ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2021 June 18; 11(6): 147-253

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

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NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Monthly

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PUBLICATION DATE
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World J Transplant 2021 June 18; 11(6): 187-202

DOI: 10.5500/wjt.v11.i6.187

ISSN 2220-3230 (online)

MINIREVIEWS

Liver transplantation in acute liver failure: Dilemmas and challenges

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Author contributions: Kumar R designed and wrote the manuscript, and collected relevant data; Anand U and Priyadarshi RN contributed in data collection and manuscript writing; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest for this article.

Manuscript source: Invited manuscript

Specialty type: Transplantation

Country/Territory of origin: India

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Abstract

Acute liver failure (ALF) refers to a state of severe hepatic injury that leads to altered coagulation and sensorium in the absence of pre-existing liver disease. ALF has different causes, but the clinical characteristics are strikingly similar. In clinical practice, however, inconsistency in the definition of ALF worldwide and confusion regarding the existence of pre-existing liver disease raise diagnostic dilemmas. ALF mortality rates used to be over 80% in the past; however, survival rates on medical treatment have significantly improved in recent years due to a greater understanding of pathophysiology and advances in critical care management. The survival rates in acetaminophen-associated ALF have become close to the post-transplant survival rates. Given that liver transplantation (LT) is an expensive treatment that involves a major surgical operation in critically ill patients and lifelong immunosuppression, it is very important to select accurate patients who may benefit from it. Still, emergency LT remains a lifesaving procedure for many ALF patients. However, there is a lack of consistency in current prognostic models that hampers the selection of transplant candidates in a timely and precise manner. The other problems associated with LT in ALF are the shortage of graft, development of contraindications on the waiting list, vaguely defined delisting criteria, time constraints for pre-transplant evaluation, ethical concerns, and comparatively poor post-transplant outcomes in ALF. Therefore, there is a desperate need to establish accurate prognostic models and explore the roles of evolving adjunctive and alternative therapies, such as liver support systems, plasma exchange, stem cells, auxiliary LT, and so on, to enhance transplant-free survival and to fill the void created by the graft shortage

Key Words: Acute liver failure; Fulminant hepatic failure; Prognosis; Kings college criteria; Liver transplantation; Acetaminophen

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 1, 2021
Peer-review started: February 1, 2021
First decision: March 8, 2021
Revised: March 17, 2021
Accepted: May 24, 2021
Article in press: May 24, 2021
Published online: June 18, 2021

P-Reviewer: Dabos KJ
S-Editor: Fan JR
L-Editor: A
P-Editor: Yuan YY

Core Tip: Liver transplantation (LT) is a lifesaving procedure for patients with acute liver failure (ALF). Its use, however, is constrained by the absence of reliable prognostic models that hampers the selection of transplant candidates in a timely and precise manner. The survival of medically treated ALF patients has increased over time, but the criteria for LT remain the same. No clear advantage of LT in acetaminophen-associated ALF appears to be present. The other problems associated with LT in ALF are diagnostic dilemmas, shortage of graft, waiting list contraindications, vaguely defined delisting criteria, pre-transplant assessment time limits, ethical concerns, and comparatively poor post-transplant outcomes. Therefore, there is a desperate need to establish accurate prognostic models and explore the roles of alternative therapies to enhance transplant-free survival and fill the gap produced by the shortage of graft.

Citation: Kumar R, Anand U, Priyadarshi RN. Liver transplantation in acute liver failure: Dilemmas and challenges. *World J Transplant* 2021; 11(6): 187-202
URL: https://www.wjgnet.com/2220-3230/full/v11/i6/187.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i6.187

INTRODUCTION

The term "acute liver failure" (ALF) refers to a condition of severe hepatic injury that leads to altered coagulation and sensorium in the absence of pre-existing liver disease [1]. This disorder was first named fulminant hepatic failure in 1970, a term that has now been largely dismissed[2]. The main features of ALF are jaundice, coagulopathy, and hepatic encephalopathy (HE) while other features include cerebral edema (CE), susceptibility to infection, shock, and multi-organ dysfunction. Drug-induced liver damage is the commonest cause of ALF in developed countries while viral hepatitis tends to comprise the majority of ALF cases globally[3]. ALF is characterized by remarkably similar clinical characteristics, despite having diverse causes.

The mortality rates of ALF used to range between 80% and 85% before the liver transplantation (LT) era[4]. In recent years, however, ALF survival rates have greatly increased because of improvements in critical care management[1,3]. Approximately half of the patients still die without emergency LT, and thus, LT plays a very important role in the management of ALF. However, LT is not widely available, and in most centers, ALF accounts for < 10% of the LT indication[5,6]. LT is an expensive therapy that requires a major surgical procedure and lifelong immunosuppression. Intraoperative and post-operative treatments are challenging in ALF patients, and survival rates are consistently lower than those associated with elective LT. In addition, there is a need to balance the risks of emergency LT in ALF patients against survival with medical care alone. In order to choose suitable candidates for LT and prevent avoidable LT, it is necessary to have a prognostic model that can predict the outcomes early and very accurately. To date, while many clinical and laboratory parameters have been found to predict outcomes in patients with ALF, in terms of accuracy, early applicability, and ease of evaluation, virtually, none is close to optimal [7]. The rarity and heterogeneity of ALF have resulted in very few evidence-based management guidelines, and these guidelines essentially represent expert opinions. In this review article, the current dilemmas and challenges in the field of ALF have been addressed with regard to the therapeutic decision, and potential directions for further research have also been proposed.

