

Acute liver failure: A practical update

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Summary

Acute liver failure is a rare and dynamic condition, with a broad aetiology and an incompletely understood pathophysiology. Management of this life-threatening disease requires critical care and organ support and frequently early liver transplantation. Proper identification, prevention and treatment of complications such as intracranial hypertension and sepsis are critical to optimising outcomes. The identification of the cause of acute liver failure and the prompt initiation of the aetiological treatment can also improve prognosis. Survival has progressively improved in parallel to advances in medical treatment. Intracranial hypertension complicating hepatic encephalopathy is less frequent than in the past and intracranial pressure monitoring now relies on non-invasive techniques. Current prognostic models have good accuracy to identify patients who will die without liver transplantation but are not able to identify those in whom transplantation is futile. New prognostic markers to select patients for transplantation are still in the pipeline. Therapeutic plasma exchange and, in some centers, early renal replacement therapy are well established treatments for the disease. The use of other artificial liver devices in clinical practice is not supported by evidence. This review is intended to provide a clinical update on the management of acute liver failure, incorporating the most recent advances in the field.

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Introduction

Acute liver failure (ALF) is a rare life-threatening condition characterised by abnormal liver tests, elevated international normalised ratio (INR) >1.5 and hepatic encephalopathy (HE) without preexisting chronic liver disease.^{1–3} Most cases are preceded by acute liver injury (ALI), a condition characterised by liver damage and impaired liver function with coagulopathy (INR >1.5) but without HE. An acute deterioration in liver function in patients with chronic liver disease or cirrhosis should be categorised as acute-on-chronic liver failure, a completely different entity which will not be considered further in this review.⁴ ALF usually affects young patients without comorbidities, yet it is associated with high mortality. This entity may progress to either spontaneous recovery or to extrahepatic complications, multiorgan failure and death. Emergency liver transplantation (ELT) is the most effective treatment for this condition given the limited effectiveness of the currently available liver support systems. ELT and extensive research in the last decades have transformed ALF from a poorly understood disease that was almost always fatal to a well-known entity with established diagnostic and treatment protocols and good prognosis in developed countries.⁵ Prompt diagnosis and treatment in expert centres can prevent ALI from progressing to ALF. Once ALF develops, rapid transfer to centres with expertise in ELT and admission to the intensive care unit (ICU) is pivotal for aetiologic diagnosis and treatment, organ support and expedited evaluation for ELT. This review will focus on practical clinical aspects and recent advances in the management of ALF.

Pathogenesis of hepatic and extrahepatic organ failures

ALF is preceded by ALI which manifests with varying degrees of hepatocyte cell death. The mechanisms involved in liver injury differ by aetiology: acute hepatitis B infection is associated with massive lysis of infected hepatocytes by the immune system, paracetamol (acetaminophen) overdose with toxic metabolites, *Amanita phalloides* intoxication with RNA synthesis blockage, shock with ischaemic necrosis, and acute fatty liver of pregnancy with mitochondrial dysfunction, among others. On the other hand, the host response to massive liver necrosis with the release of damage-associated molecular patterns from dying hepatocytes and endothelial cells^{6,7} underpins a significant immune reaction that may further cause a severe systemic inflammatory response with the release of both pro-inflammatory cytokines such as IL-6, TNF- α , HGF and anti-inflammatory cytokines. Liver failure and the deranged systemic inflammatory response may lead to the development of vasodilatory shock, acute kidney injury (AKI), metabolic abnormalities and vulnerability to infections. Moreover, the failing liver is unable to convert ammonia to urea causing an accumulation of this neurotoxin which may lead to astrocyte swelling and intracranial hypertension.⁸ Sepsis with multiorgan failure and intracranial hypertension complicated by cerebral herniation are the main causes of death in ALF. In a recent cohort of patients with ALF who were on the waitlist for ELT, 28% of the deaths were due to complications from cerebral oedema and the rest due to multiorgan failure.⁹

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<https://doi.org/10.1016/j.jhepr.2024.101131>



Keypoints

- Acute liver failure is a rare clinical condition with a broad aetiology that varies among geographical areas.
- It is the most severe clinical condition in hepatology. This life-threatening disease requires critical care admission and frequently organ support and emergency liver transplantation.
- The identification of the cause of acute liver failure and the prompt initiation of aetiological treatment can improve prognosis.
- Proper management of complications such as intracranial hypertension and sepsis is critical to optimising outcomes.
- Plasma exchange and renal replacement therapy are increasingly used in the treatment of the disease.
- Survival has progressively improved in parallel to advances in medical treatment.

Epidemiological changes and current aetiology

ALF is a rare disease with relevant differences in frequency between geographical areas (Fig. 1). A yearly incidence of 1–6 cases per million population has been reported in developed countries.^{9,10} In contrast, ALF is much more common in developing countries given the lack of extended vaccination programmes for hepatitis viruses. Prognosis is also worse in these geographical areas given the limited access to medical treatment.¹¹ Drug-induced liver injury (DILI) is currently the main cause of ALF in Europe and the US. Paracetamol is the leading drug involved in DILI. Other causes that may lead to ALF are autoimmune hepatitis (AIH), shock (ischaemic hepatitis), Wilson's disease, Budd-Chiari syndrome, toxic mushrooms, heatstroke, acute fatty liver of pregnancy, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome and malignancies.¹² Box 1 describes the whole aetiological picture in ALF. Up to 35% of cases reported worldwide are of indeterminate origin,^{11,12} a feature that may be related to limitations in the aetiological work-up, undiagnosed AIH or unrecognised viral pathogens or drugs. It is anticipated that this percentage of

Box 1. Causes of acute liver failure.

Virus

Acute hepatitis due to HAV, HBV, HCV (exceptional), HDV (HBV and HDV coinfection; HDV superinfection in HBsAg carrier) and HEV
Acute infections due to non-hepatotropic viruses: herpes simplex 1 and 2, varicella-zoster, cytomegalovirus, Epstein-Barr virus, herpesvirus type 6, parvovirus B19, adenovirus, haemorrhagic fever virus and Coxsackie B virus.

Drugs

Paracetamol (overdose; therapeutic doses in alcoholic, malnourished patients or under treatment with enzyme inducers)
Antibiotics: isoniazid, pyrazinamide, tetracyclines, amoxicillin-clavulanic acid
Halothane, sevoflurane and other derivatives
Antidepressants: MAO inhibitors, imidazopyridine derivatives, etc.
Non-steroidal anti-inflammatory drugs
Antithyroid drugs
Others: hydantoins, α -methyl dopa, ketoconazole, amphetamines, sulfonamides, etc.

Toxics

Mushrooms of the Amanita group: *A. phalloides*, *A. verna* and *Lepiota*
Industrial solvents: carbon tetrachloride, trichlorethylene, white phosphorus
Illegal drugs: cocaine, ecstasy (3,4-methylenedioxy methamphetamine)
Others: traditional Chinese medicine, chaparral, other "natural" products

Vascular diseases

Ischaemic hepatitis: shock liver, heart failure
Ligation of the hepatic artery (especially if portal thrombosis coexists)
Acute Budd-Chiari syndrome

Others

Chronic autoimmune hepatitis (as presentation of the disease)
Wilson's disease
Pregnancy (third trimester): acute fatty liver, HELLP syndrome
Hyperthermia, heat stroke
Massive tumour infiltration (due to solid neoplasms, lymphomas, leukaemia)
Reye syndrome (in children and adults)
Urea cycle disorders
Partial hepatectomy

Undetermined

HELLP, haemolysis, elevated liver enzymes and low platelets; MAO, monoamine oxidase.

