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ORIGINAL ARTICLE

# Neonates with acute liver failure have higher overall mortality but similar posttransplant outcomes as older infants

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## Abstract

Neonatal acute liver failure (ALF) carries a high mortality rate; however, little data exist on its peritransplant hospital course. This project aimed to identify factors associated with outcomes in neonates with ALF using large multicenter databases. Patients with International Classification of Diseases, Ninth Revision/International Classification of Diseases, Tenth Revision codes for liver failure (2004–2018) from linked Pediatric Health Information System and Scientific Registry of Transplant Recipients databases were assigned to two groups: neonates aged $\leq 30$ days or older infants aged 31–120 days at admission. Billing data were used to assign diagnoses and assess patient comorbidities (sepsis, extracorporeal membrane oxygenation, total parenteral nutrition, intensive care unit, and cardiac/renal/respiratory failure). Statistical analysis included Kaplan–Meier survival curve analysis and univariate and multivariate analyses with the Cox proportional hazards model. We identified 1807 neonates and 890 older infants. Neonates had significantly lower survival to 90 days ($p = 0.04$) and a lower rate of liver transplantation (2.0% vs. 6.4%; $p < 0.001$). Common risk factors associated with death or transplant were present between groups: diagnosis, respiratory failure, cardiac failure, and renal failure. Among neonates versus older infants who received a transplant, there was no significant differences in posttransplant lengths of stay (median 38 vs. 32 days; $p = 0.53$), posttransplant mortality (15% vs. 11%; $p = 0.66$), or graft loss (9.7% vs. 8.1%; $p = 0.82$). We present the largest multicenter study on peritransplant

**Abbreviations:** ALF, acute liver failure; BW, birth weight; CI, confidence interval; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; GALD, gestational alloimmune liver disease; HLH, hemophagocytic lymphohistiocytosis; HR, hazard ratio; HSV, herpes simplex virus; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; NA, not applicable; NS, not significant; OLT, orthotopic liver transplantation; OR, odds ratio; OPTN, Organ Procurement and Transplantation Network; PELD, Pediatric End-Stage Liver Disease; PHIS, Pediatric Health Information System; SRTR, Scientific Registry of Transplant Recipients; TPN, total parenteral nutrition.

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outcomes in neonatal ALF and show similar risk factors for death or transplant in neonates compared with older infants. Despite lower transplantation rates, neonates demonstrate similar posttransplant outcomes as older infants. Further studies are needed to better risk stratify neonates eligible for transplant and improve outcomes.

## INTRODUCTION

Neonatal acute liver failure (ALF) is a rare condition defined by liver synthetic dysfunction with an international normalized ratio (INR) $\geq 2.0$ in the first 30 days of life. Neonatal ALF is distinct from ALF in older infants both in etiology, management, and outcomes. The most common etiologies of neonatal ALF are gestational alloimmune liver disease (GALD), viral infections, hemophagocytic lymphohistiocytosis (HLH), and metabolic or genetic disorders.[1,2] In contrast, GALD does not present out of the neonatal period, whereas other etiologies, including unidentified causes of ALF, are more frequent in older infants.[2] ALF in the neonate carries a high mortality rate with death often secondary to multiorgan failure, cardiovascular compromise and hemodynamic instability, or bleeding.[3] In addition, neonates with ALF have been reported to have a lower rate of liver transplantation than older children, further contributing to poor outcomes in this group.[4,5]

Multiple factors are thought to contribute to the lower rate of liver transplantation for neonatal ALF; however, the impact of these factors on outcome is controversial. Various etiologies of neonatal ALF may be a contraindication to transplant such as active viral infection or mitochondrial disorders exhibiting rapid neurologic decline. Neonates may also be at greater risk for short-term complications such as longer duration of intubation, infection, or reoperation attributed to their immune susceptibility and small size.[3,6] However, young infants eligible for transplant have been shown to have similar overall patient and graft survival rates as older children, suggesting that technical factors such as recipient size may carry less impact.[7,8] In the present study, we aimed to more precisely define how differences in etiology, demographics, and disease severity in neonatal ALF compared with older infants impact outcomes, particularly death and peritransplant complications. Specifically, we characterized the etiology at presentation and the natural history of neonatal ALF across multiple centers using the Pediatric Health Information System (PHIS), with a more granular evaluation of posttransplant outcomes using Scientific Registry of Transplant Recipients (SRTR) database. The findings from our study may identify a subset of neonates with ALF who may be eligible for transplant to reduce mortality and improve patient outcomes.

## PATIENTS AND METHODS

We performed a retrospective analysis using deidentified data from the PHIS and SRTR databases. PHIS is a comprehensive database from the Children's Hospital Association (Lenexa, KS) that includes clinical and resource use data for inpatient, observation, ambulatory surgery, and emergency department patient encounters from 49 tertiary children's hospitals in the United States. The SRTR database system includes data on all donors, waitlist candidates, and transplant recipients in the United States submitted by members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR database contractors. A previously established linkage of PHIS and SRTR databases by Godown et al. using indirect identifiers for patients who received transplants allows patient-specific integration of data from both resources and includes a total of 13,388 patients.[9] The study was reviewed and approved by the Office of Research Integrity and Compliance at Ann and Robert H. Lurie Children's Hospital of Chicago.

