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ORIGINAL RESEARCH

Risk Factors for 30-Day Prognosis of Hemorrhagic Fever with Renal Syndrome in the Dali Region, China

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Objective: To analyze the risk factors for 30-day prognosis in patients with hemorrhagic fever with renal syndrome (HFRS) in the Dali region of China, and to provide a theoretical basis for the diagnosis and treatment of HFRS.

Methods: A retrospective analysis was conducted on the data of patients diagnosed with HFRS at the First Affiliated Hospital of Dali University and People's Hospital of Dali Bai Autonomous Prefecture from January 1, 2015, to January 31, 2025. Based on the 30-day prognosis, patients were categorized into the survival group (n = 341) and the deceased group (n = 32). Least Absolute Shrinkage and Selection Operator (LASSO) regression was applied to screen for influential factors affecting the 30-day prognosis of HFRS, followed by binary logistic regression analysis to identify risk factors for short-term prognosis of HFRS. Finally, a nomogram model was constructed based on the identified prognostic risk factors.

Results: A total of 373 patients with HFRS from the Dali region of China were included, with a 30-day mortality rate of 8.579%. LASSO-logistic regression analysis revealed that low levels of prothrombin time (PT), white blood cell (WBC), lactate dehydrogenase-to-albumin ratio (LAR), and free triiodothyronine (FT3) were risk factors for the 30-day prognosis of HFRS patients ($P < 0.05$). Based on these risk factors, a 30-day prognostic risk nomogram model for HFRS patients was constructed. The results indicated that the observed values in the nomogram model were largely consistent with the predicted values ($\chi^2 = 2.834$, $P = 0.944$), and the C-index was 0.946 (95% CI: 0.914–0.978), demonstrating clinical validity. Monitoring these indicators is conducive to the early identification of HFRS patients with poor prognosis, providing a scientific basis for the implementation of individualized treatment and management in clinical practice.

Conclusion: PT, FT3, WBC levels, and LAR values are risk factors for 30-day mortality in patients with HFRS. Moreover, we have, for the first time, identified a close association between FT3 and LAR and the prognosis of HFRS. The developed nomogram demonstrates favorable predictive performance and can serve as an intuitive quantitative tool for the early identification of high-risk patients, thereby guiding clinical intervention strategies.

Keywords: hemorrhagic fever with renal syndrome, prognosis, risk factors, nomogram model

Introduction

HFRS is an acute natural focal infectious disease caused by hantavirus infection,[1] characterized clinically by fever, hemorrhage, and renal impairment. The typical course of the disease is divided into five phases: febrile phase, hypotensive shock phase, oliguric phase, polyuria phase, and convalescent phase. A meta-analysis has reported a mortality rate ranging from 1% to 15% for HFRS.[2] Research conducted by Swedish scholars found an overall case fatality rate of 0.4% for HFRS, with the rate reaching 6% among the elderly.[3] A study in northwestern China suggested a mortality rate of 4.73% for HFRS,[4] indicating regional variations in HFRS mortality. Dali is located in the mid-west of

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Yunnan Province, at the transitional zone between the Yunnan-Guizhou Plateau and the Hengduan Mountains. It features a significant elevation disparity and complex terrain, and is characterized by a subtropical monsoon climate. The diverse and intricate terrain provides favorable conditions for rodent reproduction.[5–7] According to research reports, from 2004 to 2021, a cumulative total of 1367 HFRS cases were reported in the Dali region, accounting for 53.48% of the total cases in Yunnan Province during the same period, ranking first among all prefectures in Yunnan Province.[8] In addition, our research team previously utilized the LASSO-logistic regression statistical approach to analyze the risk factors for HFRS complicated by acute pancreatitis and for the progression of HFRS patients to severe states in the Dali region of Yunnan, China, and constructed nomogram models based on these risk factors[9,10.] However, the short-term prognosis and prognostic factors of HFRS patients in the Dali region of Yunnan Province remain unclear. Therefore, this study aims to retrospectively analyze the prognostic outcomes of HFRS patients in the Dali region over the past decade and construct a nomogram model [A nomogram is a graphical tool designed for the intuitive visualization of results from multifactorial predictive models. By constructing a multivariate regression model, it assigns scores to each value level of every indicator (influencing factor) based on their respective contributions (magnitude of regression coefficients) to the outcome variable. These individual scores are then summed to obtain a total score. Finally, through a functional transformation relationship between the total score and the probability of clinical outcome events, the predicted value for an individual's outcome event can be calculated] based on LASSO-Logistic regression (LASSO-logistic regression incorporates an L1 regularization term into logistic regression, which contains a tuning parameter λ. As λ increases, the coefficients of some independent variables shrink to zero, achieving variable selection and retaining only the important variables. In this study, the prognosis of HFRS is influenced by numerous potential factors, and there may be collinearity among them. LASSO-logistic regression can screen key prognostic factors, avoiding model complexity and overfitting, resulting in a concise and interpretable model that is beneficial for clinical application) analysis to identify factors influencing HFRS prognosis, with the aim of providing a reference basis for the local prevention and control of HFRS.

