Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: www.tandfonline.com/journals/iann20

Logistic regression analysis of risk factors for hemorrhagic fever with renal syndrome complicated with acute pancreatitis

Wenjie Wang, Dongqing Fan, Bin Quan, Weishun Hou & Jinsun Yang

To cite this article: Wenjie Wang, Dongqing Fan, Bin Quan, Weishun Hou & Jinsun Yang (2023) Logistic regression analysis of risk factors for hemorrhagic fever with renal syndrome complicated with acute pancreatitis, Annals of Medicine, 55:1, 2232355, DOI: 10.1080/07853890.2023.2232355

To link to this article: https://doi.org/10.1080/07853890.2023.2232355

Published online: 11 Jul 2023.

ANNALS OF MEDICINE
2023, VOL. 55, NO. 1, 2232355
https://doi.org/10.1080/07853890.2023.2232355

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Logistic regression analysis of risk factors for hemorrhagic fever with renal syndrome complicated with acute pancreatitis

Wenjie Wang[a#], Dongqing Fan[b#], Bin Quan[a], Weishun Hou[a] and Jinsun Yang[a]

[a]Department of Infectious Diseases, The First Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, P. R. China; [b]Department of Public Health, Wannan Medical College, Wuhu, Anhui, P. R. China

ABSTRACT

Background: Hantavirus infection is the main cause of hemorrhagic fever with renal syndrome (HFRS), which is common in Asia and Europe. There is a considerable risk of morbidity and mortality from the uncommon Hantavirus complication known as acute pancreatitis (AP).

Methods: Retrospective analysis of the medical records of individuals with HFRS was performed. Relevant variables were assessed by univariate analyses and the variables with a p value <.05 were entered into the multivariable regression analysis.

Results: In this study, 114 individuals with HFRS in total were included, and 30 of them (26.32%) had AP. The univariate analyses showed that living in Xuancheng city (Anhui Province); an alcohol consumption history; white blood cell (WBC) count; lymphocyte (lym%) and eosinophil percentages (EO%); neutrophil (neut), eosinophil (EO), and red blood cell (RBC) counts; hemoglobin (Hb); hematocrit (HCT); proteinuria; hematuria; albumin (ALB), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), cystatin-C (Cys-C) levels; carbon dioxide-combining power (CO_2CP); fibrinogen degradation products (FDPs); and D-dimer level were significantly associated with HFRS complicated with AP ($p<.05$). In the multivariable regression analysis, an alcohol consumption history, lym%, proteinuria, FDPs and D-dimer level were found to be risk factors for HFRS complicated with AP ($p<.05$).

Conclusion: Our findings indicate that HFRS patients with a history of consuming alcohol, a high lym%, intense proteinuria, high levels of FDPs, and a low level of D-dimer might be more prone to the development of AP.

KEY MESSAGES

- This is the first report employing Logistic regression analysis methods for exploring the risk factors for HFRS complicated with AP in China.
- Many factors (most are laboratory parameters) were significantly associated with HFRS complicated with AP.
- We found that HFRS patients with a history of consuming alcohol, a high lym%, intense proteinuria, high levels of FDPs, and a low level of D-dimer might be more prone to the development of AP.

ARTICLE HISTORY
Received 4 May 2023
Revised 27 June 2023
Accepted 28 June 2023

KEYWORDS
Hemorrhagic fever with renal syndrome; acute pancreatitis; risk factors; logistic regression analysis

Introduction

Hantavirus infection causes rodent-borne zoonotic illness hemorrhagic fever with renal syndrome (HFRS), which is mostly spread to people by aerosolized viral particles found in rodent urine, feces, and saliva [1]. China has the greatest incidence of HFRS worldwide, with Asia and Europe having the highest prevalence rates [2]. In mainland China, 209,209 HFRS cases and 1855 related fatalities were documented from 2004 to 2019. This represents a considerable illness burden [3]. One of the most severely afflicted regions in China is the province of Anhui, home to more than 60 million people. The southern regions of Anhui, including Xuancheng City and Wuhu City, are the most hit. Fever, bleeding, renal failure, thrombocytopenia, and shock are among the clinical signs of HFRS [4]. Currently, there is no effective antiviral treatment for HFRS; consequently, the mortality rate in critically ill patients is high.

Acute pancreatitis (AP) is an inflammatory condition of the pancreas, with severity ranging from mild and

CONTACT Jinsun Yang yangjinsun999999@163.com Department of Infectious Diseases, The First Affiliated Hospital of Wannan Medical, College. 2, Zheshan West Road, Wuhu, Anhui 241001, P.R. China
#These authors contributed equally to this study

self-limiting to rapidly progressive, eventually resulting in multiple organ failure (MOF) and death. Gallstones and excessive alcohol use are the two most often cited etiologies of AP [5,6]. Many academics have discovered in recent years that AP is an uncommon but serious consequence of hantavirus infection, with high rates of morbidity and death [7–10]. However, because the primary clinical presentation is vague and the likelihood of misdiagnosis is quite high, early prediction and detection of HFRS complicated with AP remain difficult.