### Patient cohort

We first used only the PHIS database to identify 2859 patients up to 120 days of age with International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) codes for liver failure during an inpatient admission between January 1, 2004, and December 31, 2018 (Supplemental Table S1). We collected demographic, diagnosis, and hospitalization outcome data on all patients and further stratified our cohort into two groups: neonates aged $\leq 30$ days at admission and older infants aged 31–120 days at admission. Cases without billing data in PHIS (109 neonates and 53 older infants) were excluded because of limitations in the analysis. Etiology was defined by ICD-9 and ICD-10

codes and classified as viral, GALD, genetic (metabolic and mitochondrial diagnoses), HLH, multiple (if more than one etiology was present), or unidentified (did not meet criteria by available codes). Codes for viral diagnoses included those for general viral hepatitis or congenital viral infection as well as specific codes for herpes simplex virus (HSV), enterovirus, adenovirus, cytomegalovirus (CMV), and Epstein–Barr virus. The diagnosis of GALD was assigned to patients with a diagnosis code for neonatal hemochromatosis without another assigned etiology or the GALD-specific ICD-10 code. Patients without an assigned etiology on this first search were next classified as cardiac, ischemia, or unidentified. We further reviewed diagnosis and procedure codes as well as charge data and clinical transaction classification codes to assign comorbidities of extracorporeal membrane oxygenation (ECMO), total parenteral nutrition (TPN), intensive care unit (ICU) stay, occurrence of organ failures (respiratory, cardiac, and renal), and sepsis. Respiratory failure was defined as the need for mechanical ventilation, cardiac failure as the use of vasoactive medications, and renal failure as the need for renal replacement therapy. Sepsis was defined as the diagnosis of sepsis plus the use of intravenous or intramuscular antibiotics for at least 7 days. Detailed information on codes and the specific criteria used for diagnoses and comorbidities is provided in Supplementary Table S1.

Outcomes from the first hospitalization to the time of discharge in PHIS were defined using discharge disposition in combination with transplant codes and classified as alive without transplant, died without transplant, alive with transplant, or died after transplant. Hospital course during possible subsequent readmissions were not analyzed in the present study. Additional peritransplant information in the linked PHIS/SRTR database was obtained on patients who received transplants. Data collected from the SRTR database in the linkage on patients who received transplants included candidate status at listing and transplant, transplant procedure information, donor characteristics, and patient and graft outcomes. SRTR database for all patients 30 days of age or less who were listed for transplantation were also analyzed.

## Data analysis

Comparisons between continuous and ordinal clinical variables were made using either the Mann–Whitney U test or Pearson chi-square test, respectively. Kaplan–Meier survival curve analysis was performed from the time of admission to death or discharge for both the entire hospitalization and the first 90 days of hospitalization, and Mantel–Cox log-rank $p$ values are reported for time-to-event comparisons between groups. Univariate and multivariate analyses were performed using a Cox proportional hazards model for the outcome of death or transplant within each age group. Factors tested on univariate analysis in each group included diagnosis, sex, age of admit in days, birth weight (BW) $\geq 3$ kg (neonates only), and comorbidities. Diagnosis and other variables with a $p$ value $<0.15$ from univariate analysis were included in the multivariate analysis. Odds ratios (ORs) and hazard ratios (HRs) are reported with the 95% confidence interval (CI) for significant variables. Significance was defined as a $p$ value $<0.05$. Statistical analyses were performed using IBM SPSS Statistics software (Versions 27 and 28) and GraphPad Prism 9. R Studio (Version 1.2.1335) was used to identify patients matching our coding criteria for diagnoses and comorbidities (Supplemental Table S1). The database was assembled, organized, and stored in FileMaker Pro 16.01.162 (Claris International).

# RESULTS

## Multicenter cohort demonstrates distinct clinical characteristics for neonatal ALF

We identified 1807 neonates with ALF at $\leq 30$ days of life at the time of admission and 890 older infants with ALF at 31–120 days of life on admission (Figure 1). Median age at admission and death/discharge was 3 days (interquartile range [IQR], 0–9 days) and 30 days (IQR, 13–58 days) for neonates compared with 72 days (IQR, 47–96 days) and 99 days (IQR, 70–127 days) for older infants (both with $p < 0.001$). Among patients who were alive at discharge, neonates had a significantly longer duration of hospitalization (median, 33 days; IQR, 18–62 days) compared with older infants (median, 20 days; IQR, 9–43 days; $p < 0.001$). Neonates also had overall increased rates of respiratory failure, cardiac failure, ECMO, TPN use, and ICU status compared with older infants, with $p < 0.001$ for all (Table 1).

We show a significant difference in etiology by age group ($p < 0.001$) with viral infection, GALD, cardiac etiologies, and perinatal origins for ischemia being more common in neonates compared with a higher proportion of cases with HLH, genetic, and unidentified etiologies in older infants (Table 1). Among all neonates with a viral diagnosis, 59% had a code for HSV followed by enterovirus as the second most common viral diagnosis (23%). In contrast, the top two viral codes in older infants were enterovirus and CMV, each comprising 39% of total cases with a viral diagnosis. More neonates were assigned multiple diagnoses than older infants (Table 1). Among neonates with multiple diagnoses, the combination of ischemia and cardiac diagnoses was most common at 52% (Supplemental Table S2).

