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Acute Kidney Injury in Patients with Hemorrhagic Fever with Renal Syndrome Caused by Hantaan Virus: Comparative Evaluation by RIFLE and AKIN Criteria

Dan Han,[1] Zhengwen Liu,[1] Qunying Han,[1] Zhu Li,[1] Guoyu Zhang,[1] Jianming Qiu,[2] Sai Lou,[1] Na Li,[1] Yawen Wang,[1] and Man Li[1]

Abstract

Acute kidney injury (AKI) is one of the most prominent characteristics of hemorrhagic fever with renal syndrome (HFRS) caused by Hantaan virus. The present study evaluated the incidence and severity of AKI classified by both the RIFLE and AKIN criteria in 120 HFRS patients at 48 h and 1 week of the patient admission. The agreements between RIFLE and AKIN and RIFLE and AKIN defined by serum creatinine (AKINc and RIFLEc) were examined by Kappa statistics. AKI occurred in 79.2% and 82.5% at 48 h and in 84.2% and 89.2% at 1 week of admission by RIFLE and AKIN criteria, respectively. RIFLE and AKIN showed very good agreement in classifying AKI at 48 h and 1 week of admission ($\kappa > 0.900$). RIFLE and RIFLEc and AKIN and AKINc at 48 h and 1 week of admission had almost perfect agreement ($\kappa > 0.900$). The classifications of RIFLE and RIFLEc and AKIN and AKINc at 48 h and 1 week were in good agreement ($\kappa > 0.650$). AKI classifications by RIFLE and AKIN were associated with mortality, occurrence of complications, and length of hospital stay. We conclude that AKI occurs in nearly 90% of HFRS patients during the disease course. RIFLE and AKIN classify AKI in HFRS with similar sensitivity. RIFLEc and AKINc may be used as alternatives of standard RIFLE and AKIN in the settings of general wards. The AKI classifications defined at 48 h of admission have predictive value for HFRS disease progression and severity.

Key Words: Acute kidney injury—AKIN—Hantaan virus—HFRS—RIFLE.

Introduction

Hantaviruses, members of genus Hantavirus of the family Bunyaviridae, cause two human febrile diseases: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (Schmaljohn and Hjelle 1997, Bi et al. 2008). HFRS caused by hantaviruses includes a severe form HFRS, previously also known as epidemic hemorrhagic fever, mainly prevailing in Asia, and a mild form HFRS, known as nephropathia epidemica, mainly prevailing in Europe (Schmaljohn and Hjelle 1997). HFRS is a severe public health problem in China (Chen et al. 1986, Zhang et al. 2004, Bi et al. 2008). Among the 31 provinces, municipalities, and autonomous regions in mainland China, HFRS is endemic in 28 (Song 1999, Zhang et al. 2004, Yan et al. 2007). Hantaan virus (HTNV) and Seoul virus (SEOV) are the two etiologic agents of HFRS in China and they have epidemiologically specific geographical distribution (Chen et al. 1986, Song 1999, Zhang et al. 2004). Clinically, HTNV causes more severe disease than SEOV (Schmaljohn and Hjelle 1997, Song. 1999). The patients with HFRS manifest abrupt onset of fever, hemorrhage, and renal dysfunction. The typical cases usually experience febrile, hypotensive, oliguric, polyuric, and convalescent five consecutive clinical stages (Schmaljohn and Hjelle 1997, Bi et al. 2008). The disease severity of HFRS varies greatly from a mild self-limited febrile disease to severe disease with shock, massive hemorrhage, acute renal failure, and even death (Schmaljohn and Hjelle 1997, Bi *et al*. 2008). Until now, no objective classification criteria for the disease severity of HFRS are available. Acute kidney injury (AKI) is one of the most prominent and characteristic manifestations of the HFRS disease, especially in the severe form HFRS (Schmaljohn and

[1]Department of Infectious Diseases, First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an, Shaanxi Province, People's Republic of China.
[2]Department of Microbiology, Molecular Genetics, and Immunology, University of Kansas Medical Center, Kansas City, Kansas.

Hjelle 1997, Kim et al. 2007, Bi *et al*. 2008). Therefore, to implement objective classification criteria taking the degree of AKI into account may be helpful for the evaluation of disease severity and the prediction of patient prognosis of HFRS.

