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MINIREVIEWS

Hypertransaminasemia in non-cirrhotic critically-ill patients

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Abstract

Hypertransaminasemia - acute elevation of alanine aminotransferase and aspartate aminotransferase - is prevalent in non-cirrhotic adults admitted to the intensive care unit (ICU) and often signals extra-hepatic pathophysiology rather than intrinsic liver disease. To synthesise contemporary evidence on aetiology-driven diagnosis, management and emerging biomarkers of hypertransaminasemia in critically ill patients. We performed a structured search of PubMed, EMBASE and CENTRAL (January 2010-June 2025). The search was restricted to full-text articles that were published in English in peer-reviewed journals. Hypoxic liver injury is the leading cause of hypertransaminasemia in non-cirrhotic ICU patients and is characterized by a ≥ 50% alanine aminotransferase/aspartate aminotransferase fall within 72 hours after haemodynamic stabilisation. Idiosyncratic drug-induced liver injury remains uncommon yet explains about 13% of acute liver-failure cases in Western registries. Sepsis-associated liver injury presents mainly as conjugated hyperbilirubinaemia with modest transaminase rise, whereas parenteral-nutrition-associated liver disease is dominated by cholestasis after > 2 weeks of parenteral feeding. Early optimisation of macro-/micro-circulation, rational deprescribing of hepatotoxins, rapid source control of infection and prompt transition to enteral nutrition are outcome-modifying interventions across all phenotypes. In the ICU, aminotransferase elevation should be interpreted as a dynamic biomarker of systemic distress. A pattern-recognition algorithm integrating clinical context, enzyme kinetics and novel biomarkers (glutamate dehydrogenase, microRNA-122, high-mobility group box-1) can expedite aetiology-specific therapy and deserves prospective validation.

Key Words: Critically ill patients; Drug-induced liver injury; Hypertransaminasemia;

Hypoxic liver injury; Intensive care unit; Liver dysfunction; Parenteral nutrition-associated liver disease; Sepsis-associated liver dysfunction

Core Tip: Hypertransaminasemia in non-cirrhotic intensive care unit patients is more often the biochemical echo of hypoperfusion, sepsis, drug toxicity or parenteral-nutrition cholestasis than a sign of primary hepatopathy. A structured, pattern-based algorithm - degree of aspartate aminotransferase/alanine aminotransferase rise, timing, haemodynamic milieu and medication exposure - enables rapid discrimination among hypoxic liver injury, drug-induced liver injury, sepsis-associated liver injury and parenteral nutrition-associated liver disease, guides targeted intervention and prevents futile diagnostics. Novel biomarkers such as glutamate dehydrogenase and microRNA-122 provide muscle-independent, early detection of hepatocellular injury and represent the next frontier for precision hepatology in critical care.

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INTRODUCTION

Hypertransaminasemia is a frequent biochemical finding in critically ill patients and frequently prompts extensive diagnostic evaluation. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can range from mild to severe, with levels sometimes exceeding 1000 U/L[1,2]. Although many of such derangements are transient and reversible, some reflect clinically significant liver injury and carry prognostic implications[3].

In this context, it is crucial to distinguish hypertransaminasemia occurring in critically ill patients without pre-existing cirrhosis, where hepatic enzyme elevations are more likely to represent systemic stress responses than decompensation of chronic liver disease[4]. Non-cirrhotic liver injury refers to hepatic damage that occurs in the absence of established cirrhosis. It typically results from acute systemic insults such as hypoxia, septic shock, or drug toxicity rather than intrinsic chronic liver disease. Secondary liver injury of this type is the most frequent hepatic abnormality observed in the intensive care unit (ICU), often serving as an early, dynamic marker of critical-illness severity and remaining potentially reversible with timely intervention. Recognition of non-cirrhotic liver injury is essential to prevent misattribution to chronic hepatic pathology, guide appropriate management strategies, and improve clinical outcomes in the ICU setting [5]. The absence of underlying hepatic pathology creates a diagnostic challenge, as baseline aminotransferase levels are typically normal, and any acute increase demands thorough etiological exploration.

This narrative review focuses on the most prevalent causes of hypertransaminasemia in non-cirrhotic ICU patients, offering a structured approach to diagnostic evaluation and clinical therapeutic approach based on current evidence and practice guidelines. For this updated narrative review we conducted a structured search of PubMed, EMBASE and Cochrane CENTRAL for studies published between January 1, 2010, and June 17 2025. The search combined the terms "critically ill patients", "drug-induced liver injury", "hypertransaminasemia", "hypoxic liver injury", "parenteral nutrition-associated liver disease" and "sepsis-associated liver dysfunction". The evaluation was restricted to full-text articles that were published in English in peer-reviewed journals.

