HEPATOLOGY

HEPATOLOGY, VOL. 68, NO. 6, 2018

Liver Transplant Listing in Pediatric Acute Liver Failure: Practices and Participant Characteristics

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Liver transplant (LT) decisions in pediatric acute liver failure (PALF) are complex. Three phases of the PALF registry, containing data on 1,144 participants over 15 years, were interrogated to characterize clinical features associated with listing status. A decrease in the cumulative incidence of listing ($P < 0.005$) and receiving ($P < 0.05$) LT occurred without an increase in the cumulative incidence of death ($P = 0.67$). Time to listing was constant and early (1 day; quartiles 1-3 = 0-2; $P = 0.88$). The most frequent reasons for not listing were "not sick enough" and "medically unsuitable." Participants listed for LT were more likely male, with coma grade scores >0; had higher international normalized ratio, bilirubin, lactate, and venous ammonia; and had lower peripheral lymphocytes and transaminase levels compared to those deemed "not sick enough." Participants listed versus those deemed "medically unsuitable" were older; had higher serum aminotransferase levels, bilirubin, platelets, and albumin; and had lower lactate, venous ammonia, and lymphocyte count. An indeterminate diagnosis was more prevalent in listed participants. Ventilator (23.8%) and vasopressor (9.2%) support occurred in a significant portion of listed participants but less frequently than in those who were not "medically suitable." Removal from the LT list was a rare event. *Conclusion:* The cumulative incidence of listing for and receiving LT decreased throughout the PALF study without an increase in the cumulative incidence of death. While all participants fulfilled entry criteria for PALF, significant differences were noted between participants listed for LT and those deemed "not sick enough" as well as those who were "medically unsuitable." Having an indeterminate diagnosis and a requirement for cardiopulmonary support appeared to influence decisions toward listing; optimizing listing decisions in PALF may reduce the frequency of LT without increasing the frequency of death. (Hepatology 2018;68:2338-2347).

Pediatric acute liver failure (PALF) is a clinical manifestation for a subgroup of heterogeneous injuries that include immune-mediated, infectious, metabolic, and genetic diseases as well as medications, toxins, and trauma.[1] In the pre–liver transplantation (LT) era, outcomes from PALF were binary as patients either survived with their native liver or died. PALF was a devastating process, with mortality rates ranging from 70% to 95%.[2,3] With the advent and advancement of pediatric LT, a third outcome was introduced, providing a potential life-saving therapeutic option for children with liver derangements. The success of LT in PALF is reflected not only in its use, whereby up to 12.5% of all pediatric LTs are now performed for the indication of PALF,[4] but also in the reduction in mortality, with recent studies showing a 21-day mortality rate of 11% in the setting of PALF.[5] However, it is important to recognize that LT perturbs the natural history of PALF and that individuals within the LT

Abbreviations: ALF, acute liver failure; ALT, alanine aminotransferase; APAP, acetaminophen; GALD, gestational alloimmune liver disease; HLH, hemophagocytic lymphohistiocytosis; INR, international normalized ratio; LT, liver transplantation; P1/P2/P3, phases 1/2/3; PALF, pediatric ALF; PALFSG, Pediatric Acute Liver Failure Study Group; WBC, white blood cell.

Received December 22, 2017; accepted May 24, 2018.
Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30116/suppinfo.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.30116

Potential conflict of interest: Dr. Ng consults for Albireo. Dr. Horslen received grants from Shire.

cohort would have either lived or died had transplant not interrupted their clinical trajectory.

The Pediatric Acute Liver Failure Study Group (PALFSG) was formed in 1999 with the goal of developing a prospective clinical registry to facilitate improved understanding of the etiopathogenesis, treatment, and outcome of acute liver failure (ALF) in children and identifying factors to help predict the likelihood of death or need for LT.[1] Notably, entry criteria for the PALF study does not "define" PALF with the inference of a poor prognosis or urgent need for LT. Rather, PALF study entry criteria identify a broader cohort of individuals who should be considered for early referral to an experienced pediatric LT center, where coordinated evaluation and management can be conducted. Once this distinction has been made, the decisions to proceed with LT listing and subsequent surgery within PALF are complex and ultimately based on the alignment of physician experience, clinical assessment, and suitable organ availability.