Although AKI is a common clinical problem encountered in the hospital settings with poor outcomes, especially in critically ill patients, the diagnosis and definition had no uniform criteria until recent years (Mehta and Chertow 2003, Schrier et al. 2004). The Acute Dialysis Quality Initiative (ADQI) group proposed a classification for AKI, the RIFLE (risk, injury, failure, loss of kidney function, and endstage kidney disease) classification, to standardize the diagnosis and classification of AKI in 2004 (Bellomo et al. 2004). The RIFLE classification has been evaluated in a number of clinical studies of critically ill patients with AKI (Ahlström et al. 2006, Hoste et al. 2006, Lin et al. 2006, Uchino et al. 2006, Ostermann and Chang 2007, Bagshaw et al. 2008). These criteria have been generally demonstrated to have clinical relevance for the diagnosis of AKI, the classification of AKI severity, the monitoring of AKI progression, and the prediction of mortality. However, the RIFLE classification is considered to have two shortcomings: one is the inaccuracy in reflecting the renal functional impairment based on prior knowledge of the baseline creatinine, and the other is the uncertainty of the influence requiring renal replacement therapy (RRT) on RIFLE stages. Therefore, the Acute Kidney Injury Network (AKIN) group proposed a classification for AKI based on RIFLE with some modifications, to increase the sensitivity and specificity of AKI diagnosis, in 2007 (Mehta et al. 2007). The comparisons of AKIN staging system and RIFLE classification system have been performed in several studies, showing no significant differences between the two systems (Bagshaw et al. 2008, Lopes et al. 2008, Joannidis et al. 2009, Chang et al. 2010).

In this study, we analyzed the data from a sample of patients with HFRS caused by HTNV, which is associated with the severe form of HFRS, to evaluate the incidence and severity of AKI defined by both the RIFLE and AKIN criteria and the relationship of AKI categories with the disease severity and patient prognosis. In addition, the agreement between RIFLE and AKIN and RIFLE and AKIN defined by serum creatinine (AKINc and RIFLEc) was examined to see whether the AKINc and RIFLEc had equivalent sensitivity and specificity with the standard criteria to define AKI in the setting of general wards. The agreement of RIFLE, AKIN, RIFLEc, and AKINc performed at 48 h and 1 week of the patient admission was also examined to see whether the early definition of AKI by RIFLE and AKIN systems was predictive of the disease severity and prognosis.

Patients and Methods

Patients and data collection

This was a retrospective study including patients with HFRS admitted to the First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, from January 2008 to December 2009. This hospital is a tertiary-care hospital located in Xi'an, northwest China. The patients were from the surrounding areas of Xi'an, where the severe form of HFRS associated with HTNV is epidemic. *Post hoc* analysis was performed on the accumulated data of patients with HFRS during the mentioned period. The diagnosis of HFRS in all the patients was confirmed by the serological positivity tested for HTNV-specific IgM antibody. The following patients were excluded: pediatric patients (age <18 years); patients with chronic kidney diseases, including chronic uremic patients undergoing RRT; patients with any other disorders that may cause kidney injury, such as hypertension and diabetes; and patients with other infections such as hepatitis B, hepatitis C, and human immunodeficiency virus infection. Patients whose hospital stay was <24 h were also excluded. Demographic, clinical, and laboratory data, including age, sex, clinical diagnosis, stages of the disease, main clinical manifestations, presence of complications associated with HFRS, RRT, routine blood and urine tests, biochemical kidney and liver functions, and urine output were retrieved from all the patients.

AKI definitions

RIFLE, AKIN, RIFLEc, and AKINc classification was performed at two time-points, 48 h and 1 week, respectively, after hospital admission of the patients. The RIFLE system proposed by ADQI group uses individual criteria for serum creatinine (Scr) levels and urine output. Patients are classified into three severity categories (risk, injury, and failure) and two clinical outcome categories (loss and end-stage renal disease). The AKIN criteria classify AKI into three stages of severity: Stages 1, 2, and 3. The AKIN classification differs from the RIFLE classification as follows: it reduces the need for baseline Scr but requires at least two creatinine values within 48 h. AKIN Stage 1 is similar to RIFLE risk but includes abrupt (within 48 h) reduction in kidney function (increase in Scr $\geq$0.3 mg/dL [$\geq$26.4 μmol/L]). Injury and failure are the same as Stages 2 and 3, respectively. Stage 3 also includes patients who need RRT in any stage. Two outcome classes, loss and end-stage kidney disease, were omitted.

Baseline Scr concentration was measured first during hospitalization. Most patients had abnormal Scr level at admission. The Modification of Diet in Renal Disease (MDRD) equation ($GFR = 186 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (female \times 0.742) \times (male \times 1)$) was applied for patients who were admitted directly to the hospital, and their Scr concentrations at admission were abnormal as recommended (assuming a lower limit of normal baseline GFR of 75 mL/min) (Bellomo et al. 2004) to estimate baseline Scr values.

Because only a cumulative 24-h urine output was recorded and we did not have patient weights, we used the description by Bagshaw et al. (2008), in which a minor modification of the RIFLE and AKIN urine output criteria was applied, assuming an average patient weight of 70 kg, and AKI was classified as <35 mL/h (Risk or Stage 1), <21 mL/h (Injury or Stage 2), or <4 mL/h (Failure or Stage 3). Patients using RRT were defined as Stage 3 in AKIN classification irrespective of the frequency, duration, and type of the therapy. The worst RIFLE or AKIN category according to either Scr or urine output criteria and the worst RIFLEc and AKINc according to Scr criteria were performed at 48 h and 1 week of admission for analysis (Bellomo et al. 2004). The criteria of RIFLE and AKIN for AKI used in this study are summarized in Table 1.

