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ORIGINAL RESEARCH

Predictors of Severity in Hemorrhagic Fever with Renal Syndrome

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Objective: To explore the risk factors for the severity of hemorrhagic fever with renal syndrome (HFRS) and construct a nomogram model.

Methods: A retrospective analysis was conducted on the data of 191 patients diagnosed with HFRS at the First Affiliated Hospital of Dali University between January 1, 2013, and September 30, 2024. Based on whether severe disease occurred, the patients were divided into a severe HFRS group (n=42) and a mild HFRS group (n=149). The clinical data of the two groups were compared, and after eliminating the influence of collinearity, LASSO-Logistic regression analysis was used to screen for factors influencing the severity of HFRS. Additionally, a nomogram model was constructed to predict the severity of HFRS.

Results: Compared with the mild HFRS group, patients in the severe HFRS group had a prolonged length of stay, increased usage rates of Continuous Renal Replacement Therapy (CRRT) and ventilators, and an elevated 30-day mortality rate ($P<0.001$). Procalcitonin (PCT, OR= 0.86), Albumin (ALB, OR: 0.86), Platelet count-to-Albumin ratio (PAR, OR: 0.64), and pleural effusion (OR: 4.49) were identified as independent risk factors for severe HFRS. The Area Under Curve (AUC) of the nomogram model was 0.890. The Hosmer-Lemeshow test result was $\chi^2=2.92$, $P=0.94$, and in combination with the Calibration curve, it indicated a good fit between the calibration curve and the ideal curve. Most of the Decision Curve Analysis (DCA) curves of the nomogram model were above the two extreme lines, suggesting that using this model to predict severe HFRS patients could clinically benefit those with severe HFRS, demonstrating the clinical practicality of the nomogram model.

Conclusion: PCT, ALB, PAR, and pleural effusion are risk factors for the severity of HFRS. The constructed nomogram model exhibits good discriminatory power, fit, and clinical practicality, enabling early identification of patients with severe HFRS in southwestern China.

Keywords: hemorrhagic fever with renal syndrome, severity, risk factors, nomogram

Introduction

HFRS is an acute zoonotic infection primarily transmitted by rodent hosts, caused by Hantavirus infection.[1] Its diagnosis is primarily based on the detection of serotype-specific antibodies (IgM, IgG) in serum samples. HFRS is widely prevalent across the Eurasian continent, with an annual incidence of 100,000 to 150,000 reported cases and a mortality rate fluctuating between 1% and 15%,[2–5] posing a significant threat to human health and constituting a major public health issue. China is one of the countries with the most severe outbreaks, accounting for 70% to 90% of the total reported cases.[6,7]

The clinical manifestations of HFRS often exhibit diversity and heterogeneity due to various factors such as the causative virus strain, geographical location, season of onset, and the immune status of the infected individual.[8–10] Additionally, the number of cases with extrarenal manifestations[11–13] has been increasing annually. Notably, new genotypes of Hantavirus have been reported,[14] all posing significant challenges for early identification and diagnosis. Although recent studies have found that biomarkers such as Exosomal microRNA (miRNA)-155, miRNA-146a,[15] Serum

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superoxide dismutase,[16] and pentraxin-3 (PTX3)[17] can be somewhat helpful in the early identification of severe HFRS, these tests are complex and costly, currently limited to research use and not yet widely applied in clinical practice.

Although Yu et al[18] proposed a novel scoring system named the HFRS-related Organ Failure Assessment Score (H-SOFA), which has high early warning value for the progression of HFRS to severe cases, its clinical application is limited due to insufficient validation. Additionally, research has also developed a nomogram model for early identification of severe HFRS in the Jingzhou region.[19] However, there are few studies on the risk factors for severe HFRS in southwestern China and the construction of predictive models for this condition.

We recognize that early identification of severe cases of hemorrhagic fever with renal syndrome poses a significant challenge for healthcare workers, hindering timely intervention and patient benefits. The aim is to explore the predictive factors for severe HFRS patients in Southwest China. To address these challenges, we will develop a nomogram model utilizing the predictive factors for severe HFRS patients, which will facilitate early identification and management of severe cases.

Materials and Methods

Ethics

This study was approved by the Ethics Committee of the First Affiliated Hospital of Dali University (DFY20240521001). As this study was a retrospective study, the Ethics Committee of the First Affiliated Hospital of Dali University granted a waiver of informed consent for the patients. All research procedures involving human participants were conducted in accordance with the 1964 helsinki Declaration and its later amendments or similar ethical standards.

Study Subjects and Grouping

The data were collected from 220 patients with HFRS, with 29 patients excluded and 191 included, according to the inclusion and exclusion criteria established in the study, as shown in Figure 1. All enrolled patients satisfied the standardized diagnostic criteria for HFRS,[20] with clinical subclassifications determined according to evidence-based guidelines referenced in peer-reviewed literature.[9,19,21]

Collection of Case Data

General baseline data for the two patient groups were collected through the Hospital Information System (HIS), including age, gender, smoking and alcohol consumption habits, underlying diseases (Hypertension, Diabetes), clinical manifestations and/or signs (Fever, Headache, Stomachache, Diarrhea, Nausea and vomiting, Muscular soreness, Conjunctiva hyperemia, Flush, Hepatosplenomegaly, Lymphadenectasis), complications (Multidrug-Resistant Organism infection, Disseminated Intravascular Coagulation, Intracranial hemorrhage, Acute Pancreatitis, Hemophagocytic Lymphohistiocytosis, Pneumonia, Pleural effusion, Seroperitoneum, Arrhythmia), and laboratory parameters [C-Reactive Protein (CRP), Procalcitonin (PCT), White Blood Cell count (WBC), Neutrophil count (N#), Lymphocyte count (L#), Red blood cell count (RBC), Hemoglobin (HGB), Platelet count (PLT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Albumin (ALB), Urea nitrogen, Creatinine (CREA), Urine acid (UA), serum potassium, serum sodium, Serum chloride, serum calcium, Glucose (Glu), Total cholesterol (TC), Triglyceride (TG), High-density lipoprotein (HDL), Low-density lipoprotein (LDL), Creatine Kinase (CK), Creatine kinase isoenzyme MB (CK-MB), Lactic Dehydrogenase (LDH), Hydroxybutyrate dehydrogenase (HBDH), Prothrombin time (PT), Activated partial thromboplastin time (APTT), Thrombin time (TT), Fibrinogen (FIB)]. The following indices were also calculated: Systemic Immune-Inflammation Index (SII) = neutrophil count × platelet count / lymphocyte count; Neutrophil-to-Lymphocyte Ratio (NLR) = neutrophil count-to-lymphocyte count Ratio; Platelet-to-Lymphocyte Ratio (PLR) = platelet count-to-lymphocyte count Ratio; Lymphocyte-to-Monocyte Ratio (LMR) = lymphocyte count-to-monocyte count Ratio; Neutrophil-to-Platelet Ratio (NPR) = neutrophil count-to-platelet count Ratio; Systemic Immune-Inflammation Response Index (SIRI) = neutrophil count × monocyte count / lymphocyte count; Platelet-to-Albumin Ratio (PAR) = platelet count-to-albumin Ratio; CRP-to-Albumin Ratio (CAR) = CRP-to-albumin Ratio; and CRP-to-Lymphocyte count Ratio (CLR) = CRP-to-Lymphocyte count Ratio.

