Published in final edited form as:

J Clin Virol. 2013 September ; 58(1): 11–17. doi:10.1016/j.jcv.2013.06.027.

Clinical and Molecular Epidemiological Features of Hemorrhagic Fever with Renal Syndrome in Korea over a 10-year Period

Ji Yun Noh¹, Hee Jin Cheong², Joon Young Song², Woo Joo Kim², Ki-Joon Song¹, Terry A Klein³, Sam H. Lee³, Richard Yanagihara⁴, and Jin-Won Song¹

¹Department of Microbiology, College of Medicine, Korea University, Seoul 136-705, Korea

²Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, Korea University, Seoul 152-703, Korea

³Force Health Protection and Preventive Medicine, 65th Medical Brigade, U.S. Army MEDDAC-Korea, Unit 15281, APO AP 96205-5281

⁴Departments of Pediatrics and Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii 96813

Abstract

Background—Laboratory diagnosis of hemorrhagic fever with renal syndrome (HFRS), an infectious disease caused by rodent-borne hantaviruses in Asia and Europe, depends primarily on serological methods. Since the advent of such serodiagnostic tests, few reports are available about the clinical and molecular epidemiological features of HFRS.

Objectives—To investigate the epidemioclinical features of HFRS treated at a tertiary-care teaching hospital in Seoul over a 10-year period.

Study design—Medical records of HFRS patients, visited to a tertiary-care teaching hospital during February 2002 to February 2012, were reviewed. Sera from patients were tested for Hantaan virus (HTNV) and Seoul virus (SEOV) RNA using RT-PCR.

Results—Among 35 HFRS patients (mean age was 44.2 ± 14.7 years), 29 were male (82.9%). Acute renal failure developed in 27 patients (77.1%), and 12 patients (34.3%) were admitted to the intensive care unit (ICU). Conjunctival injection (OR 10.32, 95% CI 1.09–97.77, $P = .04$) and initial serum albumin less than 3 g/dL (OR 22.83, 95% CI 1.45–359.93, $P = .03$) were risk factors for ICU admission. Of 35 acute-phase sera, 11 (31.4%) were positive for HTNV RNA. None were positive for SEOV RNA.

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Correspondence: Jin-Won Song, M.D., Ph.D., Department of Microbiology, College of Medicine, Korea University, Anam-dong 5-ga, Seongbuk-gu, Seoul 136-705, Korea, Tel: 82-2-920-6408, Fax: 82-2-923-3645, jwsong@korea.ac.kr.

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Competing interests: None declared

Conclusions—HFRS was characterized by the clinical triad of fever, renal insufficiency and gastrointestinal symptoms. Conjunctival injection and serum albumin level were related to severity. Large scaled multi-center study is needed to enhance an insight to epidemioclinical characteristics of HFRS in Korea.

Keywords

Hantaan virus; Hantavirus; Hemorrhagic fever with renal syndrome; Korea

Background

Hemorrhagic fever with renal syndrome (HFRS) is a clinical syndrome characterized by fever, thrombocytopenia, and acute renal insufficiency. Pathological changes are typical of acute interstitial nephritis.¹ Following the isolation of Hantaan virus (HTNV), the prototype virus of HFRS, from lung tissues of the striped-field mouse (*Apodemus agrarius*) in Korea in 1976,² several other hantavirus species, including Seoul virus (SEOV),³ Puumala virus (PUUV),^{4, 5} and Dobrava/Belgrade virus (DOBV/BGDV)⁶ have been found to cause HFRS in Asia and Europe.

Historically, HTNV has accounted for approximately 70% of the HFRS cases in Korea, followed by SEOV in 20%. The remaining 10% of HFRS cases are presumably caused by other hantaviruses, such as Soochong virus (SOOV)⁷ and Muju virus (MUJV),⁸ harbored by the Korean field mouse (*Apodemus peninsulae*) and the royal vole (*Myodes regulus*), respectively, but definitive serological or molecular evidence is unavailable. Recently, genetically distinct hantaviruses, designated Imjin and Jeju viruses, have been detected in crocidurine shrews in Korea.^{9, 10} However, whether or not HFRS cases may be caused by these shrew-borne hantaviruses remains unclear.