Laboratory determinations

Routine blood test was performed using Sysmex XT-1800i Hematology Analyzer (Sysmex Corporation, Wakinohama-Kaigandori, Chuo-ku, Kobe, Japan). Biochemical renal and

Table 1. Definition and Classification/Staging for Acute Kidney Injury in Terms of RIFLE, AKIN, and Urine Output Criteria

RIFLE Scr criteria		*AKIN Scr criteria*		*UO criteria*
Risk	Increase in Scr $\geq$1.5$\times$baseline	Stage 1	Increase in Scr $\geq$0.3 mg/dL ($\geq$26.4 μmol/L) or increase $\geq$1.5$\times$baseline	$<$35 mL/h
Injury	Increase in Scr $\geq$2.0$\times$baseline	Stage 2	Increase in Scr $\geq$2$\times$baseline	$<$21 mL/h
Failure	Increase in Scr $\geq$3.0$\times$baseline	Stage 3	Increase in Scr $\geq$3$\times$baseline or Scr $\geq$4.0 mg/dL (354 μmol/L) with an acute rise of at least 0.5 mg/dL (44 μmol/L) or initiation of RRT	$<$4 mL/h

AKIN, acute kidney injury network; RIFLE, risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure; RRT, renal replacement therapy; Scr, serum creatitine; UO, urine output.

liver functions were determined using Olympus AU5400 automatic biochemistry Analyzer (Olympus Optical, Tokyo, Japan).

Clinical management

The clinical management of the patients was implemented according to the suggestions of Prevention and Treatment Strategy of HFRS issued by the Ministry of Health, P.R. China (1988). Briefly, intravenous fluids were administered to all HFRS patients depending on their volume status referred to disease stages, hemoglobin, and urine output. Patients at febrile stage routinely received antiviral therapy with ribavirin. The volume of fluid infusion was $\sim$1000–1500 mL per 24 h for patients at febrile stage. The volume of fluid infusion might be increased if the volume of body fluid loss was large. Patients with hypotension or shock were administered rapid blood volume expanders including balanced salt fluid and colloid fluid such as fresh frozen plasma and human albumin. Stress–dose steroid therapy was administered for infective shock. Other treatments included appropriate use of 5% bicarbonate fluid for acidosis and vasoactive drugs such as dopamine for blood pressure stabilization. In patients developing signs of acute renal failure (increase in Scr and/or oliguria), blood volume expansion with albumin or low dose of 20% mannitol (100–125 mL) was given to improve renal function and increase urine volume. If oliguria persisted after inadequate blood volume had been corrected or excluded, a diuretic, usually furosemide, was prescribed. If acute renal failure was severe or progressive and measures to improve renal function had been unsuccessful, RRT was implemented. The management in patients at polyuric stage was mainly the maintenance of water–electrolyte balance. For patients with massive hemorrhage, appropriate use of platelets and coagulation factors was implemented. In all patients, the development of bacterial and fungal infections during hospitalization was investigated with appropriate diagnostic methods and cultures. Patients were started on appropriate empiric antibiotic or antifungal therapy intravenously once a diagnosis of infection was established.

Statistical analysis

Data were analyzed using SPSS16.0 for Windows (SPSS, Chicago, IL). Quantitative data were expressed as mean $\pm$ standard deviation or median (range of 25th percentile to 75th percentile [P25, P75]). Statistical analysis was performed using the analysis of variance or Kruskal–Wallis rank sum test. Qualitative data, expressed as frequency (percentage), were analyzed using the chi-square test or Fisher exact test. A p-value of $<$0.05 was considered statistically significant. We categorized the classification of AKI into non-AKI (RIFLE-Normal and AKIN Stage 0) as 0 points and AKI of RIFLE-Risk and AKIN Stage 1 as 1 point, RIFLE-Injury and AKIN Stage 2 as 2 points, and RIFLE-Failure and AKIN Stage 3 as 3 points for analysis. The measurement of observer agreement for categorical data between groups was performed using Kappa statistics (Landis and Koch 1977). For interpreting Kappa statistics, values between 0.81 and 1.00 indicate almost perfect agreement or very good agreement, 0.61–0.80 substantial agreement or good agreement, 0.41–0.60 moderate agreement, 0.21–0.40 fair agreement, and $<$0.21 poor or slight agreement (Landis and Koch 1977).