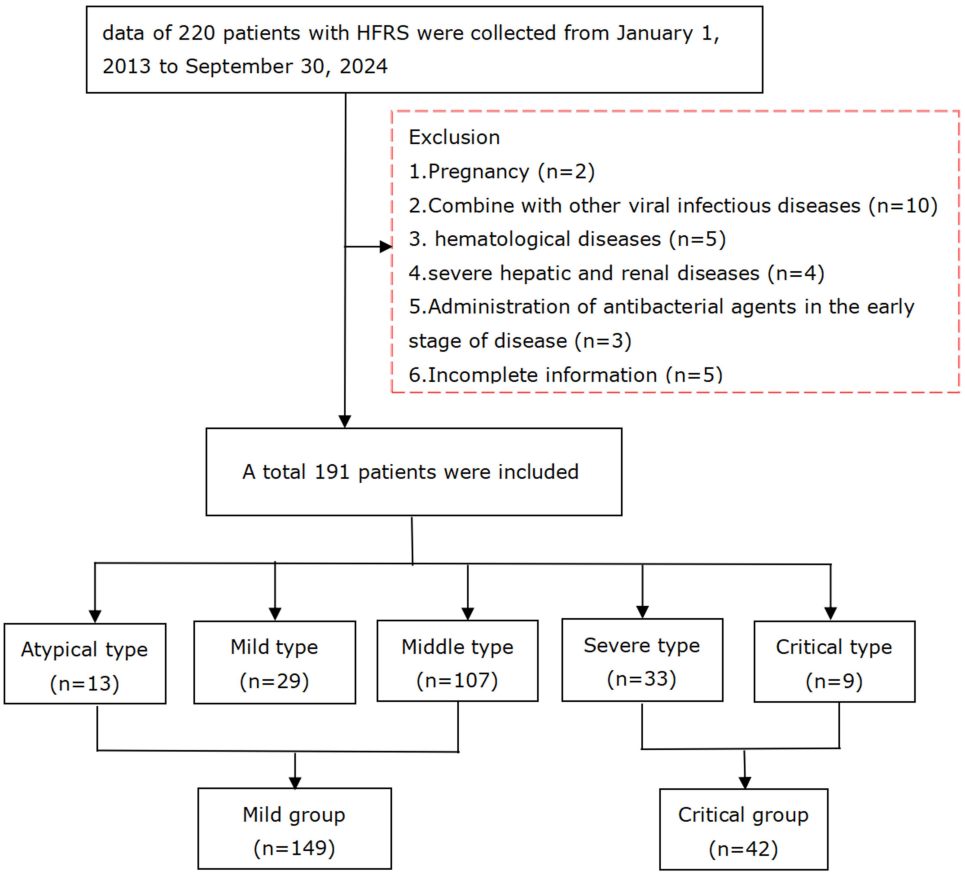

Figure 1 Schematic flow chart for Hemorrhagic Fever with Renal Syndrome.

Statistical Analysis

Statistical analyses were conducted using R Studio and SPSS version 26.0. Measurement data that conform to a normal distribution are presented as the mean ± standard deviation (SD), and comparisons between groups are conducted using the student's test. For measurement data that do not conform to a normal distribution, they are presented as the median (interquartile range) [M (P25, P75)], and comparisons between groups are performed using the Mann–Whitney *U*-test or Fisher's exact test. Count data are presented as the number of cases and percentage [n (%)], and comparisons between groups are conducted using the chi-squared (χ^2) test. The indicators with significant differences between the two aforementioned groups were subjected to multicollinearity analysis among variables, excluding those with a Variance Inflation Factor (VIF) > 10. Subsequently, based on whether severe HFRS occurred as the outcome variable, Stomachache, Diarrhea, Nausea and vomiting, Conjunctival injection, Pleural effusion, PCT, WBC, CREA, Glu, CK, CK-MB, NPR, CAR, PT, ALB, TC, LDL, Systemic Immune-Inflammation Index (SII), and Platelet-to-albumin ratio (PAR) were included as independent variables in the Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis. LASSO adds a penalty term to the least squares method to compress the estimated parameters, thereby selecting the factors that have the greatest impact on the dependent variable. Subsequently, based on the LASSO regression, variables (PCT, ALB, Glu, WBC, PAR, Stomachache, Diarrhea, Pleural Effusion) that can be used for model fitting are identified. The variables obtained from the LASSO regression analysis that are suitable for model fitting (PCT, ALB, Glu, WBC, PAR, stomach pain, diarrhea, and pleural effusion) were subjected to a multivariate logistic regression analysis to identify the risk factors for predicting severe HFRS, which include PCT, ALB, PAR, and pleural effusion. Next, a Nomogram prediction model is constructed based on the screened risk factors. Finally, a Receiver Operating Characteristic (ROC) curve is plotted, and the AUC of the ROC curve is calculated to analyze the predictive performance of the model. The Hosmer-Lemeshow test is used for calibration assessment, and a calibration curve is plotted to evaluate

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the goodness of fit. Lastly, a DCA curve is plotted to assess the clinical utility of the model. *P*-value < 0.05 indicates statistical significance.

Results

Comparison of Clinical Data Between Mild and Severe Cases in Patients with HFRS

Compared with patients in the mild group, patients in the severe group had higher incidence rates of stomachache, diarrhea, nausea and vomiting, conjunctival injection, pleural effusion, the need for continuous renal replacement therapy, ventilator use, longer hospital stays, and higher 30-day mortality ($P < 0.05$). Additionally, there were elevations in PCT, WBC, CREA, Glu, CK, CKMB, NPR, and CAR. Furthermore, PT was prolonged, while PLT, ALB, TC, LDL, SII, PLR, and PAR were significantly decreased ($P < 0.05$) (Table 1 and Table 2).

