Changing Etiologies and Prognostic Factors in Pediatric Acute Liver Failure

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After the implementation of universal hepatitis A virus vaccination in Argentina, the outcome of pediatric acute liver failure (PALF) remains unknown. We aimed to identify variables associated with the risk of liver transplantation (LT) or death and to determine the causes and short-term outcomes of PALF in Argentina. We retrospectively included 135 patients with PALF listed for LT between 2007 and 2016. Patients with autoimmune hepatitis (AIH), Wilson's disease (WD), or inborn errors of metabolism (IEM) were classified as PALF–chronic liver disease (CLD), and others were classified as "pure" PALF. A logistic regression model was developed to identify factors independently associated with death or need of LT and risk stratification. The most common etiologies were indeterminate (52%), AIH (23%), WD (6%), and IEM (6%). Overall, transplant-free survival was 35%, whereas 50% of the patients underwent LT and 15% died on the waiting list. The 3-month risk of LT or death was significantly higher among patients with pure PALF compared with PALF-CLD (76.5% versus 42.5%; relative risk, 1.8 [1.3-2.5]; $P < 0.001$), and 3 risk factors were independently associated with worse outcome: international normalized ratio (INR) ≥3.5 (odds ratio [OR], 3.1; 95% confidence interval [CI], 1.3-7.2]), bilirubin ≥17 mg/dL (OR, 4.4; 95% CI, 1.9-10.3]), and pure PALF (OR, 3.8; 95% CI, 1.6-8.9). Patients were identified by the number of risk factors: Patients with 0, 1, or ≥2 risk factors presented a 3-month risk of worse outcome of 17.6%, 36.6%, and 82%, respectively. In conclusion, although lacking external validation, this simple risk-staging model might help stratify patients with different transplant-free survival rates and may contribute to establishing the optimal timing for LT.

Liver Transplantation 26 268–275 2020 AASLD.
Received July 2, 2019; accepted September 29, 2019.

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Pediatric acute liver failure (PALF) is an uncommon life-threatening condition in which a previously healthy child rapidly progresses to synthetic liver dysfunction within 8 weeks of the onset of symptoms.[1] Unlike in adults, in PALF, the presence of hepatic encephalopathy is not required to make the diagnosis. PALF is a common indication for liver transplantation (LT) in children, representing 23% of the patients on the pediatric transplant waiting list in Argentina.[2]

LT for PALF has experienced significant changes over time in Latin America. Historically, hepatitis A virus (HAV) infection accounted for 43% of all PALF patients in a large cohort study from our region.[3] Particularly in Argentina, HAV infection was the main cause of PALF in approximately 60% of patients and the first indication for LT in children.[4,5] In 2005, universal HAV vaccination with

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; AOR, adjusted odds ratio; AST, aspartate aminotransferase; CI, confidence interval; CLD, chronic liver disease; GALD, gestational alloimmune liver disease; HAV, hepatitis A virus; IEM, inborn errors of metabolism; INCUCAI, Instituto Nacional Central Unico Coordinador de Ablación e Implante; INR, international normalized ratio; IQR, interquartile range; LT, liver transplantation; OLT, orthotopic liver transplantation; OR, odds ratio; PALF, pediatric acute liver failure; RR, relative risk; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; WD, Wilson's disease.

a single dose in children at 12 months was implemented in Argentina; consequently, since 2007, no cases of PALF secondary to HAV infection in children have been reported.[5,6]

Short-term survival after LT in PALF has improved in the last years; however, longterm survival still remains poor when compared with other indications for transplantation.[7] The ability to predict the need of LT in PALF and to determine the severity of illness is an unmet need in the clinical care of these patients. Several scoring systems have been developed to aid the decision whether to transplant a patient with acute liver failure (ALF) or not.[8-10] The etiology of PALF differs worldwide, depending on geographical and socioeconomic characteristics. Thus, the application of these scores is questionable, and clear standard criteria for LT are difficult to establish.

