The association between serum albumin and LOS of patients with acute heart failure: a retrospective study based on the MIMIV-IV database

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Research

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Abstract

Objective: To assess the relationship between serum albumin and length of stay (LOS) of the intensive care unit (ICU).

Design and Participants: we retrospectively analyze 2280 patients with acute heart failure(AHF) from the medical information mart for intensive care IV (the MIMIC-IV) database.

Materials and Methods: The exposure variable of the present study was serum albumin. The outcome variable was LOS. The final models were established by multivariate linear regression, and subgroup analysis was performed. Trend test and smooth fitting curves were used to evaluate the association between serum albumin and LOS.

Results: When the value of serum albumin was less than 5.1g/dl, the analysis of 2280 patients showed that the linear relationship between albumin and LOS. LOS was gradually shortened with the albumin increasing (β : -0.636; 95%CI: -0.819, -0.453; $P < 0.001$). In subgroup, sepsis and serum albumin_{initial} had an interactive effect on LOS ($P = 0.036$), and there was significantly different between AHF patients with sepsis (β : -1.927; 95%CI: -3.823, -0.030) and without sepsis(β : -1.412; 95%CI: -1.737, -1.087) .

Conclusion: When serum albumin was less than 5.1g/dl, the negative association was presented between serum albumin level and LOS among patients with AHF, and this association is even closer in patients with sepsis.

1. Introduction

As a common and growing medical problem, heart failure(HF) is one of the most frequent causes of admission and hospital mortality.[1] The limitation of options for the management of patients with HF lead to long length of stays (LOS). Especially, some patients with acute heart failure (AHF) in the intensive care unit (ICU) might have many underlying diseases, which might lead to long LOS. As a major problem of cardiovascular disease, AHF not only seriously affects the quality of life of patients, but also weighs their economic burden. Therefore, it is essential for us to pay more attention to LOS.

As an inexpensive and powerful indicator, serum albumin is an essential protein in the human body produced by liver, and often used to evaluate the prognosis of a variety of diseases, such as HF, acute pulmonary embolism, diabetic nephropathy and patients with severe illness in ICU.[2–5] Previous studies had shown that serum albumin was a powerful indicator to short-term and long-term prognosis of patients with HF, high albumin levels would significantly reduce their hospital mortality and rehospitalization.[6–8] Hypoalbuminemia often occurs in ICU,[9] and it is closely related to the long LOS. However, there were few studies on whether serum albumin level affects LOS in patients with AHF, especially, a specific association was not revealed between albumin level and LOS of patients with AHF. Thus, it is difficult to apply albumin level as a predictive indicator for LOS of patients with AHF to clinical practice.

Therefore, it is necessary to reassess the relationship between serum albumin and LOS in patients with AHF. In the present study, we analyzed the association between serum albumin level and LOS of patients with AHF from the medical information mart for intensive care IV (the MIMIC-IV) database, and we conducted a subgroup analysis of the relationship between serum albumin levels and LOS under different age, genders, malignancy, liver cirrhosis, nephrotic syndrome, chronic kidney disease and sepsis. In particular, the trend relationship between albumin level and LOS was explained.

2. Materials And Methods

2.1 Study population

2280 AHF patients whose years more than 18 were enrolled from the MIMIC-IV database (AHF icd_code = 42821, 42823, 42831, 42833, 42841, 42843, I5021, I5023, I5031, I5033, I5041, I5043, I50811, I50813) in our study. The data provided by the above database was the original data. Thus, data used for the study was retrieved from MIMIC-IV by author Liu (ID: 9008147, **Supplemental Table S1.**), who had completed the online training course of the National Institutes. The selection process of study participants is shown in Fig. 1.

2.2 Variables

The exposure variable of the present study was initial albumin (albumin_{initial}), minimum serum albumin (albumin_{min}) and maximum serum albumin (albumin_{max}). Serum albumin_{initial} was defined as the first serum albumin level at the time of admission to ICU, serum albumin_{min} was defined as minimum albumin level during ICU, serum albumin_{max} was defined as maximum albumin level during ICU. The outcome variable was LOS of ICU. Categorical variables [including gender, ethnicity, insurance, comorbidities and drugs use] and continuous variables [including age, systolic blood pressure (SBP), diastolic blood pressure (DBP) and body mass index (BMI)] were analyzed in the present study (Table 1).

