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Clinical Characteristics Analysis of Hemorrhagic Fever with Renal Syndrome in 145 Children of Different Age Groups

Lu Cao[1,a], Yufeng Zhang[2,b,*], Xiaoyan Wang[2,c], Kairui Lei[2,d]

[1]School of Public, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]The 2nd Department of Infectious Diseases, Xi'an Children's Hospital, Xi'an, 710003, China
[a]2471834343@qq.com, [b]568276013@qq.com, [c]wangxiaoyan509@126.com, [d]lkrui98@163.com
**Corresponding author*

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Abstract: To summarize and analyze the clinical characteristics of Hemorrhagic Fever with Renal Syndrome (HFRS) in children of different age groups, we aim to provide important information for the diagnosis, treatment, and prevention of the disease. Clinical data of 145 pediatric cases of Hemorrhagic Fever with Renal Syndrome (HFRS) from Xi'an Children's Hospital between 2019 and 2021 were collected through a cross-sectional survey. The three-dimensional distribution of HFRS in children was described, and the clinical characteristics and laboratory indicators of HFRS across different age groups were analyzed. Of the 145 children, 105 (72.4%) were males and 40 (27.5%) were females, with a mean age of (9.17±3.69) years. The cases were mainly concentrated in rural and suburban areas (85.5%). It peaked in winter. The main symptoms of 145 children were fever (144 cases, 99.3%), congestion (91 cases, 62.8%), bleeding (89 cases, 61.4%), and abdominal pain (89 cases, 61.4%). The 145 children were divided into four groups according to age: <5 years, 5-9 years, 9-12 years, and >12 years. Some of the typical clinical symptoms such as petechial hemorrhage, hemorrhagic shock, oliguria, orbital pain, and electrolyte disorders were more typical between the ages of 9-12 years than the other age groups ($P < 0.05$). Some blood indices such as ALT, BUN, PCT, ALB, PLT, Hb, Na, Ca were more typical between 9-12 years of age than other age groups ($P < 0.05$).The clinical manifestations of Hemorrhagic Fever with Renal Syndrome (HFRS) in children are often atypical, predominantly affecting school-age boys, with peaks in November and December. During high-incidence seasons or in endemic areas, healthcare providers maintain heightened vigilance for children presenting with liver and kidney function abnormalities or electrolyte imbalances, promptly conducting comprehensive relevant tests to avoid missed or misdiagnoses.

1. Introduction

HFRS is a natural epidemic disease caused by Hantavirus [1-2]. Its mortality rate is 0.3%-10%, and about 100,000 cases of HFRS occur globally each year, with China being the country with the largest number of cases, accounting for 70%-90% of all HFRS cases, and HFRS is still a great threat to public health [3-4]. In recent years, the prevalence of the disease has shown new characteristics and trends due to factors such as increased population mobility and environmental pollution. Currently, there are relatively few studies on HFRS in children, and the clinical symptoms of HFRS in children are mostly atypical, which makes it easy to be misdiagnosed and underdiagnosed. Therefore, this study aims to systematically analyze the epidemiological features and clinical characteristics of HFRS, which is of great significance in guiding clinical diagnosis and treatment and formulating public health policies.

2. Date and Methods

2.1. Clinical Date

Collection of 145 children with confirmed nephrotic syndrome hemorrhagic fever in Xi'an Children's Hospital, 2019-2021.The diagnostic criteria were referred to the Diagnostic Criteria for Epidemic Hemorrhagic Fever: WS 278-2008 issued by the former Ministry of Health of the People's Republic of China in 2008 [5] and the Expert Consensus on the Prevention and Control of Hemorrhagic Fever in Renal Syndrome issued in 2021 [6]. That is, confirmed cases need to have a positive serum-specific IgM antibody on the basis of a suspected or clinical diagnosis, or detection of hantavirus RNA from patient specimens, or a more than 4-fold increase in serum-specific IgG antibody potency during the recovery phase compared with the acute phase, or isolation of hantavirus from patient specimens.Exclusion of comorbidities such as severe kidney disease, liver disease, autoimmune disease, congenital disease, and inherited metabolic disease.

