

## Serum Albumin Level Correlates with Disease Severity in Patients with Hemorrhagic Fever with Renal Syndrome

Hypoalbuminemia frequently occurs in Hemorrhagic Fever with Renal Syndrome (HFRS), but clinical significance of hypoalbuminemia is not well known. This study was designed to evaluate hypoalbuminemia as a marker of severity of disease in patients with HFRS. We evaluated the relationship between the level of serum albumin and clinical parameters representing the severity of disease in 144 patients with HFRS. The patients were divided into three groups based on the level of serum albumin; Group I (normal serum albumin), Group II (serum albumin  $<3.5$  g/dL and  $\geq 3.0$  g/dL), and Group III (serum albumin  $<3.0$  g/dL). Of the total of 144 patients, 42 patients (29.2%) were categorized as Group I, 39 patients (27.1%) as Group II, and 63 patients (43.8%) as Group III. Group III had a higher rate of incidence in episode of hypotension, pulmonary edema than did Group I and Group II. The lowest level of serum albumin was positively correlated with platelet count ( $r=0.505$ ,  $p<0.001$ ) and was negatively correlated with leukocyte count ( $r=-0.329$ ,  $p<0.001$ ), BUN ( $r=-0.484$ ,  $p<0.001$ ), serum creatinine ( $r=-0.394$ ,  $p<0.001$ ), and AST ( $r=-0.251$ ,  $p=0.002$ ). Our data suggest that hypoalbuminemia frequently occurs in the acute stage of HFRS, and level of serum albumin is associated with the disease severity of HFRS.

**Key Words :** Hemorrhagic Fever With Renal Syndrome; Serum Albumin, Hypoalbuminemia; Hypotension; Thrombocytopenia

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### INTRODUCTION

Hemorrhagic Fever with Renal Syndrome (HFRS) is an acute infectious disease caused by Hantavirus. The clinical manifestations of HFRS comprise the triad of fever, hemorrhage, and acute renal failure (1-3). The central physiologic derangement in HFRS is widespread vascular dysfunction, leading to impaired vascular tone and increased vascular permeability (4-6). Therefore, the disease severity of HFRS depends on the degree of vascular dysfunction (4). The clinical parameters representing the severity of disease in patients with HFRS are hypotension, severe acute renal failure, thrombocytopenia, leukocytosis, hepatic dysfunction, and pleural effusion (4-6). Besides these clinical factors, encephalopathy, sepsis, anuria, acidosis, electrolyte abnormality, proteinuria of long duration, increased hemoconcentration during hypotensive stage are known to represent the severity of disease of HFRS (7-9).

Hypoalbuminemia frequently occurs in acute stage of HFRS. Its mechanism seems to be multifactorial; increased catabolism of protein, vascular leakage of serum protein due to increased vascular permeability, loss of urinary protein, decreased intestinal absorption of protein due to poor oral intake, and decreased synthesis of albumin due to hepatic dysfunction. We have previously reported that loss of protein via intestinal tracts was common in HFRS, and it was associated with the level of serum

albumin and clinical parameters representing increased vascular permeability (10). Generally, hypoalbuminemia is known to be associated with complications and mortality in patients with acute infectious disease (11). Based on the findings, we hypothesized that hypoalbuminemia may be associated with the disease severity in patients of HFRS, and we also studied relationship between level of serum albumin and clinical parameters representing severity of disease (hypotension, severe acute renal failure, thrombocytopenia, leukocytosis, hepatic dysfunction, and pleural effusion) in patients with HFRS.

### MATERIALS AND METHODS

#### Study Population

One hundred forty-four patients with HFRS, who admitted between January 1993 and December 2001 in Uijongbu St. Mary's Hospital, Uijongbu, Korea, were included in this study. The diagnosis of HFRS was based on clinical manifestations (high fever, flank pain, acute renal failure, proteinuria, and thrombocytopenia) and indirect immunofluorescence antibody test against the Hantavirus. The patients with chronic liver disease, congestive heart failure, chronic renal failure, hematologic disease, and inflammatory bowel disease were

excluded. Out of the total 144 patients, 110 were male (76.4%) and the mean age was  $42 \pm 15$  yr (range: 11-82 yr).