Table 1
Baseline characters comparsion among the different LOS of patients with acute heart failure in ICU

Variables	< 2.14 days (N = 570)	2.14 ≤ to < 3.67 days (N = 570)	3.67 ≤ to < 5.31 days (N = 570)	≥ 5.31 days (N = 570)	P value
Age, years	70.51 ± 13.22	70.81 ± 13.99	69.71 ± 13.37	68.47 ± 14.19	0.024
Male, n(%)	307 (53.86%)	317 (55.61%)	333 (58.42%)	338 (59.30%)	0.222
Ethnicity, n(%)					0.013
Whites	387 (67.89%)	404 (70.88%)	373 (65.44%)	383 (67.19%)	
Black	65 (11.40%)	46 (8.07%)	47 (8.25%)	38 (6.67%)	
Other	118 (20.70%)	120 (21.05%)	150 (26.32%)	149 (26.14%)	
SBP, mmHg	115.34 ± 19.73	114.55 ± 20.26	114.62 ± 21.43	116.81 ± 21.57	0.379
DBP, mmHg	58.20 ± 15.07	56.77 ± 14.50	57.37 ± 16.87	59.01 ± 19.22	0.382
BMI, kg/m ²	28.93 ± 6.56	28.98 ± 6.23	29.39 ± 6.31	29.18 ± 6.78	0.529
Insurance, n(%)					0.12
Medicare	320 (56.14%)	332 (58.25%)	317 (55.61%)	299 (52.46%)	
Medicaid	34 (5.96%)	25 (4.39%)	37 (6.49%)	23 (4.04%)	
Other	216 (37.89%)	213 (37.37%)	216 (37.89%)	248 (43.51%)	
Comorbidities					
Diabetes, n(%)	106 (18.60%)	129 (22.63%)	97 (17.02%)	103 (18.07%)	0.082
Hypertension, n(%)	23 (4.04%)	29 (5.09%)	16 (2.81%)	32 (5.61%)	0.099
Chronic obstructive pulmonary disease, n(%)	54 (9.47%)	62 (10.88%)	66 (11.58%)	71 (12.46%)	0.431
Respiratory failure, n(%)	114 (20.00%)	171 (30.00%)	223 (39.12%)	279 (48.95%)	< 0.001
Malignancy, n(%)	3 (0.53%)	3 (0.53%)	2 (0.35%)	3 (0.53%)	0.965
Atrial fibrillation, n(%)	293 (51.40%)	304 (53.33%)	310 (54.39%)	319 (55.96%)	0.472
Acute myocardial infarction, n(%)	71 (12.46%)	85 (14.91%)	86 (15.09%)	78 (13.68%)	0.547
Liver cirrhosis, n(%)	14 (2.46%)	11 (1.93%)	7 (1.23%)	12 (2.11%)	0.492
Chronic kidney disease, n(%)	215 (37.72%)	210 (36.84%)	239 (41.93%)	229 (40.18%)	0.277
Nephrotic syndrome, n(%)	5 (0.88%)	8 (1.40%)	1 (0.18%)	1 (0.18%)	0.025
Sepsis, n(%)	25 (4.39%)	29 (5.09%)	45 (7.89%)	49 (8.60%)	0.007
Drugs use					

Variables	< 2.14 days (N = 570)	2.14 ≤ to < 3.67 days (N = 570)	3.67 ≤ to < 5.31 days (N = 570)	≥ 5.31 days (N = 570)	P value
Nitroglycerin, n(%)	360 (63.16%)	334 (58.60%)	320 (56.14%)	292 (51.23%)	< 0.001
Diuretics, n(%)	554 (97.19%)	552 (96.84%)	549 (96.32%)	548 (96.14%)	0.747
β blocker, n(%)	496 (87.02%)	490 (85.96%)	491 (86.14%)	491 (86.14%)	0.955
Cardiotonic drugs, n(%)	111 (19.47%)	146 (25.61%)	174 (30.53%)	196 (34.39%)	< 0.001
Albumin _{initial}	3.67 ± 0.60	3.51 ± 0.59	3.37 ± 0.61	3.30 ± 0.64	< 0.001
Albumin _{max}	3.88 ± 0.56	3.76 ± 0.57	3.72 ± 0.57	3.66 ± 0.62	< 0.001
Albumin _{min}	3.37 ± 0.64	3.24 ± 0.62	3.06 ± 0.61	3.04 ± 0.62	< 0.001
SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; albumin _{initial} , the first serum albumin level when entering the ICU; albumin _{min} , minimum albumin level during ICU; albumin _{max} , maximum albumin level during ICU; ICU, intensive care unit. Data are present as MD ± SD or N(%).					