Often in PALF, clinical research studies are performed based on outcomes: survival or nonsurvival with the native liver, LT, and death. Importantly, receiving LT is contingent upon the clinical team's decision to proceed with an LT evaluation that may or may not result in listing the patient. Current models used to predict death in PALF are poor[6-8]; therefore, listing for and proceeding to LT in a patient who may have survived with the native liver are likely unavoidable. In support of this scenario, the PALFSG previously identified distinct patterns of immune and inflammatory mediators in children with ALF that differentiated those who survived from those who died with their native liver, while those receiving LT had a unique pattern that was more like those seen in spontaneous survivors than in those who died.[9] Furthermore, in adults it has long been recognized that there is an inherent risk of "unnecessary transplantation" in patients with ALF who were likely to recover spontaneously; and while prognostic models have been proposed, they remain imperfect.[10] As such, it is imperative to understand the patient characteristics and clinical patterns that drive listing status in PALF to optimize LT. Previous investigations by the PALFSG have described the clinical characteristics and outcomes in specific subpopulations, including PALF associated with acetaminophen (APAP) exposure,[11] neonatal PALF,[12] and those with an indeterminate etiology[13]; however, comprehensive analyses related to LT listing have not been performed. The aim of this study was to analyze the entire PALFSG data set to characterize those patients listed and not listed for LT and understand the patterns of LT listing that have occurred over time.

Patients and Methods

The PALF registry contains demographic, clinical, laboratory, and outcome data on 1,144 participants (age 0-17 years) enrolled between December 1999 and December 2014. Data were collected over three phases (phase 1 [P1], phase 2 [P2], and phase 3 [P3]) comprising participants enrolled with a clinical diagnosis of PALF meeting the following criteria:

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(1) the presence of severe hepatic dysfunction occurring within 8 weeks of onset of illness, (2) no known underlying chronic liver disease, and (3) a liver-based coagulopathy (not corrected with vitamin K) with an international normalized ratio (INR) ≥1.5 or prothrombin time ≥15 seconds in patients with encephalopathy or an INR ≥2.0 or prothrombin time ≥20 seconds in patients without encephalopathy. Phases were defined by funding cycles and protocol modifications. Data were collected over 6.5 years in P1, 4.5 years in P2, and 2.5 years in P3. Enrollment occurred as soon as possible after hospital admission to the study site. Institutional review boards at the individual centers approved the study protocol. Evaluating and managing each participant were based on local standard of care; however, the PALFSG had agreed-on guidelines for optimal evaluation of PALF at different ages.[1] Data collected by each site were transmitted to a central data-coordinating center for management and analysis.

Case report forms were completed for up to 7 days following enrollment and included LT listing status, reasons for not listing, and reasons for withdrawing a participant from the LT list. The reasons for not listing a participant were determined by the principal investigator at each site and included the following: not sick enough, medically unsuitable, sepsis, irreversible brain damage, and other (Fig. 1). Participants who were listed before enrollment or whose listing date could not be determined were not included in the listing analysis. Participants who were listed after 7 days are included in the analysis and considered to be not listed. Minimum and maximum lab values included lab values up to 7 days after enrollment or the first event (LT, death, or discharge). Participants who were discharged without LT before 7 days were considered to be alive at 7 days. Resource limitation restricted intensive data collection in P1 to up to 7 days following enrollment. Hence, 7 days was the maximum data collection across all phases.

STATISTICAL ANALYSIS

Differences in categorical variable percentages between participant groups were tested for using Pearson or exact chi-square statistics. Continuous variable distributions were tested using Kruskal-Wallis statistics. Trends across phases were tested using the Cochran-Armitage or Jonckheere-Terpstra test. Seven-day cumulative incidence rates are reported. The cumulative incidence rates take into account the competing risks of LT and death or listing for transplant and death. Cumulative incidence functions were estimated from survival models accounting for the competing risks and tested for difference using Gray's statistic and linear trend statistics. Cumulative probability of death at 7 days is reported for participants who were not listed. Participants who were listed after 7 days were treated as not listed. For the analysis of participants listed for LT versus those deemed