HYPOXIC LIVER INJURY

Hypoxic liver injury (HLI), also referred to as ischemic hepatitis or "shock liver", is one of the most common causes of abrupt aminotransferase elevation in ICU patients. It results from a sudden decrease in hepatic oxygen delivery, frequently due to systemic hypotension, cardiac dysfunction, or severe hypoxemia[2,6,7]. The centrilobular regions of the hepatic lobules, being furthest from arterial and portal venous blood supply, are particularly vulnerable to ischemic injury[8].

HLI is typically characterized by a sharp rise in ALT and AST levels, frequently exceeding 20 times to 50 times the upper limit of normal. Bilirubin and alkaline phosphatase levels can remain normal or demonstrate only mild elevations [9]. In the absence of ongoing hypoxia or hypotension, transaminase levels usually return to baseline within 5 days to 10 days[6].

The diagnosis of hypoxic hepatitis (HH) is chiefly clinical and hinges on identifying an acute haemodynamic insult - most commonly cardiogenic or septic shock, major haemorrhage, or severe respiratory failure. Supportive imaging may show hepatic venous congestion and echocardiographic signs of right-sided cardiac dysfunction, but these findings complement rather than replace clinical assessment[10]. Exclusion of viral hepatitis, autoimmune liver disease, and biliary obstruction is essential.

Management focuses on reversing the underlying hemodynamic insult through fluid resuscitation, oxygen supplementation, vasopressor support, and, when appropriate, inotropic agents. The prognosis depends largely on the reversibility of the primary cause of hypoperfusion rather than the degree of liver enzyme elevation itself[2,11].

DRUG-INDUCED LIVER INJURY

Drug-induced liver injury (DILI) represents a major and frequently underrecognized cause of hypertransaminasemia in ICU patients. DILI is traditionally classified into intrinsic and idiosyncratic type[12]. Idiosyncratic DILI is rare in the general population, but it is nevertheless a major aetiology of acute liver failure (ALF): Data from the United States ALF Study Group show that idiosyncratic DILI accounts for about 13% of adult ALF cases in North America, that is comparable across Western cohorts[13].

The pathogenesis of DILI varies and may involve direct hepatotoxicity, idiosyncratic reactions, or immune-mediated mechanisms. Drugs' metabolites can either interfere with cellular biochemistry (intrinsic pathway) or trigger an immune response (extrinsic pathway). Cell death occurs in both types, and it is a result of cell and nuclear disassembly[14].

The polypharmacy common in critical care - including antibiotics (*e.g.*, amoxicillin-clavulanate, flucloxacillin), antifungals (*e.g.*, voriconazole), antiepileptics, sedatives, and acetaminophen - increases the risk of hepatocellular or cholestatic injury[15,16]. DILI can present as hepatocellular (predominant ALT/AST elevation), cholestatic (elevated alkaline phosphatase and bilirubin), or mixed patterns. Symptoms are nonspecific and can include malaise, nausea, jaundice, and abdominal discomfort. In severe cases, DILI can progress to fulminant hepatic failure[17].

Diagnosis relies on clinical suspicion, a thorough drug exposure history, exclusion of other causes, and time-course correlation. The Roussel Uclaf Causality Assessment Method (RUCAM) can be helpful, though its utility is limited in ICU settings due to overlapping confounders[18]. Although the RUCAM remains the benchmark algorithm for DILI, its diagnostic performance deteriorates in the ICU. Critically ill patients typically receive multiple agents, experience overlapping non-drug hepatic stressors (hypoxia, sepsis, ischaemia) and follow complex pharmacokinetic trajectories that obscure the latency criteria integral to RUCAM. In addition, true de-challenge or re-challenge is rarely feasible. Consequently, both the specificity and sensitivity of the score decline, and expert clinical judgement - supplemented by alternative tools - is required in this setting[19]. Management begins with prompt discontinuation of the offending agent. N-acetylcysteine is indicated for acetaminophen toxicity and can also offer benefit in non-acetaminophen acute liver injury[20]. In immune-mediated reactions, corticosteroids can be considered, although guidelines don't recommend routinary corticosteroids administration for patients with DILI other than Drug Reaction with Eosinophilia and Systemic Symptoms syndrome. A single-center retrospective study used two kinds of GCs administration methods (Methylprednisolone, range: 60-120 mg/day or prednisone, range: 40-60 mg/day for 3-5 days and then prednisone 20 mg/day and 5-10 mg weekly reduction) or (methylprednisolone, range: 60-120 mg/day for 3-5 days) to treat severe DILI patients[21]. Supportive measures include monitoring hepatic function, managing coagulopathy, and preventing progression to hepatic failure.

