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Hypoxic hepatitis — its biochemical profile, causes and risk factors of mortality in critically-ill patients: A cohort study of 565 patients☆

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ABSTRACT

Purpose: A retrospective analysis of critically-ill patients with hypoxic hepatitis (HH) to characterize the biochemical profile and to identify predictors of mortality using the Medical Information Mart for Intensive Care III database.

Methods: HH was defined as a rapid increase in AST/ALT ≥ 800 IU/L after exclusion of other causes. We investigated the correlation between various clinical and laboratory parameters and mortality rates using regression models.

Results: Among 38,645 ICU-patients, 565 (1.46%) were diagnosed with HH; 57.9% were males; median age was 63 years. The unique biochemical profile of HH was confirmed; lactate dehydrogenase (LDH) was higher than both ALT and AST; AST > ALT for the first 2 days then the ratio is reversed until recovery. All-cause hospital mortality was 44.1%. All-cause hospital mortality was 44.1%. On multivariate analysis, older age, higher SAPS-II, higher INR, higher bilirubin, higher LDH, acute kidney injury (AKI), and the need for vasopressors were independently associated with mortality.

Conclusion: Older age, higher SAPS-II, LDH, INR and bilirubin levels, concomitant AKI and the need for vasopressors were all factors associated with increased mortality. The diagnosis of HH was an important harbinger of mortality in this population, which appears to be driven mainly by the severity of the underlying conditions.

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1. Background

Hypoxic hepatitis (HH) is a form of acute liver injury characterized by rapid, often dramatic, increases in serum aminotransferases, which can reach into the thousands or tens of thousands, associated with hypovolemic, cardiogenic or septic shock or other serious states of hemodynamic instability. The diagnosis should be considered in any of these settings after the exclusion of drug-induced liver injury, acute viral hepatitis, or other causes of acute hepatotoxicity [1-5]. HH is commonly known as “ischemic hepatitis” or “shock liver”; however, Henrion et al. proposed the term “hypoxic hepatitis” after demonstrating that a true shock state was absent in half of their cases when studied hemodynamically [2]. These investigators suggested that the terms “ischemic hepatitis” or “shock liver” were in fact, often misnomers [2,6,7]. Histologically, hypoxic hepatitis is characterized by centrilobular liver cell necrosis, but liver biopsy is rarely needed to make the diagnosis [5,8,9]. Although HH may contribute to many cases in which elevated AST or ALT are observed in an ICU setting [4,10], it is likely often missed, and has been the subject of many case reports describing the difficulties encountered in making this diagnosis [11-16]. While an uncommon condition overall, HH has been estimated to occur in about two of every 1000 hospital admissions (0.2%), two to three of every 100 ICU admissions (2.5%) and four of every 10 (40%) admissions in which the aminotransferases are greater than ten times the upper limit of normal [8]. However, the in-hospital mortality associated with this diagnosis has been shown to be upwards of 50% [8].

The pathophysiology of hypoxic hepatitis is not fully understood but different mechanisms have been proposed, including ischemia, venous congestion, arterial hypoxemia, and inability of the liver to extract and use oxygen [2]. Complications associated with HH have included spontaneous hypoglycemia, respiratory insufficiency due to hepatopulmonary syndrome, and hyperammonemia [17]. Since there is no specific treatment for HH per se, early recognition is of key importance [18]. Amassing clinical data regarding HH in literature has been hampered by the relative rarity of the disease, with most studies being limited by a relatively small number of patients. The largest study of HH published to date was a Japanese/US cohort reported by *Birrer* et al. that included 322 patients [19]

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followed by the Austrian group at the Vienna University Hospitals, who analyzed 295 patients [20]. Most of the HH studies have been conducted in Europe and very few were conducted solely on a US-based population [21]. The most recent US-based study was conducted by the Acute Liver Failure Study Group (ALFSG) which included only 51 patients [22]. Moreover, results from previous HH studies regarding predictors of mortality and other outcomes have not always been uniform, and have also been limited by the number of patients. To overcome some of these limitations, we reviewed data from the Medical Information Mart for Intensive Care III (MIMIC-III) critical care database which includes about forty thousand patients from a single center, and is freely available on line [23,24]. The aims of this study were to investigate the frequency of hypoxic hepatitis in a large cohort of ICU patients and to characterize its biochemical profile as well as the predictors of mortality in this population.

2. Methods

2.1. Study design

We conducted a retrospective cohort study to characterize the biochemical profile of hypoxic hepatitis and the predictors for in-hospital mortality in a study population composed of critically-ill patients from a single large medical center database.

2.2. Study population

We used the Medical Information Mart for Intensive Care III (MIMIC-III) research database developed by researchers from the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT), Cambridge, MA, USA, and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC) Boston, MA, USA [23,24]. This database contains detailed information about intensive care unit patient stays, including high-resolution vital sign trends and waveforms, laboratory data, therapeutic interventions, discharge summaries, radiology reports, and International Classification of Diseases, 9th Revision (ICD-9) codes for all patients admitted to the BIDMC ICU between 2001 and 2012 [23,24]. Patients were de-identified in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. The institutional review boards of BIDMC and MIT approved the use of the MIMIC-III database [23,24].

