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Clinical and laboratory predictors of severe pediatric Crimean−Congo hemorrhagic fever: A retrospective study

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ABSTRACT

Objective: To identify clinical and laboratory parameters associated with severe disease requiring intensive care among pediatric Crimean-Congo hemorrhagic fever (CCHF) patients.

Methods: Twenty-three children with confirmed CCHF were divided into two groups: Pediatric intensive care unit (PICU) patients (n=12) and general ward patients (n=11). Laboratory parameters including platelet count, platelet mass index (PMI), liver enzymes, and inflammatory markers were analyzed at admission through univariate and multivariate logistic regression as well as receiver operating characteristic curve analysis.

Results: PICU patients had significant lower platelet counts and PMI (P=0.002 for both), and higher aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and ferritin levels (P<0.01). Univariate analysis identified platelet count (*OR* 0.99, P=0.026), PMI (*OR* 0.98, P=0.021), AST (*OR* 1.03, P=0.025), and alanine aminotransferase (*OR* 1.03, P=0.050) as significant predictors of PICU admission. Multivariate analysis demonstrated PMI as an independent predictor (adjusted *OR* 0.98; 95% *CI* 0.97-0.99, P=0.021). The area under the curve (AUC) was the highest for aspartate aminotransferase (AUC=0.886, 95% *CI* 0.69-0.98), followed by lactate dehydrogenase (AUC=0.879, 95% *CI* 0.68-0.98), platelet mass index (AUC=0.864, 95% *CI* 0.66-0.97), platelet count (AUC=0.860, 95% *CI* 0.65-0.97), ferritin (AUC=0.811, 95% *CI* 0.59-0.94), and alanine aminotransferase (AUC=0.796, 95% *CI* 0.58-0.93).

Conclusions: PMI showed promising predictive value for intensive care requirement in pediatric CCHF patients, maintaining significance in multivariate analysis. Several laboratory parameters including AST, LDH, and platelet count showed high diagnostic accuracy for identifying severe disease. These readily available parameters can guide early risk stratification and resource allocation in pediatric CCHF management.

KEYWORDS: Biomarkers; Crimean-Congo hemorrhagic fever; Intensive care units; Pediatric; Prognosis

1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is recognized as a viral infection characterized by high mortality rates and rapidly deteriorating symptoms. Approximately 10 000 to 15 000 cases are

Summary

Question: What clinical and laboratory parameters predict intensive care requirement in pediatric Crimean-Congo hemorrhagic fever (CCHF) patients?

Findings: In this retrospective study of 23 confirmed pediatric CCHF cases, platelet mass index was an independent predictor of pediatric intensive care unit admission (adjusted *OR* 0.98; 95% *CI* 0.97-0.99, P=0.021). The area under the curve (AUC) was the highest for aspartate aminotransferase (AUC=0.886), followed by lactate dehydrogenase (AUC=0.879), platelet mass index (AUC=0.864), platelet count (AUC=0.860), ferritin (AUC=0.811), and alanine aminotransferase (AUC=0.796).

Meaning: Platelet mass index and readily available laboratory parameters enable early risk stratification and resource allocation in pediatric CCHF management.

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reported annually worldwide, with transmission primarily occurring through tick bites or contact with blood from infected animals. In endemic regions such as Central Asia, Eastern Europe, the Middle East, and Africa, CCHF poses a significant threat to public health, increasing the burden on healthcare systems and causing substantial economic impacts at the societal level[1,2].

The epidemiological patterns of CCHF demonstrate significant geographical variation, with regions characterized by suitable climate conditions for tick vectors showing higher disease prevalence. These regions typically experience seasonal peaks in CCHF cases, coinciding with increased agricultural activities and heightened human-vector interactions[2,3].

Pediatric CCHF presents with distinct clinical and pathophysiological characteristics compared to adult cases. Children often exhibit different manifestations, including milder hemorrhagic symptoms in some cases, but potentially more severe neurological complications[4]. The immunological response in pediatric patients differs significantly, with evidence suggesting variations in cytokine profiles and inflammatory responses[5]. Furthermore, children's smaller blood volume makes them particularly vulnerable to rapid clinical deterioration following hemorrhagic manifestations. Diagnosis in pediatric populations is frequently complicated by nonspecific initial symptoms that may mimic common childhood illnesses, potentially delaying critical interventions[6].