Therefore, in this study, we aimed to identify variables associated with the risk of death or LT and to investigate the etiologies and short-term outcomes of children with PALF after the implementation of universal vaccination for HAV.

Patients and Methods

This was a multicenter retrospective cohort study of children with PALF listed for orthotopic LT in Argentina from March 2007 to December 2016. The study included pediatric patients (younger than 18 years) listed with PALF with emergency status at our National Transplant Registry, Instituto Nacional Central Unico Coordinador de Ablación e Implante (INCUCAI). All enrolled patients met entry criteria as defined by the PALF study group:

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.25658

Potential conflict of interest: Nothing to report.

1. No known evidence of chronic liver disease (CLD).
2. Chemical evidence of acute liver injury.
3. Coagulopathy defined as international normalized ratio (INR) ≥1.5 following parenteral administration of vitamin K with clinical hepatic encephalopathy, or INR ≥2.0 with or without hepatic encephalopathy.[11]

Hepatic encephalopathy was evaluated on physical examination and/or electroencephalogram in accordance with standard recommendations.[12] The underlying cause of PALF was based on standard laboratory tests obtained clinically at each transplant center and by investigator judgment. Patients were divided into 2 groups according to the European Association for the Study of the Liver[13] and as recently proposed by Di Giorgio et al. from the Hospital Papa Giovanni XXIII in Bergamo, Italy[14]: patients with CLD presenting with a PALF phenotype (PALF-CLD) and another group that included all other patients ("pure" PALF). PALF-CLD was established if patients were eventually diagnosed with 1 of the following conditions: Wilson's disease (WD), inborn errors of metabolism (IEM), autoimmune hepatitis (AIH), Budd-Chiari syndrome, or chronic hepatitis B reactivation. Patients considered to have had an acute insult occurring on a previously healthy liver were classified as pure PALF. Etiological diagnosis was made according to international guidelines at each study center based on clinical history, imaging studies, laboratory values, and, in some cases, histopathological characteristics.[1,13,15] To confirm the diagnosis of AIH, the simplified criteria were retrospectively applied. Those patients who presented a score ≥6 were identified as AIH.[16] If a specific etiology was not identified, the patient was classified as having an indeterminate cause. Even though patient management and candidacy for LT was determined at each site, listing for transplantation criteria was uniform and followed published clinical guidelines.[1,13,15]

Data were obtained from a survey previously discussed by all participating centers. Participating LT programs represented >90% of all of the children listed for LT during the study period in the INCUCAI database. All data records were checked for missing values and inconsistencies. Queries were referred to the participating institution, and corrections were made at the data coordinating center.

All procedures followed were in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and complied with the ethical standards of the

responsible committee on human experimentation and with the Declaration of Helsinki 1975, as revised in 2008.[17] The institutional review board at the Hospital Universitario Austral and of each participating center approved the study.

STATISTICAL ANALYSIS

Patients included in the study were divided into 2 groups and compared (pure PALF versus PALF-CLD). Data were presented as numbers and percentages, medians and interquartile ranges (IQR), or means and standard deviations (SD) with 95% confidence interval (CI). Comparisons of baseline parameters between patient groups were performed with Student *t* test, Mann-Whitney U test for continuous variables, and χ^2 test for categorical variables. We defined worse outcomes as either the need for LT or death. The transplant-free survival group included those patients treated by supportive management who survived without LT. Total bilirubin ≥17 mg/dL and INR ≥3.5 cutoffs were defined according to King's College criteria.[18] To identify factors associated with LT or death, we developed a logistic regression model. Variables significantly associated with death or the need of LT in the crude analysis were added 1 at a time in the multivariate model. The final variable selection was based on clinical relevance and statistical significance. Calibration and discrimination of the model were evaluated with the Hosmer-Lemeshow goodness-of-fit test and area under the curve. Internal validation of coefficient estimation was performed by using bootstrapping. Tests were 2-sided, and significance was accepted at $P < 0.05$. Statistical analysis was performed by STATA, version 13 (StataCorp., College Station, TX).