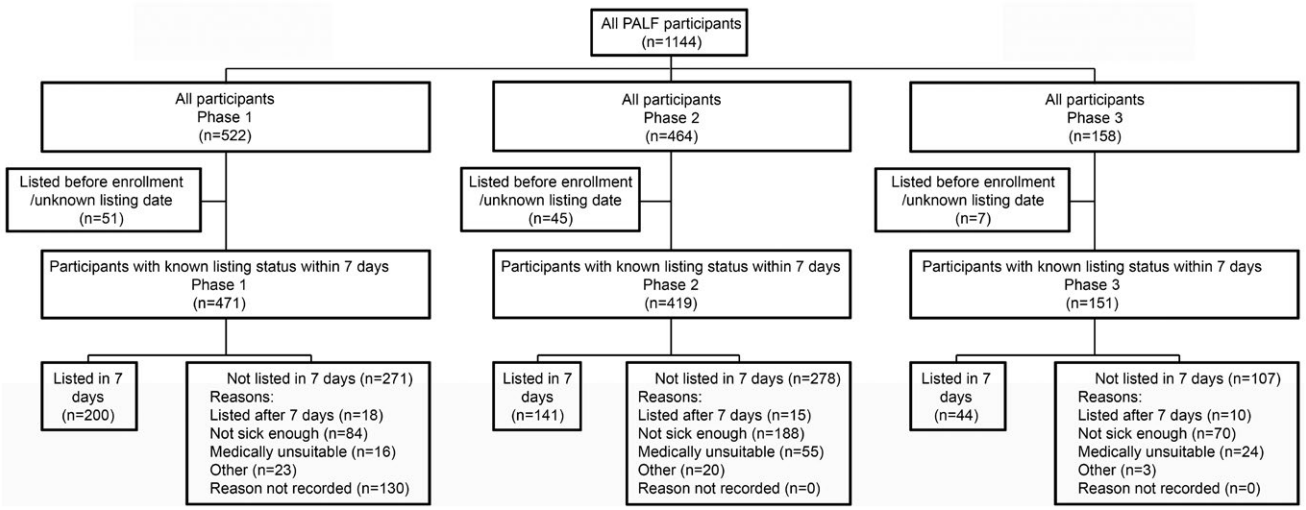

FIG. 1. PALF participants transplant listing status within 7 days after enrollment.

"medically unsuitable," only P2 and P3 data were used secondary to missing data in P1. All statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC).

Results

LISTING STATUS AND TRANSPLANTATION

Of the 1,144 participants enrolled between December 1999 and December 2014 (522 in P1, 464 in P2, and 158 in P3), 87 were listed for LT prior to study enrollment, and when they were listed was unknown for 16. These participants were excluded from listing analyses. Across the phases there was a decrease in the 7-day cumulative incidence for listing (P1 = 43.6%, P2 = 34.9%, P3 = 30.1%; $P < 0.005$) and receiving (P1 = 24.7%, P2 = 22.2%, P3 = 17.1%; $P < 0.05$) LT (Fig. 2). The distributions of time to listing after enrollment were similar across the three phases (median = 1 day; 25th-75th percentiles = 0-2; $P = 0.88$). For all participants who were listed in the first 7 days (n = 384), the median number of days from hospital admission to listing for LT was 3 (25th-75th percentiles = 1-6). For those listed, the cumulative incidence of death within 7 days of enrollment did not differ significantly among phases (P1 = 3.6%, P2 = 5.0%, P3 = 2.3%; $P = 0.67$). These results were found despite differences noted in the degree of synthetic liver dysfunction present across the three phase populations (Supporting Table S1).

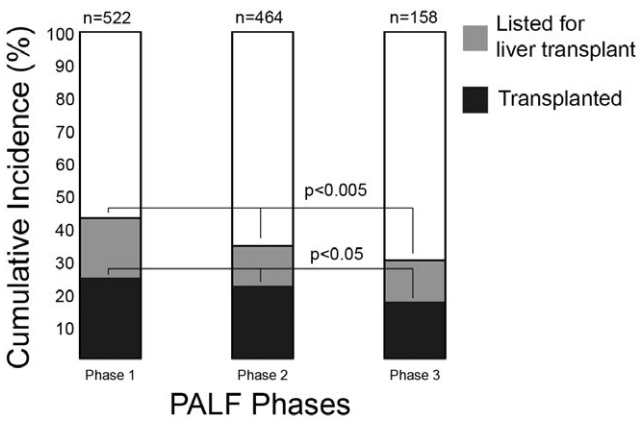

FIG. 2. Cumulative incidences of listing for and receiving LT over the three phases of PALF.

PARTICIPANT CHARACTERISTICS BY LISTING STATUS

Listing for LT was most likely to occur over the first 24 hours following study enrollment. Consequently, clinical parameters at the time of study entry, rather than dynamic clinical and biochemical changes associated with subsequent days, were most likely to be associated with decisions for listing. Therefore, comparisons of listing status are based upon clinical features at or near the time of listing.

Participants not listed for LT fell into two broad categories: those deemed "not sick enough" and those deemed to be "too sick."