Results

Characteristics of the patients

During the study period, 167 patients with HFRS were admitted to the hospital. The following 47 patients were excluded because of age, pregnancy, and complicated diseases unrelated to HFRS: 9 patients aged $<$18 years, 1 pregnant patient, 1 patient with chronic renal failure under hemodialysis, 3 patients with other infections before onset of HFRS (1 with chronic osteomyelitis in left ankle joint, 1 with lung infection, and 1 with septicemia), 4 patients accompanied other diseases (1 with acute myocardial infarction, 1 with acute myeloid leukemia, 1 with rheumatic valvular disease with atrial fibrillation, and 1 with upper gastrointestinal bleeding), 21 patients with possible renal-affecting disorders (1 with Behcet's disease, 11 with hypertension, 4 with diabetes, 3 with diabetes and hypertension, 1 with hepatitis B cirrhosis and diabetes, 1 with hepatitis B, diabetes, and hypertension), and 8 patients with chronic viral hepatitis (7 with chronic hepatitis B and 1 with chronic hepatitis C). The remaining 120 patients were included in the analysis of the study. Of the 120 patients analyzed, 35 patients received acute RRT. The demographic, clinical, and laboratory data of the 120 patients at hospital admission are shown in Table 2.

AKI classified at 48 h and 1 week of admission in HFRS patients

The incidence of AKI classified by RIFLE, RIFLEc, AKIN, and AKINc criteria at 48 h of admission in the 120 HFRS

Table 2. Demographic and Laboratory Parameters of the Patients with Hemorrhagic Fever with Renal Syndrome at Admission

	Values in HFRS patients	*Values of normal range*
Gender (male/female)	95/25	—
Age (years)	40.23 ± 15.35[a]	—
Admission phase (*n*)		—
Febrile	78	
Hypotensive	6	
Oliguric	29	
Polyuric	7	
WBC ($\times 10^9$/L)	15.13 ± 9.60[a]	(4–10)
PLT ($\times 10^9$/L)	38 (20, 63)[b]	(100–300)
ALT (IU/L)	43 (28, 73)[b]	0–40
AST (IU/L)	83 (46, 136)[b]	0–40
ALB (g/L)	29.84 ± 4.88[a]	35–55
Scr (μmol/L)	260.01 ± 191.26[a]	40–140

HFRS, hemorrhagic fever and renal syndrome; WBC, white blood cell; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; Scr, serum creatinine.

[a]Mean ± SD.

[b]Nonnormal distribution, presented as median (P25, P75: range of 25th to 75th percentile).

patients were 79.2%, 74.2%, 82.5%, and 80.8%, respectively (Table 3). The incidence of AKI according to RIFLE, RIFLEc, AKIN, and AKINc criteria at 1 week of admission was 84.2%, 80.8%, 89.2%, and 87.5%, respectively (Table 3). AKIN and AKINc system was slightly more sensitive than RIFLE and RIFLEc at both 48 h and 1 week of admission.

Table 3. Acute Kidney Injury in the Patients with Hemorrhagic Fever with Renal Syndrome Defined at 48 h and 1 Week of Admission

	At 48 h of admission			
	RIFLE (%)	*RIFLEc (%)*	*AKIN (%)*	*AKINc (%)*
Normal/Stage 0	25 (20.8)	31 (25.8)	21 (17.5)	23 (19.2)
Risk/Stage 1	17 (14.2)	13 (10.8)	21 (17.5)	21 (17.5)
Injury/Stage 2	13 (10.8)	11 (9.2)	12 (10.0)	11 (9.2)
Failure/Stage 3	65 (54.2)	65 (54.2)	66 (55.0)	65 (54.2)
Total AKI	95 (79.2)	89 (74.2)	99 (82.5)	97 (80.8)
	At 1 week of admission			
	RIFLE (%)	*RIFLEc (%)*	*AKIN (%)*	*AKINc (%)*
Normal/Stage 0	19 (15.8)	23 (19.2)	13 (10.8)	15 (12.5)
Risk/Stage 1	9 (7.5)	7 (5.8)	15 (12.5)	15 (12.5)
Injury/Stage 2	16 (13.3)	14 (11.7)	16 (13.3)	14 (11.7)
Failure/Stage 3	76 (63.3)	76 (63.3)	76 (63.3)	76 (63.3)
Total AKI	101 (84.2)	97 (80.8)	107 (89.2)	105 (87.5)

AKI, acute kidney injury; RIFLEc, RIFLE defined by serum creatinine; AKINc, AKIN defined by serum creatinine; normal/Stage 0, RIFLE/normal or AKIN/Stage 0; risk/Stage 1, RIFLE/risk or AKIN/Stage 1; injury/Stage 2, RIFLE/injury or AKIN/Stage 2; failure/Stage 3, RIFLE/failure or AKIN/Stage 3.

Agreement of different AKI classification criteria

The agreement of different classification criteria of AKI was tested by Kappa statistics. RIFLE and AKIN showed very good agreement in classifying AKI in the 120 HFRS patients at 48 h of admission ($\kappa = 0.934$). The agreement of RIFLE and AKIN at 1 week of admission in the patients was also very good ($\kappa = 0.947$; Table 4). RIFLEc and AKINc at 48 h of admission showed very good agreement ($\kappa = 0.894$) and the agreement of RIFLEc and AKINc at 1 week of admission was also very good ($\kappa = 0.894$; Table 4).

