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EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF HEMORRHAGIC FEVER WITH RENAL DISEASE SYNDROME IN THE AUTONOMOUS PROVINCE OF VOJVODINA

EPIDEMIOLOGIJA I KLINIČKE KARAKTERISTIKE HEMORAGIJSKE GROZNICE SA BUBREŽNIM SINDROMOM U AUTONOMNOJ POKRAJINI VOJVODINI

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Summary

Introduction. The aim of this study was to determine the epidemiological and clinical characteristics of hemorrhagic fever with renal syndrome in Vojvodina from 2008-2015 and to examine the factors associated with acute renal failure and hemorrhagic syndrome. **Material and Methods.** Data were extracted from medical records spanning 2008 to 2015, including demographic, epidemiological, clinical, and laboratory findings at hospital admission, as well as the course and outcome of treatment. The study investigated the correlation between disease incidence and climate, focusing on acute renal failure, its risk factors, the incidence of hemorrhagic syndrome, and factors influencing hospital stay duration. **Results.** The highest incidence for hemorrhagic fever with renal syndrome was recorded in 2014, with a rate of 0.5 per 100.000 inhabitants. Acute renal failure was observed in 40% of patients, while mild manifestations of hemorrhagic syndrome were noted in 46.7% of cases. Factors contributing to acute renal failure included lumbar pain (p=0.005), creatinine concentrations (p=0.011), and Simplified Acute Physiology score (p=0.013). The average length of hospitalization was 10 days (range 7-13 days) and was correlated with increased leukocytosis (p=0.028; ρ=0.566), higher C-reactive protein values (p=0.014; ρ=0.686), lower serum sodium levels (p=0.009; ρ=0.772), higher serum creatinine concentrations (p=0.002; ρ=0.742), the Sequential Organ Failure Assessment score (p=0.013; ρ=0.612) and the Simplified Acute Physiology score (p=0.023; ρ=0.582). **Conclusion.** Climatic factors are associated with the incidence of hemorrhagic fever with renal syndrome. The overall outcome of the disease was favorable.

Key words: Hemorrhagic Fever with Renal Syndrome; Epidemiology; Incidence; Signs and Symptoms; Risk Factors; Renal Insufficiency; Climate; Treatment Outcome

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Sažetak

Uvod. Ciljevi istraživanja su utvrđivanje epidemioloških i kliničkih karakteristika hemoragijske groznice sa bubrežnim sindromom u Vojvodini, 2008−2015. godine i faktora povezanih sa razvojem akutne bubrežne insuficijencije i hemoragijskog sindroma. **Materijal i metode.** Podaci su uzeti iz istorija bolesti (2008−2015): demografski, epidemiološki, klinički i laboratorijski nalazi pri prijemu u bolnicu, tok i ishod lečenja. Ispitana je povezanost incidencije bolesti sa klimatskim uslovima; incidencija pojave akutne bubrežne insuficijencije, faktori rizika za njen nastanak, incidencija pojave hemoragijskog sindroma i faktori povezani sa dužinom hospitalizacije. **Rezultati.** Stope incidencije hemoragijske groznice sa bubrežnim sindromom su u porastu u Vojvodini; najviša incidencija je zabeležena 2014. godine (0,5/100.000 stanovnika). Iste godine zabeležen je porast količine padavina, više prosečne temperature vazduha zimi i veća vlažnost vazduha. Razvoj akutne bubrežne insuficijencije zabeležen je kod 40%, blage manifestacije hemoragijskog sindroma kod 46,7% bolesnika. Faktori rizika za nastanak akutne bubrežne insuficijencije su: bol u lumbalnim ložama (p = 0,005), koncentracija kreatinina (p = 0,011) i *Simplified Acute Physiology score* (p = 0,013). Prosečna dužina hospitalizacije iznosila je 10 (7−13) dana i korelirala je sa: izraženijom leukocitozom (p = 0,028; ρ = 0,566), višim vrednostima C-reaktivnog proteina (p = 0,014; ρ = 0,686), nižim koncentracijama natrijuma (p = 0,009; ρ = 0,772) i višim koncentracijama kreatinina u serumu (p = 0,022; ρ = 0,585). **Zaključak.** Klimatski faktori povezani su sa incidencijom hemoragijske groznice sa bubrežnim sindromom. Klinička slika je bila blaga, sa povoljnim ishodom.

