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Low serum albumin as a risk factor for infection-related in-hospital death among hemodialysis patients hospitalized on suspicion of infectious disease: a Japanese multicenter retrospective cohort study

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Abstract

Background: Serum albumin is a marker of nourishment and inflammation. Although hypoalbuminemia in hemodialysis patients is reported as a risk factor for poor prognosis, few studies describe its effects on infectious diseases specifically. This study aimed to examine the relationship between the serum albumin level on admission and infection-related in-hospital death among hemodialysis patients.

Methods: This was a multicenter retrospective observational study that was undertaken in Japan. We reviewed the medical records of 507 hemodialysis patients aged > 18 years, whose blood cultures were obtained based on suspicion of infectious disease, and who were managed at seven Japanese tertiary dialysis units from August 2011 to July 2013. The outcome measure was infection-related in-hospital death. Multivariate logistic regression models adjusted for age, sex, the dialysis vintage, diabetes mellitus, bacteremia, and log C-reactive protein levels were used for the statistical analysis.

Results: Four hundred patients were analyzed and allocated to three groups based on their serum albumin levels: marked hypoalbuminemia (< 2.5 mg/dL), mild hypoalbuminemia (≦ 2.5–< 3.5 mg/dL), and normal albumin levels (≦ 3.5 mg/dL). The infection-related in-hospital death rates were 22.9% ($n = 11$), 12.5% ($n = 25$), and 4.6% ($n = 7$), respectively. The multivariate logistic regression models determined that a low serum albumin level was an independent risk factor for infection-related in-hospital death (odds ratio 0.35, 95% confidence interval 0.18–0.66).

Conclusions: A low serum albumin level strongly predicts infection-related in-hospital death in hemodialysis patients hospitalized on suspicion of infection. Like those with bacteremia or diabetes mellitus, hemodialysis patients with hypoalbuminemia require careful management of their infections.

Keywords: Albumin, Dialysis, Hypoalbuminemia, Infection, Mortality

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Background

Infectious disease is one of the most important causes of morbidity and mortality among patients with end-stage renal disease (ESRD) [1–3]. According to the United States Renal Data System, infection is the second leading cause of death among patients with ESRD, and it comprises almost 9% of all deaths [4]. Similarly, almost 6000 hemodialysis patients in Japan die of infectious diseases annually, which amounts to approximately 20% of all-cause mortality of hemodialysis patients, and this rate is increasing every year [5, 6]. Given the high prevalence of infectious disease, early predictions of infection-related mortality could improve the outcome for hemodialysis patients.

Reports from previous studies have described diabetes, cancer, multisystem disease, vascular access type, serum albumin level, and being female as risk factors for infection-related mortality in patients who undergo renal replacement therapy [1, 7–9]. In this study, our focus was on serum albumin levels. Serum albumin is a known marker of nourishment, and it is also recognized as a marker of inflammation because it is an acute phase reactant [10–12]. Hypoalbuminemia in hemodialysis patients has been described as a risk factor for poor prognosis such as all-cause and cardiovascular-related mortality [8, 13–17]. However, infection-related mortality has been discussed in only two articles. Wang et al. [17] showed an association between serum albumin levels and bacteremia-related mortality, but did not discuss non-bacteremic infectious disease. Mehrotra et al. [8] discussed baseline and time-averaged serum albumin levels and changes in serum albumin levels, but they did not mention serum albumin levels at the onset of infectious disease.

In the general population, hypoalbuminemia has been described as a risk factor that is associated with poor clinical outcomes in acute illness [18], and it has been reported that the serum albumin level on admission is an independent risk factor associated with death, length of stay, and re-admission [19].

Although demonstrated in the general population, there has been insufficient evidence to support an association between hypoalbuminemia on admission and short-term mortality among hemodialysis patients who are usually more prone to develop hypoalbuminemia than the general population [10].

Therefore, we hypothesized that a low serum albumin level on admission is an important prognostic factor that is associated with short-term mortality, such as infection-related in-hospital death, among hemodialysis patients, as is the case within the general population. This study aimed to examine the influence of the serum albumin level on infection-related in-hospital death among chronic dialysis patients from whom blood cultures were obtained and who were hospitalized on suspicion of infectious disease.