Materials and Methods

Ethics

This study was approved by the Ethics Committee of the First Affiliated Hospital of Dali University (DFY20231011001). 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

This study is a case-control study that retrospectively analyzed the clinical data of 373 patients diagnosed with HFRS at the First Affiliated Hospital of Dali University and People's Hospital of Dali Bai Autonomous Prefecture from January 1, 2015, to January 31, 2025. All patients were diagnosed in accordance with the diagnostic criteria for "Hemorrhagic Fever with Renal Syndrome"[11] meeting the following criteria (items 1–4): 1. Within 2 months prior to disease onset, the patient has a history of residing in an epidemic area or has been in contact with rodents and their excreta or secretions. 2. The patient exhibits clinical manifestations such as fever, hemorrhage, renal injury, and hypotensive shock. 3. Laboratory indicators show an increase in white blood cell count, a decrease in platelet count, the presence of abnormal lymphocytes, positive urinary protein, and elevated levels of serum creatinine and blood urea nitrogen. 4. The presence of any one of the following items: ①. Positive serum-specific IgM antibody. ②. A more than four-fold increase in the titer of serum-specific IgG antibody in the convalescent phase compared to the acute phase. ③. Detection of Hantavirus RNA in patient specimens. ④. Isolation of Hantavirus from patient specimens. Based on the 30-day prognosis of HFRS, patients were divided into the deceased group (n = 32) and the survival group (n = 341). Exclusion criteria included: age < 18 years, presence of primary renal diseases (such as nephrotic syndrome, IgA nephropathy, chronic renal failure), liver diseases, malignant tumors, thyroid diseases (including hyperthyroidism, hypothyroidism, subacute thyroiditis), patients during pregnancy, those with a hospital stay of less than 48 hours, and those with incomplete data (Figure 1).

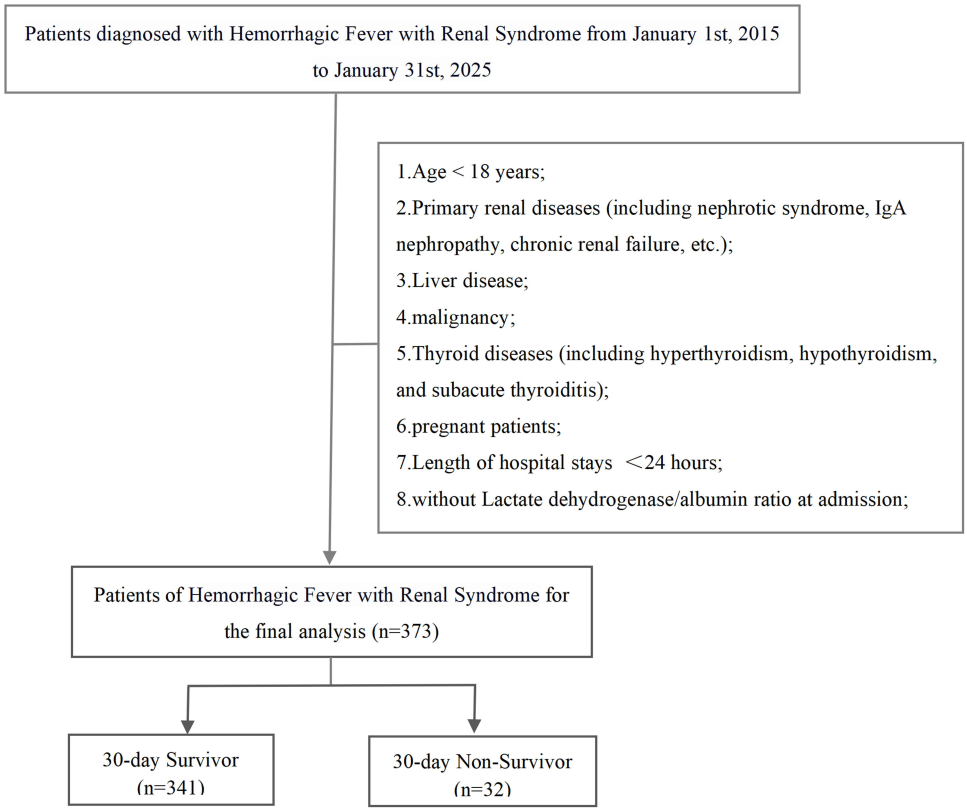

Figure 1 Flowchart of Hemorrhagic Fever with Renal Syndrome Enrollment.

Case Data Collection

General baseline data of patients in both groups were collected through the Hospital Information System (HIS), including: age, gender, smoking status, alcohol consumption, history of hypertension and diabetes mellitus, clinical manifestations (such as headache, lumbar pain, orbital pain, facial or neck flushing, conjunctival congestion), splenomegaly, presence of gastrointestinal bleeding, presence of neurological disorders, presence of pneumonia, presence of septic shock, presence of cardiac arrhythmia, laboratory data [WBC, red blood cell (RBC), hemoglobin (HB), platelet (PLT), total bilirubin (TBI), direct bilirubin (DBI), indirect bilirubin (IBI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin (ALB), blood urea nitrogen (BUN), creatinine (CREA), uric acid (UA), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatine kinase (CK), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), prothrombin time(PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), free triiodothyronine (FT3), triiodothyronine (TT3), free thyroxine (FT4), thyroxine (TT4), thyroid-stimulating hormone (TSH), procalcitonin (PCT), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)]. Additionally, the lactate dehydrogenase-to-albumin ratio (LAR) was calculated as the ratio of lactate dehydrogenase to serum albumin.