Results

DEMOGRAPHIC CHARACTERISTICS AND CLINICAL DATA

A total of 135 patients with PALF were listed for LT during the study period. Overall, 54.1% of the patients were female, median age at diagnosis was 3.7 years (IQR, 1.3-11.1 years), and only 14 patients (10.3%) were infants. Hepatic encephalopathy was manifested in 74% of the patients. Median (IQR) baseline parameters were INR, 3.5 (2.4-5.2); creatinine, 0.5 mg/dL (0.3-0.6); and total bilirubin, 19.5 mg/dL (11.1-26.3 mg/dL). Patients with AIH presented at a median (IQR) age of 9.7 (2.9-13.5) years, and 23 (74.2%) patients were female. Type 2 AIH was diagnosed in 8 (25.8%) patients. Median (IQR) age of patients with WD and IEM was 14.0 years (9.9-14.5 years) and 0.7 years (0.3-1.2 years), respectively. Extrahepatic organ dysfunction was frequently reported during hospitalization. Ventilatory support was required in 60 patients (44%), vasopressors in 58 (43%), and renal replacement therapy in 23 (17%) during intensive care unit stay. Intracranial pressure monitoring was placed in only 7 (5%) patients. Table 1 provides an overview of relevant baseline differences comparing patients with pure PALF and PALF-CLD. We found a higher proportion of women in the PALF-CLD group (33 [69%] versus 40 [46%]; $P = 0.01$) and a higher median age at diagnosis (8.6 versus 2.6; $P = 0.02$). Patients presenting with PALF-CLD also had a lower median (IQR) INR (3.2 [2.5-4.9] versus 3.5 [2.2-5.9]; $P = 0.05$) and lower median values of aspartate aminotransferase (AST; 782 versus 1702 U/L; $P = 0.006$) and alanine aminotransferase (ALT; 499 versus 1365 U/L; $P = 0.001$). There were no differences in the other biochemical clinical parameters.

DISTRIBUTION OF ETIOLOGIES IN PALF

The etiologies and outcomes of PALF in the patient population are presented in Fig. 1. The majority of cases were due to indeterminate cause accounting for 70 (52%) patients, followed by AIH with 31 (23%) patients. WD and IEM accounted for 8 (6%) patients each; drug toxicity accounted for 6 (4%) patients, gestational alloimmune liver disease (GALD) accounted for 4 (3%) patients; and other indications accounted for 8 (6%) patients. Drugs associated with PALF in our cohort were isoniazid (4 patients), valproate (1 patient), and paracetamol (1 patient). Children classified as having IEM presented with ornithine transcarbamylase deficiency (5 patients) and tyrosinemia (3 patients). Etiologies classified as others included the following: acute Epstein-Barr virus infection (3 patients), ischemic hepatitis (2 patients), herpes simplex virus infection (2 patients), and giant cell hepatitis with hemolytic anemia (1 patient). No patients with Budd-Chiari syndrome or hepatitis B reactivation were identified.