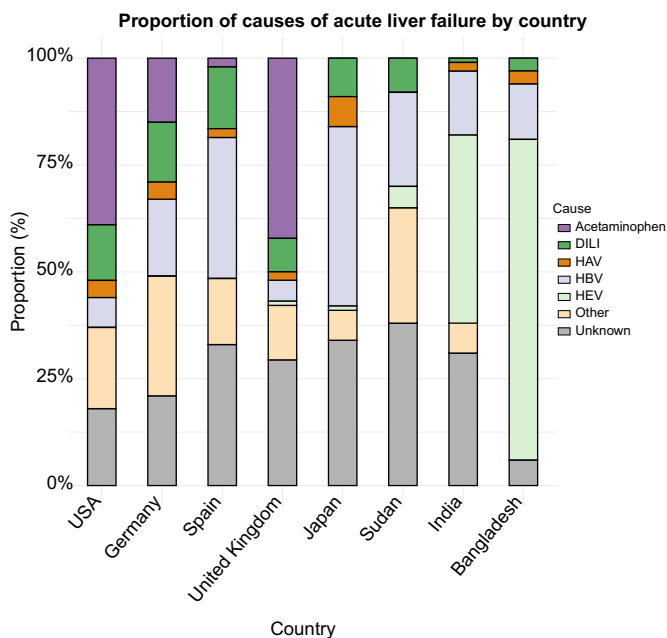


Fig. 1. Causes of acute liver failure by country. DILI, drug-induced liver injury.

indeterminate causes of ALF may decrease when data from more recent cohorts are published.

ALF may present as a hyperacute disease with an interval between jaundice and HE of a few days (≤ 1 week) or as acute or subacute forms with an interval that can last several weeks. Intracranial hypertension is mainly observed in hyperacute forms of ALF which are associated with a higher probability of spontaneous recovery. Paracetamol, viral hepatitis, heat-stroke, and hypoxic hepatitis tend to follow a hyperacute course. Subacute aetiologies may develop features of chronic liver disease such as irregular liver borders on imaging, ascites and even hepatorenal syndrome. Development of those features is associated with low probability of spontaneous recovery. Examples include non-paracetamol DILI or some cases of AIH.¹

Viral infection

Viruses account for most ALF cases worldwide. In Japan, 40% of cases of ALF are due to hepatitis B virus (HBV) infection, whereas hepatitis E virus (HEV) causes half of cases in India and Bangladesh.^{1,13} Even in developed countries with extended vaccination programmes and blood product monitoring, hepatitis viruses currently account for 12% of cases of ALF.¹ ALF due to HBV is a severe condition leading to death or ELT in 80% of cases.¹² Also, coinfection with hepatitis delta virus may lead to a more aggressive phenotype. In addition, there has been an increase in cases of reactivation of HBV in patients with subclinical chronic HBV infection treated with immunosuppressive therapy, especially steroids and rituximab. This reactivation may lead to acute or subacute ALF that can be fatal.¹⁴ Therefore, screening for past or chronic HBV infection is mandatory in all patients before initiating immunosuppression and specific recommendations regarding either prophylactic treatment or regular monitoring must be defined.¹⁴ Hepatitis A virus is the second most common viral cause of ALF globally. However, it is a decreasing entity in developed countries due to the extension of vaccination programmes and sanitization measures, and is currently a marginal cause of ELT in these countries.¹² HEV-related ALF is relatively rare in developed countries since acute viral infection is usually self-limited, but it should always be suspected. In fact, there is data estimating nearly 2 million cases of locally acquired HEV infections in Europe every year.¹⁵ It should be suspected in patients with neurologic abnormalities such as encephalitis, Guillain-Barre syndrome, or neuralgic amyotrophy.¹⁵ Acute hepatitis C is rare and generally not associated with ALF, but some cases have been reported and specific treatment with direct-acting antiviral agents should be promptly initiated. In immunocompromised (but also in immunocompetent) patients, other viruses such as herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr virus, parvovirus, and adenovirus may cause a disseminated infection with ALF, multiorgan failure, and high mortality despite antiviral treatment. Disseminated herpes simplex infection must be suspected in relatively young patients or pregnant women with high fever, very high transaminase and LDH levels and rapid progression to multiorgan failure. ELT is usually contraindicated in the setting of disseminated herpes infection.

Drugs and herbal products

Paracetamol overdose, either intentional or accidental, is the most common cause of ALF in developed countries, especially in the UK (60% of cases) and the US (46%).¹² Paracetamol-related ALF follows a hyperacute phase with very high transaminases and INR elevation and relatively low bilirubin levels. It usually self-limits with supportive therapy and N-acetylcysteine treatment. Of all ELT for ALF, only 8% were related to paracetamol overdose.¹²

Non-paracetamol DILI is a leading cause of ALF in developed countries (5% to 20% of all cases of ALF). DILI may have different phenotypes depending on the responsible drug. Most cases of DILI are idiosyncratic, *i.e.* unpredictable, variable from person to person and generally dose-independent drug reactions related to the exposure to antimicrobials, anticonvulsants, rheumatologic and antineoplastic drugs. Patterns of liver injury may be hepatocellular, cholestatic or mixed. However, a large variety of phenotypes exists. Some drugs may cause an immunoallergic reaction with eosinophilia and systemic symptoms (DRESS), others may induce an AIH, a secondary sclerosing cholangitis, a granulomatous hepatitis or even a ductopenic syndrome. There has been a recent increase in herbal medicines causing ALF. In fact, in the US, almost 20% of all DILI cases are caused by such products. Recreational drugs such as cocaine and ecstasy may cause severe cases of ALF and should be suspected in young patients with ALF of unknown origin with hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and multiorgan failure.¹⁶ Exertional heatstroke is a severe condition characterised by the presence of hyperthermia above 40 °C, associated with neurological impairment that may lead to multiple organ failure. Liver injury may develop in this context, mainly manifesting as variable elevations of serum aminotransferases. While most patients will regain normal liver function with medical treatment, some may progress to ALF requiring ELT or even death.¹⁷ Rising global temperatures, more frequent heatwaves, and intense exercise routines make this condition increasingly important to monitor and treat.

Autoimmune and metabolic diseases

The onset of AIH can lead to the development of acute or subacute forms of liver failure. Both phenotypes are increasingly observed in routine clinical practice. AIH should be suspected in young women with high transaminase and bilirubin levels, and high IgG levels and autoantibodies (*e.g.* smooth muscle antibody, antinuclear antibody). Liver biopsy is often required for the diagnosis since autoantibodies are negative in up to half of AIH-related cases.¹⁸

The fulminant presentation of Wilson's disease almost always follows a fatal clinical course without ELT. It must be suspected in young patients with a family history of liver disease and psychiatric conditions, mild increase in transaminases, a alkaline phosphatase/total bilirubin ratio < 2 and Coombs negative haemolysis.