### Study Design

We retrospectively studied medical records of the patients with HFRS. We obtained medical records of clinical symptoms and signs and the following laboratory values from each patient with HFRS; hemoglobin, hematocrit, platelet count, leukocyte count, blood urea nitrogen (BUN), serum creatinine, serum albumin level, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and proteinuria and 24 hr urine protein amount. We also evaluated plain chest and abdomen radiography and abdominal ultrasonography. Finally, we investigated the episodes of hypotension, admission duration, and outcome from the patients. Hypotension was defined as systolic pressure below 90 mmHg. Hypoalbuminemia was defined as a serum albumin less than 3.5 g/dL. Thrombocytopenia was defined as a platelet count below  $100,000/\mu\text{L}$ . Leukocytosis was defined as a leukocyte count over  $10,000/\mu\text{L}$ . Acute renal failure was defined as a serum creatinine over 2 mg/dL. Abnormal liver function was defined as an AST or ALT over 80 IU/L. Platelet transfusion was performed, when there was severe thrombocytopenia less than  $50,000/\mu\text{L}$  or hemorrhagic manifestation or central vein cannulation for hemodialysis in case of moderate thrombocytopenia more than  $50,000/\mu\text{L}$ . Hemodialysis treatment was individualized according to the degree of acute renal failure and volume status. The patients were divided into three groups based on the level of serum albumin; Group I (normal serum albumin), Group II (serum albumin  $<3.5$  g/dL and  $\geq 3.0$  g/dL), and Group III (serum albumin  $<3.0$  g/dL). Laboratory and clinical values were then compared among the three groups, and the correlation between the lowest level of serum albumin and laboratory values was evaluated.

### Statistical Analysis

Data were expressed as mean  $\pm$  standard deviation (SD). The differences among groups were analyzed by a one-way analysis of variance (ANOVA), followed by Schffe's test for multiple comparisons. Pearson's correlation coefficient was used to determine the relationship between the lowest level of serum albumin and laboratory values. The significance of differences between proportions was tested by the chi-square test. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

### Clinical Characteristics

Indirect immunofluorescence antibody tests against the Hantavirus were positive in all patients. Fever developed in 128

(88.9%) patients, flank pain in 47 (32.6%), abdominal pain in 81 (56.3%), myalgia in 65 (45.1%), and headache in 44 (30.6%). Episode of hypotension occurred in 29 (20.1%) patients. Acute renal failure developed in 113 (78.5%) patients, and 55 patients of those (38.2%) received hemodialysis treatment. Proteinuria (more than 1+ by urinalysis) developed in 115 (79.9%) patients, and it disappeared  $7.3 \pm 8.2$  days after admission. Quantitative measurement of urine protein performed in 106 patients showed  $1.9 \pm 1.6$  g/day. Thrombocytopenia developed in 118 (81.9%) patients, and 75 (52.1%) patients received platelet transfusion. Abnormal liver function developed in 86 (59.7%) patients. Laboratory findings at admission are listed in Table 1. Pulmonary edema developed in 24 (16.7%) patients. Hemorrhage manifestation developed in 18 (12.5%) patients: gastrointestinal bleeding (n=9), nasal bleeding (n=5), pulmonary hemorrhage (n=2), and intracranial hemorrhage (n=1). Ten (6.9%) patients were expired due to hypotensive shock (n=8), pulmonary hemorrhage (n=1), and intracranial hemorrhage (n=1). Mean duration value of the admission among the survivors (n=134) was  $11.6 \pm 7.7$  days (2-57 days).

### Incidence of Hypoalbuminemia

The rate of incidence of hypoalbuminemia at admission developed in 89 (61.8%) patients and increased up to 70.8% after admission. The level of serum albumin at admission ( $3.2 \pm 0.4$  g/dL) also decreased to  $3.1 \pm 0.4$  g/dL after admission. Based on the lowest level of serum albumin, 42 (29.2%) patients were categorized as Group I (normal serum albumin), 39 (27.1%) as Group II (serum albumin  $<3.5$  g/dL and  $\geq 3.0$  g/dL), and 63 (43.8%) as Group III (serum albumin  $<3.0$  g/dL). The patients in Group III were older than those in Group I ( $50 \pm 17$  vs.  $37 \pm 11$ ,  $p < 0.01$ ) and Group II ( $50 \pm 17$  vs.  $36 \pm 11$  yr,  $p < 0.05$ ), but there was no statistical difference between Groups I and II. There was no statistical difference in

