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ORIGINAL ARTICLE

Correlation of CD38 expression with the progression of hemorrhagic fever with renal syndrome

Han-Dong Zhao[1] · Yan-Ping Li[1] · Wei-Wei Zhao[2] · Peng Li[1] · Hong-Li Liu[3]

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Abstract

To assess the relationship between the expression of CD38 and the progression of hemorrhagic fever with renal syndrome (HFRS), we determined the levels of CD38 during different phases of HFRS and evaluated the relationship between changes in CD38 expression and the progression of HFRS. The expression of CD38 in 68 patients with HFRS was analyzed by flow cytometry, and this method was also used to determine the levels of $CD4^+$T, $CD8^+$T, and B lymphocytes and NK cells. Furthermore, creatinine (Cr), uric acid (UA), and urea in serum at each stage of HFRS were measured using commercial kits. The basic clinical reference values for leukocytes, platelets (PLT), and red blood cells were determined by conventional methods. The colloidal gold method was used to measure HFRS antibody levels in the patients. A significant change in CD38 expression was observed from the fever phase to the recovery phase in patients with HFRS. Moreover, the expression of CD38 was proportionally correlated with the levels of Cr, UA, and urea in serum. In contrast, there was an inverse correlation between CD38 and PLT. Interestingly, an increase in CD38 expression correlated with an increase in $CD8^+$T lymphocytes, B cells, and NK cells, but with a decrease in $CD4^+$T lymphocytes. The expression of CD38 is associated with the progression of HFRS, suggesting that it may be a potent indicator of the stages of this disorder.

Introduction

Hemorrhagic fever with renal syndrome (HFRS) has attracted increasing attention because it is a threat to public health around the world. HFRS was first diagnosed in Korea in 1978, and it is characterized by fever, hemorrhage, renal impairment, and thrombocytopenia [1, 2]. According to its clinical manifestations, HFRS can be divided into five sequential stages: fever, hypotension, oliguria, polyuria, and recovery [3]. It is believed that Hantaan virus (HTNV) is one of the causative agents of HFRS. This virus was first isolated from the lungs of infected striped field mice near the Hantaan River, and it can be transmitted to humans via inhalation of aerosols [4]. HFRS is a fulminant infectious disease with a fatality rate of 15%. Although vaccination has greatly reduced the prevalence of this disease, approximately, 100,000 cases of HFRS are reported annually in Asia and European countries. Surprisingly, China accounts for almost 90% of the total cases worldwide [5].

Much research in recent years has focused on the pathogenesis of hantavirus cardiopulmonary disease and HFRS, and it has been shown that pathological changes in HFRS are characterized by increased permeability of microvascular beds of affected organs, and kidney and endothelial cells are considered to be the primary targets of hantaviruses [4, 6]. It has also been shown that immune-mediated mechanisms, in particular, T cell activation in the acute phase, are involved in the pathogenesis of the HFRS [7, 8]. Terajima *et al.* reported that the increased capillary permeability observed in HFRS may be due to hantavirus-specific cytotoxic T cells attacking endothelial cells presenting viral antigens on their surface [9]. It has been proposed that immune dysfunction and pathological damage caused by disorders of immune regulation may also contribute to the onset of HFRS [10]. Although many efforts have been made to elucidate the pathogenic mechanism of HFRS, there remains a need for

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✉ Hong-Li Liu
liuhongli1965@163.com

[1] Central Laboratory of Virology, Shaanxi Infectious Disease Hospital, The Eighth Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China

[2] Department of Bioscience, Becton, Dickinson and Company, Shanghai 200040, China

[3] Department of Clinical Laboratory, Xi'an Forth Hospital, 21 Jiefang Road, Xi'an 710004, China

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a reliable indicator that reflects the progression of HFRS during clinical treatment.