Methods

Study population

This was a Japanese, multicenter, retrospective, observational study that involved hemodialysis patients who were managed at seven Japanese tertiary dialysis units from August 2011 to July 2013. We reviewed the medical records of consecutive hemodialysis patients who were over 18 years of age and from whom blood cultures were obtained at least twice based on the suspicion of infectious disease in an outpatient setting or within 48 h after admission. The dialysis units involved were participants in the Japanese Investigators with Innovative Network about Kidney Disease group (JOINT-KD group), which includes Chubu Rosai Hospital, Toyohashi Municipal Hospital, St. Marianna University School of Medicine Hospital, Kawasaki Municipal Tama Hospital, Inagi Municipal Hospital, Showa University Fujigaoka Hospital, and Iizuka Hospital. A total of 507 patients who were undergoing hemodialysis were enrolled to participate in this study. Patients who were not hospitalized or whose serum albumin level data were missing were excluded from the study.

Data collection

The patients' demographic, clinical, and laboratory data were extracted from their medical records. The laboratory data, including the serum albumin levels, were extracted from the results of the blood tests that were undertaken on admission.

Outcome measures

The study's primary outcome measure was infection-related in-hospital death. The definition of infection-related in-hospital death was death during hospitalization with a final diagnosis of an infectious disease. The final diagnoses were determined by the attending physicians in each hospital.

Statistical analyses

We allocated the patients to three groups based on their serum albumin levels: marked hypoalbuminemia (group 1 < 2.5 mg/dL), mild hypoalbuminemia (group 2 $\leq 2.5 - < 3.5$ mg/dL), and normal albumin levels (group 3 ≤ 3.5 mg/dL) and then the groups were evaluated by their baseline characteristics. The cutoff values were based on those of a previous study of hypoalbuminemia [20]. The continuous variables are expressed as the medians and interquartile ranges, and the categorical variables are expressed as numbers and percentages.

A logistic regression model was used to calculate the odds ratios (ORs) for infection-related in-hospital death, using group 3 as the reference category. This model was adjusted for age, sex, the dialysis vintage, diabetes mellitus, and bacteremia. These covariates were selected based on previous reports that describe the risk factors for infection-related mortality among hemodialysis patients [1, 21, 22]. We also calculated the ORs using the serum albumin levels as continuous variables in four models. Model 1 was unadjusted; model 2 was adjusted for age, sex, and present bacteremia; model 3 was adjusted for age, sex, present bacteremia, diabetes mellitus, and the dialysis vintage; and model 4 was adjusted for age, sex, present bacteremia, diabetes mellitus, the dialysis vintage, and the logarithmic (log) C-reactive protein (CRP) levels. A log transformation was applied to the CRP levels because of positive skewness (1.5). Multicollinearity among all of the covariates was evaluated using the variance inflation factor (VIF). A VIF > 10 indicates serious multicollinearity, and VIF values > 4 may be causes for concern.

In addition, we carried out a sensitivity analysis. We calculated the ORs using logistic regression models that incorporated all of the in-hospital cases, which included the cases for whom the serum albumin data were missing. The cases in which serum albumin data were missing were included after multiple imputation.

All of the analyses, with the exception of the sensitivity analysis, were performed using IBM SPSS Statistics, version 24.0 (IBM Corporation, Armonk, NY, USA). The sensitivity analysis was performed using R software, version 3.3.1 (The Comprehensive R Archive Network: https://cran.r-project.org). The multiple imputation was performed using the "mice" package [23]. A P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 507 hemodialysis patients were included in this study, and 400 patients were analyzed after excluding the patients who were not hospitalized and those whose serum albumin data were missing (Fig. 1). Table 1 shows the patients' baseline characteristics categorized according to the serum albumin groups. Mean age was 74 years. Table 2 presents the outcomes after admission, including bacteremia, infectious diseases, and mortality. The proportions of hemodialysis patients with final infectious disease diagnoses were 68.8% (n = 33), 62.0% (n = 124), and 56.6% (n = 86), in group 1, group 2, and group 3, respectively. The infection-related in-hospital death rates were 22.9% (n = 11), 12.5% (n = 25), and 4.6% (n = 7), and the proportions of patients with bacteremia were 18.8% (n = 9), 16.5% (n = 33), and 13.8% (n = 21) in group 1, group 2, and group 3, respectively.