2.2. Methods

General information about the children was collected through the hospital management information system, including epidemiologic information, clinical symptoms, signs, and laboratory tests.

Excel and Spss26.0 software were used for descriptive statistical analysis, spatial and time series analysis, and plotting. Count data were expressed as the number of cases or percentages, and intergroup comparisons were made by $\chi 2$ test, and those that conformed to normally distributed data were expressed by $x \pm s$, and the difference was considered statistically significant at $P<0.05$.

3. Conclusions

3.1. Epidemiological Information

3.1.1. Geographical Distribution Characteristics

In this study, the cases were from Shaanxi Province, including Xi'an City (118 cases, 81.4%), Weinan City (9 cases, 6.2%), Xianyang City (7 cases, 4.8%), Baoji City (4 cases, 2.8%), Yan'an City (3 cases, 2.1%), Shangluo City (3 cases, 2.1%), and Yulin City (1 case, 0.7%). The children were from rural and suburban areas (124 cases, 85.5%) and towns (21 cases, 14.5%).

3.1.2. Characteristics of Population Distribution

Among the 145 children, boys (105 cases, 72.4%) and girls (40 cases, 27.5%) were found, with a male to female ratio of 2.63:1. The age of the 145 children ranged from a minimum of 5 months and 5 days to a maximum of 17 years, with a mean age of 9.17±3.69 years. Further analysis of age showed that the highest number of cases was 48 (33.10%) in the age group of 9-12 years, with 36 cases in boys and 12 cases in girls; see Figure 1 for details.The number of cases in each age group was higher in boys than in girls, with a high prevalence in the age group of 9-12 years (P < 0.05).

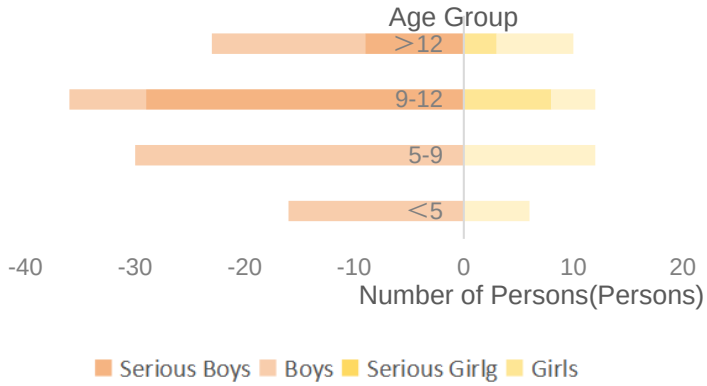

Figure 1 Distribution of population in each age group

The age of the heavy and critically ill children was mainly concentrated at 11 years old, and the mean age of the heavy male children (11.32±0.79) years old is shown in Table 1

Table 1 Characteristics of disease type and age distribution in 145 children

	Male (average age)	Female (average age)	Total	x^2	*P*
Light and Medium	67(8.07±4.10)	29(7.93±4.07)	96(8.07±4.10)	0.64(0.02)	<0.05
Serious and Critical	38(11.32±0.79)	11(11.21±0.61)	49(11.32±0.79)		
Total	105(9.17±3.69)	40(9.13±3.75)	145(9.17±3.69)		

3.1.3. Characteristics of Time Distribution

Childhood nephrotic syndrome hemorrhagic fever peaked in November and December (112/145, 77.2%), as detailed in Figure 2.