Screening of Variables Influencing the Severity of HFRS

During the variable selection process, PLT (VIF=62.43) and PLR (VIF=10.38) were excluded due to severe multicollinearity (both Variance Inflation Factors >10). Ultimately, 19 indicators demonstrating statistically significant differences between mild and severe groups (stomachache, diarrhea, nausea and vomiting, conjunctival injection, pleural effusion, PCT, WBC, CREA, Glu, CK, CKMB, NPR, CAR, PT, PAR, ALB, TC, LDL, SII) were incorporated into LASSO regression for non-zero coefficient variable screening (Figure 2A). The optimal λ value was selected through 10-fold cross-validation, aiming to include the minimum number of variables while ensuring goodness of fit. Ultimately,

Table 1 Comparison of Clinical Characteristics Between Mild and Severe Group of Hemorrhagic Fever with Renal Syndrome Patients

Variables	Mild Group (n=149)	Critical Group (n=42)	z/t/χ^2	*P*-value
Patient characteristics				
Age, years	47.44 ± 13.50	49.62 ± 16.09	0.88	0.378
Male sex, (%)	100 (67.11%)	27 (64.29%)	0.12	0.732
Height (cm)	167.00 (160.00, 170.00)	168.00 (162.50, 170.00)	0.75	0.454
Weight (kg)	61.68 ± 10.60	64.68 ± 11.14	−1.60	0.110
Body Mass Index (kg/m²)	22.27 (19.97, 24.50)	23.17 (21.86, 24.88)	−1.55	0.121
Smoking, n (%)	64 (42.95%)	22 (52.38%)	1.18	0.278
Drinking, n (%)	47 (31.54%)	16 (38.10%)	0.64	0.425
Hypertension, n (%)	23 (15.44%)	5 (11.90%)	0.33	0.568
Diabetes, n (%)	6 (4.03%)	4 (9.52%)	1.04	0.308
Vital signs				
Body temperature (°C)	39.00 (38.20, 39.60)	38.95 (37.05, 40.58)	−0.54	0.590
Breath rate (beats/min)	20.00 (20.00, 21.00)	20.00 (20.00, 21.00)	−0.89	0.375
Pulse rate (beats/min)	87.00 (76.00, 100.00)	85.50 (77.00, 101.75)	−0.05	0.960
Systolic blood pressure (mmHg)	110.00 (100.00, 125.00)	106.50 (98.25, 129.00)	−0.09	0.924
Diastolic blood pressure (mmHg)	71.00 (62.00, 79.00)	67.00 (62.25, 77.75)	−0.81	0.420

(*Continued*)

Table 1 (Continued).

Variables	Mild Group (n=149)	Critical Group (n=42)	z/t/χ^2	*P*-value
Signs and symptoms				
Fever, n (%)	129 (86.58%)	33 (78.57%)	1.63	0.202
Headache, n (%)	77 (51.68%)	21 (50.00%)	0.04	0.848
Stomachache, n (%)	27 (18.12%)	19 (45.24%)	13.18	<0.001
Diarrhea, n (%)	11 (7.38%)	12 (28.57%)	13.89	<0.001
Nausea and vomiting, n (%)	30 (20.13%)	15 (35.71%)	4.42	0.036
Muscular soreness, n (%)	51 (34.23%)	19 (45.24%)	1.71	0.191
Conjunctiva hyperemia, n (%)	17 (11.41%)	12 (28.57%)	7.49	0.006
Flush, n (%)	7 (4.70%)	2 (4.76%)	0.00	1.000
Hepatosplenomegaly, n (%)	22 (14.77%)	6 (14.29%)	0.01	0.938
Lymphadenectasis, n (%)	3 (2.01%)	1 (2.38%)	-	1.000
Comorbidities				
Multidrug-Resistant Organism infection, n (%)	5 (3.36%)	2 (4.76%)	0.00	1.000
Disseminated Intravascular Coagulation, n (%)	2 (1.34%)	2 (4.76%)	-	0.211
Intracranial hemorrhage, n (%)	1 (0.67%)	2 (4.76%)	-	0.211
Acute Pancreatitis, n (%)	5 (3.36%)	4 (9.52%)	1.57	0.210
Hemophagocytic Lymphohistiocytosis, n (%)	2 (1.34%)	1 (2.38%)	-	0.527
Pneumonia, n (%)	57 (38.26%)	21 (50.00%)	1.87	0.171
Pleural effusion, n (%)	45 (30.20%)	29 (69.05%)	20.83	<0.001
Seroperitoneum, n (%)	4 (2.68%)	1 (2.38%)	0.00	1.000
Arrhythmia, n (%)	70 (46.98%)	20 (47.62%)	0.01	0.942
Treatment and prognosis				
Continuous Renal Replacement Therapy, n (%)	8 (5.37%)	9 (21.43%)	8.54	0.003
Ventilator, n (%)	1 (0.67%)	7 (16.67%)	17.09	<0.001
Length of hospital stay (d)	10.00 (8.00, 13.00)	15.00 (11.25, 18.75)	−5.16	<0.001
30-day mortality, n (%)	4 (2.68%)	12 (28.57%)	25.33	<0.001

Note: Body Mass Index= Weight (kg)/Height (m^2).

lambdause was chosen as the optimal λ value (λ=0.054), resulting in the selection of 8 non-zero coefficient predictor variables (Figure 2B), including PCT, ALB, Glu, WBC, PAR, Stomachache, Diarrhea, and Pleural Effusion.

