J Anesth (2011) 25:50–56
DOI 10.1007/s00540-010-1058-3

ORIGINAL ARTICLE

Hypoxic hepatitis in critically ill patients: incidence, etiology and risk factors for mortality

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Received: 25 August 2010 / Accepted: 15 November 2010 / Published online: 9 December 2010

Abstract
Purpose Hypoxic hepatitis may be induced by hemodynamic instability or arterial hypoxemia in critically ill patients. We investigated the incidence, etiology, association with systemic ischemic injury and risk factors for mortality in this population.
Methods Retrospective analysis of patients with hypoxic hepatitis admitted to a multidisciplinary intensive care unit (ICU) of a university hospital. Hypoxic hepatitis was defined as the existence of a compatible clinical setting (cardiocirculatory failure or arterial hypoxemia) and aminotransferase levels higher than 1000 IU/L.
Results During the 8-year study period, 182 out of the 7674 patients admitted presented hypoxic hepatitis (2.4%). The most common cause was septic shock. The rate of in-hospital mortality in hypoxic hepatitis was 61.5% (112 patients), and was higher in patients with septic shock (83.3%) and cardiac arrest (77.7%). Ischemic pancreatitis (25.6%), rhabdomyolysis (41.2%) and renal failure (67.2%) were common in these patients. Risk factors of mortality were prolonged INR ($p = 0.005$), need for renal replacement therapy ($p = 0.001$) and septic shock ($p = 0.005$).
Conclusions Hypoxic hepatitis was not a rare condition, and was frequently accompanied by multiorgan injury, with high mortality. Risk factors for increased mortality were prolonged INR, need for renal replacement therapy, and septic shock.

Keywords Hypoxic hepatitis · Ischemic hepatitis · Pancreatitis · Rhabdomyolysis · Renal failure

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Introduction

Hypoxic hepatitis (also known as ischemic hepatitis or shock liver) is a liver injury characterized by a centrilobular liver cell necrosis with a rapid increase in serum aminotransferases [1–8]. A rapidly resolving elevation of serum enzyme activities, a profound fall in prothrombin activity, and an altered renal function form a triad of biochemical abnormalities that suggest a diagnosis of hypoxic hepatitis [1–4]. Proposed mechanisms responsible for the liver cell necrosis in hypoxic hepatitis are ischemia, venous congestion, arterial hypoxemia, and inability of the liver to extract and use oxygen [2].

In several studies, the incidence of hypoxic hepatitis in the intensive care unit (ICU) population was found to be close to 1% [1–3], although a recent and prospective study found a prevalence of 12% [4]. These studies showed that

hypoxic hepatitis was frequently accompanied by renal dysfunction [1–4], but ischemia of other organs or systems, such as pancreas (ischemic pancreatitis) or muscle tissue (rhabdomyolysis), has not been reported yet.

The objective of our study was to investigate the incidence and underlying etiology, the existence of associated ischemic injury of other organs, and the risk factors for increased mortality of critically ill patients with hypoxic hepatitis.

Material and methods

Patients

We performed a retrospective analysis of patients with hypoxic hepatitis admitted to the ICU of a tertiary university hospital (Hospital Universitari Son Dureta, Palma de Mallorca) from January 2001 to December 2008. The Institutional Research Committee of our hospital approved the study and waived the need to obtain informed consent, since this was a retrospective and observational study.

Patients were screened for the presence of hypoxic hepatitis from a clinical database and selected if they presented abnormal levels of serum aminotransferases [aspartate aminotransferase (AST) or alanine aminotransferase (ALT)], i.e., higher than 1000 IU/L. We excluded patients from the analysis who had an aminotransferase increase secondary to biliary diseases, to hepatitis of viral, pharmacological or toxic origin, and to rhabdomyolysis. Patients with incomplete data were also excluded, as well as cases with creatine kinase levels higher than 975 IU/L (five times the upper limit of normal) and AST/ALT ratios greater than 3. Indeed, this enzymatic profile more likely suggests a muscular origin [9].

Definitions

Hypoxic hepatitis was defined as follows [2, 4]: (1) a clinical setting of circulatory shock or arterial hypoxemia; (2) an early rapid but reversible rise in serum aminotransferase levels above 1000 IU/L (higher than 20-fold the upper limit of reference values in our laboratory; and (3) the exclusion of other potential causes of increased aminotransferases. The following clinical settings were compatible with the diagnosis of hypoxic hepatitis: acute heart failure, septic shock, trauma/hemorrhagic shock, obstructive shock, cardiac arrest, exacerbated chronic obstructive pulmonary disease, and arterial hypoxemia.

