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Research Article

Pediatric Acute Liver Failure in Central African Republic: Epidemiology and Prognostic Modeling

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ABSTRACT

Objective: Pediatric acute liver failure (PALF) is a potential lethal disease. Few data are available regarding its prevalence, mostly in developing countries. Over the years, several prognostic scores were proposed for the management. However, none of them predicted PALF outcome. The aim of this study is to identify the prevalence, and propose a prognostic score that can be used in pediatric settings.

Study design: It was a retrospective and prospective cross-sectional study, focused on children aged from 1 month to 15-year-old, with acute liver failure (ALF). We tested whether the clinical outcome was influenced by variables and we applied a Logistic regression.

Results: The study included 117 cases of ALF with a prevalence of 2.2‰ in the pediatric ward and 14.5‰ in Intensive Care Unit (ICU). The mean age was 39.5 months. Factors associated with the clinical outcome were: age, hepatic encephalopathy (HE), INR, alanine aminotransferase (ALT), hyperleukocytosis and anemia. Sensitivity and specificity of each prognostic parameter indicated the values that are associated with death are: age>14.5 months, HE stage III or IV, INR>4.55, ALT<219 IU/l, and pallor.

Conclusion: PALF has a significant prevalence in Central African Republic. The prognostic parameters provided in this study could be a useful tool to identify patients with low survival likelihood. However, further researches are still needed in order to focus on the causes.

Keywords: Children liver injury; Prevalence; Prognostic parameters; Developing countries

INTRODUCTION

Paediatric Acute Liver Failure (PALF) is a dynamic clinical condition, resulting from loss of liver function, due to rapid death of a large proportion of hepatocytes. Although rare, this disease is potentially lethal, and accounts for 10-15% of all paediatric liver transplantations [1].

PALF is defined as a liver disease of abrupt onset, with hepatic-based coagulopathy, not corrected by vitamin K administration, and International Normalised Ratio (INR) ≥ 2 if HE is absent, or INR ≥ 1.5 in case of HE, occurring in children with no evidence of chronic liver disease [2].

The exact prevalence of this illness is unknown, and almost all the information available come from developed countries. The PALF study group, created in order to deepen the knowledge on this disease, enrolled 348 patients over 5 years, coming from 24 centres located in Europe and North America. Data from developing countries are scarce, with the few studies available realized in India and South Africa [3-5].

Aetiology in PALF varies significantly according to age and worldwide location. Identifiable causes include infections, metabolic diseases, Drug-Induced Liver Injury (DILI), immune-mediated damage, malignancies, and vascular/ischemic injury

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[6]. In the developed world, most cases have undetermined aetiology. On the contrary, poor hygienic conditions, widespread use of potentially toxic traditional herb-made remedies, and frequent use of over-the-counter drugs, make infections and DILI the 2 most probable causes of PALF in developing countries [7]. Considering the causes, one would expect acute liver failure to be more common in low-income nations, than in the richest areas of the world.

PALF represents one of the most challenging paediatric illnesses, owing to the presence of a rapidly progressive multisystem organ failure and potential neurologic deterioration. One of the most crucial steps in the management of this emergency consists of urgent decision making in regards to prompt liver transplant. Unfortunately, in most African Countries organ transplantation is still a utopian project [8]. In this context, treatment consists of general supportive care, management of associated infections and prevention of HE [9].

The creation of multicentre registers of PALF patients has given the opportunity to improve its treatment, especially in the western world, where nowadays the spontaneous survival rate reaches 73% [10]. Unfortunately, mortality due to PALF remains high in developing countries [3,4].

A prognostic score, identifying patients at higher risk of mortality, could be very useful in both high and low-income countries. In the first case, it could help to identify transplant candidates. In the second one, it could prevent from therapeutic relentlessness. Over the years, several prognostic scoring systems were proposed, such as the Paediatric End-Stage Liver Disease (PELD) or the King's College Hospital Criteria (KCH). However, none of these constituted a satisfactory tool to predict PALF outcome [11].

As far as we know, this is the first article dealing with this issue in Central African Republic (CAR), the second worst country in terms of Human Development Index, with one of the highest child and infant mortality rates in the world [12]. The aim of this observational study is to define the prevalence, prognostic determinants and outcome of PALF in children admitted to a tertiary paediatric care hospital in Bangui, Central African Republic.