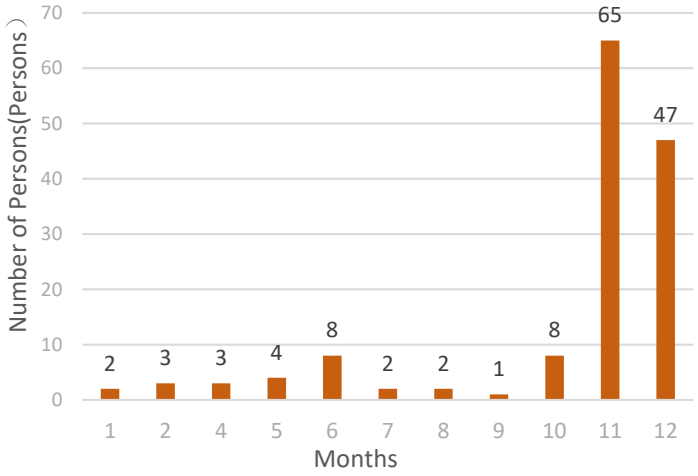

Figure 2 The month of onset of 145 children

3.2. Clinical Features of the Disease

3.2.1. Course of Disease

The mean duration of illness in 145 children was (10.11±5.32) days. The mean duration of the disease was (9.64±2.48) d in the age group <5 years, (12.52±3.56) d in the age group 5-9 years, (16.96±6.32) d in the age group 9-12 years and (14.76±6.42) d in the age group >12 years.

3.2.2. Clinical Symptom

Among the febrile children, the shortest duration of fever was 1 d and the longest was 13 d, with a mean duration of fever of (5.02±2.25) d. The main symptoms of the cases were fever (144 cases, 99.3%), congestion (91 cases, 62.8%), hemorrhage (89 cases, 61.4%), abdominal pain (89 cases, 61.4%), nausea and vomiting (79 cases, 54.5%), back pain (76 cases, 52.4%), electrolyte disorders (71 cases, 49.0%), headache, oliguria, and orbital pain. Among them, shock, petechial hemorrhage, oliguria, orbital pain, hemorrhage, bulbar conjunctival edema, lethargy, multiple plasma cavities with mucosal effusion and electrolyte disorders were more ($P<0.05$) in children aged 9-12 years compared to the number of cases in other age groups. See Table 2 for details.

Table 2 Clinical characteristics of 145 children grouped by age [number of cases (%)]

symptomatic	<5 (n=23)	5-9 (n=42)	9-12 (n=47)	>12 (n=33)	Total (n=145)	χ^2	*P*
feverish	22(95.7)	42(100)	47(100)	33(100)	144(99.3)	5.341	0.148
shock	0	0	7(14.9)	1(3.0)	8(5.5)	12.114	0.007
bruising	0	2(4.8)	13(27.7)	2(6.1)	17(11.72)	17.576	0.001
oliguria	0	0	19(40.4)	10(30.3)	29(20)	30.695	0.000
anuria	0	0	3(6.4)	1(3.0)	4(2.8)	4.155	0.245
headaches	9(39.1)	15(35.7)	23(48.9)	17(51.5)	64(44.1)	2.610	0.456
orbital pain	0	5(11.9)	11(23.4)	9(27.3)	25(17.2)	9.208	0.027
abdominal pain	13(56.5)	21(50)	34(72.3)	21(63.6)	89(61.4)	4.976	0.174
lumbago	8(34.8)	19(45.2)	27(57.4)	22(66.7)	76(52.4)	6.899	0.075
Vomiting and nausea	9(39.1)	23(54.8)	29(61.7)	18(54.5)	79(54.5)	3.175	0.365
constipation	0	1(2.4)	4(8.5)	1(3.0)	6(4.1)	3.687	0.297
hyperemia	11(47.8)	25(59.5)	33(70.2)	22(66.7)	91(62.8)	3.715	0.294
bleeding	8(34.8)	23(54.8)	39(83.0)	19(57.6)	89(61.4)	17.091	0.001
bulbar edema	0	0	5(10.6)	4(12.1)	9(6.2)	7.870	0.049
convulsion	0	1(2.4)	3(6.4)	1(3.0)	5(3.5)	2.198	0.532
drowsiness	0	0	4(8.5)	0	4(2.8)	8.577	0.035
excitable	0	0	4(8.5)	1(3.0)	5(3.4)	5.957	0.114
Multiple plasma cavities	0	0	6(12.8)	6(18.2)	12(8.3)	11.379	0.010
electrolyte disorder	3(13.0)	16(38.1)	36(76.6)	16(48.5)	71(49.0)	30.468	0.000