Other aetiologies

HELLP syndrome and acute fatty liver of pregnancy are complications of preeclampsia occurring in the third trimester of

pregnancy. Despite immediate delivery some patients may progress to ALF and require ELT. Hypoxic hepatitis, also called shock liver or ischaemic hepatitis, is a rare cause of ALF in patients with decompensated congestive heart failure or acute cardiac failure. It follows a hyperacute clinical course and it usually resolves with the treatment of cardiovascular disease. HE is usually mild.

Diagnostic work-up

Once diagnosis of ALF has been established (abnormal liver test, severe coagulopathy, and HE), efforts should be made to rapidly determine its aetiology as it impacts prognosis, may delineate specific treatments, and can also unveil a contraindication for LT (*i.e.* malignant infiltration). Diagnostic evaluation of ALF requires a comprehensive approach (Fig. 2). Clinical

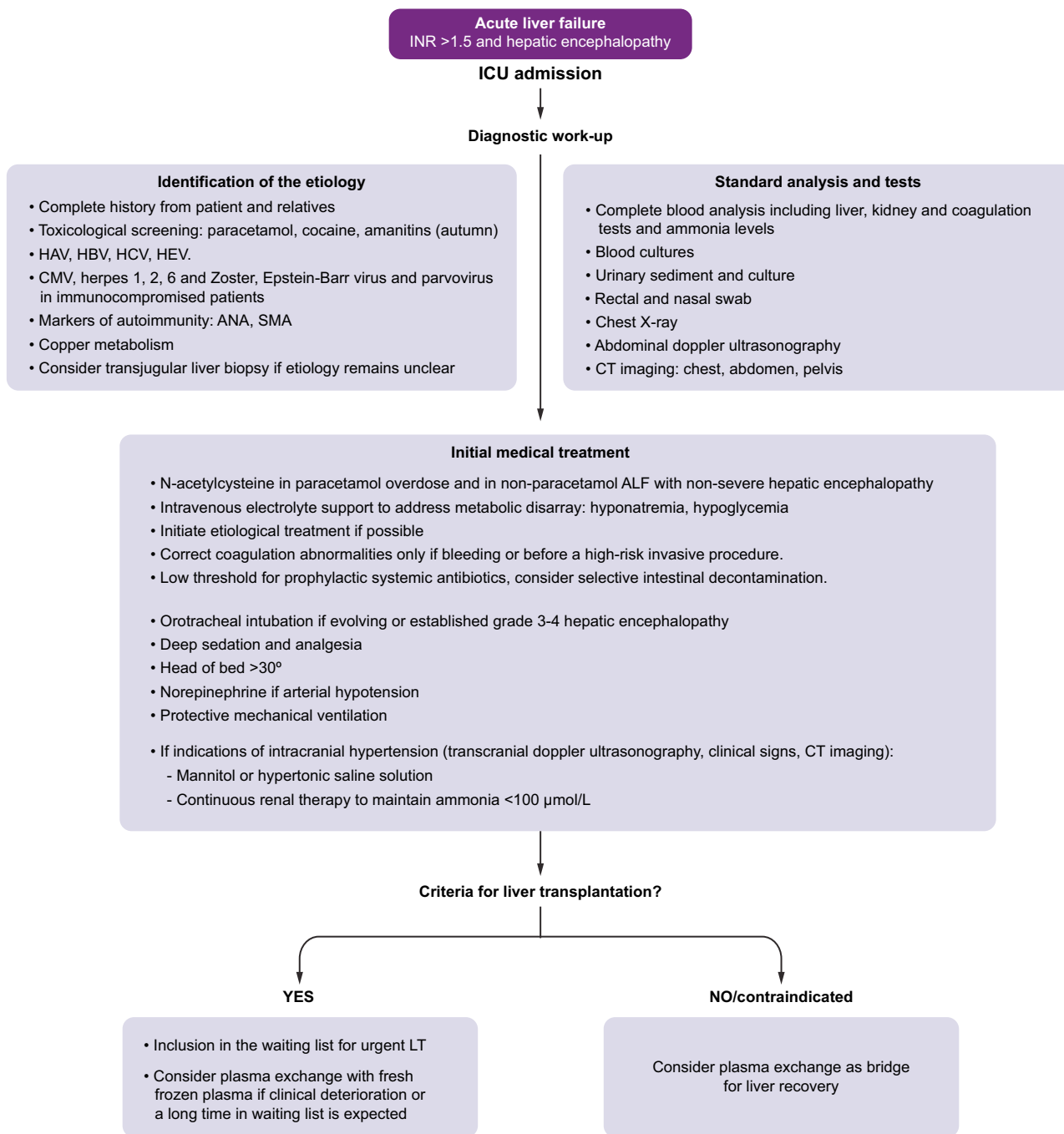


Fig. 2. Recommended initial management of acute liver failure. ALF, acute liver failure; ANA, antinuclear antibody; CMV, cytomegalovirus; INR, international normalised ratio; LT, liver transplantation; SMA, smooth muscle antibody.

assessment should be exhaustive at the time of admission, asking both the patient and their family members about recent consumption of medications or herbs, risky sexual behaviour, and recent travel. Consumption of such herbs should be actively investigated since many patients do not consider them as a potentially harmful drug. Comorbid conditions should also be investigated.^{1,3,19}

At admission, specific laboratory tests should be obtained to determine not only the aetiology, severity, and prognosis of ALF but also to identify potential complications (infection, AKI, among others) (See [Box 2](#)). Chest X-ray and abdominal ultrasonography are also required at baseline assessment. Abdominal ultrasonography should evaluate the patency of the hepatic veins (exclusion of acute Budd-Chiari syndrome), portal vein and hepatic artery, liver morphology and spleen size (data from chronic liver disease) and exclude potential infiltrative disorders. Echocardiography should always be performed in haemodynamically unstable patients or in candidates for ELT. Abdominal tomography is sometimes required to characterise vascular anatomy or upon suspicion of acute pancreatitis.^{1,3}

In all cases of suspected viral ALF, blood viral load determination by quantitative PCR techniques is recommended in addition to serologic screening ([Box 2](#), [Fig. 2](#)).^{1,3,19}

The diagnosis of other entities such as acute Wilson's disease, HELLP or acute fatty liver of pregnancy is mainly based on clinical grounds. Copper metabolism should be evaluated if Wilson's disease is suspected. The determination of copper excretion in urine (8-24 h) is the simplest and fastest diagnostic biomarker of Wilson's disease, having an excellent positive

predictive value. The usefulness of relative exchangeable copper in ALF remains to be elucidated.^{20,21}

There are other aetiologies of ALF that may only be diagnosed by liver biopsy like malignant infiltration of the liver or granulomatous hepatitis.²² It has been demonstrated that transjugular liver biopsy is safe in patients with ALF and provides enough tissue sample to establish the diagnosis. Current guidelines recommend its use if clinically indicated.^{1,23} [Table 1](#) shows the clinical, analytical and histological characteristics of the main causes of ALF.