Develop a Predictive Model

A multivariate Logistic regression prediction model was constructed with the occurrence of severity in HFRS as the dependent variable and the eight variables selected by LASSO regression as the independent variables. The results

Table 2 Comparison of Laboratory Indicators Between Mild and Severe Group of Hemorrhagic Fever with Renal Syndrome Patients

Variables	Mild Group (n=149)	Critical Group (n=42)	z/t/χ^2	*P*-value
C-Reactive Protein (mg/L)	35.82 (18.97, 58.89)	48.88 (18.81, 73.94)	Z=−1.24	0.216
Procalcitonin (ng/mL)	0.90 (0.38, 1.59)	2.50 (1.91, 4.29)	Z=−6.16	<0.001
White Blood Cell (×10^9/L)	8.32 (6.42, 11.98)	13.42 (9.52, 14.94)	Z=−4.38	<0.001
Neutrophil count (×10^9/L)	5.19 (3.91, 7.54)	5.62 (2.89, 10.34)	Z=−0.43	0.665
Lymphocyte count (×10^9/L)	1.88 (1.21, 2.64)	1.60 (0.99, 2.99)	Z=−0.99	0.324
Red blood cell (×10^{12}/L)	4.63 ± 0.78	4.53 ± 0.80	t=0.72	0.471
Hemoglobin (g/L)	143.00 (124.00, 155.00)	139.50 (121.25, 157.00)	Z=−0.45	0.651
Platelet (×10^9/L)	76.00 (42.00, 151.00)	37.00 (26.25, 60.00)	Z=−4.56	<0.001
Alanine aminotransferase (U/L)	84.00 (51.00, 160.00)	82.50 (47.50, 219.75)	Z=−0.14	0.886
Aspartate aminotransferase (U/L)	111.00 (50.00, 211.00)	88.50 (64.00, 203.75)	Z=−0.02	0.986
Albumin (g/L)	29.80 (26.40, 33.60)	25.45 (22.98, 27.85)	Z=−5.55	<0.001
Urea nitrogen (mmol/L)	7.14 (4.84, 15.38)	12.29 (5.29, 22.41)	Z=−1.65	0.100
Creatinine (umol/L)	102.00 (72.00, 231.00)	149.00 (73.50, 478.00)	Z=−2.08	0.038
Urine acid (umol/L)	346.00 (229.00, 532.00)	358.50 (251.00, 596.50)	Z=−0.91	0.361
Serum potassium (mmol/L)	3.76 ± 0.53	3.80 ± 0.57	t=−0.44	0.662
Serum sodium (mmol/L)	137.00 (134.00, 140.00)	136.00 (131.25, 139.75)	Z=−0.76	0.449
Serum chloride (mmol/L)	102.00 (98.60, 105.00)	101.25 (97.55, 107.10)	Z=−0.28	0.778
Serum calcium (mmol/L)	1.96 (1.82, 2.07)	1.89 (1.82, 2.02)	Z=−1.10	0.272
Glucose (mmol/L)	5.67 (4.84, 6.85)	6.97 (5.59, 10.14)	Z=−4.05	<0.001
Total cholesterol (mmol/L)	3.08 (2.64, 3.91)	2.75 (2.28, 3.45)	Z=−2.50	0.013
Triglyceride (mmol/L)	2.21 (1.58, 3.11)	2.27 (1.68, 3.50)	Z=−0.51	0.612
High density lipoprotein (mmol/L)	0.58 (0.38, 0.80)	0.46 (0.41, 0.67)	Z=−1.32	0.188
Low density lipoprotein (mmol/L)	1.35 (0.92, 1.76)	0.88 (0.77, 1.57)	Z=−2.65	0.008
Creatine Kinase (U/L)	59.00 (28.00, 157.00)	77.50 (56.00, 165.00)	Z=−2.41	0.016
Creatine kinase isoenzymes (ng/mL)	14.00 (8.00, 24.00)	23.50 (12.50, 32.00)	Z=−3.01	0.003
Lactic Dehydrogenase (U/L)	432.00 (328.00, 659.00)	485.50 (389.25, 650.00)	Z=−1.22	0.224
Hydroxybutyrate dehydrogenase (U/L)	364.00 (274.00, 544.00)	464.50 (303.25, 615.75)	Z=−1.57	0.117
Prothrombin time (s)	12.40 (11.40, 13.50)	13.05 (12.05, 14.40)	Z=−2.14	0.033
Activated partial thromboplastin time (s)	37.10 (31.10, 45.20)	38.15 (31.75, 44.75)	Z=−0.49	0.621
Thrombin time (s)	18.70 (16.90, 23.30)	19.80 (17.55, 24.60)	Z=−0.97	0.332
Fibrinogen (g/L)	3.08 (2.43, 4.10)	2.92 (2.40, 3.71)	Z=−0.75	0.455
SII	210.56 (89.00, 521.14)	148.46 (64.64, 234.40)	Z=−2.45	0.014

(*Continued*)

Table 2 (Continued).

Variables	Mild Group (n=149)	Critical Group (n=42)	z/t/χ^2	*P*-value
NLR	2.75 (1.74, 4.51)	3.67 (1.64, 7.70)	Z=−1.36	0.174
PLR	41.74 (18.22, 100.00)	25.25 (12.62, 37.61)	Z=−3.38	<0.001
LMR	2.59 (1.80, 3.80)	1.82 (1.41, 3.72)	Z=−1.46	0.146
NPR	0.06 (0.03, 0.14)	0.11 (0.08, 0.32)	Z=−4.18	<0.001
SIRI	2.07 (1.02, 3.80)	2.77 (1.04, 5.22)	Z=−1.25	0.212
PAR	2.42 (1.38, 5.35)	1.49 (1.06, 2.50)	Z=−3.68	<0.001
CAR	1.22 (0.63, 2.06)	1.95 (0.75, 2.96)	Z=−2.18	0.029
CLR	18.29 (8.30, 36.88)	30.13 (8.49, 71.95)	Z=−1.40	0.162

Notes: SII= Neutrophil count × Platelet count / Lymphocyte count.
Abbreviations: NLR, Neutrophil count-to-Lymphocyte count ratio; PLR, Platelet count-to-Lymphocyte count ratio; LMR, Lymphocyte count-to-Monocyte count Ratio; NPR, Neutrophil count-to-Platelet count; SIRI, Neutrophil count ×Monocyte count /Lymphocyte count; PAR, Platelet count-to-Albumin ratio; CAR, C-Reactive Protein-to-Albumin ratio; CLR, C-Reactive Protein-to-Lymphocyte count ratio.

indicated that PCT, ALB, PAR, and Pleural Effusion were independent risk factors for the severity of HFRS ($P < 0.05$) (Table 3).

Drawing of a Nomogram

Based on the results of the LASSO-Logistic regression analysis, a predictive nomogram model for the severity of HFRS was constructed, incorporating 4 risk factors: PCT, ALB, PAR, and Pleural Effusion (Figure 3).

