associated infection (32.3%) and sinusoidal obstruction syndrome (9.2%). Presence of HH was statistically associated with lower increases of liver enzymes (AST and ALT: 66 and 74UI/L vs 166 and 198UI/L  $p<0.001$ ), more important cytopenias, higher SOFA score (7 vs 5,  $p=0.009$ ), and higher HScore (174 vs 119,  $p<0.0001$ ). Analysis of HLH subgroup versus no HLH subgroup showed higher ferritin level (5728 vs 3038  $\mu\text{g/L}$ ,  $p=0.005$ ), more important cytopenias, more frequent diagnosis of medullar hemophagocytosis (73.9% vs 27.3%,  $p=0.005$ ), higher SOFA score (8 vs 5.5,  $p=0.0029$ ) and higher HScore (200 vs 127,  $p<0.0001$ ). HH group had a poorer prognosis (one-year overall survival: 35% vs 58%  $p=0.026$ ), even more if a HLH was diagnosed (one-year overall survival: 24% vs 50% if HH without HLH,  $p=0.019$ ).

### **Conclusions**

Hepatic hemophagocytosis impacts prognosis in patients with underlying hematological malignancy. Early recognition of HLH is crucial and HScore appears as a useful tool. Future studies are needed, to pave the way for guidance on optimal systematic diagnostic strategy and therapeutic approach of ALD and HLH in hematology patients.

## List of abbreviations

ALD: Acute liver dysfunction

HSCT: Hematopoietic stem cell transplantation

Allo-HSCT: Allogenic hematopoietic stem cell transplantation

GVHD: Graft-versus-host disease

SOS: Sinusoidal obstruction syndrome

HLH: Hemophagocytic lymphohistiocytosis

HH: Hepatic hemophagocytosis

ICU: Intensive care unit

HBV: Hepatitis B virus

HCV: Hepatitis C virus

SOFA score: Sepsis-related Organ Failure Assessment score

CMV: Cytomegalovirus

EBV: Epstein-Barr virus

PCR: Polymerase chain reaction,

HSV: Herpes simplex virus

OS: Overall survival

## **Introduction**

Acute liver dysfunction (ALD) is common in patients with hematological malignancies. Its occurrence is difficult to determine as the definition of hepatic dysfunction varies widely across studies, either defined by hyperbilirubinemia or elevated transaminases, with different thresholds<sup>1,2,3,4</sup>. Moreover, hepatic dysfunction is underestimated and infrequently investigated<sup>5</sup>.

Many situations can lead to ALD in this population. The causes can be infections, sepsis, treatments including chemotherapy (Cytarabine, high-dose Methotrexate or Asparaginase)<sup>6,7</sup>, targeted therapies<sup>8</sup>, immunoconjugate antibodies<sup>9</sup>, immunotherapies<sup>10</sup>, hematopoietic stem cell transplantation (HSCT) procedure<sup>2</sup>, antibiotics, antifungals and immunosuppressive therapies<sup>11</sup>, responsible of drug-induced liver injury. Etiologies can also be related to the underlying malignancy, specific tumoral infiltration<sup>12</sup>, or complications such as tumor lysis syndrome<sup>13</sup>, hepatic graft-versus-host disease (GVHD)<sup>14</sup>, sinusoidal obstruction syndrome (SOS)<sup>15</sup>, post-transfusional iron overload<sup>16</sup>, prolonged parenteral nutrition<sup>17</sup>, underlying chronic liver disease decompensation<sup>18</sup> or hemophagocytic lymphohistiocytosis (HLH)<sup>19</sup>. Causes of hepatic dysfunctions are often multifactorial and represent a diagnostic and therapeutic challenge.

ALD appears to impact outcome and total serum bilirubin level is the main criteria used in severity assessment scores to define liver injury severity in intensive care unit (ICU) patients<sup>20</sup>. ALD is associated with increased hospital mortality<sup>3,5</sup>.

Etiological diagnosis of ALD etiology in hematology patients is difficult as clinical, biological and radiological findings are frequently nonspecific. ALD etiology remained undetermined in 73% of patients in a recent study<sup>5</sup>. There are no systematic guidelines for the diagnostic approach of hepatic failure and the role of liver biopsy in this context is under-evaluated. Liver biopsy can provide evidence of hepatic hemophagocytosis (HH)<sup>19</sup>.



Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome is an acute life threatening hyperinflammatory syndrome. HLH is a result of highly stimulated lymphocytes and macrophage/monocytes leading to highly active but ineffective immune response<sup>21</sup>, which can lead to multi-organ failure<sup>22</sup>. HLH is usually classified into primary and secondary (or reactive) forms caused by malignancy, infections (bacterial, fungal and viral), rheumatic diseases and autoimmune diseases, mainly in the setting of underlying immunosuppression. Diagnosis of HLH can be challenging since there are no specific clinical, biologic, or pathologic features. Several diagnostic criteria sets or scores have been proposed to help for HLH diagnosis such as the 9-variables HScore for secondary HLH in adults<sup>23</sup>. Diagnostic approach is crucial for optimal therapeutic management, as early administration of corticosteroids or etoposide may improve survival<sup>24</sup>.

Data are scarce concerning liver involvement in HLH. Significance and prognostic of hemophagocytosis in liver biopsy is poorly understood. Cases of cholestasis and fulminant hepatic failure have been reported<sup>25,26</sup>. A study of 30 cases of hepatic manifestations of hemophagocytic syndrome was reported in 2001, characterizing histological features of hepatic involvement in the hemophagocytic syndrome. Hepatic lesions were characterized by non-specific sinusoidal dilatation with hemophagocytosis and in 50% of the patients by alterations specific to the underlying condition<sup>27</sup>. More recently, a series of 12 patients with hepatic sinusoidal hemophagocytosis found in liver biopsy was reported, half of them meeting HLH-2004 diagnostic criteria, with 67% mortality rate<sup>28</sup>.

Our study aimed to investigate the prognostic impact of liver involvement of hemophagocytosis in patients with hematological malignancy presenting with ALD. The objectives were to characterize patients with ALD and hepatic hemophagocytosis, to assess the impact of HLH diagnosis using HScore in patients with hepatic hemophagocytosis (HH),

and to assess the prognosis of hepatic hemophagocytosis (HH) on outcome in onco-hematology patients.

## **Material and Methods**

### *Patients' selection*

We conducted a retrospective single center study in our institution (Institut Paoli Calmettes, Marseille, France), an adult cancer-reference center. All patients with hematological malignancy who underwent liver biopsy during their hospital stay between June 2016 and December 2019 were included. Liver biopsy indication relied on liver biomarkers abnormalities (hyperbilirubinemia, elevated transaminases and/or cholestasis) in the absence of evident diagnosis after routine biological exams or when several diagnostic hypotheses were suspected. Liver biopsy was percutaneous or transjugular in case of significant coagulopathy or severe thrombopenia, abundant ascites or if measurement of hepatic venous pressure gradient was needed. Exclusion criteria were obstructive causes on hepatic ultrasound, viral hepatitis reactivation (HBV, HCV) and outpatient liver biopsies. This study was approved by our Institutional Review Board.