Table 1. Laboratory findings in 144 patients with HFRS at admission

	Mean $\pm$ SD	Range	Normal range
Hb (g/dL)	$14.8 \pm 2.4$	8.9-21.4	12-16
Hct (%)	$43.5 \pm 7.4$	26.9-63.7	34-49
WBC ( $\times 10^3/\mu\text{L}$ )	$15.9 \pm 11.2$	3.7-59.3	5-10
Plt ( $\times 10^3/\mu\text{L}$ )	$70 \pm 69$	8-341	150-450
BUN (mg/dL)	$53.8 \pm 32.1$	5.9-121.9	8-23
Scr (mg/dL)	$5.1 \pm 3.4$	0.6-12.9	0.5-1.2
AST (IU/L)	$137 \pm 155$	14-890	13-36
ALT (IU/L)	$79 \pm 76$	4-453	5-33
Alb (g/dL)	$3.2 \pm 0.4$	2.1-4.6	3.8-5.3
Upro (g/day)	$1.93 \pm 1.66$	0.10-7.01	$<0.15$

Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell; Plt, platelet; BUN, blood urea nitrogen; Scr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alb, serum albumin; Upro, amount of 24 hr urine protein.

sex ratio between 3 groups (male percent; 80.9%, 79.4%, and 71.4%).

**Table 2.** The comparison of morbidity and mortality among the three groups

	Group I (n=42)	Group II (n=39)	Group III (n=63)
Hypotension (%)	0 <sup>†</sup>	7.6 <sup>‡</sup>	41.2
ARF (%)	42.8 <sup>*,†</sup>	94.8	92.1
Hemodialysis Tx (%)	0 <sup>*,†</sup>	34.8 <sup>‡</sup>	60.3
Thrombocytopenia (%)	54.7 <sup>*,†</sup>	89.7	95.2
Platelet transfusion (%)	19.0 <sup>*,†</sup>	58.9	69.8
Abnormal liver function (%)	42.8 <sup>†</sup>	64.1	68.2
Pulmonary edema (%)	0 <sup>†</sup>	2.5 <sup>‡</sup>	36.5
Admission duration (day)	7.9±4.6 <sup>†</sup>	10.5±5.5 <sup>‡</sup>	15.2±9.4
Death (%)	0 <sup>†</sup>	0 <sup>†</sup>	15.8

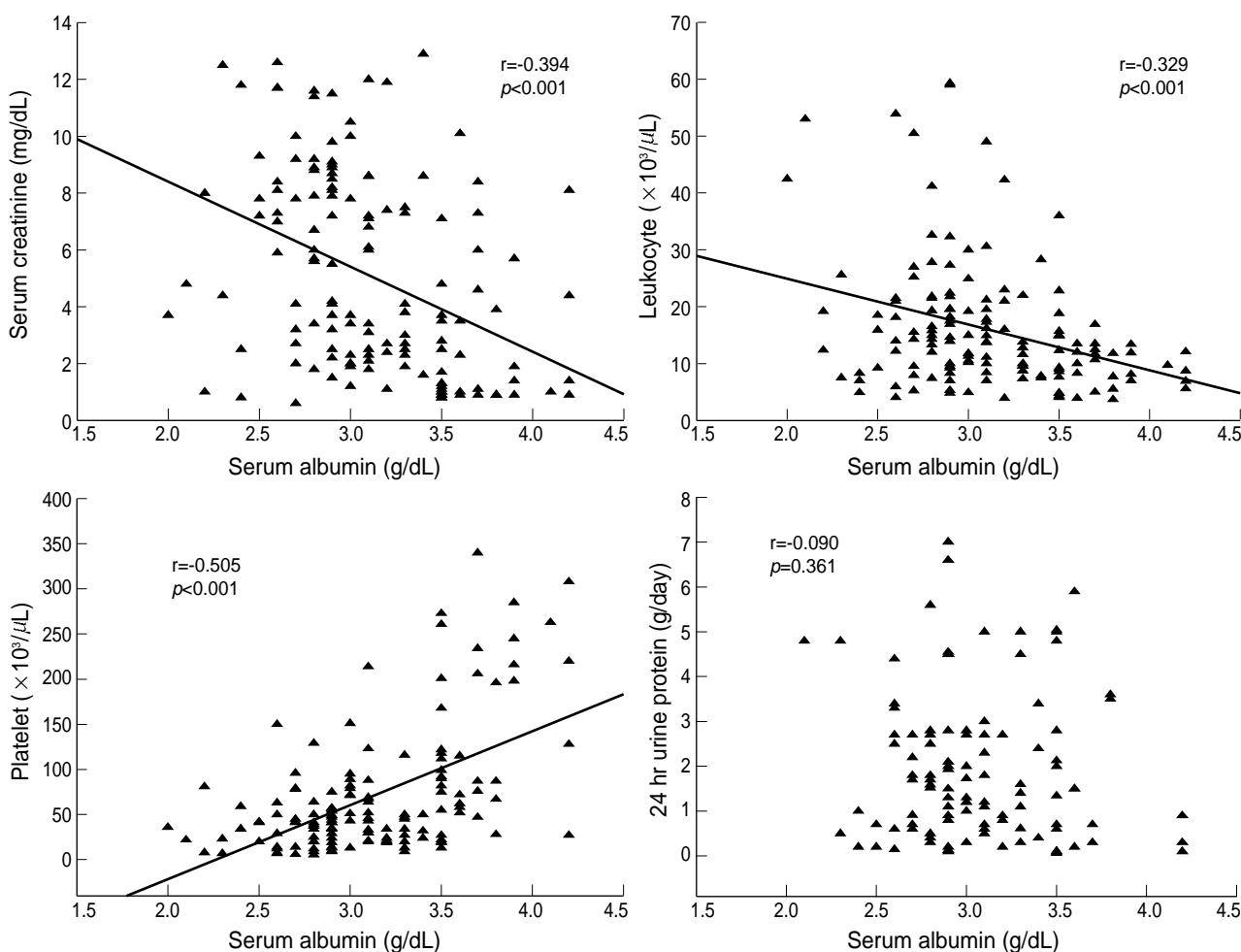
\*group I vs. group II,  $p < 0.05$ ; <sup>†</sup>group I vs. group III,  $p < 0.05$ ; <sup>‡</sup>group II vs. group III,  $p < 0.05$ .