Model Validation

The discriminatory ability of the predictive model for the severity of HFRS was evaluated using the ROC curve, with results showing an AUC of 0.890 (95% CI: 0.84–0.94) (Figure 4A). The Hosmer-Lemeshow goodness-of-fit test for the

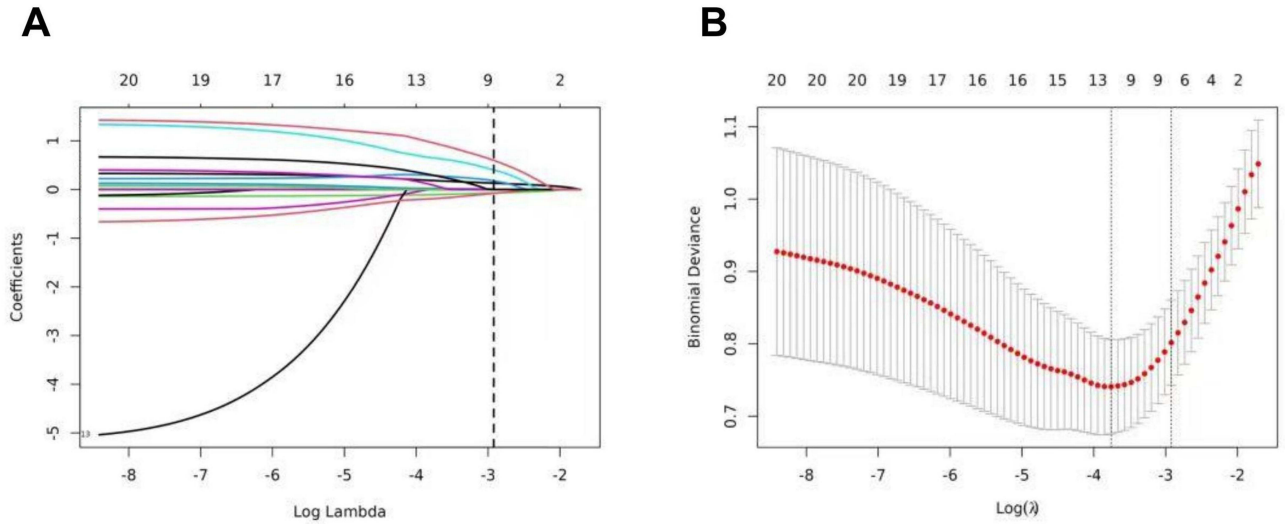

Figure 2 Screening predictor variables based on LASSO regression. (**A**) LASSO Regression Coefficient Path Diagram. This diagram illustrates the selection of non-zero coefficients through LASSO regression modeling. The analysis incorporated 19 variables, each represented by a distinct colored trajectory. Each curve traces the coefficient value of a predictor variable across varying penalty intensities (λ). The y-axis denotes coefficient magnitude, while the lower x-axis shows log(λ), and the upper x-axis indicates the number of non-zero coefficients retained in the model at each λ. (**B**) LASSO Regression Cross-Validation Plot, This plot displays model performance metrics across penalty coefficients. The x-axis represents log(λ), and the y-axis shows likelihood deviation. The overlaid numerals indicate the number of variables retained in the model at each λ. Two vertical dashed lines highlight critical λ thresholds: the left line marks λmin, and the right line denotes λ1se.

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Table 3 Multivariate Logistic Regression Analysis of Severity Progression in Hemorrhagic Fever with Renal Syndrome

Variables	β	S. E	Z	OR (95% CI)	*P*-value
Procalcitonin	0.28	0.11	2.52	1.33 (1.07–1.66)	0.012
Albumin	−0.15	0.06	−2.47	0.86 (0.76–0.97)	0.014
Glucose	0.02	0.07	0.35	1.02 (0.90–1.17)	0.727
White Blood Cell	0.06	0.04	1.30	1.06 (0.97–1.15)	0.193
Platelet-to-albumin ratio	−0.45	0.18	−2.47	0.64 (0.45–0.91)	0.014
Stomachache	0.43	0.52	0.83	1.54 (0.55–4.26)	0.408
Diarrhea	0.65	0.61	1.07	1.91 (0.58–6.24)	0.286
Pleural effusion	1.5	0.49	3.04	4.49 (1.71–11.82)	0.002

Abbreviation: OR, Odds Ratio.

model yielded χ^2=2.92, *P*=0.94. The calibration curve (Figure 4B) indicated no significant difference between the calibration curve of the nomogram model and the ideal curve, demonstrating good agreement between the predicted and actual values of the model. The net benefit of the model was assessed using the DCA (Figure 4C), which showed that the model curves were above the two extreme scenarios. According to the nomogram model, the net benefit was comparable, but with some overlap.

Discussion

The pathological characteristics of HFRS include increased vascular permeability, thrombocytopenia, and renal dysfunction. The disease is complex, progresses rapidly, and currently lacks specific medications for treatment, leading to increased mortality in severe cases. Early and accurate assessment of HFRS patient conditions is crucial for guiding clinical treatment. Based on these objectives, the following findings were obtained in this study: 1. Severe HFRS patients experienced prolonged hospital stays, increased rates of CRRT and Ventilator use, and higher 30-day mortality; 2. PCT, ALB, PAR, and pleural effusion emerged as significant predictors of HFRS severity progression. 3. A nomogram model

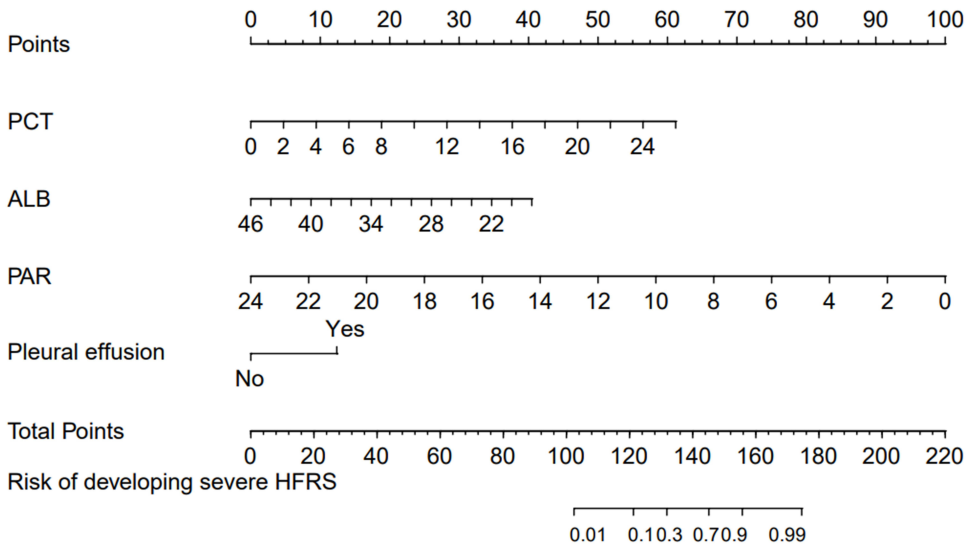

Figure 3 Nomogram model diagram for predicting severe Hemorrhagic Fever with Renal Syndrome.