### *Definitions and data collection*

Clinical and biological data were retrospectively collected. The following data were collected: age, gender, underlying malignancy, disease status, performance status<sup>29</sup>, comorbidity according to Charlson comorbidity index<sup>30</sup>, previous anti-tumoral and immunosuppressive treatments, history of allogenic transplantation, clinical and biological characteristics at day 0 (D0) which was the day of liver biopsy, sepsis-related organ failure assessment score (SOFA)<sup>20</sup> at D0, hospitalization in hematology ward or in the ICU, pathology findings of liver

biopsy, histological diagnosis and HScore<sup>23</sup> (<http://saintantoine.aphp.fr/score/>). For HScore calculation, hepatic hemophagocytosis was rated as an organ infiltration, similarly to bone marrow hemophagocytosis. Bone marrow hemophagocytosis relied on a bone marrow examination from 7 days before to 7 days after liver biopsy. We considered viral reactivation for Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV) if a replication detected by polymerase chain reaction (PCR) occurred from 7 days before to 7 days after the biopsy.

### *Liver biopsy procedure*

Percutaneous liver biopsies were ultrasound guided, performed by experienced radiologists or gastroenterologists, using semi-automatic systems to obtain hepatic samples, the biopsy device Coaxial TemnoEvolution™, Care fusion which is a 18-gauge needle-catheter. Transjugular liver biopsies were performed by interventional radiologists. A 14-gauge catheter was placed in internal jugular vein under ultrasound guidance. A cannula from a Liver Access and Biopsy set (Cook, Bloomington, Indiana) inserted through the catheter, was positioned in the selected hepatic vein. A 19-gauge core biopsy needle was then delivered through the cannula into the hepatic lobe, and biopsy specimens were obtained under fluoroscopic guidance. Biopsy samples were immediately placed in formalin for histologic analysis. In patients managed in the ICU who rapidly died before liver biopsy while it was indicated, a post-mortem biopsy was performed, after family information and agreement.

### *Histological analyzes*

Liver biopsies were reviewed by two different expert pathologists. Analyses consisted of standard staining (hematoxylin erythrosine, HES), Masson trichrome for the assessment of

fibrosis and special stains and immunohistochemical according to etiological hypothesis. Perls staining showed ferric overload, and Grocott's staining showed the presence of spores and mycelial filaments. GVHD was characterized by CD8 + lymphocytic cholangitis lesions associated with dystrophic lesions of the bile duct epithelial lining of the vanishing bile duct syndrome type without neo-ductular neogenesis. Sinusoidal obstruction syndrome was characterized by sinusoidal congestion with confluent or non-confluent centrilobular hepatocyte necrosis. Hepatic hemophagocytosis was defined by hyperplasia of the Kupffer cells (massive expansion of highly activated histiocytes) in the hepatic sinusoids, associated with erythrophagocytosis. Additional immunohistochemistry staining with antibody CD163 may be helpful in hepatic hemophagocytosis diagnosis. Ischemic cholangiopathy was characterized by a polymorphic inflammatory infiltrate rich in neutrophils, a marked demarcation of portal spaces and especially dystrophic epithelial lesions of vascular bile ducts, associated with neoductular neogenesis and sometimes cholangiolitis with biliary thrombi. It also associates aspects of cholestatic hepatitis with double expression of a biliary and hepatocyte phenotype of the hepatocytes of the border blade. The hypothesis of drug toxicity was proposed, after considering all the treatments administered to the patient, and consultation of possible liver lesions induced by them on the "livertox" website. Immune-allergic or autoimmune hepatitis was characterized by severe interface hepatitis associated with centrilobular involvement and the presence of endotheliitis lesions, and plasma cell involvement with inflammatory infiltrate. The presence of neutrophils and micro abscesses in the lobule associated with confluent necrosis suggested infection of the hepatic parenchyma. The presence of mycelial filaments and / or spores was considered as a suspected hepatic fungal infection. Anti-HSV and anti-CMV immunostaining with nuclear positivity and cytopathic effect was indicative of viral HSV or CMV infection, whereas Fluorescence In Situ Hybridization technique with EBER probe showed evidence of active EBV infection.

Hepatosiderosis was evaluated according to the Searle/Scheuer<sup>31</sup> classification and fibrosis by analogy to the METAVIR system<sup>32</sup>.

### *Statistical analysis*

Characteristics and outcome of patients were compared according to the presence of hepatic hemophagocytosis on liver biopsy. In patients with hepatic hemophagocytosis, we analyzed patients according to HScore HLH criteria, with a defined threshold of 169 (<169 or ≥169). Qualitative variables were described by numbers and percentages and compared using Chi-square test. Quantitative data were described by their median value and interquartile range (IQR) and compared using Mann-Whitney U test. Overall survival (OS) was calculated using the Kaplan Meier method, starting at the time of liver biopsy and Log-rank test was used for statistical comparison. Patients with post-mortem liver biopsy were not included in survival analysis. For patients who had several liver biopsies over time, OS was computed from the most recent one. Statistical significance was defined by a p-value < 0.05. Statistical analyses were performed using the software 'R'.

## **Results**

Between June 2016 and December 2019, 3127 patients were hospitalized in our institution, including 448 who underwent allogenic stem cell transplantation. One hundred and sixteen hepatic biopsies were performed on 110 patients as represented in the flow chart (Figure 1). Seventy-six were transjugular biopsies. Forty were percutaneous, including 9 postmortem biopsies in critically ill patients. Among these 116 biopsies, 65 revealed hepatic hemophagocytosis, of which 33 met HScore HLH diagnostic criteria.

### *Patients' characteristics according to hepatic hemophagocytosis*

Patients' characteristics are described in Table 1. Among the 116 biopsies, HH was diagnosed in 65 biopsies and absent in 51 biopsies. In patients with HH, 78.5% of patients were male, median age was 59 (45-66). The most frequent underlying malignancies were acute myeloid leukemias (36.9%), myelodysplastic syndromes (18.5%), myeloproliferative neoplasms (16.9%) and non-Hodgkin lymphoma (12.3%). Half of patients were in complete or partial remission and 78.5% had a history of allogenic transplantation, with a majority of reduced intensity conditioning. More than 60% were still under immunosuppressive treatments. The main clinical features were weight gain (40%), hepatomegaly (43%), fever (33.8%), sepsis (46.2%), ascites (27.7%) and jaundice (15.4%). Median hepatic biomarkers were as following: aspartate aminotransferase 66 UI/L, alanine aminotransferase 74 UI/L, alkaline phosphatase 202 UI/L, GGT 197 UI/L and bilirubinemia 83  $\mu\text{mol/L}$ . Triglycerides were 2.3 g/L and ferritin 4927  $\mu\text{g/L}$ . CMV and EBV reactivations were diagnosed in blood samples in 16.9% and 10.8% respectively. Pathology analyses founded mostly iron overload (67.7%), fibrosis (49.2%), steatosis (20%) and sinusoidal congestion (4.6%). Hepatic hemophagocytosis was frequently associated with GVHD (55,4%), histological signs of associated infection (32.3%) defined by a viral hepatitis or an acute lobular hepatitis or a fungal infection, and SOS (9.2%). Median SOFA score was 7 (5-10) and 40% patients required ICU management. HLH diagnosis was suspected in 29.2% of cases by the clinician. Median HScore was 174 (129-200) in patients with HH. When comparing to patients with no HH, the statistically significant differences were found on biological hepatic biomarkers, hematology blood test, histological signs of associated infection, SOFA score and HScore (174 vs 119,  $p < 0.0001$ ). Figure 2 represents HScore according to the presence of hepatic hemophagocytosis. With a threshold of 169, positive predictive value for the presence of

hepatic hemophagocytosis according to HScore was 77% and negative predictive value was 56%.

