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RESEARCH LETTER
Miscellaneous

Impact of hypoxic hepatitis in cardiogenic shock: a substudy of the DOREMI trial

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Hypoxic hepatitis (HH), or 'shock liver' is characterized by hepatocyte necrosis caused by decreased blood flow. Hepatic congestion, hypoxemia, and impaired oxygen utilization play secondary roles.[1] Existing HH definitions require appropriate clinical context, elevated aspartate aminotransferase (AST), and excluding other etiologies.[1] Clinically HH manifests as encephalopathy, hyperammonemia, and coagulopathy.[2] HH is the most common cause of liver failure in critically ill patients affecting 2.5–10% of ICU admissions.[1] Up to 90% of cases are attributable to heart failure, respiratory failure, and sepsis, all associated with poor outcomes.[3]

Cardiogenic shock (CS) is defined by low cardiac output with biochemical/haemodynamic manifestations of end-organ hypoperfusion. Despite therapeutic advances, outcomes remain unfavourable.[2] CS results in hypoperfusion and passive congestion representing a physiologically plausible etiology of HH. Limited prospective data are available on the frequency and prognosis of HH in CS patients.

The Dobutamine Compared with Milrinone (DOREMI) trial examined both agents in a cohort of 192 patients with CS; with similar outcomes in both groups.[4] This post-hoc analysis investigates the association between HH and outcomes among CS patients. Study protocols, eligibility criteria, and methods are reported elsewhere.[4] The primary outcome was a composite of all-cause inhospital mortality, resuscitated cardiac arrest, receipt of cardiac transplant/mechanical circulatory support device, nonfatal acute myocardial infarction, transient ischaemic attack (TIA)/stroke, or initiation of renal replacement therapy (RRT).

HH was defined as AST elevation exceeding five times the upper limit of normal (145 U/L).[3] This analysis included 179 patients from the DOREMI trial. Thirteen patients were excluded due to preexisting liver disease. Eighty-nine (50%) had HH, and 90 (50%) did not. Baseline characteristics were similar between groups and are available upon reasonable request. Thirty-one (35%) and 34 (38%) patients in the HH and nonHH groups were female. Dobutamine was used for 46 (52%) and 43 (48%) patients, respectively. Median LVEF was similar between groups, nonHH group: 25.5% (20.0–40.0), HH group 25.0% (20.0–40.0). Lactate (mmol/L) was higher in the HH group, 3.80 (2.40–5.60) compared with 2.45 (1.60–3.65) in the non-HH group ($P < 0.0001$).

Data were analysed by the intention-to-treat principle. Categorical data are expressed as numbers/percentages and continuous variables are expressed as means (SDs) for normally distributed variables and medians (IQRs) for non-normally distributed variables. Outcomes were assessed using unadjusted chi-square analyses. All reported *P*-values are two-sided, and statistical significance set at a *P*-value less than 0.05. (SAS version 9.4, SAS Institute, Cary, North Carolina, USA). All data available upon request from the authors.

The composite primary outcome occurred in 90 patients (50.2%), occurring more frequently in the HH group in 53 (59.6%) participants compared with 37 (41.1%) participants in nonHH groups (unadjusted hazard ratio 1.77; 95% confidence interval (CI) 1.15–2.70, $P = 0.008$) (*Figure 1A*).

Cardiac arrest was more common in with HH, occurring in 11 (12.4%) patients, compared with 3 (3.3%) among those without HH (Unadjusted HR 4.14, 95% CI: 1.15–14.83, $P = 0.03$). No difference in all-cause mortality was seen likely to the cohort being underpowered, with death occurring in 39 (43.8%) patients with HH and 29 (32.2%) patients without HH (Unadjusted HR 1.53, 95% CI 0.95–2.48, $P = 0.08$) (*Figure 1B* and *C*).

To examine the association of the primary outcome with transaminase rise; AST was separated into tertiles (tertile 1; 0–84, tertile 2; ≥ 84–438.16, and ≥438.16), representing $n = 57, 60, 58$ patients, respectively. Compared to tertile 1, tertiles 2 and 3 were more strongly associated with the primary outcome (Unadjusted HR 1.49 (95% CI, 0.86–2.56; $P = 0.16$)—tertile 2, Unadjusted HR 1.73 (95% CI, 1.01–2.96; $P = 0.045$)—tertile 3) (*Figure 1D*). On univariable analysis Society for Cardiovascular Angiography and Interventions cardiogenic shock Class C, and lactate level >2 were associated with HH.