Listed Versus not Listed Due to "Not Sick Enough"

The initial analysis compared those listed for LT (n = 385) within 7 days of enrollment with those not listed because the participant was considered "not sick enough" (n = 342) (Table 1). Participants who were listed for LT versus those not listed were more likely to be male (58% versus 46%); have an indeterminate diagnosis (59% versus 29%); have coma grade scores >0; have higher INR (median 3.0 versus 2.2), total bilirubin (15 versus 3.2 mg/dL), lactate (2.8 versus 2.1 mmol/L), and venous ammonia (63 versus 50.5 μmol/L); and have lower white blood cell (WBC) counts (7.7 versus 8.6 1,000/mm^2) and alanine aminotransferase (ALT) levels (1,635 versus 2,449 IU/L) at study enrollment. Cardiorespiratory support with ventilator-assisted breathing (26% versus 12%) and/or vasopressor administration (12% versus 5%) up to the day of listing was more common in participants listed for LT compared to those deemed "not sick enough." In each phase of PALF, approximately 70% of the participants who were not listed in the first 7 days and for whom a reason(s) was provided were "not sick enough."

Listed Versus Not Listed Due to "Too Sick"

For participants not listed because they were considered "too sick," reasons for not listing for LT changed over time, with the most frequent reason being that those participants were deemed "medically

TABLE 1. Participant Characteristics of Listed Versus "Not Sick Enough"

Characteristic	Total (N = 1,041)	Listed in the First 7 Days After Enrollment (n = 385)	Not Listed Due to Not Sick Enough (n = 342)	Listed Versus Not Listed *P* Value
Age (years), median, Q1-Q3*	4.4, 0.8-13.5	5.6, 1.6-12.6	5.9, 1.0-15.0	0.46
Male, n (%)	537 (51.6)	223 (57.9)	156 (45.6)	<0.001
Final diagnosis, n (%)				<0.0001
Indeterminate	436 (41.9)	227 (59.0)	100 (29.2)	
APAP	144 (13.8)	28 (7.3)	86 (25.1)	
Metabolic	99 (9.5)	36 (9.4)	33 (9.6)	
Viral	91 (8.7)	24 (6.2)	30 (8.8)	
Autoimmune	70 (6.7)	28 (7.3)	31 (9.1)	
Shock/ischemia	39 (3.7)	0 (0.0)	12 (3.5)	
Non-APAP drug-induced	31 (3.0)	9 (2.3)	15 (4.4)	
GALD	30 (2.9)	12 (3.1)	7 (2.0)	
HLH	32 (3.1)	9 (2.3)	5 (1.5)	
Veno-occlusive disease	12 (1.2)	2 (0.5)	3 (0.9)	
Multiple	19 (1.8)	4 (1.0)	6 (1.8)	
Other	38 (3.7)	6 (1.6)	14 (4.1)	
At study enrollment				
Baseline coma grade >0, n (%)	442 (46.6)	205 (56.5)	111 (34.8)	<0.001
Not assessable, n (%)	62 (6.0)	11 (2.9)	13 (3.8)	
Coma grade missing, n (%)	31 (3.0)	11 (2.9)	10 (2.9)	
ALT (IU/L), median, Q1-Q3	1,629, 479-3,547	1,635, 588-2,980	2,449, 801-5,288	<0.001
ALT missing, n (%)	87 (8.4)	23 (6.0)	21 (6.1)	
INR, median, Q1-Q3	2.5, 2.0-3.7	3.0, 2.3-4.6	2.2, 1.8-3.0	<0.001
INR missing, n (%)	93 (8.9)	27 (7.0)	28 (8.2)	
Total bilirubin (mg/dL), median, Q1-Q3	8.5, 2.7-16.5	15.0, 7.5-20.2	3.2, 1.4-9.7	<0.001
Total bilirubin missing, n (%)	91 (8.7)	25 (6.5)	37 (10.8)	
Lactate (mmol/L), median, Q1-Q3	2.6, 1.8-4.5	2.8, 1.9-4.4	2.1, 1.5-3.2	<0.001
Lactate missing, n (%)	453 (43.5)	166 (43.1)	161 (47.1)	
Venous ammonia (μmol/L), median, Q1-Q3	59, 37-93	63, 41-102	50.5, 33.0-75.5	<0.001
Venous ammonia missing, n (%)	384 (36.9)	135 (35.1)	102 (29.8)	
WBC (1,000/mm^2), median, Q1-Q3	8.4, 5.6-11.9	7.7, 5.3-10.9	8.6, 5.9-12.0	<0.01
WBC missing, n (%)	23 (2.2)	4 (1.0)	14 (4.1)	
Platelet count (1,000/mm^2), median, Q1-Q3	154, 88-230	167, 108-253	174.0, 103.5-236.5	0.58
Platelet count missing, n (%)	24 (2.3)	5 (1.3)	14 (4.1)	
Glucose (mg/L), median, Q1-Q3	97, 75-125	96, 74-123	100.0, 77.5-128.0	0.46
Glucose missing, n (%)	62 (5.9)	18 (4.7)	15 (4.4)	
Albumin (g/dL), median, Q1-Q3	2.8, 2.4-3.2	2.8, 2.5-3.2	2.9, 2.5-3.3	0.21
Albumin missing, n (%)	27 (2.6)	7 (1.8)	9 (2.6)	
Any use up to day of listing				
Ventilator, n (%)	292 (28.0)	101 (26.2)	42 (12.3)	<0.001
Pressor, n (%)	170 (16.3)	46 (12.0)	18 (5.3)	<0.01
7-day cumulative incidence				
LT	19.4%	49.1%	0%	—
Death	6.5%	4.0%	0.5%	0.002
21-day cumulative incidence†				
LT	32.1%	68.6%	—	—
Death	17.1%	10.4%	3%	<0.001