Sample Size Calculation

In constructing a logistic regression model for the 30-day prognostic risk factors of patients with HFRS, we adhered to the Events per Variable (EPV) principle[12] for each independent variable, where "events" denote the less frequent category among the covariates. By setting EPV = 10, we anticipated including 5 to 6 covariates. Given that previous research reported an approximate mortality rate of 15% among HFRS patients, the calculated required number of HFRS patients was (5–6) × 10 = (50–60) cases. Consequently, the total required sample size was (50–60) ÷ 15% = (333–400)

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cases. In this study, a total of 373 HFRS patients were included, which falls within the range of the minimum sample size requirement.

Statistical Analysis

Statistical analysis was conducted using R Studio and SPSS 26.0 statistical software. For measurement data conforming to a normal distribution, the mean ± standard deviation was used for representation, and the *T*-test was employed for inter-group comparisons. For measurement data with a non-normal distribution, the median [interquartile range (M (P25, P75)] was used, and the Mann–Whitney *U*-test or Fisher's exact probability method was applied for inter-group comparisons. LASSO-logistic regression analysis was utilized to identify risk factors for the 30-day prognosis of HFRS patients, and a nomogram model was constructed based on these risk factors to predict the 30-day prognosis of HFRS. A *P*-value of less than 0.05 was considered statistically significant.

Results

Comparison of Clinical Data Between the Non-Survival Group and the Survival Group of Patients with HFRS

The proportions of HFRS patients in the deceased group experiencing headache, gastrointestinal bleeding, proteinuria, pneumonia, septic shock, and requiring hemodialysis and mechanical ventilation, as well as their age, respiratory rate, and pulse rate, were all significantly higher than those in the survival group ($P < 0.05$) (Table 1).

Table 1 Demographics and Clinical Characteristics of Patients with HFRS

Variables	Total (n = 373)	Survivors (n = 341)	Non- survivors (n = 32)	*P*-value
Age (years), Mean ± SD	45.92 ± 14.38	45.16 ± 13.96	53.97 ± 16.45	<0.001
Sex, n (%)				0.064
Male	263 (70.51)	245 (71.85)	18 (56.25)	
Female	110 (29.49)	96 (28.15)	14 (43.75)	
Hospitalization (day), median (IQR)	10.00 (8.00, 14.00)	10.00 (8.00, 14.00)	9.50 (5.00, 20.25)	0.461
Maximum body temperature (°C), median (IQR)	39.00 (38.10, 39.50)	39.00 (38.20, 39.60)	38.50 (37.95, 39.05)	0.053
Breathe (breaths per minute), median (IQR)	20.00 (20.00, 20.00)	20.00 (20.00, 20.00)	20.00 (20.00, 21.00)	<0.001
Pulse, (breaths per minute), median (IQR)	85.00 (70.00, 98.00)	84.00 (70.00, 98.00)	94.00 (83.75, 101.75)	0.004
Systolic pressure (mmHg), median (IQR)	108.00 (97.00, 123.00)	107.00 (97.00, 120.00)	112.00 (97.75, 137.25)	0.158
Diastolic pressure, (mmHg), median (IQR)	70.00 (61.00, 78.00)	70.00 (61.00, 77.00)	69.00 (61.75, 82.00)	0.561
History of smoking, n (%)				0.205
No	217 (58.18)	195 (57.18)	22 (68.75)	
Yes	156 (41.82)	146 (42.82)	10 (31.25)	
History of Alcohol, n (%)				0.780
No	260 (69.71)	237 (69.50)	23 (71.88)	
Yes	113 (30.29)	104 (30.50)	9 (28.12)	
Hypertension, n (%)				0.486
No	334 (89.54)	307 (90.03)	27 (84.38)	
Yes	39 (10.46)	34 (9.97)	5 (15.62)	
Diabetes, n (%)				1.000
No	359 (96.25)	328 (96.19)	31 (96.88)	
Yes	14 (3.75)	13 (3.81)	1 (3.12)	
Headache, n (%)				0.005
No	215 (57.64)	189 (55.43)	26 (81.25)	
Yes	158 (42.36)	152 (44.57)	6 (18.75)	

