



Prognostic Factors for Pediatric Acute Liver Failure: A Systematic Review and Meta-analysis of Prognostic Studies

Junwen Mao ^{1,2}, Junhua Chen ^{1,2,*} and Zhu Chen^{1,2}

¹Department of Infectious Disease, Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing, China

²Chongqing Key Laboratory of Pediatrics, Chongqing Key Laboratory of Child Infection and Immunity, Chongqing, China

*Corresponding author: Department of Infectious Disease, Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing, China. Email: cjh460@163.com

Received 2020 December 25; Revised 2021 April 11; Accepted 2021 April 20.

Abstract

Context: Pediatric acute liver failure (PALF) is a disease with high mortality, characterized by a multisystem disorder and acute liver dysfunction.

Objectives: A systematic review and meta-analysis of prognostic studies is necessary to summarize the general prognostic factors for PALF. Also, these factors can contribute to the development of a new prognostic model.

Methods: An electronic literature search was conducted systematically in PubMed, Embase and Cochrane databases to identify prognostic factors of pediatric acute liver failure and evaluate outcomes, including spontaneous survival, death without LT, and undergoing LT. Prospective or retrospective cohort designs were included. The methodological quality of studies was analyzed and scored, using the QUIPS tool. Also, a meta-analysis was performed to calculate the pooled odds ratio (OR) of the factors

Results: 1465 citations were identified, 30 studies were reviewed, and 16 studies were included in the meta-analysis. The indicators extracted from the studies were divided into four categories: (1) general markers, (2) bio-markers, (3) scoring systems, and (4) treatments. Several prognostic factors were associated with the poor outcomes, including etiology (indeterminate disease and drugs), INR, ammonia, ALT levels, AST levels, bilirubin, albumin, severe HE (grade 3/4), sex (male), lactate. In addition, ammonia, bilirubin, albumin, AST levels, severe HE (grade 3/4) and etiology (indeterminate disease, drugs, metabolic disease) were associated with death (no LT).

Conclusions: Etiology, ammonia, bilirubin, albumin, AST levels, severe HE (grade 3/4) were found associated with the poor outcomes or death (without LT) of PALF. Although these factors may contribute to the new prognostic model, they must be considered with caution. Further prognostic studies of PALF with larger cohorts are also needed.

Keywords: Prognosis, PALF, Meta-analyze

1. Context

Acute liver failure (ALF) is a life-threatening disease, characterized by a multi-system disorder, severe liver dysfunction with or without encephalopathy, and hepatocellular necrosis. Although the true incidence of ALF is unknown in pediatric patients, it has a high mortality rate, ranging from 24 to 53% (1). Pediatric ALF (PALF) has a variety of age- and geography-related etiologies. In a large number of children, the cause of PALF remains undetermined (2) due to several factors, such as limitations of detection instruments.

Due to the insufficient number of liver donations, it is necessary to identify patients with a poor prognosis to determine whether liver transplantation (LT) must be per-

formed. Multiple prognostic factors have been studied so far, including the international normalized ratio (INR), severity of hepatic encephalopathy (HE), and serum ammonia level (3, 4). However, no optimal prognostic model has been developed for PALF so far. Generally, an optimal predictive model should include some static and dynamic parameters (5). To the best of our knowledge, there are no systematic reviews to determine the prognostic factors that may provide an ideal predictive model for PALF.

2. Objectives

In the present study, a systematic review and meta-analysis of prognostic studies was carried out, and the gen-

eral prognostic factors predicting poor outcomes in studies on PALF were investigated for the development of a new prognostic model.

3. Methods

3.1. Study Selection

This systematic review and meta-analysis was conducted based on the PRISMA guidelines (6). The PubMed, Embase, and Cochrane databases (from 1950 to November 20, 2020) were searched to identify prognostic studies on PALF. The keywords included “pediatric acute liver failure”, “prediction”, “prognosis”, “epidemiology”, “child”, and “risk factors”. Also, “liver failure” and “prognosis” were used as the MeSH terms. The literature search strategy is presented in Appendix 1. The reference lists of all included studies were also reviewed to retrieve relevant publications.

The inclusion criteria for all publications were defined before the search. The inclusion criteria were as follows: (1) a study population of children aged 0 - 18 years; (2) identification of prognostic factors for PALF; (3) evaluation of outcomes, including spontaneous survival, death without undergoing LT, and undergoing LT; (4) a prospective or retrospective cohort design; and (5) published studies in English. On the other hand, the exclusion criteria were as follows: (1) focus on only the prognostic factors for PALF complications or LT; (2) comparison of the groups without prediction; and (3) assessment of treatment effects (e.g., transplantation or supportive devices). After omitting duplicates in the Endnote software, two independent reviewers selected studies by screening their titles and abstracts, according to the inclusion and exclusion criteria. They identified potentially eligible articles by reviewing the full-texts independently and subsequently. Disagreements were discussed and resolved in a consensus meeting.

3.2. Quality Assessment

The quality in prognosis studies (QUIPS) tool was used to examine the methodological quality (7). Since prognostic studies evaluated the possible prognostic factors, we did not assess the confounding variables; therefore, the QUIPS tool was used in this study. We developed a scoring algorithm to discriminate and summarize the quality of studies (Appendix 1). The total score was measured by summing the scores (maximum total score = 75). If the score was ≥ 60 , the quality of the study was ranked as high; if the score was 45 - 59, it was considered moderate; and if it was < 45 , it was considered low (8).

3.3. Data Extraction and Reporting

We extracted the data using a standardized extraction form (Table 1). The prognostic factors with statistical significance were selected from the multivariate and univariate analyses ($P < 0.05$). In the meta-analysis, we defined death (with or without LT) and LT as poor outcomes, regardless of the short- and long-term outcomes.

3.4. Statistical Analysis

For the meta-analysis, we extracted the mean and SD of variables in the included studies. Data reported as median and range were transformed into mean and SD using statistical methods (36). Due to anticipated heterogeneity, we used the random-effects model, as it is more conservative. The effect size and 95% confidence intervals (CIs) are also presented in the forest plots. Moreover, Cochran's Q and Higgins I^2 tests were used to examine the heterogeneity of studies. The Cochran's Q P -value < 0.1 and $I^2 > 50\%$ indicated the high level of heterogeneity among studies. In case of significant heterogeneity, a sensitivity analysis was conducted by eliminating studies one at a time. Besides, funnel plot and Egger's test were used for evaluating the potential publication bias. If publication bias was detected, Duval's trim-and-fill method was applied. Since different measurement methods were used in different studies, we used the standardized mean difference (SMD) and odds ratio (OR) for the groups. The RevMan software was used for statistical analysis. P -value < 0.05 was considered statistically significant, unless otherwise specified (registration number: INPLASY202040116).

4. Results

4.1. Search Results and Inclusion of Studies

A total of 1465 studies were extracted in the initial search (Figure 1). Thirty articles were finally included in this study. Generally, prognostic models are scores derived by biochemical or clinical variables and cannot be included as variables on their own. Therefore, we did not include the prognostic models or factors that were discussed only once in the studies in our meta-analysis. We also excluded studies collecting data related to prognostic factors at their peaks. The study by Kaur (2013) (17) was ranked as low quality and was excluded. Finally, 16 studies were included in the meta-analysis.

There were six definitions of PALF in 30 included articles (Table 2). The heterogeneity of the definitions was small. The main differences were related to coagulopathy, high bilirubin level, jaundice, course of the disease, and HE. Generally, the definition proposed by the PALF study group is widely accepted (22), and most of the retrieved studies used this definition.