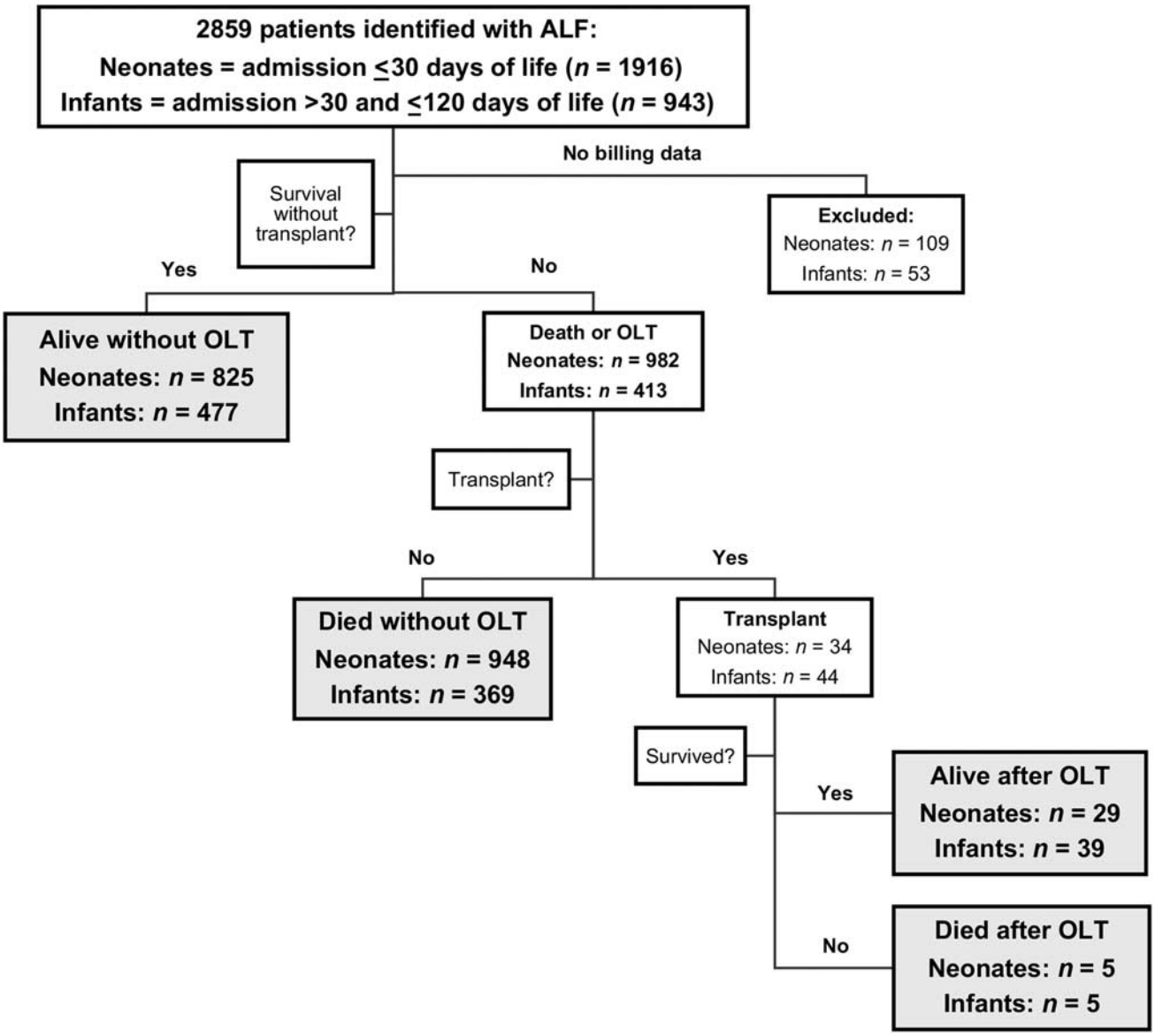


**FIGURE 1** Consort diagram of the entire cohort shows assignment of patients in each group to four primary outcomes: alive without transplant (OLT), died without OLT, alive after OLT, and died after OLT

## Patients with neonatal ALF experience worse outcomes than older infants

Overall, neonates had a higher mortality rate and a lower transplantation rate when compared with older infants (Table 1 and Figure 2A). Of neonates, 53% died without a transplant in contrast to 42% of older infants ($p < 0.001$); however, the rate of death after liver transplantation did not differ between groups (Figure 2A). Kaplan–Meier survival curve analysis demonstrated that neonates had a lower median survival of 57 days (95% CI, 47–67 days) compared with 72 days (95% CI, 56–88 days) for older infants. Although this was not significantly different for the overall duration of hospitalization ($p = 0.06$), survival within the first 90 days of hospital admission was lower for neonates ($p = 0.04$) (Figure 2B).