At present, there have been very few reports on the risk factors for HFRS complicated with AP. Therefore, we carried out this retrospective analysis to investigate the risk factors for AP among patients with HFRS by logistic regression analysis in an endemic area in China.

Method

Study participants

This study retrospectively analyzed a total of 114 consecutive patients diagnosed with HFRS in the First Affiliated Hospital of Wannan Medical College from July 2012 to September 2021. The identification of HFRS was primarily based upon the detection of specific IgM antibodies against hantavirus in acute-phase serum specimens by enzyme-linked immunosorbent assay (ELISA). These tests were conducted by the Center for Disease Control and Prevention in Wuhu, Anhui Province.

Diagnostic criteria

The diagnosis of AP requires two of the following three characteristics [11]: (1) a tendency to have abdominal pain with pancreatitis (epigastric pain often radiating to the back), the onset of which is considered to be the beginning of AP; (2) a serum lipase concentration (or amylase concentration) at least three times higher than the upper limit of normal; and (3) a specific presentation of AP detected by computed tomography (CT) and/or magnetic resonance imaging (MRI) or transabdominal ultrasonography (US).

The inclusion criteria for HFRS complicated with AP were a simultaneous diagnosis of HFRS and AP. Exclusion criteria included (1) age < 8 years, (2) pregnancy, and (3) acute or chronic renal and hematologic disease; or (4) gallstones, hyperlipidemia, drug treatment, genetic disease, a postoperative state or other types of pancreatic injury. Additionally, those for whom the daily intake of alcohol met the criteria of alcoholic pancreatitis were excluded [12]. Patients with incomplete clinical data were also excluded.

Ethical statement

This study was approved by the ethics committee of The First Affiliated Hospital of Wannan Medical College. Informed consent was waived due to the retrospective nature of the study. All research procedures involving human participants comply with the Declaration of Helsinki of 1964 and its subsequent amendments or similar ethical standards.

Data collection

Patient blood samples were collected as soon as possible after admission, and testing was carried out after sample collection. Well-trained doctors collected patient demographic, underlying disease, clinical manifestation, and laboratory parameter data from the electronic medical record system (including complete blood cell count; routine urine tests (proteinuria and hematuria were classified into 5 categories: –, 1+, 2+, 3+, and 4+); biochemical tests; electrolyte, C-reactive protein (CRP), coagulation function measurements). Additionally, daily alcohol intake was classified as exceeding 15 g or not exceeding 15 g, but alcohol consumption for more than half a year was considered a positive 'alcohol drinking history'.

Data analysis and statistics

Univariate and multivariable regression analyses were performed to identify the risk factors for HFRS complicated with AP. The univariate logistic regression analyses were performed according to basic demographic characteristics, clinical characteristics, and laboratory parameters. These parameters were further stratified and ranked according to their emergence during the clinical course. After excluding irrelevant variables, 54 variables were finally included in the univariate logistic regression analyses. The odds ratio (OR) with a 95% confidence interval (CI) were used to quantify the strengths of associations between variables. Variables with p values <.05 in the univariate analyses were included in the multivariable regression analysis. A two-tailed p value < .05 was considered to manifest a significant difference. Data processing was performed using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA).

Result

A total of 114 patients diagnosed with HFRS were admitted to the First Affiliated Hospital of Wannan Medical College during the research period; 30 patients

had HFRS complicated with AP (all of them developed AP during hospitalization), with an incidence of 26.32%. Among all 114 HFRS patients, there were 94 males and 20 females, and the mean age was 49.31 ± 14.82 years. Among the 30 patients with HFRS complicated with AP, there were 27 males and 3 females, and the mean age was 51.60 ± 11.11 years (patient characteristics are summarized in Table 1).

To explore the risk factors for HFRS complicated with AP, univariate logistic regression analyses were performed to identify the basic demographic characteristics, clinical characteristics, and laboratory parameters that were correlated with the incidence. Finally, the univariate logistic regression analysis results showed that 20 factors were significantly associated with HFRS complicated with AP ($p < .05$): living in Xuancheng city (Anhui Province); an alcohol consumption history; white blood cell (WBC) count; lymphocyte (lym%) and eosinophil percentages (EO%); neutrophil (neut), eosinophil (EO), and red blood cell (RBC) counts; hemoglobin (Hb) level; hematocrit (HCT); proteinuria; hematuria; albumin (ALB), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), and cystatin-C (Cys-C) levels; carbon dioxide-combining power (CO_2CP); fibrinogen degradation products (FDPs); and D-dimer level (for details, see Tables 2–4). All other factors were weakly correlated or not correlated with HFRS complicated with AP. In addition, the results also showed no significant differences in clinical signs/symptoms between patients with and without AP.