Multivariate analysis of the risk factors for infection-related in-hospital death

Figure 2 presents the logistic regression model of infection-related in-hospital deaths that used group 3 as the reference category. The ORs for infection-related in-hospital deaths were 8.17 (95% CI 2.45–29.96) for group 1 and 3.03 (95% CI 1.13–8.12) for group 2. The logistic regression models in which the serum albumin levels were used as continuous variables are shown in Tables 3 and 4. The serum albumin level, diabetes mellitus, and bacteremia were significant risk factors for poor clinical outcomes in hemodialysis patients (Table 3). The four models used to analyze the serum albumin levels (Table 4) all showed significant associations between the serum albumin level on admission and infection-related in-hospital death. We assessed the covariates'

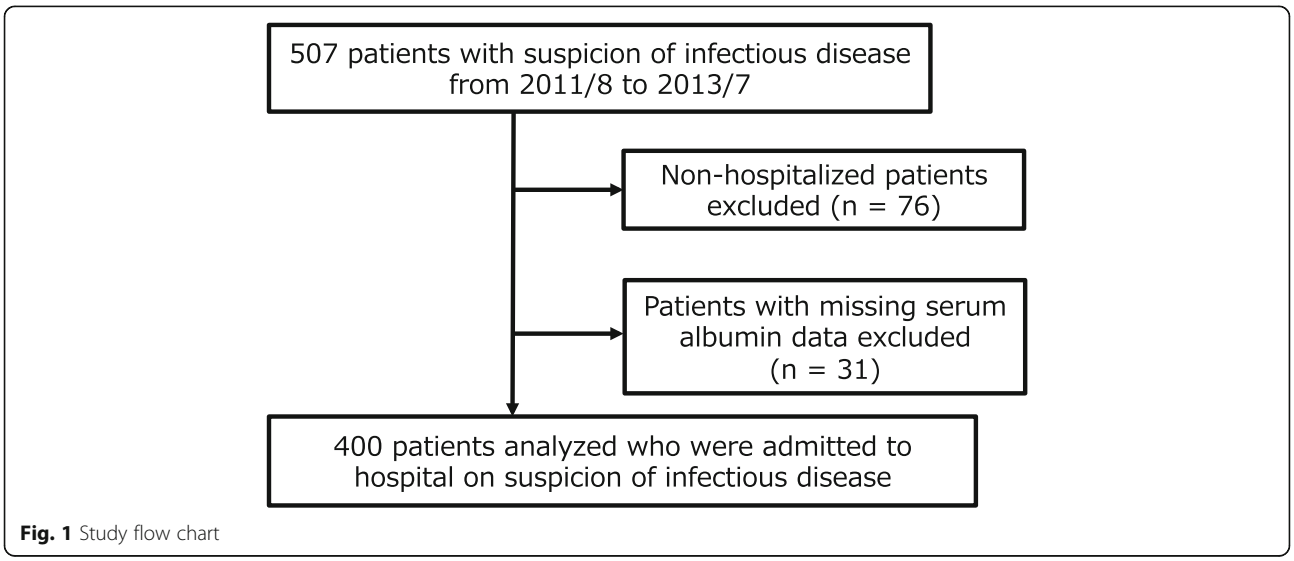

Fig. 1 Study flow chart

Table 1 Baseline characteristics ($N = 400$)

	Alb < 2.5 $n = 48$	2.5 ≤ Alb < 3.5 $n = 200$	3.5 ≤ Alb $n = 152$	Total $n = 400$	P value
Albumin (g/dL)	2.2 (2.0, 2.4)	3.1 (2.9, 3.3)	3.8 (3.6, 4.0)	3.3 (2.9, 3.7)	< 0.01*
Age (years)	72 (66, 80)	75 (69, 81)	71 (62, 79)	74 (66, 81)	< 0.01*
Sex (male)	25 (52.1)	125 (62.5)	110 (72.4)	260 (65.0)	0.021*
Dialysis vintage (month)	54 (25, 130)	63 (24, 119)	62 (24, 108)	62 (24, 116)	0.924
BMI (kg/m^2)	19.7 (17.2, 21.6)	19.5 (17.5, 22.0)	21.5 (19.0, 23.7)	20.1 (17.9, 22.8)	< 0.01*
Diabetes mellitus	19 (40.4)	84 (42.0)	74 (48.7)	177 (44.4)	0.387
Malignancy	7 (14.6)	27 (13.5)	16 (10.5)	50 (12.5)	0.633
Artificial devices	10 (20.8)	77 (38.5)	36 (23.7)	123 (30.8)	< 0.01*
Creatinine (mg/dL)	4.8 (4.0, 6.9)	6.2 (4.5, 8.3)	7.3 (5.4, 9.8)	6.4 (4.6, 8.6)	< 0.01*
Potassium (mEq/L)	3.8 (3.4, 4.4)	4.3 (3.7, 4.8)	4.3 (4.1, 5.2)	4.3 (3.8, 4.8)	< 0.01*
CRP (mg/dL)	10.1 (4.5, 21.5)	7.7 (3.4, 14.4)	4.0 (0.7, 9.7)	6.6 (1.9, 12.9)	< 0.01*
Hemoglobin (g/dL)	9.7 (8.4, 11.5)	10.6 (9.5, 11.5)	11.3 (10.2, 12.4)	10.7 (9.5, 11.9)	< 0.01*