Rhabdomyolysis was defined as a serum creatine kinase value greater than 5 times the upper limit of normal (>975 IU/L) [10, 11].

Pancreatitis was defined as a serum amylase value greater than 3 times the upper limit of normal values (>375 U/L) [12, 13] in a plausible clinical context. Imaging techniques that were routinely performed were taken into account for the diagnosis.

Acute renal failure was defined as a serum creatinine value greater than 2 mg/dL [14, 15]. The number of patients requiring renal replacement therapy was also noted [16].

Shock was defined as persistent arterial hypotension and inadequate tissue perfusion in the setting of sepsis (septic shock), trauma or hemorrhage (traumatic or hemorrhagic shock), or extracardiac obstruction (obstructive shock) that required vasopressors to revert hypotension [17, 18]. Hypotension was defined by a persistent systolic arterial pressure below 90 mmHg, a mean arterial pressure below 60 mmHg, or a reduction in systolic blood pressure of >40 mmHg from baseline. Obstructive shock included cardiac tamponade or pulmonary embolism.

Acute heart failure included acute pulmonary edema, cardiogenic shock (low output syndromes), right heart failure, and hypertensive heart failure [19].

Data collection

We recorded age, sex, weight, comorbidities, and underlying condition of hypoxic hepatitis. Severity of illness was evaluated with the Simplified Acute Physiology Score II (SAPS II) during the patient's first 24 h in the ICU [20].

Peak laboratory data, including serum AST, ALT, lactic dehydrogenase (LDH), bilirubin, amylase, creatinine, creatine kinase, and international normalized ratio (INR), were obtained during the first week of ICU admission. We also recorded the percentage of patients with mechanical ventilation, inotropic and vasoactive support, and in-hospital outcome.

The hemodynamic and blood gas analysis values at the start of the episode of hypoxic hepatitis were used. Arterial blood gas analysis and systolic arterial pressure measurements were performed through an arterial line. Central venous pressure was monitored by a central venous catheter, and pulmonary capillary wedge pressure and cardiac index by thermodilution catheter (where available). In patients who received transthoracic or transesophageal ecocardiography, we evaluated the ejection fraction and the right heart overload. We considered a normal or low reduction ejection fraction to be a value higher than 40%, a moderate reduction to be an ejection fraction of between 30 and 40%, and a severe reduction to be an ejection fraction of less than 30%. Right heart overload was diagnosed on the basis of right heart chamber enlargement (right ventricular/left ventricular end-diastolic area ratio >0.6, or right ventricular end-

diastolic volume diameter >30 mm) and/or acute pulmonary hypertension (central venous pressure higher than pulmonary artery occlusion pressure, paradoxical septal motion in systole, or rising central venous pressure and pulmonary vascular resistance with failing cardiac output).

Statistical analysis

Categorical data are expressed as numbers and percentages. Continuous variables are expressed as mean ± SD or median and interquartile range (IQR), as appropiate. Differences between groups were compared using the independent Student's t test or the Mann–Whitney U test (for continuous variables) and chi-square or Fisher's exact test (for categorical variables), as appropriate. To determine the relationship between in-hospital mortality (dependent variable) and ischemic hepatitis (independent variable), a multiple logistic regression model was used to identify independent predictors of in-hospital mortality. Results of the logistic regression analysis are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). The variables included in the logistic regression were those with a significance level of $p < 0.10$ in the univariate analysis. The Hosmer–Lemeshow test was used to assess the goodness of fit of the model. A one-way ANOVA and the Kruskal–Wallis test were utilized to compare groups, as appropriate. Data were analyzed using the SPSS statistical package, version 15.0 (SPSS Inc., Chicago).

Results

During an 8-year period, 9822 patients were admitted to the ICU. In 7674 of these patients, ASL/ALT levels were determined at least once. Among them, 235 had serum aminotransferase levels higher than 1000 IU/L. This was attributed to hypoxic hepatitis in 182 cases, which represents a prevalence of 2.4%. The reasons for excluding 53 patients with serum aminotransferase levels higher than 1000 IU/L are summarized as follows: blunt hepatic trauma (8 patients), toxic hepatitis (6 patients), biliary disease (8 patients), rhabdomyolysis (21 patients), miscellaneous in 6 cases (3 patients with HELLP disease, 1 hemolytic uremic syndrome, and 2 patients with leukemia), and insufficient data for 4 patients.