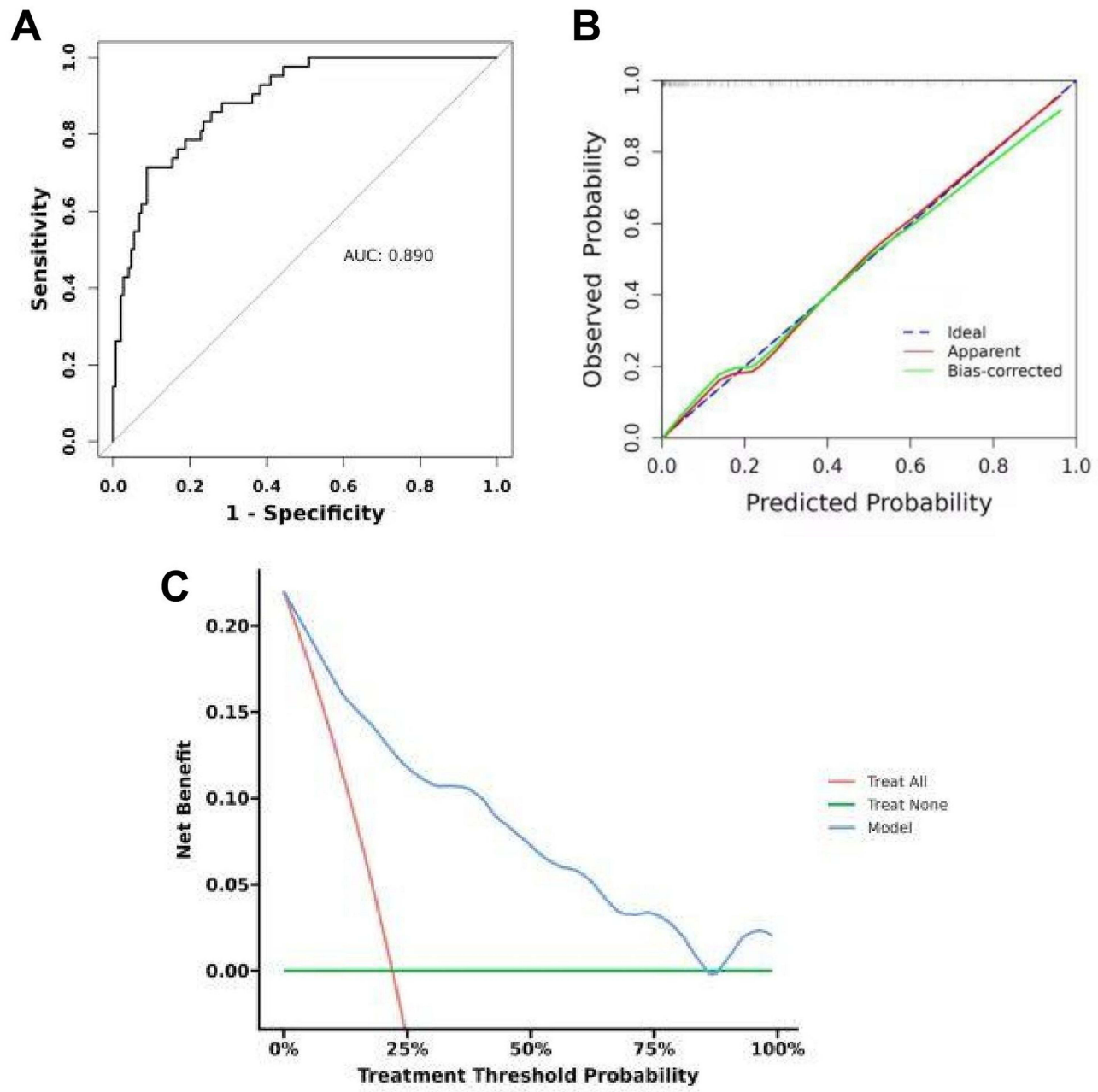

Figure 4 Performance evaluation diagrams of the nomogram model. (**A**) ROC curve of the nomogram model; (**B**) Calibration curve of the nomogram model; (**C**) Decision curve analysis of the nomogram model.

developed using these predictors demonstrated robust discriminatory power, adequate calibration, and favorable net benefit for clinical decision-making in HFRS management.

Previous studies have found that severe Acute Kidney Injury (AKI) often requires CRRT treatment, and AKI is a common cause of death in HFRS patients.[22] In cases where the condition progresses to acute respiratory distress syndrome, mechanical ventilation can improve symptoms and reduce the risk of mortality. Similarly, research[23] has shown that, depending on the severity of the disease in HFRS patients, hemodialysis can control volume load, stabilize blood flow, remove inflammatory mediators, protect the kidneys, and reduce the incidence of hypervolemic syndrome and/or pulmonary edema. In this study, it was found that the severe group had prolonged hospital stays, increased use of CRRT and Ventilators, and a higher 30-day mortality rate. This may be due to Hantavirus infection of endothelial cells causing endothelial barrier disruption, increased vascular permeability, and immune system imbalance, leading to

respiratory failure, pulmonary edema, and multiple organ dysfunction syndrome, and even death in patients.[8] Clearly, the prognosis for severe HFRS patients is poorer. Thus, elucidating predictors of HFRS severity progression and constructing a nomogram model hold substantial clinical value for early recognition and stratified management of severe HFRS cases.

Subsequent analyses identified PCT, ALB, PAR, and pleural effusion as significant predictors of HFRS severity progression. A study by Kim[24] found that ALB levels are closely associated with the severity of HFRS. When Hantavirus invades vascular endothelial cells, the integrity of the endothelial barrier is compromised. Simultaneously, the coagulation system and immune system are activated, leading to the release of cytokines and triggering a cytokine storm.[25] The loss of blood-tissue barrier function increases vascular permeability, resulting in edema and hemorrhage,[6] which subsequently leads to decreases in PLT and ALB levels, as well as pleural effusion.