Based on reports from the Korea Centers for Disease Control and Prevention, the annual number of HFRS cases in Korea ranges from 300 to 500.¹¹ However, there are few recent studies on the clinical and molecular epidemiological trends of HFRS in Korea, possibly because of the availability of rapid serodiagnostic tests.

Objectives

In this report, we aimed to present the epidemioclinical features of HFRS patients treated at a tertiary-care teaching hospital in Seoul over a 10-year period.

Study design

Patients and Data Collection

Medical records of HFRS patients who were treated at Korea University Guro Hospital, a 900-bed tertiary-care teaching hospital located in southwestern Seoul, between February 2002 and February 2012, were reviewed retrospectively. The diagnosis of HFRS was based on clinical findings and confirmed by the detection of anti-HTNV IgG antibodies in a 1:32 dilution of serum, using the indirect immunofluorescent antibody (IFA) test. In the event of a negative IFA test result in the face of clinical findings suggestive of HFRS, the IFA test

was repeated with paired sera collected during the convalescent phase to determine seroconversion.

Molecular Analysis

RT-PCR for HTNV and SEOV was performed as described elsewhere with modification.^{12, 13} Briefly, total RNA was extracted from HFRS patient sera using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany), then reverse transcribed into cDNA using M-MLV Reverse Transcriptase (Promega, Madison, WI). Viral sequences were amplified by PCR, using oligonucleotide primers designed for the partial M segment: outer primer set for HTNV, 5'-TGGGCTGCAAGTGC-3', 5'-ACATGCTGTACAGCCTGTGCC-3'; inner primer set for HTNV, 5'-TGGGCTGCAAGTGCATCAGAG-3', 5'-ATGGATTACAACCCAGCTCG-3' (373bp); outer primer set for SEOV, 5'-GATATGAATGATTGYTTTGT-3', 5'-CGATCAGGGTCTYTCCA-3'; inner primer set for SEOV, 5'-GATATGAATGATTGYTTTGT-3', 5'-GCAAAGTTACATTTYTTCCT-3' (242bp). PCR cycling consisted of initial denaturation at 95°C for 4 minutes, followed by 6 cycles of denaturation at 94°C for 30 seconds, annealing at 37°C for 30 seconds, and elongation at 72°C for 1 minute, 32 cycles of denaturation at 94°C for 30 seconds, annealing at 42°C for 30 seconds, and elongation at 72°C for 1 minute, and final extension at 72°C for 5 minutes. DNA sequences were determined in both directions using the Applied Biosystems Automatic Sequencer ABI 3730xl and ABI Prism® BigDye Terminator v3.1 sequencing system (Applied Biosystems, Foster City, CA). Before testing of samples, the primer set was tested with HTNV 76–118 and SEOV 80–39 strain as positive controls and was verified also. For phylogenetic analysis, the neighbor-joining (N–J) and maximum likelihood methods were employed.¹⁴ Representative hantaviruses, including HTNV isolates from China and Russia and HTNV sequences from *Apodemus* rodents captured in Korea were included in the phylogenetic analysis.^{15, 16} Genetic distances were computed using PAUP version 4.0b and topologies were evaluated by bootstrap analysis of 1000 iterations.¹⁴

Statistical Analysis

All statistical analyses were carried out using SPSS 12.0 (SPSS Inc., Chicago, IL). Data were expressed as mean $\pm$ standard deviation for continuous variables and count with percent for categorical variables. Mann-Whitney test was used to analyze continuous variables and Fisher's exact test was adopted to analyze categorical variables. Variables with *P* value $<.1$ were moved to multivariate logistic regression model and analyzed and a *P* value of $<.05$ was considered statistically significance.