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 373)	Survivors (n = 341)	Non- survivors (n = 32)	*P*-value
Low back Pain, n (%)				0.889
No	295 (79.09)	270 (79.18)	25 (78.12)	
Yes	78 (20.91)	71 (20.82)	7 (21.88)	
Orbital pain, n (%)				0.356
No	356 (95.44)	327 (95.89)	29 (90.62)	
Yes	17 (4.56)	14 (4.11)	3 (9.38)	
Conjunctival hyperemia, n (%)				0.173
No	352 (94.37)	324 (95.01)	28 (87.50)	
Yes	21 (5.63)	17 (4.99)	4 (12.50)	
Splenomegaly, n (%)				0.241
No	362 (97.05)	332 (97.36)	30 (93.75)	
Yes	11 (2.95)	9 (2.64)	2 (6.25)	
Gastrointestinal bleeding, n (%)				<0.001
No	340 (91.15)	317 (92.96)	23 (71.88)	
Yes	33 (8.85)	24 (7.04)	9 (28.12)	
Continuous renal replacement therapy, n (%)				<0.001
No	355 (95.17)	330 (96.77)	25 (78.12)	
Yes	18 (4.83)	11 (3.23)	7 (21.88)	
Mechanical ventilation, n (%)				<0.001
No	365 (97.86)	340 (99.71)	25 (78.12)	
Yes	8 (2.14)	1 (0.29)	7 (21.88)	
Urine protein, n (%)				<0.001
1	295 (79.09)	277 (81.23)	18 (56.25)	
2	78 (20.91)	64 (18.77)	14 (43.75)	
Pneumonia, n (%)				<0.001
No	302 (80.97)	284 (83.28)	18 (56.25)	
Yes	71 (19.03)	57 (16.72)	14 (43.75)	
Intracranial hemorrhage, n (%)				0.061
No	368 (98.66)	338 (99.12)	30 (93.75)	
Yes	5 (1.34)	3 (0.88)	2 (6.25)	
Septic shock, n (%)				0.007
No	356 (95.44)	329 (96.48)	27 (84.38)	
Yes	17 (4.56)	12 (3.52)	5 (15.62)	
Arrhythmia, n (%)				0.710
No	267 (71.58)	245 (71.85)	22 (68.75)	
Yes	106 (28.42)	96 (28.15)	10 (31.25)	

Notes: Urine protein categorized as 1 for −, +, and 2+, and 2 for 3+ and 4+. Data were expressed as median (IQR) or count (percentage, %) and were compared using the Chi-square test or Mann Whitney *U*-test.

Abbreviations: HFRS, Hemorrhagic Fever with Renal Syndrome; SD, Standard deviation; IQR, interquartile range.

Comparison of Laboratory Data Between the Deceased Group and the Survival Group of Patients with HFRS

The levels of PCT, CRP, PT, APTT, BUN, CREA, FBG, TG, LDH, WBC, and the LAR were all significantly higher in the non-survival group of HFRS patients compared to the survival group ($P < 0.05$). Conversely, the levels of FT3, TT3, FT4, and ALB were significantly lower in the deceased group than in the survival group ($P<0.05$) (Table 2).

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Table 2 Laboratory Results of Patients with HFRS at Admission