Multivariable regression analysis was then performed. The results indicated that alcohol consumption history (OR, 19.516; CI, 1.222–311.716), lym% (OR, 1.184; 95% CI, 1.004–1.396), proteinuria (OR, 101.271; 95% CI, 1.383–7415.481), FDPs (OR, 1.226; 95% CI, 1.015–1.482) and D-dimer level (OR, 0.515; 95% CI, 0.286–0.929) were risk factors for HFRS complicated with AP (Table 5). The results indicated HFRS patients with the above five factors were more likely to develop AP than HFRS patients without the above five factors ($p < .05$).

Discussion

HFRS is a global public health problem and the outbreak situation in China is worrisome. There are a series reports of HFRS accompanied by acute pancreatitis [13–15]. In the present study, we retrospectively analyzed the data of 114 laboratory-confirmed HFRS patients; 30 had HFRS complicated with AP, and the incidence rate of HFRS complicated with AP was 26.32% (30/114). Furthermore, we investigated the risk factors for HFRS complicated with AP by logistic regression analysis. The univariate logistic regression analyses showed that living in Xuancheng city (Anhui Province); an alcohol consumption history; WBC count;

Table 1. General information of all patients with HFRS.

Basic data	HFRS ($n = 114$) n or mean ± SD	HFRS with AP ($n = 30$) n(%) or mean ± SD	HFRS without AP ($n = 84$) n(%) or mean ± SD
Age (years)	49.31 ± 14.82	51.60 ± 11.11	48.49 ± 15.92
Sex			
Male	94	26 (86.77)	68 (80.95)
Female	20	4 (13.33)	16 (19.05)
Living in Xuancheng city (Anhui Province)			
Yes	95	29 (96.67)	66 (78.57)
No	19	1 (3.33)	18 (21.43)
Having underlying diseases			
Yes	21	5 (16.67)	16 (19.05)
No	93	25 (83.33)	68 (80.95)

SD: Standard deviation.

Table 2. Results of univariate logistic regression analyses of the demographic characteristics associated with HFRS complicated with AP.

Variables	B	Standard error	Wald	p	Odds ratio	95% confidence interval	
Age	−0.014	0.015	0.975	.323	0.986	0.958	1.014
Sex	0.425	0.605	0.494	.482	1.529	0.468	5.003
Living in Xuancheng city (Anhui Province)	2.068	1.051	3.870	**.049**	7.909	1.008	62.084
Basic diseases	−0.163	0.563	0.083	.773	0.850	0.282	2.563
Season of onset	0.361	0.463	0.608	.435	1.435	0.579	3.560
Smoking history	0.441	0.465	0.900	.343	1.555	0.625	3.869
Alcohol consumption history	1.037	0.463	5.021	**.025**	2.821	1.139	6.986

Living in Xuancheng city (Anhui Province) was assigned 1, and no was assigned 2. Male was assigned 1; female was assigned 2. Having basic diseases was assigned 1, and no basic diseases was assigned 2. The onset season was assigned 1 in spring and autumn and 2 in summer and winter. Have smoking history and Alcohol consumption history were assigned 1, and no smoking and Alcohol consumption history was assigned 2.
B: β coefficient. Statistically significant correlations ($p < .05$) are highlighted by bold print.

Table 3. Results of univariate logistic regression analyses of the clinical characteristics associated with HFRS complicated with AP.

Variables	B	Standard error	Wald	*p*	Odds ratio	95% confidence interval	
Fever	−0.505	0.519	0.947	.331	0.604	0.219	1.668
Duration of fever	0.055	0.110	0.253	.615	1.057	0.852	1.310
Muscle soreness	0.283	0.587	0.233	.630	1.327	0.420	4.194
Cough and expectoration	−1.670	1.061	2.477	.116	0.188	0.024	1.506
Abdominal pain	−0.305	0.689	0.195	.658	0.737	0.191	2.847
Diarrhea	0.167	0.431	0.150	.698	1.182	0.508	2.750
Vomiting	−0.118	0.433	0.074	.786	0.889	0.380	2.077
Skin ecchymosis	0.201	0.725	0.077	.782	1.222	0.295	5.065
Headache	−0.223	0.523	0.182	.670	0.800	0.287	2.232

Fever, muscle soreness, cough and expectoration, abdominal pain, diarrhea, vomiting, skin ecchymosis and headache were assigned 1, and the absence of these symptoms was assigned 2. B: β coefficient.

Table 4. Results of univariate logistic regression analyses of the laboratory parameters associated with HFRS complicated with AP.