CD38 is a 46-kDa type II transmembrane glycoprotein that is expressed by immature or activated lymphocytes, plasma cells, monocytes, and most peripheral blood NK cells. It has been shown that CD38 is associated with surface receptors such as CD3, surface Ig, and CD16, which are crucial for the function of T and B lymphocytes and NK cells [11, 12]. Furthermore, it has been reported that the expression of CD38 is correlated with several diseases, including HIV infection, autoimmune diseases, type II diabetes mellitus, osteoporosis, and cancer [13–16]. Increased expression of CD38 is also observed in some hematological malignancies, such as multiple myeloma, Waldenstrom's macroglobulinemia, primary systemic amyloidosis, NK cell leukemia, and plasma cell leukemia [17–20]. However, little attention has been paid to the expression characteristics of CD38 in patients with HFRS.

In the present study, we investigated the expression of CD38 in patients with HFRS at different stages, analyzed the correlation between CD38 levels and renal impairment in HFRS patients, and evaluated the correspondence between changes in CD38 levels and the progression of HFRS.

Materials and methods

Participants

A total of 68 adults (37 men, 31 women; median age, 48.4 years) who were diagnosed with HFRS at the Infectious Diseases Department of the Eighth Affiliated Hospital of Xi'an Jiaotong University (Shaanxi Provincial Hospital of Infectious Diseases) were enrolled in this study. All patients were positive for HTNV antibody. HFRS was diagnosed according to the diagnosis and classification criteria established by the Ministry of Health of the People's Republic of China (PRC) in 1997 (fever phase, body temperature >37.3℃, leukocytes $>9 \times 10^9$/L; hypotension phase, systolic pressure < 90 mmHg; oliguria phase, urine output < 500 ml/day; polyuria phase, urine output >3000 ml/day; recovery phase, urine output 1500-2000 ml/day, and return of basic clinical reference values to the normal level). None of the patients had kidney disease, diabetes, cardiovascular disease, hematological disease, autoimmune disease, viral hepatitis, or other liver diseases. Sixty-three healthy volunteers (32 men, 31 women; median age, 47.5 years) were also recruited as controls for the present study. All procedures involving human participants were carried out in accordance with the ethical standards of the Institutional Review Board of Xi'an Jiaotong University (2015284) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Cr, UA, and urea measurements

Each morning, 3 mL of venous blood was aspirated aseptically into a tube containing sodium heparin, which was then incubated in a 37 ℃ water bath for 10 min. After that, the serum was isolated by centrifugation at 3,000 rpm for 5 min. The sarcosine oxidase method, the uricase-peroxidase method, and the ultraviolet-glutamate dehydrogenase method were used to determine creatinine (Cr), uric acid (UA), and urea levels, respectively, using a Mindray BS800 system (Mindray Urea, UA, Cr Kit; Mindray Medical Co., Ltd, Shenzhen, China) according to the manufacturer's protocol.

HTNV antibody examination

Levels of IgG or IgM against HTNV were measured by the colloidal gold method (Bosheng Biotechnology Co., Ltd, Xiamen, China). Briefly, 100 µL of diluted sample diluents was mixed with 2 µL of EDTA-K_2-anticoagulated plasma, and 70 µL of this mixture was pipetted onto a test strip and incubated for 20 min according to the manufacturer's instructions. The assay sensitivity and specificity were 96.71% and 98.72%, respectively.

CD38 determination

Flow cytometry (FCM) was used to determine the level of CD38 in patients and donors. One hundred µL of EDTA-K_2-anticoagulated blood was mixed with twenty µL FITC-conjugated anti-CD38 antibody (Becton Dickinson, Franklin, NJ, USA) and incubated in the dark for 15 min. Two ml of lysing solution was then added, the mixture was incubated for 15 min and centrifuged at 300 *g* for 5 min, and the supernatant was discarded. After three extensive washes with PBS, each sample was resuspended in 500 µL of PBS, and data were collected using Diva software and analyzed using Flow Jo version 10.5.2 (Becton Dickinson, Franklin, NJ, USA).