#### *Patients with hepatic hemophagocytosis characteristics according to HScore*

Patients characteristics are described in Table 2. HLH diagnosis was retained if HScore  $\geq 169$ . Demographic characteristics were similar between both groups. Interestingly, 100% of patients with HScore  $\geq 169$  received chemotherapy the month preceding liver biopsy and  $>80\%$  were allo-HSCT recipients. The main biological and pathologic statistically differences between the 2 groups were ferritin level (5728 vs 3038  $\mu\text{g/L}$ ,  $p=0.005$ ), platelet count (12 vs 22  $\text{G/L}$ ,  $p=0.002$ ), neutrophils count (1.4 vs 3.6  $\text{G/L}$ ,  $p=0.05$ ), bone marrow hemophagocytosis (73.9% vs 27.3%,  $p=0.005$ ), severity score (SOFA score 8 vs 5.5,  $p=0.0029$ ) and HScore (200 vs 127,  $p<0.0001$ ). Seventeen patients had a HScore higher than 169 without histological component of HScore.

#### *Long-term outcome*

Figure 3 illustrates outcome of patients with or without HH in the whole cohort. One-year overall survival (OS) was 35% in patients with HH, significantly lower compared to 58% in patients with no HH ( $p=0.026$ ).

Figure 4 shows 1-year OS in patients with HH according to the HScore threshold. In patients with HScore  $\geq 169$ , 1-year OS was 24% compared to 50% in patients with HScore  $< 169$  ( $p=0.019$ ).

## Discussion

Our study aimed to investigate the meaning and prognostic impact of liver involvement of hemophagocytosis in 110 patients with hematological malignancy presenting with ALD who benefited from liver biopsy. Sixty-five biopsies found HH, of which 33 met HScore HLH diagnostic criteria. Forty percent of patients were critically ill requiring ICU admission. HScore was significantly higher in patients with HH. One-year overall survival was poorer in patients with HH versus not and even more when HLH HScore criteria were fulfilled.

Few studies focused on hepatic dysfunction from any causes in patients with hematological malignancies. Van de Louw and al.<sup>3</sup> found an occurrence of 20% for hepatic dysfunction in critically ill hematology patients with significant increase in mortality. Similarly, Bisbal and al.<sup>5</sup> reported the same occurrence in a comparable population, associated with a ICU mortality twice as high in case of hepatic dysfunction (45% vs 24%). In more than 70% of patients, there was no determined etiology for the hepatic dysfunction. In our study, only 2 biopsies (1.7%) brought insufficient samples leading to lack of diagnosis. Data concerning liver biopsies in patients with hematological malignancies are scarce. Kis<sup>33</sup> and Ruggiu<sup>34</sup> studied usefulness and safety of transjugular liver biopsy in allo-HSCT patients. Major complications were under 2% and diagnosis was possible in more than 90% of cases, which is consistent with our results.

Because hepatic dysfunction worsens the prognosis, absence of diagnosis for this dysfunction is common and liver biopsy is safe, the use of histological analyses should be encouraged and generalized in case of lack of diagnosis for hepatic dysfunction.

Concerning histological results in the whole cohort, we mainly found 56% of hemophagocytosis, 55.2% of GVHD, 24.1% of histological signs of associated infection, 14.7% of sinusoidal obstruction syndrome and 10.3% of drug toxicity. In previous studies



such as those of Kis<sup>33</sup> or Ruggiu<sup>34</sup>, GVHD, infectious hepatitis, SOS and drug toxicity were the most common diagnoses, with rates consistent with our results. The main difference with previous studies is the presence of hemophagocytosis in more than half of our biopsies. In Ruggiu and al.<sup>34</sup> for example, there was no diagnosis of hemophagocytosis among 54 biopsies. In 2019, De Gottardi<sup>28</sup> looked for each case of hepatic hemophagocytosis and found 12 cases among 3855 liver biopsies. Included patients had not necessarily an underlying hematological malignancy. There are also few case-reports of patients with hepatic failure and then multi organ failure with a diagnosis of HLH and hemophagocytosis found in liver biopsies<sup>25,26</sup>. Since data are scarce concerning HH, its clinical meaning is difficult to understand. In the first place, presence of HH can be related to HLH diagnosis, as organ involvement.

Diagnosis of HLH can be challenging. HScore was developed to help to diagnose HLH with 9 nine clinic-biological items. However, population used to validate HScore was completely different from our patients as they were neither critically ill patients, nor patients with hematological malignancies<sup>23</sup>. Indeed, these patients have more frequently cytopenias, splenomegaly, fever related to the underlying disease or treatments, which can affect diagnostic performance of HScore. In our study, 40% of our patients required ICU management.

Many studies evaluated diagnosis performance of HScore in the ICU context. Diagnosis of HLH according to HScore or to experts was compared. Knaak and al.<sup>35</sup> reported good diagnosis performance in ICU with a cut-off of 169 for HScore with a sensitivity of 100% and a specificity of 94.1%. Recently, Valade and al.<sup>36</sup> studied performances of HScore by comparing patients hospitalized in ICU with severe HLH versus patients without HLH but with hematological malignancies. Diagnostic performance remained excellent in this population. In our study, we calculated HScore and retained HLH diagnosis if HScore was

≥169. We also considered HH as organ involvement, similarly to bone marrow hemophagocytosis. Our main result was a one-year mortality rate 1.5 times higher for HLH subgroup. This result shows that, even in a population of critically ill hematologic patients with all patients presenting histological evidence of hemophagocytosis, HScore appears as a good tool to distinguish very different groups of patients in terms of disease severity. It is concordant with previous studies analyzing diagnosis performance of HScore. This seems to demonstrate that HScore remains interesting to confirm or reject HLH diagnosis in our population.

The implications of our study are therefore numerous. First, liver biopsy is safe and useful for ALD diagnosis in oncohematology patients. In addition, HLH is a little-known diagnosis for ALD which can be common in this specific population. It can be suggested by the presence of hepatic hemophagocytosis, which needs to be sought. Nine patients (27.3%), in whom no bone marrow aspiration was performed or with no medullar hemophagocytosis, would not have fulfilled HLH criteria diagnosis without liver biopsy. Furthermore, HScore appears as a good tool for HLH diagnosis even in hematology and ICU patients with ALD and its use should be encouraged in this population. This diagnosis of HLH could involve introduction of specific treatments, such as etoposide.

We acknowledge some limitations of our study. First, its retrospective design prevents some analyses, for example the determination of risk factors for hemophagocytosis in overall population of patients with hematological malignancies. It can also be limited by patient's heterogeneity, including allo-HSCT recipients or not. Moreover, our study was conducted in a highly-specialized hematology and allogenic hematopoietic stem cell transplantation center, which can question the generalization of our results. Nevertheless, to the best of our knowledge, there is no data available on this topic.