Given the known etiology-specific mortality trends and the effect the different diagnoses may have on transplant candidacy, we next compared etiologies among patients who died in each group. Significant differences in etiology among patients who died overall paralleled our observations from the entire cohort except for cardiac and HLH diagnoses (Figure 2C). Notably, more patients with viral and ischemic etiologies died in the neonatal group, whereas cases with genetic or unidentified diagnoses comprised a greater proportion of older infants who died (Figure 2C).

## Risk factors for death or transplant by group for neonates and older infants

Despite a lower rate of liver transplantation and higher mortality, only the comorbidities of ECMO and TPN use

**TABLE 1** Differences in overall clinical characteristics between neonates with ALF compared with older infants

| Patient variable | Neonates | Older infants | *p* value |
|---|---|---|---|
| Sex | 1805 | 889 | 0.39 |
| Male | 1004 (56) | 510 (57) | |
| Female | 801 (44) | 379 (43) | |
| Diagnosis | 1807 | 890 | < 0.001 |
| Viral | 185 (10) | 61 (6.9) | 0.004 |
| GALD | 48 (2.7) | 4 (0.4) | < 0.001 |
| Genetic | 160 (8.9) | 116 (13) | 0.001 |
| HLH | 27 (1.5) | 28 (3.1) | 0.004 |
| Cardiac | 440 (24) | 159 (18) | < 0.001 |
| Ischemia | 207 (12) | 19 (2.1) | < 0.001 |
| Multiple diagnoses | 154 (8.5) | 39 (4.4) | < 0.001 |
| Unidentified | 586 (32) | 464 (52) | < 0.001 |
| Outcome | 1807 | 890 | |
| Died during primary admission | 953 (53) | 374 (42) | < 0.001 |
| Liver transplantation | 34 (1.9) | 44 (4.9) | < 0.001 |
| Comorbidities | 1807 | 890 | |
| Respiratory failure | 1657 (92) | 679 (76) | < 0.001 |
| Cardiac failure | 1472 (82) | 606 (68) | < 0.001 |
| Renal failure | 165 (9.1) | 66 (7.4) | 0.13 |
| Sepsis | 678 (38) | 339 (38) | 0.77 |
| ECMO | 233 (13) | 67 (7.5) | < 0.001 |
| TPN | 1462 (81) | 488 (55) | < 0.001 |
| ICU | 1731 (96) | 750 (84) | < 0.001 |

*Note*: Data are provided as *n* or *n* (%).
Abbreviations: ALF, acute liver failure; ECMO, extracorporeal membrane oxygenation; GALD, gestational alloimmune liver disease; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; TPN, total parenteral nutrition.

were significantly higher in neonates who died or received a transplant (Supplemental Table S3). Furthermore, risk factors associated with death or transplant by multivariate analysis were overall similar between groups (Table 2). Common risk factors included diagnosis, respiratory failure, cardiac failure, and renal failure, whereas ECMO was only a risk factor in older infants. Respiratory failure was the strongest factor associated with death or transplant in both groups with a HR of 5.2 (95% CI, 2.4–11) in neonates and 12 (95% CI, 5.3–25) in older infants. In contrast, TPN and sepsis were inversely associated with death or transplant. To explore the possibility that the inverse association between sepsis and death or transplant was confounded by a longer duration of hospitalization, we compared the median duration of admission between patients with and without sepsis. Median duration for admission until discharge, death, or transplant was 35 days (IQR, 14–88 days) for neonates with sepsis compared with 17 days (IQR, 4.0–36 days) for those without sepsis ($p < 0.001$). A similar difference in duration of admission was present in older infants with median of 30 days (IQR, 14–77 days) in those with sepsis compared with 9 days (IQR, 3.0–23 days) in those without.

## Peritransplant characteristics of neonates with ALF

Comparison of recipient and donor characteristics by group for patients who received transplants is shown in Table 3. Overall etiology did not significantly differ between groups, and no patients with ischemia or HLH received transplants in either group (Table 3). There were also no significant differences in the prevalence of comorbidities between groups with similar rates of respiratory failure, cardiac failure, renal failure, ECMO, TPN, ICU, and sepsis identified in the PHIS. Furthermore, preoperative candidate use of life support, ventilatory support, dialysis, inotropes, and ECMO as identified in the SRTR database did not differ significantly between the two groups. Median age at transplant was 32 days (IQR, 19–46 days) for neonates and 102 days (IQR, 67–119 days) for older infants ($p < 0.001$). Median days from admittance to transplant was 14 days for both groups (IQR, 9.0–40 days for neonates; IQR, 7.0–31 days for older infants; $p = 0.24$). In addition, there was no difference in time on the wait list between groups, with a median of 5 days (IQR, 2–8 days) in neonates and 8 days (IQR, 3–16 days) in older infants ($p = 0.09$) with the available SRTR database. Significantly different clinical variables at transplant in neonates included lower median height and weight and increased INR, serum creatinine, and serum sodium ($p < 0.05$ for all; Table 3). In contrast, older infants had a higher rate of moderate ascites ($p = 0.008$). Although INR was significantly higher in neonates, there was no statistically significant difference in the laboratory-based Pediatric End-Stage Liver Disease (PELD) score at transplant, although a trend toward more neonates with a PELD score >40 was noted (32.3% vs. 14% in older infants). The majority of patients in both groups were listed as Status 1, comprising 94% of neonates and 78% of older infants ($p = 0.08$).

