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EDITORIAL

Prediction of mortality from hepatitis A virus-related acute liver failure in children—Do we have the perfect prognostic model?

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Pediatric acute liver failure (PALF) is characterized by acute onset of severe hepatic dysfunction resulting from various etiologies and can be potentially fatal. Timely etiological diagnosis and specific treatment, appropriate intensive care management with liver support care and early referral for liver transplantation (LT) in a subset with irreversible PALF remain the cornerstone of management.

PALF though not very common accounts for 10% to 15% of all pediatric LTs in the west and 28% in India, respectively [1, 2]. In the era of LT, overall mortality due to PALF in the last decade has been reported to be around 35% to 40% from India [3, 4]. Studies from the pre-LT era report a mortality of 40% to 44% [5, 6]. Spontaneous survival of native liver has improved due to early diagnosis of the etiology, advances in the intensive care management and wider availability of organ support systems. However, it is still difficult to predict the cohort of patients who would survive without LT. Pediatric LT is technically challenging. In India, this is compounded by scarcity of deceased donors more so for children, lack of easy access to a center with expertise in pediatric LT, financial constraints and delayed referral.

In the given scenario, it becomes even more relevant to have an objective prognostic scoring system. This system should have the ability to stratify the patients at risk for poor outcomes thereby ensuring early referral for LT. On the other hand, the scoring system should also identify patients likely to recover without LT. In India, although it has become relatively easy to raise funds for LT through various charitable or crowd-funding platforms, especially for children, the post-LT care with immunosuppression and regular follow-up still remains a logistic and financial challenge, which emphasizes conscientious selection of PALF cases for LT.

Acute viral hepatitis remains the most common cause for PALF in India and other Asian countries and in parts of South America, with hepatitis A virus (HAV) being the commonest implicated agent. HAV accounts for 40% to 60% cases of PALF [3]. HAV-related PALF is associated with significant mortality (20% to 30%) and its incidence is likely to be increased in older children due to widespread vaccination and shift in the endemicity. None of the previously available scoring systems is etiology specific or validated in the Indian population. The Peds HAV model was devised by Lal et al. in 2020 for identification and timely referral of children with hepatitis A-related PALF for LT [7]. It is etiology specific, dynamic, easy to use bedside scoring system comprising of international normalized ratio (INR), jaundice to hepatic encephalopathy (HE) interval and grade of HE with INR > 3.1, jaundice to HE interval > 10 days and HE Grades 3 and 4 associated with death. The sensitivity and specificity were 92.6% and 83.3%, respectively, for predicting death when two or more components were positive.

This issue of the *Journal* reports the results of an externally validated Peds HAV model of PALF [8]. Verma and colleagues have externally validated the Peds HAV model in 96 PALF cases from two non-transplant centers and compared its accuracy to the King's College Hospital (KCH) criteria and Pediatric End-stage Liver Disease (PELD) score.

Similar to the original study by Lal et al., the sensitivity and specificity of predicting death were close to 90% when more than two components were positive with higher prognostic accuracy. The authors also found that the model has better discriminative ability than other available models such as the KCH and PELD score.

We would, however, like to discuss a few limitations of the study and compare the findings of the study with previously available scoring systems.

Prognostic models use information from multiple predictive factors to derive a score or an equation that can

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predict outcomes in patients. Several factors are important while evaluating and using prognostic models and include:

1) Ease of Use: The components of the prognostic system should be objective, easily measurable and limited in number and inclusive of all clinically relevant factors. The Peds HAV model is an excellent bedside tool for prognostication. However, one of the limitations of the study is inclusion of HE in the score. Assessment of HE is not only subjective, but it may also be difficult to identify it in younger children which can possibly lead to erroneous calculation of jaundice to HE interval. Another limitation is that ammonia and lactate, which have been shown to be prognostic variables in previous studies, were not evaluated due to missing data in the study by Verma and colleagues in this issue of the *Journal*.
2) Validity: For any prognostic score to be used reliably, it should have good calibration and discriminatory power (ideal AUROC being 1 and an AUROC more than 0.8 acceptable). It should be reproducible and valid in population other than the derivation cohort. Verma et al. have validated the Peds HAV score in two non-transplant centers with good accuracy. In the study by Verma et al., the area under the receiver operator characteristics curve (AUROC) for the Peds HAV score for predicting death at listing cut-off ≥ 2 was 0.952 with positive predictive value (PPV) of 95.2% and negative predictive value (NPV) of 78.7%, which reliably demonstrates its ability to distinguish those who are likely to die in the absence of LT.
3) Dynamicity: PALF is a rapidly evolving process with variable clinical course with the possibility of development of poor prognostic factors or improvement later in the disease course. The score should be dynamic in nature to accurately identify those at high risk of mortality as the disease evolves and those who need to be delisted with recovering liver function. The major strength of the Peds HAV model was being dynamic in nature, but the dynamicity was not validated in the study by Verma et al. In fact, almost a third of patients who succumbed could have been referred for LT had the Peds HAV score been calculated on subsequent days also. We would like to highlight the ALF early dynamic model (ALFED) score, which predicts outcomes based on changes in values of four prognostic variables (ammonia, INR, serum bilirubin and HE), over three days and was found to be superior to KCC and MELD score [9]. Though the ALFED derivation cohort did include adolescents, it has not been validated in children. Saluja et al. compared the diagnostic accuracy of the ALFED score to other prognostic scores in a cohort of 100 ALF cases, which also included adolescents with predominantly viral etiology and found it to be superior to both KCC and the MELD criteria with better specificity [10].
4) Etiology: The natural history of PALF due to different etiologies is variable and the availability of specific treatment may alter the outcome, thereby necessitating an etiology-specific prognostic scoring system. Peds HAV model is etiology specific, which increases its accuracy as compared to the commonly used KCH, where non-HAV criteria make it unreliable in those with PALF due to HAV.
5) Age: The etiology of PALF varies with age and etiologies with multi-system involvement being more common in younger age group. Younger children and infants pose technical challenges with management as well resulting in higher mortality. The prognostic score thus should be validated across all age groups of children. One of the limitations of KCH is that the criteria of age < 10 years exclude adolescents with PALF. Though the Peds HAV model overcomes this drawback of KCH, its derivation cohort as well as the cohort in the study by Verma et al. predominantly included older children with no infants thereby questioning its applicability in infants and very young children (although infants usually do not suffer from HAV).