## **Conclusion**

Hepatic hemophagocytosis impacts prognosis in patients with underlying hematological malignancy. It deserves to be investigated in case of liver abnormalities in the absence of etiological diagnosis. Early recognition of HLH is crucial and HScore appears as a useful tool. Future studies are needed, to pave the way for guidance on optimal systematic diagnostic strategy and therapeutic approach of ALD and HLH in hematology patients. Collaborative and multidisciplinary clinical and research networks are crucial both to improve our understanding to develop diagnostic strategies and adapted therapeutic options, as well as prevention of liver injury.

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## Tables

**Table 1.** Patients' characteristics according to hepatic hemophagocytosis (n=116)

	<b>HH (n=65)</b>	<b>No HH (n=51)</b>	<b>P</b>
Gender (male)	51 (78,5%)	29 (56,9%)	0,02
Age (years)	59 [45-66]	58 [48-65,5]	0,99
Performans status >1 at D0	50 (76,9%)	33 (64,5%)	0,21
Charlson comorbidity index >2	43 (66,2%)	34 (66,7%)	1
<b>Underlying malignancy</b>			0,19
Acute myeloblastic leukemia	24 (36,9%)	20 (39,2%)	
Acute lymphoblastic leukemia	4 (6,2%)	8 (15,7%)	
Chronic lymphocytic leukemia	1 (1,5%)	0	
Myelodysplastic syndrome	12 (18,5%)	2 (3,9%)	
Myeloproliferative neoplasm	11 (16,9%)	9 (17,6%)	
Hodgkin lymphoma	3 (4,6%)	2 (3,9%)	
Non-Hodgkin lymphoma	8 (12,3%)	5 (9,8%)	
Multiple myeloma	1 (1,5%)	4 (7,8%)	
Bone marrow failure	1 (1,5%)	1 (2%)	
<b>Disease status</b>			
Complete remission	29 (44,6%)	24 (47,1%)	0,94
Partial remission	4 (6,2%)	6 (11,8%)	0,46
Progression	12 (18,5%)	9 (17,6%)	1
Unknown	19 (29,2%)	13 (25,5%)	0,81
<b>Previous treatment</b>			
Chemotherapy the month before biopsy	63 (96,9%)	50 (98%)	1
Allo-HSCT patients	51 (78,5%)	35 (68,6%)	0,32
<b>Conditioning regimen for allo-HSCT patients</b>			
Reduced intensity conditioning regimen	23 (35,4%)	15 (29,4%)	0,63
Reduced toxicity conditioning regimen	20 (30,8%)	14 (27,5%)	0,85
Sequential intensified conditioning regimen	11 (16,9%)	6 (11,8%)	0,61
<b>Ongoing Immunosuppressive treatment at Day 0</b>			
Any immunosuppressive agent <sup>‡</sup>	41 (63,1%)	31 (60,8%)	0,95
Corticosteroids	22 (33,8%)	12 (23,5%)	0,31
Ciclosporin	26 (40%)	25 (49%)	0,43



**Clinical features at Day 0**

Ascites	18 (27,7%)	13 (25,5%)	0,96
Weight gain	26 (40%)	16 (31,4%)	0,44
Hepatalgy	14 (21,5%)	14 (27,5%)	0,6
Hepatomegaly	28 (43,1%)	19 (37,2%)	0,66
Skin or gastro-intestinal GVHD	15 (23,1%)	13 (25,5%)	0,93
Jaundice	10 (15,4%)	4 (7,8%)	0,34
Fever	22 (33,8%)	13 (25,5%)	0,44
Sepsis <sup>†</sup>	30 (46,2%)	15 (29,4%)	0,1
Ongoing antimicrobial treatment	47 (72,3%)	28 (54,9%)	0,08

**Biological characteristics at Day 0**

Aspartate aminotransferase (UI/L)	66 [23-145]	166 [48-595]	0,0005
Alanine aminotransferase (UI/L)	74 [31-156]	198 [63-532]	0,001
Total Bilirubinemia (µmol/L)	83 [41-169]	49 [19-162]	0,08
Ferritin (µg/L)	4927 [2840-6353]	3387 [2220-6186]	0,15
Alkaline phosphatase (UI/L)	202 [96-417]	230 [117-397]	0,41
Gamma glutamyltranspeptidase (UI/L)	197 [100-461]	231 [79-623]	0,81
Triglycerides (g/L)	2,3 [1,8-3,4]	2,6 [1,6-3,5]	0,86
Prothrombin Time (%)	74 [61-82]	78 [47-90]	0,67
Leucocytes (G/L)	2,3 [0,2-4,6]	5,3 (1,1-8,6)	0,003
Platelets (G/L)	15 [9-30]	44 [13-118]	0,001
Hemoglobin (g/dL)	8,8 [7,8-9,7]	9,2 [8,4-10,3]	0,046
Lactate dehydrogenase (UI/L)	229 [174-368]	320 [207-515]	0,049
Fibrinogen (g/L)	3,9 [2,9-5,4]	3,7 [2,6-4,3]	0,23
Serum creatinine (µmol/L)	80 [57-116]	74 [59-122]	0,85
Procalcitonin (µg/L)	1,5 [0,5-6,7]	2,1 [0,7-8,8]	0,99
Patients with neutrophils<0.5G/L	27 (41,5%)	14 (27,5%)	0,17
Patients with CMV reactivation	11 (16,9%)	7 (13,7%)	0,83
Patients with EBV reactivation	7 (10,8%)	8 (15,7%)	0,61
Bone marrow hemophagocytosis	23/45 (51,1%)	7/24 (29,2%)	0,13

**Hepatic lesions on liver biopsy**

Sinusoidal congestion	3 (4,6%)	2 (3,9%)	1
Iron overload (scheuer's classification>1)	44 (67,7%)	23 (45,1%)	0,03
Hepatic steatosis (>30%)	13 (20%)	7 (13,7%)	0,55
Hepatic fibrosis (score> F1)	32 (49,2%)	19 (37,3%)	0,31

**Histological diagnosis**

Hemophagocytosis	65 (100%)	0	
GVHD	36 (55,4%)	28 (54,9%)	1
Histological signs of associated infection	21 (32,3%)	7 (13,7%)	0,035
Suspected fungal infection	9 (13,8%)	1 (2%)	
HSV2 hepatitis	0	1 (2%)	

EBER probe positivity	6 (9,2%)	1 (2%)	
Acute lobular hepatitis	8 (12,3%)	5 (9,8%)	
Sinusoidal obstruction syndrome	6 (9,2%)	11 (21,6%)	0,23
Drug toxicity	3 (4,6%)	9 (17,6%)	0,048
Tumoral infiltration	4 (6,2%)	6 (11,8%)	0,46
Ischemic cholangitis	4 (6,2%)	3 (5,9%)	1
Autoimmune or immunoallergic hepatitis	1 (1,5%)	4 (7,8%)	0,23

#### Severity scores and presence in ICU at D0

SOFA score without bilirubin level	4 [3-7]	3 [1,5-5]	0,005
SOFA score	7 [5-10]	5 [2-8]	0,0087
ICU stay	26 (40%)	15 (29,4%)	0,32

#### Suspicion of HLH

HScore	174 [129-200]	119 [72-155]	<0,0001
HLH diagnosis suspected by clinician	19 (29,2%)	0 (0%)	<0,0001