We further demonstrate that transplant procedure variables and overall posttransplant outcomes were similar between groups (Table 3). There was no difference in the use of technical variant grafts, use of living donors, or warm and cold ischemia times between groups. During the primary transplant admission, the median posttransplant length of stay until death or discharge was similar between groups at 37 days (IQR, 19–53 days) for neonates and 31 days (IQR, 17–60 days) for older infants ($p = 0.84$). In addition, the rate of patient death during the primary ALF admission did not differ and was 15% in Group 1 and

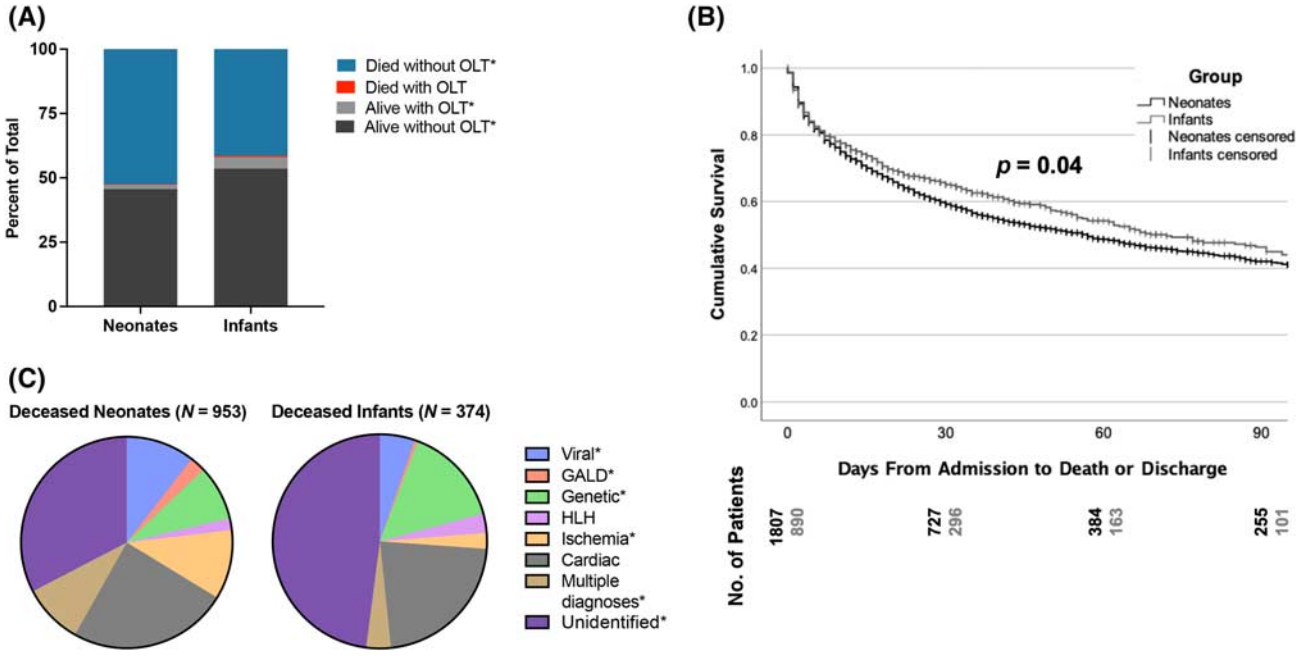


**FIGURE 2** (A) Overall outcomes by patient group show significant differences for all outcomes except patients who died with transplant (OLT). (B) Kaplan–Meier survival curve analysis for the first 90 days of primary admission shows lower survival rates in neonates (black line) compared with older infants (gray line; $p = 0.04$). (C) Viral, GALD, genetic, ischemia, multiple diagnoses, and unidentified etiologies for ALF significantly differed among neonates who died versus older infants. *Significant differences between groups ($p < 0.05$)

11% in Group 2 ($p = 0.66$). Longer term follow-up outcome data were available for 30 neonates and 37 older infants with a median duration of follow-up of 1848 days (IQR, 403–3160 days) and 1851 days (IQR, 710–3817 days) for each group, respectively ($p = 0.53$). A similar proportion of patients were alive, dead, or retransplanted at last follow-up in both groups ($p = 0.53$; Figure 3). Graft loss was reported for three patients in each group ($p = 0.82$), with vascular thrombosis being the most common reported cause. Reported causes of death across both groups included sepsis, fungal infection, viral infection, acute respiratory distress syndrome, multiple organ system failure, vascular thrombosis, rejection, arrythmia, congestive heart failure, and cardiac arrest.

### Waitlist characteristics for neonates at 0–30 days of life

Lastly, we evaluated characteristics among all neonates listed for transplant in the SRTR database even though granular PHIS coding data from the linkage are only available for patients who received transplants. Among all patients aged 0–30 days who were listed for transplant in the SRTR database regardless of diagnosis, 62% (145 of 234) received transplants and 38% (88 of 234) were removed from the wait list. A greater proportion of the group removed from the wait list were documented to require life support ($p = 0.03$) and ventilatory support ($p = 0.009$) before transplant. There were no significant differences in rates of inotropic support, ECMO, or dialysis between patients who did and did not receive a transplant. Weight at the time of listing also differed, with a median weight of 4 kg in the group that was removed from the wait list compared with a median weight of 4.6 kg in the group that received transplants ($p = 0.001$).