Ključne reči: hemoragijska groznica sa bubrežnim sindromom; epidemiologija; incidenca; znaci i simptomi; faktori rizika; bubrežna insuficijencija; klima; ishod lečenja

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Abbreviations

HFRS	– Hemorrhagic fever with renal syndrome
ARI	– Acute renal injury
AKIN	– Acute Kidney Injury Network
SOFA	– Sequential Organ Failure Assessment
SAPS II score	– Simplified Acute Physiology Score
CRP	– C-reactive protein
ALT	– Alanine aminotransferase
AST	– Aspartate aminotransferase
Aptt	– Activated partial thromboplastin time
APV	– Autonomous province of Vojvodina
PUUV	– Puumala virus

Introduction

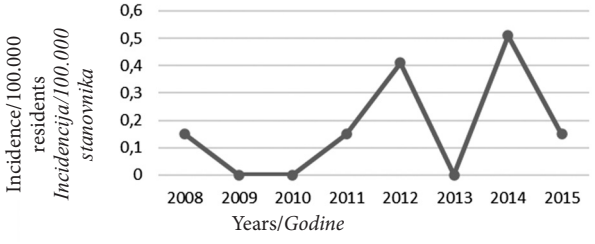
Hemorrhagic fever with renal syndrome (HFRS), caused by the Hantaan virus, is a zoonosis disease with a global distribution, posing significant challenges to public health worldwide [1–3]. Key factors affecting the virus's viability outside the host include temperature, humidity, exposure to ultraviolet light and sunlight, and the organic composition of the contaminated fluid. The optimal environmental conditions for virus survival can vary among different strains of the Hantaan virus, contributing to the distinct infection dynamics observed in both rodents and humans [4–6].

Material and Methods

This study adheres to established scientific methodologies in medical research, having obtained approval from the University Clinical Center Clinical Etics Committee (No. 6, 00-53). Conducted as a retrospective observational study, data were sourced from the medical records of patients admitted to the Infectious Diseases Clinic at the Clinical Center of Vojvodina. Additionally, epidemiological data regarding HFRS in the Autonomous Province (AP) of Vojvodina were retrieved from the annual publication "Infectious Diseases in AP Vojvodina", published by the Disease Control and Prevention Center of the Institute for Public Health of Vojvodina in collaboration with healthcare centers across the region. The data sources included disease histories and infectious disease surveillance. HFRS supervision in our region is conducted through passive collection of reports on documented cases and mortality. We employed a descriptive epidemiological methodology, analyzing registered HFRS cases chronologically and demographically. The results, including an analysis of the association between climatic factors and disease frequency as well as the clinical characteristics of the illness, are presented in both tabular and graphical formats. Standard epidemiological and clinical indicators, such as percentages, incidence rates, median, interquartile ranges, and correlation coefficients were utilized. The study covered eight consecutive years from 2008 to 2015. Eligibility criteria included individuals with suspected HFRS, characterized by a sudden onset of illness in those who had either traveled to HFRS-endemic regions or had contact with rodent excreta within two months prior to symptom onset. The illness had to manifest with at least two of the following clinical features: tremors, chills, headache, back pain, bleeding, hypotension, abdominal pain, and acute renal failure. Confirmation of HFRS required meeting at least one laboratory criterion: a positive result for Hantaan virus-specific IgM or a fourfold increase in the titer of Hantaan virus-specific IgG. For the clinical component of the research, data were gathered from medical records including patient age, gender, symptoms reported at the time of hospital admission, duration of symptoms prior to admission, and initial laboratory parameters recorded at admission. These parameters comprised a complete blood count, concentrations of C-reactive protein, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, urinalysis findings, and calculated Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score (SAPS II score) [7]. Patients were monitored throughout hospitalization, documenting the occurrence of hemorrhagic syndrome, the highest recorded creatinine values, the development of acute renal failure as defined by the Acute Kidney Injury Network (AKIN), disease outcomes, and length of hospital stay [8]. According to AKIN criteria, acute renal failure is defined by an increase in serum creatinine of at least 26 μmol/L or more than 150% of baseline values, or urine output less than 0.5 ml/kg of body weight over 6-12 hours. Statistical data were processed using SPSS version 23.0. Results for categorical variables are presented as total number (n) and percentage (%), with differences between groups assessed using the chi-square (χ^2) test. Continuous variables are reported as median and interquartile range, based on the Shapiro-Wilk test findings indicating statistically significant deviations from normal distribution for most variables. Differences between the two groups were compared using the Mann-Whitney U test. Spearman's rank correlation was used for correlation analysis, with statistical significance set at $p < 0.05$.