DIAGNOSTIC DILEMMAS IN ALF

In the early 1970s, Trey and Davidson originally identified ALF as a fulminant hepatic failure and defined it as "a severe liver injury, potentially reversible in nature and with onset of HE within 8 wk of the first symptoms in the absence of pre-existing liver disease"[2]. Many revised definitions have subsequently been proposed. There is,

however, no definitive consensus to date. In addition, in clinical practice, diagnostic dilemmas are frequently caused by ALF-mimicking infections, uncertainty about the presence of pre-existing liver disease, confusion over HE, and variations in international normalized ratio (INR) testing.

ALF: One disease, many definitions

A systematic analysis of 130 published ALF studies has identified a substantial variability in the definition of ALF. Over 81 studies have used 41 different ALF definitions, and no clear definition has been reported in the remaining 16 studies[8]. Currently, the most widely accepted ALF definition is "the occurrence of severe acute liver injury (ALI) with any degree of HE and INR of 1.5 or greater in a patient without pre-existing liver disease and a period of illness of < 26 wk"[9]. However, the icterus-encephalopathy interval is still considered to be < 4 wk to describe ALF in the Indian subcontinent[10]. Such a wide diversity in ALF definitions hinders comparability among studies. Thus, there is an unmet need for a widely agreed definition of ALF in order to facilitate standardized clinical management and research in ALF patients.

Acute vs acute-on-chronic dilemmas

The absence of underlying chronic liver disease (CLD) is a criterion for the diagnosis of ALF. Nevertheless, ALF is primarily a clinical diagnosis where the absence of CLD is presumed without sufficient investigation support. Radiological imaging may not detect early changes of CLD when a significant alteration in liver morphology is absent. In addition, a collapse of hepatic sinusoids, systemic vasodilation, and hyperkinetic circulation in ALF may contribute to the development of significant portal hypertension and ascites, making it difficult to rule out the underlying CLD[11, 12]. Differentiating ALF from the more common entity, acute-on-chronic liver failure (ACLF), can also become complicated at times in the real-world scenario. In a study carried out on 54 patients, the presumed clinical diagnosis of ALF has altered in 16.7% (9 out of 54) patients after transjugular liver biopsy[13]. On the other hand, there are some exceptions, such as Wilson's disease, autoimmune hepatitis, and Budd-Chiari syndrome, where ALF diagnosis is acceptable despite the presence of underlying CLD [1]. Also, there is no consensus-based clarity as to whether ALF or ACLF should be considered in patients with non-alcoholic fatty liver disease or chronic viral hepatitis who present with liver failure.

ALF-mimicking infections

Jaundice, coagulopathy, and altered mentation that can mimic ALF may occur with many infectious diseases, such as dengue, malaria, enteric fever, leptospirosis, rickettsial infection, cytomegalovirus infection, herpes simplex virus infection, or tuberculosis[14]. However, the liver injury in these conditions is usually secondary. To allow a diagnosis of ALF, there should be a primary liver insult, and coagulopathy and altered sensorium should be attributed to liver disease *per se*, which can be difficult at times to decide. On the one hand, several non-hepatotropic viruses, such as dengue and herpes simplex, can cause severe hepatic damage leading to ALF, and on the other hand, common hepatotropic viruses can have mainly systemic manifestations of the extra-hepatic disease[15]. Such a diagnostic dilemma may not be so uncommon in the tropical world.

Uncertainty about HE

For making a diagnosis of ALF, HE is necessary to be clinically manifested. However, there is a lack of a well-validated and standardized assessment tool for early diagnosis and grading of HE. Several scales have been developed for this purpose, and the most often used is the West Haven criteria (WHC), which differentiate overt HE between four grades[16]. The subjectivity and considerable interobserver variability of the WHC, however, hinder low-grade HE assessments. Modified versions of WHC are suggested; however, external validation is lacking[17,18]. As patients who develop coagulopathy without evidence of HE are defined as having ALI, efforts should be made to develop more sensitive measures to detect early grades of HE in order to distinguish between ALI and ALF. In infants and young children, however, ALF can be diagnosed in the absence of HE if a greater degree of coagulopathy (INR of > 4) is present[1].

Variation in INR testing

INR has been developed as a tool to assess the efficacy of vitamin-K antagonist therapy. However, it is also used to assess the degree of coagulopathy in patients with

liver disease, including ALF. INR is calculated after adjusting the prothrombin time value with a correction factor applied to adjust for differences in sensitivity of instrument and reagent. While INR testing has been available for decades, a significant interlaboratory variance continues to exist[19,20]. The variations in the combination of thromboplastin and instrument and correction values assigned to different reagents as used by various laboratories are the key reasons for the interlaboratory variance in INR testing. Since INR is used not only to define ALF but also to prognosticate it, patient assessment and management can be seriously affected by such laboratory variability.

IMPROVED SURVIVAL ON MEDICAL TREATMENT

Over the past 30 years, ALF has been transformed from a poorly known condition with a near-fatal outcome to one with a well-characterized phenotype and improved outcome. The ALF survival rate has improved dramatically in recent years due to a better understanding of pathophysiology and improvements in critical care management[1,3,4]. A substantial decrease in the incidence of CE and intracranial hypertension, a much-feared complication, has been observed over time, which may be attributed to earlier identification of the condition and better initial care[21]. The liver has an immense regenerative capacity, rendering ALF a potentially reversible disease in which survivors usually recover completely without sequelae. Therefore, intensive supportive care during the acute event, with particular attention to the prevention and treatment of fatal complications, such as CE and infection, can increase the likelihood of transplant-free survival (TFS).