BMI body mass index; *CRP* C-reactive protein
Continuous data are medians (IQR). Categorical data are *n* values (%)
Differences among groups were evaluated by a chi-square test for categorical variables and a Kruskall-Wallis test for continuous variables
*$P < 0.05$

multicollinearity using the VIF in this analysis, and all of the VIFs were < 4.0.

Table 5 shows the results of the sensitivity analysis that comprised multivariate logistic regression analysis after multiple imputation, which determined that a low serum albumin level was an independent risk factor for infection-related in-hospital death, consistent with the results from the multivariate analysis without multiple imputation.

Discussion

The results from the present study showed that the serum albumin level on admission was a significant risk factor for in-hospital infection-related death among hemodialysis patients from whom blood cultures were obtained and who had been hospitalized on suspicion of infectious disease. Hemodialysis patients who are hospitalized with infectious diseases have high infection-related mortality and readmission rates [24]. Indeed, infection-related mortality is significantly higher in ESRD patients with bacteremia compared with patients without bacteremia [21]. In our study, the bacteremia-related in-hospital death rate was 6.3%, which represented 58.1% of all of the infection-related in-hospital deaths. However, mortality in patients with infectious diseases in the absence of bacteremia is not negligible. Dalrymple et al. [24] reported that the in-hospital mortality rates for infection-related hospitalization without bloodstream infections or sepsis were between 2 and 16%, which concurs with the findings from our study that showed that the rate of infection-related in-hospital death without bacteremia was 4.5%. In addition, although there is a strong association between bacteremia and poor clinical outcomes, it is difficult to determine whether or not patients have bacteremia on admission. In contrast, the serum albumin levels are assessable on admission; hence, our study's findings suggest that the serum albumin levels

Table 2 Outcomes after admissions ($N = 400$)

	Alb < 2.5 $n = 48$	2.5 ≤ Alb < 3.5 $n = 200$	3.5 ≤ Alb $n = 152$	Total $n = 400$	P value
Bacteremia	9 (18.8)	33 (16.5)	21 (13.8)	63 (15.8)	0.657
Final diagnosis of infectious disease	33 (68.8)	124 (62.0)	86 (56.6)	243 (60.8)	0.282
Duration of hospitalization (days)	22 (9, 52)	19 (11, 37)	13 (7, 25)	16 (9, 35)	< 0.01*
In-hospital death (infection related)	11 (22.9)	25 (12.5)	7 (4.6)	43 (10.8)	< 0.01*
Duration from admission to infection-related death (days)	9 (5, 29)	15 (6, 25)	11 (2, 45)	14 (6, 28)	0.913
In-hospital death (infection related, with bacteremia)	5 (10.4)	15 (7.5)	5 (3.3)	25 (6.3)	0.121
In-hospital death (infection related, without bacteremia)	6 (12.5)	10 (5.0)	2 (1.3)	18 (4.5)	< 0.01*
In-hospital death (all cause)	15 (31.3)	40 (20.0)	12 (7.9)	67 (16.8)	< 0.01*

Continuous data are medians (IQR). Categorical data are n values (%)
Differences among groups were evaluated by a chi-square test for categorical variables and a Kruskall-Wallis test for continuous variables
*$P < 0.05$