2.3 Statistical analysis

Continuous variables were represented by mean ± standard deviation or median (25th quartile, 75th quartile) in the table. If the test of normality and the homogeneity test of variance are performed, the T test is appropriate, otherwise, the Kruskal Wallis test is appropriate. Categorical variables are presented as a percentage in the tables and compared using the X^2 test. Multivariate linear regression with significant difference of 0.05 was used to build the final models. The subgroup analysis was performed by stratified multivariate linear regression analysis under different age, genders, nephrotic syndrome, malignancy, liver cirrhosis, nephrotic syndrome, chronic kidney disease and sepsis. Trend test and smooth fitting curves were used to evaluate the association between serum albumin level and LOS. All statistical analyses were performed using the software Stata15. All P value < 0.05 was significant.

3. Results

3.1 Baseline characteristics

The mean age of 2280 patients were 69.88 ± 13.72 , and men made up 56.80% of the total. All patients were grouped by the quartile range of LOS (< 2.14 days; $2.14 \leq$ to < 3.67 days; $3.67 \leq$ to < 5.31 days; ≥ 5.31 days) during the ICU (Table 1). albumin_{initial}, albumin_{max} and albumin_{min} in the quartile grouping of LOS had significant difference. Except age, ethnicity, respiratory failure, nephrotic syndrome, sepsis, nitroglycerin, cardiotonic drugs ($P < 0.05$), all variables were not significant in other subgroups ($P > 0.05$). Comparison of baseline characteristics among albumin level was provided in **Supplemental Table S2**.

3.2 Analysis of association between serum albumin_{initial} and LOS

We further analyzed the relationship between serum albumin and LOS based on serum albumin_{initial}. In the model adjusted for all variables, serum albumin_{initial} could reduce LOS of patients with AHF (β : -0.636; 95%CI: -0.819, -0.453; $P < 0.001$). the β (95% CI) for LOS across the albumin quartile were -0.611 (-0.925, -0.298), -0.722 (-1.056, -0.388), and -1.117 (-1.441, -0.792), compared with the first quartile of albumin (P for trend < 0.001). Both unadjusted and adjusted only age, gender, and ethnicity models showed statistical similar significance to the above. (Table 2). The analysis of the relationship between serum albumin and LOS based on serum albumin_{max} and serum albumin_{min} was provided in **Supplemental Table S3**.

Table 2
Association of serum albumin_{initial} with length of stay in ICU

Variables	Model 1	Model 2	Model 3
	β (95%CI)	β (95%CI)	β (95%CI)
Albumin	-0.873 (-1.048, -0.699)***	-0.872 (-1.047, -0.697)***	-0.636 (-0.819, -0.453)***
Quartile of albumin _{initial}			
Q1 (< 3.0 g/dl), (Ref.)	Ref.	Ref.	Ref.
Q2 (3.0 ≤ to < 3.5 g/dl)	-0.805 (-1.120, -0.490)***	-0.800 (-1.114, -0.485)***	-0.611 (-0.925, -0.298)***
Q3 (3.5 ≤ to < 3.9 g/dl)	-1.022 (-1.351, -0.693)***	-1.018 (-1.346, -0.690)***	-0.722 (-1.056, -0.388)***
Q4 (≥ 3.9 g/dl)	-1.526 (-1.838, -1.214)***	-1.525 (-1.838, -1.213)***	-1.117 (-1.441, -0.792)***
<i>P</i> for trend	< 0.001	< 0.001	< 0.001
Model 1: None was adjusted. Model 2: Age, gender and ethnicity were adjusted. Model 3: Age, gender, ethnicity, SBP, DBP, BMI, insurance, diabetes, hypertension, chronic obstructive pulmonary disease, respiratory failure, malignancy, atrial fibrillation, acute myocardial infarction, liver cirrhosis, chronic kidney disease, nephrotic syndrome, septicemia, nitroglycerin, diuretics, β blocker, cardiotonic drugs were adjusted. *** <i>P</i> < 0.001; <i>P</i> for trend was presented as comparison of quartile of albumin _{initial} ; albumin _{initial} , the first serum albumin level when entering the ICU; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ICU, intensive care unit; CI, confidence interval.			