TABLE 1. Baseline Parameters in Patients With PALF

Variables	Overall (n = 135)	Pure PALF (n = 88)	PALF-CLD (n = 47)	*P* Value
Age, years	3.7 (1.3-11.1)	2.6 (1.2-8.7)	8.6 (1.5-13.3)	0.02
Sex, female	73 (54.1)	40 (45)	33 (70)	0.01
Jaundice on admission	120 (89)	80 (91)	40 (85)	0.12
Encephalopathy	100 (74)	65 (74)	35 (74)	0.83
Encephalopathy grade >2	50 (37)	35 (40)	15 (32)	0.31
Hemoglobin, g/dL	11.0 ± 2.2	11.4 ± 2.2	10.2 ± 2.1	0.98
White blood cells, $\times 10^3/\mu L$	11.7 ± 5.5	11.8 ± 5.5	11.7 ± 5.8	0.98
Platelets, $\times 10^3/\mu L$	219 ± 118	228 ± 122	203 ± 110	0.23
INR	3.5 (2.4-5.2)	3.5 (2.2-5.9)	3.2 (2.5-4.9)	0.05
Creatinine, mg/dL	0.5 (0.3-0.6)	0.4 (0.3-0.5)	0.5 (0.3-0.8)	0.15
Total bilirubin, mg/dL	19.5 (11.1-26.3)	19.9 (13.2-26.1)	17.1 (8.0-27.8)	0.44
AST, U/L	1216 (268-2692)	1702 (554-3048)	782 (171-1361)	0.006
ALT, U/L	1269 (321-2461)	1365 (673-2851)	499 (73-1893)	0.001
Albumin, g/dL	3.1 (2.7-3.5)	3.2 (2.7-3.6)	2.8 (2.3-3.3)	0.06
Vasopressors	58 (43)	37 (42)	21 (45)	1.00
Ventilatory support	60 (44)	40 (45)	20 (43)	0.45
Renal replacement therapy	23 (17)	16 (18)	7 (15)	0.64
Intracranial pressure monitoring	7 (5)	6 (7)	1 (2)	0.43

NOTE: Data are given as mean ± SD, median (IQR), or n (%).

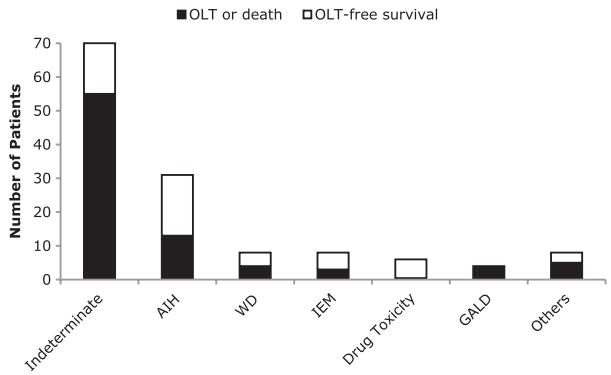

FIG. 1. Etiologies and outcomes of 135 pediatric patients with ALF.

The risk of death or LT appeared to be particularly high for patients with pure PALF due to an indeterminate cause (81%) or with GALD (100%). No suggestive signs of CLD or cirrhosis were found in the explanted livers of patients with pure PALF. The PALF-CLD group included 47 patients with the following etiologies: AIH, WD, and IEM. On the other hand, 88 patients composed the pure PALF group with indeterminate cause, drug-toxicity, GALD, and other causes.

OUTCOME

The overall outcomes of the 135 patients with PALF listed for LT are shown in Fig. 2. Altogether, 68 (50%) patients received a liver graft; 11 of the 68 (16%) LT recipients died after surgery, and 20 (15%) patients died without LT. The etiologies of those children who died after transplantation (n = 11) were indeterminate in 8 patients, and 1 patient each for AIH, GALD, and IEM. Patients who died while on the waiting list (n = 20) presented with indeterminate cause in 11 patients, IEM in 3, AIH and GALD in 2 patients, WD in 1 patient, and ischemic hepatitis in 1 patient. From those patients who underwent LT, 28 (41%) received a whole cadaveric donor, 26 (38%) received a split donor, and 14 (21%) underwent living donation. Only 47 (35%) patients recovered spontaneously with support therapy, and these patients were removed from the waiting list and discharged. The median time from transplantation listing to actual transplantation was 5 days (IQR, 2-9 days). Overall, 104 (77%) PALF patients were discharged from the hospital alive.