*Quartile 1-quartile 3.
†In P1 participants were only followed for 21 days; therefore, only 21-day cumulative incidence postenrollment is provided.

TABLE 2. Reasons for Not Listing for LT in PALF*

	Total, N (%)	P1, n (%)	P2, n (%)	P3, n (%)
Sepsis	15 (10.6)	5 (12.8)	10 (13.3)	0 (0.0)
Medically unsuitable	95 (67.4)	16 (41.0)	55 (73.3)	24 (88.9)
Irreversible brain damage	6 (4.3)	3 (7.7)	2 (2.7)	1 (3.7)
Active psychiatric issue	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Other	24 (17.0)	15 (38.5)	7 (2.7)	2 (7.4)

*Reasons for not listing (excluding not sick enough) are significantly different across phases (exact Pearson chi-square $P = 0.0002$).

unsuitable" (Table 2). In P2 and P3 (n = 570), significant differences were seen between those participants listed in the first 7 days following study enrollment (n = 185) and those deemed "medically unsuitable" (n = 79) (Table 3). Compared to "medically unsuitable" participants, those listed for LT were older (5.6 versus 0.2 years), more likely to have an indeterminate diagnosis (55.7% versus 12%), and less likely to have a diagnosis of viral (5.9% versus 25.3%), shock/ischemia (0% versus 12.7%), or hemophagocytic lymphohistiocytosis (HLH) (4.3% versus 12.7%). Also, those who were listed tended to have higher ALT (1,170 versus 670 IU/L), INR (median 2.9 versus 2.6), total bilirubin (15.1 versus 6.2 mg/dL), platelet count (165.5 versus 94 1,000/mm^2), and albumin (2.9 versus 2.6 g/dL), with lower lactate (2.8 versus 4.2 mmol/L), venous ammonia (63 versus 83 μmol/L), and WBC counts (7.4 versus 9.5 1,000/mm^2). Listed participants were less likely to have required cardiorespiratory support in the form of ventilator-assisted breathing (23.8% versus 70.9%) or vasopressor administration (9.2% versus 57%). Notably, "irreversible brain damage," a major finding in adults with ALF who do not receive LT,[14] was an uncommon reason for not placing a child on the LT wait list (P1 = 7.7% [3/39], P2 = 2.7% [2/75], P3 = 3.7% [1/27]) (Table 2).

PARTICIPANTS REMOVED FROM THE LT LIST

Removal from the wait list was a rare event. A participant listed before enrollment or during the first 7 days after enrollment (n = 472) was unlikely to be removed during the first 7 days of the study (n = 27, ~6%). Reasons for removal were improved (n = 16, 59%), medically unsuitable (n = 5, 19%), irreversible brain damage (n = 3, 11%) sepsis (n = 2, 7%), and parent refusal (n = 1, 4%).