3.2.3. Laboratory Tests

Blood routine liver function: blood bilirubin was elevated in 22 cases (15.17%); alanine aminotransferase was elevated in 47 cases (32.4%); albumin was decreased in 103 cases (71.03%). Renal function: urea nitrogen was elevated in 83 cases (57.24%); blood creatinine was elevated in

135 cases (93.1%). Calcitoninogen test: PCT was elevated in 129 cases (88.97%). Cardiac enzyme examination: creatine kinase isoenzyme was elevated in 86 cases (59.31%). Electrolytes: potassium decreased in 122 cases (84.14%), sodium decreased in 83 cases (57.24%), chloride decreased in 67 cases (46.21%), calcium decreased in 62 cases (42.76%).

Among 145 cases, White Blood Cell (WBC) was elevated in 64 cases (44.13%); Platelets (PLT) was decreased in 129 cases (88.97%); Hemoglobin (Hb) was decreased in 29 cases (20%). Blood Bilirubin (TBIL) was higher than the normal range in 22 cases (15.17%), Alanine aminotransferase (ALT) was abnormal in 47 cases (32.4%), Albumen (ALB) was abnormal in 103 cases (71.03%), Urea nitrogen (Urea nitrogen (BUN) was abnormal in 83 cases (57.2%). There were also sodium (Na) abnormalities in 84 cases (57.9%), chloride (Cl) abnormalities in 47 cases (32.4%), and calcium (Ca) abnormalities in 62 cases (42.8%). Creatine kinase isoenzyme (CKMB) was above the normal value range in 87 cases (60%).

The composition ratio of each age group is shown in Figure 3.

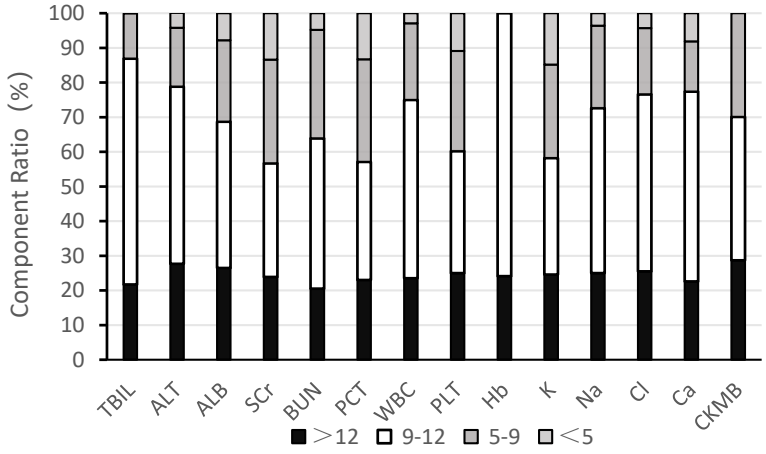

Figure 3 Score map of blood indexes grouped by age in 145 children

The 145 study subjects were divided into 4 groups according to age: <5 years old, 5-9 years old, 9-12 years old, and >12 years old, and the differences in TBIL, ALT, SCr, BUN, PCT, WBC, and CKMB among children of different ages were statistically significant ($P<0.05$). Differences in ALB, PLT, Hb, Na, Cl, Ca were statistically significant in children of different age groups ($P<0.05$).

The mean values of various blood indices of different groups were analyzed and compared with the normal reference range of each index.The mean values of ALT, SCr, BUN, PCT, WBC, CKMB were above the normal range in the age group of 9-12 years old and in other age groups the values of these indices were within the normal range.For the indices such as ALB, PLT, Na, Cl, Ca, etc. the mean values of the 9-12 years old were below the normal range and in other age groups the values were within the normal range.The mean values of Hb, TBIL were within the normal reference range in all the groups. normal value range, children in other age groups had values within the normal value range, and Hb and TBIL indicators in all groups had values within the normal reference value range. See Figure 4.