In-hospital mortality in hypoxic hepatitis was 61.5% (112 patients). Mortality rates according to the etiology of hypoxic hepatitis were as follows: septic shock 83.3% (50/60 patients), cardiac arrest 77.7% (7/9 patients), trauma/hemorrhagic shock 71.0% (27/38 patients), acute heart failure 45.8% (22/48 patients), obstructive shock 14.2% (2/14 patients), and miscellaneous 30.7% (4/13 patients) (Fig. 1).

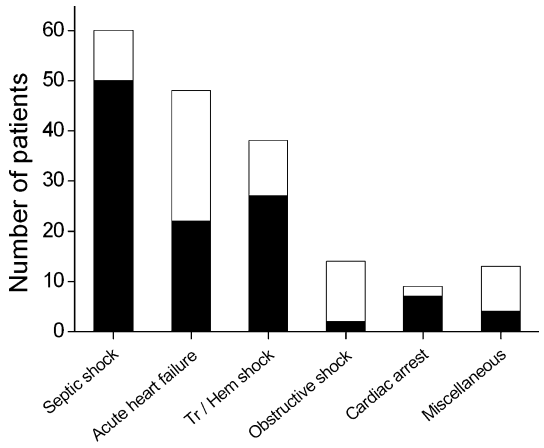

Fig. 1 Number of patients with hypoxic hepatitis (*white columns*) and number of nonsurvivors (*black columns*) distributed by etiology

The clinical characteristics of patients with hypoxic hepatitis who survived and those who did not are detailed in Table 1. Both groups differed in severity of illness (as evaluated by SAPS II score) and in the underlying condition of hypoxic hepatitis (Table 1). The main clinical diagnosis complicated with hypoxic hepatitis was septic shock, followed by cardiac failure and trauma/hemorrhagic shock. Obstructive shock included 10 patients with cardiac tamponade and 4 patients with massive pulmonary embolism.

Peak serum AST, ALT and LDH levels were reached within 2 days of the beginning of the clinical process that accompanied hypoxic hepatitis (Fig. 2). Differences in peak laboratory data between survivors and nonsurvivors were found in their serum AST, LDH, INR and creatinine levels, but not in their serum ALT, total bilirubin, amylase and creatine kinase levels (Table 2). Hypoxic hepatitis was accompanied by acute renal failure in 67.2% of patients, ischemic pancreatitis in 25.6%, and rhabdomyolysis in 41.2%. No differences were found between survivors and nonsurvivors except in relation to acute renal failure, which was more frequently present in nonsurvivors (73 vs. 59%, $p = 0.049$).

We found no differences in PaO_2, $PaCO_2$, and systolic blood pressure in the four main diagnosis groups (Table 3). Septic and traumatic or hemorrhagic shock had lower pH and hemoglobin than the other groups (Table 3). Pulmonary artery catheterization was performed in 71 patients, and transthoracic echocardiography in 85 patients. The results of the hemodynamic evaluation are detailed in Table 3.

Nonsurvivors required treatment with mechanical ventilation, norepinephrine and renal replacement therapy more frequently than survivors (Table 4). Risk factors associated with mortality in patients with hypoxic hepatitis were prolonged INR, need for renal replacement therapy, and presence of septic shock (Table 5). Other variables included in the univariate analysis that did not reach statistical significance were SAPS II score, peak serum AST,