Figure 2 showed the relationship between albumin_{initial}, albumin_{max} and albumin_{min} and LOS by using smooth fitting curve and scatter plot. Both smooth fitting curve and scatter plot all showed that LOS of patient with AHF was gradually shortened when serum albumin was gradually increased. However, this result was based on the fact that albumin_{initial}, albumin_{max} and albumin_{min} were smaller than their maximum (maximum albumin_{initial}: 5.1g/dl; maximum albumin_{max}:5.2g/dl; maximum albumin_{min}: 5.0g/dl).

3.3 Subgroup analysis of association between serum albumin_{initial} and LOS

The present study based on subgroup analysis of age, genders, malignancy, liver cirrhosis, nephrotic syndrome, chronic kidney disease and sepsis showed the relationship between serum albumin_{initial} and LOS. Among subgroups, there was significant trend association between serum albumin_{initial} and LOS. Sepsis and serum albumin_{initial} had an interactive effect on the LOS (*P* = 0.036). there was significantly different between AHF patients with sepsis (β : -1.927; 95%CI: -3.823, -0.030) and without sepsis (β : -1.412; 95%CI: -1.737, -1.087). Except for the subgroup of sepsis, the interaction of serum albumin_{initial} in subgroups for age, gender, malignancy, liver cirrhosis, nephrotic syndrome and chronic kidney disease with LOS were no significant (Table 3).

Table 3
Subgroups analysis for the associations of serum albumin_{initial} with length of stay in ICU

Variables	Q1(< 3.0g/dl)	Q2(3.0 ≤ to < 3.5 g/dl)	Q3(3.5 ≤ to < 3.9 g/dl)	Q4(≥ 3.9 g/dl)	P for trend	P for interaction
	(Ref.)	β (95%CI)	β (95%CI)	β (95%CI)		
Age, years						0.573
< 65	Ref.	-0.411(-1.016,0.193)	-1.029(-1.655,-0.403)**	-1.539(-2.108,-0.969)***	< 0.001	
≥ 65	Ref.	-0.964(-1.330,-0.598)***	-1.017(-1.401,-0.634)***	-1.535(-1.907,-1.163)***	< 0.001	
Gender						0.708
Male	Ref.	-0.864(-1.290,-0.438)***	-1.023(-1.465,-0.580)***	-1.519(-1.936,-1.103)***	< 0.001	
Female	Ref.	-0.736(-1.204,-0.269)**	-1.033(-1.524,-0.542)***	-1.563(-2.035,-1.090)***	< 0.001	
Malignancy						0.202
No	Ref.	-0.805(-1.121, -0.490)***	-1.008(-1.338, -0.679)***	-1.518(-1.831, -1.205)***	< 0.001	
Yes	Ref.	-1.673(-7.193, 3.847)	-4.782(-9.821, 0.257)	-4.582(-9.621, 0.457)	0.061	
Liver cirrhosis						0.953
No	Ref.	-0.800(-1.119,-0.481)***	-1.048(-1.379,-0.717)***	-1.530(-1.845,-1.215)***	< 0.001	
Yes	Ref.	-0.804(-2.855,1.247)	0.660(-2.088,3.408)	-1.642(-4.158,0.873)	0.395	
Nephrotic syndrome						0.5902
No	Ref.	-0.798(-1.114, -0.481)***	-1.028(-1.358, -0.698)***	-1.529(-1.842, -1.216)***	< 0.001	
Yes	Ref.	-0.276 (-2.391, 1.838)	1.109 (-1.080, 3.298)	-0.017(-2.205, 2.172)	0.662	
Chronic kidney disease						0.932
No	Ref.	-0.703(-1.111,-0.295)***	-0.955(-1.372,-0.538)***	-1.491(-1.888,-1.093)***	< 0.001	
Yes	Ref.	-0.956(-1.453,-0.459)***	-1.116(-1.652,-0.581)***	-1.568(-2.072,-1.064)***	< 0.001	
Sepsis						0.036
No	Ref.	-0.697(-1.029,-0.365)***	-0.911(-1.254,-0.567)***	-1.412(-1.737,-1.087)***	< 0.001	
Yes	Ref.	-1.333(-2.458,-0.207)*	-1.520(-3.000,-0.041)*	-1.927(-3.823,-0.030)*	0.006	
*P < 0.05, **P < 0.01, ***P < 0.001; P for trend was presented as comparison of quartile of albumin _{initial} in subgroups; P interaction was presented as the interaction of age, gender, malignancy, liver cirrhosis, nephrotic syndrome, chronic kidney disease and sepsis with serum albumin _{initial} on length of ICU stay; albumin _{initial} , the first serum albumin level when entering the ICU; ICU, intensive care unit; CI, confidence interval.						