The most significant determinant of TFS in patients with ALF appears to be the cause of liver injury[1,22]. Causes with favorable TFS include paracetamol (75%), hepatitis E virus (56%), hepatitis A virus (56%), and ischemic liver injury (74%). On the other hand, hepatitis B virus (26%), drug-induced liver injury (41%), autoimmune hepatitis (25%), and indeterminate causes (37.5%) are associated with poor TFS rates[1,23,24]. The survival rates in acetaminophen-associated ALF (AALF) have become very close to the post-transplant survival rates. In a prospective cohort study that included 2070 ALF patients over 16 years from 31 transplant centers in the United States, 21-d TFS rates increased throughout the 16-year period. The TFS was 45.1% during the period 1998 to 2005 and 56.2% during the period 2006 to 2013[22]. While the improved survival rate on medical treatment has reduced the need for emergency LT in many patients with ALF, the challenge for the clinician to recognize patients who cannot live without a transplant has greatly increased.

PROGNOSTICATING THE OUTCOMES IN ALF PATIENTS

Recognizing the feasibility of LT in ALF in the 1980s, the need for prognostic markers to determine the subset of patients most likely to benefit from this procedure emerged. In order to select an appropriate patient for LT and prevent avoidable LT, it is necessary to have a very precise prognostic model. The fundamental requirements of a prognostic model in the context of ALF are accuracy, early applicability, and ease of evaluation. When selecting a candidate for LT, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the prognostic model are important determinants. Sensitivity and PPV preferences ensure that all patients who require a transplant receive it whereas a preference for specificity and NPV minimizes unnecessary LT. From time to time, a large number of prognostic markers and models have been proposed so that patients predicted to have poor outcomes can be directed toward LT (Table 1). The King's College Criteria (KCC), Model for End-Stage Liver Disease (MELD) score, and Clichy criteria are the most commonly used and studied criteria.

KCC

The KCC developed in 1989 is the most thoroughly studied and widely used criteria. Owing to variations in the characteristics of parameters correlating with prognosis, the criteria are stratified into AALF and non-acetaminophen-associated ALF (NAALF). The performance of KCC was evaluated in patients with NAALF by a meta-analysis of 18 studies with data on 1105 patients[25]. The pooled sensitivity and specificity were 68% and 82%, respectively. This means that up to 32% of ALF patients who die may

Table 1 Prognostic scoring systems for patients with acute liver failure

Prognostic model/marker	Parameters included	Predictive values	Remarks/drawbacks
KCC[25,26]	Age, INR, serum bilirubin, icterus-encephalopathy interval, drug toxicity	For NAALF, Pooled Sn and Sp are 68% and 82%, respectively. For AALF, Pooled Sn and are 58.2% and 94.6%, respectively	Major limitation is poor sensitivity, only 58% in recent studies (after 2005). Perform better with advanced HE which is a late event. Combining lactate with the KCC improves sensitivity but reduces specificity
MELD score[34,37]	Serum bilirubin, serum creatinine and INR	For NAALF, DOR, Sn, and Sp of MELD scores > 30 are 8.42, 76%, and 73%, respectively. For AALF, DOR, Sn, and Sp of MELD scores > 30 are 6.6, 80%, and 53%, respectively	The discriminatory cut-offs and predictive values vary across the studies. Laboratory variations in the determination of serum bilirubin, creatinine and INR
Clichy criteria[38]	Advanced HE with factor V levels < 20% in patients < 30 years and < 30% in patients ≥ 30 yr	For NAALF, Sn 69%, Sp 50%, PPV 64%, and NPV 55%. For AALF, Sn 75%, Sp 56%, PPV 50%, and NPV 79%	Inferior to KCC and MELD in validation studies. Poor Sp and PPV. Factor V level assay is not a routine parameter
Arterial ammonia[51,52]	Baseline arterial ammonia > 124 mol/L	Sn 78.6%, Sp 76.3%, and DA 77.5%	Ammonia levels can be influenced by renal impairment, sepsis, bleeding, haemolysis, drugs *etc*. Not validated at LT centres. Persistent hyperammonemia is better predictor, but decision is delayed[52]
Blood lactate[28]	Post-resuscitation arterial lactate cut-off 3.0 mmol/L in AALF	Sn 76%, Sp 97%, PLR 30, and NLR 0.24	Variability in the timing of lactate measurements. Contradictory results with regard to its performance in NAALF
Serum phosphate[43,54]	Level of 1.2 mmol/L at 48 to 96 h after acetamenophen overdose	Sn 89%, Sp 100%, PPV 100%, and NPV 98%	Such results could not be replicated in subsequent studies[43]
Serum Gc globulin[53]	A cut-off level of 80 mg/L in the NAALF	Sn 49%, Sp 90%, PPV 85%, and NPV 43%	Poor sensitivity and NPV. Lacks validation studies
Cytokeratin 18-based modification of the MELD[55]	CK18 M65, INR, MELD. A baseline cut-off of 53.5 modified MELD	Sn 81%, Sp 82%, PPV 65%, and NPV 91%	Reported to be better than MELD and KCC, but lack validation studies
APACHE II[46]	Multiple parameters. APACHE II >15	Sn 82% and Sp 98% for AALF	Not specific to liver disease. Lacks validation studies. Cumbersome for routine clinical use
SOFA[45]	SOFA score of > 6 by 72 h post-acetamenophen overdose	Sn 90%, Sp 69%, PPV 42%, and NPV 96% for AALF	Not specific to liver disease. Relatively lower specificity and PPV. Difficulties in calculating the neurological component in intubated patients
Monocyte HLA-DR expression[50]	Monocyte HLA-DR expression 15% or less in AALF	Sn 96%, Sp 100%, DA 98%	Lacks validation studies. Reduction in monocyte HLA-DR expression was not associated with outcome in NAALF
BiLE score[49]	Bilirubin, lactate, and etiology	Sn 79% and Sp 84%	Scores derived from retrospective analysis. No validation study
ALFED model[27]	Over 3 d values of arterial ammonia, serum bilirubin, INR, and advanced HE	AUROC for ALFED: 0.92. ALFED score of ≥ 4 had a PPV 85% and NPV 87%	Needs further validation. Decision will be delayed. Patients died before 3 d were excluded from analysis. Advanced HE is a late feature
ALFSG index[47]	Coma grade, INR, serum bilirubin and phosphorus levels, and log(10) M30	Sn 85.6% and Sp 64.7%	Requires additional laboratory testing and costs for M30. Found better than MELD and KCC, but requires validation studies