SEPSIS-RELATED LIVER INJURY

Liver dysfunction constitutes a core component of sepsis-associated multiple-organ dysfunction syndrome and usually presents as a mixed pattern of hepatocellular necro-inflammation, cholestasis, and loss of synthetic capacity (*e.g.*, rising international normalized ratio, falling albumin)[22]. The pathophysiology involves inflammatory cytokine release, microvascular dysfunction, impaired oxygen extraction, mitochondrial damage, and endotoxin-mediated injury[23,24]. A hallmark of sepsis-associated liver dysfunction is sepsis-induced cholestasis, where conjugated hyperbilirubinemia is prominent despite the absence of biliary obstruction[25]. Aminotransferase levels are typically mildly elevated (< 5 × upper limit of normal), although more significant elevations can occur in severe cases or in combination with hypoperfusion. In septic patients, diagnostic work-up must first exclude alternative causes of liver dysfunction - most notably biliary obstruction (*e.g.*, choledocholithiasis, cholangitis) and exposure to hepatotoxic drugs. Bed-side imaging such as abdominal ultrasound or computed tomography/magnetic resonance cholangiopancreatography is therefore routinely employed to rule out extra-hepatic cholestasis. Once mechanical and pharmacological insults have been discounted, dynamic liver-function testing with indocyanine-green plasma-disappearance rate offers an early, quantitative marker of hepatic dysfunction and correlates with 28-day mortality in the ICU setting[26].

Management is focused on controlling the underlying infection, ensuring adequate tissue perfusion, and minimizing hepatotoxic exposure. Early initiation of appropriate antibiotics, source control (*e.g.*, drainage of abscess or infected devices), and hemodynamic resuscitation are cornerstones of Surviving Sepsis Campain[27]. Prognosis is frequently linked to the degree of systemic organ dysfunction rather than isolated liver indices[28].

PARENTERAL NUTRITION-ASSOCIATED LIVER DISEASE

Parenteral nutrition-associated liver disease (PNALD), also known as intestinal failure-associated liver disease, is a significant concern in ICU patients requiring prolonged parenteral nutrition (PN). The pathogenesis is multifactorial and includes overfeeding, lack of enteral stimulation, lipid emulsions rich in omega-6 fatty acids, and recurrent catheter-

related infections[29,30].

Clinical features frequently begin with biochemical cholestasis, characterized by elevated gamma-glutamyl transpeptidase, alkaline phosphatase, and bilirubin. Transaminase elevations are typically mild to moderate and can precede overt cholestasis. In long-term cases, progression to fibrosis or cirrhosis can occur[30].

Diagnosis is based on clinical context - particularly prolonged PN use in the absence of other identifiable causes of liver dysfunction. Imaging is typically unremarkable but used to rule out biliary obstruction. Liver biopsy can be considered in cases of persistent cholestasis or clinical deterioration.

Management strategies include minimizing PN duration, initiating early enteral nutrition whenever feasible, and using fish oil-based lipid emulsions that appear to reduce the risk of cholestasis. Avoiding overfeeding, cycling PN infusions, and preventing infections through strict catheter care protocols are also essential components of therapy[29,30].

EMERGING BIOMARKERS OF LIVER INJURY IN THE ICU

Traditional liver-function tests (ALT, AST, bilirubin, alkaline phosphatase) provide essential but nonspecific information about hepatic status. In critically ill patients these indices are easily distorted by extra-hepatic factors. Recent work underscores the need for adjunctive biomarkers with higher organ-specificity and earlier kinetic change.

Glutamate dehydrogenase (GLDH) is a mitochondrial enzyme released only after hepatocyte necrosis; it is not influenced by muscle injury or haemolysis. A 2025 multi-centre study (n = 338) reported an area under the receiver operating characteristic curve of 0.99 for GLDH *vs* 0.90 for ALT and demonstrated a faster decline during recovery, supporting its utility for dynamic monitoring in multiorgan failure[31]. MicroRNA-122 (miR-122) is a liver-specific, non-coding RNA that rises early in hepatocellular stress. In a 2024 clinical cohort, miR-122 increased 12-24 hours before ALT in DILI and remained unchanged by skeletal-muscle damage, improving diagnostic specificity in patients with rhabdomyolysis[32]. High-mobility group box-1 has emerged as a prognostic mediator in paediatric ALF, correlating with inflammatory network activation and outcome[33]. Circulating cytokeratin-18 fragments (M65/M30) reflect mixed apoptosis-necrosis; a 2023 Biomolecules study of 312 subjects showed that cytokeratin 18-M65 discriminated nonalcoholic fatty liver disease patients at very-high cardiovascular-risk and tracked disease severity[34].