Lymphocyte detection

The levels of lymphocytes, including $CD4^+$T lymphocytes, $CD8^+$T lymphocytes, B cells, and NK cells, were determined using an IMK Kit (Becton Dickinson, Franklin, NJ, USA) according to the manufacturer's instructions. Fifty µL of EDTA-K_2-anticoagulated plasma and 20 µL of reagent were mixed in a TruCount tube (Becton Dickinson, Franklin, NJ, USA) and incubated in the dark for 15 min., after which 450 µL of lysing solution was added and the

sample was incubated in the dark for 10 min. All samples were analyzed using FACSCanto Clinical software (Becton Dickinson, Franklin, NJ, USA).

Leukocyte and platelet assays

Flow cytometry and electrical impedance were used to determine the levels of leukocytes and platelets (PLT) using a Mindray CAL 8000 system (Mindray Leukocyte, PLT Kit; Mindray Medical Co., Ltd, Shenzhen, China) according to the manufacturer's instructions.

Statistical analysis

Data were analyzed statistically using SPSS software version 17.0. The significance between groups was evaluated using a two-sample Student's *t*-test. Associations between CD38 and Cr, UA, urea and PLT levels were analyzed using Spearman correlation test. Differences between groups were considered significant at a level of $p < 0.05$.

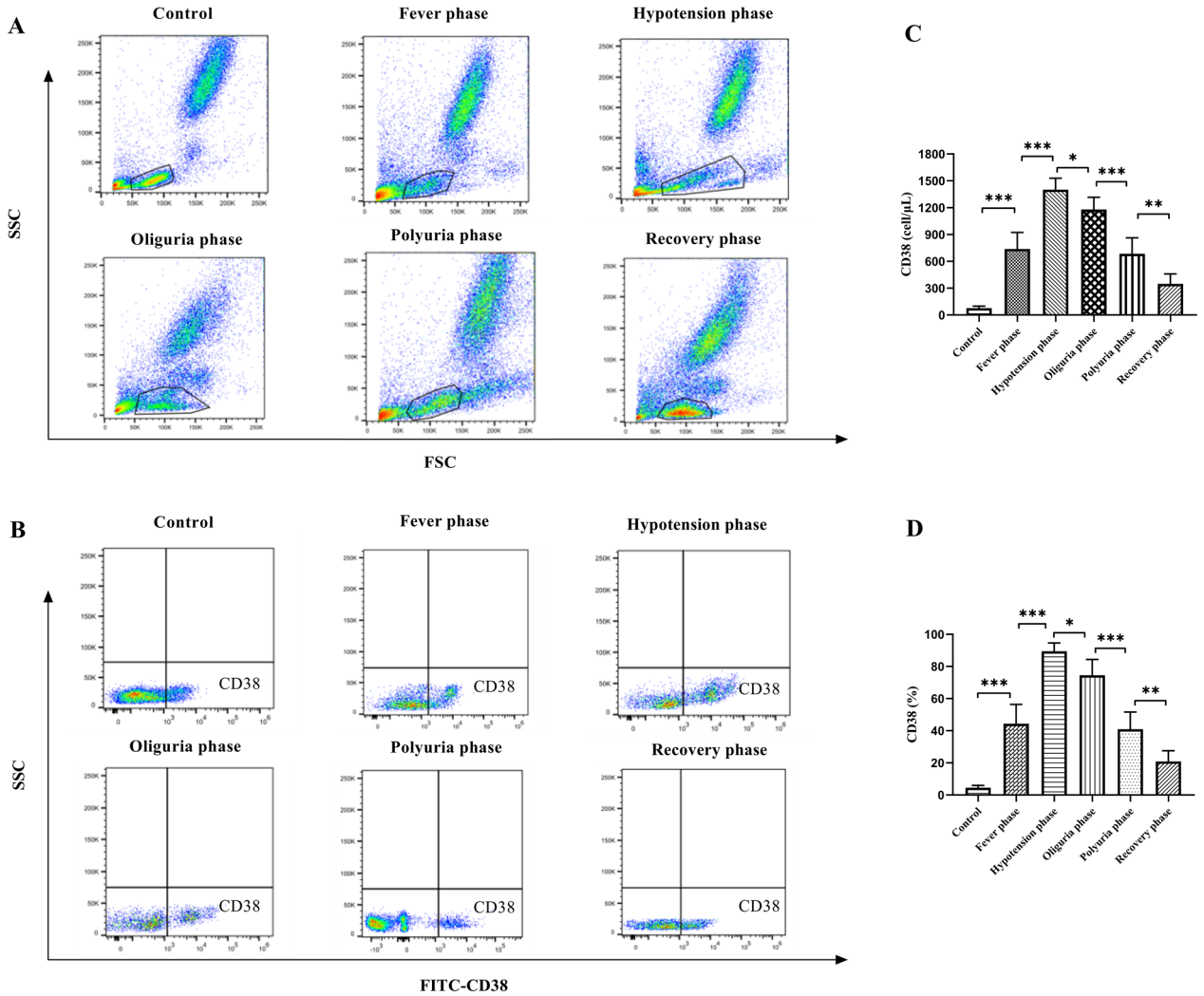

Fig. 1 The level of CD38 in patients with hemorrhagic fever with renal syndrome (HFRS) at different phases. (A-D) The expression and rate (CD38/lymphocytes) of CD38 at different stages of HFRS (n = 68) as determined by FCM. (C-D) A significant difference was observed between the control group and patients in the recovery phase. Notably, the