Variables	Total (n = 373)	Survivors (n = 341)	Non-Survivors (n = 32)	*P*-value
PCT (ng/mL), median (IQR)	1.27 (0.43, 2.87)	1.17 (0.41, 2.51)	3.80 (1.82, 10.43)	<0.001
CRP (pg/mL), median (IQR)	37.90 (19.01, 70.73)	36.30 (18.46, 67.44)	64.82 (33.01, 104.74)	<0.001
ESR (mm/h), median (IQR)	14.00 (7.00, 34.00)	14.00 (7.00, 31.00)	22.00 (7.75, 50.25)	0.171
PT (s), median (IQR)	15.60 (14.60, 16.50)	15.50 (14.50, 16.40)	16.85 (16.28, 17.40)	<0.001
APTT (s), median (IQR)	35.20 (29.50, 42.70)	34.60 (28.90, 42.10)	41.55 (35.50, 49.42)	<0.001
TT (s), median (IQR)	19.70 (17.50, 23.10)	19.60 (17.50, 23.10)	19.85 (17.48, 25.30)	0.778
FIB (g/L), median (IQR)	3.07 (2.44, 3.67)	3.08 (2.45, 3.65)	2.92 (1.72, 3.83)	0.370
FT3 (pmol/L), median (IQR)	4.20 (2.94, 5.04)	4.32 (3.27, 5.32)	2.25 (1.90, 2.73)	<0.001
TT3 (nmol/L), median (IQR)	1.75 (1.28, 2.37)	1.87 (1.38, 2.38)	1.04 (0.77, 1.26)	<0.001
FT4 (pmol/L), median (IQR)	16.40 (13.88, 18.50)	16.30 (13.60, 18.40)	16.48 (15.60, 19.20)	0.114
TT4 (nmol/L), median (IQR)	96.20 (78.20, 121.50)	96.40 (78.60, 123.40)	77.82 (67.72, 107.28)	0.010
TSH (μIU/mL), median (IQR)	2.24 (1.26, 3.45)	2.18 (1.21, 3.43)	2.58 (1.73, 3.47)	0.116
TBIL (umol/L), median (IQR)	13.50 (10.00, 17.90)	13.20 (10.10, 17.80)	13.75 (8.32, 21.73)	0.799
DBIL (umol/L), median (IQR)	5.00 (3.50, 7.10)	4.98 (3.50, 6.80)	5.10 (3.20, 11.32)	0.373
IBIL (umol/L), median (IQR)	7.90 (5.50, 12.00)	7.90 (5.60, 12.00)	7.95 (4.20, 13.30)	0.465
ALT (U/L), median (IQR)	85.00 (49.00, 168.00)	86.00 (52.00, 166.00)	73.50 (29.00, 214.00)	0.304
AST (U/L), median (IQR)	96.00 (48.00, 203.00)	96.00 (48.00, 201.00)	90.00 (56.75, 308.75)	0.776
ALP (U/L), median (IQR)	81.00 (63.00, 120.00)	81.00 (63.00, 118.00)	78.50 (67.75, 143.50)	0.552
GGT (U/L), median (IQR)	89.00 (49.00, 158.00)	87.00 (49.00, 150.00)	133.00 (48.00, 173.00)	0.311
ALB (g/L), median (IQR)	31.50 (27.30, 35.20)	32.00 (27.70, 36.00)	25.95 (23.35, 29.00)	<0.001
BUN (mmol/L), median (IQR)	6.87 (4.49, 14.74)	6.63 (4.35, 13.88)	16.59 (6.83, 27.07)	<0.001
Scr (umol/L), median (IQR)	105.00 (71.00, 242.00)	104.00 (71.00, 220.00)	261.85 (89.75, 474.75)	0.009
UA (umol/L), median (IQR)	381.00 (257.00, 565.00)	373.00 (257.00, 551.00)	504.00 (304.25, 684.00)	0.054
FBG (mmol/L), median (IQR)	5.84 (4.89, 7.34)	5.78 (4.88, 7.05)	7.69 (5.45, 10.20)	0.011
TC (mmol/L), median (IQR)	3.38 (2.73, 4.10)	3.39 (2.74, 4.10)	3.25 (2.52, 3.93)	0.506
TG (mmol/L), median (IQR)	2.21 (1.60, 3.02)	2.18 (1.57, 2.93)	2.92 (1.86, 3.77)	0.011
HDL-C (mmol/L), median (IQR)	0.76 (0.53, 1.03)	0.76 (0.53, 1.03)	0.71 (0.50, 1.62)	0.717
LDH-C (mmol/L), median (IQR)	1.25 (0.89, 1.76)	1.25 (0.90, 1.74)	1.42 (0.87, 2.63)	0.128
CK (U/L), median (IQR)	62.00 (35.00, 140.00)	61.00 (34.00, 131.00)	77.50 (44.25, 256.00)	0.124
CK-MB (ng/mL), median (IQR)	16.00 (10.00, 25.00)	16.00 (10.00, 25.00)	16.00 (6.75, 32.00)	0.763
LDH (U/L), median (IQR)	394.00 (293.00, 616.00)	382.00 (291.00, 578.00)	794.00 (436.00, 997.25)	<0.001
LAR, median (IQR)	13.02 (9.31, 20.20)	12.49 (9.23, 18.64)	30.82 (21.19, 38.75)	<0.001
HBDH (U/L), median (IQR)	328.00 (252.00, 462.00)	328.00 (258.00, 453.00)	277.50 (203.50, 587.50)	0.732
WBC ($\times 10^9$/L), median (IQR)	8.20 (5.95, 11.47)	8.10 (5.89, 11.03)	11.54 (7.84, 15.20)	0.008
RBC ($\times 10^{12}$/L), Mean ± SD	4.68 ± 0.81	4.69 ± 0.79	4.49 ± 0.99	0.276
HB (g/L), median (IQR)	141.00 (127.00, 152.00)	141.00 (128.00, 152.00)	132.50 (108.75, 148.25)	0.071
PLT ($\times 10^9$/L), median (IQR)	70.00 (40.00, 130.00)	70.00 (44.00, 132.00)	47.50 (26.50, 84.25)	0.024

Notes: Data were expressed as mean ± standard deviation or median (IQR) and were compared using the Wilcoxon rank-sum test, Student's *t*-test or Fisher's exact test.

Abbreviations: PCT, Procalcitonin; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; TT, Thrombin Time; FIB, Fibrinogen; FT3, Free triiodothyronine; TT3, Total triiodothyronine; FT4, Free thyroxine; TT4, Total thyroxine; TSH, Thyroid stimulating hormone; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; ALT, Alanine transaminase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyl transferase; ALB, Albumin; BUN, Blood urea nitrogen; Scr, Serum creatinine; UA, uric acid; FBG, Fasting blood glucose; TC, Total cholesterol; TG, Triglyceride; HDL, High density lipoprotein; LDL, low density lipoprotein; CK, Creatine kinase; CK-MB, creatine kinase isoenzymes; LDH, lactate dehydrogenase; LAR, lactate dehydrogenase to albumin ratio; HBDH, Hydroxybutyrate Dehydrogenase; WBC, White blood cell; RBC, Red blood count; HB, Hemoglobin; PLT, Platelet; SD, Standard deviation.

LASSO-Logistic Regression Analysis Was Employed to Screen for Risk Factors Influencing the 30-Day Prognosis of Patients with HFRS

Collinearity analysis was conducted on the statistically significant indicators (headache, gastrointestinal bleeding, proteinuria, pneumonia, septic shock, age, respiratory rate, pulse rate, PCT, CRP, PT, APTT, BUN, CREA, FBG, TG, WBC, LDH, LAR, FT3, TT3, TT4, and ALB) derived from the univariate analysis of clinical and laboratory data