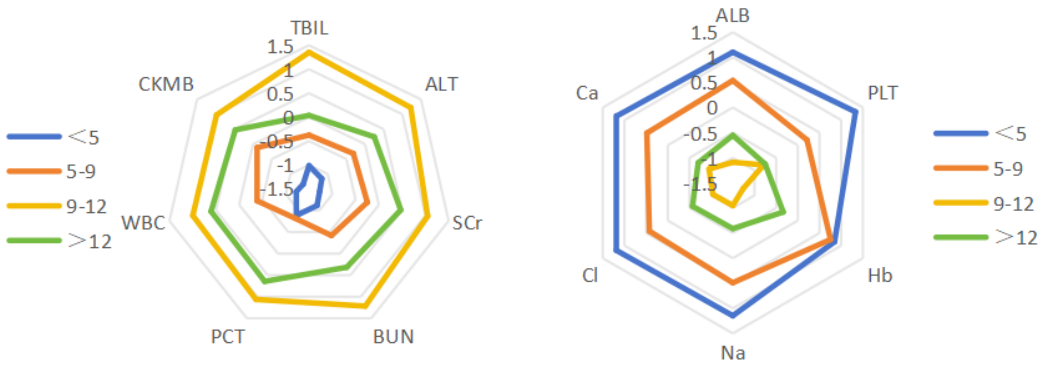

Figure 4 Comparison of radar maps of blood indexes in 145 children by age

3.3. Treatment and Prognosis

All 145 children diagnosed with renal syndrome hemorrhagic fever were cured and discharged after comprehensive medical treatment.

4. Discussions

Hemorrhagic fever of renal syndrome (HFRS) has been reported globally [7] and is endemic in several countries and regions in Asia and Europe, with a high morbidity and mortality rate, and is a public health problem of global concern [8,9] It is prevalent to varying degrees in China every year [10]. According to the official data released by Shaanxi Provincial Bureau of Statistics, between 2018 and 2021, the incidence rate of HFRS had been as high as 7.6300/100,000 in 2021, 5.2912/100,000 and 3.0121/100,000 in 2020 and 2019, respectively, and 4.5445/100,000 in 2018 [11]. A study by Deng Xuefei et al. also pointed out that Shaanxi Province and the three northeastern provinces were the hardest hit by the HFRS epidemic in China during 2004-2005 [12]. In Shaanxi province, all cities had reported incidence, and the high incidence areas were mainly concentrated in Guanzhong, which was more consistent with the regional distribution of the data in this study.

In this study 145 children with HFRS were 72.4% males and 27.5% females, with a male to female ratio of 2.625:1, which is similar to the national data of 2.70:1, showing a significantly higher prevalence in males than in females. However, there was no significant difference in the mean age between genders, which indicated that the age of onset was similar between genders [13]. Meanwhile, it was found that the prevalence of HFRS tended to be in children <15 years of age and older adults >60 years of age, and the prevalence in children under 15 years of age was on the rise [14]. This emphasizes the influence of age on the prevalence of HFRS and reveals the trend of the disease across age and gender. The present study showed that most of the children with HFRS (85.5%) were concentrated in rural and suburban areas, which is closely associated with the area of rodent activity and is consistent with the results of a previous study [15]. Therefore, special attention should be paid to hemorrhagic fever prophylaxis in these areas, especially during the peak winter months of November and December, which coincides with the behavioral pattern of rodents searching for food and sheltering from the cold by entering residential areas, and is also in line with previous studies [16].

The incidence of HFRS in children is approximately 10% of the total number of cases [17]. Pediatric patients have mild systemic toxic symptoms [18], atypical clinical manifestations that may involve the digestive, circulatory, and respiratory systems, and pediatric patients usually recover faster and have a better prognosis [6]. While retrospectively analyzing the clinical characteristics of