Table 1. Methodological Characteristics of the Included Prognostic Studies

Authors	Country (y)	Type	Uni Test/Multi	N Included	Population	Outcome	Significant Prognostic Factors from Multivariate Analysis	Significant Prognostic Factors from Univariate Analysis	Score
Kathemann 2015 (9)	Germany (2010 - 2013)	Retrospective	Univariate	37	0 - 16 (y) (mean 1y)	R or NSR		(1) Low ALT; (2) high ammonia; (3) low albumin	63.5
Alam 2017 (10)	India (2011 - 2016)	Prospective	Multivariable	109	0 - 18 (y) (mean 5.8 y)	R or death or LT	PELD-MELD (cutoff > 24), JE interval > 7 d.	Bilirubin, INR, ALT, lactate, J-E interval, KCC, PELD, cerebral edema, MODS, HE grade 3/4	61
Bariş 2012 (11)	Turkey (1987 - 2006)	Retrospective	Univariate	74	1 mo - 17 y (mean 5.8 y)	R or death		TB, DB, PT, INR, PH	61
Hussain 2014 (12)	USA (2008 - 2011)	Retrospective	Univariate	19	mean 6.9 ± 1.3 (y)	R or death		(1) The HE scores; (2) lactate; (3) AST ALT; (4) the LIU scores; (5) EEG	59.5
Ozcay 2016 (13)	Turkey (2000 - 2015)	Retrospective	Multivariable	91	11 d - 17 y (mean 5.7 y)	R or LT or Ddeath	Grade 3 - 4 HE, TB, PT	HE grades 3 - 4, (PRISM), (PELD) scores, TB, DB, ammonia, lactate, APTT, PT, INR	58.5
Öztürk 2010 (14)	Turkey (2000 - 2007)	Retrospective	Multivariable	21	1 - 14.7 (y) (median 8 y)	R or LT or death	Presence of encephalopathy, Serum phosphorus	Serum phosphorus, presence of encephalopathy	58.5
Pei 2014 (15)	China (2008 - 2013)	Retrospective	Multivariable	53	2 mo - 14 y	R or death	INR, HE and serum albumin	INR, HE, ammonia, serum albumin, MODS, gastrointestinal bleeding	58.5
Chien 2019 (1)	Taiwan (2003 - 2016)	Retrospective	Univariate	23	3 d - 15 y (mean 1.39 y)	R or NSR		Idiopathic etiology, ammonia, and AFP, plasma exchange more than six times	57
Rajanayagam 2013 (3)	Australia (1991 - 2011)	Retrospective	Multivariable	54	1 d - 15.6 y (median 1.4 y)	R or LT or death	High peak bilirubin and peak INR ANN (artificial neural network) model	(1) Bilirubin, ALT, AST, lactate, lactate dehydrogenase, platelets; (2) INR and bilirubin	55
Zhao 2014 (4)	CHINA (2007 - 2012)	Retrospective	Multivariable	32	≤ 12 y	R or death	The entry blood ammonia	INR, creatinine, LDH, BLA, PTA	54.5
Di 2017 (16)	Italy (1996 - 2012)	Retrospective	Multivariable	55	0.1 - 15.1 (y) (mean 2.6 y)	R or LT or death	Higher bilirubin and severe encephalopathy (grade 3/4) on admission	ALT, bilirubin, ammonia, INR	53.5
Kaur 2013 (17)	India (2008 - 2010)	Prospective	Multivariable	43	0 - 18 (y) (mean 4.8 y)	R or death	(1) JE interval > 7 days and HE; (2) blood glucose	(1) HE, (2) bilirubin, (3) pH	40.5
Aydoğdu 2003 (18)	Turkish (1994 - 2002)	Retrospective	Univariable	34	1 mo - 17 y	R or NSR		Encephalopathy grade, total and indirect bilirubin levels	61.5
Ciocca 2008 (19)	Argentina (1982 - 2002)	Retrospective	Multivariable	210	1 - 18 (y)	R or LT or death	Prothrombin time and encephalopathy III/IV	Peak bilirubin, PT, FV < 30 and HE III/IV	63.5
Lee 2005 (20)	UK (1991 - 2000)	Retrospective	Multivariable	97	0 - 18 (y)	R or NSR	Time to onset of HE > 7 d, PT > 55 s, ALT ≤ 2384 IU/L on admission	Time to onset of hepatic encephalopathy, PT, bilirubin, ALT	63.5
Lee 2020 (21)	Korea (2000 - 2018)	Retrospective	Multivariable	146	1 mo - 18 y	R or LT or death		Peak TB, daily TB, peak INR, daily INR, peak ammonia, mechanical ventilator, renal replacement, vasopressor	61
Squires 2006 (22)	USA (2000 - 2018)	Prospective	Multivariable	348	0 - 18 (y)	R or NR or LT	TB ≥ 5 mg/dL, INR ≥ 2.55 and HE		68.5
Sanchez 2011 (23)	Italian (2007 - 2012)	Retrospective	Multivariable	40	6 mo - 17 y	R or LT or death		TB, PELD-MELD	58.5
Núñez-Ramos 2018 (24)	Spain (2005 - 2013)	Retrospective	Multivariable	20	≤ 15 (y)	R or LT or death		PELD-MELD	56
Azhar 2013 (25)	Multi-centers (since 1999)	Retrospective	Multivariable	49	0 - 18 (y)	R or LT or death	Dynamic Bayesian Network (DBN) analysis of inflammatory mediators		63.5
Bucvalas 2013 (26)	Multi-centers	Prospective	Univariable	77	Mean 9 (y)	R or LT or death	sIL2Rα		59
Devarbhavi 2014 (27)	India (1996 - 2012)	Retrospective	Multivariable	61	Children with Wilson Disease (WD) 9.7 ± 2.8 (y)	R or NSR	Encephalopathy and total bilirubin	Encephalopathy, INR, total proteins, TB, DB, alkaline phosphatase, serum creatinine, white blood cell count, PELD/MELD score, King's College Criteria score, Nazer score	60.5
Feldman 2017 (28)	Multi-centers (1999 - 2010)	Prospective	Univariable	537	0 - 18y	R or LT or death	The initial lactate or pyruvate molar ratio (L:P) were not association with biochemical variables of clinical severity or clinical outcome.	55.5	
Grama 2020 (29)	Romania (2015 - 2018)	Prospective	Univariable	34	1 mo - 17 y	R or NSR	Vitamin D-binding protein (Gc-globulin) serum levels	59	
Lal 2020 (30)	India (2012 - 2019)	Prospective	Multivariable	120	8.6 ± 4.6 (y)	R or death	HE grade 3/4, INR ≥ 3.1, JE interval ≥ 10 s Etiology (HAV) specific prognostic model (Peds-HAV model)	INR, grade of HE, JE interval	60.5
Ibel 2003 (31)	USA (1990 - 2001)	Prospective	Univariable	24	1.1 - 17 (y)	R or NSR		TB, INR, factor VII, PABA	56.5
Lu 2013 (32)	Multi-centers (1999 - 2008)	Retrospective	Multivariable	461	1.1 - 13.5 (y)	LT or death	Liver injury units (LIU) scoring system, admission LIU (aLIU) score	65	
Quintero 2014 (33)	Spain (2005 - 2011)	Prospectively	Multivariable	48	5.15 - 9.3 (y)	R or NSR	Indocyanine green plasma disappearance rate (ICG - PDR)	61.5	
Sundaram 2013 (34)	Multi-centers (1999 - 2009)	Retrospective	Univariable	522	0 - 17.9 (y)	R or death	KCHC does not reliably predict death in PALF	60	
Uchida 2017 (35)	Japan (2005 - 2015)	Retrospective	Univariable	73	2.6 ± 3.3 (y)	LT or no LT	Scoring system established by the Intractable Hepato-Biliary Disease Study Group (JHBDG)	62.5	

Abbreviations: R, survive with native liver; LT, liver transplantation; Death, died without LT; NSR, non-recovered spontaneously; INR, international normalized ratio; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; PELD, the pediatric end-stage liver disease; KCC, King's College Criteria; MELD, the model for end-stage liver disease; HE, hepatic encephalopathy, OR, odd's ratio, SD, standard deviation; J-E interval, jaundice to encephalopathy interval; DB, direct bilirubin; PTA, prothrombin time activity; TB, total bilirubin; PRISM, pediatric risk of mortality; PABA, para-aminobenzoic acid; FV, factor V; AST, aspartate aminotransferase; LIU, liver injury units scoring system.