Criteria for referral to transplant centres

The progression of ALF is highly unpredictable, especially in its hyperacute clinical presentation. In all cases where there is significant acute liver damage, transfer of the patient to a liver transplant centre should be considered. Even patients who may not seem ideal candidates for ELT should be assessed for potential transfer, as management in specialised centres could enhance their chances of survival. Mental status changes can be subtle, and even mild HE may indicate a critical, life-threatening condition within a short timeframe. Therefore, it is highly recommended to transfer the patient upon observing any alteration in mental status, an INR >1.5, or hypoglycaemia or metabolic acidosis. [Table 2](#) describes the suggested criteria for transferring a patient with ALI or ALF related or not related to paracetamol to a LT centre. This early and proactive policy can be crucial for decision-making and improving clinical outcomes in patients with ALF.^{1,2} The only general measure advisable during patient transfer is hypertonic glucose infusion (due to the risk of hypoglycaemia).

Box 2. Suggested laboratory work-up in acute liver failure.

Disease severity and complications

Full coagulation screen including prothrombin time, INR, fibrinogen and factor V

Liver tests including LDH and conjugated and unconjugated bilirubin and creatinine kinase

Renal function tests including serum creatinine, urea* and urine output

Arterial blood gases and serum lactate

Arterial ammonia

Serum amylase and lipase

Blood and urine cultures

Aetiology

Toxicological screening in urine

Paracetamol serum levels in paracetamol overdose

Amanitin in urine in mushroom poisoning

Microbiological screen for virus infection:

- HBsAg, anti-HBc IgM, HBV DNA, delta virus if HBV
- Anti hepatitis A virus IgM
- Anti hepatitis E virus IgM, HEV RNA
- Anti hepatitis C virus, HCV RNA
- Cytomegalovirus, herpes simplex, herpes zoster, Epstein-Barr virus, parvovirus PCR

Markers of autoimmunity: serum levels of immunoglobulins, ANA, SMA, anti-soluble liver antigen

ANA, antinuclear antibody; INR, international normalised ratio; LDH, lactate dehydrogenase; SMA, smooth muscle antibody.

*Low urea levels indicate severe liver dysfunction.

^Immunocompromised patients.

General management and organ support

Critical care management of patients with ALF could resemble that of any other patient in the ICU but has specific aspects that deserve consideration. If ALF is suspected, all drugs that the patient was previously receiving should be suspended (except hormone replacement treatment if applicable). Additionally, manoeuvres that further worsen or could resemble HE (*i.e.* administering sedatives or metoclopramide) should be avoided. There is no evidence that treatment with disaccharides or rifaximin are effective in the treatment of HE in ALF. Lactulose enemas are contraindicated due to the risk of increasing intracranial pressure (ICP).²⁷ The administration of intravenous N-acetylcysteine improves transplant-free survival in cases of non-paracetamol ALF with early stage HE (grade 1 and 2). This treatment is ineffective if HE worsens to grade 3 or 4.^{28,29}

A close control of consciousness level is essential in the management of patients with ALF. It should be checked very frequently, usually every 6 or even 2 h. Patients with grade 3-4 HE require intubation for airway protection and prevention/management of intracranial hypertension. Once intubated, sedation and analgesia must be initiated.^{1,3,5} Recommended general management of patients with ALF is detailed in [Fig. 2](#) and [Table 3](#).

Aetiological treatment

Early initiation of treatment targeting the cause of ALF, when available, is of paramount clinical relevance. Administration of N-acetylcysteine in paracetamol overdose (150 mg/kg in 1 h,

Table 1. Multiparametric diagnosis guide for acute liver failure.

Aetiologic trigger	Clinical phenotype	Testing	Liver histology
HAV, HBV, HCV, HEV	Epidemiological background Viral prodromes (malaise, fever, diarrhoea) Hyperacute course High AST, ALT, and INR	Anti-HAV IgM Anti-HB core IgM, HBV surface antigen, and HBV-DNA Anti-HCV Ig and HCV-RNA Anti-HEV IgM and HEV-RNA	Massive or submassive hepatocellular necrosis Lymphocytic infiltrates Varying degrees of fibrosis in HBV reactivation Immunohistochemical staining
HSV, VZV, CMV, EBV, ADV, PB19 ²⁴	Immunocompromised (but also in immunocompetent) Hyperacute course High fever with or without skin/mucosal lesions in HSV and VZV Disseminated infection Multiorgan failure	IgM and blood viral load	Massive or submassive hepatocellular necrosis Viral inclusions Immunohistochemical staining
Paracetamol overdose	Intentional (younger) or accidental overdose Hyperacute course Metabolic acidosis and acute kidney injury	Drug serum concentration	Coagulative confluent hepatocellular necrosis in centrilobular areas
DILI	Epidemiological background Acute or subacute clinical course Varying patterns of liver injury	Exclude other causes of ALF	Necroinflammatory pattern Massive or submassive hepatocellular necrosis Lymphocytic infiltrates
Autoimmune hepatitis ²⁵	Young women History of other autoimmune disorders High transaminases and high bilirubin May follow a subacute course (ascites)	High gamma globulin levels Autoantibodies (not in 50% of cases)	Centrilobular and confluent necrosis Lymphoplasmacytic infiltration Interface hepatitis Varying degrees of fibrosis
Wilson's disease	Young patients Neurologic or psychiatric background Acute intravascular non-immune haemolysis High bilirubin and low alkaline phosphatase Modest elevations of transaminases with high AST/ALT ratio Progression to AKI	High 24h-cupruria High relative exchangeable copper Low serum copper and low ceruloplasmin	Microvesicular steatosis Glycogenated nuclei Varying degrees of fibrosis
Hypoxic hepatitis	History of congestive heart failure or refractory shock Very sudden and high increase in transaminases and INR with abrupt recovery Transient elevation of bilirubin after recovery Other signs of end-organ damage	Perform liver imaging to assess vascular permeability	Predominant centrilobular necrosis
Heatstroke	Hyperthermia > 40 °C History of physical exhaustion (exercise, heat wave) Concomitant recreational use of cocaine or MDMA Very high transaminases and INR Other signs of end-organ damage (AKI, rhabdomyolysis, ARDS)	Exclude other causes of ALF	Predominant centrilobular necrosis
Mushroom poisoning	Epidemiologic background Severe gastroenteritis High transaminases	Amatoxins in urine	Massive hepatocellular coagulative necrosis
Malignant infiltration	Lymphoma, leukaemia, breast cancer, colon cancer Toxic syndrome, B symptoms High bilirubin and cholestasis Hepatomegaly and lymphadenopathies	Liver biopsy	Atypical cell infiltration in sinusoids
HELLP syndrome ²⁶	Third trimester of pregnancy (frequent history of preeclampsia/eclampsia) Coombs negative haemolysis High transaminases and low platelets May progress to liver rupture	Exclude other causes of ALF	Microvascular fibrin deposition, neutrophilic infiltrate, fatty infiltration, lobular necrosis, and periportal haemorrhage

(continued on next page)

Table 1. (continued)

Aetiologic trigger	Clinical phenotype	Testing	Liver histology
Acute fatty liver of pregnancy ²⁶	Third trimester of pregnancy (infrequent history of preeclampsia/eclampsia) Abdominal pain and vomiting Ascites Severe coagulopathy and encephalopathy Low transaminases Progression to AKI	Swansea criteria	Microvesicular steatosis
Acute Budd-Chiari syndrome ²⁵	Myeloproliferative neoplasm or other prothrombotic disease Abdominal pain Painful hepatomegaly and ascites	Hepatic vein congestion on ultrasound Vein thrombosis identification on imaging	Centrilobular vein dilation

ADV, adenovirus; AKI, acute kidney injury; ALF, acute liver failure; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HSV, herpes simplex virus; PB19, parvovirus B19; VZV, herpes zoster virus.