*HH: Hepatic hemophagocytosis, Allo-HSCT: allogenic hematopoietic stem cell transplantation, GVHD: Graft versus host disease, CMV: Cytomegalovirus, EBV: Epstein-barr virus, SOFA: sequential organ failure assessment score, ICU: intensive care unit, HLH: hemophagocytic lymphohistiocytosis. \* Corticosteroids, Ciclosporin and/or Mycophenolate Mofetil. † any ongoing infection according to the physician*

**Table 2.** Patients' characteristics according to HScore in hepatic hemophagocytosis group (n=65)

	HScore $\geq$ 169 (n=33)	HScore < 169 (n=32)	P
Gender (male)	27 (81,8%)	24 (75%)	0,7
Age (years)	56 [45-66]	59 [46-64]	0,98
Performans status >1 at D0	31 (93,9%)	19 (59,4%)	0,003
Charlson comorbidity index >2	21 (63,6%)	22 (68,8%)	0,86
<b>Underlying malignancy</b>			<b>0,27</b>
Acute myeloid leukemia	11 (33,3%)	13 (40,6%)	
Acute lymphoblastic leukemia	2 (6,1%)	2 (6,3%)	
Chronic lymphocytic leukemia	1 (3%)	0	
Myelodysplastic syndrome	4 (12,1%)	8 (25%)	
Myeloproliferative neoplasm	7 (21,2%)	4 (12,5%)	
Hodgkin lymphoma	3 (9,1%)	0	
Non-Hodgkin lymphoma	4 (12,1%)	4 (12,5%)	
Multiple myeloma	0	1 (3,1%)	
Bone marrow failure	1 (3%)	0	

<b>Disease status</b>			
Complete remission	16 (48,5%)	13 (40,6%)	0,7
Partial remission	2 (6,1%)	2 (6,3%)	1
Progression	6 (18,2%)	6 (18,8%)	1
Unknown	8 (24,2%)	11 (34,4%)	0,53
<b>Previous treatment</b>			
Chemotherapy the month before biopsy	33 (100%)	30 (93,8%)	0,46
Allo-HSCT patients	27 (81,8%)	24 (75%)	0,73
<b>Conditioning regimen for allo-HSCT patients</b>			
Reduced intensity conditioning regimen	16 (48,5%)	7 (21,9%)	0,047
Reduced toxicity conditioning regimen	9 (27,3%)	11 (34,4%)	0,73
Sequential intensified conditioning regimen	4 (12,1%)	7 (21,9%)	0,47
<b>Ongoing immunosuppressive treatment at Day 0</b>			
Any immunosuppressive agent <sup>‡</sup>	21 (63,6%)	20 (62,5%)	1
Corticosteroids	9 (27,3%)	13 (40,6%)	0,38
Ciclosporin	13 (39,4%)	13 (40,6%)	1
<b>Clinical features at Day 0</b>			
Ascites	12 (36,4%)	6 (18,8%)	0,19
Weight gain	15 (45,5%)	11 (34,4%)	0,51
Hepatalgia	9 (27,3%)	5 (15,6%)	0,4
Hepatomegaly	18 (54,5%)	10 (31,3%)	0,998
Skin or gastro-intestinal GVHD	5 (15,2%)	10 (31,3%)	0,21
Jaundice	5 (15,2%)	5 (15,6%)	1
Fever	16 (48,5%)	6 (18,8%)	0,023
Sepsis <sup>†</sup>	21 (63,6%)	9 (28,1%)	0,009
Ongoing antimicrobial treatment	26 (78,8%)	21 (65,6%)	0,36
<b>Biological characteristics at Day 0</b>			
Aspartate aminotransferase (UI/L)	76 [30-162]	60 [20-99]	0,2
Alanine aminotransferase (UI/L)	76 [32-231]	67 [26-128]	0,62
Total bilirubinemia (µmol/L)	69 [41-162]	86 [39-176]	0,97
Ferritin (µg/L)	5728 [4037-7197]	3038 [1653-5659]	0,005
Alkaline phosphatase (UI/L)	218 [93-402]	189 [101-417]	0,68
Gamma glutamyltranspeptidase (UI/L)	179 [89-539]	213 [133-391]	0,87
Triglycerides (g/L)	2,4 [1,8-3,4]	1,9 [1,5-3,1]	0,2
Prothrombin Time (%)	68 [54-80]	76 [67-88]	0,08
Leucocytes (G/L)	1,4 [0,1-2,9]	3,6 [0,3-6,1]	0,05
Platelets (G/L)	12 [8-24]	22 [11-52]	0,02
Hemoglobin (g/dL)	8,6 [8-9]	8,9 [7,7-10]	0,45

Lactate dehydrogenase (UI/L)	242 [202-368]	224 [150-366]	0,36
Fibrinogen (g/L)	3,3 [2,2-4,8]	4,6 [3,3-5,5]	0,08
Serum creatinine (µmol/L)	86 [51-126]	79 [57-95]	0,59
Procalcitonin (µg/L)	2,2 [0,5-16]	1,3 [0,5-5,4]	0,63
Patients with neutrophils<0.5G/L	13 (39,4%)	14 (43,8%)	0,92
Patients with CMV reactivation	6 (18,2%)	5 (15,6%)	1
Patients with EBV reactivation	5 (15,2%)	2 (6,3%)	0,45
Bone marrow hemophagocytosis	17/23 (73,9%)	6/22 (27,3%)	0,005

#### Hepatic lesions on liver biopsy

Sinusoidal congestion	1 (3%)	2 (6,3%)	0,98
Iron overload (scheuer's classification>1)	24 (72,7%)	20 (62,5%)	0,54
Hepatic steatosis (>30%)	5 (15,2%)	8 (25%)	0,5
Hepatic fibrosis (score> F1)	15 (45,5%)	17 (53,1%)	0,71

#### Histological diagnosis

Hemophagocytosis	33 (100%)	32 (100%)	
GVHD	18 (54,5%)	18 (56,3%)	1
Histological signs of associated infection	12 (36,4%)	9 (28,1%)	0.66
Suspected fungal infection	5 (15,2%)	4 (12,5%)	
EBER probe positivity	3 (9,1%)	3 (9,4%)	
Acute lobular hepatitis	4 (12,1%)	4 (12,5%)	
Sinusoidal obstruction syndrome	4 (12,1%)	2 (6,3%)	0.7
Tumoral infiltration	2 (6,1%)	2 (6,3%)	1
Drug toxicity	0	3 (9,4%)	0.23
Autoimmune or immunoallergic hepatitis	0	1 (3,1%)	0.96