MATERIALS AND METHODS

Research design, participants and setting

The current study was lead in the National Pediatric Teaching Hospital of Bangui. The setting was a 22 beds intensive care unit (ICU), providing medical and surgical care for children. It was a retrospective and prospective cross-sectional study, focused on hospitalized children aged from 1 month to 15-year-old, with PALF. We used an updated definition of ALF in children that included a series of clinical and biochemical indicators:

- biochemical evidence of liver injury without previous hepatic illness,
- coagulopathy not responsive to vitamin K,
- An INR greater than 1.5 in patients presenting encephalopathy or greater than 2 in patients without encephalopathy [13,14].

Procedure

The retrospective phase was conducted using the patient discharge register to identify patients diagnosed ALF from January 2017 to July 2019. Once the file was found, we assured that the criteria were met, and then a previously elaborated questionnaire was filled out.

The prospective phase of the study was lead in intensive care unit, from October 2019 to February 2020. We enrolled patients diagnosed ALF based on the criteria above and the same questionnaire was filled out.

We excluded children less than 28 days old, children with an INR<1.5 or with an INR ≥ 1.5 corrected by parenteral vitamin K, children whose legal guardian did not consent and those with a pre-existing liver disease. Moreover, children who died before 24 h and for which there was not time to collect enough data were also excluded.

Information collected including: Demographic data (i.e. age and sex), personal medical history (i.e. underlying diseases, hepatitis B vaccine), treatment before admission (i.e. herbal medicine intake), clinical data (i.e. pallor, jaundice, hepatomegaly, ascites, and stage of encephalopathy), laboratory tests at admission (Hemoglobin (Hb), White blood cell (WBC), Bilirubin, INR, albumin, ALT, AST, glycaemia), treatment with antimalarial, and clinical outcome. The outcome was interpreted as recovery of liver function or death. Acute malnutrition is defined as low weight for height (<2 Z score) for children under 5 and weight for height less than 80% for older children [15]. Hepatic encephalopathy was classified according to the Study Group recommendations [13].

- **Grades I–II:** inconsolable crying; inattention to tasks; "not acting like self," according to parents; normal reflexes or hyperreflexia
- **Grade III:** somnolence, stupor, combativeness, hyperreflexia
- **Grade IV:** coma, reflexes absent, decerebration or decortication

Data analysis

We reported the mean, standard deviation, confidence interval at 95% of the mean, for quantitative variables (i.e. age and laboratory test results), and percentages for qualitative variables (i.e. sex, personal medical history and clinical data). We then tested whether the clinical outcome (dead or recovered patients) was influenced by these variables. We applied a Logistic regression. Categorical variables with more than 2 levels (i.e. hepatic encephalopathy and underlying disease) were entered in the logistic regression by use of dummy coding, which generates dichotomous variables by comparing each level of

the variable with a reference level (i.e. hepatic encephalopathy grade I-II and no underlying disease). The logistic regression was conducted including all the independent variables except herbal medicine intake and hepatitis B vaccine. These two variables were excluded due to high number of missing values (i.e. values were missing for 40% and 72% of the patients, respectively). The clinical outcome was unknown for 8 patients; hence they were also excluded. Due to laboratory constraints, including shortage of reagents and device breakdown, it was not possible to collect all laboratory data for some patients. Since these data are missing for technical failures, we assumed they were missing completely at random and we used a multiple imputations function by Chained Equation to impute them [16]. The number of missing and imputed values was 7.4% of the dataset.

We reduced the number of independent variables by mean of a stepwise regression with backward selection, which excludes one variable at a time, starting from the less significant one. The logistic regression models obtained were compared using the Akaike Information Criteria (AIC) and the model having the lowest AIC was selected as the best one.

We plotted the Receiver-Operating Characteristic (ROC) curves for each of the significant variables resulting from the best logistic model. Based on the ROC curve, for each variable we selected the cut-off value as the value corresponding to the highest Youden's index. Finally, for additional model performance statistics, we identified sensitivity and specificity of these parameters, when present in isolation or together.