difference between the control group and patients in the fever phase is striking (***$p < 0.001$). A similar phenomenon was also observed in the fever phase, hypotension phase, oliguria phase, and polyuria phase (***$p < 0.001$). The data in panel 1C are the mean ± SD, and those in panel D are the mean ± SEM.

Results

Correlation of expression levels of CD38 with the progression of HFRS

The CD38 expression levels in 68 patients with HFRS were analyzed at different stages of disease, as shown in Fig. 1. A striking difference was observed between the HFRS patients and the control group until the hypotension phase (Fig. 1C; $p < 0.001$), when the level of CD38 reached a peak and then gradually decreased as the patients recovered (Fig. 1C; $p < 0.01$). Interestingly, a similar change in the CD38 rate (CD38/lymphocytes) was also observed (Fig. 1D). However, the expression level of CD38 remained relatively high, even in the recovery phase (Fig. 1C), suggesting the importance of CD38 in HFRS, although its pathological role in this disorder is largely unknown.

The correlation between CD38 and Cr, UA, urea, and PLT

In previous studies, increased permeability in microvascular beds of affected organs was observed in HFRS patients, especially in the kidney, and endothelial cells were suggested to be the primary targets of hantavirus infection [4, 6]. Therefore, we measured the kidney function indices Cr, UA, and urea, which reflect the degree of kidney damage. In addition, the correlation between CD38 with either Cr or UA as well as urea was also investigated, and the corresponding results and the clinical characteristics of patients