### Correlation between the Lowest Level of Serum Albumin and Laboratory Values

The lowest level of serum albumin was positively correlated with platelet count ( $r = 0.505$ ,  $p < 0.001$ ), and was negatively correlated with leukocyte count ( $r = -0.329$ ,  $p < 0.001$ ), and BUN ( $r = -0.484$ ,  $p < 0.001$ ), and serum creatinine ( $r = -0.394$ ,  $p < 0.001$ ), and AST ( $r = -0.251$ ,  $p = 0.002$ ). But there was no correlation between the lowest level of serum albumin and hemoglobin ( $r = 0.058$ ,  $p = 0.491$ ), hematocrit ( $r = 0.050$ ,  $p = 0.553$ ), ALT ( $r = -0.120$ ,  $p = 0.153$ ), and amount of 24 hr urine protein ( $r = -0.090$ ,  $p = 0.361$ ) (Fig. 1).

### Comparison of Clinical Values and Mortality according to the Lowest Level of Serum Albumin

The rate of incidence of hypotension in Group III was higher than that of Group I (0%) and that of Group II (7.6%). The



**Fig. 1.** The correlation between the lowest serum albumin level and Scr, leukocyte count, platelet count, and amount of proteinuria. The lowest serum albumin level showed positive correlation with platelet count and negative correlation with Scr, leukocyte count. But there was no correlation with the lowest serum level and amount of 24 hr urine protein. Scr, serum creatinine; Plt, platelet; Upro, amount of 24 hr urine protein.

rate of incidence of acute renal failure in Groups II (94.8%) and III (92.1%) were higher than that of Group I (42.8%), and while more patients from Group III (60.3%) received hemodialysis treatment than did the patients from Group I (0%) and Group II (34.8%). Group I had a higher rate of incidence of thrombocytopenia and a higher incidence of platelet transfusion, when compared to Group II and Group III. Group I had a higher rate of incidence of abnormal liver function, compared to group III, but there was no statistical difference between Groups I and II. Group III had a higher rate of incidence of pulmonary edema, when compared to Groups I and II. All patients who were expired were in Group III, and the duration of admission of the survivors from Group III ( $15.2 \pm 9.4$  days) was longer than that of Group I ( $7.9 \pm 4.6$  days) and that of Group II ( $10.5 \pm 5.5$  days) (Table 2).

## DISCUSSION

Hypoalbuminemia frequently occurs in the acute stage of HFRS, but its significance is rarely reported until now. To evaluate the relationship between the level of serum albumin and the severity of disease in patients with HFRS, we have studied 148 patients with HFRS in a single center. Our data demonstrated that hypoalbuminemia frequently occurred in the acute stage of HFRS, and the lowest level of serum albumin was associated with the severity of disease of HFRS. To our knowledge, this is the first report demonstrating the relation between the level of serum albumin and the severity of disease of HFRS.