Although still under active investigation, their integration into ICU algorithms is anticipated as bedside assays become widely available, particularly when conventional liver function tests are equivocal or the aetiology of transaminasaemia is multifactorial.

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT STRATEGY

A structured approach to hypertransaminasemia in non-cirrhotic critically ill patients demands the integration of clinical, biochemical, and imaging data (Figure 1). A key first step is assessing the pattern and degree of enzyme elevation: (1) Massive elevations (*e.g.*, > 1000 U/L) are typically associated with HH or acute DILI (*e.g.*, acetaminophen); (2) Cholestatic patterns (elevated alkaline phosphatase, gamma-glutamyl transpeptidase, bilirubin) are more suggestive of sepsis-associated cholestasis or PNALD; and (3) Mixed injury patterns necessitate broader differential diagnoses.

Concurrently, the clinical context must be assessed: (1) Hypotension or cardiac dysfunction - suspect HLI; (2) Polypharmacy or known hepatotoxins - DILI; (3) Sepsis with or without jaundice - sepsis-associated liver dysfunction; and (4) Prolonged PN - PNALD.

Key investigations include serial liver function testing; serial ALT/AST should be re-checked every 24 hours; a fall of ≥ 50% from the peak within 48-72 hours is generally regarded as a favorable biochemical trajectory[2]. Abdominal ultrasound with doppler to assess hepatic flow and rule out vascular/biliary obstruction should be performed[35].

Management is primarily supportive and etiology-specific: (1) Restoration of hepatic perfusion in HLI; (2) Drug withdrawal and antidotes in DILI (*e.g.*, N-acetylcysteine); (3) Infection control and organ support in sepsis; and (4) Transition to enteral nutrition in PNALD.

In select cases, referral to hepatology or consideration of liver support therapies (*e.g.*, molecular adsorbent recirculating system, plasma exchange) can be warranted. Close monitoring of trends in enzyme levels, coagulation parameters, and overall organ function is essential for guiding therapeutic decisions. Summary of major etiologies of hypertransaminasemia in non-cirrhotic critically ill patients is summarized in Table 1.

CONCLUSION

Hypertransaminasemia in non-cirrhotic critically ill patients is not an epiphenomenon of isolated hepatic disease but rather a highly sensitive, early sentinel of global pathophysiology - including hypoperfusion, systemic inflammation, drug toxicity and nutritional derangement - frequently preceding overt failure of other organs. A pattern-recognition approach that couples the magnitude and kinetics of aminotransferase release with haemodynamic data and imaging permits rapid delineation of HH, DILI, sepsis-associated liver injury and PNALD, thereby streamlining targeted therapy. From a clinical-practice standpoint, monitoring of ALT, AST, bilirubin and international normalized ratio, prompt optimization of macro- and micro-circulatory flow, systematic deprescribing of non-essential hepatotoxins, and early enteral nutrition constitute actionable measures that directly influence short-term survival and long-term hepatic

Table 1 Major etiologies of hypertransaminasemia in non-cirrhotic critically ill patients is summarized

Etiology	Clinical context	Biochemical pattern	Key diagnostic clues	Management focus	Ref.
HLI	Shock, cardiac arrest, severe hypoxaemia	Massive ALT/AST > 1000 U/L; bilirubin initially normal	Acute haemodynamic collapse; ≥ 50 % ALT/AST decline ≤ 72 h	Fluid resuscitation, vasopressors, optimise oxygen delivery	[2,6,7]
DILI	Polypharmacy, known hepatotoxins	Hepatocellular, cholestatic or mixed	Temporal drug link; RUCAM limited in ICU	Drug withdrawal; NAC (acetaminophen); selective corticosteroids	[13,17]
SALI	Septic shock, bacteraemia/fungaemia	Mild-moderate ALT/AST; cholestatic bilirubin rise	Imaging rules-out obstruction; conjugated hyperbilirubinaemia	Source control, guideline antibiotics, perfusion optimisation	[22]
PNALD	> 2 weeks PN, minimal enteral feed	Cholestasis ± mild ALT/AST	GGT/ALP rise; exclude other cholestasis	Early enteral nutrition, fish-oil lipids, avoid overfeeding	[30]
Multifactorial/unclear	Combined shock, sepsis, drugs, PN	Variable	No single dominant trigger	Multimodal supportive care; hepatology consult	[3]

HLI: Hypoxic liver injury; DILI: Drug-induced liver injury; SALI: Sepsis-associated liver injury; PNALD: Parenteral-nutrition-associated liver disease; RUCAM: Roussel Uclaf causality assessment method; ICU: Intensive care unit; NAC: N-acetylcysteine; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PN: Parenteral nutrition; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase.