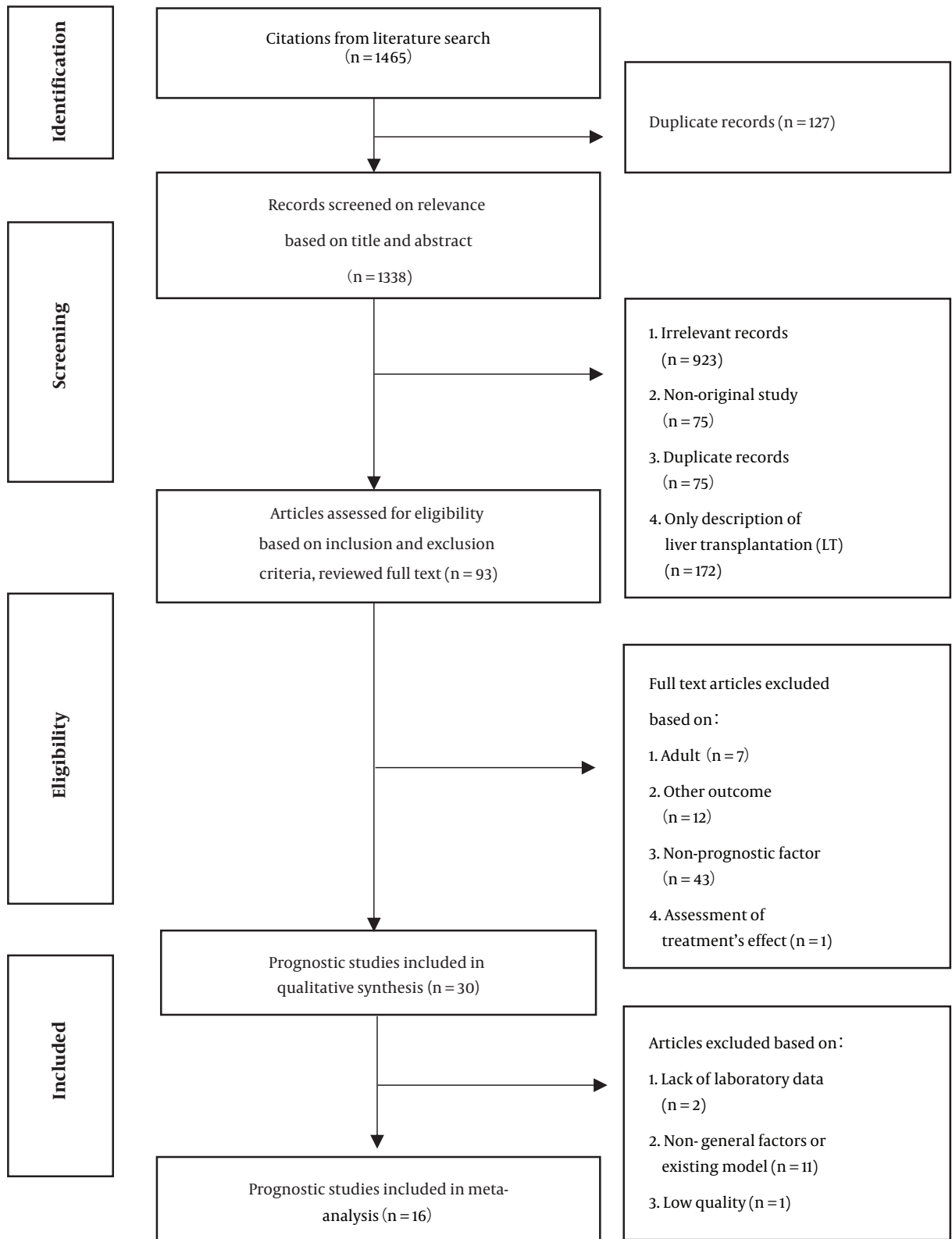


Figure 1. Selection and number of publications

Table 2. Definitions of PALF

Definition	References
Definition of PALF study group: (1) no pre-existing chronic liver disease; (2) coagulopathy that cannot be corrected by vitamin K. It was defined as INR \geq 1.5 with HE or, INR \geq 2.0 with or without HE; (3) acute liver injury.	(1, 3, 9-17, 21-30, 32-34)
(1) Coagulopathy (PT > 24s or INR > 2.0) and HE; (2) no pre-existing liver disease; (3) liver disease within 8 weeks. HE is not absolutely necessary.	(18, 20, 37)
Coagulopathy (PT < 50% and INR > 2), HE is not absolutely necessary.	(19)
Chinese definition: (1) coagulopathy (prothrombin activity (PTA) \leq 40% or INR \geq 1.5) without hematologic diseases; and (2) jaundice (total bilirubin (TB) \geq 171 μmol/L); (3) liver disease within 4 weeks; (4) no pre-existing chronic liver disease.	(4)
Acute liver failure coagulopathy (factor II and factor V (reduced by more than 50%). HE is not absolutely necessary.	(31)
(1) Acute liver injury with HE and INR > 1.5; (2) previously healthy liver.	(35)

4.2. Study Characteristics

Fifteen studies were classified as high quality, 14 studies as moderate quality, and one study as low quality. Overall, there were nine prospective studies and 21 retrospective studies. 19 studies were multivariate analyses. There were 3512 patients examined in these studies.

4.3. Prognostic Factors

The indicators extracted from the studies were divided into four categories: general markers (7), biomarkers (38), scoring systems (22), and treatments (4) (Appendix 1). Overall, 18 factors were described in at least two studies (Figure 2).

We conducted a meta-analysis of some general markers and biomarkers described in the included studies (Table 3). According to the pooled results, INR (OR, 0.78; 95% CI, 0.42 - 1.14; $P < 0.05$), ammonia (OR, 0.41; 95% CI, 0.15 - 0.67; $P < 0.05$), alanine aminotransferase (ALT) level (OR, 0.41; 95% CI, 0.21 - 0.58; $P < 0.05$), aspartate transaminase (AST) level (OR, 0.26; 95% CI, 0.01 - 0.50; $P < 0.05$), bilirubin (OR, 0.66; 95% CI, 0.49 - 0.83; $P < 0.05$), albumin (OR, 0.42; 95% CI, 0.18 - 0.66; $P < 0.05$), severe HE (grade 3/4) (OR, 0.19; 95% CI, 0.10 - 0.37; $P < 0.05$), sex (male) (OR, 0.63; 95% CI, 0.46 - 0.85; $P < 0.05$), and lactate (OR, 0.69; 95% CI, 0.40 - 0.98; $P < 0.05$) were significantly associated with poor outcomes.