Data were recorded and processed with RStudio v. 1.1.383 software. We specifically used the packages 'mice' for the multiple imputations by chained equation and 'pROC' to compute the ROC curves.

Ethical consideration

For prospective phase of the study, each child's parent or guardian was informed and the consent was obtained. All identifying information was kept confidential and patient's anonymity was protected (Table 1).

Table 1: Independent variables for which values were missing.

Variable	No. missing values
Glycaemia	26
Albuminemia	28
Total Bilirubin	25
ALT	22
AST	22
Hb	06
WBC	16

RESULTS

Overall, during the study period, we analyzed 117 cases of acute liver failure out of 52214 admissions in the pediatric ward (2.2‰) and 8071 admissions in ICU (14.5‰). The mean age was 39.5 months and the sex ratio 1.1. The majority did not present any underlying disease. However, we noticed 12% of malnutrition upon admission. Many data were missing owing to incompleteness of the files. Twenty percent of children were vaccinated against hepatitis B; but the immunization status was unknown in 72% of cases. Moreover, the traditional medicine intake was reported in only 60% of case among them one-third had taken prior to admission (Table 2). The type of traditional medicine was often unheeded.

Table 2: Demographic, clinical and anamnestic characteristics of the 117 patients (N) included in the study.

Characteristics	N=117
Age: mean (SD) months	39.47 (45.36)
Sex: Male n (%)	62 (52.99)
Underlying diseases n (%)	
None	93 (79.49)
Sickle cell disease	3 (2.6)
Acute Malnutrition	14 (11.96)
HIV	4 (3.42)
Other	5 (4.27)
Hepatitis B vaccine n (%)	
Yes	23 (19.66)
No	10 (8.55)
Not known	84 (71.80)
Herbal medicine before admission n (%)	
Yes	40 (34.19)
No	30 (25.64)
Not known	47 (40.17)
Clinical signs upon admission n (%)	
Pallor	61(52.14)
Jaundice	33 (28.21)
Hepatomegaly	57(48.72)
Ascites	10 (8.55)
Hepatic encephalopathy stages n (%)	
I-II	69 (58.97)
III	17 (14.53)
IV	31 (26.49)
Antimalarial treatment: n (%)	63 (53.85)
Outcome n (%)	
Death	60 (51.28)
Alive	49 (41.88)
Escape	8 (6.8)

The predominant reasons for admission were neurological disorders followed by fever and digestive symptoms (Figure 1). Physical examination revealed that all patients exhibited neurological disorders of various intensity and the hepatic encephalopathy was classified stage III or IV in respectively

15% and 26% of cases. Pallor and hepatomegaly were found in 53% and 49%, respectively. Half of the patients included in the study died.

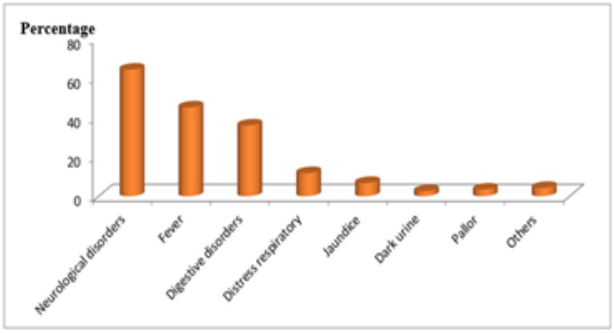

Figure 1: Main reasons for admission.

As mentioned in paragraph Data analysis, some biochemical data were missing for some patients due to laboratory constraints (Table 3). The INR mean at admission was 2.8 with range from 1.5 to 9. Hepatic cytolysis was highly marked with elevated ALT level ranging from 10 to 100 fold normal. The hematologic disorders found were moderate to severe anemia associated with hyper leukocytosis or leukopenia.

Table 3: Biochemical characteristics.