Discussion

By interrogating the data collected over the 15-year period of the Pediatric Acute Liver Failure Study, this investigation characterized clinical decision making and participant features related to LT listing. Similar to publications in adults with ALF,[14] just over one third of participants with PALF were listed for LT within the first 7 days following enrollment. LT is lifesaving for the subset of children with ALF who will not recover without such intervention. However, once LT has been undertaken, it is no longer possible to know if spontaneous recovery with native liver could have been achieved. Moreover, because some children with ALF who are listed for LT show clinical improvement prior to availability of a donor liver organ and are removed from the waiting list, there are likely to be other children who would have recovered spontaneously or with appropriate therapeutic support without LT. Differentiating who will survive without LT (LT unnecessary), who will die without LT but will survive with successful transplant (LT needed), and who will die whether or not they get transplanted (LT futile) among an equally sick cohort of children cannot be guided by current data. Single biomarkers such as ammonia,[15] actin-free Gc-globulin,[16,17] and lactate[18] are not reliable or generalizable to all ALF patients and have not been adequately studied in children. Prognostic scoring models using clinical and biochemical parameters obtained at admission or using peak values on subsequent days, such as Kings College criteria[18,19] and liver injury unit score,[20] do not reliably predict death. While more complex models that incorporate the dynamic nature of PALF, using a growth mixture model[13] or a panel of immune and inflammatory markers,[9] have shown promise, our data demonstrate that listing decisions are often made early, before these dynamic patterns are established. As decisions to list are prerequisites to decisions for LT, it is important to identify the critical factors related to decisions to list for and proceed to LT. To date, no studies of PALF have examined stated or implied reasons physicians decide to list patients for LT. The current study seeks to fill that gap.

TABLE 3. Participant Characteristics of Listed Versus Medically Unsuitable for Listing: P2 and P3 Only

Characteristic	Total (N = 570)	Listed in the First 7 Days After Enrollment (n = 185)	Not Listed Medically Unsuitable (n = 79)	*P*
Age (years), median, Q1-Q3	3.8, 0.4-13.5	5.6, 1.8-13	0.2, 0.0-3.8	<0.001
Male, n %	298 (52.3)	108 (58.4)	41 (51.9)	0.33
Final diagnosis, n (%)				<0.001
Indeterminate	208 (36.5)	103 (55.7)	12 (15.2)	
APAP	84 (14.7)	15 (8.1)	0 (0.0)	
Metabolic	56 (9.8)	20 (10.8)	10 (12.7)	
Viral	60 (10.5)	11 (5.9)	20 (25.3)	
Autoimmune	41 (7.2)	14 (7.6)	0 (0.0)	
Shock/ischemia	19 (3.3)	0 (0.0)	10 (12.7)	
Non-APAP drug-induced	14 (2.5)	3 (1.6)	1 (1.3)	
GALD	20 (3.5)	5 (2.7)	6 (7.6)	
HLH	25 (4.4)	8 (4.3)	10 (12.7)	
Multiple	6 (1.1)	1 (0.5)	0 (0.0)	
Veno-occlusive disease	5 (0.9)	0 (0.0)	2 (2.5)	
Other	32 (5.6)	5 (2.7)	8 (10.1)	
At study enrollment				
Baseline coma grade > 0 (n%)	205 (41.8)	84 (50.9)	30 (58.8)	0.32
Not assessable, n (%)	50 (8.8)	11 (5.9)	6 (7.6)	
Coma grade missing, n (%)	30 (5.3)	84 (50.9)	30 (58.8)	
ALT (IU/L), median, Q1-Q3	1,647.5, 470.0-3,721.5	1,770.0, 617.0-3,157.0	670.0, 104.0-1,513.0	<0.001
ALT missing, n (%)	26 (4.6)	8 (4.3)	6 (7.6)	
INR, median, Q1-Q3	2.5, 2.0-3.5	2.9, 2.3-4.3	2.6, 2.0-3.7	0.01
INR missing, n (%)	29(5.1)	12(6.5)	4 (5.1)	
Total bilirubin (mg/dL), median, Q1-Q3	7.7, 2.5-15.7	15.1, 7.4-20.4	6.2, 3.7-13.1	<0.001
Total bilirubin missing, n (%)	68(11.9)	17 (9.2)	10 (12.7)	
Lactate (mmol/L), median, Q1-Q3	2.5, 1.7-4.4	2.8, 2.1-4.4	4.2, 2.5-7.6	0.009
Lactate missing, n (%)	245(43.0)	82 (44.3)	20 (25.3)	
Venous ammonia (μmol/L), median, Q1-Q3	58, 37-89	63, 44-102	83, 57-155	0.01
Venous ammonia missing, n (%)	152 (26.7)	43 (23.2)	27 (34.2)	
WBC (1,000/mm^2), median, Q1-Q3	8.3, 5.6-12.1	7.4, 5.2-10.1	9.5, 6.4-13.7	0.003
WBC missing, n (%)	10 (1.8)	1 (0.5)	0 (0.0)	
Platelet count (1,000/mm^2), median, Q1-Q3	147.0, 85.0-221.0	165.5, 106.5-238.5	94.0, 53.0-131.0	<0.001
Platelet count missing, n (%)	9 (1.6)	1 (0.5)	0 (0.0)	
Glucose (mg/L), median, Q1-Q3	96.0, 73.0-125.0	97.0, 71.0-128.0	94.0, 70.3-122.0	0.62
Glucose missing, n (%)	15 (2.6)	6 (3.2)	2 (2.5)	
Albumin (g/dL), median, Q1-Q3	2.8, 2.4-3.2	2.9, 2.5-3.2	2.6, 2.2-3.0	<0.001
Albumin missing, n (%)	12(2.1)	2 (1.1)	2 (2.5)	
Creatinine (mg/dL), median, Q1-Q3	0.5, 0.3-0.7	0.4, 0.3-0.6	0.5, 0.3-1.1	0.15
Creatinine missing, n (%)	5 (0.9)	1(0.5)	0 (0.0)	
Any use up to day of listing				
Ventilator, n (%)	154 (27.0)	44 (23.8)	56 (70.9)	<0.001
Pressor, n (%)	79 (13.9)	17 (9.2)	45 (57)	<0.001
7-day cumulative incidence				
LT	18%	50.8%	0%	—
Death	6.5%	4.4%	29.20%	<0.001
30-day cumulative incidence				
LT	33.5%	77.9%	n/a*[1]	—
Death	22.9%	12.5%	63%	<0.001