AALF: Acetaminophen-associated acute liver failure; ALFED: Acute liver failure early dynamic; ALFSG: Acute liver failure study group; APACHE: Acute physiology and chronic health evaluation; AUROC: Area under receiver operating characteristic; DA: Diagnostic accuracy; DOR: Diagnostic odds ratio; INR: International normalized ratio; KCC: King's college criteria; MELD: Model of end stage liver disease; NAALF: Non-acetaminophen-associated acute liver failure; NPV: Negative predictive value; PPV: Positive predictive value; Sn: Sensitivity; Sp: Specificity; SOFA: Sequential organ assessment score; HE: Hepatic encephalopathy.

not fulfill the KCC, and 18% of patients who can survive without a transplant will meet the KCC. Thus, the fulfillment of the KCC may be an indication for LT, but lack of fulfillment does not ensure survival. The sensitivity of the KCC was even worse (58%) in studies published after 2005, further reducing the utility of this model in current clinical practice[25]. The reduced performance of the KCC in recent studies may be due to improvement in medical management. The specificity of the KCC was clinically acceptable (82%); it further improved when the KCC was dynamically

applied in the clinical course (88%) and when consideration was given to patients with only high-grade HE (93%). Nevertheless, the assessment of the grades of HE is subjective, and waiting for patients to develop advanced HE before deciding on LT may reduce the chance of a successful outcome. Furthermore, many ALF patients may become medically unfit for surgery by the time they fulfill the KCC[5].

In a meta-analysis of 14 studies (n = 1960) evaluating the performance of the KCC in AALF, the pooled specificity was good (94.6%), but the pooled sensitivity was only 58.2%[26]. It has been proposed that the KCC should not be used as a static model but rather as a dynamic model. However, it is not clear at what point in time a decision on LT should be made. In a large prospective study from India, 25.7% of ALF patients died without meeting the KCC at baseline, and 42% of ALF patients who died never met the KCC by day 3 of hospitalization[27]. The poor performance of the KCC in that series could be due to the preponderance of viral etiology and hyperacute liver failure.

The KCC has been modified to incorporate other parameters, such as blood lactate and phosphate, in order to increase diagnostic accuracy. But the results are not so promising. Bernal *et al*[28] reported that the addition of post-resuscitation lactate concentrations (30 mmol/L) to the KCC improves the speed of identification, sensitivity, and negative likelihood ratio but decreases the positive likelihood ratio. While this will reduce the proportion of patients who die without being identified as transplant candidates, the proportion of patients who do not need LT may increase [28]. Schmidt and Larsen[29] reported that applying the blood-lactate-modified KCC in patients with AALF increases their sensitivity but reduces their specificity to < 50%, showing no clear advantages over the existing KCC[29]. Chung *et al*[30] reported that the addition of serum phosphate to KCC does not offer any significant advantages[30].

MELD Score

The MELD scoring system was initially designed to assess the probability of short-term mortality in patients with cirrhosis. Subsequently, this score was also adopted to assess the mortality in patients with ALF and determine organ allocation by the United Network of Organ Sharing (UNOS)[31-35]. Yantorno *et al*[35] found that in 94% of ALF patients who died without LT, the MELD score was > 30 while it was < 30 in 91% of patients who survived with medical therapy alone[35]. Some studies indicate that the MELD score is superior to the KCC to determine the prognosis in patients with ALF[35,36], but many others do not[32,33]. In a prospective trial assessing the performance of the MELD score in patients with AALF (n = 124), a score of 33 had sensitivity, specificity, PPV, and NPV of only 60%, 69%, 65%, and 63%, respectively. Moreover, to predict mortality, the MELD score was not superior to KCC or even INR alone[33]. Katoonizadeh *et al*[33] found that an MELD score of > 30 had a high NPV (91%) in NAALF patients, but the PPV was unacceptably poor (56%)[32]. A very high MELD score cutoff of > 35 discriminates between survivors and non-survivors with a sensitivity of 86% but with a low specificity of 75%[33]. Thus, the discriminatory cutoffs and predictive values of the MELD scores vary across the studies. In addition, various laboratory methods and reagents for the determination of bilirubin, creatinine, and in particular, INR can result in a considerable variation of the MELD score, thereby affecting its performance in routine practice.

In a recent meta-analysis of 23 studies (n = 2153) published between 2001 and 2015 that compared the accuracy of the KCC with MELD scores in predicting ALF mortality, none of the two scoring systems was optimal for all patients[37]. The KCC predicted hospital mortality more accurately among patients with AALF while the MELD score was better for NAALF. In patients with AALF, the diagnostic odds ratios (DOR), sensitivity, and specificity of KCC were 10.4%, 58%, and 89%, respectively, whereas the corresponding values of the MELD scores were 6.6%, 80%, and 53%, respectively. In contrast, for patients with NAALF, the DOR, sensitivity, and specificity of the KCC were 4.16%, 58%, and 74%, respectively, whereas the corresponding values of the MELD scores were 8.42%, 76%, and 73%, respectively.