145 children with HFRS, it was found that children in the age group of 9-12 years had a longer duration of illness. This may be related to the higher proportion of severely and critically ill children in this age group, and to the abnormalities of blood indices in children in this age group, including higher levels of ALT, SCr, BUN, PCT, WBC, and CKMB, and lower levels of ALB, PLT, Na, Cl, and Ca. Abnormalities in these markers may reflect more severe liver damage, renal impairment, increased inflammatory response, increased white blood cell counts, and myocardial damage, as well as decreased protein levels, thrombocytopenia, and electrolyte imbalances. After grouping children by age, we investigated whether there were differences in the symptoms and clinical indicators of HFRS in children of different ages. Children between 9 and 12 years of age were likely to exhibit more pronounced clinical symptoms, such as fever, congestion, hemorrhage, abdominal pain, headache, oliguria, orbital pain, and petechiae, which were more frequent than those of other age groups, and a greater proportion of the abnormal clinical indicators were found in this group. Our scholars, Hongwei Ma, Tiejian X. et al. showed that HFRS is prevalent in school-age children aged 7-14 years [18], and a study in the Crimea-Congo also showed that hemorrhagic fever was more common in older boys [19]. This may be related to the increased clinical complications resulting from a strong immune response with increased antibody dependence during school age [20]. In addition, children in this age group are generally able to describe their discomfort more accurately, which helps parents and healthcare professionals to recognize relevant symptoms in a timely manner. At the same time, due to the wider range of activities of children in this age group, they have more opportunities to come into contact with rodents or their feces that may be carrying the virus [21], thus increasing the risk of infection. Therefore, special attention and preventive measures are needed for children in this age group to reduce the incidence of diseases such as hemorrhagic fever.

In the present study, the incidence of the typical symptoms of HFRS, “three reds” and “three pains”, was not high, with 64 cases of headache (44.1%), 25 cases of orbital pain (17.2%), and 91 cases of congestion (62.8%) among 145 children. These findings are consistent with previous studies [22] and suggest atypical clinical features of HFRS in pediatric patients.

HFRS can cause multi-systemic damage with statistical differences between age groups. In the present study, we found a high percentage of abnormal ALT in liver function indices, especially in children aged 9-12 years. Previous studies [23] have shown that hantavirus infection is ubiquitous, and hantavirus antigens can be detected in tissues such as the liver, spleen, heart, kidneys, lymph nodes, and nervous system in patients with HRFS [24,25], and elevated ALT is associated with the susceptibility of the liver, which is rich in small blood vessels, to involvement. In the present study, we found a high rate of abnormal ALT in children aged 9-12 years, whether it is related to the damage of abnormal immune response after hantavirus infection in this age group needs to be further investigated in the follow-up.Abnormal elevation of CKMB, especially in children aged 9-12 years, suggests that there is an increased risk of myocardial or muscular damage after hantavirus infection in this age group [26]. Among the indicators of infection, the proportion of abnormal PCT and WBC was significantly higher in the group of children aged 9-12 years, and the significant increase in PCT levels in children with HFRS was not specifically suggestive of a co-infection with bacterial infections, and may be related to the initiation of multiple immune responses in vivo by hantavirus infection [27]. Some studies have shown that elevated leukocyte counts correlate with the severity of the clinical condition [28], and children with significantly elevated leukocyte counts should be alerted to the progression of the disease.The increase in the rate of abnormal indicators in the group of children aged 9-12 years reminds clinicians that they need to monitor the condition of the children in this age group and the damage to organs, and to formulate individualized treatment plans for children of different ages, so as to be alerted to the progression of the disease.

There are some limitations of this study, such as small sample size and limited geographical scope. Therefore, larger and multicenter studies are needed in the future to validate the results of this study as well as to further confirm the characteristics and manifestations of HFRS in different populations.

In summary, this study reveals the gender, age and epidemiologic characteristics of children with HFRS, providing important clues for further prevention and diagnosis. Future studies should expand the sample size and incorporate data from more geographic areas for a more comprehensive understanding of the pathogenesis and characteristics of HFRS in children. In practice, it is recommended that health surveillance and education and publicity efforts in rural and suburban areas be strengthened, especially in winter to enhance rodent prevention and control measures. In addition, healthcare professionals should consider the age factor of patients when diagnosing and treating HFRS and adopt individualized treatment plans accordingly.

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