RIFLE and RIFLEc at 48 h of admission had almost perfect agreement ($\kappa = 0.920$). The agreement of RIFLE and RIFLEc at 1 week of admission was also almost perfect ($\kappa = 0.924$; Table 4). AKIN and AKINc at 48 h of admission had perfect agreement ($\kappa = 0.934$) and the agreement of AKIN and AKINc at 1 week of admission was also perfect ($\kappa = 0.955$; Table 4).

Agreement of AKI classifications at 48 h and 1 week of admission

Based on RIFLE criteria, three patients progressed from normal at 48 h of admission to injury at 1 week of admission, three patients progressed from normal to failure, six patients progressed from risk to injury, two patients progressed from risk to failure, and six patients progressed from injury to failure. The classification of RIFLE at 48 h of admission was in good agreement with that of RIFLE at 1 week of admission ($\kappa = 0.722$; Table 5). Based on RIFLEc criteria, one patient progressed from normal at 48 h of admission to risk at 1 week of admission, three patients progressed from risk to injury, four patients progressed from risk to failure, six patients progressed from risk to injury, and one patient progressed from risk to failure. Six patients progressed from injury at 48 h to failure at 1 week. The classification at 48 h of admission had good agreement with that at 1 week of admission ($\kappa = 0.704$; Table 5).

According to AKIN criteria, four patients with Stage 0 at 48 h of admission progressed to Stage 1 at 1 week of admission, two patients progressed from Stage 0 to Stage 2, and three patients progressed from Stage 0 to Stage 3. Seven patients progressed from Stage 1 at 48 h of admission to Stage 2 at 1 week of admission and three patients progressed from Stage 1 to Stage 3. Five patients progressed from Stage 2 at 48 h to Stage 3 at 1 week of admission. The agreement of AKIN classification at 48 h and 1 week of admission was good ($\kappa = 0.679$; Table 5). According to AKINc criteria, four patients with Stage 0 at 48 h of admission progressed to Stage 1 at 1 week of admission, two patients progressed to Stage 2, and three patients progressed to Stage 3. Seven patients with Stage 1 at 48 h of admission progressed to Stage 2 and two patients progressed to Stage 3. Six patients progressed from Stage 2 to Stage 3. The agreement of AKINc classification at 48 h and 1 week of admission was also good ($\kappa = 0.667$; Table 5).

Relationships of clinical outcome and occurrence of complications with AKI classifications

Among the 120 patients, eight patients (6.7%) died (two patients died of intracranial edema and hemorrhage leading to respiratory and circulatory failure, four patients died of serious neurological and coagulation complications and multiorgan failure, and two patients died of severe

Table 4. Agreement of Different Acute Kidney Injury Category Systems at 48 h and 1 Week of Admission in Patients with Hemorrhagic Fever with Renal Syndrome

Agreement of RIFLE and AKIN at 48 h ($\kappa = 0.934$) and 1 week ($\kappa = 0.947$) of admission

		$AKIN_{48}$						$AKIN_{wk1}$			
		Stage 0	*Stage 1*	*Stage 2*	*Stage 3*			*Stage 0*	*Stage 1*	*Stage 2*	*Stage 3*
$RIFLE_{48}$	Normal	**21**	4	0	0	$RIFLE_{WK1}$	Normal	**13**	6	0	0
	Risk	0	**17**	0	0		Risk	0	**9**	0	0
	Injury	0	0	**12**	1		Injury	0	0	**16**	0
	Failure	0	0	0	**65**		Failure	0	0	0	**76**

Agreement of RIFLEc and AKINc at 48 h ($\kappa = 0.894$) and 1 week ($\kappa = 0.894$) of admission

		$AKINc_{48}$						$AKINc_{wk1}$			
		Stage 0	*Stage 1*	*Stage 2*	*Stage 3*			*Stage 0*	*Stage 1*	*Stage 2*	*Stage 3*
$RIFLEc_{48}$	Normal	**23**	8	0	0	$RIFLEc_{WK1}$	Normal	**15**	8	0	0
	Risk	0	**13**	0	0		Risk	0	**7**	0	0
	Injury	0	0	**11**	0		Injury	0	0	**14**	0
	Failure	0	0	0	**65**		Failure	0	0	0	**76**

Agreement of RIFLE and RIFLEc at 48 h ($\kappa = 0.920$) and 1 week ($\kappa = 0.924$) of admission

		$RIFLEc_{48}$						$RIFLEc_{wk1}$			
		Normal	*Risk*	*Injury*	*Failure*			*Normal*	*Risk*	*Injury*	*Failure*
$RIFLE_{48}$	Normal	**25**	4	2	0	$RIFLE_{WK1}$	Normal	**19**	3	1	0
	Risk	0	**13**	0	0		Risk	0	**6**	1	0
	Injury	0	0	**11**	0		Injury	0	0	**14**	0
	Failure	0	0	0	**65**		Failure	0	0	0	**76**