The existing literature presents various findings regarding risk factors that influence the course and mortality of CCHF. For instance, hematological findings such as thrombocytopenia, elevated liver enzymes, prolonged coagulation times, as well as disseminated intravascular coagulation (DIC) and multi-organ failure, are closely associated with the mortality of the disease[7,8]. Since these findings may show more distinct differences in pediatric patients compared to adults, it is important to identify specific risk factors that affect prognosis in the pediatric population. Studies on pediatric CCHF cases are often based on small case series, and comprehensive analyses involving multi-center data are scarce[9,10].

This study aims to analyze and compare clinical and laboratory data of pediatric CCHF patients admitted to intensive care units versus those managed in inpatient wards. By examining these two distinct patient groups, we seek to identify critical parameters that may indicate clinical deterioration. The research will provide essential data for early detection of warning signs in children infected with CCHF and establish a foundation for optimizing patient management strategies. Our hypothesis is that specific clinical and laboratory parameters differ significantly between patients requiring intensive care and those managed in general wards, and identifying these differences will contribute to the development of improved triage and management strategies for pediatric CCHF cases. The findings are expected to facilitate the creation of evidence-based protocols for patient evaluation, enabling clinicians to predict disease progression and identify high-risk patients at earlier stages.

2. Methods

2.1. Study design and patient selection

This single-center, retrospective study was conducted at a tertiary care hospital and included pediatric patients diagnosed with CCHF between March 2020 and March 2025. Ethical approval was obtained from the Ethics Committee of the University of Health Sciences, Kayseri City Hospital (Approval number: 249-26/11/2024).

Inclusion criteria were laboratory-confirmed CCHF by either serological testing or nucleic acid amplification testing (*i.e.*, PCR) and availability of complete medical records. Exclusion criteria included negative test results, missing data, or prior treatments that could affect laboratory values. Twelve patients with negative CCHF test results were excluded based on hospital records and verification from the Provincial Health Directorate.

2.2. Case definition and data collection

CCHF diagnosis was established based on clinical presentation, epidemiologic risk factors, and laboratory confirmation by PCR or serological testing[11]. Data were collected retrospectively from hospital records, including demographic characteristics, clinical findings, laboratory results, complications, and treatments. Clinical findings included fever, fatigue, myalgia, nausea, vomiting, mucosal bleeding, petechiae, hepatomegaly, and altered mental status. Complications recorded in the PICU group included DIC, multi-organ dysfunction syndrome (MODS), encephalopathy, seizures, hypotension requiring inotropic support, and neutropenic sepsis. All data were recorded at the time of hospital admission, prior to any therapeutic intervention. In addition, the interval between symptom onset and hospital admission (in days) was documented and included in the analysis.

Laboratory parameters included complete blood count

components-white blood cell count, neutrophil count (NEU), lymphocyte count (LEU), and platelet count (PLT); derived indices-neutrophil-to-lymphocyte ratio (NEU/LEU) and platelet mass index [PMI; PLT ×mean platelet volume (MPV)]; liver function tests-aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH); coagulation parameters-international normalized ratio, prothrombin time, and activated partial thromboplastin time (APTT); and biochemical markers-creatinine and ferritin.

PICU admission criteria included development of severe complications such as DIC, MODS, neurologic involvement (*e.g.*, altered consciousness, seizures), hypotension requiring vasopressors, or neutropenia complicated by sepsis.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 24.0 (Statistical Package for the Social Sciences), and GraphPad Prism 9.0 was used for figures. The normality of data distribution was assessed, and appropriate statistical tests were applied. Continuous variables were summarized as median and interquartile range (IQR) or mean± standard deviation, as appropriate. For continuous variables, Mann-Whitney *U* test or independent samples *t*-test was used. Categorical variables were analyzed using *Chi*-square or Fisher's exact test. To identify independent risk factors associated with PICU admission, univariate logistic regression analysis was performed for all relevant variables, followed by multivariate logistic regression analysis including four variables (AST, ALT, LDH, and PMI) selected based on univariate *P*-values (<0.10), clinical relevance, and avoidance of collinearity. Backward Wald elimination was applied to determine the final model. Receiver Operating Characteristic (ROC) curve analysis was performed using GraphPad Prism 9.0 to determine the predictive value of selected parameters. A *P*-value <0.05 was considered statistically significant.