We included all adult patients (≥18 years) admitted to the medical, cardiac or surgical ICU units at BIDMC between 2001 and 2012 who met all of the following criteria for the diagnosis of hypoxic hepatitis: 1) AST and ALT ≥20-times the upper limit of normal (~800 IU/L), irrespective of the admission diagnosis; 2) daily AST and ALT values available to review until their recovery or death; 3) no evidence of drug-induced, chemical or toxic-related liver injury and acute viral hepatitis excluded by standard serology panels. Patients with suspected acetaminophen poisoning were excluded by virtue of positive serum acetaminophen levels or by an appropriate overdose history on reviewing the chart. Clinical notes and discharge summaries were reviewed to document the reason for admission, the cause of death (if any) and to rule out any suspected toxic-related liver injury or accidental hepatic artery ligation in surgical patients. Patients who had undergone liver surgery, including resection or orthotropic liver transplant, were also excluded.

The day of diagnosis of HH (designated as Day 0) was defined as the first evidence of AST and/or ALT increased ≥800 IU/L. Serial ALT, AST, lactate dehydrogenase (LDH), alkaline phosphatase, albumin, total bilirubin, international normalized ratio (INR), lactate, complete blood counts, blood urea nitrogen and creatinine levels were extracted from Day −2 to Day +10. Demographic data including age, sex, and ethnicity were obtained for each patient. Clinical data included vital signs, fluid intake/output, need for vasopressors, need for mechanical ventilator support, hospital/ICU length of stays (LOS) and discharge location. Sepsis was identified as a documented infection and acute organ dysfunction based on ICD-9 codes as studied and validated by Angus et al. [25]. We also used ICD-9 codes to look for other medical comorbidities, including congestive heart failure, cardiac arrhythmias, peripheral vascular disease, hypertension, chronic respiratory diseases, chronic kidney disease, and diabetes mellitus. Acute kidney injury (AKI) was defined as a ≥1.5 times rise in creatinine from baseline or the need for renal replacement therapy. Hypotension was defined as blood pressure <90/60 mm Hg or mean arterial pressure (MAP) <65 mm Hg. For grading of severity, we used the well-validated Simplified Acute Physiology Score II (SAPS-II) score on admission to the ICU. The SAPS-II score uses 17 variables to predict the risk of death without having to specify a primary diagnosis [26].

2.3. Statistical analysis

Age, vital signs, laboratory data, SAPS-II and LOS were defined as continuous variables; while ethnicity, gender, sepsis, vasopressors, mechanical ventilation, medical comorbidities and in-hospital mortality were defined as categorical variables. Continuous variables were reported as the mean with standard deviation (SD) or the median with interquartile range (IQR) when appropriate. Categorical variables are reported as percentages. The correlation between various clinical and laboratory data and hospital mortality rates was investigated using univariate analysis. Comparisons between groups for categorical variables were evaluated using Pearson's chi-square test for contingency, and for continuous variables, a two-sided *t*-test was used. Subsequently, a multivariate analysis was conducted using a logistic regression model. The model included potential variables from the univariate analysis with $P < 0.05$, as well as those felt to have clinical significance (even if not reaching the pre-defined statistical significance value). In the event of co-linearity between variables, only one variable was included. All statistical tests and/or confidence intervals (CI) were performed at $\alpha = 0.05$. All reported *P* values were two sided and rounded to three decimal places. Statistical analysis was performed using JMP Pro by SAS Institute, NC, USA.

3. Results

3.1. Patient characteristics

Out of 38,645 adult ICU admissions at the BIDMC between 2001 and 2012, we identified 746 patients with AST and ALT ≥800 IU/L. Of these, 565 (1.46%) satisfied all of our inclusion criteria for a diagnosis of HH, including having daily liver tests available to review. We excluded 181 patients for having either a positive serum acetaminophen level ($n = 105$), serological evidence of acute viral hepatitis ($n = 33$) or having missing or incomplete data ($n = 43$), including the absence of daily liver biochemistries. A flow diagram of the study population is shown in Fig. 1.

The baseline characteristics of the study population are summarized in Table 1. The median age of the group was 63.2 years [interquartile range (IQR) 49.2–76.1 years]; 57.9% were males; 65.1% were white, median SAPS-II score on admission was 47 [IQR 36–62.5]. The underlying conditions for the ICU admissions are summarized in Table 2. Sepsis, myocardial infarction, CHF, respiratory failure, arrhythmia and post-surgical conditions were the most frequent indications for admission in our cohort. All-cause in-hospital and 28-day mortality rates were 44.1% and 48% respectively. The causes of death are summarized in Table 3. In many cases the cause of death was not mentioned, or patients were placed on comfort measures only (31%), followed by septic shock (18%) and multiple organ failure (13%). Documented hypotension prior to the diagnosis of HH was found in only 24.4%. However, vasopressors were used in 63.2% of patients, sepsis was identified in 56.3% of patients; concomitant AKI developed in 69.4% and 75.2% required ventilatory support, suggesting that the proportion with unrecorded hypotension might have been substantially higher.

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