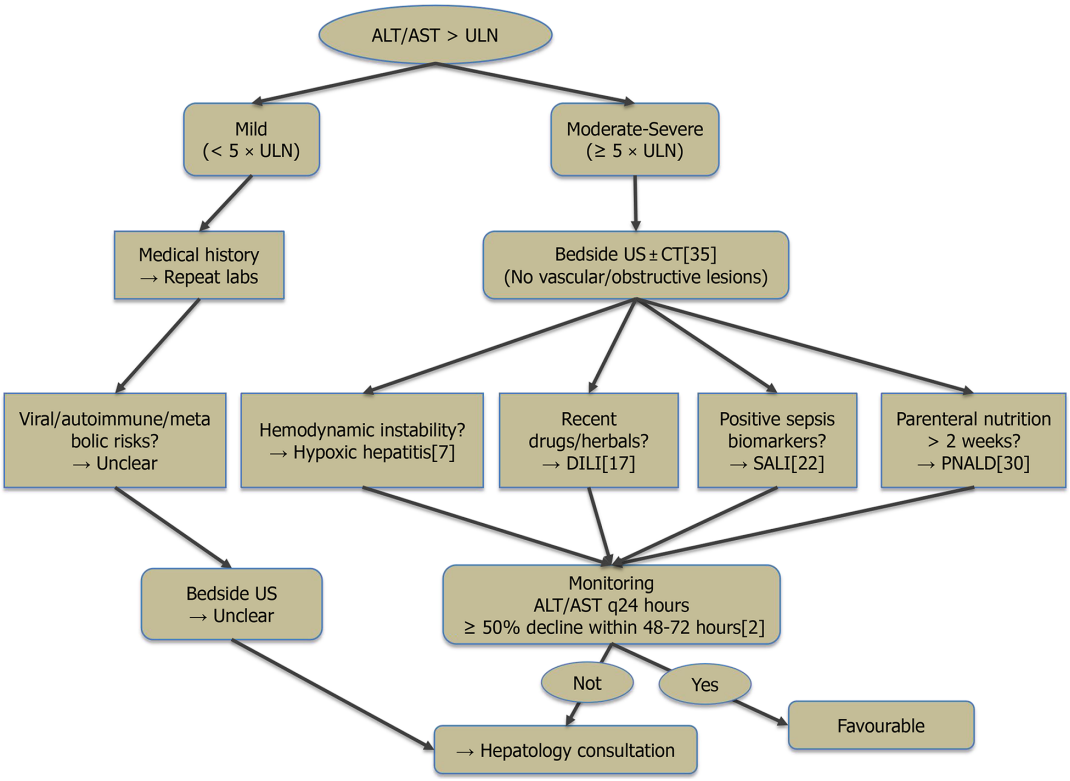

Figure 1 A structured approach to hypertransaminasemia in non-cirrhotic critically ill patients. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limit of normal; US: Ultrasound; CT: Computed tomography; DILI: Drug-induced liver injury; SALI: Sepsis-associated liver injury; PNALD: Parenteral nutrition-associated liver disease; q24: Every 24 hours.

recovery. Future research should prioritize prospective validation of combined biomarker panels such as GLDH, miR-122 and high-mobility group box-1 for their incremental prognostic yield over conventional tests, exploration of biomarker-triggered therapeutic algorithms within randomized frameworks, and integration of machine-learning models that fuse electronic medication profiles with real-time haemodynamic and laboratory data to predict clinically significant liver injury before irreversible damage ensues. Such an agenda will transform aminotransferase elevation from a descriptive laboratory anomaly into a modifiable risk signal, fostering truly precision-guided hepatoprotection in the intensive-care environment.

FOOTNOTES

Author contributions: Fiore M and Cosenza G designed the study, they contributed equally to this article, they are the co-first authors of this manuscript; Coppolino F, Pota V, and Sansone P performed the search; Pace MC supervised the manuscript; Petrou S revised the manuscript to improve and polish language; Fiore M and Cosenza G wrote the paper; and all authors thoroughly reviewed and endorsed the final manuscript.

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