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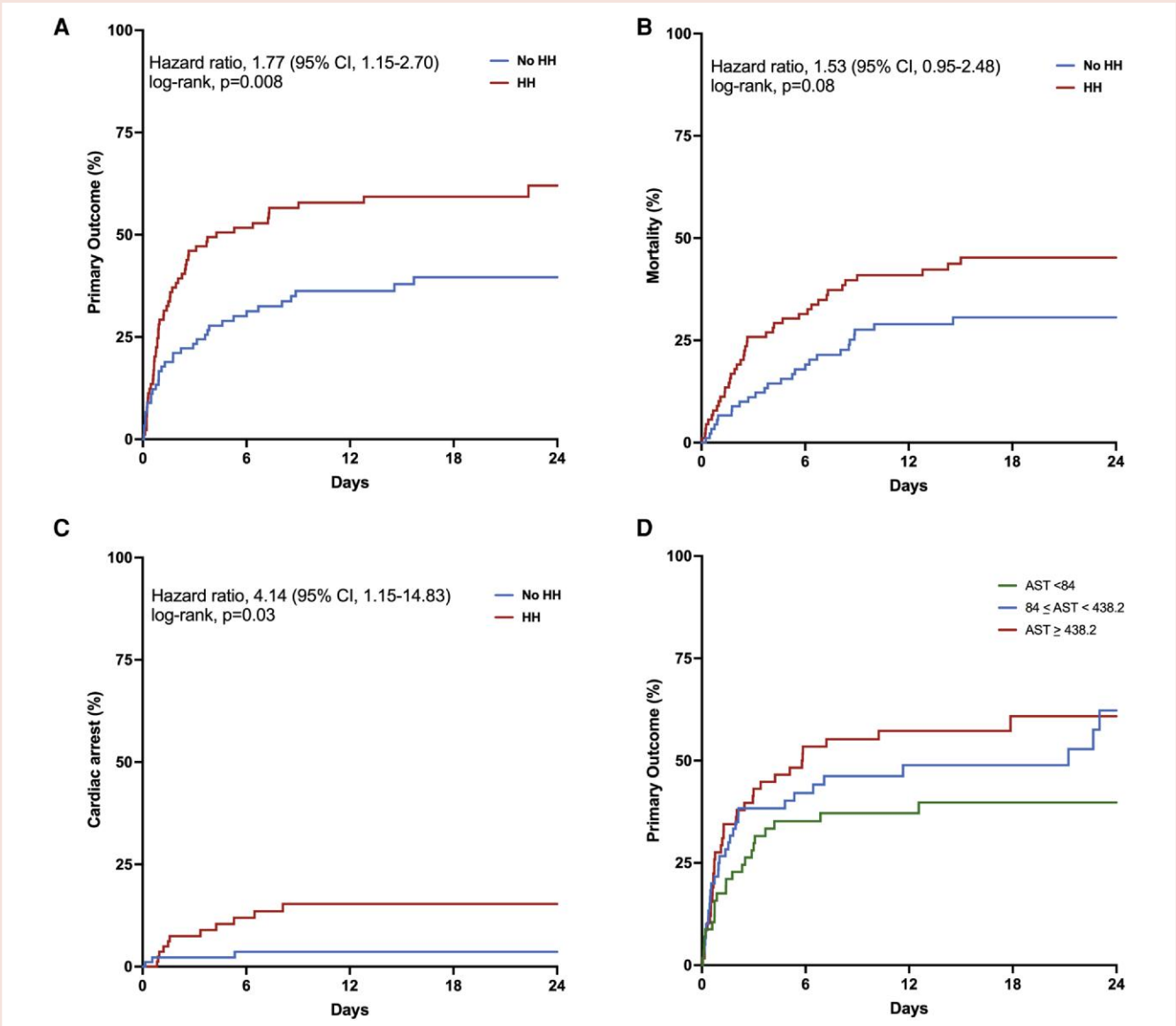

Figure 1 Time-to-Event analysis of the primary composite outcome (*A*) resuscitated cardiac arrest (*B*), death (*C*). The primary composite outcome was inhospital death from any cause, resuscitated cardiac arrest, receipt of a cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, TIA or stroke diagnosed by a neurologist, or initiation of RRT. (*D*) Time-to-Event Analysis of the primary outcome based on AST level by tertile.

Further, on multivariable analysis elevated lactate >2 was associated with HH.

This substudy reveals an association between HH and outcomes in CS. These findings are consistent with the available literature on HH and the association with worse outcomes in various clinical scenarios including ST elevation myocardial infarction, out of hospital cardiac arrest, and patients requiring intensive care.[3] HH has also been retrospectively associated with a higher inhospital mortality among patients with CS.[5] Whether HH is a prognostic marker, or a mediator of clinical deterioration remains unclear. Though definitions of CS recognize elevated liver transaminases as evidence of hypoperfusion, our study highlights the association between HH and unfavorable outcomes. This association is stronger with greater magnitude transaminase rises, however, the threshold at which HH should be defined should be the target of larger studies. Early identification of HH is potentially useful in identifying those that benefit from advanced therapy.

This analysis has limitations. First, as a post-hoc analysis it is not designed/powered to assess impact HH on outcomes in CS, specifically on the most clinically relevant outcome, inhospital mortality. Second, only inhospital outcomes were assessed, therefore long-term impact remains unknown. Finally, due to a lack of blinding to markers of hepatic injury the possibility remains that decisions regarding futility of care were influenced by the occurrence of HH thereby exaggerating the association with poor outcomes.

This study demonstrates a high frequency and significant association with adverse outcomes when HH is present in patients with CS. Considering HH in their prognostication may be valuable. Potential benefits of targeted therapies aimed at correcting liver dysfunction, and the sequelae of HH in CS remains unknown and warrants further studies.

Lead author biography

Omar Abdel-Razek, MD, MSc, is a Structural Heart Interventional Fellow at the Beth Israel Deaconess Medical Center. He completed his pre-medical and medical training at Memorial University. He completed his Honors Bachelor of Science earning the Merit Award for highest academic standing. In 2015, he completed a Doctorate of Medicine followed by Internal Medicine training at Memorial. He then went on to complete General Cardiology and Interventional Cardiology training at the University of Ottawa while also completing his M.Sc in Clinical Epidemiology. His research interests are in cardiogenic shock and the role of structural interventions in this patient population.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of interest: The authors have no conflicts of interest to declare.

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