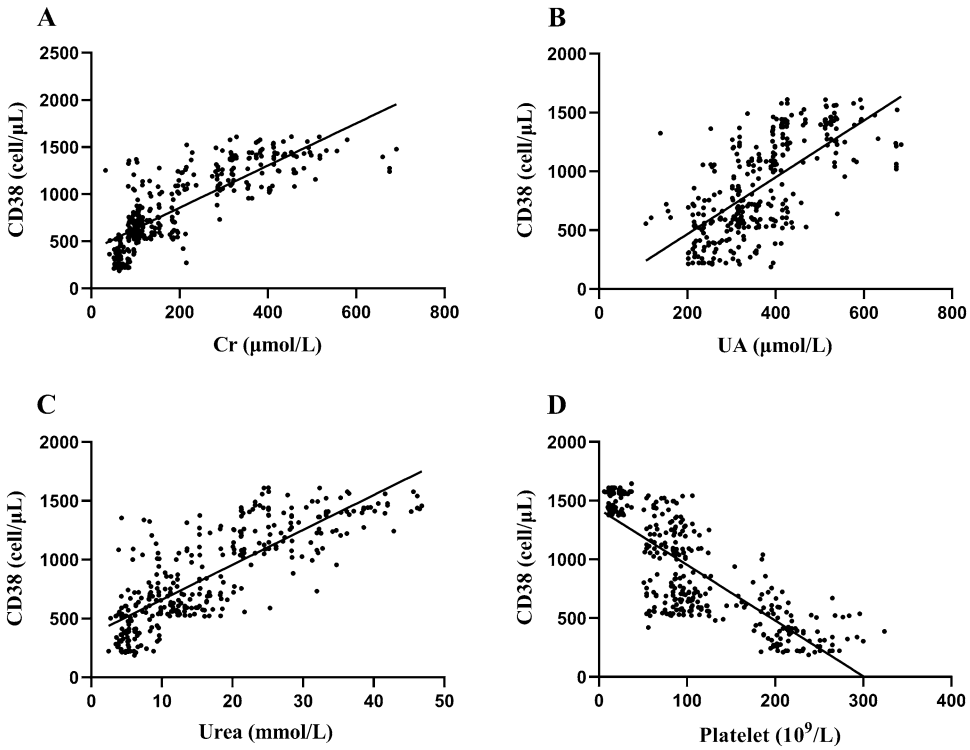

Fig. 2 The relationship between CD38 and Cr, UA, urea, and PLT. (A) Positive correlation of CD38 expression in patients with HFRS (n = 68) at different phases with the level of Cr (** $p < 0.01$, $r^2 = 0.656$). (B-C) Positive correlation of CD38 expression with UA (** $p < 0.01$, $r^2 = 0.449$) and urea (** $p < 0.01$, $r^2 = 0.652$). (D) Negative correlation of CD38 expression with PLT (** $p < 0.01$, $r^2 = 0.572$).

Table 1 Clinical characteristics of patients with HFRS

Phase	Leukocytes (10^9/L)	RBC (10^{12}/L)	Platelets (10^9/L)	Serum Cr (μmol/L)	Serum urea (mmol/L)	Serum UA (μmol/L)
Control	4.72 ± 0.84	4.63 ± 0.52	223.31 ± 32.24	68.32 ± 13.77	5.69 ± 1.34	266.45 ± 60.27
Fever	15.71 ± 4.76	4.38 ± 0.67	76.19 ± 26.33	115.93 ± 36.45	12.98 ± 5.56	341.08 ± 70.23
Hypotension	18.39 ± 2.98	4.51 ± 0.58	17.65 ± 7.22	432.65 ± 88.31	32.91 ± 7.31	491.83 ± 59.12
Oliguria	16.84 ± 3.22	4.19 ± 0.49	98.32 ± 11.52	279.56 ± 82.94	23.18 ± 5.63	421.92 ± 118.38
Polyuria	10.59 ± 1.98	4.21 ± 0.58	213.07 ± 41.52	136.31 ± 40.41	11.02 ± 3.21	332.02 ± 54.59
Recovery	4.82 ± 1.16	4.24 ± 0.61	234.76 ± 41.01	69.56 ±21.79	5.51 ± 1.63	271.41 ± 56.84

Data are the mean ± SD

are shown in Fig. 2 and Table 1, respectively. Fig. 2A illustrates the correlation between CD38 and Cr. Statistical analysis showed that the CD38 levels in patients with HFRS in different phases were proportional to the level of Cr in serum (Fig. 2A; $p < 0.01$, $r^2 = 0.656$). Similarly, as shown in Fig. 2B and C, high levels of UA and urea were associated with the increased expression of CD38 (Fig. 2B and C; $p < 0.01$, $r^2 = 0.449$; $p < 0.01$, $r^2 = 0.652$). Considering that thrombocytopenia is one of the notable clinical signs in patients with HFRS [1], the correlation between CD38 and PLT was also analyzed. Interestingly, the level of CD38 was inversely correlated with the PLT count (Fig. 2D; $p < 0.01$, $r^2 = 0.572$). Taken together, variation in CD38 levels correlated with changes in Cr, UA, and urea, suggesting that CD38 levels reflect the degree of renal impairment in HFRS patients.