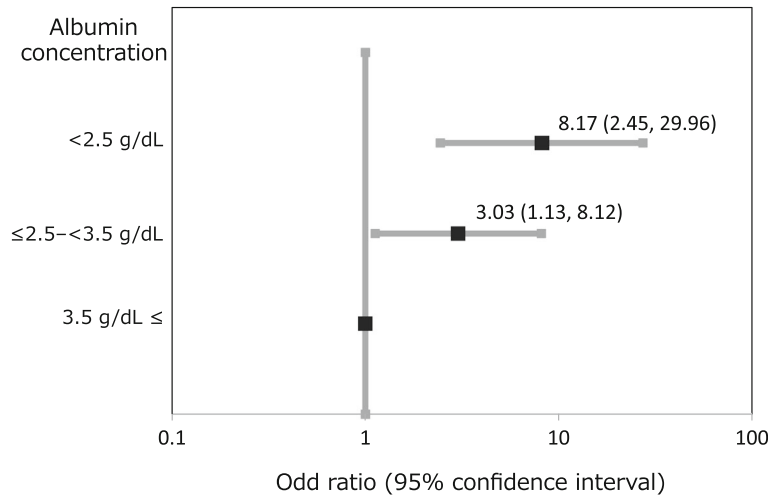

Fig. 2 Adjusted odds ratios (95% confidence intervals) for infection-related in-hospital death according to the albumin groups. The odds ratios were adjusted simultaneously for age, sex, the dialysis vintage, diabetes mellitus, and current bacteremia. Alb, albumin

may provide earlier prognostic predictions among patients who are suspected of carrying infectious diseases.

There are several strengths associated with our study that include its multicenter design. Several studies have assessed the relationship between hemodialysis and serum albumin levels, but few multicenter cohort studies that have specifically investigated infectious diseases among hemodialysis patients have been undertaken. This study focused on infectious diseases specifically, which enabled us to assess the data that were derived from the onset of the infectious diseases and their effects on the patients' prognoses. Additionally, the mean age of this cohort, which was 74 years, was important. The mean age in previous studies that assessed the relationship between hypoalbuminemia and infection-related mortalities were around 60 years [8, 17]. This is not applicable to the increased age of dialysis patients in recent years [5]. Although it has been shown that elderly patients are prone to hypoalbuminemia [25], we suggest that hypoalbuminemia is still a strong prognostic factor of infectious disease in elderly dialysis patients.

Our study has some limitations. First, the study's sample size was small compared with previous studies. This might have lowered our study's statistical power, but the findings from the multivariate analysis suggested a strong association between a low serum albumin level and poor outcomes. In addition, this was a multicenter study; hence, its external validity was high. The infection-related in-hospital death rate in our study was 10.8%, which concurs with that reported previously [24]. Second, there were no data that described the patients' courses after discharge and there was no information

Table 3 Univariate and multivariate logistic regression analysis of in-hospital infection related death

	Univariate analysis			Multivariate analysis[¶]		
	OR	[95% CI]	*P*	OR	[95% CI]	*P*
Sex (reference: female)	1.27	[0.64, 2.53]	0.49	1.68	[0.74, 3.83]	0.22
Age (per year increase)	1.01	[0.98, 1.04]	0.42	1.01	[0.97, 1.05]	0.53
Dialysis vintage (per month increase)	1.00	[1.00, 1.01]	0.09	1.00	[1.00, 1.01]	0.14
Diabetes mellitus (reference: without DM)	1.22	[0.65, 2.31]	0.53	2.35	[1.03, 5.35]	0.041*
Bacteremia (reference: without bacteremia)	11.66	[5.83, 23.32]	< 0.01*	11.47	[5.04, 26.01]	< 0.01*
log CRP (per point increase)	2.04	[1.44, 2.90]	< 0.01*	1.36	[0.94, 1.99]	0.11
Serum albumin (per g/dl increase)	0.38	[0.23, 0.63]	< 0.01*	0.35	[0.18, 0.66]	< 0.01*

[¶]Adjusted for age (years), sex, bacteremia, diabetes mellitus, dialysis vintage (months), and log CRP
*$P < 0.05$

Table 4 Odd's ratio for association of serum albumin (per g/dl increase) with infection related in-hospital death

Model	OR	[95% CI]	*P*
1[a]	0.38	[0.23, 0.63]	< 0.01*
2[b]	0.32	[0.18, 0.57]	< 0.01*
3[c]	0.30	[0.16, 0.55]	< 0.01*
4[d]	0.35	[0.18, 0.66]	< 0.01*

