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ORIGINAL ARTICLE

Coagulation Factors as Predictive Markers of Poor Outcomes in Children with Acute Liver Failure

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SUMMARY

Background: **In children, acute liver failure (ALF) is a severe condition associated with high mortality if an emergency liver transplantation (LT) is impossible. Clinical laboratory parameters and different scores or criteria are used to predict ALF evolution in children. We aimed to assess the role of coagulation factors as predictive markers of poor outcomes in children with ALF.**

Methods: **The prospective study included 40 children with ALF, diagnosed based on the Pediatric ALF study group criteria. Patients with emergency LT or deceased were considered with poor outcomes. For all patients, we analyzed clinical and laboratory parameters (including plasma level of factor V (FV), factor VII (FVII), and INR). We calculated the PELD (Pediatric End-stage Liver Disease) and MELD (Model for End-stage Liver Disease) scores, King's College Hospital (KCH), and Clichy criteria. We analyzed their performance in predicting a poor outcome.**

Results: **FV and FVII levels were significantly lower in children with poor outcomes than survivors (18.92 ± 19.95% vs. 10.72 ± 10.21%, p = 0.00139, respectively 46.51 ± 26.05% vs. 10.72 ± 10.21%, p = 0.00014). These parameters varied with ALF etiology, being the lowest in metabolic and infectious causes. The maximum value of INR (INR-max) was higher in children with poor outcomes than survivors (7.05 ± 3.20 vs. 2.96 ± 1.82, p = 0.000007), as it also was for the PELD/MELD score (30.06 ± 15.55 vs. 15.77 ± 9.64, p = 0.00092). FVII, FV, and INR-max had an excellent performance in predicting the poor outcome with an area under the ROC curve of 0.894, 0.816, and 0.861, respectively. KCH criteria had a higher sensitivity than Clichy criteria (92.86% vs. 50%) but lower specificity (53.85% vs. 95%).**

Conclusions: **Our results support the role of coagulation factors (INR, FV, and FVII) as predictive markers for the fatal evolution of children with ALF and underlined the need for monitoring along with the usual liver function tests in children with ALF.**

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KEY WORDS

acute liver failure, child, coagulation factors, predictive marker, poor outcomes

INTRODUCTION

In children, acute liver failure (ALF) is a severe condition with extremely high mortality (50%) in the absence of emergency liver transplantation (LT). According to the PALF (Pediatric Acute Liver Failure) study group criteria, ALF involves liver coagulopathy that cannot be corrected with parenteral vitamin K administration and INR (International Normalized Ratio) between 1.5 and 1.9, in the presence of liver encephalopathy or INR over 2.0, without encephalopathy, all these in the absence of chronic liver disease. Currently, 10 - 15% of LT in children are secondary to ALF, with survival up to 60 - 70% [1-7]. LT is a complicated and expensive surgery, and it is essential to choose correct and rigorous eligible patients. For this reason, several prognostic markers and scores are still the subjects of research in children. These are based on either clinical manifestation (e.g., hepatic encephalopathy), laboratory parameters (INR, albumin, bilirubin, level of factor V - FV, factor VII - FVII), age, or etiology [1-5]. In adults, the coagulation factors V or VII are closely related to the evolution of ALF, a low value of these factors being associated with a higher risk of death. Prognostic scores like PELD (Pediatric End-stage Liver Disease) score, for children below the age of 12, and MELD (Model for End-stage Liver Disease) score for adults and children older than 12 or King's College Hospital (KCH) and Clichy criteria have been used so far to predict the evolution of ALF in children and to assess the need for a liver transplant in ALF patients [1-9]. Some of these markers/ scores are used in children to prioritize potentially fatal cases requiring emergency LT. But it is not unanimously established which is the most helpful score or prognostic marker that can be used in a child with severe ALF because none of these factors can accurately predict a possible negative evolution. For this reason, more studies on markers that could predict the evolution of ALF early are needed in children.

Our research aimed to evaluate the usefulness of coagulation factors (INR, FV, FVII) in predicting the unfavorable evolution of children with ALF. As all include coagulation factors, we also analyzed the performance of PELD/MELD scores, KCH, and Clichy criteria in predicting the evolution in our cohort.