In the AIH group, 27 of 31 patients were treated with steroids according to the protocol at each institution. A total of 20 patients received oral steroids, and the remaining 7 were treated intravenously. From those patients who received steroids, 8 underwent

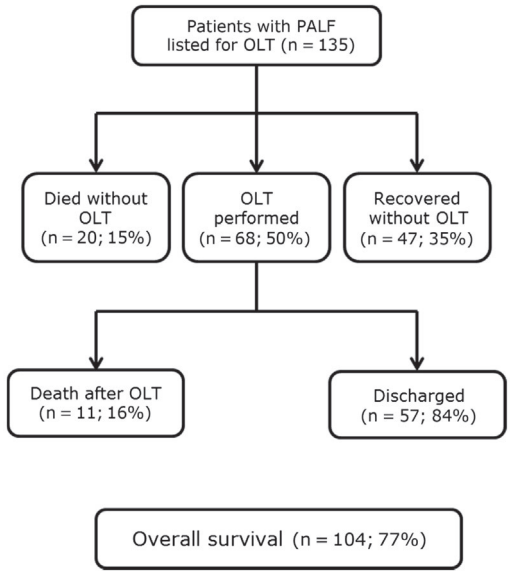

FIG. 2. Outcome of 135 pediatric patients with ALF.

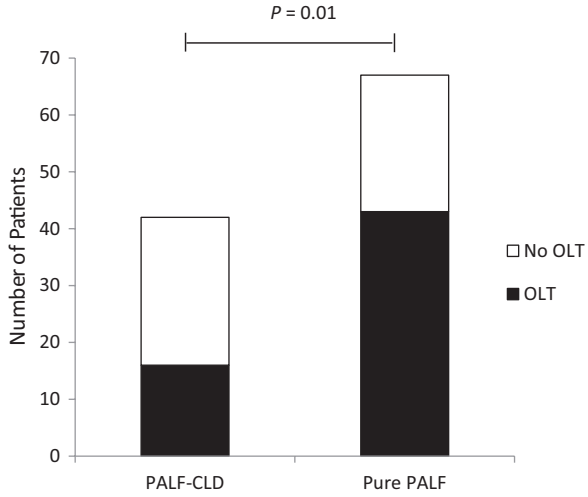

FIG. 3. Comparison among children with ALF with or without underlying liver disease according to the need for OLT.

LT, 1 died on the waiting list, and the remaining 18 were delisted and discharged. Of the 8 patients with WD, 4 received treatment: 2 patients were treated with plasmapheresis, 1 patient was treated with oral penicillamine, and 1 patient received penicillamine plus plasmapheresis. In the GALD group, only 1 of 4 patients was treated with intravenous immunoglobulin.

The 3-month risk of LT or death was significantly higher among patients with pure PALF compared with PALF-CLD (76.5% versus 42.5%; relative risk [RR], 1.8 [1.3-2.5]; $P < 0.001$). In the PALF-CLD group, 30 (64%) patients survived without LT, whereas in the pure PALF group, only 31 (35%) patients survived with medical support ($P = 0.01$; Fig. 3).

PREDICTION OF LT OR DEATH IN PALF

Among the studied variables, the presence of encephalopathy, need of ventilatory support or vasopressors, pure PALF etiology, peak INR, and peak total bilirubin were related to worse outcomes (Table 2). After adjusting using logistic regression, the model identified 3 risk factors associated with the need of LT or death: peak INR ≥3.5 (odds ratio [OR], 3.1; 95% CI, 1.3-7.2; $P < 0.001$), peak total bilirubin ≥17 mg/dL (OR, 4.4; 95% CI, 1.9-10.3; $P < 0.001$), and pure PALF (OR, 3.8; 95% CI, 1.6-8.9; $P < 0.001$). The prediction model identified risk groups according to the number of risk factors: patients with 0, 1, or ≥2 risk factors presented a 3-month risk of worse outcome of 17.6%, 36.6%, and 82%, respectively (Table 3). The model showed adequate calibration (Hosmer-Lemeshow goodness-of-fit test, $P = 0.52$). Discrimination evaluated by the receiver operating characteristic curve was 0.78 (95% CI, 0.7-0.9).