In the subgroup without LT, ammonia, bilirubin, albumin, AST, and severe HE (grade 3/4) were significantly associated with death (without LT). The INR ($P = 0.07$), ALT levels ($P = 0.26$), and sex (male) ($P = 0.50$) were not associated with death (without LT). In the subgroup of newborns, the predictive role of INR, ammonia, ALT levels, bilirubin, and severe HE (grade 3/4) were stable in newborns. In the subgroup of newborns, albumin was not associated with poor outcomes. However, regarding sex (male), in the subgroup without newborns, the relationship was not statistically significant.

Based on the results, the inclusion of newborn patients influenced the AST levels, while in two subgroups including newborns, the AST levels were not associated with poor

outcomes; generally, the role of AST level is a controversial issue. Moreover, lactate was associated with poor outcomes; however, there were only two studies reporting this finding. On the other hand, creatine and age were not associated with poor outcomes ($P = 0.39$). As for etiology, in the subgroup including LT patients, indeterminate and drug-induced diseases were associated with poor outcomes. Also, in the non-LT subgroup, indeterminate diseases, drug-induced diseases, and metabolic diseases were associated with mortality.

4.4. Heterogeneity and Publication Bias

The analysis of INR ($I^2 = 0.79$) and HE grade (3/4) ($I^2 = 0.65$) indicated heterogeneity. Based on the sensitivity analysis by excluding individual studies, it was found that studies by Ciocca in 2008 (19) and Squires in 2006 (22) affected the pooled results significantly. By reviewing these two studies, we found that the definition proposed by Ciocca in 2008 did not exclude patients with preexisting liver diseases. Generally, pre-damaged liver may affect coagulation. However, it did not influence the heterogeneity of other parameters. Although identification of higher grades of HE (grade 3/4) was not difficult in children, HE grades were still assessed subjectively. Overall, heterogeneity was unavoidable. The corresponding pooled ORs of other parameters did not significantly change by eliminating one study at a time (data not shown). A funnel plot is presented in Appendix 1. According to Egger's test ($P = 0.3731$), there was no significant publication bias.

5. Discussion

It is generally important to identify patients with a poor prognosis. However, no optimal prognostic model has been developed for PALF so far. A proper prognostic model should include stable and accessible clinical indicators; have high sensitivity and specificity; include some

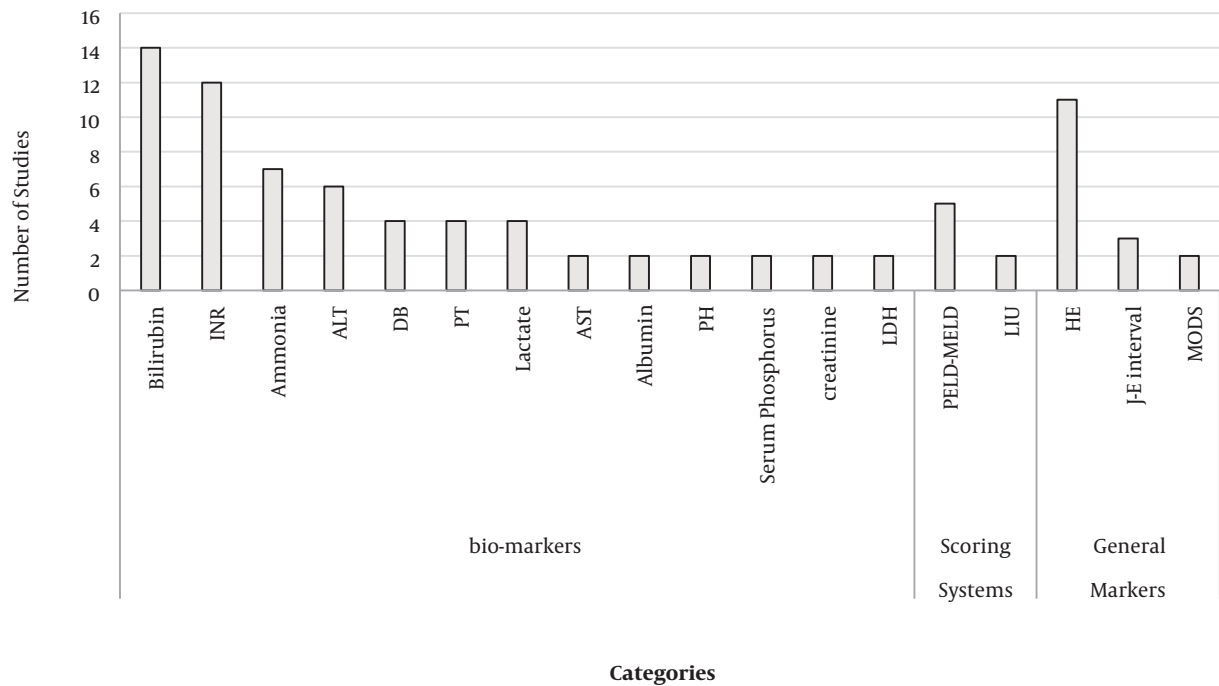


Figure 2. Indicators with the number of studies with significant

static and dynamic parameters; and comprise of a combination of single parameters (5). We aimed to determine the prognostic factors that may contribute to the development of a new prognostic model. The INR, ammonia, ALT levels, AST levels, bilirubin, albumin, severe HE (grade 3/4), sex (male), and lactate were significantly associated with poor outcomes.

Generally, the increased ammonia level in the plasma indicates the loss of functional liver mass, predisposition to HE, and the increased level of glutamine in astrocytes (2). Deep (39) found that the reduction of ammonia after 48 hours of continuous renal replacement therapy (CRRT) was associated with survival, according to the multivariate analysis ($P = 0.004$). A study by Ng revealed that severe HE was associated with mortality in 769 children (40). Nevertheless, HE is a dynamic condition, which is difficult to assess in children. Therefore, serial neurological assessments must be carried out routinely during hospitalization of patients. In this regard, Hussain found that electroencephalography (EEG) could help identify children with a possible poor prognosis or those requiring LT (12). The serum S100b and IL-6 levels can also assist us in the assessment of brain injury (41). However, use of the existing assessment tools is still limited. Therefore, there is a pressing need to develop a reliable biomarker for brain damage to be used across different pediatric age groups.

The ALT and AST levels are sensitive indices of liver func-

tion, closely related to the degree of liver damage. However, liver enzymes of children with spontaneous recovery were higher on admission. These indices were also found to be statistically significant in studies by Rajanayagam (3) and Kathemann (9). The reason may be that pre-damaged livers have lower liver enzymes, such as gestational alloimmune liver disease and Wilson's disease, which are commonly associated with poor outcomes (9).

A high INR represents severe hepatocellular dysfunction. INR is generally a predictor of poor outcomes, as reported in many studies (42, 43). In the King's College Hospital (KCH) model, $INR > 4$ showed a good predictive capability ($AUC = 0.79$). On the other hand, albumin and bilirubin levels represented the synthesizing functions of the liver (15). Besides, INR combined with arterial ammonia, HE, and serum bilirubin showed a good predictive capability ($AUC = 0.91$) (44). In the pediatric end-stage liver disease (PELD) model, INR combined with albumin, bilirubin, and age showed 81% specificity and 86% sensitivity for poor outcomes.

Only two studies examined the lactate level. Feldman found that lactate could not predict the 21-day clinical outcomes. As for gender, few studies, which were mostly univariate analyses, identified its prognostic role; therefore, further research is needed. Rajanayagam developed an artificial neural network (ANN) model (37), which consisted of 34 input variables, such as ALT, AST, ammonia, albu-

min, lactate, prothrombin time (PT), INR, and serum bilirubin. This model showed a superior predictive power for poor outcomes. Besides, in the literature, dynamic models (44), such as dynamic Bayesian network (DBN) analysis of inflammatory mediators (25) and ANN models (37), have been found to be promising.