#### Severity assessment at Day 0

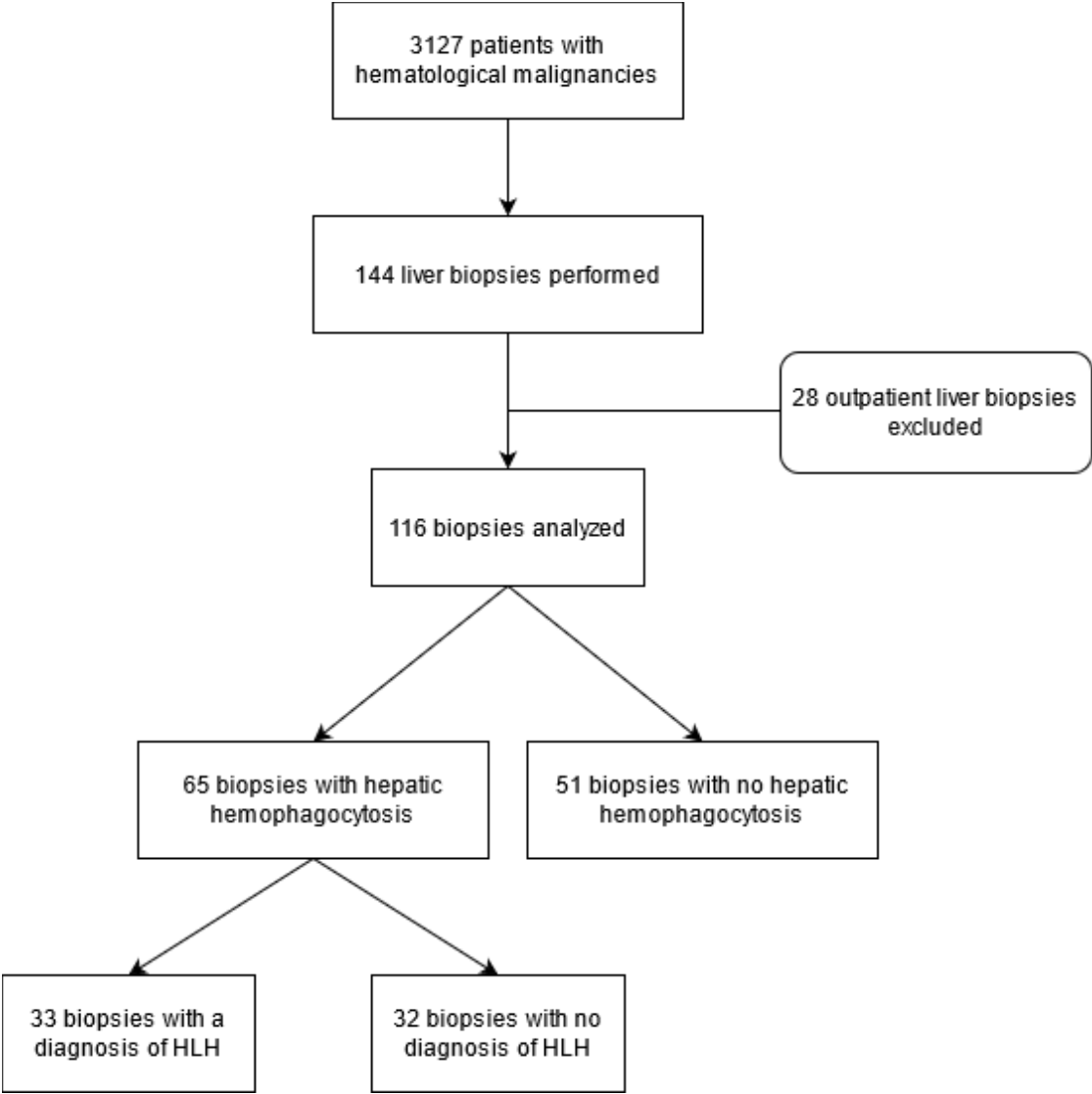
SOFA score without bilirubin level	5 [4-8]	3 [2,8-6,3]	0,01
SOFA score	8 [6-10]	5,5 [4-9]	0,029
ICU stay	16 (48,5%)	10 (31,3%)	0,24

#### Suspicion of HLH

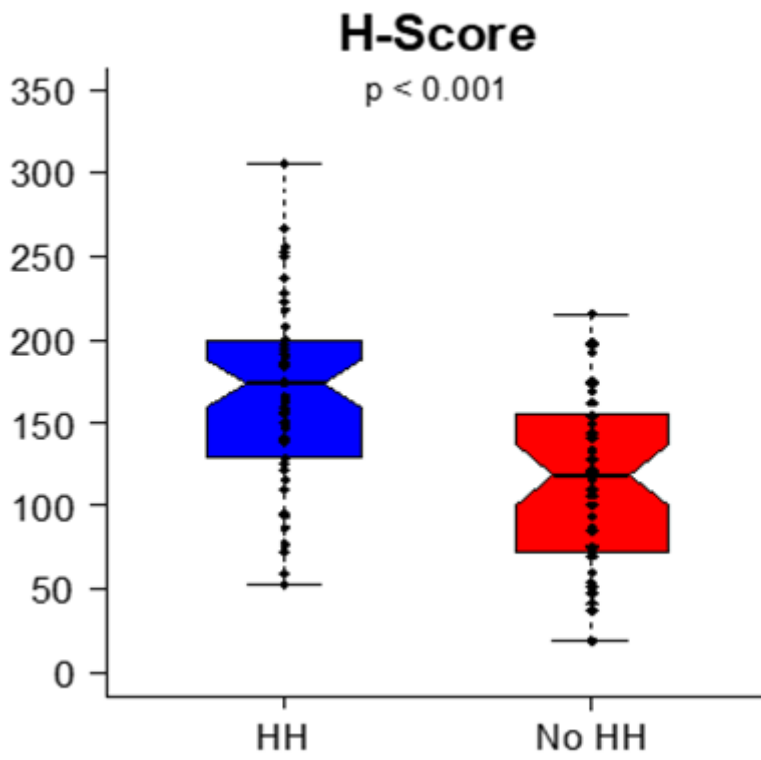
HScore	200 [190-237]	127 [95-150]	<0,0001
HLH diagnosis suspected by the clinician	12 (36,4%)	7 (21,9%)	0,31

HH: Hepatic hemophagocytosis, Allo-HSCT: allogenic hematopoietic stem cell transplantation, GVHD: Graft versus host disease, CMV: Cytomegalovirus, EBV: Epstein-barr virus, SOFA: sequential organ failure assessment score, ICU: intensive care unit, HLH: hemophagocytic lymphohistiocytosis. ‡ Corticosteroids, Ciclosporin and/or Mycophenolate Mofetil. † any ongoing infection according to the physician