It is well-known that PCT is an effective indicator for assessing the severity of sepsis.[26] However, Fan et al[27] found that PCT levels in patients with severe HFRS were significantly higher than those in patients with mild disease, and were independently associated with the severity of the illness. Che L[21] also found that PCT levels play a significant role in assessing severe HFRS. Furthermore, research by Li[28] indicated that PCT is an independent risk factor for severe HFRS in children. This may be related to the upregulation of cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) during viral infections,[29–31] which can also promote the synthesis of procalcitonin.[32]

PAR has recently been recognized as a novel marker that reflects the systemic inflammation and immune-nutritional status in various diseases, with minimal dynamic influence from various physiological and/or disease conditions.[33] In this study, PAR emerged as an independent predictor of HFRS severity progression. Huang et al[34] discovered that PAR is a potential new biomarker for assessing the severity of endoscopic inflammatory bowel disease. However, the value of PAR in the application of HFRS has not been reported in relevant literature, and more data and multicenter studies are needed to explore its potential role.

This study identified predictors of HFRS severity progression and developed a nomogram model, which demonstrated robust discriminatory capacity for severe HFRS cases in western Yunnan Province, China. Both calibration plots and Hosmer-Lemeshow tests confirmed excellent concordance between predicted probabilities derived from the nomogram and actual clinical outcomes. Additionally, to assess the clinical utility of the nomogram model, we plotted a DCA curve, and the results suggested that using the nomogram to assess the risk of severe disease in HFRS patients could benefit patients. However, there remains considerable scope for refining this nomogram model. Future investigations could enhance its predictive accuracy and reliability through prospective, multicenter study designs with expanded sample sizes and the incorporation of additional risk stratification parameters, thereby facilitating broader generalizability across geographically and epidemiologically diverse regions.

While in clinical practice, healthcare providers could integrate the nomogram model developed in this study to perform dynamic quantitative assessments of HFRS, enabling early identification of patients at high risk of progressing to severe disease and facilitating the formulation of personalized treatment protocols. Additionally, studies by Meurer et al[35] have demonstrated that implementing One Health management strategies could reduce the incidence of Q fever. Given that HFRS, as a prototypical zoonosis, involves complex transmission dynamics across reservoir hosts, environmental interfaces, and human populations, analogous One Health frameworks may be equally applicable. Specifically, integrating veterinary surveillance data with medical early-warning systems to establish multi-sectoral collaborative intervention mechanisms could disrupt HFRS transmission chains. However, current low awareness of One Health principles among healthcare providers underscores the critical need for enhanced education and training to leverage these integrated approaches for effective HFRS prevention and control.

Limitations

However, the study still has limitations. Firstly, it is a single-center retrospective study with a small and homogeneous sample size, potentially leading to selection bias. Moreover, clinical subclassification of HFRS patients (mild, moderate, severe, and critical) was not performed, nor was a further analysis conducted to determine whether the aforementioned indicators are applicable to patients with different clinical subtypes.

Secondly, only a nomogram model for predicting severe HFRS was established, without internal or external validation. Thirdly, the laboratory indicators in this study were not dynamically observed throughout the entire course of the disease. Fourthly, this study only represents the situation of severe HFRS in the western Yunnan region of southwestern China and cannot be generalized to the national level. Therefore, future research should involve multicenter studies with a longer duration and more representative large-sample data to conduct in-depth investigations and both internal and external validations.

Conclusion

Patients with severe HFRS exhibit severe disease conditions and poor prognosis. HFRS cases with elevated PCT levels, decreased ALB and PAR, and concurrent Pleural effusion are more likely to progress to severe disease. Furthermore, the nomogram model constructed in this study demonstrates good discriminative ability, goodness of fit, and clinical utility for patients with severe HFRS in the western Yunnan region of southwestern China. Subsequent research will further adopt a prospective, multi-center approach with expanded sample sizes to incorporate additional clinical/laboratory indicators, aiming to develop a comprehensive and precise predictive model with cross-regional applicability.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study conformed to the guidelines of the Helsinki Declaration. Ethics approval was obtained by the Research Ethics Committee of the first Affiliated Hospital of Dali University. And the Ethics Committee waived the requirement for informed consent due to the retrospective and observational nature of the investigation, as well as the anonymity of the data.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article, have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Vial PA, Ferres M, Vial C, et al. Hantavirus in humans: a review of clinical aspects and management. *Lancet Infect Dis*. 2023;23(9):e371–e82. doi:10.1016/S1473-3099(23)00128-7