Clichy criteria

In 1986, Bernuau *et al*[38] found that serum levels of factor V, alpha-fetoprotein, age, and absence of serum HBsAg were independent predictors of survival in a cohort of 115 patients with hepatitis-B-related ALF[38]. Originating from this study, Bismuth *et al*[39] used the so-called "Clichy criteria" to select ALF patients for LT at a liver center in Paris between 1986 and 1991[39]. The criteria predicted poor prognosis in ALF when patients had advanced HE and factor V levels < 20% in patients < 30 years of age and < 30% in patients ≥ 30 years of age[39]. The Clichy criteria are mainly used in France to determine the prognosis of ALF patients. Subsequent validation studies, however, showed that the Clichy criteria were not only less accurate than originally stated but

also less reliable to predict outcomes than KCC[40,41]. A recent study evaluated the performance of Clichy criteria retrospectively in 808 adult ALF patients listed in France for super-urgent LT between 1997 and 2010. The sensitivity, specificity, PPV, and NPV were 75%, 56%, 50%, and 79%, respectively, for AALF, and 69%, 50%, 64%, and 55%, respectively, for NAALF[42]. In that study, 13.9% of listed patients withdrew from the waiting list because their condition improved subsequent to listing. The limited specificity and PPV of the Clichy criteria can increase the risk of unnecessary transplantation.

Arterial blood lactate

In ALF, hyperlactatemia may indicate the severity of the hepatic injury as well as multi-organ dysfunction[29]. A number of studies have shown that hyperlactatemia is associated with death or LT in both AALF and NAALF[26,43]. However, there has been substantial variability in the timing of lactate measurements and fluid resuscitation procedures at different centers, making it more difficult to draw a uniform conclusion[43]. In AALF, where the duration of illness is short and multi-organ failure dominates the clinical course, the lactate level may have a better prognostic value. For NAALF, however, there are only a few studies with contradictory results available[44].

Non-liver-specific scoring systems

The prognostic roles of non-liver-specific scoring systems, such as sequential organ failure assessment (SOFA) score and the acute physiology and chronic health evaluation II (APACHE II), are also assessed in ALF patients. In a retrospective study, the SOFA score was found to be prognostically superior to the MELD score at both 72 and 96 h after acetaminophen overdose[45]. In addition, a SOFA score of > 6 by 72 h post-acetaminophen overdose predicted death or transplantation with an NPV of 96.9%. In a prospective study on 102 ALF patients, an APACHE II score of > 15 had a similar power to predict death or LT as the KCC (sensitivity 82% or 65%, respectively, and specificity 98% or 99%, respectively). On the first day, an APACHE II score of > 15 was able to identify four more patients than the KCC[46]. More studies are needed to validate these findings before they can be used in routine practice.

Other prognostic scores

The United States Acute Liver Failure Study Group (ALFSG) has developed a prognostic index for ALF based on the combination of clinical markers and levels of M30, an apoptosis biomarker[47]. In the ALFSG index, coma grade, INR, serum levels of bilirubin and phosphorus, and log(10) M30 values at study entry correctly identified patients, who would need an LT or die, with a sensitivity of 85.6% and specificity of 64.7%. However, the M30 measurement requires additional laboratory testing and costs. Moreover, this model was subsequently found to be inferior to the APACHE II and SOFA scores[48]. The ALF early dynamic model, which is based on dynamic values of arterial ammonia, serum bilirubin, INR, and advanced HE over 3 d, has been shown to have an excellent accuracy in predicting the outcomes of ALF patients[27]. The findings, however, require further confirmation. Similarly, the prognostic role of BiLE score, reduced monocyte HLA-DR expression, and arterial hyperammonemia requires further validation studies[49-52]. Serum level of Gc-globulin also predicted mortality in patients with ALF but with poor sensitivity (49%) and NPV (43%)[53]. Serum phosphate concentration of 1.2 mmol/L at 48-96 h after acetaminophen overdose was found to be very accurate in predicting mortality; however, similar results could not be replicated in the subsequent studies[43,54]. It was also found that the cytokeratin-18-based MELD score modification was better than the MELD scores and KCC, but there were no validation studies[55].

Limitations of prognostic scores for ALF

While several prognostic scores have been established to predict outcomes in ALF patients, virtually, none are close to the ideal yet (Table 2). The most prognostic models that are used worldwide today have features derived from analyses of historical patients treated without LT. In addition, in studies assessing the prognosis of ALF patients, there is gross variation in the definitions of ALF, etiologies, and management protocol. The survival rates of ALF patients on medical treatment have increased in recent years, but the models (*e.g.*, the KCC and MELD) used are still the old ones[25]. Many studies have equated transplanted patients with non-survivors; this may falsely increase the PPV of prognostic scores. While some prognostic scores have shown better performance than the KCC and/or MELD scores, reproducibility and validation studies are lacking. Dynamic models are better than models based on