MATERIALS AND METHODS

This prospective study was performed over four years (January 2015 - December 2018) in the 2nd Pediatric Clinic, Emergency Clinical Hospital for Children, Cluj-Napoca, Romania. We included 40 children with ALF (aged between 1 month and 17 years 10 months old) in the study. For ALF diagnosis, we used PALF criteria: acute onset of liver disease with hepatic-based coagulopathy (prothrombin time (PT) > 20 seconds or international normalized ratio (INR > 2) not corrected by parenteral vitamin K without hepatic encephalopathy (HE) or hepatic based coagulopathy (PT, 15 - 19.9 s; INR, 1.5 - 1.9) with HE [1,8]. We excluded the patients who did not meet the PALF criteria from this study, those with acute hepatitis A and E (followed in the Infectious Diseases Hospital), children who developed ALF in the context of multiple secondary organ failure or post-chemotherapy, and patients with incomplete or unclear data in the observation sheets.

We collected the following data from patients' clinical observation sheets: patient identification data, demographic characteristics (age, gender, date of birth, date of admission), laboratory investigations, including alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), total and direct bilirubin (TB, DB), serum albumin, hemoglobin (Hb), white blood cells (WBC), platelets (PLT), FV, FVII, INR. The normal values we referred to in the evaluation of these parameters were the following: Hb > 11g/dL, WBC 4,500 - 17,000/mm^3 (varying according to age: 6,000 - 17,500/mm^3 in neonates and infants and between 4,500 - 13,000/mm^3 in older children and teenagers), PLT > 150,000/mm^3, ASAT 35 - 50 IU/L, ALAT 35 - 60 IU/L, INR 1 - 1.5, TB < 1.2 mg/dL, BD < 0.3 mg/dL, serum albumin 3.5 - 5 g/dL, FV 60 - 140%, FVII 70 - 130% [10-15]. Unlike factors VIII, IX, XI, and XII, which have higher plasma levels with the lower age in children, FV and FVII have no relevant changes compared to teenagers and adults [16].

The patients' blood was centrifuged immediately after collection and stored at -20°C. FV and FVII levels were measured by the coagulometric method. This method consists of measuring the coagulation time of the sample in the presence of thromboplastin and plasma containing all the plasma coagulation factors except the V factor. In the presence of an excess of thrombin, the coagulation time of the citrated and diluted plasma (1/ 10), poor in platelets, is inversely proportional to the fibrinogen concentration.

The etiology of ALF was established based on specific investigations and divided into infectious, metabolic, toxic, autoimmune, or unknown causes. Depending on the evolution, the patients were grouped in favorable evolution (survival with native liver under medical treatment) and poor outcome (emergency LT or death). We analyzed the difference in the level of different laboratory parameters based on ALF outcomes.

The PELD score was used for children under 12 years of age, while for children older than 12 years, the MELD score was used. These scores were calculated on the first day of hospitalization using an online application based on the formula:

PELD = 0.436 [age (< 1 year)] - 0.687 log [albumin (g/dL)] +0.480 x log [TB (mg/dL)] + 1.87 log (INR) +

0.667 [growth retardation (< -2 standard deviations)] [17],
MELD = 3.78 × log [TB (mg/dL)] + 11.2 × log [INR] + 9.57 × log [serum creatinine (mg/dL)] + 6.43 [18].
KCH criteria were analyzed based on previously described parameters. In ALF due to paracetamol ingestion, KCH criteria are positive if arterial pH is < 7.3 or all three of prothrombin time (PT) > 100 seconds, serum creatinine level > 3.4 mg/dL, and grade III or IV encephalopathy are present. In ALF with other causes (non-paracetamol), PT > 100 seconds (INR > 6.5) or any three of the following criteria (non-A/non-B viral heapatitis, toxic or unknown cause, more than 7 days from the onset of jaundice to the start of the hepatic encephalopathy, age under 10 years or over 40 years, PT > 50 seconds (INR > 3.5) or TB > 17.5 mg/dL) are associated with an indication of LT [19-21].
Clichy criteria are based on the association of hepatic encephalopathy (grade III or IV) and FV level under 20% [19-21].

Statistics
All data were included in a database created using Microsoft Office Excel and interpreted statistically, using Statistics version 13, TIBCO Software Inc, 2018. We used descriptive statistics for variables with continuous distribution (means and standard deviations). Statistical significance testing was performed using the t-Student and Mann-Whitney tests (for PELD, MELD scores). We calculated the area under ROC curve (AUC) values, confidence intervals, and cut-off values for TB, albumin, INR, FV, and FVII from the first day of hospitalization and the maximum level of INR (INR-max), using the EasyROC software available online [22]. The selection of the cut-off values was made using the Youden Index. The results were considered statistically significant at values of $p < 0.05$.