Agreement of AKIN and AKINc at 48 h ($\kappa = 0.934$) and 1 week ($\kappa = 0.955$) of admission

		$AKINc_{48}$						$AKINc_{wk1}$			
		Stage 0	*Stage 1*	*Stage 2*	*Stage 3*			*Stage 0*	*Stage 1*	*Stage 2*	*Stage 3*
$AKIN_{48}$	Stage 0	**21**	2	0	0	$AKIN_{WK1}$	Stage 0	**13**	1	0	0
	Stage 1	0	**19**	2	0		Stage 1	0	**14**	2	0
	Stage 2	0	0	**10**	1		Stage 2	0	0	**14**	0
	Stage 3	0	0	0	**65**		Stage 3	0	0	0	**76**

$RIFLE_{48}$, $RIFLEc_{48}$, $AKIN_{48}$, and $AKINc_{48}$: RIFLE, RIFLEc, AKIN, and AKINc defined at 48 h of admission; $RIFLE_{WK1}$, $RIFLEc_{wk1}$, $AKIN_{wk1}$, and $AKINc_{wk1}$: RIFLE, RIFLEc, AKIN, and AKINc defined at 1 week of admission. Bold values show the identical numbers of two systems.

pulmonary fungal infection, requiring mechanical ventilation and continuous venous hemofiltration treatment, and multiple organ dysfunction). All the eight patients who died were classified as failure by RIFLE or RIFLEc criteria or as Stage 3 by AKIN or AKINc criteria at 48 h and 1 week of admission (Table 6).

At least one acute complication associated with HFRS occurred in 51 patients (42.5%). Of these 51 patients, 46 patients (90.2%) were classified as AKI at 48 h of admission according to the RIFLE category (2 risk, 4 injury, and 40 failure). Of these 51 patients, 47 patients (92.2%) were classified as AKI at 48 h of admission according to the AKIN category (3 Stage 1, 4 Stage 2, and 40 Stage 3). Of the 51 patients with complications, 49 patients (96.1%) had AKI at 1 week of admission according to RIFLE (5 injury and 44 failure) and 50 patients had AKI at 1 week of admission according to AKIN (1 Stage 1, 5 Stage 2, and 44 Stage 3). The incidence of complications in HFRS patients was much higher in patients classified as AKI, especially as RIFLE-failure or AKIN Stage 3 ($p < 0.01$; Table 6).

The length of hospital stay in the patients with different AKI classifications was significantly different. Patients with greater AKI classifications, particularly patients classified as RIFLE-failure or AKIN Stage 3, had longer duration of hospital stay ($p < 0.01$; Table 6).

Discussion

Acute renal injury is one of the major characteristics of the severe form of HFRS caused by HTNV. Until now, no objective classification of AKI in HFRS has been available for clinical reference. In this study, we for the first time stratified AKI in HFRS patients by both RIFLE and AKIN classification/staging systems. We showed that AKI occurred in 79.2% and 82.5% of the HFRS patients at 48 h of hospital admission

Table 5. Agreement of Acute Kidney Injury Classified by the Same System at 48 h and 1 Week of Admission

Agreement of RIFLE at 48 h and 1 week of admission ($\kappa = 0.722$) and RIFLEc at 48 h and 1 week of admission ($\kappa = 0.704$)

		$RIFLE_{WK1}$						$RIFLEc_{WK1}$			
		Normal	*Risk*	*Injury*	*Failure*			*Normal*	*Risk*	*Injury*	*Failure*
$RIFLE_{48}$	Normal	**19**	0	3	3	$RIFLEc_{48}$	Normal	**23**	1	3	4
	Risk	0	**9**	6	2		Risk	0	**6**	6	1
	Injury	0	0	**7**	6		Injury	0	0	**5**	6
	Failure	0	0	0	**65**		Failure	0	0	0	**65**

Agreement of AKIN at 48 h and 1 week of admission ($\kappa = 0.679$) and AKINc at 48 h and 1 week of admission ($\kappa = 0.667$)

		$AKIN_{wk1}$						$AKINc_{wk1}$			
		Stage 0	*Stage 1*	*Stage 2*	*Stage 3*			*Stage 0*	*Stage 1*	*Stage 2*	*Stage 3*
$AKIN_{48}$	Stage 0	**13**	4	2	2	$AKINc_{48}$	Stage 0	**14**	4	2	3
	Stage 1	0	**11**	7	3		Stage 1	1	**11**	7	2
	Stage 2	0	0	**7**	5		Stage 2	0	0	**5**	6
	Stage 3	0	0	0	**66**		Stage 3	0	0	0	**65**

Bold values show the identical numbers of two systems.

and in 84.2% and 89.2% of them at 1 week of admission by RIFLE and AKIN criteria, respectively. Less than 20% of HFRS patients had no AKI (RIFLE-normal/AKIN-Stage 0) evaluated at 1 week of hospital admission by both RIFLE and AKIN as well as by RIFLEc and AKINc criteria. More than 50% of the patients at 48 h and >60% of them at 1 week of hospital admission had severe AKI of RIFLE-failure/AKIN-Stage 3. Our study confirms the characteristic nature of the early occurrence and high incidence of AKI in HFRS by RIFLE and AKIN, which may standardize the evaluation of kidney injury in HFRS and facilitate the academic communication.