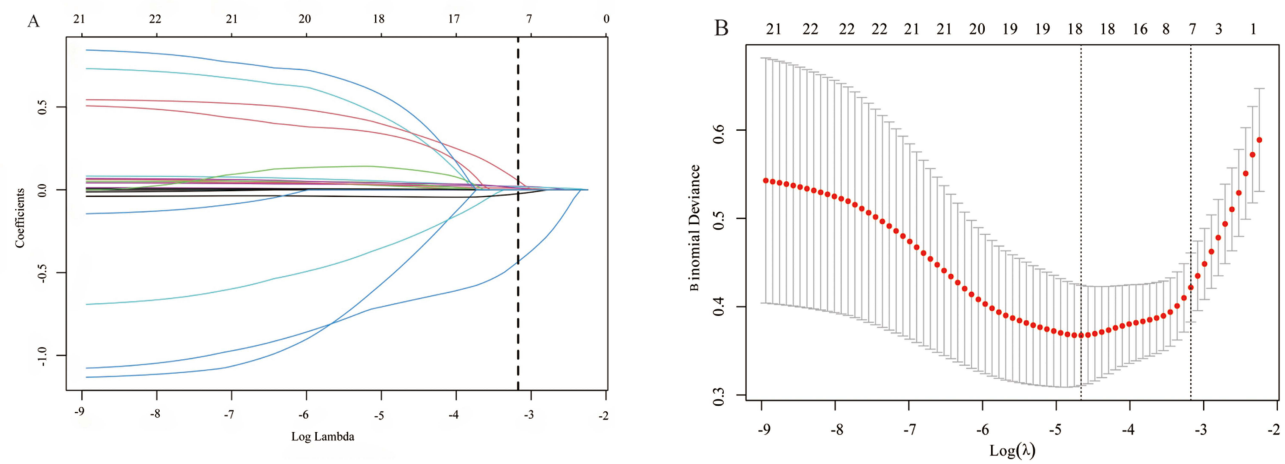

Figure 2 Screen of predictor variables by LASSO regression. (**A**) Path diagram of regression coefficients. In this study, a total of 22 independent variables were included, resulting in 22 lines of different colors. Each line represents the trajectory of changes in the coefficient for each independent variable. The vertical axis denotes the coefficient values, with the lower horizontal axis representing log lambda and the upper horizontal axis indicating the number of non-zero coefficients in the model at that point. As observed in the diagram, with an increase in the parameter log λ, the regression coefficients (ie, the values on the vertical axis) progressively converge and ultimately converge to zero. (**B**) Cross-validation curve plot for LASSO regression. The X-axis represents the logarithm of the penalty coefficient, log λ, while the Y-axis denotes the likelihood deviation. A smaller value on the Y-axis indicates a better fit of the equation. The numbers displayed at the top represent the number of variables remaining in the equation for different values of λ. The two dashed lines in the plot represent two special λ values. The left dashed line corresponds to λ min, which is the λ value at which the deviation is minimized, indicating the highest model fit at this λ value. The right dashed line represents λ-se, which is one standard deviation to the right of the minimum λ. At this λ value, the model fit is also excellent, while incorporating fewer variables into the equation, resulting in a simpler model. Clinically, λ1-se on the right side is generally chosen as the final criterion for equation selection.

(Table 1 and Table 2) between the non-survival group and the survival group of patients with HFRS. LDH, which exhibited strong collinearity (variance inflation factor > 10), was excluded from further analysis.

LASSO regression was applied to screen for predictor variables with non-zero coefficients among the 22 variables (Figure 2A). The optimal λ value was selected through 10-fold cross-validation, aiming to include the fewest variables while ensuring a good model fit. Ultimately, lambda.1se was chosen as the optimal λ value (λ=0.042). This selection identified seven predictor variables with non-zero coefficients, including the levels of PCT, PT, FT3, ALB, BUN, LAR, and WBC) (Figure 2B).

Construction of a Nomogram Model Based on the Risk Factors Screened by LASSO-Logistic Regression

A multivariate logistic regression prediction nomogram model was constructed with the occurrence of death in HFRS patients as the dependent variable and the seven variables screened by LASSO regression as the independent variables.

Table 3 Multivariate Logistic Regression Analysis of the 30-Day Mortality Risk in Patients with HFRS

Variables	OR	Multivariate Logistic 95% CI	*P*-value
PCT (ng/mL)	1.04	0.98–1.10	0.199
PT (s)	1.83	1.27–2.65	0.001
FT3 (pmol/L)	0.28	0.15–0.52	<0.001
ALB (g/L)	0.92	0.82–1.03	0.142
BUN (mmol/L)	1.01	0.96–1.07	0.639
LAR	1.08	1.03–1.13	<0.001
WBC ($\times 10^9$/L)	1.1	1.01–1.21	0.036

Abbreviations: HFRS, Hemorrhagic Fever with Renal Syndrome; PCT, Procalcitonin; PT, Prothrombin Time; FT3, Free triiodothyronine; ALB, Albumin; BUN, Blood urea nitrogen; LAR, lactate dehydrogenase to albumin ratio; WBC, White blood cell; OR, Odds Ratio; CI, Confidence interval.

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The results indicated that PT, FT3, LAR, and WBC were independent risk factors for 30-day mortality in HFRS patients (Table 3).