Results

According to epidemiological data, 28 cases of HFRS were documented within the specified period in patients from the Autonomous Province of Vojvodina (APV). Detailed information regarding the progression and outcome of the disease was accessible for 15 of these cases **(Table 1).**

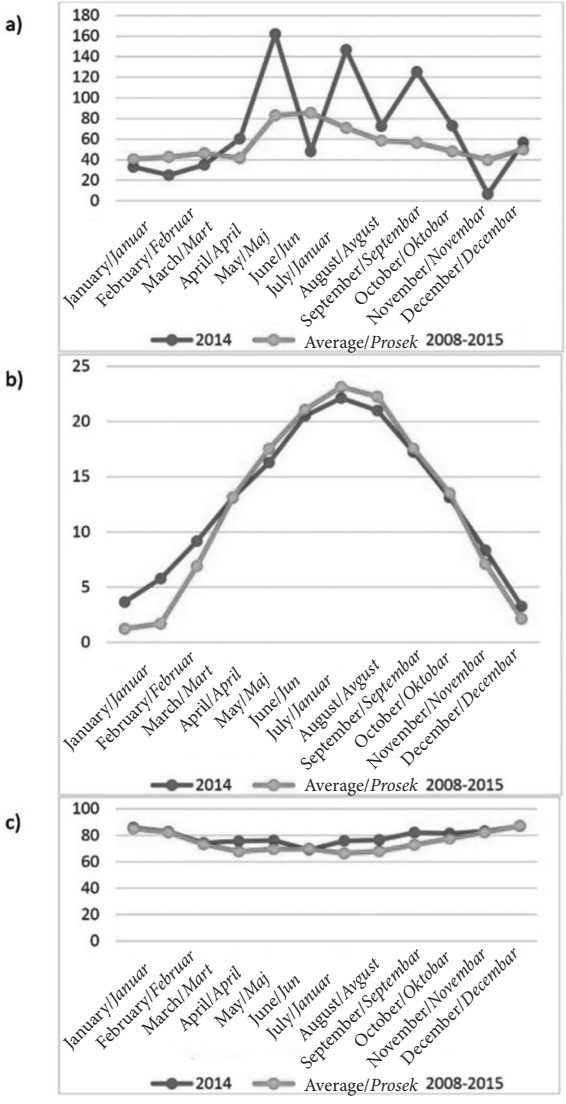


Graph 1. Chronological distribution of HFRS in the APV, from 2008 to 2015

Grafikon 1. *Hronološka distribucija HGBS u Autonomnoj pokrajini Vojvodini, 2008–2015. godine*

Table 1. Age and gender specific distribution of HFRS patients in the AP of Vojvodina in the period from 2008 to 2015
Tabela 1. *Uzrasno i rodno specifična distribucija obolelih od hemoragijske groznice sa bubrežnim sindromom u Autonomoj pokrajini Vojvodini u periodu od 2008. do 2015. godine*

	N/*Br.*	%
Age/*Uzrast*		
Under 20 years old/*Mlađi od 20 godina*	2	7.14
21-30	7	25.00
31-40	10	35.71
41-50	8	28.57
51-60	0	0.00
Over 60 years old/*Preko 60 godina*	1	3.57
Gender/*Pol*		
Male/*Muški*	26	92.90
Female/*Ženski*	2	7.10



Graph 2. Average monthly values of temperature, precipitation and air humidity in the AP of Vojvodina, from 2008 to 2015
Grafikon 2. *Prosečne mesečne vrednosti temperature, količine padavina i vlažnosti vazduha u AP Vojvodini, 2008–2015. godine*

The registered incidence rates of HFRS in the APV during the observed period ranged from 0.0 in 2009, 2010, and 2013, to 0.5 in 2014. An escalation in HFRS incidence was noted during severe flooding in Serbia in 2014 **(Graph 1).**

The average monthly values of temperature, precipitation, and air humidity in the APV from 2008 to 2015 are depicted in the graph.

In relation to the data depicted in **Graph 2**, it is evident that the most significant fluctuations occurred in the average values for rainfall. In May, July, and September, precipitation levels were recorded at twice the average amount for those respective months. Throughout 2014, higher relative air humidity values were observed compared to the average. Regarding air temperature, slightly elevated temperatures were noted during the winter months, while slightly lower temperatures were observed during the summer months, in comparison to the respective monthly averages.