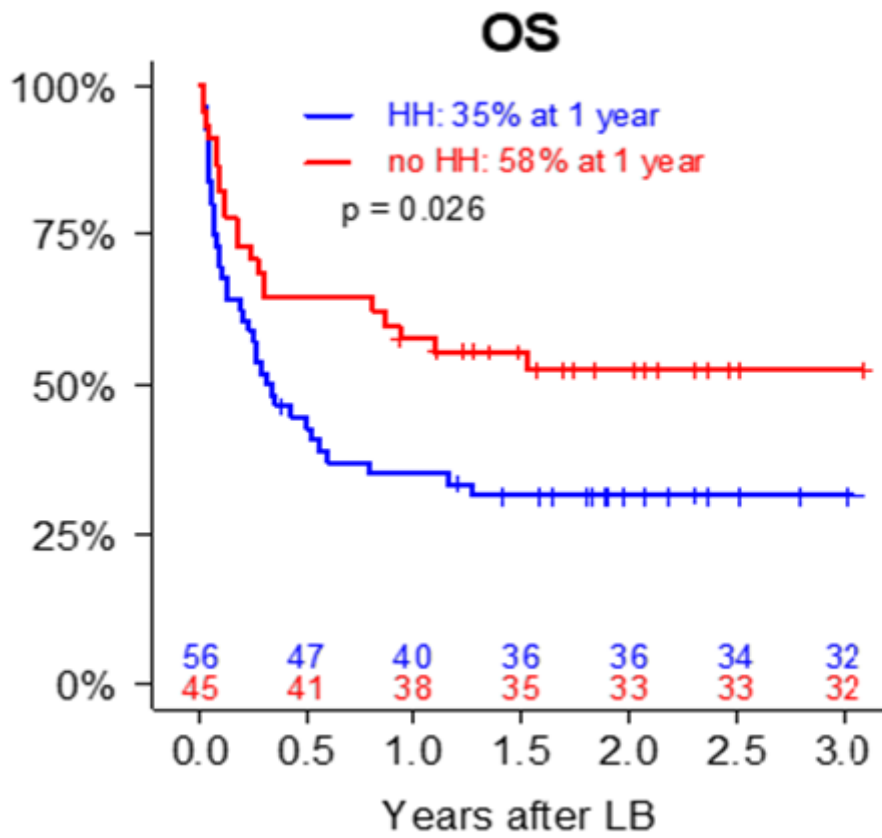
# Figures



**Figure 1:** Flow chart. *HLH: Hemophagocytic lymphohistiocytosis*

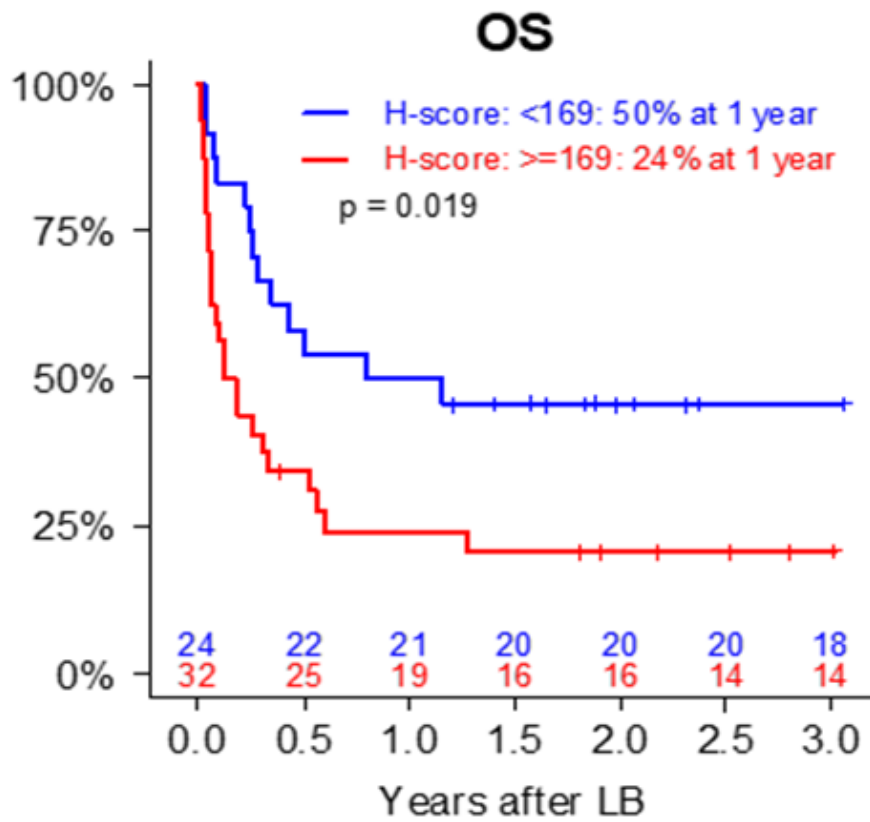


**Figure 2:** Box plot: HScore according to hepatic hemophagocytosis (HH).



**Figure 3:** Overall survival of patients according to hepatic hemophagocytosis (HH).

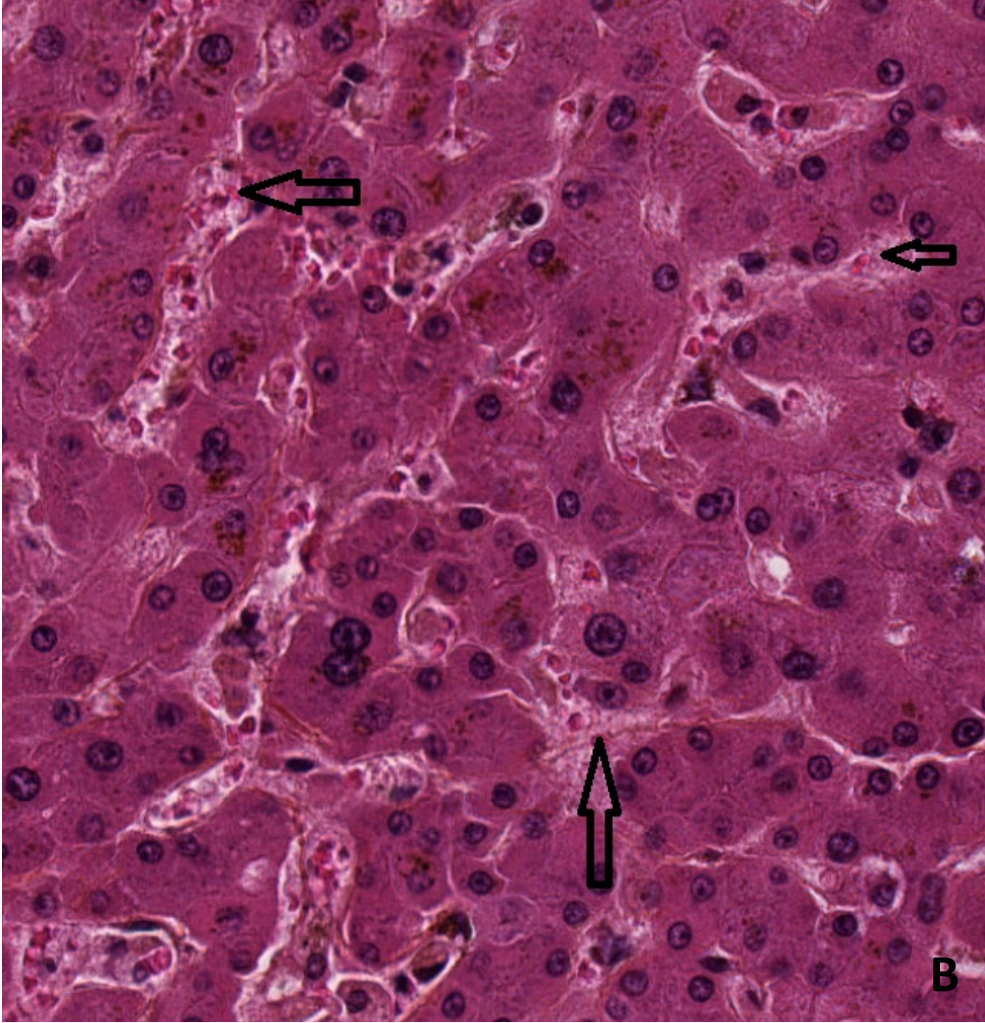
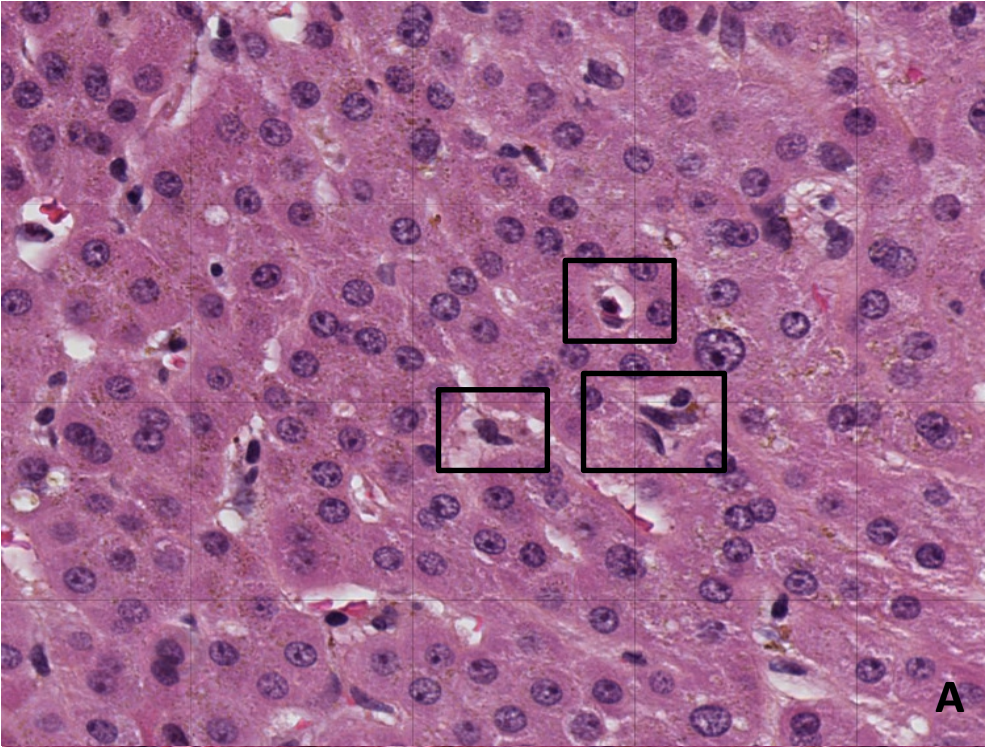
*LB: liver biopsy, OS: Overall survival.*