Age was found to be a prognostic factor in studies by Zhao (45) and Deep (39), considering the children's small size, rapidly progressive etiologies of the disease, and long waiting time for LT. While this factor is included in the PELD model, our meta-analysis was different, and further evidence is needed. Moreover, a high creatinine level is included in the model for end-stage liver disease (MELD) criteria. Nevertheless, in our study, this factor was not statistically significant, although some studies on children have confirmed its significance (38), which may be due to the fact that kidney function is rarely impaired in children, even in those with liver failure.

To reduce the effect of LT on the natural course of PALF and to investigate survival, we included studies on patients without LT. In this subgroup, ammonia, bilirubin, albumin, AST, and severe HE (grade 3/4) were significantly associated with death (without LT); this finding is important for identifying children who can recover without LT; however, the results are not replicable if LT is performed. Overall, neonatal liver failure is an independent phenomenon, which does not have a natural course like other PALFs. In this newborn subgroup, the predictive role of INR, ammonia, ALT, bilirubin, and severe HE (grade 3/4) was stable. Besides, the ALT levels and INR predicting the prognosis of neonatal liver failure have been previously reported (46).

As for etiology, children with indeterminate and drug-induced diseases were more likely to have poor outcomes due to several reasons, such as limitations of detection instruments and genetic susceptibility (47), and were more likely to receive LT (48). In the subgroup without LT, metabolic diseases were also associated with poor outcomes. In recent studies, etiology-specific prognostic models have shown optimal sensitivity and specificity, such as Peds-HAV (30) and Wilson's score (5).

5.1. Limitations

This study had some limitations. We focused on published studies written in English language in the inclusion criteria, leading to possible language bias. Also, we focused on studies assessing the prognostic value of different factors for poor outcomes; therefore, we might have missed some studies focusing less on prediction. The scoring algorithm used in our study had arbitrary cut-off points; nevertheless, readers can draw conclusions from the details presented in the studies. Besides, some studies had a retrospective design and a small sample size. Heterogeneity

was inevitable in this study, because we ignored the heterogeneity of some characteristics, such as follow-up duration; therefore, further analyses on larger prospective cohorts are needed. Also, inclusion of LT as a poor outcome was limited by the criteria for listing at respective centers, living donor liver transplantation (LDLT) vs. deceased donor liver transplant (DDLT) programs, availability of LT, and use of bridging therapies. Finally, since limited studies have been conducted on PALF, we synthesized significant univariable factors rather than multivariable factors. Therefore, the effects of these factors may be unavoidable, and further multivariable studies are necessary in the future.

6. Conclusions

We summarized several prognostic factors for the poor outcomes of PALF, including etiology (indeterminate diseases and drug-induced diseases), INR, ammonia, ALT levels, AST levels, bilirubin, albumin, and severe HE. Regardless of LT, etiology (indeterminate diseases, drug-induced diseases, and metabolic diseases), ammonia, bilirubin, albumin, AST, and severe HE (grade 3/4) were significantly associated with death (without LT). These prognostic factors might be of significance in the development of a new prognostic model. However, due to unavoidable heterogeneity, they must be considered with caution. Further high-quality studies on larger cohorts are also needed.

Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: Study concept and design and data extraction, JunWen Mao and Zhu Chen; Literature search, data extraction, and analysis, JunWen Mao and Zhu Chen; Data interpretation and manuscript writing, JunWen Mao and Zhu Chen; Critical revision of the manuscript for important intellectual content, JunHua Chen.

Conflict of Interests: We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of the manuscript.

Funding/Support: There is no funding/support.