Based on the results of LASSO-logistic regression analysis, influencing factors such as PT, FT3, LAR, and WBC were incorporated to construct a nomogram model for predicting the 30-day prognosis of HFRS (Figure 3). Receiver Operating Characteristic (ROC) curve analysis demonstrated a C-index of 0.946 (95% CI: 0.914–0.978) for the nomogram model (Figure 4A). The Hosmer-Lemeshow test indicated a good agreement between the observed and predicted values of the nomogram model ($\chi^2 = 2.834$, $P = 0.944$) (Figure 4B). Decision curve analysis revealed a high predictive value and clinical effectiveness of the nomogram model (Figure 4C).

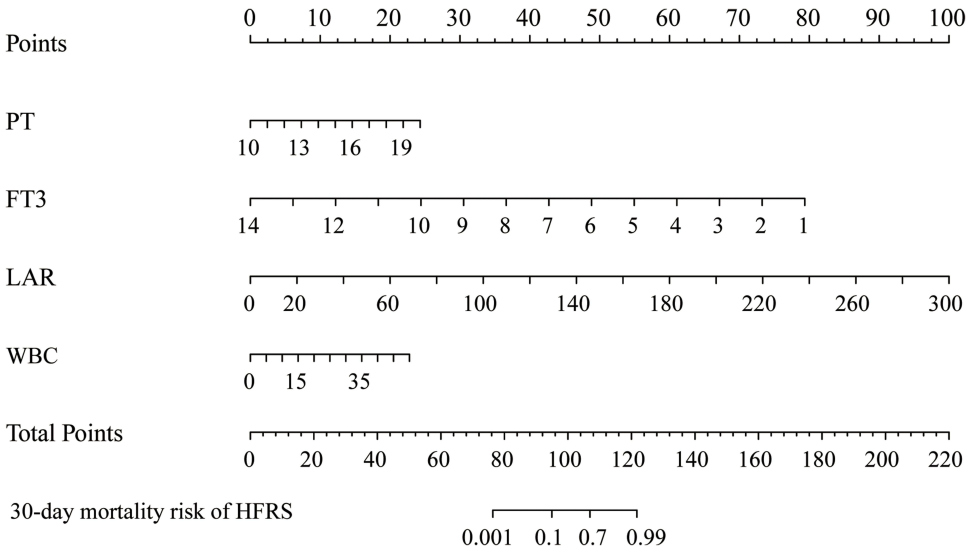

Figure 3 A 30-day mortality risk prediction nomogram for HFRS.

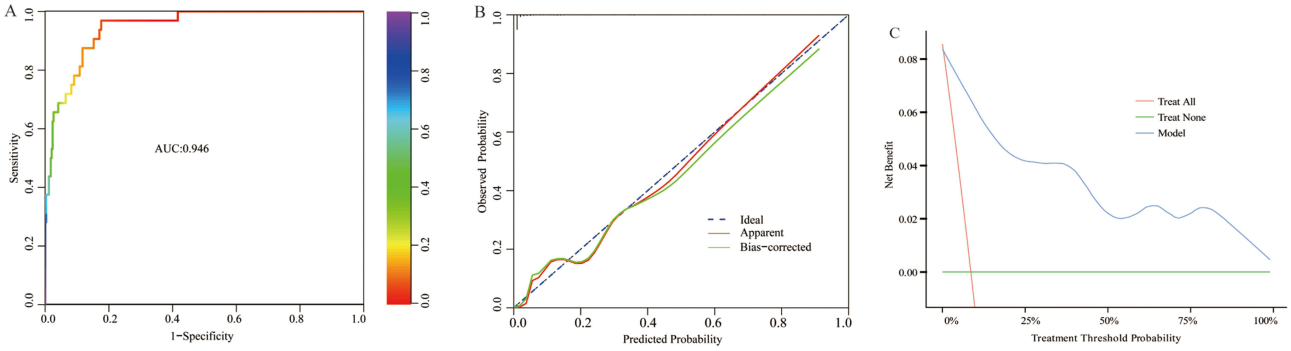

Figure 4 Diagrams illustrating the performance evaluation of the nomogram model. (**A**) The discriminatory performance of the nomogram was evaluated using the ROC curve. In this study, the Area Under the Curve (AUC) of the nomogram was 0.946, indicating a favorable discriminatory performance. (**B**) The calibration curve of the nomogram model features the predicted probability of a positive outcome on the x-axis and the actual observed probability on the y-axis. The blue dashed line represents the curve under an ideal model, serving as the reference line where the actual probability equals the predicted probability. The red solid line illustrates the fit between the predicted and actual probabilities, while the green solid line depicts the fit after calibration. The closer these two lines (red and green) are to the reference line, the more closely the predicted probabilities align with the actual probabilities, indicating a higher predictive value of the model. (**C**) Decision Curve Analysis (DCA) Graph. The x-axis represents the risk threshold, while the y-axis denotes the net benefit. The green horizontal line indicates the net benefit when no intervention is administered to any patient, ie, the net benefit under a "no-treatment" scenario. The red diagonal line reflects the net benefit when all patients receive intervention across various risk thresholds. The blue curve illustrates the net benefit derived from the risk probabilities estimated by the constructed nomogram model at different risk thresholds. As evident from the graph, within a broad range of thresholds, the model's net benefit consistently surpasses that of both the green horizontal line (no intervention) and the red diagonal line (universal intervention). Consequently, a relatively wide range of threshold values can be selected, underscoring the high predictive value of the nomogram model.