Table 2. Suggested criteria for referral of patients with acute liver failure to specialised units.³

Paracetamol and hyperacute aetiologies	Non-paracetamol
Arterial pH <7.30 or HCO ₃ <18	pH <7.30 or HCO ₃ <18
INR >3.0 day 2 or >4.0 thereafter	INR >1.8
Oliguria and/or elevated creatinine	Oliguria/renal failure or Na <130 mmol/L
Altered level of consciousness	Encephalopathy, hypoglycaemia, or metabolic acidosis
Hypoglycaemia	Bilirubin >300 µmol/L (17.6 mg/dl)
Elevated lactate unresponsive to fluid resuscitation	Shrinking liver size

INR, international normalised ratio.

50 mg/kg over 4 h, 100 mg/kg in 16 h and 150 mg/kg in 24 h for 3–4 days); glucocorticoids in AIH without severe HE (1 mg/kg); penicillin G in *Amanita phalloides* poisoning, intravenous acyclovir in herpes 1, 2 or zoster infection (10 mg/kg every 8 h), tenofovir or entecavir in HBV ALF and expedited delivery in acute fatty liver of pregnancy or HELLP are measures that should be initiated immediately after the diagnosis has been established.^{11,27} Ribavirin may also be considered in ALF caused by HEV since it may reduce morbidity, but there is no evidence of its efficacy.¹⁵ Therapeutic plasma exchange (TPE) is indicated to treat acute haemolysis in Wilson's disease.¹⁷ Once major liver damage is established (*i.e.* grade 3–4 HE) aetiological measures are much less effective and potentially harmful (*i.e.* steroids in AIH).³⁰

Cardiovascular support

Cardiovascular alterations in ALF are characterised by hyperdynamic circulation (high cardiac output and peripheral vasodilation) that could compromise end-organ perfusion causing lactic acidosis and AKI.²⁷ Hypotensive patients should be carefully resuscitated, preferably with normal saline, to avoid congestion and ensure organ perfusion. Fluid overload is especially deleterious in ALF since it increases the risk of intracranial hypertension due to worsening cerebral oedema. In a study involving patients with ALF, fluid responsiveness was observed in only 29%. Preload dependency parameters, based on pulse contour analysis, effectively predicted fluid

responsiveness.³¹ In persistently hypotensive patients, vasopressors should be initiated, norepinephrine being the preferred drug. Vasopressin should be added to norepinephrine in cases of refractory hypotension. Stress dose hydrocortisone (50 mg intravenous q6h) should be considered in vasopressor-resistant hypotension given the high prevalence of relative adrenal insufficiency in ALF.³² Several studies show that molecular adsorbent recirculating system and high-volume plasma exchange improve haemodynamic stability in patients with ALF requiring vasopressor support.^{33,34}

Respiratory support

The incidence of respiratory failure is low in ALF. However, ELT is contraindicated in patients developing refractory respiratory failure.^{35,36} Ventilatory settings should be protective using low tidal volumes (6 ml/kg/ideal body) and appropriate, usually low to moderate positive end expiratory pressure. Hypercarbia and hypocarbia should be avoided, with CO₂ targets between 4.5 and 5.5 kPa (34–41 mmHg).³ Extracorporeal membrane oxygenation could be considered as a bridge to ELT in highly selected patients with reversible respiratory failure or as rescue therapy for refractory respiratory failure in post-transplant patients.³⁷

Acute kidney injury and renal replacement therapy

AKI is highly prevalent in ALF and is associated with poor outcome.^{38,39} Up to 70% of patients in a US cohort had AKI with 30% requiring renal replacement therapy (RRT).⁴⁰ Continuous renal replacement therapy (CRRT) is the preferred modality because it is associated with a lower risk of cardiovascular instability and cerebral oedema. CRRT effectively decreases ammonia level and, in the last decade, hyperammonaemia has become an increasingly common indication for RRT in ALF independently of the presence of AKI. Several studies suggest that early CRRT improves survival in this setting by preventing severe hyperammonaemia and its associated complications.^{41–43}

Nutritional support and metabolic control

The role of nutritional therapy in ALF is to provide sufficient energy, vitamins, and trace elements, facilitate adequate protein synthesis, and avoid metabolic complications, such as hypoglycaemia and hyperammonaemia.⁴⁴ In patients with ALF with high arterial ammonia levels who are at risk of cerebral

Table 3. General management of acute liver failure.

Organs and systems	General management	Treatment
Brain	Admission and patient monitoring in the ICU (risk of rapid clinical deterioration) Assessment of arterial ammonia Orotracheal intubation in case of grade 3-4 hepatic encephalopathy Non-invasive intracranial pressure monitoring: - Transcranial Doppler ultrasound - Diameter of the optic nerve Invasive intracranial pressure monitoring (exceptional): - Extradural ICP sensor	N-acetylcysteine in all cases of paracetamol overdose and in non-paracetamol ALF with grades 1 or 2 hepatic encephalopathy Deep sedation, RASS -5 No nociceptive stimuli Raise head of bed >30° Core temperature <37 °C Avoid hyponatremia If data of intracranial hypertension: - Mannitol or hypertonic saline solution - Continuous renal therapy to maintain ammonia <100 µmol/L - Barbiturate coma or moderate hypothermia 33-34 °C if refractory intracranial hypertension
Cardiovascular	Invasive blood pressure monitoring in intubated patient Echocardiography	Avoid arterial hypotension Volume resuscitation in hypotensive patients Norepinephrine as the vasopressor of choice Hydrocortisone at stress doses in refractory shock
Respiratory	Reasons for intubation: - Grade 3 or 4 hepatic encephalopathy - Acute respiratory failure - Agitation in a patient requiring transfer to a referral centre	Protective mechanical ventilation • O ₂ saturations 94-98%, • PaO ₂ > 75 mmHg, • PaCO ₂ 34-41 mmHg
Renal	Close analytical and clinical monitoring (urinary output)	Avoid nephrotoxic drugs Early continuous renal replacement therapy
Metabolic and gastrointestinal	Tight glycaemic control (2 h)	Hypertonic glucose (10%-20%) Blood glucose levels: 110-180 mg/dl PPI: stress ulcer prophylaxis Early enteral nutrition (discontinue if worsening of hepatic encephalopathy or of arterial ammonia)
Coagulation	Close analytical monitoring Viscoelastic tests if bleeding or invasive procedures	Correct coagulation abnormalities only if bleeding or before a high-risk invasive procedure.
Infections	Rule out infection: cultures (blood, urine, respiratory secretions), chest X-ray, and urine sediment at admission and whenever patient deteriorates	Potential prophylactic role of selective intestinal decontamination or systemic antibiotics Low threshold to initiate empirical antibiotic therapy

ALF, acute liver failure; ICP, intracranial pressure; ICU, intensive care unit; PPI, proton pump inhibitor; RASS, Richmond agitation-sedation scale.

oedema, nutritional protein support can be deferred for 24–48 h until hyperammonaemia is controlled. When protein administration is started, arterial ammonia should be closely monitored to ensure no pathological elevation occurs.⁴⁵

Hypoglycaemia is a frequent manifestation in patients with ALF due to decreased hepatic glycogen stores and impaired gluconeogenesis and glycogenolysis. Hypoglycaemia can contribute to HE and has been associated with increased mortality; therefore, periodic monitoring of glycaemia is recommended every 6 h¹.