References

- Chien MM, Chang MH, Chang KC, Lu FT, Chiu YC, Chen HL, et al. Prognostic parameters of pediatric acute liver failure and the role of plasma exchange. *Pediatr Neonatol*. 2019;**60**(4):389–95. doi: [10.1016/j.pedneo.2018.09.006](https://doi.org/10.1016/j.pedneo.2018.09.006). [PubMed: [30361144](https://pubmed.ncbi.nlm.nih.gov/30361144/)].
- Devictor D, Tissieres P, Durand P, Chevret L, Debray D. Acute liver failure in neonates, infants and children. *Expert Rev Gastroenterol Hepatol*. 2011;**5**(6):717–29. doi: [10.1586/egh.11.57](https://doi.org/10.1586/egh.11.57). [PubMed: [22017699](https://pubmed.ncbi.nlm.nih.gov/22017699/)].
- Rajanayagam J, Coman D, Cartwright D, Lewindon PJ. Pediatric acute liver failure: Etiology, outcomes, and the role of serial pediatric end-stage liver disease scores. *Pediatr Transplant*. 2013;**17**(4):362–8. doi: [10.1111/petr.12083](https://doi.org/10.1111/petr.12083). [PubMed: [23586473](https://pubmed.ncbi.nlm.nih.gov/23586473/)].
- Zhao P, Wang CY, Liu WW, Wang X, Yu LM, Sun YR. Acute liver failure in Chinese children: A multicenter investigation. *Hepatobiliary Pancreat Dis Int*. 2014;**13**(3):276–80. doi: [10.1016/s1499-3872\(14\)60041-2](https://doi.org/10.1016/s1499-3872(14)60041-2). [PubMed: [24919611](https://pubmed.ncbi.nlm.nih.gov/24919611/)].
- Jain V, Dhawan A. Prognostic modeling in pediatric acute liver failure. *Liver Transpl*. 2016;**22**(10):1418–30. doi: [10.1002/lt.24501](https://doi.org/10.1002/lt.24501). [PubMed: [27343006](https://pubmed.ncbi.nlm.nih.gov/27343006/)].
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Ann Intern Med*. 2009;**151**(4):W65–94. doi: [10.7326/0003-4819-151-4-200908180-00136](https://doi.org/10.7326/0003-4819-151-4-200908180-00136). [PubMed: [19622512](https://pubmed.ncbi.nlm.nih.gov/19622512/)].
- Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;**158**(4):280–6. doi: [10.7326/0003-4819-158-4-201302190-00009](https://doi.org/10.7326/0003-4819-158-4-201302190-00009). [PubMed: [23420236](https://pubmed.ncbi.nlm.nih.gov/23420236/)].
- Samuels N, van de Graaf RA, de Jonge RCJ, Reiss IKM, Vermeulen MJ. Risk factors for necrotizing enterocolitis in neonates: A systematic review of prognostic studies. *BMC Pediatr*. 2017;**17**(1):105. doi: [10.1186/s12887-017-0847-3](https://doi.org/10.1186/s12887-017-0847-3). [PubMed: [28410573](https://pubmed.ncbi.nlm.nih.gov/28410573/)]. [PubMed Central: [PMC5391569](https://pubmed.ncbi.nlm.nih.gov/PMC5391569/)].
- Kathemann S, Bechmann LP, Sowa JP, Manka P, Dechene A, Gerner P, et al. Etiology, outcome and prognostic factors of childhood acute liver failure in a German Single Center. *Ann Hepatol*. 2015;**14**(5):722–8. [PubMed: [26256901](https://pubmed.ncbi.nlm.nih.gov/26256901/)].
- Alam S, Khanna R, Sood V, Lal BB, Rawat D. Profile and outcome of first 109 cases of paediatric acute liver failure at a specialized paediatric liver unit in India. *Liver Int*. 2017;**37**(10):1508–14. doi: [10.1111/liv.13370](https://doi.org/10.1111/liv.13370). [PubMed: [2811909](https://pubmed.ncbi.nlm.nih.gov/2811909/)].
- Baris Z, Saltik Temizel IN, Uslu N, Usta Y, Demir H, Gurakan F, et al. Acute liver failure in children: 20-year experience. *Turk J Gastroenterol*. 2012;**23**(2):127–34. doi: [10.4318/tjg.2012.0319](https://doi.org/10.4318/tjg.2012.0319). [PubMed: [22706740](https://pubmed.ncbi.nlm.nih.gov/22706740/)].
- Hussain E, Grimson M, Goldstein J, Smith CM, Alonso E, Whittington PF, et al. EEG abnormalities are associated with increased risk of transplant or poor outcome in children with acute liver failure. *J Pediatr Gastroenterol Nutr*. 2014;**58**(4):449–56. doi: [10.1097/MPG.0000000000000271](https://doi.org/10.1097/MPG.0000000000000271). [PubMed: [24345828](https://pubmed.ncbi.nlm.nih.gov/24345828/)].
- Ozcay F, Karadag Oncel E, Baris Z, Canan O, Moray G, Haberal M. Etiologies, outcomes, and prognostic factors of pediatric acute liver failure: A single center's experience in Turkey. *Turk J Gastroenterol*. 2016;**27**(5):450–7. doi: [10.5152/tjg.2016.16431](https://doi.org/10.5152/tjg.2016.16431). [PubMed: [27782894](https://pubmed.ncbi.nlm.nih.gov/27782894/)].
- Ozturk Y, Berktaş S, Soyulu OB, Karademir S, Astarcioglu H, Arslan N, et al. Fulminant hepatic failure and serum phosphorus levels in children from the western part of Turkey. *Turk J Gastroenterol*. 2010;**21**(3):270–4. [PubMed: [20931431](https://pubmed.ncbi.nlm.nih.gov/20931431/)].
- Pei L, Wen GF, Guo ZY, Song WL, Wang LJ, Liu CF. [Short-term prognostic factors in children with acute liver failure]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2014;**16**(12):1250–4. Chinese. [PubMed: [25523575](https://pubmed.ncbi.nlm.nih.gov/25523575/)].
- Di Giorgio A, Sonzogni A, Picciche A, Alessio G, Bonanomi E, Colledan M, et al. Successful management of acute liver failure in Italian children: A 16-year experience at a referral centre for paediatric liver transplantation. *Dig Liver Dis*. 2017;**49**(10):1139–45. doi: [10.1016/j.dld.2017.05.026](https://doi.org/10.1016/j.dld.2017.05.026). [PubMed: [28663066](https://pubmed.ncbi.nlm.nih.gov/28663066/)].
- Kaur S, Kumar P, Kumar V, Sarin SK, Kumar A. Etiology and prognostic factors of acute liver failure in children. *Indian Pediatr*. 2013;**50**(7):677–9. doi: [10.1007/s13312-013-0189-7](https://doi.org/10.1007/s13312-013-0189-7). [PubMed: [23255683](https://pubmed.ncbi.nlm.nih.gov/23255683/)].
- Aydogdu S, Ozgenc F, Yurtsever S, Akman SA, Tokat Y, Yagci RV. Our experience with fulminant hepatic failure in Turkish children: Etiology and outcome. *J Trop Pediatr*. 2003;**49**(6):367–70. doi: [10.1093/tropej/49.6.367](https://doi.org/10.1093/tropej/49.6.367). [PubMed: [14725414](https://pubmed.ncbi.nlm.nih.gov/14725414/)].
- Ciocca M, Ramonet M, Cuarterolo M, Lopez S, Cernadas C, Alvarez F. Prognostic factors in paediatric acute liver failure. *Arch Dis Child*. 2008;**93**(1):48–51. doi: [10.1136/adc.2006.115113](https://doi.org/10.1136/adc.2006.115113). [PubMed: [17872939](https://pubmed.ncbi.nlm.nih.gov/17872939/)].
- Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United Kingdom. *J Pediatr Gastroenterol Nutr*. 2005;**40**(5):575–81. doi: [10.1097/01.mpg.0000158524.30294.e2](https://doi.org/10.1097/01.mpg.0000158524.30294.e2). [PubMed: [15861019](https://pubmed.ncbi.nlm.nih.gov/15861019/)].
- Lee EJ, Kim JW, Moon JS, Kim YB, Oh SH, Kim KM, et al. Development of a prognostic score to predict mortality in patients with pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2020;**70**(6):777–82. doi: [10.1097/MPG.0000000000002625](https://doi.org/10.1097/MPG.0000000000002625). [PubMed: [32443030](https://pubmed.ncbi.nlm.nih.gov/32443030/)].
- Squires RJ, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: The first 348 patients in the pediatric acute liver failure study group. *J Pediatr*. 2006;**148**(5):652–8. doi: [10.1016/j.jpeds.2005.12.051](https://doi.org/10.1016/j.jpeds.2005.12.051). [PubMed: [16737880](https://pubmed.ncbi.nlm.nih.gov/16737880/)]. [PubMed Central: [PMC2662127](https://pubmed.ncbi.nlm.nih.gov/PMC2662127/)].
- Sanchez MC, D'agostino DE. Pediatric end-stage liver disease score in acute liver failure to assess poor prognosis. *J Pediatr Gastroenterol Nutr*. 2012;**54**(2):193–6. doi: [10.1097/MPG.0b013e3182349a04](https://doi.org/10.1097/MPG.0b013e3182349a04). [PubMed: [21886007](https://pubmed.ncbi.nlm.nih.gov/21886007/)].
- Nunez-Ramos R, Montoro S, Bellusci M, Del Fresno-Valencia MR, German-Diaz M, Urruzuno P, et al. Acute liver failure: Outcome and value of pediatric end-stage liver disease score in pediatric cases. *Pediatr Emerg Care*. 2018;**34**(6):409–12. doi: [10.1097/PEC.0000000000000884](https://doi.org/10.1097/PEC.0000000000000884). [PubMed: [29851917](https://pubmed.ncbi.nlm.nih.gov/29851917/)].
- Azhar N, Ziraldo C, Barclay D, Rudnick DA, Squires RH, Vodovotz Y, et al. Analysis of serum inflammatory mediators identifies unique dynamic networks associated with death and spontaneous survival in pediatric acute liver failure. *PLoS One*. 2013;**8**(11):e78202. doi: [10.1371/journal.pone.0078202](https://doi.org/10.1371/journal.pone.0078202). [PubMed: [24244295](https://pubmed.ncbi.nlm.nih.gov/24244295/)]. [PubMed Central: [PMC3823926](https://pubmed.ncbi.nlm.nih.gov/PMC3823926/)].
- Bucuvalas J, Filipovich L, Yazigi N, Narkewicz MR, Ng V, Belle SH, et al. Immunophenotype predicts outcome in pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2013;**56**(3):311–5. doi: [10.1097/MPG.0b013e31827a78b2](https://doi.org/10.1097/MPG.0b013e31827a78b2). [PubMed: [23111765](https://pubmed.ncbi.nlm.nih.gov/23111765/)]. [PubMed Central: [PMC3582763](https://pubmed.ncbi.nlm.nih.gov/PMC3582763/)].
- Devarbhavi H, Singh R, Adarsh CK, Sheth K, Kiran R, Patil M. Factors that predict mortality in children with Wilson disease associated acute liver failure and comparison of Wilson disease specific prognostic indices. *J Gastroenterol Hepatol*. 2014;**29**(2):380–6. doi: [10.1111/jgh.12356](https://doi.org/10.1111/jgh.12356). [PubMed: [24033813](https://pubmed.ncbi.nlm.nih.gov/24033813/)].
- Feldman AG, Sokol RJ, Hardison RM, Alonso EM, Squires RH, Narkewicz MR, et al. Lactate and lactate: Pyruvate ratio in the diagnosis and outcomes of pediatric acute liver failure. *J Pediatr*. 2017;**182**:217–222 e3. doi: [10.1016/j.jpeds.2016.12.031](https://doi.org/10.1016/j.jpeds.2016.12.031). [PubMed: [28088395](https://pubmed.ncbi.nlm.nih.gov/28088395/)]. [PubMed Central: [PMC5328928](https://pubmed.ncbi.nlm.nih.gov/PMC5328928/)].
- Gramma A, Burac L, Aldea CO, Bulata B, Delean D, Samasca G, et al. Vitamin D-binding protein (Gc-globulin) in acute liver failure in children. *Diagnostics (Basel)*. 2020;**10**(5). doi: [10.3390/diagnostics10050278](https://doi.org/10.3390/diagnostics10050278). [PubMed: [32375318](https://pubmed.ncbi.nlm.nih.gov/32375318/)]. [PubMed Central: [PMC7278011](https://pubmed.ncbi.nlm.nih.gov/PMC7278011/)].
- Lal BB, Sood V, Snehavardhan P, Khanna R, Pasupuleti SSR, Siloliya M, et al. A novel, bedside, etiology specific prognostic model (Peds-HAV) in hepatitis A induced pediatric acute liver failure. *Hepatol Int*. 2020;**14**(4):483–90. doi: [10.1007/s12072-020-10050-0](https://doi.org/10.1007/s12072-020-10050-0). [PubMed: [3272333](https://pubmed.ncbi.nlm.nih.gov/3272333/)].
- Lebel S, Nakamachi Y, Hemming A, Verjee Z, Phillips MJ, Furuya KN. Glycine conjugation of para-aminobenzoic acid (PABA): A pilot study of a novel prognostic test in acute liver failure in children. *J Pediatr Gastroenterol Nutr*. 2003;**36**(1):62–71. doi: [10.1097/00005176-200301000-00013](https://doi.org/10.1097/00005176-200301000-00013). [PubMed: [12499998](https://pubmed.ncbi.nlm.nih.gov/12499998/)].
- Lu BR, Zhang S, Narkewicz MR, Belle SH, Squires RH, Sokol RJ, et al. Evaluation of the liver injury unit scoring system to predict sur-