Ethical statement
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Emergency Clinical Hospital for Children Cluj-Napoca, Romania (41 SC/11.01.2016). All parents signed an informed consent before including their children in the study.

RESULTS

The study group included 40 children diagnosed with ALF, aged between 1 month and 17 years 10 months, mean age of 4.87 ± 5.30 years. There were 21 boys (51.50%) and 19 girls. The causes of ALF were toxic substances (11 children; 27.50%), metabolic diseases (9 children; 22.50%), infections, and autoimmune diseases (8 children each; 20%). The ALF etiology remained unknown in 4 children (10%).
The causes of ALF in children vary depending on the child's age. In our cohort, in neonates (0 - 1 month) and infants (1 - 12 months), infectious and metabolic disorders were the most frequent causes of ALF, while in children (1 - 14 years) and teenagers (14 - 18 years), the causes were toxic substances, autoimmune hepatitis, and Wilson's disease. Three neonates had ALF due to herpes simplex virus infections, neonatal lupus syndrome, and tyrosinemia. In infants, the leading causes were metabolic disorders (7 patients) and infections (four patients, with cytomegalovirus in 2 patients and herpes virus or Gram-negative bacteria in one patient each). Metabolic causes were galactosemia, hereditary fructose intolerance, mitochondrial disorders (two cases each), and tyrosinemia (one infant). In children, toxic hepatitis was the leading cause (7 patients). Toxic substances included mushrooms and acetaminophen (two patients each), albendazole, isoniazid and valproic acid (one patient each). There were also four patients with autoimmune hepatitis (AIH) and three with after infections (Cytomegalovirus, Epstein-Barr virus, and Echovirus). There were two children with Wilson's disease and one with a mitochondrial disorder. The etiology remained unknown in three children. Among teenagers (5 patients), the leading causes of ALF were also toxic substances (four patients, acetaminophen in three cases and mushrooms in one patient) and autoimmune hepatitis (one patient). In our study, 14 patients (35%) had unfavorable evolution (13 deaths and one child with LT), and in 26 patients, the outcome was favorable (65%). There was a significant difference between the analyzed parameters in children with poor outcomes compared to those that survived. FV, FVII, and albumin levels were significantly lower and the INR higher in patients who died than survivors. For other parameters, the differences were not significant (Table 1).
There are statistically significant differences in the coagulation parameters in different etiologies. Coagulation was the most severely affected in metabolic disorders, correlated with the evolution (Table 2).
Regarding the performance of KCH criteria in predicting the poor outcome of ALF, in our analysis, the sensitivity was 92.86%, specificity 53.85%, the positive predictive value (PPV) 52%, and the negative predictive value (NPV) 93.33%. The sensitivity of Clichy criteria was 50%, specificity was 95% with a PPV of 87.50% and NPV of 73.10%. The accuracy of Clichy criteria in our patients was 76.47%.
Analyzing the performance of different parameters in predicting the fatal outcome in ALF in children, based on AUROC analysis, FVII, FV, and maximum level of INR had the best performance with an AUC of 0.894, 0.816, and 0.861, respectively (Figure 1 and Table 3). At a cutoff of 14%, the level of FVII had the best sensitivity (78.6%), similar with INR-max (at a cutoff of 4.1) and TB level (at a cutoff of 4 mg/dL), but with higher specificity (88.5% compared to 84.6% and 57.7%). FV level at a cutoff of 5% and INR on the first day of hospitalization had the highest specificity (92.3%).

Table 1. Comparisons between children with ALF according to the outcome.

Variable	Poor outcome (Deceased or LT) n = 14	Survivors n = 26	p-value
Age (years)	*0.958 ± 0.985*	*6.984 ± 5.489*	*0.00024*
AST (IU/dL)	1,406.71 ± 1,749.22	1,402.15 ± 1,749.22	0.99488
ALT (IU/dL)	1,198.43 ± 1,680.04	1,253.77 ± 1,680.04	0.91299
TB (mg/dL)	8.83 ± 7.71	6.27 ± 6.87	0.29001
DB (mg/dL)	5.50 ± 4.26	4.64 ± 5.51	0.61523
Alb (g/dL)	*2.69 ± 0.80*	*3.29 ± 0.51*	*0.00605*
Hb (g/dL)	9.79 ± 2.63	10.76 ± 2.65	0.27397
WBC (/mm^3)	13.69 ± 7.80	14.69 ± 7.63	0.69517
PLT (/mm^3)	190.86 ± 156.86	229.96 ± 97.76	0.33678
FV (%)	*18.93 ± 19.96*	*46.52 ± 26.05*	*0.00139*
FVII (%)	*10.72 ± 10.22*	*39.33 ± 24.02*	*0.00014*
INR i	*5.18 ± 3.64*	*2.28 ± 1.10*	*0.00052*
INR max	*7.06 ± 3.20*	*2.93 ± 1.82*	*0.000007*
PELD/MELD	*30.06 ± 15.55*	*15.77 ± 9.64*	*0.00092*
KCH criteria	12 (85.71%)	12 (46.15%)	*0.01449*
Clichy criteria	9 (64.28%)	6 (23.07%)	*0.03716*