## DISCUSSION

We report findings from the largest multicenter retrospective analysis of peritransplant outcomes in neonatal ALF. Neonates ($\leq 30$ days old) had an overall higher mortality rate, increased rate of comorbidities, and lower transplantation rates compared with older infants (31–120 days old). Importantly, however, risk factors for death or transplant were similar between neonates and older infants. In addition, preoperative medical acuity and posttransplant outcomes did not differ between the groups. Therefore, our data suggest that although neonatal ALF carries overall high mortality rates, neonates without significant preoperative comorbidities can achieve similar posttransplant outcomes as older infants.

Previous studies have reported outcomes in small infants; however, limited data exist on transplant outcomes, specifically in the neonate. Technical challenges in liver transplantation of neonates and small infants include small vasculature and possible vessel mismatch from adult donors, large-for-size grafts even with reduced size grafts, and a smaller abdominal cavity.[10] These factors may predispose neonates and

**TABLE 2** Factors associated with death or transplant by patient group

| Neonates | Alive without OLT ($n$ = 825); median (IQR), $n$ (%; $N$), or $n$ (%) | Death or OLT ($n$ = 982); median (IQR), $n$ (%; $N$), or $n$ (%) | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | $p$ value | HR (95% CI) | $p$ value |
| Diagnosis | NA | NA | NS | 0.58 | NA | < 0.001 |
| Age of admit, days | 3 (0–9) | 3 (0–9) | NS | 0.62 | – | – |
| BW ≥ 3 kg | 365 (49; $N$ = 743) | 368 (41; $N$ = 889) | 0.73 (0.60–0.89) | 0.002 | NS | 0.87 |
| Sex | NA, $N$ = 825 | NA, $N$ = 980 | NS | 0.21 | – | – |
| Respiratory failure | 685 (83) | 972 (99) | 20 (10–38) | < 0.001 | 5.2 (2.4–11) | < 0.001 |
| Cardiac failure | 545 (66) | 927 (94) | 8.7 (6.4–12) | < 0.001 | 3.9 (2.9–5.2) | < 0.001 |
| Renal failure | 37 (4.5) | 128 (13) | 3.2 (2.2–4.7) | < 0.001 | 1.4 (1.2–1.8) | 0.001 |
| Sepsis | 269 (33) | 409 (42) | 1.5 (1.2–1.8) | < 0.001 | 0.70 (0.61–0.81) | < 0.001 |
| ECMO | 60 (7.3) | 173 (18) | 2.7 (2.0–3.7) | < 0.001 | NS | 0.349 |
| TPN | 687 (83) | 775 (79) | 0.75 (0.59–0.96) | 0.02 | 0.23 (0.19–0.28) | < 0.001 |
| ICU | 792 (96) | 939 (96) | NS | 0.69 | – | – |
| **Infants** | **Alive without OLT ($n$ = 477); median (IQR) or $n$ (%)** | **Death or OLT ($n$= 413); median (IQR) or $n$ (%)** | **Univariate Analysis** | | **Multivariable Analysis** | |
| | | | **OR (95% CI)** | **$p$ value** | **HR (95% CI)** | **$p$ value** |
| Diagnosis | NA | NA | NA | 0.04 | NA | < 0.001 |
| Age of admit, days | 71 (47–97) | 73 (48–96) | NS | 0.68 | – | – |
| Sex | NA, $N$ = 477 | NA, $N$ = 412 | NS | 0.39 | – | – |
| Respiratory failure | 274 (57) | 405 (98) | 38 (18–77) | < 0.001 | 12 (5.3–25) | < 0.001 |
| Cardiac failure | 225 (47) | 381 (92) | 13 (8.9–20) | < 0.001 | 2.7 (1.8–4.1) | < 0.001 |
| Renal failure | 15 (3.1) | 51 (12) | 4.3 (2.4–7.8) | < 0.001 | 1.4 (1.0–2.0) | 0.03 |
| Sepsis | 165 (35) | 174 (42) | 1.4 (1.0–1.8) | 0.02 | 0.46 (0.37–0.57) | < 0.001 |
| ECMO | 19 (4.0) | 48 (12) | 3.2 (1.8–5.5) | < 0.001 | 1.4 (1.0–2.0) | 0.049 |
| TPN | 228 (48) | 260 (63) | 1.9 (1.4–2.4) | < 0.001 | 0.32 (0.25–0.40) | < 0.001 |
| ICU | 358 (75) | 392 (95) | 6.2 (3.8–10) | < 0.001 | NS | 0.78 |

*Notes*: ORs and HRs are reported for significant variables ($p < 0.05$). Factors with $p < 0.15$ on univariate analysis were included in the multivariate analysis.
Abbreviations: BW, birth weight; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; NA, not applicable; NS, not significant; OLT, orthotopic liver transplant; OR, odds ratio; TPN, total parenteral nutrition.