Variables	B	Standard error	Wald	*p*	Odds ratio	95% confidence interval		HFRS with AP group	HFRS group
WBC	−0.033	0.015	4.691	**.030**	0.967	0.938	0.997	26.00 ± 11.10	19.25 ± 3.34
LYM%	0.058	0.022	6.921	**.009**	1.059	1.015	1.106	16.88 ± 2.79	29.35 ± 4.41
MO%	0.015	0.057	0.073	.787	1.015	0.909	1.134	9.50 ± 0.56	8.51 ± 1.16
EO%	−0.425	0.215	3.920	**.048**	0.653	0.429	0.996	1.03 ± 0.21	0.87 ± 0.23
NEUT	−0.052	0.022	5.531	**.019**	0.949	0.909	0.991	18.33 ± 7.45	11.71 ± 2.28
LYM	−0.038	0.062	0.381	.537	0.963	0.853	1.086	4.85 ± 2.61	5.25 ± 0.86
MO	−0.189	0.130	2.107	.147	0.828	0.642	1.068	2.35 ± 0.88	1.79 ± 0.48
EO	−1.552	0.696	4.964	**.026**	0.212	0.054	0.830	0.23 ± 0.09	0.22 ± 0.10
RBC	−0.620	0.262	5.623	**.018**	0.538	0.322	0.898	4.41 ± 0.60	4.31 ± 0.24
HB	−0.022	0.009	6.340	**.012**	0.978	0.962	0.995	136.25 ± 18.04	130.93 ± 6.18
HCT	−7.462	3.082	5.863	**.015**	0.001	0.000	0.241	0.40 ± 0.05	0.38 ± 0.02
PLT	0.015	0.010	2.273	.132	1.015	0.995	1.035	39.75 ± 9.57	45.71 ± 9.59
Proteinuria	1.489	0.586	6.472	**.011**	4.435	1.408	13.972	NA	NA
Hematuria	0.907	0.448	4.095	**.043**	2.476	1.029	5.959	NA	NA
TP	0.063	0.033	3.592	.058	1.065	0.998	1.137	50.68 ± 3.03	50.58 ± 1.75
ALB	0.132	0.058	5.153	**.023**	1.141	1.018	1.278	23.15 ± 1.52	26.11 ± 1.27
GLOB	0.042	0.048	0.749	.387	1.043	0.949	1.146	27.53 ± 1.57	24.47 ± 0.98
TBIL	−0.003	0.005	0.253	.615	0.997	0.987	1.008	25.29 ± 7.80	45.83 ± 25.62
DBIL	0.000	0.009	0.001	.971	1.000	0.982	1.017	9.50 ± 2.71	26.97 ± 17.06
TBA	−0.002	0.012	0.046	.831	0.998	0.975	1.021	19.16 ± 8.20	17.80 ± 8.84
BUN	−0.086	0.022	15.555	**.000**	0.918	0.880	0.958	33.43 ± 4.27	26.92 ± 2.86
Cr	−0.002	0.001	9.571	**.002**	0.998	0.996	0.999	791.45 ± 162.10	533.41 ± 65.77
UA	−0.002	0.001	4.294	**.038**	0.998	0.996	1.000	646.18 ± 67.34	623.36 ± 55.64
CyS-C	−0.259	0.083	9.798	**.002**	0.772	0.656	0.908	8.19 ± 1.47	5.34 ± 0.63
GLU	−0.043	0.036	1.454	.228	0.958	0.893	1.027	9.55 ± 1.08	9.95 ± 1.40
CK	0.000	0.000	1.733	.188	1.000	0.999	1.000	382.50 ± 161.55	894.21 ± 726.81
CKMB	−0.003	0.004	0.660	.417	0.997	0.988	1.005	40.75 ± 10.59	50.52 ± 14.81
LDH	0.000	0.000	2.872	.090	1.000	0.999	1.000	680.25 ± 150.54	1267.86 ± 658.03
K	−0.269	0.238	1.271	.260	0.764	0.479	1.220	4.79 ± 0.27	4.77 ± 0.16
Na	0.001	0.003	0.165	.684	1.001	0.995	1.007	148.28 ± 3.32	145.02 ± 0.90
Ca	0.031	0.081	0.146	.702	1.031	0.881	1.208	2.23 ± 0.10	2.03 ± 0.05
Mg	−0.644	0.845	0.581	.446	0.525	0.100	2.750	1.12 ± 0.04	1.20 ± 0.10
CO_2CP	0.140	0.061	5.207	**.023**	1.150	1.020	1.298	14.53 ± 1.41	17.24 ± 0.68
CRP	−0.003	0.004	0.512	.474	0.997	0.989	1.005	44.57 ± 4.52	96.05 ± 27.94
PT	−0.029	0.022	1.755	.185	0.972	0.931	1.014	14.28 ± 1.15	15.42 ± 1.54
APTT	−0.006	0.010	0.385	.535	0.994	0.974	1.014	37.40 ± 5.91	44.84 ± 4.45
FDPs	−0.029	0.013	5.316	**.021**	0.971	0.947	0.996	28.09 ± 9.79	14.45 ± 2.77
D-dimer	−0.102	0.044	5.273	**.022**	0.903	0.828	0.985	6.53 ± 2.86	3.85 ± 0.87