Despite its limitations, the Peds HAV model scores over the existing prognostic scoring systems to a great extent.

- **King's College Hospital (KCH) criteria**: KCH has been widely used for listing for LT in PALF for decades now. It was first outlined in 1989 primarily for predicting outcomes in acetaminophen-induced ALF in adults. It has been long used for predicting mortality in adults; however, its applicability in PALF cannot be justified owing to differences in definition, etiology, natural history of PALF and inclusion of only 29 children in the derivation cohort with exclusion of infants. Lower sensitivity (61% vs. 91%) and comparable specificity (70% vs. 90%) to adults have been reported for KCH when applied to PALF with further drop in sensitivity to 30% when it is applied to cohort of PALF caused predominantly by drugs, toxins, infections (excluding HAV and HEV) and metabolic etiology [11, 12]. Another major limitation is that the criteria of non-HAV etiology and age < 10 years will not be fulfilled by adolescents with HAV-related PALF.
- **Pediatric End-stage Liver Disease (PELD) score/ Model for End-stage Liver Disease (MELD) score**: The components of PELD score include age, growth failure, serum bilirubin, INR and albumin and were derived from a multi-centric north American cohort of patients for optimal prioritization and organ allocation in children < 12 years with end-stage liver disease listed for LT. The MELD score encompasses bilirubin, creatinine and INR for use in children > 12 years. In a cohort of PALF from Argentina, PELD score > 33 was

reported to have a sensitivity and specificity of 86% and 81%, respectively, with AUC of 0.88 for predicting death in the absence of LT; however, small sample size of 40, missing data, predominant HAV, autoimmune and indeterminate etiologies and combined analysis of death and LT as similar outcome limit its generalization [13]. A recent South African cohort of PALF with a majority of children being < 5 years in age and viral hepatitis as predominant etiology, a PELD score of > 29 predicted poor outcomes with a sensitivity and specificity of 85% and 83%, respectively, however, has limitations of retrospective design, single center and small sample size of 45 with the absence of metabolic liver disease as etiology [14]. Verma et al. have reported good sensitivity and specificity of PELD. However, the components, growth failure and albumin of PELD may not have significance in the setting of acute liver failure and hence further raise the validity of PELD in PALF.

Other scores which Verma et al. have not studied and have been described include.

- **Liver Injury Unit (LIU) score**: It was derived from a cohort of 81 children with a majority having non-viral etiology and includes peak bilirubin, INR and ammonia levels. Low risk of death was predicted with LIU ≤ 295 with AUC of 0.95 in the derivation cohort. When LIU score was validated in a cohort of 700 patients of the PALF study group, the AUC for predicting death, transplant-free survival and LT was 0.76, 0.81 and 0.84, respectively [15, 16]. However, non-inclusion of age and etiology, using peak instead of admission values of the individual components, failure of admission LIU score to predict death/LT and unreliability in infancy were major limitations of its applicability.
- **Children's Hospital of Los Angeles – liver failure score**: Derived from a cohort of 147 PALF patients and validated in the PALF study group cohort of 492 patients, it comprises albumin, ammonia and total bilirubin. A score > 30 predicts need for LT with high accuracy (AUC 0.83) [17]. Limitations being it does not involve age and is not etiology specific.

In conclusion, the Peds HAV is an excellent bed-side tool for timely identification of HAV PALF cases that would require LT thereby allowing early referral in Indian setting where there are inherent challenges with pediatric LT. There is a need for more etiology and age-specific, dynamic, objective and validated prognostic scoring systems for risk stratification in PALF. We propose that the ALFED score, which appears to be superior to KCH and MELD in adult ALF can be validated in PALF and its diagnostic accuracy can be compared to the Peds HAV score.

Data availability Not applicable.

Declarations

Conflict of interest SP and AN declare no competing interests.

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