3. Results

A total of 23 pediatric patients diagnosed with CCHF were included in the study; 12 patients (52%, 12/23) required PICU admission, while 11 patients (48%, 11/23) were managed in the pediatric infectious disease ward. A flow chart illustrating patient selection is presented in Figure 1.

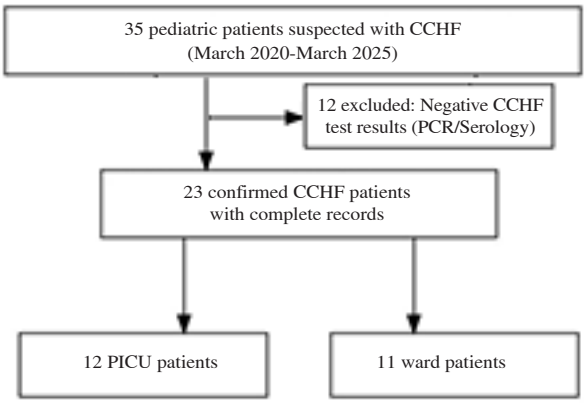

Figure 1. Patient inclusion flowchart. CCHF: Crimean-Congo hemorrhagic fever; PCR: Polymerase chain reaction; PICU: pediatric intensive care unit.

Among the 12 patients admitted to the PICU, DIC was the most common complication, occurring in 3 patients (25%, 3/12) as an isolated complication, while an additional 3 patients (25%, 3/12) presented with a combination of DIC and MODS. The remaining 6 patients (50%, 6/12) presented with various other complications, including isolated MODS (8%, 1/12), neurological manifestations (8%, 1/12), MODS with neurological manifestations (8%, 1/12), DIC with neurological manifestations (8%, 1/12), hypotension (8%, 1/12), and neutropenia with sepsis (8%, 1/12).

Treatment modalities for PICU patients included fresh frozen plasma (8/12, 67%), platelet transfusion (7/12, 58%), plasmapheresis (6/12, 50%), intravenous immunoglobulin (3/12, 25%), and erythrocyte suspension (3/12, 25%).

3.1. Patient characteristics and clinical course

Among the 12 PICU patients, 9 were male (75%) and 3 were female (25%), while the ward group consisted of 6 males (54%, 6/11) and 5 females (45%, 5/11) (Table 1). The median age was 15 years (IQR: 13-16) in the PICU group and 14 years (IQR: 4-16) in the ward group, with no significant difference (*P*=0.214).

PICU patients had significantly longer hospital stays, median of 12 (IQR: 8.5-14.3 days compared to 8.0 (IQR: 7.0-9.0) days for ward patients (*P*=0.007). The median interval from symptom onset to admission was 2 (IQR: 1-3) days for PICU *vs*. 2 (IQR: 1-2) days for ward patients (*P*=0.611). However, the median duration of fever 3 (IQR: 1-3) days for PICU *vs*. 1 (IQR: 1-3) days for ward patients did not differ significantly between the groups (*P*=0.312), as shown in Table 1.

Initial clinical presentations, summarized in Table 1, showed similar distributions between PICU and ward patients. Fever was

Table 1. Comparison of demographics and clinical parameters between pediatric intensive care unit and ward patients.