2. Kabwe E, Davidyuk Y, Shamsutdinov A, et al. Orthohantaviruses, emerging zoonotic pathogens. *Pathogens*. 2020;9(9):775. doi:10.3390/pathogens9090775
3. Mittler E, Dieterle ME, Kleinfelter LM, et al. Hantavirus entry: perspectives and recent advances. *Adv Virus Res*. 2019;104:185–224.
4. Brugger B, Chuard C. Hantavirus infections. *Rev Med Suisse*. 2022;18(799):1900–1903. doi:10.53738/REVMED.2022.18.799.1900
5. Hu H, Zhan J, Chen W, et al. Development and validation of a novel death risk stratification scale in patients with hemorrhagic fever with renal syndrome: a 14-year ambispective cohort study. *Clin Microbiol Infect*. 2024;30(3):387–394. doi:10.1016/j.cmi.2023.11.003
6. Jiang H, Du H, Wang LM, et al. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. *Front Cell Infect Microbiol*. 2016;6:1. doi:10.3389/fcimb.2016.00001
7. Avsic-Zupanc T, Saksida A, Korva M. Hantavirus infections. *Clin Microbiol Infect*. 2019;21S:e6–e16. doi:10.1111/1469-0691.12291
8. Tariq M, Kim DM. Hemorrhagic fever with renal syndrome: literature review, epidemiology, clinical picture and pathogenesis. *Infect Chemother*. 2022;54(1):1–19. doi:10.3947/ic.2021.0148
9. Douglas KO, Payne K, Sabino-Santos G, et al. Influence of climatic factors on human hantavirus infections in Latin America and the Caribbean: a systematic review. *Pathogens*. 2021;11(1). doi:10.3390/pathogens11010015
10. Rusnak JM, Byrne WR, Chung KN, et al. Experience with intravenous ribavirin in the treatment of hemorrhagic fever with renal syndrome in Korea. *Antiviral Res*. 2009;81(1):68–76. doi:10.1016/j.antiviral.2008.09.007
11. Wang W, Fan D, Quan B, et al. Logistic regression analysis of risk factors for hemorrhagic fever with renal syndrome complicated with acute pancreatitis. *Ann Med*. 2023;55(1):2232355. doi:10.1080/07853890.2023.2232355
12. Guo Q, Xu J, Shi Q, et al. Acute pancreatitis associated with hemorrhagic fever with renal syndrome: a cohort study of 346 patients. *BMC Infect Dis*. 2021;21(1):267. doi:10.1186/s12879-021-05964-5
13. Hautala N, Partanen T, Kubin AM, et al. Central nervous system and ocular manifestations in puumala hantavirus infection. *Viruses*. 2021;13(6). doi:10.3390/v13061040
14. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. *Clin Microbiol Rev*. 2010;23(2):412–441. doi:10.1128/CMR.00062-09
15. Gilyazova I, Ivanova E, Pavlov V, et al. Exosomal miRNA-155 and miRNA-146a are promising prognostic biomarkers of the severity of hemorrhagic fever with renal syndrome. *Noncoding RNA Res*. 2023;8(1):75–82. doi:10.1016/j.ncrna.2022.10.003
16. Tian Z, Yao N, Wu Y, et al. Serum superoxide dismutase level is a potential biomarker of disease prognosis in patients with hemorrhagic fever with renal syndrome caused by the Hantaan virus. *BMC Infect Dis*. 2022;22(1):446. doi:10.1186/s12879-022-07394-3
17. Du H, Hu H, Wang P, et al. Predictive value of pentraxin-3 on disease severity and mortality risk in patients with hemorrhagic fever with renal syndrome. *BMC Infect Dis*. 2021;21(1):445. doi:10.1186/s12879-021-06145-0
18. Yu Z, Zhou N, Li A, et al. Performance assessment of the SAPS II and SOFA scoring systems in Hanta virus Hemorrhagic fever with renal syndrome. *Int J Infect Dis*. 2017;63:88–94. doi:10.1016/j.ijid.2017.08.003
19. Yang Z, Hu Q, Feng Z, et al. Development and validation of a nomogram for predicting severity in patients with hemorrhagic fever with renal syndrome: a retrospective study. *Open Med*. 2021;16(1):944–954. doi:10.1515/med-2021-0307
20. National Health Commission of the People's Republic of China. *Department of Health of the People's Republic of China. Diagnostic Criteria for Epidemic Hemorrhagic Fever: WS 278-2008*. Beijing: Standards Press. Available from: http://www.nhc.gov.cn/wjw/s9491/200802/39043.shtml. Accessed April 2, 2025.
21. Che L, Wang Z, Du N, et al. Evaluation of serum ferritin, procalcitonin, and C-reactive protein for the prediction of severity and mortality in hemorrhagic fever with renal syndrome. *Front Microbiol*. 2022;13:865233. doi:10.3389/fmicb.2022.865233
22. Wang M, Wang J, Wang T, et al. Thrombocytopenia as a predictor of severe acute kidney injury in patients with Hantaan virus infections. *PLoS One*. 2013;8(1):e53236. doi:10.1371/journal.pone.0053236
23. Fan H, Zhao Y, Song FC. Acute pancreatitis associated with hemorrhagic fever with renal syndrome: clinical analysis of 12 cases. *Ren Fail*. 2013;35(10):1330–1333. doi:10.3109/0886022X.2013.828187
24. Kim YO, Yoon SA, Ku YM, et al. Serum albumin level correlates with disease severity in patients with hemorrhagic fever with renal syndrome. *J Korean Med Sci*. 2003;18(5):696–700. doi:10.3346/jkms.2003.18.5.696
25. Sehgal A, Mehta S, Sahay K, et al. Hemorrhagic fever with renal syndrome in Asia: history, pathogenesis, diagnosis, treatment, and prevention. *Viruses*. 2023;15(2):561. doi:10.3390/v15020561
26. Cecconi M, Evans L, Levy M, et al. Sepsis and septic shock. *Lancet*. 2018;392(10141):75–87. doi:10.1016/S0140-6736(18)30696-2
27. Fan X, Deng H, Sang J, et al. High serum procalcitonin concentrations in patients with hemorrhagic fever with renal syndrome caused by hantaan virus. *Front Cell Infect Microbiol*. 2018;8:129. doi:10.3389/fcimb.2018.00129
28. Li R, Sun J, Chen Y, et al. Clinical and laboratory features and factors predicting disease severity in pediatric patients with hemorrhagic fever with renal syndrome caused by Hantaan virus. *J Med Virol*. 2023;95(1):e28339. doi:10.1002/jmv.28339
29. Linderholm M, Ahlm C, Settergren B, et al. Elevated plasma levels of tumor necrosis factor (TNF)-alpha, soluble TNF receptors, interleukin (IL)-6, and IL-10 in patients with hemorrhagic fever with renal syndrome. *J Infect Dis*. 1996;173(1):38–43. doi:10.1093/infdis/173.1.38
30. Wang PZ, Li ZD, Yu HT, et al. Elevated serum concentrations of inflammatory cytokines and chemokines in patients with haemorrhagic fever with renal syndrome. *J Int Med Res*. 2012;40(2):648–656. doi:10.1177/147323001204000227
31. Lee GY, Kim WK, No JS, et al. Clinical and immunological predictors of hemorrhagic fever with renal syndrome outcome during the early phase. *Viruses*. 2022;14(3):595. doi:10.3390/v14030595
32. Gautam S, Cohen AJ, Stahl Y, et al. Severe respiratory viral infection induces procalcitonin in the absence of bacterial pneumonia. *Thorax*. 2020;75(11):974–981. doi:10.1136/thoraxjnl-2020-214896
33. Gui Y, Xu Y, Yang P. Predictive value of the platelet-to-albumin ratio (PAR) on the risk of death at admission in patients suffering from severe fever with thrombocytopenia syndrome. *J Inflamm Res*. 2021;14:5647–5652. doi:10.2147/JIR.S335727
34. Huang J, Lu J, Jiang F, et al. Platelet/Albumin ratio and plateletcrit levels are potential new biomarkers for assessing endoscopic inflammatory bowel disease severity. *BMC Gastroenterol*. 2023;23(1):393. doi:10.1186/s12876-023-03043-4
35. Meurer IR, Silva MR, Roland RK, Corrêa JOA, Coimbra ES. Evaluation of medical professionals' knowledge about Q fever. *Sci Med*. 2024;34(1):e45474