Data are given as mean ± standard deviation (SD).
LT - liver transplantation, AST - aspartate transaminase, ALT - alanine transaminase, TB - total bilirubin, DB - direct bilirubin, Alb - albumin, WBC - white blood cells/leucocytes, Hb - haemoglobin, PLT - platelets/thrombocytes, FV - factor V, FVII - factor VII, INR - International Normalized Ratio, i - initial, max - maximum value during ALF evolution, PELD - Pediatric End-stage Liver Disease, MELD - Model for End-stage Liver Disease, KCH - Kings College Hospital.

Table 2. Comparisons between FV, FVII level, INR on the first day of hospitalization (INR i) and maximum INR value (INR max), according to etiology.

Variable	Metabolic n = 9	Infectious n = 8	Autoimmune n = 8	Toxic substance n = 11	Unknown n = 4
Age (years)	0.57 ± 0.64	1.55 ± 2.53	7.09 ± 5.01	9.83 ± 5.00	3.12 ± 3.91
INR i	5.89 ± 4.03	2.74 ± 1.70	1.98 ± 0.46	2.61 ± 2.06	3.04 ± 0.83
INR max	7.61 ± 3.21	4.11 ± 2.28	2.17 ± 0.72	3.05 ± 2.28	5.68 ± 3.53
F V (%)	16.44 ± 20.18	38.43 ± 23.70	34.38 ± 12.26	61.41 ± 28.00	17.13 ± 18.13
F VII (%)	11.13 ± 9.96	29.74 ± 29.14	29.89 ± 14.22	45.45 ± 27.39	23.88 ± 23.19

Age: toxic substance vs. unknown, p = 0.031.
FV: toxic substance vs. unknown p = 0.012, metabolic vs. autoimmune p = 0.046, metabolic vs. toxic substance p = 0.001.
FVII: metabolic vs. autoimmune p = 0.006, metabolic vs. toxic substance p = 0.02.
INRi: unknown vs. autoimmune p = 0.015; metabolic vs. autoimmune p = 0.015; metabolic vs. toxic substance p = 0.03.
INR max: unknown vs. autoimmune p = 0.017; metabolic vs. autoimmune p = 0.0003; metabolic vs. toxic substance p = 0.002; metabolic vs. infectious p = 0.021; infectious vs. autoimmune p = 0.037.

Data are given as mean ± standard deviation (SD).
FV - factor V, FVII - factor VII, INR - International Normalized Ratio, i - initial, max - maximum value during ALF evolution.

Table 3. The area under ROC analysis for total bilirubin, albumin, INR, FV, FVII level on the first day and maximum INR value in predicting the poor outcomes of ALF in children.

Variable	AUC	AUC limits	Cut-off	Se	Sp	PPV	NPV
TB	0.592	0.391 - 0.793	4 mg/dL	78.6%	57.7%	50.0%	83.3%
Alb	0.746	0.588 - 0.904	2.9 g/dL	57.1%	80.8%	61.5%	77.8%
INR i	0.775	0.596 - 0.954	3	57.1%	92.3%	80.0%	80.0%
INR max	0.861	0.735 - 0.988	4.1	78.6%	84.6%	73.3%	88.0%
F V	0.816	0.671 - 0.961	7 %	64.3%	92.3%	81.8%	82.8%
F VII	0.894	0.793 - 0.995	14 %	78.6%	88.5%	78.6%	88.5%

TB - total bilirubin, Alb – albumin, FV - factor V, FVII - factor VII, INR - International Normalized Ratio, i - initial, max - maximum value during ALF evolution, AUC - area under the curve, Se – sensitivity, Sp – specificity, PPV - positive predictive value, NPV - negative predictive value.