Variable	PICU (n=12)	Ward (n=11)	P-value
Sex, n (%)			
Male	9 (75)	6 (55)	0.400
Female	3 (25)	5 (45)	
Age, years, median (IQR)	15 (13-16)	14 (4-16)	0.214
Hospital stay, days, median (IQR)	12.0 (8.5-14.3)	8.0 (7.0-9.0)	0.007
Symptom onset to admission, days, median (IQR)	2 (1-3)	2 (1-2)	0.610
Duration of fever, days, median (IQR)	3 (1-3)	1 (1-3)	0.312
Initial clinical presentations, n (%)			
Headache	5 (42)	4 (36)	0.567
Abdominal pain	8 (67)	7 (64)	0.611
Fever	11 (92)	9 (82)	0.476
Bleeding manifestations	11 (92)	3 (27)	0.003
Neurological manifestations	2 (17)	0 (0)	0.478
Widespread myalgia	5 (42)	2 (18)	0.371

Statistically significant at P<0.05. P-values were calculated using Fisher's exact (1-sided) test for categorical variables and Mann-Whitney U test for continuous variables. IQR: Interquartile range.

Table 2. Comparison of laboratory parameters between ward and pediatric intensive care unit patients.

Parameter	Ward (n=11)	PICU (n=12)	P-value
WBC, $\times 10^3$/μL	3980 (1 530-7 020)	2 785 (1 652-3 690)	0.406
NEU, $\times 10^3$/μL	2310 (450-5 310)	2 140 (1 147-2 637)	0.951
LEU, $\times 10^3$/μL	920 (380-1 370)	565 (415-747)	0.406
NLR	2.18 (0.60-6.79)	3.60 (2.36-6.22)	0.424
PLT, $\times 10^3$/μL	128 (94-213)	71 (28-99)	0.002
PMI, $\times 10^3$	1488 (996-1 917)	751 (348-1 090)	0.002
AST, U/L	34 (22-75)	135 (86-256)	<0.001
ALT, U/L	15 (13-46)	59.5 (21-112)	0.014
LDH, U/L	302 (216-362)	472 (334-917)	0.001
INR	1.29 (1.04-1.48)	1.36 (1.21-2.31)	0.291
APTT, s	32.0 (27.9-35.7)	40.7 (30.7-57.3)	0.079
CREAT, mg/dL	0.56 (0.36-0.84)	0.71 (0.59-0.82)	0.096
FER, ng/mL	440 (237-850)	2 062 (705-21 370)	0.010

Values are presented as median (IQR: 25%-75%). WBC: White blood cell count; NEU: Neutrophil count; LEU: Lymphocyte count; NLR: Neutrophil-to-lymphocyte ratio; PLT: Platelet count; PMI: Platelet mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; INR: International normalized ratio; APTT: Activated partial thromboplastin time; KREAT: Creatinine; FER: Ferritin; PICU: Pediatric intensive care unit.

the most common symptom (92% in PICU *vs*. 82% in ward), followed by abdominal pain (67% *vs*. 64%) and headache (42% *vs*. 36%). Neurological manifestations (17% *vs*. 0.0%) were observed although this difference did not reach statistical significance. Bleeding manifestations were significantly more common in PICU patients (11/12, 92%) compared to ward patients (3/11, 27%) (P=0.003). Detailed bleeding types included petechial rash in 9 patients, with additional gastrointestinal bleeding in 2 patients, prolonged menstrual bleeding in 1 patient, hematuria in 1 patient, and subconjunctival hemorrhage in 1 patient.

3.2. Comparison of laboratory parameters between ward and PICU patients

The comparison of laboratory parameters between patients managed in the ward and those admitted to the PICU revealed several statistically significant differences (Table 2). PLT and PMI were significantly higher in ward patients than in PICU patients (PLT: 128×10^3/μL *vs*. 71×10^3/μL, P=0.002; PMI: $1\,488\times10^3$ *vs*. 751×10^3, P=0.002).

AST and ALT levels were significantly elevated in PICU patients

Table 3. Univariate and multivariate logistic regression results for predicting pediatric intensive care unit admission.