[a]Unadjusted
[b]Adjusted for age (years), sex, and bacteremia
[c]Adjusted for age (years), sex, bacteremia, diabetes mellitus, and dialysis vintage(months)
[d]Adjusted for age (years), sex, bacteremia, diabetes mellitus, dialysis vintage (months), and log CRP
*$P < 0.05$

regarding the patients' courses when they changed hospitals. In this study, 67 patients died during hospitalization, 265 patients were discharged from hospital, 64 patients were transferred to different hospitals, and 4 patients' courses were unknown. There were no data that described the mortality of the patients who were transferred. Third, the inclusion criteria were not very clear. Suspicion of infectious disease was subjectively assessed by each physician thereby creating a sampling bias. However, this does reflect the actual clinical management of dialysis patients. Fourth, we did not have data regarding other malnutrition and inflammation markers such as prealbumin, cholesterol, other rapid turnover proteins, and liver enzymes. Although low albumin levels are linked to a poor prognosis in this study, reasons for the hypoalbuminemia were not clear. There are many factors that affect serum albumin levels and our data showed that body mass index (BMI), CRP, and creatinine levels in the three albumin groups were statistically different. This means that the reasons for hypoalbuminemia in each case could be different. We could not estimate how malnutrition and inflammation impacted hypoalbuminemia due to the lack of data regarding other more specific markers, which could be a limitation. However, serum albumin levels are commonly assessed by clinicians and are very useful regardless of what causes the hypoalbuminemia. Fifth, as mentioned above, CRP levels in group 1 were negligible. This suggests high CRP levels are linked to poor prognosis, and the OR in the logistic regression model with CRP levels (Table 4, model 4) increased compared with the model without CRP levels (Table 4, model 3). The effect of hypoalbuminemia was attenuated by CRP due to the common causal pathway of inflammation. However, CRP has not been identified as a prognosis factor for infectious disease in past studies despite its predictive association with bacteremia and elevated inflammatory conditions [26, 27]. Finally, the timing of the serum albumin measurements was an important limitation. The serum albumin levels were only measured on admission in this study. Although we discussed serum albumin levels as an acute inflammatory reactant rather than a nutrient marker, single measurement of albumin levels was not enough to judge whether the hypoalbuminemia was chronic, whether it had occurred as a result of acute illness, or both. So, we assessed the multicollinearity between serum albumin levels and BMI, a known nutritional marker, and the VIF was < 4.0. This suggests that hypoalbuminemia in this study reflected not only malnutrition, which could be chronic hypoalbuminemia, but also acute reaction from inflammation. We did not evaluate the nutritional status of the participants other than BMI, so this could be a limitation. Furthermore, the serum albumin levels of hemodialysis patients fluctuate depending on the volume status; therefore, compared with the pre-dialysis levels, the post-dialysis serum albumin levels are higher, and the degrees of fluctuation correlate with the intra-dialysis volume loss. Kubrusly et al. [28] reported a comparative analysis of the pre- and post-dialysis albumin levels, and the mean albumin levels were 3.45 ± 0.55 g/dL and 3.90 ± 0.73 g/dL, respectively. Although these findings indicated that the intra-dialysis albumin fluctuations are not large, the timing of the serum albumin measurements could be a study limitation as we did not have any data that described the relationship between the timing of the blood tests and dialysis.

Table 5 Sensitivity analysis: multivariate logistic regression analysis of in-hospital infection-related death after multiple imputation

	Multivariate analysis (MI data)		
	OR	[95% CI]	*P*
Sex (reference: female)	1.68	[0.75, 3.75]	0.20
Age (per year increase)	1.02	[0.98, 1.06]	0.38
Dialysis vintage (per month increase)	1.00	[1.00, 1.01]	0.14
Diabetes mellitus (reference: without DM)	2.16	[0.98, 4.73]	0.06
Bacteremia (reference: without bacteremia)	10.88	[4.91, 24.11]	< 0.01*
log CRP (per point increase)	1.42	[0.98, 2.07]	0.07
Serum albumin (per g/dl increase)	0.34	[0.18, 0.64]	< 0.01*

Adjusted for age (years), sex, bacteremia, diabetes mellitus, dialysis vintage (months), and log CRP
*$P < 0.05$

Conclusions

The present study's findings showed that the serum albumin level was a significant risk factor for infection-related in-hospital death among hemodialysis patients who had been hospitalized on suspicion of infectious disease. Like those with bacteremia or diabetes mellitus, hemodialysis patients with hypoalbuminemia and infections should be carefully managed.

Abbreviations
BMI: Body mass index; CRP: C-reactive protein; ESRD: End-stage renal disease; ORs: Odds ratios; VIF: Variance inflation factor

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Availability of data and materials
The datasets of the current study is available from the corresponding author on a reasonable request.

Authors' contributions
SM and AN designed the study. SM performed the statistical analysis and wrote the manuscript. All other authors contributed to the study design, data collection, analysis, and writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was conducted with approval from the St. Marianna University School of Medicine's Ethics Committee (No. 2713), and it was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was not obtained from the participants, because of the retrospective nature of the study.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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