Table 1 Clinical characteristics of 182 patients with hypoxic hepatitis

	All patients ($n = 182$)	Survivors ($n = 70$)	Nonsurvivors ($n = 112$)	p Value
Age (years)	59 ± 17	56 ± 18	61 ± 15	0.10
Sex female, *n* (%)	49 (26.9)	16 (22.9)	33 (29.5)	0.33
Weight (kg)	75 ± 14	73 ± 13	76 ± 14	0.12
SAPS II	48 ± 21	40 ± 18	54 ± 20	<0.001
Comorbidities, *n* (%)				
Diabetes mellitus	45 (24.7)	18 (25.7)	27 (24.1)	0.81
Chronic pulmonary disease	34 (18.7)	14 (20.0)	20 (17.9)	0.72
Chronic heart disease	63 (34.8)	23 (32.9)	40 (36.0)	0.66
Chronic renal disease	18 (9.9)	5 (7.1)	13 (11.6)	0.33
Chronic hepatic disease	22 (12.1)	5 (7.1)	17 (15.2)	0.11
Alcohol abuse	39 (21.4)	13 (18.6)	26 (23.2)	0.46
Active cancer	10 (5.5)	3 (4.3)	7 (6.3)	0.74
Pulmonary hypertension	9 (4.9)	4 (5.7)	5 (4.5)	0.74
Underlying condition, *n* (%)				
Septic shock	60 (33.0)	10 (14.3)	50 (44.6)	<0.001
Pneumonia	36 (19.8)	6 (8.6)	30 (26.8)	
Acute abdominal infection	16 (8.8)	2 (2.9)	14 (12.5)	
Urinary tract infection	2 (1.1)	1 (1.4)	1 (0.9)	
Other	6 (3.3)	1 (1.4)	5 (4.5)	
Acute cardiac failure	48 (26.4)	26 (37.1)	22 (19.6)	0.009
Traumatic or hemorrhagic shock	38 (20.9)	11 (15.7)	27 (24.1)	0.18
Obstructive shock	14 (7.7)	12 (17.1)	2 (1.8)	<0.001
Cardiac arrest	9 (4.9)	2 (2.9)	7 (6.3)	0.49
Miscellaneous	13 (7.1)	9 (12.9)	4 (3.6)	0.02

SAPS simplified acute physiology score

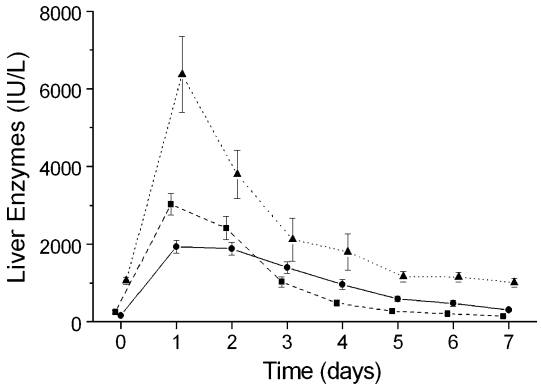

Fig. 2 Mean and SE of serum aspartate aminotransferase (*dotted line*), alanine aminotransferase (*solid line*), and lactate dehydrogenase (*dashed line*) in patients with hypoxic hepatitis during the first week of ICU admission

LDH and creatinine, the need for mechanical ventilation and norepinephrine use.

Discussion

In the ICU of our hospital, hypoxic hepatitis was not a rare condition, and it was frequently accompanied by ischemic injuries to other organs, especially acute renal failure. ICU patients who developed hypoxic hepatitis presented high mortality. Risk factors associated with mortality were prolonged INR, need for renal replacement therapy, and presence of septic shock.

In our study, we found an incidence of hypoxic hepatitis of 2.4%, similar to those described for most series of critically ill patients [1–3], and lower than the 12% described by Fuhrmann et al. [4]. We believe that these disparities are due to the different baseline characteristics of the populations studied, and to a lesser extent, to the different diagnostic criteria used to define hypoxic hepatitis, which range from 8- to 20-fold the upper limit of normal reference serum aminotransferase levels [1–5]. For a diagnosis of hypoxic hepatitis, we required that serum aminotransferase levels must be more than 20 times the upper limit, in order to rule out other causes that can moderately increase serum aminotransferases in critically ill patients [2]. This constitutes the most commonly used criteria [2, 4]. We found septic shock was the most common condition accompanying hypoxic hepatitis, similarly to Whitehead et al. [5]. In a previous study, we found an incidence of 14% of hypoxic hepatitis in septic shock patients [8]. Unfortunately, we lack accurate information

Table 2 Peak laboratory data for 182 patients with hypoxic hepatitis during the first week: liver, pancreatic, renal and muscular function tests