WBC: white blood cell; lym%: lymphocyte percentage; Mo%: monocyte percentage; EO%: eosinophil percentage; neut: neutrophil; lym: lymphocyte; Mo: monocyte; EO: eosinophil; RBC: erythrocyte; HB: hemoglobin; HCT: hematocrit; PLT: platelet; TP: Total protein; ALB: albumin, GLOB: globulin; TBIL: total bilirubin; DBIL: direct bilirubin; TBA: bile acid; BUN: urea nitrogen; Cr: creatinine; UA: uric acid; Cys-C: cystatin-C; Glu: glucose; CK: creatine kinase; CKMB: creatine kinase isoenzyme; LDH: lactate dehydrogenase; K: potassium; Na: sodium; Ca: calcium; Mg: magnesium; CO_2CP: carbon dioxide binding force; CRP: C-reactive protein; PT: prothrombin time; APTT: activated partial thromboplastin time; FDPs: fibrinogen degradation products; proteinuria and hematuria 3+ and 4+ were assigned 2, and 2+, 1+ and − were assigned 1; NA: not applicable. Statistically significant correlations ($p < .05$) are highlighted by bold print. B: β coefficient. Statistically significant correlations ($p < .05$) are highlighted by bold print.

lym%; EO%; neutrophil, EO, and RBC counts; Hb level; HCT; proteinuria; hematuria; ALB, BUN, Cr, UA, and Cys-C levels; CO_2CP; FDPs; and D-dimer level were significantly associated with HFRS complicated with AP ($p < .05$). Subsequent multivariable analysis showed that and alcohol consumption history, lym%, proteinuria, FDPs and D-dimer level were risk factors for HFRS complicated with AP ($p < .05$). This result indicated that HFRS patients who had a history of alcohol consumption, a high lym%, intense proteinuria, a high level of

Table 5. Results of multivariable regression analyses of the high-risk factors associated with HFRS complicated with AP.

Variables	B	Standard error	Wald	*p*	Odds ratio	95% confidence interval	
Alcohol consumption history	2.971	2.011	2.961	**.036**	19.516	1.222	311.716
LYM%	0.169	0.084	4.023	**.045**	1.184	1.004	1.396
Proteinuria	4.618	2.191	4.444	**.035**	101.271	1.383	7415.481
FDPs	0.204	0.097	4.453	**.035**	1.226	1.015	1.482
D-dimer	−0.663	0.301	4.857	**.028**	0.515	0.286	0.929

B: β coefficient. Statistically significant correlations ($p < .05$) are highlighted by bold print.

FDP and a low level of D-dimer were more prone to a complication with AP.

In general, there is an incubation period of two to three weeks after infection with the hantavirus, followed by a typical 5-period clinical course, namely, a febrile phase, a hypotensive phase, an oliguric phase, a diuretic phase, and a convalescent-phase [16]. Although renal dysfunction is the main symptom of hantavirus infection, various extrarenal symptoms have also been noted. Up to 33.3% of HFRS patients also have extra-renal organ involvement in addition to acute renal insufficiency, with the pancreaticobiliary illness being the most frequent symptom [17]. The activation of inflammatory mediators during the hypotensive phase of HFRS appears to be caused by an inflammatory cascade of responses mediated by cytokines, immunocytes, and the complement system. Inflammatory cytokines cause macrophages to migrate into tissues far from the pancreas, including the lungs and kidneys [18]. This could be a possible pathogenic mechanism of AP in HFRS patients. In recent years, the number of cases complicated with AP has increased annually [19]. In this study, the incidence of AP in patients with HFRS was 26.32%, far exceeding the incidence rates of 8.4% reported by Guo et al. in Xi'an, China [11], and 8% reported by Zhu et al. in Nanchang, China [20]. The proportions of patients with HFRS complicated with AP differ in different regions. The univariate analysis results of this study showed that the incidence of HFRS complicated with AP was higher in the population living in the Xuancheng area (Anhui Province) than in other areas. These areas are mainly located in southeastern Anhui Province and are mostly mountainous. Therefore, it is speculated that the incidence of HFRS complicated with AP is related to geographic region, as population characteristics, eating habits, and living habits in different regions vary.