Discussion

This study aimed to analyze the prognosis of patients with HFRS, explore the risk factors associated with HFRS prognosis, and construct a nomogram model to provide references for the local prevention and treatment of HFRS. The following findings were obtained: (1) The 30-day mortality rate of HFRS in the study region was 8.579%; (2) Through LASSO-Logistic regression analysis, PT, FT3, LAR, and WBC were ultimately identified as influential factors for 30-day mortality in HFRS; (4) A nomogram model for predicting 30-day mortality in HFRS was further constructed based on the four differential variables screened by LASSO-Logistic regression. The results suggested that the model exhibited good discriminatory ability. In clinical practice, healthcare professionals can measure the levels of PT, WBC, and FT3, and calculate the LAR. They then locate the corresponding values on the respective variable axes and draw lines upwards to the total score axis to compute the total score. Subsequently, they draw lines downwards from the total score position to the risk probability axis and directly read the numerical value to swiftly determine the likelihood of death within 30 days for patients with HFRS. This model enables quantitative risk assessment through graphical tools, offering an intuitive and convenient reference for clinical prognostic evaluation and intervention decision-making.

After hantavirus infects the host, it can trigger innate immunity, cellular immunity, and humoral immunity, leading to the formation of antigen-antibody complexes. These complexes activate various cytokines, inflammatory factors, complement components, and NK cells, which cause damage to host cells and tissues, disrupt the integrity of the vascular endothelial barrier, and impair platelet function. This, in turn, increases vascular permeability, resulting in plasma extravasation, tissue edema, and hemorrhage.[13,14] Additionally, hantavirus exhibits a pan-tropic nature, affecting not only the kidneys, which are its primary target organs, but also the liver, myocardium, muscles, pituitary gland, and other tissues and organs.[15–17] Since most coagulation factors are synthesized in the liver, impaired liver function can further exacerbate coagulation disorders and reduce ALB levels. In this study, it was found that prolonged PT is a risk factor for 30-day mortality in HFRS, which is consistent with findings from previous studies.[18]

LDH, which is indicative of cellular energy status or damage, is present in nearly all living cells. Both viral infection and cytokine storms associated with inflammation can lead to elevated levels of LDH. A meta-analysis[2] revealed that HFRS patients in the non-survival group had higher levels of LDH and WBC compared to those in the survival group, while ALB levels were lower. In this study, by calculating the ratio of LAR, it was found that a high LAR is a risk factor for 30-day mortality in HFRS. Prior studies[19] have elucidated that COVID-19 patients with an elevated LAR demonstrate a significantly increased propensity for mortality. Additionally, studies have identified LAR as a predictor of mortality in patients with severe fever with thrombocytopenia syndrome.[20]

This study identified low levels of FT3 as a risk factor for 30-day mortality in HFRS. This finding is considered to be associated with hypopituitarism, which may occur in HFRS patients due to the following reasons: Firstly, it may result from hemorrhage and ischemia.[21] Autopsy analyses of HFRS patients have revealed that 50–100% of them exhibit hemorrhage and necrosis in the anterior pituitary gland.[22,23] Secondly, it may be related to hantavirus directly invading the human body and spreading throughout the body via the bloodstream, leading to viremia. Previous studies have indicated that hantavirus RNA can be detected in the blood and is closely correlated with disease severity.[24] Additionally, some studies have detected hantavirus in the pituitary tissues of deceased HFRS patients, suggesting that hantavirus directly infects pituitary tissues and is associated with hypopituitarism.[25] Thirdly, hantavirus may induce an immune response, forming immune complexes in the pituitary gland, which subsequently leads to impaired immune function. Therefore, in clinical practice, appropriate assessment of pituitary function in HFRS patients can aid in the early identification of those with a poor prognosis, enabling timely intervention.

Limitations

To our knowledge, this is the first study to analyze the prognostic significance of FT3 and the LAR in HFRS, identifying them as risk factors for 30-day mortality in HFRS patients. As FT3 levels decrease and LAR increases, close observation is warranted for early-stage HFRS patients. However, this study has several limitations. Firstly, being a retrospective study, it may be susceptible to selection bias. Secondly, the laboratory data in this study were not continuously monitored for analytical purposes. Thirdly, this study only established a nomogram model for predicting 30-day mortality in HFRS

patients without external validation. Fourthly, the prognostic findings of this study are specific to HFRS patients in the Dali region of China and may not be representative of other regions. Therefore, future research necessitates a multi-center approach, a longer study duration, and more representative large-sample data for in-depth analysis and external validation.

Conclusion

This study found that prolonged PT, elevated WBC, increased LAR, and decreased FT3 levels could serve as predictive indicators for the 30-day prognosis of patients with HFRS. The nomogram model constructed based on these predictive indicators can assist clinicians in early identification of patients at high risk of mortality, thereby enabling the timely implementation of individualized treatment and comprehensive management strategies. However, the applicability of the developed nomogram predictive model to different populations in other regions remains to be validated. Future research should involve prospective, multicenter studies with large sample sizes, extend the follow-up duration for HFRS patients, continuously monitor experimental data, conduct external validation of the model, and further explore the intrinsic associations among Hantavirus infection, pituitary function, and FT3 levels.

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

The authors report no conflicts of interest in this work.

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