Results

Demographic Findings

There were 35 HFRS patients between February 2002 and February 2012. The mean age of patients was 44.2 ± 14.7 years and 29 patients were male (82.9%). Most cases occurred in November (11, 31.4%) and December (5, 14.3%) (Figure 1). No cases occurred between June and August. Most patients (31, 88.6%) were previously healthy without underlying chronic diseases, except for four patients (11.4%) who had diabetes mellitus. A history of

outdoor activities, including occupational exposure, was found in more than half (18, 51.4%). Only one patient (2.9%) had previously received the HTNV vaccine (Hantavax®), prepared from HTNV-infected suckling mouse brain.

Clinical Manifestations and Disease Outcome

The clinical and initial laboratory findings of the patients are shown in Tables 1 and 2. The mean time from symptom onset to hospital visit was 5.1 ± 2.7 days (range 1–14). A history of fever was the most frequent symptom (34, 97.1%) and 16 (45.7%) patients were febrile ($> 37.8^{\circ}\text{C}$) at the time of hospital visit. Myalgia (23, 65.7%) and headache (18, 51.4%) were common, as were gastrointestinal symptoms (29, 82.9%): nausea (23, 65.7%), vomiting (15, 42.9%), diarrhea (16, 45.7%), and abdominal pain (13, 37.1%). Abdominal tenderness was observed in 15 patients (42.9%). Conjunctival injection was detected in 8 patients (22.9%). Microscopic hematuria was found in 17 patients (48.6%) and proteinuria (more than 1+ by urine analysis) developed in 29 patients (82.9%). Oliguria (hourly urine output of <0.5 mL/Kg) was documented in 12 patients (34.3%), and diuresis (urine output > 3 L/day) in 26 patients (74.3%) during the course of disease.

Acute renal failure (ARF) developed in 27 patients (77.1%), and renal replacement therapy was required in five patients (14.3%). Twelve patients (34.3%) were admitted to the ICU, and the mortality was 2.9% (one death). Hypotension (systolic blood pressure <90 mmHg) was documented in only one patient. The mean hospital stay was 11.7 ± 5.3 days. Multivariate analysis showed that the conjunctival injection (OR 10.32, 95% CI 1.09–97.77, $P = .04$) and initial albumin of less than 3 g/dL (OR 22.83, 95% CI 1.45–359.93, $P = .03$) were risk factors for ICU admission (Table 3).

Molecular Epidemiology

Of the 35 sera with anti-HTNV IgG antibodies, 11 (31.4%) sera, collected 5.2 ± 2.7 days after symptom onset (range 2–10), were positive for HTNV RNA by RT-PCR. None of the samples were positive for SEOV RNA. Nine sera (9/26, 34.6%) were positive among the samples collected within 7 days from symptom onset, and the PCR-positive rate was 25.0% (2/8) in samples collected from 1 to 2 weeks of symptom onset. There were no significant differences in time to blood sampling from symptom onset (5.2 ± 2.7 vs. 6.6 ± 3.6 days, $P = .15$) and time to hospital visit from symptom onset (4.7 ± 2.4 vs. 5.3 ± 2.9 days, $P = .52$) between of RT-PCR-positive patients and RT-PCR-negative groups. RT-PCR-positive HFRS patients showed higher rate of ARF (100% vs. 66.7%, $P = .03$) and ICU admission (63.6% vs. 20.8%, $P = .02$) than RT-PCR-negative patients. Table 4 shows the characteristics of the 11 RT-PCR-positive HFRS patients. Five patients had a history of outdoor activity prior to illness and specific sites were identified in four patients: KU 02-1993, KU 04-1469, KU 08-327 and KU 10-1359. Phylogenetic analysis confirmed that the viral sequences belonged to the HTNV group (Figure 2).