small infants to developing a higher rate of surgical complications after liver transplantation than older children. However, despite these technical challenges, the short- and long-term outcomes in infants aged younger than 3 months have been shown to be similar to older infants, particularly in experienced centers.[8,11,12] Furthermore, comparable outcomes between infants <5–6 kg and older patients has been demonstrated; however, the sample size of neonates was limited.[10,13]

As ALF remains a leading indication for liver transplantation in neonates, our findings significantly add to the current literature on transplant outcomes in neonates. A comprehensive evaluation of factors influencing transplant candidacy for neonatal ALF in the linked PHIS-SRTR database is limited because of the diagnosis codes obtained in SRTR database. However, we acknowledge that neonatal ALF is a leading indication to list a patient for liver transplantation within the first 30 days of life, so we compared candidate weight between listed patients who received transplants and those removed from the wait list. Patients who were removed from the wait list had a lower median weight and higher rates of life support and ventilatory support compared with those who received transplants. This suggests that smaller neonates may be at higher risk for pretransplant comorbidities that may affect waitlist candidacy.

However, despite significantly lower patient height and weight in neonates versus older infants who received a transplant, neonates did not have longer posttransplant

**TABLE 3** Peritransplant characteristics in neonates with ALF compared with older infants

| Patient variable | Neonates | Older infants | *p* value |
|---|---|---|---|
| Diagnosis, *n* (%) | *N* = 34 | *N* = 44 | 0.29 |
| Viral | 7 (21) | 3 (6.8) | |
| GALD | 4 (12) | 2 (4.5) | |
| Genetic | 7 (21) | 9 (21) | |
| HLH | 0 | 0 | |
| Cardiac | 2 (5.9) | 2 (4.5) | |
| Ischemia | 0 | 0 | |
| Multiple diagnoses | 3 (8.8) | 8 (18) | |
| Unidentified | 11 (32) | 20 (46) | |
| Transplant admission comorbidities, *n* (%) | *N* = 34 | *N* = 44 | |
| Respiratory failure | 34 (100) | 42 (96) | 0.21 |
| Cardiac failure | 30 (88) | 39 (89) | 0.96 |
| Renal failure | 6 (18) | 7 (16) | 0.84 |
| Sepsis | 12 (35) | 13 (30) | 0.59 |
| ECMO | 0 | 1 (2.3) | 0.38 |
| TPN | 31 (91) | 41 (93) | 0.74 |
| ICU | 34 (100) | 43 (98) | 0.38 |
| Peritransplant clinical status | | | |
| Median days from admittance to transplant (IQR; *N*) | 14 (9.0–40; *N* = 34) | 14 (7.0–31; *N* = 44) | 0.24 |
| Median age at transplant, days (IQR; *N*) | 32 (19–46; *N* = 34) | 102 (67–119; *N* = 44) | < 0.001 |
| Median weight, kg (IQR; *N*) | 3.7 (3.4–4.5; *N* = 31) | 4.4 (3.9–6.1; *N* = 37) | 0.005 |
| Median height, cm (IQR; *N*) | 52 (50–54; *N* = 31) | 55 (52–58; *N* = 37) | 0.001 |
| Median last albumin, g/dl (IQR; *N*) | 2.7 (2.3–3.2; *N* = 31) | 2.7 (2.3–3.3; *N* = 37) | 0.99 |
| Median last bilirubin, mg/dl (IQR; *N*) | 13.8 (7.2–23.9; *N* = 31) | 13.9 (8.2–21.1; *N* = 37) | 0.59 |
| Median last INR (IQR; *N*) | 3.4 (2.8–4.5; *N* = 31) | 2.7 (2.1–3.4; *N* = 37) | 0.009 |
| Median last serum creatinine, mg/dl (IQR; *N*) | 0.3 (0.2–0.5; *N* = 31) | 0.2 (0.2–0.3; *N* = 37) | 0.04 |
| Median last serum sodium, mEq/L (IQR; *N*) | 143.5 (137.8–146.3; *N* = 30) | 137.5 (134.0–143.8; *N* = 36) | 0.03 |
| Median posttransplant length of stay, days (IQR; *N*) | 38 (20–54; *N* = 31) | 32 (14–57; *N* = 37) | 0.53 |
| Presence of moderate ascites, N (%; total *N*) | 4 (16%; *N* = 25) | 15 (50%; *N* = 30) | 0.008 |
| Last candidate laboratory-based PELD score, *n* (%) | *N* = 31 | *N* = 37 | 0.28 |
| PELD score <15 | 1 (3.2) | 3 (8.1) | |
| PELD score 15–30 | 7 (23) | 11 (30) | |
| PELD score 31–40 | 13 (42) | 18 (49) | |
| PELD score >40 | 10 (32) | 5 (14) | |
| Transplant procedure variables | | | |
| Median donor age, months (IQR; *N*) | 27.0 (13.0–110.0; *N* = 31) | 72.00 (15.0–277.5; *N* = 37) | 0.29 |
| Graft type, *n* (%) | *N* = 31 | *N* = 37 | 0.93 |
| Whole liver | 11 (36) | 14 (38) | |
| Partial liver | 14 (45) | 15 (41) | |
| Split liver | 6 (19) | 8 (22) | |
| Donor type, *n* (%) | *N* = 31 | *N* = 37 | 0.50 |
| Living donor | 4 (13) | 7 (19) | |
| Deceased donor | 27 (87) | 30 (81) | |
| Median warm ischemia time, min (IQR; *N*) | 40.0 (32.0–46.0; *N* = 19) | 38.5 (28.8–46.3; *N* = 26) | 0.73 |
| Median cold ischemia time, min (IQR; *N*) | 6.95 (5.2–54.0; *N* = 30) | 6.4 (4.7–8.6; *N* = 35) | 0.24 |
| Posttransplant outcome during primary admission | | | |
| Median posttransplant length of stay, days (IQR; *N*) | 37 (19–53; *N* = 34) | 31 (17–60; *N* = 44) | 0.84 |
| Patient death, *n* (%; *N*) | 5 (15; *N* = 34) | 5 (11; *N* = 44) | 0.66 |