Incidence of Acute Renal Injury (ARI) and clinical characteristics associated with its development in patients with HFRS

Initially elevated creatinine values were recorded in 4 patients (26.7%), while subsequent increases beyond the reference limits were observed in another 4 patients (26.7%), totaling 53.3% of patients with elevated creatinine levels. Six patients met the criteria for diagnosing ARI. Proteinuria was documented in 7 patients (46.7%), with 5 classified as mild (57.1%), 1 as moderate (14.3%), and 2 as severe (28.6%) proteinuria.

Tables 2 and 3 display pertinent data concerning hospital admission symptoms in patients with and without ARI, as well as age, duration of symptoms prior to hospitalization, time from admission to appropriate diagnosis, and predictive scores (SAPS II and SOFA score).

Table 4 presents the values of laboratory parameters recorded upon hospital admission, categorized by the presence of ARI.

The correlation analysis revealed statistically significant positive correlations between the highest

Table 2. Symptoms reported by patients at hospital admission, in the group with and without ARI
Tabela 2. *Simptomi koje su bolesnici prijavljivali pri prijemu u bolnicu, u grupi sa i bez ABI*

Symptoms *Simptomi*	Yes/No *Da/Ne*	ARI/*ABI* n (%)	Without ARI/*Bez ABI* n (%)	p/*p*
Fever/*Povišena telesna temperarura*	Yes/*Da*	6 (100%)	9 (100%)	–
Headache/*Glavobolja*	Yes/*Da*	5 (83%)	1 (11.1%)	0.475
Abdominal pain/*Abdominalni bol*	Yes/*Da*	1 (11.1%)	5 (83%)	0.475
Nausea, vomiting/*Muka*, *povraćanje*	Yes/*Da*	3 (50%)	3 (50%)	0.833
Lumbar pain/*Bol u lumbalnom delu leđa*	Yes/*Da*	5 (83.3%)	1 (11.1%)	0.005
Hemorrhagic syndrome/*Hemoragijski sindrom*	Yes/*Da*	0 (0%)	6 (100%)	0.389
Vision problems/*Problemi sa vidom*	Yes/*Da*	1 (11.1%)	5 (83%)	0.475
Diarrhea/*Dijareja*	Yes/*Da*	1 (11.1%)	5 (83%)	0.475

Table 3. Age, duration of complaints before admission, time from admission to suspicion of HFRS and predictive scores in patients who developed ARI compared to patients who did not develop ARI; Group of patients with and without acute renal failure in relation to symptoms recorded at hospital admission
Tabela 3. *Uzrast, dužina tegoba pre prijema, vreme proteklo od prijema do postavljanja sumnje na HGBS i prediktivni skorovi kod bolesnika kod kojih je došlo do razvoja ABI u odnosu na bolesnike kod kojih se ABI nije razvila; Grupa pacijenata sa i bez akutne bubrežne insuficijencije u odnosu na simptome zabeležene pri prijemu u bolnicu*

	ARI *ABI*	Median *Medijana*	Interquartile range *Interkvartilni raspon*	p/*p*
Age *Uzrast*	Without ARI/*Bez ABI*	32.00	26.00-47.00	0.723
	With ARI/*Sa ABI*	34.00	28.00-40.00	
Duration of symptoms before admission *Trajanje tegoba pre prijema*	Without ARI/*Bez ABI*	4.00	3.00-4.00	0.077
	With ARI/*Sa ABI*	6.00	5.00-7.00	
Time from admission to suspicion of HFRS *Vreme od prijema do postojanja sumnje na HGBS*	Without ARI/*Bez ABI*	4.50	3.00-6.00	0.850
	With ARI/*Sa ABI*	5.00	4.00-6.50	
SOFA *SOFA*	Without ARI/*Bez ABI*	2.00	0.00-2.00	0.101
	With ARI/*Sa ABI*	3.50	2.00-6.00	
SAPS II *SAPS II*	Without ARI/*Bez ABI*	12.00	9.00-13.00	0.013
	With ARI/*Sa ABI*	20.00	16.00-24.00	

Table 4. Laboratory data in patients who developed ARI compared to the ones who did not develop ARI
Tabela 4. *Laboratorijski podaci kod bolesnika kod kojih je došlo do razvoja ABI u odnosu na bolesnike kod kojih se ABI nije razvila*