The results of the multivariate analysis in this study showed that HFRS patients with an alcohol consumption history were more likely to have AP than patients without an alcohol consumption history, and an alcohol consumption history may be a risk factor. Alcohol consumption predisposes patients to various infections (including bacterial infections and viral infections) [21,22]. Epidemiological data have established that excessive alcohol consumption is the second leading cause of AP after gallstones [11] and the most prevalent risk factor for CP [23]. It is also a risk factor for recurrent pancreatitis after the first AP attack and increases the risk of progression to CP [24]. Alcohol exposure contributes to the initiation and progression of pancreatitis. However, how alcohol consumption predisposes the pancreas to disease is not entirely understood. Additionally, several studies have shown that the risk of getting AP is higher if the patient is a current or an ex-smoker compared with nonsmokers [25,26], but our study did not find that smoke is a risk factor of HFRS complicated with AP.

Thrombocytopenia and leukocytosis are characteristics of hantavirus infection. Thrombocytopenia can lead to petechiae on the skin or mucous membranes, conjunctivitis, bleeding, hemolysis, hematuria, and fatal intracranial hemorrhage [1]. In addition, platelet dysfunction may also lead to abnormal blood coagulation [27]. It has been demonstrated that platelet adhesion to infected endothelial cells is directed by pathogenic hantavirus strains through the β3 integrin receptor [28]. This results in altered platelet activation, a reduction in the platelet count, and loss of vascular integrity; consequently, endothelial lesions may promote coagulation activation and fibrinolysis, effects induced by increased prothrombin and D-dimer levels [29]. A study performed by Maeda et al. showed that hemostatic system parameter measurement represents a valuable diagnostic tool for the early recognition of events leading to serious and life-threatening complications during the course of AP [30]. The results of the multivariate analysis in our study showed that HFRS patients with high FDP levels and low D-dimer levels were extremely vulnerable to complication with AP. However, there have been limited research reports and mechanistic studies on these factors. Therefore, the relationship between abnormal coagulation and AP in HFRS patients is an interesting subject for further investigation.

In addition, the multivariable regression analysis results of this study showed that the more severe the degree of proteinuria was, the higher the risk of HFRS complicated with AP was, and proteinuria may be

another risk factor for HFRS complicated with AP. Patients with HFRS can develop acute renal failure, usually caused by tubular and glomerular injury [31,32], and proteinuria is detected in almost all of these patients. There are few relevant studies on whether there is a causal relationship between proteinuria and HFRS complicated with AP and the mechanism of such a relationship, which made us interested in developing more research for answers. In this study, we also found that the incidence of HFRS complicated with AP was significantly increased in those with higher lym%, and lym% was a risk factor for HFRS complicated with AP. The molecular mechanism by which an increase in lymphocytes promotes the occurrence of AP may involve the secretion of inflammatory cytokines, such as IL-1, IL-6 and TNF-α, from lymphocytes [33]. TNF-α and IL-1 can activate leukocytes and vascular adhesion cells, causing activated granulocytes to penetrate pancreatic tissue, causing an inflammatory response and aggravating tissue damage. Some studies have shown that Red cell distribution width (RDW) is an independent risk factor related to the severity of AP [34,35], but our study did not find that RDW is a risk factor of HFRS complicated with AP.

It is widely recognized that early identification of HFRS complicated with AP is important to improve the clinical outcome of this potentially life-threatening disease. The high mortality rate among HFRS patients in critical condition highlights the significance of clinicians being aware of the occurrence of potentially fatal complications (like AP) and changes in biochemical status to ensure that supportive treatment can be started promptly and systematically when necessary. Since both diseases overlap similar clinical signs and symptoms, it may be challenging to make an early diagnosis of AP in HFRS patients. For this reason, it is especially crucial to identify risk factors for HFRS complicated with AP. Additionally, in HFRS-endemic areas, more emphasis should be placed on encouraging comprehensive health education and behavior adjustments among at-risk people. Medical personnel need to consider the lym%, presence of proteinuria, and abnormal coagulation function; prevent exposure to other inducing factors; and strive for early prediction and prevention of disease progression. Based on the five risk factors identified in this study, clinicians can assess the individual risk of HFRS complicated with AP in patients to a certain extent, make the greatest clinical judgments and give patients the finest treatment possible.

To our knowledge, this is the first report on the risk factors for HFRS complicated with AP in China, even though these results should be considered preliminary. The present study provides some valuable results, but there are some limitations to this study, which must be acknowledged. First, it was a single-center, retrospective, observational study, and the participants' selection is obviously impacted by the inherent constraints of this form of study, thus resulting in selection bias. Second, particularly for the multivariable regression analysis conducted to identify risk variables for HFRS complicated with AP, the comparatively low number of cases rendered the statistical power extremely poor, and confounding bias is unavoidable during the statistical analysis process. Third, the study's sample sizes did not adequately capture the stark contrasts between the two groups. This study represents the situation of patients with HFRS complicated with AP in only southern Anhui Province and not China as a whole. Therefore, future studies on this topic require a longer study period, representative large-sample data, as well as more thorough studies, are needed for statistical analysis.