*Nine participants who underwent LT within 30 days of enrollment were listed more than 7 days after enrollment.
Abbreviation: n/a, not applicable.

Notably, despite a comparable degree of synthetic liver dysfunction, there was a decrease in both the cumulative incidence of listing for LT over time and the cumulative incidence of actual LT without an identifiable increase in mortality in more recent cohorts. These data demonstrate that over the course of the PALFSG, participants who were likely to survive with their native liver were increasingly identified. There are likely multiple contributing factors associated with this finding. Improvements in directed therapies and supportive care,[21,22] improved PALFSG-associated health care provider experience in managing the complexity of PALF, recommendations for age-appropriate evaluations within the PALFSG,[23] and published diagnostic strategies and practice guidelines[24] collectively have enhanced the care afforded to these critically ill patients. While difficult to quantitate, these factors have assuredly impacted the multifaceted decisions surrounding the pursuit of LT as a therapeutic option.

When ALF is the indication to list for LT, it presumes the child has progressive, irreversible hepatic dysfunction and can only be rescued by acceptance of a donor organ with tolerable risk factors. Once that clinical judgement is made, and an organ becomes available, a decision to refuse an organ can be challenging. Therefore, it is notable that, despite improvements in clinical management, the time to listing was constant and early throughout the phases of the PALF study. On average, if pursued, listing children with ALF occurred within the first 24 hours of study enrollment. This pattern suggests that prior publications looking to establish prognostic tools based on clinical trajectories[13,25] and "peak" values[7] over the clinical course may be less applicable to the process of listing. Thus, medical decisions related to listing for LT in PALF may be less reflective of the dynamic nature of the disease course following attainment of PALSG entry criteria and more representative of the child's early clinical status leading up to the development of ALF.

Early, anticipatory listing may be influenced partly by the realities of overall organ shortages.[14] The act of placing patients on the LT list enables a better chance of locating a potential donor candidate whose anatomy and size would be suitable to a pediatric recipient. However, one consequence of early listing may be the acceptance of an organ in an individual whose clinical course would have improved with continued aggressive supportive therapy. Consequently, LT would be an unnecessary intervention, inflicting the short-term risks of LT surgery and the long-term sequelae of lifelong immunosuppression. On the contrary, a delay in listing would risk disease progression or the development of complications or comorbidities which could result in the patient becoming "too sick" for LT. Yet we found that disease progression resulting in removal from the transplant list was an infrequent occurrence over the first 7 days following study enrollment. It is therefore worth considering that more conservative approaches to patient listing may enable a clearer picture of disease trajectory, optimizing the selection of patients listed for LT and further minimizing the chances of replacing an organ with the potential to recover.