Management of coagulopathy

Global assessment of haemostasis in ALF indicates a “rebalanced” state. Compensatory mechanisms have been identified for each phase of haemostasis. Pro-haemostatic drivers may overcompensate for deficient liver-derived coagulation factors and result in a relative hypercoagulable state.⁴⁶ Therefore, prophylactic transfusion of fresh frozen plasma (FFP) or other blood products is unwarranted and may expose patients to harmful effects, such as volume overload, brain oedema and transfusion reactions, without any clinical benefit.⁴⁷ A recent study by Stravitz *et al.*, identified an association between coagulopathy assessed by rotational thromboelastometry, bleeding events, and mortality in patients with ALF, highlighting the clinical utility of rotational thromboelastometry in this setting.⁴⁸

Prevention and treatment of infections

In patients with ALF, sepsis can manifest at any time in the course of the disease. Early infections are mainly attributed to immune dysfunction, while late episodes are also facilitated by the high degree of instrumentation required in the management of these patients (hospital-acquired infections occurring in the setting of disease progression).⁴⁹ Bacteria implicated in early infections arise from the patient’s normal flora while later infections involve exogenous bacteria and fungi. Most endogenous infections occur within the first week.⁵⁰

The susceptibility to bacterial and fungal infections, sepsis, and septic shock is notably increased in patients with ALF, with infectious complications being a leading cause of death in this setting. Bacterial infections have been documented in 60–80% of patients, most commonly presenting as pneumonia (50%), urinary tract infections (22%), catheter-related bacteraemia (12%), and spontaneous bacteraemia (16%). Infections by multidrug-resistant organisms are associated with a higher incidence of grade 3-4 HE, multiorgan failure, longer hospital stay and a trend towards higher mortality.⁵¹ Fungal infections, largely caused by *Candida* species, occur in about one-third of patients requiring prolonged critical care support.⁵²

The diagnosis of infection in patients with ALF is difficult; the clinical features are non-specific and tests such as C reactive protein and procalcitonin measurements are frequently unhelpful. A high level of clinical suspicion should be maintained.

Empirical broad-spectrum antibiotics should be administered to patients with ALF who have signs of sepsis, persistent hypotension or unexplained progression to higher grades of HE. Antifungal therapy should be considered in patients with prolonged organ support. Use of biomarkers to guide treatment for invasive fungal infections is recommended (serum galactomannan antigen and 1,3- β -D glucan).³ Empiric antibiotics are recommended for patients listed for super urgent LT, since the development of infection and sepsis may prompt delisting.⁵²

Cerebral oedema and intracranial hypertension

Intracranial hypertension is a complication mainly observed in hyperacute forms of ALF, having declined in incidence in recent years (50% in the past vs. 30% in more recent series).⁵³ The two main pathogenic factors are: high ammonia levels leading to astrocyte swelling and systemic inflammation. Patients with more than one of the following: young patients with acute or hyperacute forms, persistent increase in ammonium >150-200 μ mol/L, AKI and norepinephrine >0.1 μ g/kg/min are at higher risk of intracranial hypertension.^{3,54} Clinical monitoring of this complication is essential. Insertion of an ICP sensor, mainly in the extradural space, was frequently used in the past for this purpose. This sensor allows for the continuous evaluation of ICP and the estimation of cerebral perfusion pressure; ICP should be maintained <20 mmHg and cerebral perfusion pressure (CPP) >50 mmHg. This invasive technique has been replaced by non-invasive methods, mainly transcranial Doppler ultrasound of cerebral arteries (cerebral flow, pulsatility index) and by the evaluation of the optic nerve sheath diameter (a measure >0.48 cm is suggestive of intracranial hypertension).⁵⁵ The disadvantage of non-invasive methods is that the information given is discontinuous.

Several measures are applied to prevent cerebral oedema and intracranial hypertension in ALF including facilitating venous drainage (head elevation 30° or more, semiflexed head), avoidance of nociceptive stimuli; control of agitation (sedoanalgesia); avoidance of hyponatremia (serum sodium between 140 and 145 mEq/L), prevention of hypo- and hyperglycaemia and avoidance of fever and hyperhydration.^{3,54} Osmotic therapy with mannitol (0.5-1 g/kg) or hypertonic saline (10-30%) is the first line treatment for intracranial hypertension. CRRT can be used if there is no response to osmotic therapy in the presence of serum ammonia >150-200 mmol/L. Muscle relaxants and moderate hyperventilation (pCO₂ 30-35 mmHg) are other measures that can help to control intracranial hypertension. Second-level interventions, indicated in refractory cases (CPP <50 mmHg, ICP >20 mmHg), are moderate hypothermia (central temperature of 33-34 °C) and barbiturate coma.³² In desperate cases of uncontrolled intracranial hypertension, refractory shock and toxic liver due to massive necrosis, emergent hepatectomy is indicated in some centres, with the aim of achieving a clinical improvement while awaiting an organ.^{3,56}

Liver support systems

Hepatic failure in ALF is reversible in many cases given the huge regenerative capacity of the liver. This explains why liver support systems could have great potential in ALF, as a bridge to liver regeneration or to ELT. These systems should support all liver functions including synthesis, excretion, and

metabolism. Unfortunately, such a system does not exist. The greatest clinical experience is with artificial liver support systems (without liver cells). Albumin dialysis systems (MARS [molecular adsorbent recirculation system] and Prometheus) are based on the scavenger capacity of albumin that is capable of removing water-soluble and albumin-bound toxic substances, which accumulate and promote systemic and hepatic inflammation. Unfortunately, these systems have not been shown to improve survival in ALF and are not recommended in current guidelines.⁵⁷ Bioartificial liver support systems contain hepatocytes in the bioreactor. Published studies performed in the past also failed to show a consistent reduction in mortality.⁵⁸ Currently, bioartificial liver support systems are not available on the market.

TPE is the most effective liver support treatment currently available and the only one indicated according to current guidelines.^{3,34} It is used as a bridge to LT or to spontaneous recovery in cases with good prognosis (paracetamol, hepatitis A virus) and when LT is contraindicated. It has detoxifying and immunomodulatory effects. High-volume plasma exchange (3 plasma volumes) improves transplant-free survival. Recent studies suggest the effectiveness of TPE using lower doses (1.5-2 volumes of plasma) with fewer adverse events. In recent years, TPE has become a routine therapy in patients with ALF in several centres given its effectiveness, safety, ease of use, and low cost compared to other therapies such as albumin dialysis.⁵⁹ It is important to remark that the replacement solution used is FFP. Therefore, INR cannot be used as a prognostic marker after the initiation of TPE.