Discussion

As reported previously, most of the HFRS cases in this study occurred in late autumn and early winter. Peak incidence has been associated with the breeding season of the reservoir

rodent host and increased infectious excreta in the environment.¹⁷ Dry weather during these seasons also contributes to respiratory transmission of hantaviruses to humans. National report during 1996–2005 showed a low number of hantavirus-seropositive HFRS cases between June and August (119/1,415, 8.4%).¹⁷ In our study, there were no cases during the summer months. The preponderance of male and mean age of patients might reflect the higher risk associated with occupational and recreational exposure to the outdoor environment.

Previously, Kim and Han attributed the 74% of failure rate of recognizing HFRS as the cause of ARF on admission to the absence of the five classical sequential phases of fever, shock, oliguria, diuresis, and convalescence.¹⁸ That is, while most HFRS patients exhibit the febrile and diuretic phases, shock and oliguria are noted less frequently.¹⁹ In fact, abdominal pain is oftentimes more common. Frequency of abdominal pain was 47.7%–86% in HFRS patients and there is a report that all patients infected HTNV and SEOV complained of at least one of the gastrointestinal symptoms: abdominal pain, nausea, vomiting, and diarrhea.^{18, 20–22} Consequently, it has been suggested that the clinical diagnosis of HFRS should be based on the triad of fever, renal insufficiency, and gastrointestinal symptoms.¹⁸ In our study, 29 (82.9%) patients complained at least one gastrointestinal symptom including abdominal pain, abdominal discomfort, nausea, vomiting, and diarrhea. Such a clinical triad would have correctly diagnosed 62.9% (22/35) serologically confirmed HFRS patients.

Various extrarenal complications have been reported in HFRS patients. Besides pulmonary complications, pancreatobiliary and cardiovascular complications were not unusual.²¹ In addition, cochlear hemorrhage, abducens nerve palsy, severe hyponatremia associated with hypopituitarism, compartment syndrome, and hemophagocytic lymphohistiocytosis complicated with HFRS were reported in Korea.^{21, 23, 24} In this study, four patients (11.4%) had acalculous cholecystitis and three had pancreatitis (8.6%). Cerebrospinal fluid analysis was performed in three patients due to persistent headache. However, there was no evidence for the central nervous system infection.

Conjunctival injection and less than 3.0 g/dL of serum albumin were risk factors for ICU admission. Comparing to other studies in which the frequency of conjunctival injection was 68%–74%^{20–22}, only eight patients (22.9%) exhibited this finding. In a previous study, hypoalbuminemia was associated with HFRS disease severity.²⁵ The mechanism of hypoalbuminemia in HFRS is multifactorial: increased catabolism of protein, increased vascular permeability followed by vascular leakage of serum protein, urinary loss of protein, decreased intestinal absorption of protein, and decreased synthesis of albumin due to hepatic dysfunction.²⁵ Disease severity was not associated with the level of creatinine in this study.

HTNV RT-PCR positivity was 31.4% (11/35) in this study. By contrast, in a one-year prospective study in China, 131 of 151 (86.8%) serum samples from HFRS patients were positive for hantavirus RNA by RT-PCR.²² In another study in Russia during the winter of 2006–2007, the RT-PCR positivity rate was 50% (5/10) in the patients with DOBV infection.²⁶ The comparatively lower RT-PCR positivity rate in our study may have been due to the retrospective design, and possibly RNA degradation despite storage at –70°C.

Although SEOV causes HFRS in urban setting,³ we could not detect SEOV in this study, and all 11 RT-PCR-positive HFRS patients were infected with HTNV. Clinical findings of SEOV infection appear to be milder and less typical than HTNV infection.²² Liver injury is more prominent than renal involvement and hemorrhagic manifestation in SEOV infection.^{22, 27} Therefore, physician may have overlooked the diagnosis of HFRS in favor of self-limiting viral hepatitis. Moreover, since this study was restricted to patients treated in a tertiary-care teaching hospital, selection bias might have excluded patients with mild HFRS.