Diagnosis appears to associate with listing status, although a final diagnosis was not always established at the time of listing. Listed participants were more likely to have an indeterminate diagnosis, while non-listed participants were more likely to have a confirmed diagnosis. Among those who were "not sick enough," a diagnosis of APAP toxicity was the most common and no participants with APAP-induced ALF were deemed "medically unsuitable." One report has shown that 61% of PALF participants with acute APAP toxicity had no clinical encephalopathy at baseline.[11] Thus, the majority met PALF entry criteria based upon an uncorrectable liver-based coagulopathy. Individuals with APAP toxicity meeting PALF entry criteria should be carefully monitored by an LT center; however, additional factors, such as the presence of or advancing encephalopathy, might prompt considerations to list for LT. Diagnoses associated with being "medically unsuitable" for listing included viral, gestational alloimmune liver disease (GALD), HLH, and shock/ischemia. Herpes simplex virus, enterovirus, and GALD are among the most common causes of ALF in the neonate. Infants with these conditions are often desperately ill and have associated multiorgan failure. Thus, it is not surprising that participants with these diagnoses, compounded by the size of the patient, would be considered "medically unsuitable" for listing. Congenital or, more commonly, idiopathic HLH also has multisystem involvement and has historically been considered a contraindication to LT as chemotherapy with or without bone marrow transplantation is the preferred treatment. However, recent reports of transplant outcomes in HLH have shown that a benefit can be achieved in select patients.[26]

Important clinical and biochemical differences are noted depending upon listing status. Clinical parameters among those "medically unsuitable" for listing reflect the severity of the participant's illness with ventilator and pressor support required in over 70% and 57%, respectively. As might be expected, lactate levels were highest in this group. In addition, the lowest median platelet count was present in this cohort, which is likely reflective of the disease severity as well as the underlying diagnoses of viral etiology and HLH that accounted for 38% of this cohort. For those deemed "not sick enough" to list for LT, median ALT was the highest and total bilirubin was the lowest among the three cohorts likely impacted by the clinical phenotype of APAP toxicity that accounted for 25% of this cohort. For those listed for LT, total bilirubin was the most distinguishing feature compared to the two cohorts that were not listed. The reasons for this are not clear but may be related to a vigorous inflammatory process seen in many indeterminate cases as well as hemolysis associated with Wilson disease. The need for ventilator (23.8%) and vasopressor (9.2%) support occurred in a significant portion of listed subjects but less frequently than those who were not medically suitable for LT listing.

Male patients were more likely to be listed for LT than female patients in our cohort. This sexual disparity related to listing, though unexplained, appears to mirror national trends in LT. Recent data from the US Department of Health and Human Services Organ Procurement and Transplantation Network demonstrates that in 2017 only 35.7% of all LT recipients were female.[27] Review of the data over the past 20 years shows a clear trend in sexual inequality in LT recipients.[27] Future efforts to more completely understand these disparities are needed.

Several limitations of the current study should be acknowledged. First, while age-appropriate evaluations and management strategies within the PALFSG have been presented, variation in clinical care existed across centers and across time. Second, the decision to list, remove, or inactivate a participant was site-specific and not directly dictated by PALFSG protocols or by the site principal investigator. Also, the analyzed data were limited by what had been collected. For example, while increased granularity into the decision to designate an individual as "medically unsuitable" would have enabled greater insight into the principal investigator's thought processes, the determination was made by checking a box on the case report forms, without free text. Thus, we cannot know what an individual clinician used to determine what is "medically unstable," and we would not want to infer what that might be. Additionally, PALF study data collection did not begin until study enrollment; therefore, it is unknown how the clinical course of each participant prior to study enrollment influenced the teams' decision to list. Finally, we recognize the inherent bias in including only children whose families agreed to participate in the prospective study, potentially limiting the generalizability of our findings.

In conclusion, we characterized clinical features of PALF participants who were listed and not listed for LT during the 15 years of enrollment. Our findings show that the cumulative incidences of listing for and receiving LT decreased over time without an increase in the cumulative incidence of death. The process of listing generally occurred early after study enrollment and was therefore less likely to be influenced by the clinical trajectory of the participant's disease following attainment of PALF entry criteria. The large majority of patients who were listed proceeded to transplant, with only 3% removed from the list because they had improved. While all participants fulfilled entry criteria for PALF, significant differences were noted between participants listed for LT versus those deemed "not sick enough" as well as listed participants versus those who were "medically unsuitable." Having an indeterminate diagnosis and a requirement for cardiopulmonary support appeared to influence decisions toward listing. Research focused on testing and optimizing listing decision algorithms in PALF could reduce the frequency of LT while preserving patient survival.

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