Table 2 Problems with prognostic scoring systems in acute liver failure

Sr No	Issues	Remarks
1	All available prognostic scoring systems have limited accuracy	Error of both commission and omission can happen
2	Heterogeneity in the studies evaluating prognosis in ALF: Variations in the definitions of ALF, etiologies, & management protocol	The heterogeneity makes it difficult to compare the results between studies and draw a uniform conclusion
3	Survival rates of ALF patients on medical treatment have improved but models used are still the old ones	Reduced performance of old models (*e.g.*, KCC) have been noted in the newer studies compared to the old ones
4	Many studies have considered and analyzed transplanted patients as 'non-survivors'	This may falsely elevate the positive predictive value of a prognostic, increasing the risk of unnecessary LT in some patients
5	Lack of reproducibility and validation studies for many prognostic scores	A model cannot be implemented in the clinical practise without adequate validation studies
6	Dynamic models are better than models based on baseline parameters, but critical time at which decision should be made is not clear	A very late decision may results in loss of opportunity to transplant, and very early decision may lead to unnecessary LT
7	Many models have included non-ideal parameters, such as factor V, apoptotic markers, monocyte HLA, *etc*	These markers are not routinely available and their measurement involve additional investigations and cost
8	Some prognostic markers, such as serum bilirubin and INR, are subject to laboratory variations	This may cause error in selection of LT candidates
9	Inclusion of advanced HE in some prognostic models	HE is subjective markers, and advanced HE is usually a late feature of ALF
10	Inclusion of CE in prognostic models	CE is difficult to diagnosed clinically, and a clinically overt CE is usually a late feature

ALF: Acute liver failure; CE: Cerebral edema; HE: Hepatic encephalopathy; KCC: Kings college criteria; LT: Liver transplantation; INR: International normalized ratio; HLA: Human leukocyte antigen.

baseline parameters, but the critical time at which a decision should be made is not clear[27]. A very late decision may result in a loss of opportunity to transplant. Several models have used parameters that are not routinely usable, such as serum level of factor V, apoptotic markers, and monocyte HLA. Thus, the measurement of these parameters requires additional investigation and expense. Some prognostic markers are subject to laboratory variations, such as serum bilirubin and INR, which can cause errors in the prognosticating ALF. Several prognostic models have included advanced HE and/or CE as prognostic variables. However, these are usually the late feature of ALF and may reduce the chances of early implementation.

TIME AND DECISION OF LT

The timing of LT is difficult to determine in ALF patients. ALF is a dynamic state in which the condition of patients can change very rapidly, making it difficult to predict the outcomes in the early course of the disease. A very late decision may result in a loss of opportunity to transplant, and a very early decision may lead to unnecessary LT (Figure 1). In the event of too early LT, the patients who would otherwise have survived with medical treatment would be subject to needless major surgery and lifelong immunosuppression, apart from major resource utilization and a loss of graft that could be used for another more suitable candidate. In the case of a very delayed decision, the patient may become too sick for LT, resulting in a potentially preventable death. The selection of timing for LT also depends on the probability of the potential for survival after LT. In a study from King's College Hospital, out of 310 ALF patients listed for emergency LT, 52 (17%) died before the organ became available, and 15 (5%) became too sick for LT. The death occurred at a median of only 2 d after listing[56]. Fortunately, the median time from listing to LT has now decreased to 1 d in some centers[57].Pre-transplant waiting time of > 5 d was correlated with an increased post-LT mortality rate in one study by Yuan *et al*[58]. Therefore, a very limited window of opportunity appears to exist for LT in ALF patients, which could fall from day 2 to day 5 of admission. For better results, early applicability of prognostic models for listing and expedited donor evaluation will be essential. Dynamic models are better than models based on baseline parameters, but it is important to evaluate the crucial time at

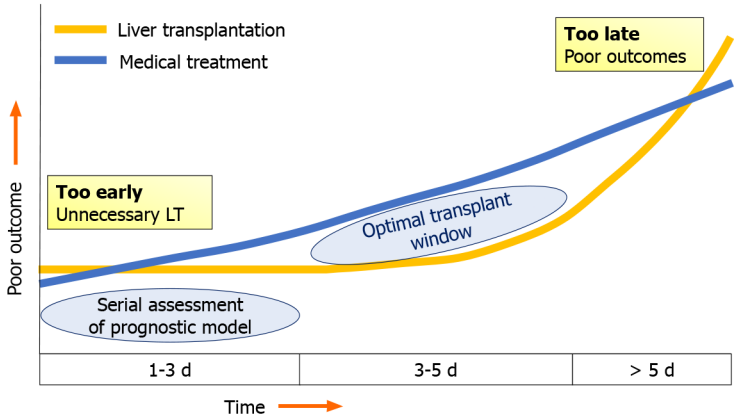

Figure 1 Time and decision for liver transplantation in acute liver failure patients. There appears to be a very limited optimal window of opportunity for liver transplantation (LT) in acute liver failure patients. In the event of too early LT, the patients who would otherwise have survived with medical treatment would be subject to needless transplantation. In the case of a very delayed decision, the patient may become too sick for LT, resulting in a potentially preventable death. For better results, serial assessment of prognostic models with early applicability is needed along with the expedited donor evaluation. LT: Liver transplantation.

which a decision should be made. Criteria for LT should also take into account the waiting time, and once the graft is available, indication for LT should be reassessed in real-time. Another concern is the absence of well-defined delisting criteria while patients are on the waiting list. It is not clear what degree of clinical deterioration predicts LT futility in order to abandon a scheduled LT.

ETHICAL ISSUES

LT in ALF patients is associated with many ethical dilemmas. A pre-operative psychosocial assessment is a critical problem in ALF patients due to the presence of HE. In certain ALF patients, such as those with a history of acetaminophen overdose, alcohol abuse, or suicide attempts, such evaluation is necessary because there may be some risk of underlying psychological issues in them. In addition, knowledge of patients' financial and social support prior to LT is important. It can be difficult to predict compliance with post-LT treatment without a proper psychosocial assessment. The urgency of transplantation in ALF patients can result in the selection of unsuitable liver donors, and in the case of a living donor LT (LDLT), the fear of imminent death of the patient can easily influence the donor who is usually a close relative. A number of complications, such as biliary leaks, pleural effusion, bacterial infections, neuropraxia, incisional hernia, and venous thrombosis, are associated with donor hepatectomy[59-61]. Accordingly, the risk to the donor must be justified by the recipient's chance of recovery.