Hemodynamic alterations leading to hypotension and shock have been well characterized in patients with HFRS. These alterations appear to be the consequence of widespread vascular dysfunction, including impaired vascular tone and increased vascular permeability (4). Marked capillary congestion and the episode of hypotension reflect the impairment of vascular tone, while retroperitoneal edema, pleural effusion, ascites, and pericardial effusion reflect the vascular leakage due to increased vascular permeability (5). Increased vascular permeability has been confirmed by tracer studies of blood and plasma volume (12). Vascular endothelial cell injury is an important cause of thrombocytopenia. Besides these clinical factors, severe acute renal failure requiring hemodialysis, leukocytosis, abnormal liver function, encephalopathy, sepsis, anuria, acidosis, electrolyte abnormality, proteinuria of long duration, increased hematocrit during hypotensive stage are reported to represent the severity of disease of HFRS (4-9).

Although the mechanism of hypoalbuminemia in patients with HFRS is not well known until now, it is considered to be associated with protein leakage through the vessel wall due to increased vascular permeability (4). We first demonstrated the loss of protein via intestinal tracts in the acute stage of HFRS by abdominal scintigraphy using technetium-99m-labeled human serum albumin and fecal clearance of alpha-

antitrypsin and it was associated with serum albumin level and clinical parameters representing increased vascular permeability (10). We also reported that hypoalbuminemia was associated with gallbladder wall edema in the acute stage of HFRS (13).

Based on these findings, we hypothesized that hypoalbuminemia in the acute stage of HFRS might be associated with the increased vascular permeability in patients of HFRS. We also studied the relationship between the level of serum albumin and clinical parameters representing the severity of disease. The lowest level of serum albumin was found to be associated with clinical parameters representing the severity of disease (hypotension, thrombocytopenia, leukocytosis, acute renal failure, abnormal liver function, pulmonary edema, and pleural effusion). Therefore, we suggest that hypoalbuminemia, which commonly occurs in acute stage of HFRS, is associated with the severity of disease of HFRS.

We also evaluated whether the lowest level of serum albumin influences on the morbidity and mortality in patients with HFRS. In this study, ten patients (6.9%) out of the total of 144 patients with HFRS died, and most of them ( $n=8$ ) died from hypotensive shock. This mortality ratio in patients with HFRS was similar to other reports (2, 3, 14). To evaluate the impact of serum albumin on the morbidity and mortality in patients of HFRS, we divided the patients into three groups based on the lowest level of serum albumin; Group I (normal serum albumin), Group II (serum albumin  $<3.5$  g/dL and  $\geq 3.0$  g/dL), and Group III (serum albumin  $<3.0$  g/dL). And then we compared the factors among the three groups. Group III had a higher rate incidence of episode of hypotension, pulmonary edema, and pleural effusion than did other groups. Duration of admission of survivors from Group III ( $15.2 \pm 9.4$  days) was longer than that of Group I ( $7.9 \pm 4.6$  days) and that of Group II ( $10.5 \pm 5.5$  days). All ten patients who died of HFRS were in Group III ( $p < 0.01$ ). Therefore, our data suggest that the level of serum albumin is associated with morbidity and mortality in patients with HFRS.

Interestingly, the amount of proteinuria did not correlate with serum albumin level in this study. Furthermore, it was not associated with the severity of renal failure. The loss of urinary protein in patients with HFRS results from both tubular and glomerular injury (4, 15). Proteinuria frequently occurs in the acute stage of with HFRS, but the amount of proteinuria is usually mild and transient. In addition, it is reported that the amount of proteinuria in patients with HFRS does not correlate with the severity of renal biopsy findings (16). In this study, the mean amount of proteinuria was  $1.93 \pm 1.66$  g/day, and was similar to the other reports (17). It did not correlate with the severity of renal failure and the level of serum albumin. Furthermore, it completely disappeared in most patients within 7 days. Therefore, we think, besides urinary protein loss, that other factors such as intestinal protein loss or increased catabolism of protein as a consequence of negative acute phase response of serum albumin may contribute

to hypoalbuminemia.

In conclusion, our data suggest that hypoalbuminemia frequently occurs in the acute stage of HFRS and the lowest level of serum albumin is closely associated with the clinical parameters representing disease severity and mortality. But it does not correlate with the amount of proteinuria.

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