	All patients ($n = 182$)	Survivors ($n = 70$)	Nonsurvivors ($n = 112$)	p Value
Liver function test				
AST (IU/L)	3353 ± 3616	2862 ± 3188	3666 ± 3846	0.02
ALT (IU/L)	2225 ± 2211	2122 ± 2032	2289 ± 2323	0.82
LDH (IU/L)	6196 ± 10530	5264 ± 10009	6788 ± 10852	0.003
INR	2.7 ± 1.6	2.2 ± 1.0	3.1 ± 1.8	<0.001
Total bilirubin (mg/dL)	3.8 ± 5.5	2.5 ± 2.2	4.6 ± 6.7	0.12
Other organ function tests				
Creatinine (mg/dL)	2.8 ± 1.8	2.3 ± 1.3	3.1 ± 2.1	0.003
Amylase (IU/L)	413 ± 698	415 ± 675	412 ± 715	0.74
Creatine kinase (IU/L)	3202 ± 7364	2141 ± 6309	3865 ± 7907	0.79
Lactate (mmol/L)	11.4 ± 7.8	7.0 ± 6.9	14.2 ± 7.1	<0.001

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *INR* international normalized ratio

Table 3 Laboratory/arterial blood gas analysis and hemodynamic data according to underlying condition

	SS	ACF	THS	OS	p Value
Patients (n)	60	48	38	14	
PaO_2 (mmHg)	76 (66–91)	80 (67–96)	75 (58–95)	76 (61–89)	0.81
$PaCO_2$ (mmHg)	42 (34–53)	37 (32–47)	41 (33–51)	40 (32–50)	0.59
pH	7.21 (7.12–7.31)	7.36 (7.26–7.44)	7.23 (7.10–7.32)	7.32 (7.26–7.44)	<0.001
Hb (mg/dL)	8.8 (8.0–10.2)	10.3 (8.6–12.4)	6.4 (5.3–7.5)	9.1 (6.9–11.4)	<0.001
SBP (mmHg)	83 (70–93)	84 (69–90)	78 (70–96)	88 (72–98)	0.92
CVP (mmHg)	14 (12–17)	15 (13–20)	11 (8–15)	19 (10–22)	0.005
Patients (n)	32	25	9	5	
PCWP (mmHg)	17 (14–19)	21 (18–24)	15 (9–18)	16 (14–22)	0.02
CI (L/min/m^2)	2.8 (2.0–3.6)	1.8 (1.6–2.4)	2.2 (1.9–5.2)	2.0 (1.2–3.4)	0.03
Patients (n)	31	41	7	10	
EF, n (%)					0.001
>40%	25 (81)	7 (17)	5 (71)	6 (60)	
30–40%	2 (6)	7 (17)	–	2 (20)	
<30%	4 (13)	27 (66)	2 (29)	2 (20)	
RHO, n (%)	13 (42)	33 (80)	5 (71)	5 (50)	0.007

Results are expressed as medians (IQR)

SS septic shock, *ACF* acute cardiac failure, *THS* traumatic or hemorrhagic shock, *OS* obstructive shock, *Hb* hemoglobin, *SBP* systolic arterial blood pressure, *CVP* central venous pressure, *PCWP* pulmonary capillary wedge pressure, *CI* cardiac index, *EF* ejection fraction, *RHO* right heart overload

for the other groups studied. Other series reported heart failure as the most common underlying process in hypoxic hepatitis patients [1–4, 21].

Patients with hemodynamic instability or arterial hypoxemia leading to hypoxic hepatitis could likewise present ischemia in other organs or systems [22]. Our study underscores that hypoxic hepatitis was frequently associated with ischemia in other organs, such as pancreas (ischemic pancreatitis), muscle (rhabdomyolysis), and especially the kidney (acute renal failure with acute tubular necrosis). Our serum creatinine levels were similar to those found in other studies [1–4, 21]. However, these studies did not report the level of serum amylase and creatine kinase. We considered that the elevation of serum amylase was caused by ischemia of the pancreas, and not by translocation of intraluminal enteric pancreatic enzymes [23] or some other diseases [12]. We did not exclude all patients with elevation of creatine kinase, as was done in the study of Whitehead et al. [5]. In those cases with increased serum creatine kinase, we evaluated if the increase of aminotransferase was due to hypoxic

Table 4 Treatment received by 182 patients with hypoxic hepatitis

	All patients ($n = 182$)	Survivors ($n = 70$)	Nonsurvivors ($n = 112$)	p value
Mechanical ventilation, n (%)	155 (85.2)	51 (72.9)	104 (92.9)	<0.001
Mechanical ventilation (days)	9.0 ± 13.3	8.4 ± 13.2	9.3 ± 13.5	0.73
Norepinephrine, n (%)	152 (83.5)	48 (68.6)	104 (92.9)	<0.001
Norepinephrine (days)	6.5 ± 9.3	3.6 ± 3.4	7.8 ± 10.8	0.08
Dobutamine, n (%)	93 (51.1)	39 (55.7)	54 (48.2)	0.32
Dobutamine (days)	3.3 ± 3.5	3.1 ± 2.3	3.5 ± 4.2	0.34
Renal replacement therapy, n (%)	79 (43.4)	12 (17.1)	67 (59.8)	<0.001
Renal replacement therapy (days)	5.2 ± 6.8	6.2 ± 4.6	5.0 ± 7.2	0.03