Discussion

Large epidemiological national surveys of PALF involving more than 1 center are scarce in Latin America. Information regarding the etiologies, management, and outcomes of PALF is usually obtained from other regional studies, especially from Europe and the United States. In our study, we included patients from 6 transplant centers representing almost the whole PALF population in Argentina. This gives us a comprehensive overview of the outcomes and evolution of PALF after the implementation of the national HAV vaccination program. We described how after eliminating HAV as a cause of PALF, an indeterminate cause was the main etiology followed by children with CLD presenting with ALF, such as AIH, WD, and IEM. In this new epidemiological scenario, we identified 3 factors associated with worse outcomes (total bilirubin, INR, and pure PALF), which allowed us to stratify patients into 3 risk groups.

TABLE 2. Univariate Analysis of Patients With PALF

Variables	Spontaneous Survivors (n = 47)	Death or LT (n = 88)	OR	95% CI	*P* Value
Age, years	6.3 ± 5.6	6.0 ± 5.5	0.9	0.9-1.1	0.78
Sex, female	30 (64)	43 (49)	1.8	0.9-3.9	0.09
Encephalopathy during hospitalization	27 (57)	73 (83)	3.6	1.6-8.1	0.002
INR ≥3.5	13 (28)	50 (57)	3.5	1.6-7.6	0.001
Creatinine, mg/dL	0.5 ± 0.5	0.7 ± 0.6	1.8	0.8-4.2	0.16
Total bilirubin ≥17 mg/dL	16 (34)	61 (69)	4.5	2.1-9.7	<0.001
Albumin, g/dL	3.2 ± 0.7	3.0 ± 0.7	0.7	0.4-1.2	0.17
Vasopressors	13 (28)	45 (51)	2.8	1.4-6.3	0.008
Ventilatory support	11 (23)	49 (56)	4.3	1.9-9.8	<0.001
Renal replacement therapy	5 (11)	18 (20)	2.1	0.7-6.1	0.23
Pure PALF	21 (45)	66 (75)	3.7	1.8-7.9	0.001

NOTE: Data are given as mean ± SD or n (%). Additional variables evaluated as nonsignificant were the numbers of white blood cells and platelets and the levels of AST and ALT.

TABLE 3. Multivariate Logistic Regression Analysis and Risk Stratification Model for Predictors of LT or Death 3 Months After Listing Pediatric Patients With ALF (n = 135)

	AOR (95% CI)	*P* Value
Pure PALF	3.8 (1.6-9.9)	<0.001
Peak INR ≥3.5	3.1 (1.3-7.2)	<0.001
Peak total bilirubin ≥17 mg/dL	4.4 (1.9-10.3)	<0.001

Number of Variables	3-Month Risk
No variables	17.6%
Any 1 variable	36.6%
Any ≥2 variables	82%

It is important that transplant teams taking care of patients with these complex illnesses know detailed PALF epidemiology in their regions to allow a prompt and proper diagnosis and a better management of their patients.[19] We confirm previous reports regarding the almost null incidence of paracetamol-related PALF in our country.[5,20] Our data showed that indeterminate cause is the major etiology in Argentina accounting for 50% of patients, which is a similar finding to those reported in Italy (47%), the United States (50%), and Germany (43%).[21-23] AIH was also one of the most prevalent etiologies of PALF in our study. This finding is expected given that AIH is a common cause of pediatric end-stage liver disease in Argentina[2] and the second most common cause of ALF in adults.[24] Correct diagnosis of patients with an acute presentation of AIH is always challenging. These patients often have elevated γ-globulin levels and positive autoantibodies, but these indications can be absent in a proportion of patients.[13,25] Patients presenting with AIH can benefit from the early use of corticosteroids. Although the risks and benefits of corticosteroid administration in this setting should be weighed carefully, prompt diagnosis and treatment of these patients might preclude LT or death.[26-28]