POST-TRANSPLANT OUTCOMES

The post-LT survival rates of ALF patients have improved over the last three decades. The 1- and 5-year post-LT survival rates are 79% and 72% in Europe and 84% and 73% in the United States, respectively[6,62]. In a recent study based on 30-year single-center experience from Sweden, the 1-year, 5-year, 10-year, and 20-year post-LT survival rates in ALF patients were 71%, 63%, 52%, and 40%, respectively[63]. Between 2000 and 2014, the survival rates were even better (1 year-82%, 5 years-76%, and 10 years-71%).However, 1-year post-LT survival rate is still approximately 10% lower for ALF patients than for other transplanted non-ALF patients[6,62-64]. There is an increased risk of complications and mortality during the early post-operative period for transplanted ALF patients. Infections remain the commonest cause of early mortality after LT. Multiple factors affect the outcomes of patients transplanted for ALF (Table 3). Among the causes of ALF, the best post-LT results are seen in Wilson disease whereas the worst results are seen in cases of drug-induced or autoimmune ALF[56,65]. The prognosis of AALF is very distinct as survival with medical treatment is now approaching that of LT, creating a therapeutic dilemma in the management of such patients[66]. The age of the recipient has an important influence on the outcome of LT

Table 3 Factors associated with poor outcomes of liver transplantation in acute liver failure patients

Ref.	Country	Patients	Determinant of poor outcomes
Barshes *et al*[67], 2006	United States	*n* = 1457	Body mass index > or = 30 kg/m^2. Serum creatinine > 2.0 mg/Dl. Recipient age > 50 years old. History of life support.
Bernal *et al*[56], 2009	United Kingdom	*n* = 310	Age > 45 years old. Vasopressor requirement. Transplantation before 2000. Use of high-risk grafts.
Park *et al*[88], 2010	South Korea	*n* = 44	Older age. Higher MELD.
Germani *et al*[6], 2012	Europe	*n* = 4903	Recipient > 50 yr. Incompatible ABO matching. Donors > 60 yr. Reduced size graft.
Yuan *et al*[58], 2012	China	*n* = 20	Pre-transplant waiting time > 5 d.
Yamashiki *et al* [77], 2012	Japan	*n* = 209	Older age of recipient and donor. Incompatible ABO.
Hoyer *et al*[89], 2014	Germany	*n* = 57	Lowest pH of the recipient before LT. PH ≤ 7.26 have the worst outcome.
Pamecha *et al*[90], 2019	India	*n* = 61	Postoperative worsening of cerebral edema. Systemic inflammatory response syndrome. Preoperative culture positivity. Longer duration of anhepatic phase.

LT: Liver transplantation; MELD: Model for end stage liver disease; ABO: Arquivos brasileiros de oftalmologia.

for ALF. The UNOS and European Liver Transplant Registry (ELTR) database studies have shown that age over 50 years is an independent risk factor for poor outcomes[6,56,64,67]. Poor outcomes have also been reported to occur in recipients of small-sized, steatotic, or arquivos brasileiros de oftalmologia (ABO)-incompatible grafts[6,39,56,68]. A graft quality compromise can result in a higher proportion of primary non-function rates, as high as 13%[62]. A recent large ELTR study of 4903 recipients undergoing LT for ALF found that recipients of > 50 years, incompatible ABO matching, donors of > 60 years, and reduced-size grafts were independent risk factors for patient/graft survival[6]. Following an analysis of the UNOS database, including 1457 recipients who underwent LT for ALF, four adverse risk factors were identified: Body mass index of > 30, serum creatinine of > 2 mg/dL, recipient age of over 50 years, and history of life-support[67]. Thus, the determinant of the poor post-LT outcome should also be taken into consideration when selecting ALF patients for LT.

SPECIFIC GROUP OF ALF PATIENTS

Therapeutic dilemmas may occur while deciding on LT in ALF patients with advanced HE, infection, or acute kidney injury (AKI). A study assessing the outcome of LT in ALF patients with grade 4 HE found a poor outcome unless LT was performed within 48 h of the onset of hepatic coma. In those LT performed after 48 h of hepatic coma, the 3-year survival rate was only 50% compared with 85% where LT was performed within 48 h[69]. If LT is completed within 48 h, a successful neurological recovery can be expected. It may not always be feasible, however, to perform LT within such a limited window of chance. Infection is very common in ALF patients, accounting for 37% of all causes of ALF mortality[70,71]. Therefore, early and successful prevention and treatment of infection are of utmost importance. Approximately 5% of ALF infections are fungal infections, and a confirmed invasive fungal infection should preclude LT[71,72].

AKI is very common in patients with ALF. In a study involving 1604 ALF patients, 70% were found to have AKI. While AKI reduced the overall survival time, the TFS rate was over 50% in patients with AALF or ischemic ALF, compared with 19% in patients with ALF due to other causes[73]. AKI is usually transient and is potentially reversible in ALF patients after LT. While AKI decreases post-LT survival to some degree, an LT should not be deferred because of AKI when other contraindications are absent[74]. However, there is a lack of robust evidence supporting and justifying the use of LDLT in ALF patients with AKI, and such a decision can only be taken on a case-by-case basis. The use of continuous renal replacement therapy (CRRT) can play a role in TFS or bridging LT in ALF patients with AKI[74]. In a recent study including 62 ALF patients, early institution of CRRT was found to be associated with the prevention of severe hyperammonemia and increased TFS compared with those without CRRT

(55% *vs* 13%; $P = 0.05$)[75].