The oligonucleotide primers were designed to also detect SOOV, but none of the RT-PCR-positive samples showed SOOV sequences. Similarly, no molecular evidence was found for MUJV, a hantavirus detected in the royal vole in Korea, which is antigenically related to PUUV, the causative agent of nephropathia epidemica. Further studies are warranted to determine if SOOV and MUJV account for any of the HFRS burden in Korea.

This study had some limitations. Because of the retrospective design and the total dependence on the available medical records, detailed information about certain key parameters, such as outdoor exposure, was missing. Serodiagnostic examination was conducted by anti-HTNV IgG IFA test solely. Anti-HTNV IgG IFA test could detect anti-SEOV IgG also because of their cross-reactivity, however, we did not separate HFRS cases into HTNV infections and SEOV infections. Moreover, the study was conducted in single medical center, so the results may not be representative of nationwide trends. Nevertheless, these data provide valuable clinical clues about HFRS over a 10-year period in Korea. Large scaled multi-center study is required to enhance an insight to HFRS in Korea.

Acknowledgments

Funding: This work was supported in part by the National Institute of Allergy and Infectious Diseases, National Institutes of Health [R01AI075057] and the Armed Forces Health Surveillance Center, Division of Global Emerging Infections Surveillance and Response System [AFHSC-GEIS], Silver Spring, MD.

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Figure 1. HFRS cases treated in a tertiary-care teaching hospital in Korea (A) during each year between 2002 and 2012 and (B) during each month over the 2002–2012 period.

Figure 2.

(A) Phylogenetic tree generated by the neighbor-joining method, based on a 320-nucleotide region of the M segment amplified from sera of HFRS patients (shown in bold). The GenBank accession numbers of sequences from HFRS patients are as follows: KU 02-1993, JX177435; KU 03-1223, JX177436; KU 03-1321, JX177437; KU 04-1469, JX177438; KU 04-1536, JX177439; KU 06-1308, JX177440; KU 07-197, JX177441; KU 07-1481, JX177442; KU 08-327, JX177443; KU 09-13, JX177444; KU 10-1359, JX177445; KU 10-1372, JX177446. GenBank accession numbers of reference hantavirus sequences are: Amur virus (AMRV) H5, AB127993; AMRV JilinAP06, EF371454; Soochong virus (SOOV) 1, AY675353; SOOV2, DQ056293; SOOV3, DQ056294; SOOV4, DQ056295; Hantaan virus (HTNV) 76-118, Y00386; HTNV Lee, D00377; HTNV Galkino AA57 2002, AB620032; HTNV z251, GQ120966; HTNV CGHu3, EU363818; HTNV TJ16, EU074672; Dobrava virus (DOBV), AJ410616; Seoul virus (SEOV) 80-39, S47716; Jeju virus (JJUV), HQ834696; Andes virus (ANDV), AF291703; New York virus (NYV), U36082; Sin Nombre virus (SNV), L37903; Muju virus (MUJV), EF198413; Puumala virus (PUUV), NC_005223; Prospect Hill virus (PHV), X55129; Imjin virus (MJNV) 05-11, EF641798; Thottapalayam virus (TPMV), DQ825771. (B) The capture sites of rodents of which sequences were entered into phylogenetic tree were shown on the map of South Korea. Identified travel sites of HFRS patients (shown in bold) are also presented. KU 04-1469 and Aa08-555 Suwon were from Gyeonggi-do, and KU 08-327, KU 10-1359 and HTNV NS 94-20 were from Chungcheongnam-do (map adopted from National Geographic Information Institute, Korea, www.ngii.go.kr).