Levels of $CD4^+$T lymphocytes, $CD8^+$T lymphocytes, B lymphocytes, and NK cells in patients with HFRS during the different phases

As mentioned above, CD38 is associated with surface receptors such as CD3, surface Ig, and CD16, that are crucial for the function of T and B lymphocytes and NK cells. Furthermore, hantavirus infection can induce a vigorous cellular immune response in humans and especially influences T cell activation in the acute phase [11, 12, 21]. Therefore, the levels of $CD4^+$T, $CD8^+$T, and B lymphocytes and NK cells were determined in the present study. As shown in Fig. 3A, the population of $CD8^+$ T lymphocytes, B lymphocytes, and NK cells was significantly higher in patients with HFRS in the hypotension phase than in the controls, with a trend similar to that of the expression levels of CD38 ($p < 0.01$). In contrast, the population of $CD4^+$T lymphocytes decreased dramatically in patients with HFRS during the hypotension phase, in striking contrast to other cell types examined (Fig. 3D), although the physiological significance remains unclear. It seems that the role of $CD4^+$T lymphocytes in

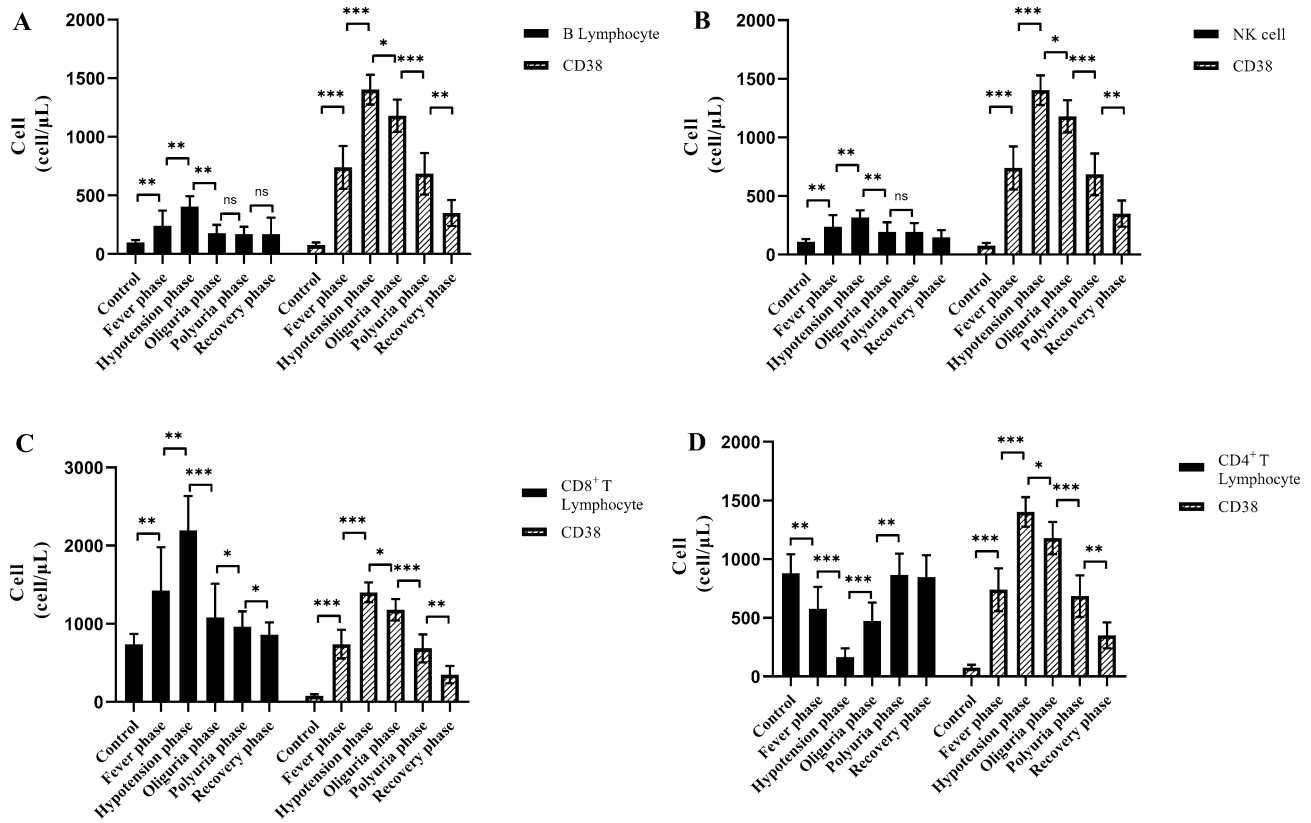

Fig. 3 Levels of $CD4^+$T lymphocytes, $CD8^+$T lymphocytes, B lymphocytes, and NK cells in patients with HFRS (n = 68) at various phases, determined by FCM. (A) A significant difference in B lymphocyte levels was found in patients in the oliguria phase compared to controls (** $p < 0.01$) (B-D). A similar trend was also observed in $CD4^+$T lymphocytes, $CD8^+$T lymphocytes, and NK cells (** $p < 0.01$, *** $p < 0.001$). (C) A clear difference in $CD8^+$T lymphocyte levels was observed from the oliguria phase to the recovery phase (* $p < 0.05$). The data shown are the mean ± SD.

the progression of HFRS is distinct from those of $CD8^+$T lymphocytes, B lymphocytes, and NK cells. In addition, as can be seen in Fig. 3, a significant change in CD38 levels was observed from the oliguria phase to the recovery phase. However, no such change was observed in the levels of B lymphocytes and NK cells, and the level of $CD8^+$T lymphocytes did not change to the same degree as CD38, suggesting that CD38 levels are more sensitive to Hantavirus infection, and therefore might be a better indicator of the HTNV infection status.

Discussion