Liver transplantation for ALF

Selection of candidates for emergency liver transplantation in ALF

The standard clinical approach to the care of the patient with ALF is to deliver supportive critical care to the multiple organ systems involved and identify (and where possible treat) the specific agent responsible for liver injury. In doing so, conditions for native liver regeneration are optimised and with effective regeneration and return of liver function, multiorgan failure will resolve. Prioritised ELT is reserved for those patients in whom sufficient regeneration will not occur and death is inevitable. Since its first introduction, patient outcomes have incrementally improved over time (Fig. 3) reflecting better understanding of the matching of liver grafts with recipients and progressive improvement in pre-, intra-, and post-operative care.^{8,9,60}

Successful utilisation of ELT requires a reliable means of identifying patients who will benefit at an early enough stage (*i.e.* before the severity of their illness precludes surgery). Recipient selection criteria therefore require a rapid result with high accuracy, as the consequences of incorrect selection are huge. A false positive result from a selection test will result in unnecessary transplantation in a patient who would otherwise survive with medical management and loss of a graft from the donor pool. The consequences of a false negative selection test are even greater, resulting in a missed ELT candidate and a likely preventable death.

A number of prognostic systems are in current use and share common features. The presence of HE is generally a prerequisite for consideration for ELT, given that in its absence,

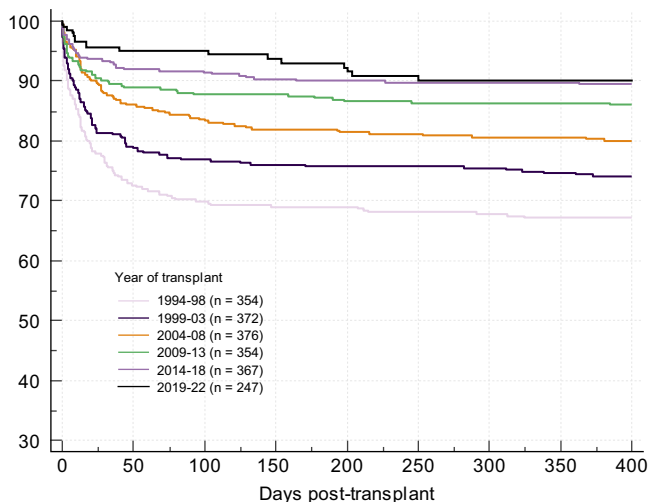


Fig. 3. Patient survival after liver transplantation for ALF, United Kingdom 1994–2022. ALF, acute liver failure.

transplant-free survival (TFS) is generally very good.⁶¹ Criteria then consider severity of liver injury, usually assessed through laboratory measures including bilirubin and coagulation disturbance, as reflected by INR or factor V levels.^{62,63} In some criteria the aetiology of liver injury is also considered, reflecting that for ‘favourable’ causes of liver injury such as paracetamol, TFS may be good despite apparently very severe liver injury, as capacity for native liver regeneration is retained.⁶⁴ In ‘unfavourable’ aetiologies – exemplified by indolent presentations of ALF of indeterminant cause – equivalent measures of liver injury may be associated with a markedly worse TFS.^{65,66} Criterion thresholds triggering consideration for ELT may thus vary by aetiology.

The King’s College criteria (KCC) are amongst the most widely utilised prognostic criteria and illustrate this approach and its strengths and weaknesses (Box 3). They were derived and validated from two large retrospective cohorts of patients with ALF treated without ELT between 1973 and 1986.⁶⁷ The KCC mandate the presence of HE, differentiate between patients with paracetamol-induced hepatotoxicity and other causes of ALF, and utilise basic clinical features and standard laboratory parameters. Initial validation analyses of criteria performance suggested a high specificity such that few cases fulfilling criteria would be unnecessarily transplanted. This performance and apparent simplicity of their clinical application led to their widespread adoption and use. Several meta-

Box 3. The original Kings College criteria.

Non-paracetamol aetiology

Consider transplantation if: encephalopathy and INR >6.7, or any three of: unfavourable aetiology (non-APAP DILI, indeterminate), acute/sub-acute presentation, bilirubin >300 µmol/L, INR >3.5

Paracetamol aetiology

Consider transplantation if: arterial pH <7.3 after adequate intravenous volume resuscitation or concurrent findings of: HE ≥ Grade 3, creatinine >300 µmol/L, INR >6.5

Source: 64.

analyses have subsequently assessed criteria performance. One of the largest assessed 23 studies comprising 2,153 patients from 1983–2012 and demonstrated high pooled specificity (79%, 95% CI 77–81%) but lower pooled sensitivity (59%, 95% CI 56–62%).⁶⁸ Subgroup analyses found these findings to be consistent when exploring key confounding factors including size and quality of studies, inclusion/exclusion of transplanted patients as ‘non-survivors’ and the era of the cases reported.^{68,69}

Issues in practical application

The widespread use of the KCC has made apparent some issues in their practical application. What constitutes ‘adequate intravenous fluid administration’ in paracetamol ALF is difficult to quantify and will have significant impact on both KCC parameters of arterial pH and blood lactate concentration. Both may also be modulated by very high concentrations of circulating paracetamol early after overdose, through its impact on mitochondrial function that may precede hepatocellular necrotic injury by many hours.^{70,71} Further, the clinical and laboratory features of an unintentional, staggered overdose may differ significantly from those of single time-point consumption.⁷²

Medical interventions may also act as confounders and affect the variables assessed. The administration of sedation may make assessment of HE severity difficult, and RRT will affect both arterial pH and blood creatinine concentration. Administration of blood products such as FFP or TPE will artefactually alter the INR and factor levels.^{34,73} Finally, ALF may be a dynamic and rapidly progressive illness and patient’s condition, and clinical and laboratory features, may change for better or worse over hours.⁷⁴

Alternative and supplementary predictive scores and biomarkers

To address the shortfalls in the diagnostic performance of the KCC, proposals have included its replacement with alternate scoring systems and/or the supplemental inclusion of standard laboratory variables or non-standard biomarkers most often reflecting hepatic injury, and less commonly regeneration or severity of multiorgan failure.^{75,76} To date, most reports of their performance are in cohorts of limited size and are subject to the systematic limitations in assessment as outlined above.⁶⁹ External validation has been limited for most, and many of the non-standard biomarkers are not measured in routine clinical laboratory settings. Examples of different approaches are presented in Table 4.

With the exception of arterial blood lactate measurement, few have been widely adopted. Lactate has the advantage of being routinely, rapidly and accurately measured in most critical care settings and persistent elevation is closely related to poor outcomes in many critical illnesses.⁷⁰ In 2002, blood lactate was proposed for inclusion into the KCC to address their limited sensitivity.⁷⁸

The UK revised criteria

In the UK, the ELT selection criteria have been revised and recalibrated, recognising marked improvements in TFS over

Table 4. Illustrative alternative systems and biomarkers for mortality prediction in acute liver failure.