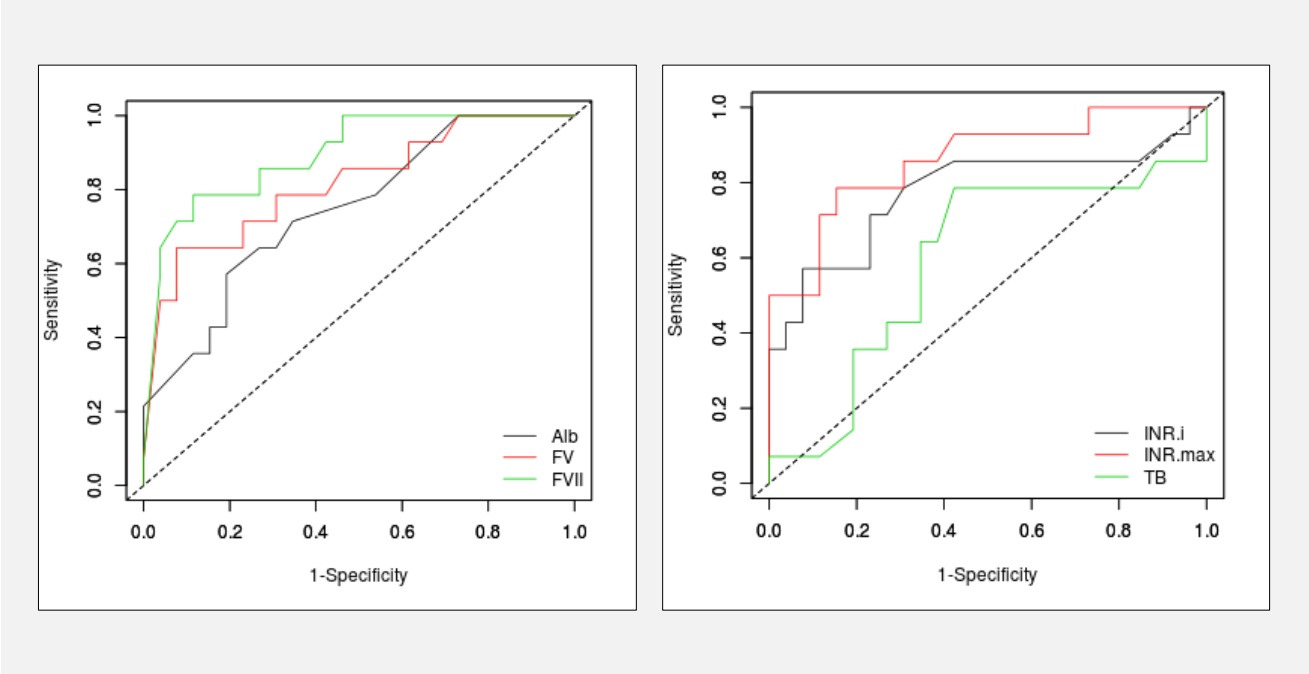

Figure 1. The area under the ROC curve for different parameters in predicting the poor outcomes of ALF in children.

Alb – albumin, FV - factor V, FVII - factor VII, TB - total bilirubin, INR - International Normalized Ratio, i - initial, max - maximum value during ALF evolution.

DISCUSSION

ALF occurs after exposure of the liver parenchyma to various aggressions: infections, endogenous or exogenous toxic substances, and aberrant immune responses. Even though it is a rare disease in children, ALF is responsible for 10 - 15% of all pediatric LT, causing high mortality in the absence of this intervention [22,24]. The evolution of children with ALF is different and quite unpredictable. Although they have severe damage with encephalopathy or coagulation disorders, some recover their liver function, while others progress extremely severely until death. Early identification of this group of patients is crucial because it can allow an early referral to LT centers. For this reason, various markers or scores have been developed to predict the negative evolution of ALF. In children, the existence of a liver injury and its severity is monitored by analyzing parameters as transaminases, bilirubin, cholestasis enzymes, clotting times, albumin, cholinesterase. Changes in these parameters confirm liver damage and provide an overview of the severity of ALF but do not offer an