Small change in renal function has been evidenced to have a significant impact on outcomes in a variety of clinical settings and patient types (Lassnigg et al. 2004, Brandt et al. 2007, Coca et al. 2007a, 2007b). To compare the performance of the RIFLE and AKIN systems, the agreement of different classification/grading criteria of AKI was tested by Kappa statistics. RIFLE and AKIN showed very good agreement in classifying the AKI in the HFRS patients at 48 h and 1 week of admission, although the AKIN criteria appeared a little more sensitive than RIFLE criteria with no statistical significance. It appears reasonable that the AKIN criteria should be more sensitive than RIFLE criteria because the proposal of AKIN was based on RIFLE and aimed to improve the sensitivity and specificity of AKI diagnosis (Mehta et al. 2007). However, it seems that most of the comparative studies did not demonstrate the

Table 6. Clinical Outcomes of the Patients with Hemorrhagic Fever with Renal Syndrome Stratified by the RIFLE and AKIN Systems

	Classification system			
Clinical outcome	$RIFLE_{48}$	$AKIN_{48}$	$RIFLE_{wk1}$	$AKIN_{wk1}$
Mortality, *n* (%)				
	Normal, 0 Risk, 0 Injury, 0 Failure, 8 (6.7)	Stage 0, 0 Stage 1, 0 Stage 2, 0 Stage 3, 8 (6.7)	Normal, 0 Risk, 0 Injury, 0 Failure, 8 (6.7)	Normal, 0 Risk, 0 Injury, 0 Failure, 8 (6.7)
Patients with at least one acute complication, *n* (%)[a]				
	Normal, 0 Risk, 2 (1.67) Injury, 4 (3.33) Failure, 40 (33.33)	Stage 0, 0 Stage 1, 3 (2.50) Stage 2, 4 (3.33) Stage 3, 40 (33.33)	Normal, 0 Risk, 0 Injury, 5 (4.17) Failure, 44 (36.67)	Stage 0, 0 Stage 1, 1 (0.83) Stage 2, 5 (4.17) Stage 3, 44 (36.67)
Length of hospital stay (days)[b]				
	Normal, 9 (6,10) Risk, 9 (6,10) Injury, 10 (7,13) Failure, 14 (10,18)	Stage 0, 9 (6,10) Stage 1, 9 (6,11) Stage 2, 10 (7,13) Stage 3, 14 (10,19)	Normal, 8 (5,9) Risk, 6 (5,8) Injury, 9 (7,10) Failure, 14 (10,18)	Stage 0, 7 (5,9) Stage 1, 8 (5,9) Stage 2, 9 (7,10) Stage 3, 14 (10,18)

[a] $p < 0.01$, when the occurrence of complications was compared between different categories of RIFLE and AKIN at 48 h and 1 week of admission.

[b] $p < 0.01$, when the length of hospital stay was compared between different categories of RIFLE and AKIN at 48 h and 1 week of admission.

expectedly improved sensitivity and specificity of the AKIN criteria in comparison with RIFLE criteria. For instance, one comparison in critically ill patients showed that the AKIN criteria do not materially improve the sensitivity, robustness, and predictive ability of the definition and classification of AKI in the first 24 h after admission to the intensive care unit (ICU) compared with the RIFLE criteria (Bagshaw et al. 2008). Other two comparisons of the RIFLE and AKIN criteria for diagnosing and classifying AKI and for predicting hospital mortality in critically ill patients also showed that AKIN classification does not improve the sensitivity and ability of outcome prediction in critically ill patients compared with RIFLE criteria (Lopes et al. 2008, Chang et al. 2010). Further, one comparison of the two classification systems with respect to the outcome of ICU patients showed that AKI classified by either RIFLE or AKIN is associated with increased hospital mortality but RIFLE even shows better robustness and a higher detection rate of AKI during the first 48 h of ICU admission despite presumed increase of sensitivity by the AKIN classification (Joannidis et al. 2009). Therefore, the AKIN staging system seems to have not generally increased the sensitivity and specificity of the definition and predictive ability of AKI. The small inconsistencies of the studies may at least partly contribute to the great heterogeneity in the critically ill patients. Our comparison in the patients with the same disease entity showed that the AKIN system was slightly more sensitive than RIFLE in defining AKI in HFRS patients but the difference was not significant. This is in accord with the findings of the most comparisons in the critically ill patients (Bagshaw et al. 2008, Lopes et al. 2008, Chang et al. 2010).