LOS length of stay, *ICU* intensive care unit

Table 5 Independent risk factors in multivariate analysis for in-hospital mortality in hypoxic hepatitis

Risk factor	OR (95% CI)	p value
International normalized ratio	1.6 (1.2–2.2)	0.005
Renal replacement therapy	3.7 (1.7–8.0)	0.001
Septic shock	3.3 (1.4–7.7)	0.005

The Hosmer–Lemeshow test indicated a good model fit (χ^2 7.15, $df = 8$, $p = 0.52$)

hepatitis, or if it was secondary to rhabdomyolysis according to clinical presentation and AST/ALT ratio [9]. Serum lactate level was very high, as found in the other two studies on hypoxic hepatitis [2, 4], probably because of increased lactate production in the context of acute circulatory failure or arterial hypoxemia and reduced metabolism due to hepatic dysfunction [24].

Since we did not continuously monitor the different variables in relation to the intensity and duration of the different mechanisms involved in HH (ischemia, hypoxemia and venous congestion), it is difficult to establish the major contributing factor in each group of patients. However, all our patients presented arterial hypotension and low cardiac output, except for patients in septic shock. Since hypoxia is usually rapidly corrected in the ICU environment, we consider ischemia to be the major factor in our patients. Other contributing factors, depending on the group studied, are venous congestion in the obstructive shock group and cardiac dysfunction (high pulmonary capillary wedge pressure and low ejection fraction) in acute cardiac failure patients.

The in-hospital mortality of patients with hypoxic hepatitis is high compared to patients with the same underlying systemic disease. Thus, in a previous study of septic shock patients, we found that mortality increased from 53 to 84% in septic patients complicated with hypoxic hepatitis [8]. The serum levels of AST, ALT and bilirubin were not independent factors of hospital mortality in hypoxic hepatitis patients. This may be because the level of aminotransferases and bilirubin are indicators of hepatic hepatocellular necrosis and elimination function respectively, while INR expresses synthetic function. In the multiple logistic regression analysis, INR was found to be an independent factor associated with in-hospital mortality, along with etiology and need for renal replacement therapy. However, two of these factors, INR and need for renal replacement therapy should probably be considered the same pathology (ischemic insult to hepatic and renal cells), rather than different entities, since—as previously pointed out [22]—associated ischemia in different organs is common in patients with hypoxic hepatitis.

These results are similar to those reported by Fuhrmann et al. [4], who showed that etiology (septic shock), INR and severity of illness were independent factors related to mortality. These results conflict with those of Malinoski et al. [23], who found that elevated serum pancreatic enzymes predicted organ failure and death in a different subset of patients with hemorrhagic shock. In our series, serum amylase and creatine kinase were not predictive of in-hospital mortality. Lactate was not included in the multiple regression model because the peak value occurred pre-mortem and not during the hypoxic hepatitis episode in several patients.

Translating our results into clinical practice, ICU physicians should consider screening for systemic ischemic injury in patients with increased aminotransferase levels. This may lead to prompt recognition of hypoperfusion and the implementation of specific cardiocirculatory support treatments. We propose that hypoxic hepatitis should be considered another liver manifestation of multiple organ dysfunction syndrome (MODS), rather than ICU jaundice, which presents with increased bilirubin levels, decreased albumin, and only a slight elevation of aminotransferases [25].

The major limitation of our study is the retrospective nature of the analysis, which implies inherent limitations. However, this is one of the largest series of patients with hypoxic hepatitis studied, and we carefully selected the patients included. In addition, serum aminotransferases were not determined daily in all patients.

In conclusion, we found that hypoxic hepatitis was not a rare condition in a multidisciplinary ICU, and was frequently accompanied by ischemic injury to other organs with high mortality. Risk factors associated with the highest risk of mortality were prolonged INR, need for renal replacement therapy, and presence of septic shock.

Conflict of interest All authors declare no conflict of interest.

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