Parameters	Number of patients	Mean (SD)
Glycemia (mg/dl)	88	67.4 (69.13)
INR	117	2.8 (1.7)
Albuminemia (g/dl)	87	2.25 (0.76)
Total Bilirubinemia (mg/dl)	90	13.32 (56.38)
ALT (IU/l)	93	466 (543)
AST (IU/l)	93	593 (568)
Hb (g/dl)	109	9.2 (8.8)
WBC (/mm3)	98	11764 (7438)

The odds of dying are 0.3% lower for every single month of increasing age. Likewise, the odds of dying are 0.04% lower for every 1 point increase in ALT; in other words, 4% lower for each 100 IU/l increment in ALT. Conversely, hepatic encephalopathy stage IV, higher INR values and presence of pallor increase the odds of the death. Specifically, the odds of dying are 35.9% higher for hepatic encephalopathy stage IV compared to stage I-II. For every 1 point increment in INR, the odds of dying are 6.1% higher and the patient who presented with pallor increases his odd of death by 24.4%. In summary, factors that were associated with death a poor prognosis in our study were a younger age, low transaminases, higher INR, HE stage IV and pallor (Table 4).

Table 4: Factors associated with the clinical outcome resulting from the best logistic regression model (lower AIC value) obtained after backward selection. For each variable of the model, we report the odds ratio and the p-value.

Variable	Odds ratio (OR)	95% C.I.	P-value
Age	0.997	0.996-0.998	0.009
Hepatic encephalopathy stage III	1.163	1.029-1.315	0.221
Hepatic encephalopathy stage IV	1.359	1.227-1.506	0.003
INR	1.061	1.034-1.090	0.027
ALT	0.999	0.999-0.999	0.003
WBC	1.0	1.0-1.0	0.079
Hb	1.041	1.019-1.065	0.069
Pallor	1.244	1.116-1.387	0.048

The hepatic encephalopathy stage, followed by ALT and age were the best predicting factors, as demonstrated by the AUC value of the ROC curves generated for each parameter (Figure 2). Indeed, the AUC summarizes how good the factor is at discriminating between clinical outcomes. The cut-off values for each prognostic parameter, obtained from the ROC curves, indicate the values of the parameters that are likely associated with death or recovery. Specifically, we predict death for patients younger than 14.5 months, with a hepatic encephalopathy stage III or IV, INR>4.55, ALT<219 IU/l and showing pallor. The accuracy of the prediction is reported in (Table 5).

Table 5: Sensitivity and specificity at the cut-off value of each prognostic parameter. The direction (e.g. <14.5 months) indicates the values that are associated with death.

Variable (Cut-off values)	Sensitivity (%)	Specificity (%)
Age (<14.5 months)	45.0	77.6
Hepatic encephalopathy (>I-II)	56.7	73.5
INR (>4.55)	16.7	93.9

ALT (<219 IU/l)	53.3	69.4
Pallor	60.0	55.1

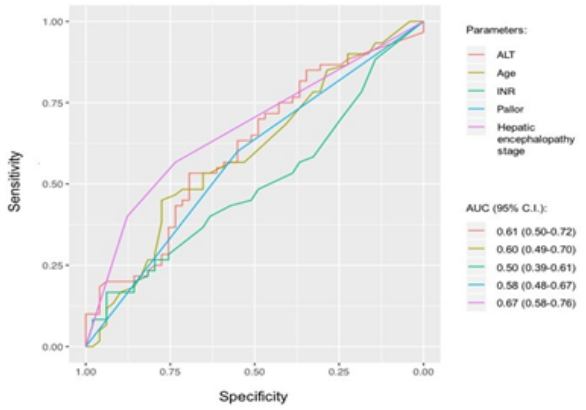

Figure 2: ROC curves for the single prognostic variables and relative Area under the curve (AUC).

When all the 5 prognostic parameters are considered together and death is predicted if at least 1, 2, 3 or 4 of the conditions associated to death are present in a patient, the goodness of the prognosis increases compared to considering the factors individually, as indicated by an AUC value of 0.8 (Figure 3, Table 6). An AUC of "1.0" would be ideal, representing 100% discrimination; however, in practice, AUC>0.8 is considered acceptable [11] .

Table 6: Sensitivity and specificity at the variable.