Table 1**Clinical Manifestations and Outcome of HFRS Patients**

Clinical features	N (%)
Initial body temperature (°C), mean $\pm$ SD	37.7 $\pm$ 1.0 (range 36.2–40.0)
Time from symptom onset to hospital visit (day)	5.1 $\pm$ 2.7 (range 1–14)
General	
Fever at hospital visit ($> 37.8^{\circ}\text{C}$)	16 (45.7)
History of fever	34 (97.1)
Malaise	19 (54.3)
Myalgia	23 (65.7)
Headache	18 (51.4)
Dizziness	4 (11.4)
Cough	5 (14.3)
Dyspnea	4 (11.4)
Orbital pain	3 (8.6)
Arthralgia	2 (5.7)
Rash	2 (5.7)
Abdominal	
Anorexia	24 (68.6)
Nausea	23 (65.7)
Vomiting	15 (42.9)
Diarrhea	16 (45.7)
Abdominal pain	13 (37.1)
Abdominal discomfort	6 (17.1)
Abdominal tenderness	15 (42.9)
Renal	
Oliguria ($< 0.5 \text{ mL/Kg/hr}$)	12 (34.3)
Low back pain	5 (14.3)
Bleeding	
Conjunctival injection	8 (22.9)
Epistaxis	2 (5.7)
Gingival hemorrhage	1 (2.9)
Petechiae	1 (2.9)
Skin oozing	2 (5.7)
Gastrointestinal bleeding	0 (0)
Hemoptysis	0 (0)
Macroscopic hematuria	2 (5.7)
Complication	
Pulmonary edema	7 (20.0)
Pleural effusion	8 (22.9)
Pericardial effusion	1 (2.9)
Pancreatitis	3 (8.6)

Clinical features	N (%)
Acalculous cholecystitis	4 (11.4)
Acute renal failure	27 (77.1)
Treatment and Outcome	
Renal replacement therapy	5 (14.3)
Vasopressor infusion	2 (5.7)
Mechanical ventilation	1 (2.9)
ICU admission	12 (34.3)
Hospital day	11.7 ± 5.3 (range 4–24)
Mortality	1 (2.9)

Abbreviation: ICU, intensive care unit.

Table 2

Initial Laboratory Findings of HFRS Patients

Parameter	Value (range)	Normal range
Hemoglobin (g/dL), mean $\pm$ SD	15.5 $\pm$ 2.3 (range 10.7–19.5)	11.7–16.1
WBC (/ μ L)	12,562.6 $\pm$ 7,932.7 (2,300–35,800)	4,500–11,000
Platelet ($\times$ 1,000/ μ L)	62.5 $\pm$ 50.0 (11–209)	150–400
Blood urea nitrogen (mg/dL)	34.6 $\pm$ 24.2 (4.6–88.8)	8.0–23.0
Creatinine (mg/dL)	2.8 $\pm$ 2.0 (0.6–6.8)	0.6–1.1
Protein (g/dL)	6.3 $\pm$ 0.7 (4.5–7.8)	6.0–8.0
Albumin (g/dL)	3.4 $\pm$ 0.5 (2.4–4.6)	3.2–4.6
AST (IU/L)	323.6 $\pm$ 996.7 (24–5,970)	5–45
ALT (IU/L)	137.6 $\pm$ 193.5 (21–1,037)	10–40
ESR (mm/hr)	29.1 $\pm$ 27.4 (2–100)	0–20
C-reactive protein (mg/L)	54.9 $\pm$ 40.3 (2.1–157.0)	0–3
Lactate dehydrogenase (IU/L)	1,331.0 $\pm$ 940.5 (321–5,112)	263–450
Creatine phosphokinase (IU/L)	732.5 $\pm$ 1,137.4 (35–4,613)	32–269
Glucose (mg/dL)	129.1 $\pm$ 36.4 (72–225)	74–106
Sodium (mmol/L)	134.1 $\pm$ 6.0 (118–146)	136–145
Potassium (mmol/L)	4.0 $\pm$ 0.6 (3–6)	3.5–5.3
Urine specific gravity	1.017 $\pm$ 0.009 (1.005–1.050)	1.005–1.030

Abbreviations: AST, aspartate aminotransferase; ALT, alanin aminotransferase; ESR, erythrocyte sedimentation rate.