Criteria	Era	Aetiology	Cases assessed	Diagnostic performance*	Comment
SOFA score	1993-2010	APAP	125	Sensitivity 0.67, specificity 0.80	MOF scoring system ⁷⁷
ALFSG model	1998-2013	All	1,974	Sensitivity 0.37, specificity 0.95	Combined clinical criteria ⁶⁵
Arterial lactate	1998-2000	APAP	210	Sensitivity 0.81, specificity 0.97	Addition to original KCC ⁷⁸
MELD	2001-2015	All	2,153	AUROC 0.78	Meta-analysis ⁶⁸
Dynamic	2004-2014	APAP	762	AUROC 0.91	Dynamic clinical model ⁷⁴
MicroRNA	1998-2014	APAP	194	AUROC 0.83	Regeneration biomarker model ⁷⁹
FABP1	1998-2014	APAP	198	AUROC 0.82	Cellular injury biomarker ⁸⁰
Factor V	2001-2017	All	90	AUROC 0.86	Coagulation factor ⁸¹
IL-10	2007-2009	APAP	51	AUROC 0.92	Immunoparesis biomarker ⁸²
M-30	2010-2012	APAP	26	Sensitivity 0.89, specificity 0.61	Apoptosis biomarker ⁸³
¹³ C-MBT	2016-2019	All	62	AUROC 0.88	Hepatic metabolic function test ⁸⁴

¹³C-MBT, ¹³C-methacetin breath test; ALFSG, Acute Liver Failure Study Group; APAP, acetaminophen; FABP1, fatty acid binding protein 1; IL-10, interleukin 10; M-30, caspase cleaved cytokeratin-18; MELD, model for end-stage liver disease; MOF, multiorgan failure; SOFA, sequential organ failure assessment score.

*diagnostic performance in discriminating survivors and non-survivors.

Box 4. The United Kingdom revised ELT selection criteria for acute liver failure in adults.

Category 1

Paracetamol: pH <7.25 more than 24 hours after overdose and after fluid resuscitation.

Category 2

Paracetamol: co-existing INR >6.5, creatinine >300 µmol/L or anuria, and grade 3–4 HE

Category 3

Paracetamol: significant liver injury and coagulopathy following exclusion of other causes of hyperlactatemia (e.g. pancreatitis, intestinal ischaemia) after adequate fluid resuscitation: Arterial lactate >5 mmol/L on admission and >4 mmol/L 24 hours later in presence of HE.

Category 4

Paracetamol: two of the three criteria from category 2 with clinical evidence of deterioration (e.g. increased ICP, FiO₂ >50%, increasing inotrope requirements) in the absence of clinical sepsis.

Category 5

Favourable non-paracetamol aetiologies such as acute viral hepatitis or ecstasy/cocaine-induced ALF: the presence of clinical hepatic encephalopathy is mandatory and: prothrombin time >100 seconds, or INR >6.5, or any three from the following: age >40 or 50 seconds or INR >3.5; any grade of hepatic encephalopathy with jaundice to encephalopathy time >7 days; serum bilirubin >300 µmol/L.

Category 6

Unfavourable non-paracetamol aetiologies such as seronegative or idiosyncratic drug reactions: a) prothrombin time >100 seconds, or INR >6.5, or b) in the absence of clinical hepatic encephalopathy then INR >2 after vitamin K repletion is mandatory and any two from the following: age >40 or 50 seconds or INR >3.5; if hepatic encephalopathy is present then jaundice to encephalopathy time >7 days; serum bilirubin >300 µmol/L.

Category 7

Acute presentation of Wilson's disease, or Budd-Chiari syndrome. A combination of coagulopathy, and any grade of encephalopathy.

ELT, emergency liver transplantation.

time in some aetiologies of ALF, and increased confidence in the poor prognosis of others (Box 4).^{8,85,86} These UK Revised Criteria (UKRC), though based around the original KCC, now have seven categories, and include new thresholds for key

variables. Recognising the issues in their application, specific guidance is now offered about their interpretation: By example, for the paracetamol criteria, arterial pH thresholds have been lowered and those for blood lactate increased, with specific guidance on their utilisation and interpretation. A further transplant criterion (selection category number 4) has been introduced to give more scope for clinical judgement, recognising that some patients may die without fulfilling the standard criteria. For non-paracetamol cases different laboratory marker thresholds are now provided for favourable and unfavourable causes, and waitlisting is now permitted for some specific cases in advance of the onset of HE (i.e. idiopathic aetiology or idiosyncratic drug reactions with gradual illness onset, deep jaundice and significant coagulopathy and shrinking liver volume). External validation of the UKRC has been limited, but to date the indications are of good performance, with maintained specificity and enhanced sensitivity.

Transplant selection criteria and cases transplanted

It is important to recognise that fulfilling ELT selection criteria may identify a patient with poor survival without ELT, but it does not identify those who will tolerate the procedure or have acceptable longer term post-transplant survival. The principal determinants of recipient survival after ELT are age – with an upper threshold of 40-50 years – the severity of multiorgan failure, and the use of a sub-optimal graft.^{87–89} Impaired early graft function is poorly tolerated by critically ill recipients and predisposes to sepsis, the most common cause of early post-ELT death. Many potential recipients may have an underlying comorbidity or acute abdominal complications contraindicating surgery, meaning that ELT may never be an option for them. Other contra-indications include active sepsis or fungal infection, irreversible brain injury from intracranial hypertension, and overwhelming multiorgan failure. Thresholds for the latter must be individualised and take into account candidate age and underlying physical condition – though respiratory failure or high-level vasopressor dependence are a particular concern. Multiorgan failure is generally more severe in cases of paracetamol-related ALF who are more likely to be removed from the waitlist due to deterioration.^{9,64} A particular challenge is the patient who has been waitlisted for ELT after fulfilling poor prognosis criteria and is now showing signs of

improvement: is it better to proceed with transplantation or to remove from the waitlist? Paradoxically, this is also a particular issue for paracetamol-induced ALF, wherein native liver recovery is still possible even in the setting of severe multiorgan

failure, and decision-making must be individualised. In more unfavourable aetiologies decision-making is more straightforward and removal from the waitlist is seldom undertaken.

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Abbreviations

AIH, autoimmune hepatitis; AKI, acute kidney injury; ALF, acute liver failure; ALI, acute liver injury; CRRT, continuous renal replacement therapy; DILI, drug-induced liver injury; ELT, emergency liver transplantation; FFP, fresh frozen plasma; HBV, hepatitis B virus; HE, hepatic encephalopathy; HELLP, haemolysis, elevated liver enzymes and low platelets; HEV, hepatitis E virus; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalised ratio; KCC, King's College criteria; RASS, Richmond agitation-sedation scale; RRT, renal replacement therapy; TFS, transplant-free survival; TPE, therapeutic plasma exchange; UKRC, UK Revised criteria.

Financial support

The authors did not receive any financial support to produce this manuscript.

Conflict of interest

The authors of this study declare that they do not have any conflict of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed equally to this work by writing the assigned sections. Sections were suggested by JF and approved by DT, OB and WB.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2024.101131>.

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Author names in bold designate shared co-first authorship

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Keywords: prognosis; mortality; liver transplantation; liver support; intracranial hypertension.

Received 18 March 2024; received in revised form 17 May 2024; accepted 22 May 2024; Available online 10 June 2024