In recent years, much attention has been paid to HFRS as a global health issue. Studies focused on the pathogenesis of HFRS have revealed that immune dysfunction may contribute to the development of HFRS [9]. Meanwhile, it has also been shown that HTNV infection induces a strong cellular immune response in humans, with trafficking of $CD4^+$T, $CD8^+$T, and $CD25^+$ lymphocytes promoting the progression of this disorder [22–24]. However, the relationship between the progression of HFRS and the expression of CD38 is still poorly understood.

In the present study, we investigated the expression of CD38 at different stages of HFRS. Our results show that the expression of CD38 increases significantly from the fever phase to the hypotension phase. It has been documented that vascular endothelial cells are the primary targets of HTNV and that T lymphocytes recognize the viral antigen on the surface of endothelial cells and eliminate cells that are infected with HTNV. In this process, CD38 also plays an important role in regulating the adhesion of circulating lymphocytes to endothelial cells [4, 25, 26]. Therefore, the increased expression of CD38 during the fever and hypotension phases of HFRS may be related to the activation and migration of lymphocytes. During the polyuria and recovery phases, with the elimination of virus-infected cells, a decrease in the immune response and feedback regulation of lymphocytes may synergistically contribute to a decrease in CD38. Given that CD38 is expressed by immature or activated lymphocytes, plasma cells, monocytes, and most peripheral blood NK cells [11], the level of CD38 remains relatively high during the recovery phase, probably due to the persistence of CD38-expressing cells.

Considering that renal impairment or failure is a significant feature of HFRS. Cr, UA, and urea are important indicators of the degree of kidney damage [27, 28]. We measured the levels of Cr, UA, and urea in serum and investigated the correlation between the level of CD38 and these indices. The results revealed that the expression levels of CD38 in patients with HFRS are proportionally correlated with an increase in Cr, UA, and urea, suggesting that increased levels of CD38 may indirectly reflect the damage done to vascular endothelial cells, as well as aggravated renal impairment during the hypotension and oliguria phases. This is supported by the fact that, with the gradual improvement of the kidney condition and the elimination of infected cells, the level of CD38 also decreased correspondingly. Apparently, the expression of CD38 parallels renal impairment in HFRS, which provides a new parameter for evaluating the progression or severity of HFRS.