Table 3

Risk Factors for ICU Admission in HFRS Patients

	General ward and outpatient care (N=23)		ICU admission (N=12)	<i>p^a</i>	OR (95% CI)	<i>p^b</i>
Conjunctival injection						
Yes	2 (25.0)		6 (75.0)	.01	10.32 (1.09–97.78)	.04
No	21 (77.8)		6 (22.2)			
Blurred vision						
Yes	2 (50.0)		2 (50.0)	.60		
No	21 (67.7)		10 (32.3)			
Pulmonary edema						
Yes	3 (42.9)		4 (57.1)	.20		
No	20 (71.4)		8 (28.6)			
Proteinuria						
Yes	18 (62.1)		11 (37.9)	.64		
No	5 (83.3)		1 (16.7)			
Microscopic hematuria						
Yes	8 (47.1)		9 (52.9)	.04	3.79 (0.46–31.45)	.22
No	15 (83.3)		3 (16.7)			
Oliguria						
Yes	6 (50.0)		6 (50.0)	.26		
No	17 (73.9)		6 (26.1)			
Initial creatinine						
3.0 mg/dL	8 (61.5)		5 (38.5)	.73		
< 3.0 mg/dL	15 (68.2)		7 (31.8)			
Initial WBC count						
20,000 / μ L	1 (20.0)		4 (80.0)	.04	2.16 (0.10–46.27)	.62
< 20,000 / μ L	22 (73.3)		8 (26.7)			
Initial albumin						
< 3.0 g/dL	1 (16.7)		5 (83.3)	.01	22.83 (1.45–359.93)	.03
3.0 g/dL	22 (75.9)		7 (24.1)			

Abbreviations: ICU, intensive care unit; OR, odds ratio; CI, confidence interval; WBC, white blood cell.

d ; drawn by univariate analysis
 b ; drawn by multivariate logistic regression

Table 4
Clinical Characteristics of 11 HFRS Patients with Detectable HTNV RNA in Serum by RT-PCR

	02-1993	03-1223	03-1321	04-1469	04-1536	06-1308	07-1481	08-327
Sex/Age	M/37	M/42	M/43	M/56	M/50	M/56	M/26	M/45
Year	2002	2003	2003	2004	2004	2006	2007	2008
Month	Nov	Nov	Dec	Nov	Dec	Oct	Dec	May
Comorbidity	–	–	DM	–	DM	–	–	–
Outdoor activity	Fishing	–	–	Agriculture	Fishing	–	–	Fishing
IFA test result	w+	3+	1+	1+	2+	w+	1+	2+
Day from symptom onset to hospital visit	5	4	4	10	3	2	7	3
Duration of fever (day)	5	6	6	10	6	6	9	3
Conjunctival injection	–	Yes	–	Yes	–	–	–	Yes
Minimum platelet ($\times 1,000/\mu\text{L}$)	11	18	33	25	40	27	22	34
Peak WBC count $/\mu\text{L}$	18,500	24,200	20,900	22,600	24,100	13,600	11,500	32,900
Peak BUN (mg/dL)	94.1	96.7	40.2	63.2	61.5	31.4	21	49.3
Peak Cr (mg/dL)	7.1	11.3	2.3	7.8	5.9	3.7	4.5	7.2
Initial serum albumin (g/dL)	3.1	3.8	2.8	3.4	3.6	4.0	4.1	2.5
Admission	General ward	ICU	ICU	ICU	ICU	General ward	ICU	ICU
Complication	ARF	ARF	ARF, pleural effusion	ARF, pleural effusion, pulmonary edema	ARF, cholecystitis, pancreatitis	ARF	ARF	ARF, cholecystitis, pericardial effusion
Hospital day	8	19	13	10	21	15	12	23
Outcome	recovered	recovered	recovered	recovered	recovered	recovered	recovered	recovered

Abbreviations: DM, diabetes mellitus; IFA, immunofluorescent antibody; WBC, white blood cell; BUN, blood urea nitrogen; Cr, creatinine; ICU, intensive care unit; ARF, acute renal failure.