Conclusions

In conclusion, our study results showed that a history of alcohol consumption, lym%, proteinuria, FDPs and D-dimer levels were risk factors for HFRS complicated with AP. This study provides new insights into the risk factors for the occurrence of AP in HFRS patients and can effectively improve the vigilance of medical staff and provide useful guidance for early prediction, recognition, and intervention strategies.

Author contributions

Study conception/design: Jinsun Yang; Methodology: Wenjie Wang, Dongqing Fan; Data curation: Dongqing Fan; Investigation: Bin Quan, Weishun Hou; Supervision: Jinsun Yang. Writing – original draft: Wenjie Wang. Writing – review & editing: Wenjie Wang, Jinsun Yang.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Wannan Medical College 1 Key Project of Young and Middle-aged Scientific Research Fund: Areas in the South of Anhui Kidney Syndrome Hemorrhagic Fever Virus Gene Sequence Analysis and Molecular Epidemiological Studies (2020; No. WK2020ZF08).

ORCID

Wenjie Wang http://orcid.org/0000-0003-2067-1250
Jinsun Yang http://orcid.org/0000-0001-6285-5504

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, [Jinsun Yang].

References

[1] Avsic-Zupanc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect. 2019;21:1–9. doi: 10.1111/1469-0691.12291.

[2] Wu H, Wang X, Xue M, et al. Spatial-temporal characteristics and the epidemiology of haemorrhagic fever with renal syndrome from 2007 to 2016 in Zhejiang province, China. Sci Rep. 2018;8(1):10244. doi: 10.1038/s41598-018-28610-8.

[3] Zou LX, Sun L. Analysis of hemorrhagic fever with renal syndrome using wavelet tools in mainland China, 2004–2019. Front Public Health. 2020;8:571984. doi: 10.3389/fpubh.2020.571984.

[4] Tian HY, Yu PB, Luis AD, et al. Changes in rodent abundance and weather conditions potentially drive hemorrhagic fever with renal syndrome outbreaks in xi'an, China, 2005–2012. PLOS Negl Trop Dis. 2015;9(3):e0003530. doi: 10.1371/journal.pntd.0003530.

[5] Iannuzzi JP, King JA, Leong JH, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. Gastroenterology. 2022;162(1):122–134. doi: 10.1053/j.gastro.2021.09.043.

[6] Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol. 2019;16(3):175–184. doi: 10.1038/s41575-018-0087-5.

[7] 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.

[8] Qiu FQ, Li CC, Zhou JY. Hemorrhagic fever with renal syndrome complicated with aortic dissection: a case report. World J Clin Cases. 2020;8(22):5795–5801. doi: 10.12998/wjcc.v8.i22.5795.

[9] Puca E, Harxhi A, Pipero P, et al. Pancreatitis in patients with hemorrhagic fever with renal syndrome: a five-year experience. J Infect Dev Ctries. 2017;11(11):900–903. doi: 10.3855/jidc.9567.

[10] 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):267–275. doi: 10.1186/s12879-021-05964-5.

[11] Boxhoorn L, Voermans RP, Bouwense SA, et al. Acute pancreatitis. Lancet. 2020;396(10252):726–734. doi: 10.1016/S0140-6736(20)31310-6.

[12] Lee P, Papachristou G. New insights into acute pancreatitis. Nat Rev Gastroenterol Hepatol. 2019;16(8):479–496. doi: 10.1038/s41575-019-0158-2.

[13] D'Souza MH, Patel TR. Biodefense implications of new-world hantaviruses. Front Bioeng Biotechnol. 2020;8:925. doi: 10.3389/fbioe.2020.00925.

[14] Zhang Y, Ma R, Wang Y, et al. Viruses run: the evasion mechanisms of the antiviral innate immunity by hantavirus. Front Microbiol. 2021;12:759198. doi: 10.3389/fmicb.2021.759198.

[15] Wang WJ, Zhao J, Yang JS, et al. Clinical analysis of patients with acute pancreatitis complicated with hemorrhagic fever with renal syndrome and acute biliary pancreatitis. Medicine. 2020;99(5):e18916. doi: 10.1097/MD.0000000000018916.

[16] Kim HK, Chung JH, Kim DM, et al. Hemorrhagic fever with renal syndrome as a cause of acute diarrhea. Am J Trop Med Hyg. 2019;100(5):1236–1239. doi: 10.4269/ajtmh.18-0974.