Recently, Di Giorgio et al. compared the outcomes of children with PALF-CLD with those with PALF and no preexisting liver disease.[14] In their study, the transplant-free survival was significantly higher in the PALF-CLD group when compared with the pure PALF group. This outcome might be the consequence of PALF-CLD etiologies (ie, AIH and WD) presenting a more indolent evolution allowing physicians to use medical therapies and to eventually find a suitable organ to allow transplantation. In our study, a high proportion of patients presented with PALF-CLD. This can be attributable to the elimination of HAV as a cause of PALF after the successful implementation of our universal vaccination program in 2005. Moreover, if we compare our outcomes with reports from the HAV era, we also found a substantial improvement in spontaneous survival, wait-list mortality, and overall survival.[4,5] We can speculate that these findings might be explained by 2 reasons:

1. HAV-associated PALF infection has a hyperacute presentation with an associated mortality and need of LT of approximately 40% and 45%, respectively.[3]
2. There have been some relevant improvements in the medical management of children with PALF.[1,9]

Thus, in this new scenario, early diagnosis of PALF-CLD etiologies is crucial to evaluate the need of medical therapy and to eventually establish the optimal timing for LT. Our results confirmed that children with pure PALF and PALF-CLD have different clinical characteristics at presentation and, more importantly, different outcomes. The clinical course of PALF can be dynamic, fast, and unpredictable. Therefore, there is urgency in establishing a specific diagnosis because timely therapeutic intervention can affect clinical outcomes, especially in patients with PALF-CLD.

Determining the likelihood of either spontaneous native liver recovery or death in patients with PALF is the most challenging assessment in this setting. Several prognostic scores have been developed to aid decision making for LT. Previous studies from the HAV era described prognostic factors (low prothrombin time and advanced hepatic encephalopathy) and King's College criteria to be strongly associated with death or the need of LT.[4] In our study, we solely focused on patients with PALF who were listed. Using traditional PALF scoring systems in this population to identify patients who will benefit from LT can represent a bias. Thus, we did not analyze traditional dynamic prognostic scores, such as King's College criteria, Clichy, and Model for End-Stage Liver Disease/PELD. Using these scores in patients with PALF who are already listed can overestimate the need of LT.

To gain a better understanding of variables associated with death or LT in our cohort, we performed a logistic regression analysis. In the final model, we described biochemical (total bilirubin ≥17 mg/dL and INR ≥3.5) and clinical features (pure PALF) to be significantly associated with a poor prognosis. We identified 3 risk groups according to the number of risk factors presented. The presence of 2 or more risk factors was strongly associated with a very high risk of death or need for LT. The variables included in our risk stratification model are easy to measure and use. Our model highlights the importance of distinguishing the type of PALF. We believe that 1 prognostic score that fits all patients will be really hard to find and that different prognostic variables or PALF scoring systems should be adapted according to regional variables significantly associated with worse outcomes in different areas. In a population with a high prevalence of PALF-CLD, these variables can be used as another tool to help identify patients who will benefit from LT.

As with all observational studies, the results of this study are subject to certain limitations. First, our study is retrospective and cannot account for undocumented patients' characteristics. Thus, we checked for missing values and inconsistencies, and queries were referred to the participating institution. Lastly, our model was not tested outside of the derivation data set. However, the model showed good calibration and discrimination, and it was internally validated by bootstrapping.

In summary, our study confirms that indeterminate causes and AIH are the most frequent etiologies in our population after the elimination of HAV as a cause of PALF. In line with previous studies,[14] we confirmed that patients with PALF-CLD present better transplant-free survival compared with those without a preexisting liver disease. We also described 3 prognostic variables, including PALF type, and we created a prediction model identifying risk groups according to the number of risk factors. We consider that this simple risk stratification model could assist physicians and other health care providers in their clinical evaluation and therapeutic decision-making processes. We believe future studies should focus on more accurate prognostic markers of liver regeneration with potential inclusion of metabolomic and inflammatory parameters to better select candidates for LT and prolong survival in these patients.

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