- vival in a multinational study of pediatric acute liver failure. *J Pediatr*. 2013;**162**(5):1010–6 e1-4. doi: [10.1016/j.jpeds.2012.11.021](https://doi.org/10.1016/j.jpeds.2012.11.021). [PubMed: [23260095](https://pubmed.ncbi.nlm.nih.gov/23260095/)]. [PubMed Central: [PMC3786160](https://pubmed.ncbi.nlm.nih.gov/PMC3786160/)].
33. Quintero J, Miserachs M, Ortega J, Bueno J, Dopazo C, Bilbao I, et al. Indocyanine green plasma disappearance rate: A new tool for the classification of paediatric patients with acute liver failure. *Liver Int*. 2014;**34**(5):689–94. doi: [10.1111/liv.12298](https://doi.org/10.1111/liv.12298). [PubMed: [24112412](https://pubmed.ncbi.nlm.nih.gov/24112412/)].
 34. Sundaram V, Shneider BL, Dhawan A, Ng VL, Im K, Belle S, et al. King's College Hospital criteria for non-acetaminophen induced acute liver failure in an international cohort of children. *J Pediatr*. 2013;**162**(2):319–23 e1. doi: [10.1016/j.jpeds.2012.07.002](https://doi.org/10.1016/j.jpeds.2012.07.002). [PubMed: [22906509](https://pubmed.ncbi.nlm.nih.gov/22906509/)]. [PubMed Central: [PMC3504621](https://pubmed.ncbi.nlm.nih.gov/PMC3504621/)].
 35. Uchida H, Sakamoto S, Fukuda A, Sasaki K, Shigeta T, Nosaka S, et al. Sequential analysis of variable markers for predicting outcomes in pediatric patients with acute liver failure. *Hepatol Res*. 2017;**47**(12):1241–51. doi: [10.1111/hepr.12859](https://doi.org/10.1111/hepr.12859). [PubMed: [28032939](https://pubmed.ncbi.nlm.nih.gov/28032939/)].
 36. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;**5**:13. doi: [10.1186/1471-2288-5-13](https://doi.org/10.1186/1471-2288-5-13). [PubMed: [15840177](https://pubmed.ncbi.nlm.nih.gov/15840177/)]. [PubMed Central: [PMC1097734](https://pubmed.ncbi.nlm.nih.gov/PMC1097734/)].
 37. Rajanayagam J, Frank E, Shepherd RW, Lewindon PJ. Artificial neural network is highly predictive of outcome in paediatric acute liver failure. *Pediatr Transplant*. 2013;**17**(6):535–42. doi: [10.1111/ptr.12100](https://doi.org/10.1111/ptr.12100). [PubMed: [23802584](https://pubmed.ncbi.nlm.nih.gov/23802584/)].
 38. Zhao P, Wang C, Liu W. Can experience from adults regarding acute liver failure fit children? *Indian J Pediatr*. 2014;**81**(5):501–3. doi: [10.1007/s12098-013-1262-x](https://doi.org/10.1007/s12098-013-1262-x). [PubMed: [24135945](https://pubmed.ncbi.nlm.nih.gov/24135945/)].
 39. Deep A, Stewart CE, Dhawan A, Douiri A. Effect of continuous renal replacement therapy on outcome in pediatric acute liver failure. *Crit Care Med*. 2016;**44**(10):1910–9. doi: [10.1097/CCM.0000000000001826](https://doi.org/10.1097/CCM.0000000000001826). [PubMed: [27347761](https://pubmed.ncbi.nlm.nih.gov/27347761/)].
 40. Ng VL, Li R, Loomes KM, Leonis MA, Rudnick DA, Belle SH, et al. Outcomes of children with and without hepatic encephalopathy from the pediatric acute liver failure study group. *J Pediatr Gastroenterol Nutr*. 2016;**63**(3):357–64. doi: [10.1097/MPG.0000000000001178](https://doi.org/10.1097/MPG.0000000000001178). [PubMed: [27367788](https://pubmed.ncbi.nlm.nih.gov/27367788/)]. [PubMed Central: [PMC4992416](https://pubmed.ncbi.nlm.nih.gov/PMC4992416/)].
 41. Toney NA, Bell MJ, Belle SH, Hardison RM, Rodriguez-Baez N, Loomes KM, et al. Hepatic encephalopathy in children with acute liver failure: Utility of serum neuromarkers. *J Pediatr Gastroenterol Nutr*. 2019;**69**(1):108–15. doi: [10.1097/MPG.0000000000002351](https://doi.org/10.1097/MPG.0000000000002351). [PubMed: [31058776](https://pubmed.ncbi.nlm.nih.gov/31058776/)]. [PubMed Central: [PMC6591057](https://pubmed.ncbi.nlm.nih.gov/PMC6591057/)].
 42. Dhawan A, Cheeseman P, Mieli-Vergani G. Approaches to acute liver failure in children. *Pediatr Transplant*. 2004;**8**(6):584–8. doi: [10.1111/j.1399-3046.2004.00292.x](https://doi.org/10.1111/j.1399-3046.2004.00292.x). [PubMed: [15598330](https://pubmed.ncbi.nlm.nih.gov/15598330/)].
 43. Sturm E, Lexmond WS, Verkade HJ. Pediatric acute liver failure: Variations in referral timing are associated with disease subtypes. *Eur J Pediatr*. 2015;**174**(2):169–75. doi: [10.1007/s00431-014-2363-x](https://doi.org/10.1007/s00431-014-2363-x). [PubMed: [25005716](https://pubmed.ncbi.nlm.nih.gov/25005716/)].
 44. Kumar R, Sharma H, Goyal R, Kumar A, Khanal S, Shalimar, et al. Prospective derivation and validation of early dynamic model for predicting outcome in patients with acute liver failure. *Gut*. 2012;**61**(7):1068–75. doi: [10.1136/gutjnl-2011-301762](https://doi.org/10.1136/gutjnl-2011-301762). [PubMed: [22337947](https://pubmed.ncbi.nlm.nih.gov/22337947/)].
 45. Zhao P, Wang C, Liu W, Chen G, Liu X, Wang X, et al. Causes and outcomes of acute liver failure in China. *PLoS One*. 2013;**8**(11):e80991. doi: [10.1371/journal.pone.0080991](https://doi.org/10.1371/journal.pone.0080991). [PubMed: [24278360](https://pubmed.ncbi.nlm.nih.gov/24278360/)]. [PubMed Central: [PMC3838343](https://pubmed.ncbi.nlm.nih.gov/PMC3838343/)].
 46. Zozaya Nieto C, Fernandez Caamano B, Munoz Bartolo G, Menendez Suso JJ, Frauca Remacha E, Valverde Nunez E. Presenting features and prognosis of ischemic and nonischemic neonatal liver failure. *J Pediatr Gastroenterol Nutr*. 2017;**64**(5):754–9. doi: [10.1097/MPG.0000000000001501](https://doi.org/10.1097/MPG.0000000000001501). [PubMed: [28437325](https://pubmed.ncbi.nlm.nih.gov/28437325/)].
 47. Dhawan A. Acute liver failure in children and adolescents. *Clin Res Hepatol Gastroenterol*. 2012;**36**(3):278–83. doi: [10.1016/j.clinre.2012.03.022](https://doi.org/10.1016/j.clinre.2012.03.022). [PubMed: [22521555](https://pubmed.ncbi.nlm.nih.gov/22521555/)].
 48. Squires JE, McKiernan P, Squires RH. Acute liver failure: An update. *Clin Liver Dis*. 2018;**22**(4):773–805. doi: [10.1016/j.cld.2018.06.009](https://doi.org/10.1016/j.cld.2018.06.009). [PubMed: [30266162](https://pubmed.ncbi.nlm.nih.gov/30266162/)].