Variable	*OR*	95% *CI*	*P*-value	a*OR*	95% *CI*	*P*-value
PLT	0.99	0.98-0.99	0.026	-	-	-
AST	1.03	1.00-1.06	0.025	1.01	0.97-1.04	0.67
ALT	1.03	1.00-1.06	0.050	-	-	-
LDH	1.01	1.00-1.02	0.068	1.00	0.99-1.02	0.61
Ferritin	1.00	1.00-1.00	0.290	-	-	-
PMI	1.00	0.99-1.00	0.021	1.00	0.99-1.00	0.021

Multivariate logistic regression included AST, LDH, and PMI. *P*<0.05 was considered statistically significant. *OR*: Odds ratio; a*OR*: Adjusted odds ratio; *CI*: Confidence interval; PLT: Platelet count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; FER: Ferritin; PMI: Platelet mass index; PICU: Pediatric intensive care unit.

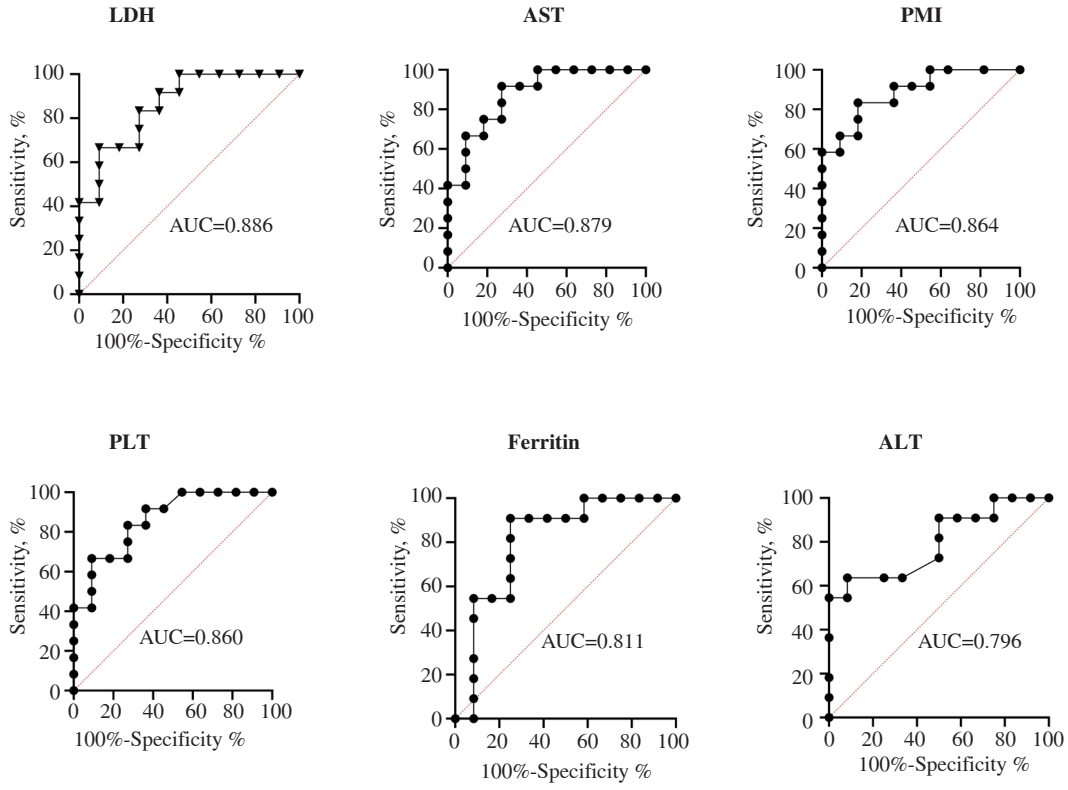

Figure 2. Receiver operating characteristic (ROC) curves of laboratory parameters in pediatric Crimean-Congo hemorrhagic fever (CCHF). ROC curves of aspartate aminotransferase (AST), lactate dehydrogenase (LDH), platelet count (PLT), platelet mass index (PMI), ferritin, and alanine aminotransferase (ALT) are presented to evaluate their predictive performance for admission to the pediatric intensive care unit (PICU). The area under the ROC curve (AUC) was 0.886 for AST, 0.879 for LDH, 0.864 for PMI, 0.860 for PLT, 0.811 for ferritin, and 0.796 for ALT.