Variable	Sensitivity (%)	Specificity (%)
Any 1	100.0	18.4
Any 2	81.7	59.2
Any 3	43.3	91.8
Any 4	6.7	100.0

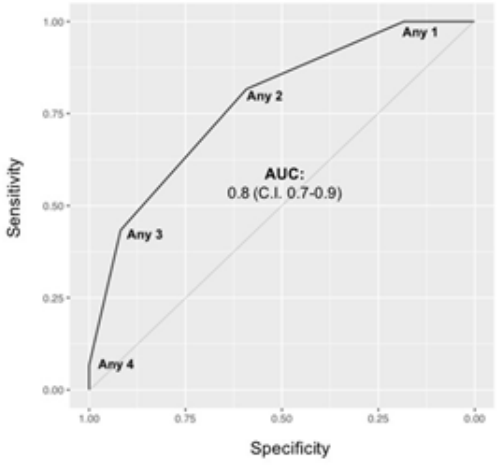

Figure 3: ROC curve considering all the 5 prognostic variables. Any 1, 2, 3 and 4 indicate the values of sensitivity and specificity when death is predicted if at least 1, 2, 3 or 4 conditions associated to death are present in a patient.

The best prognosis is obtained if the criterion used to predict death is that at least 2 of the conditions associated to death are present in a patient. If this is the case, there is an 82% probability of correctly identify the patients that will die and a 59% probability of correctly identify the patients that will recover. When at least 3 of the conditions are met in the patient, the probabilities of correctly identifying the one who will die decreases to 43% while the probability of identifying patients who recover increases to 92%. Finally, when 4 conditions are associated, the probability of identifying the patient who will die reached its lowest rate (6.7%) while it reached its highest rate for identifying patients who will be cured (100%) (Table 6).

DISCUSSION

This study is one of the few works available on PALF in sub-Saharan Africa and the first in Central African Republic. We collected 117 cases of acute liver failure over a period of 36 months. It consists of a significant number, when compared to some of the biggest multi-center studies ever realised on this subject in developed countries, [2,10] showing that PALF is probably more frequent in low-income nations.

Unfortunately, the aetiologies were not accurately defined in most of cases due to the lack of information in the medical records and the investigations restriction subsequent of a limited technical platform.

The main symptoms of admission were neurological disorders, and 41% of patients had a grade III-IV HE. This could be explained by the critical health situation in CAR, which in many cases results in delayed access to a proper medical treatment.

The mortality recorded was unacceptably high (51.28%) when compared to that of USA [10] but similar to the rate reported by other authors in developing countries [3,4]. The high mortality rate in developing countries may be related to the delayed access to care and the level of intensive care unit.

The main prognostic determinants in our study were: young age (<14.5 months), hepatic encephalopathy (III-IV), INR (>4.55), ALT (<219 IU/l) and pallor. It has already been demonstrated that severity of HE [2,11,17,18] and high INR values [2,14,19] are two strong predictors of negative outcome in both adults and children. As it concerns age, many studies, highlighted that young age is associated with poor outcome [2,11,19,20] partly due to the high frequency of multisystemic diseases (metabolic diseases, hemophagocytic lymphohistiocytosis, and herpes simplex virus infection) in this group. We also found out that a higher level of ALT was correlated with a better chance of survival, confirming findings from previous studies [17,21,22]. Lower liver enzymes could reflect the presence of massive organ damage, with loss of a large proportion of hepatocytes. Moreover, the presence of undiagnosed pre-damaged liver or chronic exposure to toxic substances as those contained in traditional herb remedies might be explanation [3,23]. Finally, we discovered that pallor was a predictor of poor outcome; even though Hb values were not found to have an impact on the

outcome. Pallor being a clinician-dependent parameter, it was mentioned in the medical files each time it was noticed; while we had a limited number of Hb due to laboratory constraints. This data could probably suggest the presence of worse health and nutritional status in patients who died.

Based on these results, a score was proposed to estimate prognosis in paediatric patients with ALF. According to ROC curve analysis the best discriminatory capacity of this score occurs when a patient presents any 2 of our prognostic markers.

This study has several limitations. The main one is the lack of data due to the retrospective design of a consistent part of the work, as well as technical problems typical of the developing countries. Another great limit is the inability to detect the causes of PALF in our population. Future research could fill this gap, by means of prospective observational studies and use of serological and toxicological analyses in enrolled patients.

We conclude that PALF has a significant prevalence and mortality in CAR. The study presented the main prognostic parameters in Central African children and provided clinicians a valid tool to identify patients with low survival likelihood. However, future research is needed in order to focus on the causes of this disease.

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Potential conflict of interests

Nothing to report.

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