	ARI/*ABI*	Without ARI/*Bez ABI*	p/*p*
Leukocytes/*Leukociti* (x10^9/l)	10.05 (5.16-10.69)	8.70 (6.51-9.60)	0.724
Erythrocytes/*Eritrociti* (x10^9/l)	4.98 (4.73-5.57)	4.57 (4.52-5.02)	0.099
Platelets/*Trombociti* (x10^9/l)	70.75 (55.0-207.00)	74.00 (57.00-178.00)	0.906
Aptt a second/*Aptt sekunda*	0.97 (0.97-0.98)	2.89 (1.86-4.92)	0.564
Prothrombin time a second/*Protrombinsko vreme u sekundi*	7.15 (0.91-13.40)	1.11 (1.01-5.75)	0.767
CRP/*CRP* (mg/l)	59.15 (30.45-93.55)	54.85 (31.15-145.400)	0.865
Urea/*Urea* (mmol/L)	7.950 (5.80-15.00)	6.00 (5.00-6.30)	0.157
Serum creatinine/*Kreatinin u serumu* (µmol/L)	98.50 (90.0-253.00)	92.00 (92.0-98.00)	0.375
Highest recorded creatinine values *Najviše zabeležene vrednosti kreatinina* (µmol/L)	215.50 (140.0-402.00)	93.00 (92.0-117.00)	0.011
Sodium/*Natrijum* (mmol/L)	139.00 (136.0-140.00)	139.00 (138.0-141.00)	0.599
AST/*AST* (U/L)	44.50 (38.0-62.00)	26.00 (19.0-31.00)	0.077
ALT/*ALT* (U/L)	36.50 (31.0-48.00)	28.00 (19.0-41.00)	0.346

recorded creatinine values during hospitalization and:

– The duration of symptoms before admission to the hospital, of both the mean and high intensity (p=0.047; p=0.608), with the former being statistically significant.

– Leukocyte values, of moderate intensity (p=0.048; p=0.517).

– Initially recorded values of urea (p=0.002; p=0.742) and creatinine (p=0.05; p=0.685) of high intensity.

– The initially recorded values of predictive SOFA score (p=0.013; p=0.612) and SAPS II (p=0.023; p=0.582), of moderate to high intensity.

No statistically significant correlation was observed between the highest recorded creatinine values and other laboratory parameters (p>0.05).

Hemorrhagic syndrome, clinical and laboratory manifestations in HFRS patients

Thrombocytopenia was documented in 9 out of 15 patients (60%), prolonged prothrombin time in 2 out of 15 patients (13%), and manifestations of hemorrhagic syndrome, including epistaxis, microhematuria, skin hemorrhages, and gum bleeding, in 7 out of 15 patients (46.7%).

There was no statistically significant difference observed in gender or disease symptoms concerning the occurrence of hemorrhagic syndrome (p>0.05). Similarly, no statistically significant differences were noted in age, duration of complaints before hospital admission, predictive scores, or laboratory parameters between patients with and without hemorrhagic syndrome (p>0.05).

Hemorrhagic fever with renal syndrome - Duration of hospitalization and disease outcome among all subjects

The mean duration of hospitalization was 10 days (range 7-13).

None of the documented disease symptoms exhibited a statistically significant impact on the duration of hospitalizations (p>0.05).

Correlation analysis revealed associations between the duration of hospitalization and the following laboratory parameters:

– Leukocytosis exhibited a positive correlation of moderate intensity (p=0.028; ρ=0.566).

– CRP showed a positive correlation of moderate to high intensity (p=0.014; ρ=0.686).

– The highest recorded creatinine values demonstrated a positive correlation of moderate intensity (p=0.022; ρ=0.585).

– Serum sodium concentrations exhibited a negative correlation of high intensity (p=0.009; ρ= -0.772).

Discussion

Infectious diseases have historically emerged following major natural disasters, particularly after the flooding of river basins and acute food shortages caused by severe storms. As long as microorganisms persist, alongside their primary vectors and reservoirs among animals, this correlation will continue to exist [9, 10].