(median AST: 135 U/L *vs*. 34 U/L, *P*<0.001; ALT: 59.5 U/L *vs*. 15 U/L, *P*=0.014). Similarly, LDH and ferritin values were markedly higher in the PICU group (LDH: 472 U/L *vs*. 302 U/L, *P*=0.001; ferritin: 2 062 ng/mL *vs*. 440 ng/mL, *P*=0.010).

There were no statistically significant differences between groups in white blood cell count (*P*=0.406), NEU (*P*=0.951), LEU (*P*=0.406), neutrophil-to-lymphocyte ratio (*P*=0.424), APTT (*P*=0.079), creatinine (*P*=0.096), or international normalized ratio (*P*=0.291), although APTT and creatinine tended to be higher in PICU patients.

3.3. Predictive factors for PICU admission

In the univariate logistic regression analysis (Table 3), PLT (*OR* 0.99; 95% *CI* 0.98-0.99; *P*=0.026), AST (*OR* 1.03; 95% *CI* 1.00-1.06; *P*=0.025), ALT (*OR* 1.03; 95% *CI* 1.00-1.06; *P*=0.050), and PMI (*OR* 0.98; 95% *CI* 0.97-0.99; *P*=0.021) were found to be significantly associated with intensive care admission. Due to the limited sample size, a multivariate logistic regression analysis including four variables (AST, ALT, LDH, and PMI) was performed

using a backward Wald elimination method. Variables were selected based on univariate *P*-values (<0.10), clinical relevance, and avoidance of collinearity. PLT was not included in the multivariate model because of its collinearity with PMI, as PMI is calculated by multiplying PLT and MPV, which could bias the results. Including four variables allowed a comprehensive assessment of potential predictors while maintaining an acceptable events-per-variable ratio given the small cohort size. In the multivariate model, only PMI remained an independent predictor of PICU admission (adjusted *OR* 0.98; 95% *CI* 0.97-0.99; *P*=0.021). These results indicate that decreased PMI values independently predict the need for intensive care in pediatric CCHF patients.

3.4. Discriminative power of laboratory parameters in severe pediatric CCHF

To evaluate the predictive ability of laboratory parameters in identifying children with CCHF who require admission to the PICU, ROC curve analysis was performed for six biomarkers (Figure 2, Supplementary Table 1). Among the evaluated parameters, AST, LDH, PLT, and PMI showed high diagnostic accuracy.

The area under the curve (AUC) was highest for AST (AUC=0.886, 95% *CI* 0.69-0.98), followed by LDH (AUC=0.879, 95% *CI* 0.68-0.98), PMI (AUC=0.864, 95% *CI* 0.66-0.97), PLT (AUC=0.860, 95% *CI* 0.65-0.97), ferritin (AUC=0.811, 95% *CI* 0.59-0.94), and alanine aminotransferase (ALT) (AUC=0.796, 95% *CI* 0.58-0.93). The differences between the AUC values of these biomarkers were not statistically significant.

The optimal cut-off value for AST was ⩾84 U/L, yielding a sensitivity of 83.3% and a specificity of 81.8%. LDH had a cut-off of ⩾326 U/L, achieving 91.7% sensitivity and 72.7% specificity. PMI, inversely associated with PICU admission, had a cut-off of ⩽872, providing 66.7% sensitivity and 90.9% specificity. PLT levels ⩽90 000/mm^3 also demonstrated a strong predictive value with 66.7% sensitivity and 90.9% specificity. Ferritin levels ⩾1 256 ng/mL and ALT levels ⩾118 U/L were also significant predictors of PICU admission. These findings suggest that elevated AST, LDH, and ferritin, as well as decreased platelet count and PMI, are valuable predictors of critical illness in pediatric CCHF patients.

4. Discussion

This study aimed to identify clinical and laboratory parameters that differentiate pediatric CCHF patients requiring intensive care from those manageable in general wards. Our findings confirm that elevated LDH and AST levels and decreased PMI and platelet counts serve as significant predictors of intensive care need in pediatric CCHF patients, providing valuable tools for early risk stratification and management decisions.