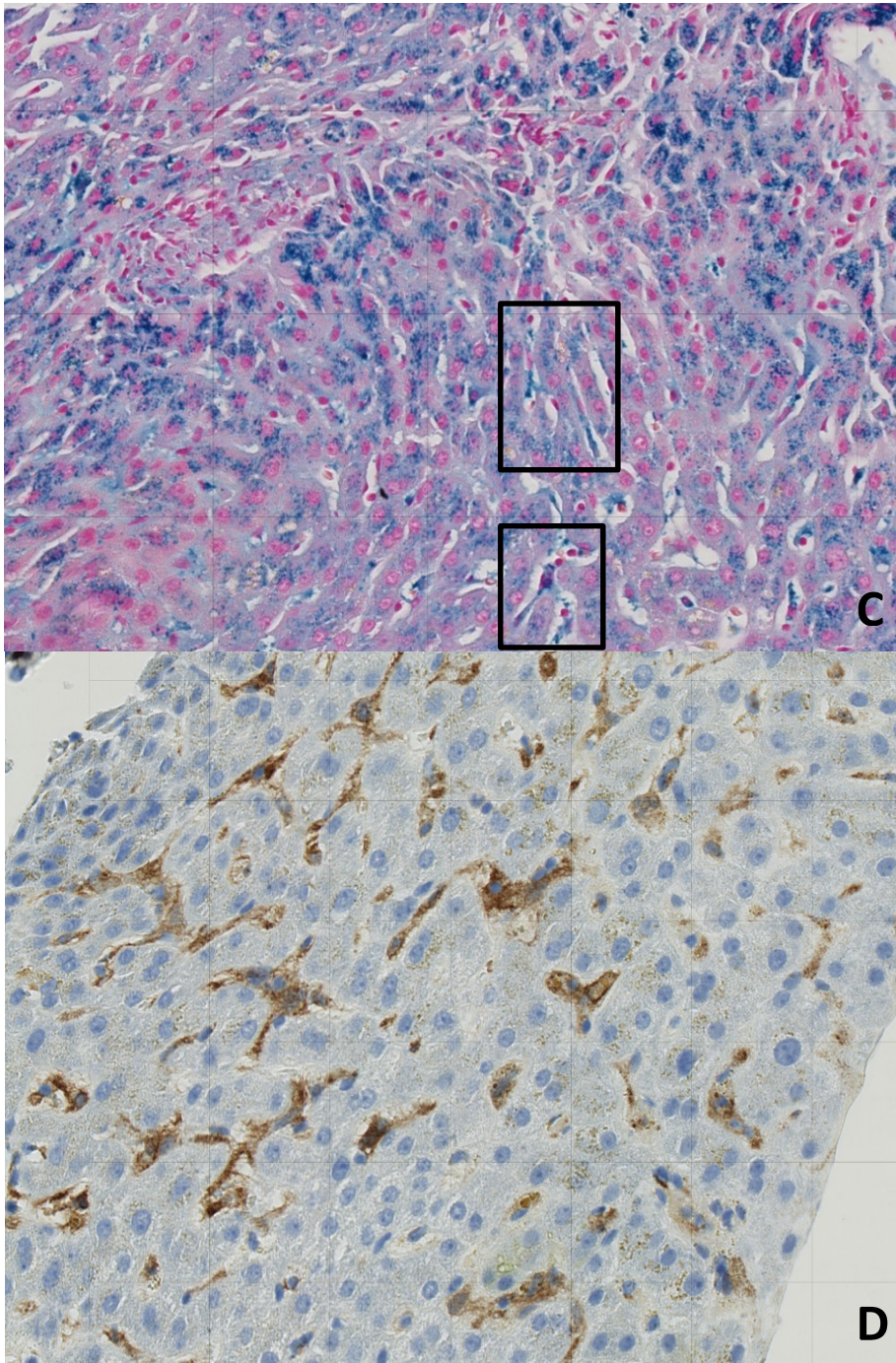
**Figure 4:** Overall survival of patients with hepatic hemophagocytosis according to HScore.

*LB: liver biopsy, OS: Overall survival.*









**Figure 5.** A. Standard Hematoxylin and Eosin Stain: kuppfer cell hyperplasia framed. B. Standard Hematoxylin and Eosin Stain: erythrophagocytosis (the end of the arrow shows red blood cells trapped by macrophages). C. Staining Perls allows the detection of heminic iron in kuppfer cells (framed). D. Immunohistochemistry: anti-CD163 shows kuppfer cells increase in number and plump.

## “ Au moment d’être admis(e) à exercer la médecine, je promets et je jure d’être fidèle aux lois de l’honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J’interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l’humanité.

J’informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n’exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l’indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l’intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l’intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l’indépendance nécessaire à l’accomplissement de ma mission. Je n’entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J’apporterai mon aide à mes confrères ainsi qu’à leurs familles dans l’adversité.

Que les hommes et mes confrères m’accordent leur estime si je suis fidèle à mes promesses; que je sois déshonoré(e) et méprisé(e) si j’y manque. ”