Table 3. Meta-analysis of Parameters

Parameters	Studies	Participants	Effect Estimate	I ² (%)	P
1.1. INR	11	776	0.78 [0.42 - 1.14]	79	< 0.05
1.2. INR (subgroup)	11	776	0.78 [0.42 - 1.14]	79	< 0.05
1.2.1. No newborn	7	589	0.83 [0.32 - 1.33]	86	< 0.05
1.2.2. Include newborn	4	187	0.71 [0.33 - 1.08]	27	< 0.05
1.3. INR (no LT)	6	261	0.73 [0.06 - 1.51]	86	0.07
2.1. Ammonia	8	471	0.41 [0.15 - 0.67]	44	< 0.05
2.2. Ammonia (subgroup)	8	471	0.41 [0.15 - 0.67]	44	< 0.05
2.2.1. No newborn	5	304	0.46 [0.06 - 0.86]	62	0.02
2.2.2. Include newborn	3	167	0.33 [0.02 - 0.65]	0	0.04
2.3. Ammonia (no LT)	2	68	0.70 [0.19 - 1.20]	0	0.007
3.1. ALT levels	9	572	0.41 [0.24, 0.58]	0	< 0.05
3.2. ALT (subgroup)	9	572	0.41 [0.24, 0.58]	0	< 0.05
3.2.1. No newborn	6	366	0.40 [0.17, 0.62]	7	< 0.05
3.2.2. Include newborn	3	206	0.43 [0.14, 0.71]	0	0.003
3.3. ALT (no LT)	3	122	0.21 [-0.16, 0.59]	0	0.26
4.1. Bilirubin	15	986	0.66 [0.49 - 0.83]	32	< 0.05
4.2. Bilirubin (subgroup)	15	986	0.66 [0.49 - 0.83]	32	< 0.05
4.2.1. No newborn	9	648	0.72 [0.55 - 0.89]	0	< 0.05
4.2.2. Include newborn	6	338	0.57 [0.14 - 1.00]	69	0.01
4.3. Bilirubin (no LT)	7	288	0.65 [0.40 - 0.89]	0	< 0.05
5.1. Albumin	7	310	0.42 [0.18, 0.66]	0	< 0.05
5.2. Albumin (subgroup)	7	310	0.42 [0.18, 0.66]	0	< 0.05
5.2.1. No newborn	4	172	0.54 [0.16, 0.92]	28	< 0.05
5.2.2. Include newborn	3	138	0.26 [-0.10, 0.61]	0	0.15
5.3. Albumin (no LT)	4	103	0.52 [0.12, 0.92]	0	0.01
6.1. AST levels	5	284	0.26 [0.01, 0.50]	0	0.04
6.2. AST levels (subgroup)	5	284	0.26 [0.01, 0.50]	0	0.04
6.2.1. No newborn	4	230	0.23 [-0.08, 0.54]	21	0.14
6.2.2. Include newborn	1	54	0.37 [-0.17, 0.91]	Not	0.18
6.3. AST levels (no LT)	5	259	0.30 [0.05, 0.56]	0	0.02
7.1. Creatinine	3	131	-0.16 [-0.52, 0.20]	0	0.39
8.1. Lactate	2	200	0.69 [0.40 - 0.98]	0	< 0.05
9.1. HE grade 3/4	9	948	0.19 [0.10, 0.37]	65	< 0.05
9.2. HE grade 3/4 (subgroup)	9	948	0.19 [0.10, 0.37]	65	< 0.05
9.2.1. No newborn	4	386	0.19 [0.07, 0.55]	65	0.002
9.2.2. Include newborn	5	562	0.18 [0.07, 0.49]	66	0.0008
9.3. HE grade 3/4 (no LT)	5	408	0.08 [0.01, 0.54]	83	0.009
10.1. Age	8	483	0.07 [-0.26, 0.11]	0	0.45
11.1. Sex (male)	8	706	0.63 [0.46, 0.85]	0	0.003
11.2. Sex (subgroup)	8	706	0.63 [0.46, 0.85]	0	0.003

11.2.1. No newborn	4	192	0.71 [0.39, 1.31]	0	0.28
11.2.2. Include newborn	4	514	0.60 [0.42, 0.85]	0	0.004
11.3. Sex (no LT)	4	308	0.79 [0.41, 1.54]	15	0.50
12.1. Etiology (include LT)	9				
12.1.1. Indeterminate	8	914	0.40 [0.29, 0.54]	0	< 0.05
12.1.2. Metabolic	6	665	0.73 [0.41, 1.29]	23	0.28
12.1.3. Autoimmune	7	692	1.06 [0.57, 1.98]	1	0.86
12.1.4. Drugs	8	801	4.02 [2.52, 6.43]	0	< 0.05
12.1.5. Infective	8	801	1.32 [0.76, 2.30]	40	0.32
12.2. etiology (no LT)	9				
12.2.1. Indeterminate	8	615	0.36 [0.16, 0.80]	62	0.01
12.2.2. Metabolic	6	431	0.52 [0.28, 0.94]	0	0.03
12.2.3. Autoimmune	7	458	0.97 [0.43, 2.22]	0	0.95
12.2.4. Drugs	8	552	2.94 [1.62, 5.37]	0	< 0.05
12.2.5. Infective	8	552	1.44 [0.77, 2.69]	37	0.26

Abbreviation: LT, liver transplantation.