[17] Park KH, Kang YU, Kang SJ, et al. Short report: experience with extrarenal manifestations of hemorrhagic fever with renal syndrome in a tertiary care hospital in South Korea. Am J Trop Med Hyg. 2011;84(2):229–233. doi: 10.4269/ajtmh.2011.10-0024.

[18] Kim YO, Yang CW, Yoon SA, et al. Intestinal protein loss in patients with haemorrhagic fever with renal syndrome. Nephrol Dial Transplant. 2000;15(10):1588–1592. doi: 10.1093/ndt/15.10.1588.

[19] Wu G, Xia Z, Wang F, et al. Investigation on risk factors of haemorrhagic fever with renal syndrome (HFRS) in Xuancheng city in Anhui province, mainland China. Epidemiol Infect. 2020;148:e248. doi: 10.1017/S0950268820002344.

[20] Zhu Y, Chen YX, Zhu Y, et al. A retrospective study of acute pancreatitis in patients with hemorrhagic fever with renal syndrome. BMC Gastroenterol. 2013;13:171–176. doi: 10.1186/1471-230X-13-171.

[21] Simou E, Britton J, Leonardi-Bee J. Alcohol and the risk of pneumonia: a systematic review and meta-analysis. BMJ Open. 2018;8(8):e022344. doi: 10.1136/bmjopen-2018-022344.

[22] Jerrells TR, Pavlik JA, DeVasure J, et al. Association of chronic alcohol consumption and increased susceptibility to and pathogenic effects of pulmonary infection with respiratory syncytial virus in mice. Alcohol. 2007;41(5):357–369. doi: 10.1016/j.alcohol.2007.07.001.

[23] Beyer G, Habtezion A, Werner J, et al. Chronic pancreatitis. Lancet. 2020;396(10249):499–512. doi: 10.1016/S0140-6736(20)31318-0.

[24] Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol. 2016;14(5):738–746. doi: 10.1016/j.cgh.2015.12.040.

[25] Lugea A, Gerloff A, Su HY, et al. The combination of alcohol and cigarette smoke induces endoplasmic reticulum stress and cell death in pancreatic acinar cells. Gastroenterology. 2017;153(6):1674–1686. doi: 10.1053/j.gastro.2017.08.036.

[26] Tang QY, Yang Q, Yu XQ, et al. Association of demographic and clinical factors with risk of acute pancreatitis: an exposure-wide mendelian randomization study. Mol Genet Genomic Med. 2023;11(1):e2091.

[27] Cosgriff TM, Lee HW, See AF, et al. Platelet dysfunction contributes to the haemostatic defect in haemorrhagic fever with renal syndrome. Trans R Soc Trop Med Hyg. 1991;85(5):660–663. doi: 10.1016/0035-9203(91)90386-d.

[28] Gavrilovskaya IN, Gorbunova EE, Mackow ER. Pathogenic hantaviruses direct the adherence of quiescent platelets to infected endothelial cells. J Virol. 2010;84(9):4832–4839. doi: 10.1128/JVI.02405-09.

[29] Laine O, Mäkelä S, Mustonen J, et al. Enhanced thrombin formation and fibrinolysis during acute puumala hantavirus infection. Thromb Res. 2010;126(2):154–158. doi: 10.1016/j.thromres.2010.05.025.

[30] Maeda K, Hirota M, Ichihara A, et al. Applicability of disseminated intravascular coagulation parameters in the assessment of the severity of acute pancreatitis. Pancreas. 2006;32(1):87–92. doi: 10.1097/01.mpa.0000186248.89081.44.

[31] Muranyi W, Bahr U, Zeier M, et al. Hantavirus infection. J Am Soc Nephrol. 2005;16(12):3669–3679. doi: 10.1681/ASN.2005050561.

[32] Krautkrämer E, Grouls S, Stein N, et al. Pathogenic old world hantaviruses infect renal glomerular and tubular cells and induce disassembling of cell-to-cell contacts. J Virol. 2011;85(19):9811–9823. doi: 10.1128/JVI.00568-11.

[33] Zhang XP, Wang L, Zhou YF. The pathogenic mechanism of severe acute pancreatitis complicated with renal injury: a review of current knowledge. Dig Dis Sci. 2008;53(2):297–306. doi: 10.1007/s10620-007-9866-5.

[34] Zhang T, Liu H, Wang D, et al. Predicting the severity of acute pancreatitis with red cell distribution width at early admission stage. Shock. 2018;49(5):551–555. doi: 10.1097/SHK.0000000000000982.

[35] Yalcin MS, Tas A, Kara B, et al. New predictor of acute necrotizing pancreatitis: red cell distribution width. Adv Clin Exp Med. 2018;27(2):225–228. doi: 10.17219/acem/67590.