To investigate whether the RIFLE and AKIN criteria classified only by Scr (RIFLEc and AKINc) can be used as alternatives of the standard RIFLE and AKIN criteria, which use both Scr and urine output per hour, we compared the agreement of RIFLE and RIFLEc as well as AKIN and AKINc at 48 h and 1 week of admission in the patients. The results showed that the agreement between RIFLE and RIFLEc at 48 h and 1 week was almost perfect ($\kappa > 0.900$). The agreement between AKIN and AKINc at 48 h and 1 week of admission was also perfect ($\kappa > 0.900$). It was suggested that RIFLE and AKIN defined by Scr may be used as alternatives to evaluate AKI in HFRS patients at the non-ICU settings. This omitted the need to record the precise urine output per hour and provided a convenient method for evaluating AKI in HFRS patients.

To investigate whether the early classifications of AKI in HFRS patients is predictive of the disease progression and severity in HFRS patients, we examined the agreement of AKI classified at 48 h with that classified at 1 week of admission. The classification of RIFLE, RIFLEc, AKIN, and AKINc at 48 h and 1 week of admission were all in good agreement, although the AKI classifications progressed in a small number of patients during the disease course. *Scilicet*, the AKI classified by both the standard criteria and the Scr criteria at 48 h of admission had good agreement with that classified at 1 week of admission, indicating the predictive role of the early (48 h of admission) classifications.

The prognostic implication of AKI classification has been demonstrated in critically ill patients (Hoste et al. 2006, Bagshaw et al. 2008, Lopes et al. 2008, Joannidis et al. 2009, Chang et al. 2010). So far, no systematics and predictive assessments are available for the disease severity and prognosis of HFRS. We correlated the AKI classified by RIFLE and AKIN to disease severity and prognosis in the HFRS patients. In our study, all the eight patients who died had the worst of AKI classifications (RIFLE-failure/AKIN-Stage 3) at 48 h and 1 week of admission. The incidence of complications was significantly higher in patients with the worst AKI classifications (RIFLE-failure/AKIN-Stage 3) at 48 h and 1 week of admission, accounting for >85% of the patients with complications. The length of hospital stay in the patients with the worst AKI classifications (RIFLE-failure/AKIN-Stage 3) at 48 h and 1 week of admission was also significantly longer. It was indicated that the AKI classifications of RIFLE and AKIN were associated with the disease severity and early implementation of AKI assessment may have predictive value during the clinical course.

Our evaluation of AKI by RIFLE and AKIN systems in the present study was performed in patients with the severe form of HFRS caused by HTNV. To our knowledge, no evaluation of the two AKI systems has been conducted in the mild forms of HFRS caused by Puumala virus or SEOV. It can be expected that the evaluation of AKI in the mild forms of HFRS by the standardized criteria will well define the clinical profiles of HFRS disease caused by various hantaviruses and facilitate the academic communication associated with HFRS.

In conclusion, we in the present study first applied the two AKI category systems, RIFLE and AKIN, in evaluating kidney injury in HFRS patients. We showed that nearly 90% of the patients with HFRS induced by HTNV had AKI during the course of the disease. The two AKI category systems had similar sensitivity of power in classifying AKI in HFRS patients. The AKI defined by Scr criteria of the two systems had good agreement with their standard criteria by Scr and urine output per hour. The categories of AKI defined at the early stage (48 h of hospital admission) were predictive of the categories defined at the later stage (1 week of hospital admission) of the disease. The classifications of AKI by the two systems, RIFLE-failure and AKIN-Stage 3 in particular, were associated with the disease severity and the patients' prognosis. It is suggested that both systems can be used for evaluating AKI and predicting the disease severity and prognosis in HFRS patients, and the Scr criteria of the two systems may provide an objective and convenient approach for these evaluations under the non-ICU condition.

The findings of our study are intriguing and put forward for the standardization of AKI in HFRS and the use of RIFLE and AKIN systems in a disease manifested with AKI. However, our study is a retrospective analysis performed in a sample of relatively small number of patients with the severe form HFRS, and the data were from the experience of a single hospital. Therefore, further prospective multicenter studies in larger patient samples including both the severe and mild forms of HFRS caused by various hantaviruses are warranted to confirm the value of RIFLE and AKIN in evaluating the incidence and severity of AKI and the predictive ability of prognosis in HFRS.

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Disclosure Statement

The authors declare that they have no conflict of interest related to the publication of this manuscript.

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Address correspondence to:
Zhengwen Liu
Department of Infectious Diseases
First Affiliated Hospital
School of Medicine
Xi'an Jiaotong University
Xi'an 710061, Shaanxi Province
The People's Republic of China

E-mail: liuzhengwen@medmail.com.cn