To the best of our knowledge, this is the first study comprehensively comparing pediatric CCHF patients managed in intensive care versus general wards with a specific focus on PMI as a predictive marker. The identification of reliable laboratory indicators for disease severity addresses a critical gap in the literature, as most previous studies on pediatric CCHF consist of small case series or focus primarily on mortality rather than early indicators of clinical deterioration. Our study design, which captured laboratory parameters at admission before any therapeutic intervention, provides valuable insights into baseline predictors of subsequent disease progression.

In the univariate logistic regression analysis, PLT, AST, ALT, and PMI were found to be significantly associated with intensive care admission, indicating that lower platelet counts and PMI values, as well as higher AST and ALT levels, are potential predictors for ICU requirement. In the multivariate analysis, which included AST, ALT, LDH, and PMI, only PMI remained an independent predictor of PICU admission (adjusted *OR* 0.98; 95% *CI* 0.97-0.99, *P*=0.021). These findings are consistent with previous studies highlighting the importance of thrombocytopenia, liver enzyme elevations, and other biomarkers in predicting CCHF severity and bleeding risk[12-16].

Elevated AST levels showed remarkable diagnostic accuracy for identifying patients requiring intensive care. The higher predictive value of AST compared to ALT in our study is noteworthy and may reflect the broader tissue distribution of AST, suggesting more widespread organ damage in severe cases. Previous studies have demonstrated that AST elevations often precede clinical deterioration in CCHF patients and may serve as an early warning sign for impending complications[17,18]. The robust predictive performance of AST in our pediatric cohort underscores its value as a readily available laboratory parameter for risk stratification in resource-limited settings.

Decreased PMI emerged as the only independent predictor of PICU admission in the multivariate analysis. This novel finding extends beyond the established correlation between thrombocytopenia and CCHF severity by incorporating platelet size, potentially offering a more comprehensive assessment of hemostatic capacity. Recent studies have proposed bleeding risk scoring systems and validated various biomarkers for predicting hemorrhagic complications in CCHF, further supporting the importance of platelet-related

indices[12–14,19,20]. The role of PMI in pediatric viral hemorrhagic fevers has not been previously established, and our findings may encourage further research into its application as a composite marker of hemostatic function.

The significant association between decreased platelet counts and PICU admission in univariate analysis confirms the clinical importance of thrombocytopenia in CCHF progression. While PLT was not included in the multivariate model due to its collinearity with PMI (as PMI is calculated by multiplying PLT and MPV), the strong univariate association reinforces the central role of platelet dysfunction in disease severity. Our findings reinforce previous research showing that profound thrombocytopenia is a hallmark of severe CCHF in pediatric patients. The development of thrombocytopenia in CCHF reflects both direct viral effects on megakaryocytes and peripheral consumption of platelets, with the latter becoming increasingly prominent as the disease progresses to DIC[21]. This hemostatic dysfunction manifested clinically as bleeding complications in 91.7% of PICU patients compared to only 27.3% of ward patients (P=0.003), with manifestations ranging from petechiae to severe hemorrhage. The strong correlation between laboratory abnormalities and clinical bleeding underscores the value of PMI and platelet count as predictors of hemorrhagic complications requiring intensive care[12].

Markedly elevated ferritin levels in PICU patients suggest hyperferritinemia as an important marker of disease severity. Hyperferritinemia in severe CCHF likely reflects the intense inflammatory response and potential development of secondary hemophagocytic lymphohistiocytosis (HLH) in critically ill patients. Recent studies have demonstrated that extreme hyperferritinemia correlates with cytokine storm syndromes in various viral infections, supporting its use as a marker for immunopathology requiring aggressive immunomodulatory interventions[22,23].