*Notes*: Data were obtained from the PHIS and SRTR databases: 78 patients who received a transplant had data available in the PHIS and 68 in the SRTR database.
Abbreviations: ECMO, extracorporeal membrane oxygenation; GALD, gestational alloimmune liver disease; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; PELD, Pediatric End-Stage Liver Disease; TPN, total parenteral nutrition.

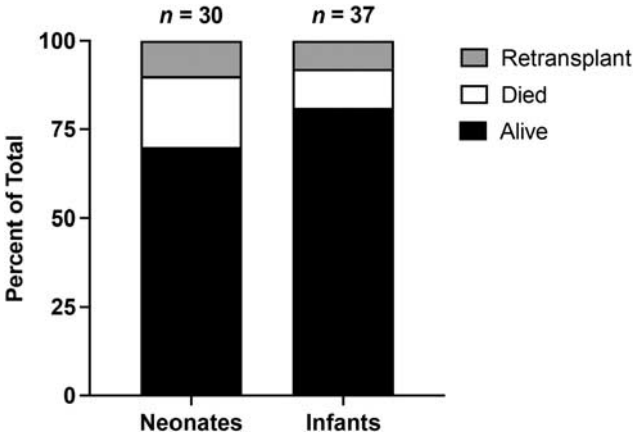


**FIGURE 3** Posttransplant outcomes for patients with follow-up data in SRTR database were not significantly different between neonates and older infants ($p = 0.53$)

hospital stays or higher mortality rates during their transplant hospitalization. Furthermore, a similar frequency of graft loss was reported between groups, with similar numbers of patients alive, dead, and retransplanted at the time of the last recorded follow-up in SRTR database between the two groups. These data support a favorable role for liver transplantation in eligible neonates $\leq$30 days of life to improve patient outcomes despite possible age-specific surgical and medical challenges. Additional studies are necessary to reduce medical acuity in the lower weight neonates and increase candidacy for transplant in this group.

Our study also adds to established epidemiologic data on differences in diagnoses between neonates and older infants.[1,2,14] We show a higher rate of viral infections and GALD, cardiac, and ischemic etiologies in neonates compared with older infants, in which HLH, genetic, and unidentified etiologies were more prevalent. Interestingly, although CMV is understood to be a less common viral etiology for ALF in infants, CMV was among the top two viral codes in older infants along with enterovirus. However, we are unable to confirm a possible causal relationship between CMV and the infants' liver failure without additional clinical information. Not unexpectedly, HSV was the most common viral code in neonates, present in 59% of cases. Although HSV carries high mortality rates even with prompt initiation of acyclovir, and active infection is a contraindication to transplant, it is important to note that identified viral infections comprised an overall small proportion of total neonates who died (11%). Further studies are therefore needed to better define neonates with ALF who meet transplant criteria to improve patient outcomes.

We acknowledge several limitations to our retrospective study. First, the nature of the PHIS database relies on documentation by providers and billing coders, which can lead to missing data or errors in data entry. Furthermore, PHIS data do not allow for a more detailed evaluation of laboratory data or timing of an event. For example, coding reports limit our ability to confirm diagnoses based on clinical data and further characterize patients with an unidentified etiology. In addition, the linkage between PHIS and SRTR databases is limited only to patients who received a transplant and does not include deaths while on the wait list or patients removed from the wait list. Although the SRTR database does have data for patients removed from the wait list, diagnosis codes are limited. We also recognize that the small sample size of patients who received transplants limits comparisons of specific posttransplant outcomes between groups. Lastly, the intricacies of transplant candidacy are difficult to evaluate in a retrospective study, and identifying subgroups of additional neonates suitable for transplant may be better served by a prospective clinical study design.

In summary, despite the aforementioned limitations, our data significantly expand on current knowledge of neonatal ALF and peritransplant outcomes. We demonstrate that neonates with ALF have an overall higher rate of mortality, more comorbidities, and lower transplantation rates when compared with older infants. However, risk factors for death or transplant were similar between groups, as are posttransplant outcomes, suggesting that more neonates with ALF may benefit from liver transplantation. Further studies are needed to improve preoperative medical management of patient comorbidities and increase candidacy for listing in neonatal ALF.

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## CONFLICT OF INTEREST

Nothing to report.

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