CD38 is not only recognized as a differentiation and activation marker of lymphocytes but also plays an important role in regulating the function of T lymphocytes, B lymphocytes, and NK cells [13]. NK cells have been shown to play a significant role in the host response to virus infection [29, 30], and patients with primary immunodeficiencies affecting NK cell numbers and/or NK cell function have been shown to have an altered response to infection [31, 32]. In the present study, a significant increase in NK cells was observed from the fever phase to the hypotension phase, and levels of NK cells at all phases of HFRS were significantly higher than that in controls. This observation is consistent with the earlier observation of rapid expansion and long-term persistence of elevated NK cell counts in humans infected with HTNV [33]. On the other hand, an elevation of plasmablasts (CD3neg CD19low CD20neg CD38hi CD27hi CD138+/- IgA+/-) in patients with hantavirus pulmonary syndrome (HPS), suggests a possible role and relevance of this cell type in the pathogenesis and outcome of HTNV-related disease [34]. Interestingly, an increase in B lymphocytes was also found from the fever phase to the hypotension phase. These findings suggest that both B and NK cells are an important part of the host response to HTNV infection, especially at the early stage.

Given that T cell activation and a change in the $CD8^+$/$CD4^+$T lymphocyte ratio in HFRS patients has been demonstrated, suggesting an important role of T cell-mediated cytotoxicity in the immune response against HTNV infection [7, 35], the levels of $CD8^+$T and $CD4^+$T lymphocytes were also examined in the present study. Indeed, a significant increase in $CD8^+$T lymphocytes was observed from the fever phase to the hypotension phase. Surprisingly, the population of $CD4^+$T lymphocytes decreased during the period of the progression but increased again from the hypotension phase to the polyuria phase. Thus, $CD8^+$T lymphocytes may play a major role in eliminating the virus at the early stage of HFRS, while the function of $CD4^+$T lymphocytes is probably inhibited by the virus by reducing their population.

Interestingly, the increase in $CD8^+$ T and B lymphocytes and NK cells in patients with HFRS follows a trend similar to that of CD38 expression, with $CD8^+$ T lymphocytes and CD38 showing the most similarity in their expression patterns. This phenomenon seems to indicate that the CD38 measured in the present study was mainly present on $CD8^+$

T lymphocytes, although it can be also expressed by immature or activated lymphocytes, plasma cells, monocytes, and most peripheral blood NK cells [12]. Studies have shown that $CD8^+$T lymphocytes play a major role in other severe acute viral diseases, and the activation of $CD8^+$T lymphocytes is the primary response, which is in line with our observation [3]. In addition, effector $CD8^+$ T lymphocytes ($Ki67^+CD38^+HLA\text{-}DR^+$), which contribute a large proportion of the total $CD8^+$ T lymphocyte population, also play an important role in acute hantavirus infection [36].

In conclusion, the increased expression of CD38 in the blood cells from patients with HFRS is in line with the elevated levels of Cr, UA, and urea, implicating its potential value as a clinical marker. Notably, the expression of CD38 is consistent with the progression of HFRS. Although a larger cohort of patients is needed to confirm our results, the findings from this study suggest that CD38 may be a potent indicator for monitoring the progression of HFRS and an effective therapeutic target for treating this disease.

Author contributions H.-D. Zhao: data curation, writing—original draft preparation. Y.-P. Li: visualization, investigation, supervision. W.-W. Zhao: conceptualization, methodology, software. P. Li: software, validation. H.-L. Liu: writing—reviewing, funding acquisition and editing.

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Declarations

Conflict of interest The authors report no conflicts of interest.

Consent to participate Informed consent was obtained from all participants included in the study.

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