Its markedly higher levels in PICU patients and excellent performance in ROC analysis suggest LDH remains an important marker for disease severity. Elevated LDH likely reflects the extent of tissue damage and cellular destruction caused by CCHF virus infection, serving as a marker of widespread organ involvement. Several studies have identified LDH as a consistent prognostic marker across viral hemorrhagic fevers, suggesting its utility as part of a severity assessment panel in resource-limited settings where specific viral testing may be delayed. In line with our findings, previous reports have also demonstrated that increased LDH activity correlates with higher bleeding risk and worse clinical outcomes in CCHF patients[24,25].

The treatment modalities employed in our PICU patients, including plasmapheresis, fresh frozen plasma, platelet transfusions, and erythrocyte suspensions, reflect the intensive supportive care required for severe CCHF. The use of specific antiviral therapy (ribavirin) in both groups reflects the ongoing debate regarding the clinical benefit of this agent[26,27].

Our ROC curve analysis demonstrated the high diagnostic accuracy of multiple laboratory parameters in identifying children who would require PICU admission. These findings indicate that these biomarkers effectively distinguish between patients who will develop severe disease requiring intensive care versus those who can be safely managed in general wards. The lack of statistically significant differences between these AUC values suggests that clinicians can utilize multiple markers for risk assessment based on test availability and laboratory capabilities, particularly valuable in resource-limited settings[18,28].

Our study has several limitations, including its retrospective design, relatively small sample size, and single-center nature. The limited sample size particularly affected the multivariate analysis, potentially reducing its statistical stability and limiting the number of variables that could be included. This constraint may have influenced our ability to detect all independent predictors of PICU admission. Additionally, we did not have access to viral load data, which has been shown in some studies to correlate with disease severity. Despite these limitations, our study provides valuable insights into predictors of disease severity in pediatric CCHF and identifies parameters that can be readily assessed in most healthcare settings.

In conclusion, this study identifies PMI as an independent predictor of intensive care requirement in pediatric CCHF patients, providing a novel and practical tool for early risk stratification. The comprehensive assessment of laboratory parameters revealed that while multiple markers including AST, LDH, and platelet count show excellent diagnostic accuracy, PMI emerges as the most robust predictor when adjusted for other variables. These findings have important implications for clinical practice, enabling early identification of high-risk pediatric patients who may benefit from closer monitoring and timely interventions. Future research should focus on prospective validation of PMI in larger multicenter cohorts, development of pediatric-specific CCHF severity scoring systems, and investigation of whether early risk stratification based on these markers can improve clinical outcomes.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Ethics approval

The study protocol was reviewed and approved by the Ethics Committee of the University of Health Sciences, Kayseri City Hospital (Approval number: 249, date: 26 November 2024). All procedures were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments.

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Authors´ contributions

M.A.D. contributed to concept, design, literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, and manuscript review. M.O.D. was involved in data acquisition and manuscript preparation. F.B. contributed to data acquisition and definition of intellectual content. I.H.D. participated in data acquisition and concept development. S.Y.D. supervised the project and contributed to manuscript preparation. M.A.D. served as the guarantor of the study, ensuring the integrity of the work from inception to published article. All authors have read and approved the final manuscript. The requirements for authorship have been met, and each author believes that the manuscript represents honest work.

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Supplementary Table 1. ROC curve analysis for predicting PICU admission in pediatric CCHF patients.

Biomarker	AUC (95% CI)	p-value	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AST	0.89 (0.69–0.98)	<0.001	84 U/L	83.33	81.82	83.33	81.82
LDH	0.88 (0.68–0.98)	<0.001	326 U/L	91.67	72.73	78.57	88.89
PMI	0.86 (0.66–0.97)	<0.001	872 × 10^3	66.67	90.91	88.89	71.43
PLT	0.86 (0.65–0.97)	<0.001	90000/mm^3	66.67	90.91	88.89	71.43
Ferritin	0.81 (0.59–0.94)	0.002	1256 ng/mL	75.00	90.91	90.00	76.92
ALT	0.80 (0.58–0.93)	0.003	118 U/L	91.67	63.64	73.33	87.50

AUC: Area Under the Curve; CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; PMI: Platelet Mass Index; PLT: Platelet Count; ALT: Alanine Aminotransferase