Hemorrhagic Fever with Renal Syndrome is endemic in the Balkan countries, with periodic outbreaks and sporadic cases. Annually, about 100 cases are reported in the Balkan Peninsula, with a noticeable seasonal distribution, showing higher prevalence during the summer months, with occupation being the predominant risk factor [11, 12]. Epidemiologically, it is well-established that extraordinary conditions such as floods, earthquakes, and wars facilitate the transmission of infectious diseases. However, a higher frequency of HFRS is observed in the AP of Vojvodina, despite its lack of direct exposure to these phenomena. In our study, the rise in the number of patients during specific years can be attributed to findings from mainland China, which demonstrated that increased rainfall, higher temperatures, and elevated air humidity are conducive to the survival and proliferation of the causative agent [11, 12]. This infection occurs more frequently in regions where the annual average temperature is around 20°C, the annual average relative humidity ranges between 50-80%, and the annual total precipitation ranges from 400 to 1600 mm. In contrast, no cases have been reported in western China, where the average altitude exceeds 2000 m, and precipitation is infrequent, resulting in relative humidity typically exceeding 50% and fewer than 60 rainy days per year. Based on the aforementioned data, most researchers believe that precipitation, coupled with lower air temperatures, are the most significant meteorological factors influencing the abundance and activity of rodents, the primary vector of the HFRS causative agent of [13–16]. The average duration of illness prior to hospitalization in our study was 5 days. Among the 15 patients with available data on laboratory parameters, disease course, and outcome, no fatalities were recorded. Different authors, employing diverse sample populations and diagnostic criteria for ARI, have identified different predictors for its etiology. In contrast to data from Asian regions, where high mortality rates are documented, in our country, all patients presented with a less severe clinical presentation, with no reported fatalities, and none necessitated hemodialysis among those who developed ARI. These findings align with global data suggesting that Puumala virus (PUUV) induces milder disease manifestations [17–19]. The objective of our study was to investigate factors associated with the occurrence of ARI and hemorrhagic manifestations, and to determine the primary determinants of hospitalization duration among patients with HFRS. ARI, a primary complication of HFRS, is a multifaceted disorder characterized by clinical manifestations ranging from a minimal elevation in serum creatinine levels to the requirement for hemodialysis [17, 24]. Recent epidemiological studies indicate considerable diversity in etiology and risk factors, and highlight the elevated mortality rates linked with this disease, particularly when dialysis

is required. These studies suggest an association with the subsequent development of HFRS and dependency on dialysis. Emerging evidence also suggests that even minor elevations in serum creatinine levels are correlated with increased patient mortality [8]. Utilizing the AKIN definition of ARI, our findings reveal that among the 15 patients with a confirmed diagnosis of HFRS, 6 developed ARI. Factors associated with elevated creatinine levels and the development of ARI during hospitalization included the initially recorded values of urea and creatinine, the duration of symptoms before hospital admission, SAPS II score, and leukocytosis upon hospital admission [7].

In one of the numerous studies on HFRS conducted in China, the SAPS II score was positively correlated with mortality in ARI cases. Conversely, SOFA score, widely used for assessing hospitalization duration, mortality risk, and as a major prognostic indicator for severe sepsis, also showed significant correlation with the severity of HFRS. This suggests that these scoring systems possess strong predictive value for the progression of severe HFRS [8]. Our study also demonstrates a positive correlation between SAPS II score values and the occurrence of acute renal failure. While the findings for the SOFA score exhibit a clear trend towards statistical significance, we hypothesize that this was not reached due to the sample size limitations.

Regarding the development of hemorrhagic syndrome, data from various studies suggest diverse factors associated with the occurrence of hemorrhagic manifestations [20, 21].

Our study did not demonstrate a difference in the presentation of specific symptoms/signs or laboratory findings between patients with and without hemorrhagic manifestations. This observation may be explained by the mild nature of the hemorrhagic manifestations observed in our patients, which were limited to isolated instances of epistaxis, microhematuria, and skin and gum bleeding. In contrast, more pronounced hemorrhagic manifestations are documented in endemic regions with other virus subtypes. Another explanation could be the small sample size, which may be insufficient to detect statistically significant differences.

Our results indicate that the average duration of hospitalization was 10 days (range 7-13), and none of the symptoms significantly influenced the length of hospital stay. However, the duration of hospitalization was associated with leukocytosis, CRP values, highest creatinine values, and serum sodium concentration. Consistent with our findings, a study conducted in Slovenia reported an average hospital stay of 10.4 days [22, 23].

Conclusion

In our study, the clinical presentation of hemorrhagic fever with renal syndrome was predominantly mild among most patients, with acute renal failure observed in 40% of cases, none of which required hemodialysis. The peak incidence of the disease occurred in 2014, coinciding with a significant rise in precipitation levels, slightly elevated average air temperatures in winter, lower temperatures in summer months, and increased air humidity. Further detailed investigation into environmental conditions, as well as other contributing factors, is warranted to better understand the rise in the number of patients with hemorrhagic fever with renal syndrome.

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