exact picture of the evolution of the disease. There is no universally valid criterion for assessing the prognosis of children with ALF. Several negative predictive factors have been described in children with ALF, including age under 10 years, non-A-G virus infections, some etiologies such as Wilson disease (WD), grade III/IV hepatic encephalopathy, a sudden decrease in liver size or transaminases, marked increase of serum bilirubin, INR > 4 or level of FV < 20%, vitamin D binding protein, and creatinine level. Different scores or prognostic criteria are also used: KCH and Clichy criteria, PELD/MELD scores, and Wilson Index in WD [4,7,10,24-29].
This study assesses the role of FV, FVII, and INR in predicting the evolution of children with ALF. The levels of these parameters were significantly lower in children with poor outcomes of ALF compared with survivors. Moreover, FV was < 20% in deceased or transplanted patients, a value that requires emergency LT, according to some authors. The unfavorable course of a child with ALF may be predicted by the association of FV level of less than 20% and the hepatic encephalopathy (grade III or IV) after Clichy criteria [12].
FVII is another important prognostic marker in the evolution of ALF [11]. In our analysis, the FVII level was even lower than FV. The plasma concentrations of these factors decrease quickly after severe liver injury due to the shortest half-life of FV and FVII: 12 and 4 - 6 hours, respectively [12,13].
FV and INR are currently considered the main negative prognostic factors of ALF in children regardless of etiology [1]. Our results support the role of INR in predicting the evolution of children with ALF. Children with poor outcomes had significantly higher INR levels at admission to the hospital or during the disease evolution than those who survived. So, we can say that in the absence of other parameters that predict the evolution of children with ALF, the use of INR represents an option of choice for assessing the severity of the liver injury and the potential for death.
The performance of FV and FVII from the first day of hospitalization and the maximum level of INR in predicting the poor outcome in ALF in children proved very good in our cohort. With an AUC between 0.8 and 0.9, these parameters may be used for their predictive role. In our study, the cutoff for FV level was lower than 20% used in Clichy criteria in adults (7% with excellent specificity, 92%). Also, our results are similar to other researchers' results regarding the INR cutoff of 4 as a predictive value for poor outcomes.
The level of INR, FV, or FVII in ALF patients varied depending on the etiology. We found that FV and FVII were lower and INR higher in ALF due to metabolic and infectious causes than the autoimmune or toxic substance etiology. This can be explained by the degree of liver destruction, which is much more severe in metabolic diseases and infections. In the group of patients with toxic substance or autoimmune ALF, the values of FV and FVII were almost within the normal range.
However, none of these factors can accurately predict a possible negative evolution of ALF patients. For this reason, some authors use various scores like PELD, MELD, and KCH or Clichy criteria to predict ALF evolution. Based on these parameters and predictive scores, we can decide whether to perform LT. In our analysis, the KCH criteria sensitivity was 92.86% and the specificity 53.85%, while the sensitivity of Clichy criteria was 50% and the specificity 95%. KCH criteria may predict the course of death in a patient with ALF, but their absence does not necessarily imply survival. The mortality rate in children with ALF predicted to die (positive predictive value) was 52%. In fact, according to most authors, KCH criteria do not significantly predict the unfavorable evolution in children with ALF, which can lead to overutilization of LT [30]. We have also analyzed PELD/MELD scores and the evolution of ALF. Children with poor outcomes had significantly higher PELD/MELD scores than those who survived. Despite all the new investigations and therapeutic measures, mortality in children with ALF remains high (over 50%) in the absence of emergency LT because of the limited defense resources, immaturity of organs or systems, or childhood-specific conditions that can be extremely severe (metabolic diseases). However, assessing the plasmatic levels of FV, FVII, and INR, or the use of predictive scores, may predict the severity of the liver injury and the outcome of ALF in children. Although LT is a life-saving procedure in ALF, the patients often have a worse long-term outcome than spontaneous survivors. FV, FVII, and INR cannot predict the post-transplant evolution of these patients, but would help to predict the need for LT. Cryoprecipitate, frozen plasma, and platelet concentrate are administered with recombinant activated factor VII to restore hemostasis in acute bleeding from liver failure. As a result, bleeding can be controlled, INR was shortened, and FVII clotting activity increased considerably.
The main limitation of our study was the small number of children included in the analysis, as ALF is rare in the pediatric population. Also, the fact that these parameters and scores were not evaluated in different moments of disease evolution limited the significance of the coagulation factor performance in predicting the poor outcomes in ALF in children.

CONCLUSION

Our study underlines the importance of coagulation factors in assessing the severity of ALF in children. These parameters are used to evaluate prognostic scores at admission and during hospitalization. Based on these predictive scores, the decision of the emergency transfer to a specialized center in performing LT will increase the chances of survival in children with ALF.

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Declaration of Interest:
The authors declare no conflicts of interest.

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