PROBLEMS OF ORGAN SHORTAGE

An increasing global problem is the donor liver shortage, leading to a dilemma as to whether the sickest group of ALF patients should be prioritized. LDLT, auxiliary LT, and incompatible ABO graft can provide an alternative choice to solve the problem of organ shortages. In Asian countries, LDLT accounts for the bulk of LT[76-78]. However, inadequate time and expedited donor assessment for emergency LT could raise some concerns about the potential donor coercion, inappropriate donor selection, and increased risk of donor complications, including psychological problems in the donor. Between LDLT and deceased donor LT, the post-LT outcomes appear to be similar; the former, however, is associated with the risk of donor complications. In ALF patients, auxiliary LT may be an attractive alternative for providing temporary liver support until spontaneous hepatic regeneration takes place. However, since the procedure involves partial resection of the native liver in a critically ill patient and complex vascular reconstruction, the surgical technique is very challenging. There is, thus, not only a high risk of complications but also higher retransplant rates in auxiliary LT. In addition, it is difficult to predict which patients may develop native liver regeneration[79,80]. Because of the pressing demand for grafts for ALF, incompatible ABO grafts have also been used. The early experience with incompatible ABO grafts was disappointing due to the increased risk of serious graft rejection, biliary complications, and vascular thrombosis. However, procedure refinements, including perioperative plasmapheresis, rituximab administration, splenectomy, and triple systemic immunosuppression, have resulted in better outcomes[81]. Such a protocol, however, needs full expertise and is related to an increased risk of complications, largely due to infection.

CONCERNS RELATED TO CORONAVIRUS DISEASE 2019

The current coronavirus disease 2019 (COVID-19) pandemic has had a major impact on surgical treatment for patients worldwide, including LT. Because of concerns about virus transmission, donor unavailability due to lockdown, and increased demand for intensive care unit beds for severe COVID-19 patients, many centers across the world have had to suspend their elective LT. There is concern that COVID-19 puts immunocompromised patients at a higher risk of morbidity and mortality. It is also presumed that post-LT immunosuppression may cause COVID-19 to be severe and long-lasting, though evidence for this is lacking[82]. Nevertheless, an emergency LT in ALF is a lifesaving procedure that cannot be refused due to COVID-19 issues. Extra caution is needed to avoid nosocomial COVID-19 infection among recipients, donors, and healthcare workers. The donors and recipients should be screened for COVID-19 before LT. Standard immunosuppression can be continued in the post-transplant period till further information becomes available[83].

NOVEL ADJUNCTIVE THERAPIES

ALF is a devastating condition that may lead to the death of patients while awaiting a graft. Therefore, to provide a bridge to LT or spontaneous recovery, these patients may need an artificial liver support system. A variety of support systems, such as the molecular adsorbent recirculating system, the fractionated plasma separation and adsorption system, and the single-pass albumin dialysis system, have been developed over the last two decades. While these systems have been shown to have beneficial effects on different biochemical parameters, there is contradictory evidence on improved survival[84]. However, the careful use of these devices as salvage therapy cannot be questioned, given the shortage of available evidence from adequately powered randomized controlled trials. Warrillow *et al*[75] have recently reported the prevention of severe hyperammonemia and enhanced TFS in ALF patients with early CRRT[75]. High-volume plasma exchange therapy (HV-PET), defined as an exchange of 8%-12% or 15% of ideal body weight with fresh frozen plasma, has been found to improve survival in ALF patients[85,86]. Larsen *et al*[85] in a randomized controlled trial ($n = 182$) found that HV-PET improves survival in ALF patients by 10% in

comparison to standard medical therapy (58.7% *vs* 47.85%)[85]. Moreover, significant changes in hemodynamic and biochemical parameters are also noted. The efficacy of PET in ALF patients with acetaminophen or other drug/toxin-associated ALF is plausible, but further studies are needed to validate the efficacy of PET in NAALF patients where liver damage is mainly due to inflammatory and immunological processes. Even in the study by Larsen *et al*[85], the majority of patients had AALF. In a recent meta-analysis, three studies on ALF reported improvement in outcome with PET[86]. In recent years, a growing number of studies have shown that stem cells can effectively treat liver failure. Mesenchymal stem cells (MSCs) are the most widely used stem cells to study liver diseases because they are easy to acquire without any ethical problems. Several pre-clinical and few clinical trials have shown that MSCs are capable of treating liver failure with short-term benefits, but there is no consistent long-term efficacy[87]. Therefore, it could be a promising field for potential studies to investigate the therapeutic role of stem cells in ALF.

CONCLUSION

LT is a lifesaving treatment for patients with ALF. Despite a substantial increase in survival rates after medical therapy, a little less than half the patients will die without a transplant. Nevertheless, there are several issues that complicate the therapeutic decision in ALF patients. An absence of reliable prognostic models hampers the selection of transplant candidates in a timely and precise manner. Sometimes, even a diagnostic dilemma happens due to the lack of a universally accepted definition. The shortage of graft, development of contraindications while on the waiting list, uncleared delisting criteria, time constraints, ethical concerns, and poor post-transplant outcomes are the other limiting factors. There is an unmet need for a widely agreed definition of ALF in order to facilitate standardized clinical management and research in ALF patients. Further study on disease pathogenesis and clinical course is needed to develop a more reliable prognostic model and identify new therapeutic targets with the aim to enhance TFS and limit the need for emergency LT.

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