4. Discussion

In the present study, multivariate linear regression analysis showed that serum albumin_{initial} was closely related to LOS of patients with AHF. Trend test and smooth curve fittings suggested that LOS was gradually shortened when serum albumin_{initial} level was gradually increased (based on serum albumin being less than its maximum; maximum albumin_{initial}: 5.1g/dl). In our subgroups, sepsis and serum albumin_{initial} had an interactive effect on LOS ($P = 0.036$), and there was a significant difference between AHF patients with sepsis (β : -1.927; 95%CI: -3.823, -0.030) and without sepsis (β : -1.412; 95%CI: -1.737, -1.087).

The nutritional status of patients with AHF in ICU significantly affects their prognosis and LOS, albumin not only maintains the colloidal osmotic pressure, but also plays an important role in their nutritional status. Hypoalbuminemia, occurred commonly in patients with AHF in ICU, might be related to their poorer heart function and more underlying diseases, and it could result in serious adverse events. Previous studies showed that hypoalbuminemia significantly affected prognosis and LOS of various diseases, such as patients for severe sepsis, acute decompensated chronic obstructive pulmonary disease and requiring surgery.[10–13] But none of them proposed the specific relationship between albumin and LOS. In the present study, negative relationships between serum albumin and LOS in patients with AHF was found, and elevation of serum albumin level could reduce the LOS. Serum albumin could maintain the colloidal osmotic pressure, the proper serum albumin is beneficial to the recovery of AHF patients, however, with the levels of serum albumin increasing, heart load will inevitably be aggravated, the topic on the optimal value of serum albumin has not been widely explored. The further increases of albumin might weight the heart load, which may be not conducive to the prognosis of patients with AHF. Therefore, the above findings were based on the fact that albumin is less than 5.1g/dl.

Currently, several studies had suggested that serum albumin level < 3.5g/dL was an independent risk factor for prolonged LOS,[12–14] Clinicians are more inclined to treat moderate and severe hypoalbuminemia, but albumin level are divided into normal albumin levels (≥ 3.5 g/dl), mild hypoalbuminemia (3.0g/dl-3.5g/dl), moderate hypoalbuminemia (2.5g/dl-3.0g/dl) and severe hypoalbuminemia (< 2.5g/dl). The present study found that compared with low albumin level, high albumin level could significantly reduce the LOS. Therefore, the treatment of mild albuminemia is also vital to shorten the LOS.

Age and gender are important indicators for risk stratification and treatment of patients with AHF. Previous literature demonstrated that age not only was an independent risk factor for mortality of various diseases, but also determined the length of their hospital stay, and with age increasing, LOS was prolonged.[15–17] This might be because the elderly in ICU often had multiple organ failure, including poor heart function and other serious underlying diseases, which lead to poor prognosis and long LOS. For gender, women may be closely related to longer LOS.[18] Compared with men, female had higher systolic blood pressure, and the article published by Redfield et al. on circulation thought as patients grew older, female could have heavier arteriosclerosis.[19, 20] Severe coronary arteriosclerosis reduced blood supply of heart, and made prognosis of patients with AHF worse. In our study, neither of different age and gender had an impact on the relationship between serum albumin and LOS.

For AHF patients with malignancy, liver cirrhosis, nephrotic syndrome, chronic kidney disease and sepsis, these comorbidities can affect the synthesis and concentration of albumin.[21–24] In subgroup analysis, it can be found that only sepsis had an impact on the relationship between serum albumin and LOS. Sepsis is systemic infectious disease that often leads to dysfunction of various organs of the body. Demissei et al. pointed out AHF patients often had elevated inflammation indicators and had poor prognosis, [25] but there is currently no clear guideline for the treatment of AHF patients with sepsis.[26] In the present study, we found that compared to without sepsis, serum albumin can significantly reduce the LOS in AHF patients with sepsis, which might guide clinical practice. Explanation from the clinical mechanism, serum albumin enhances immunity, regulates inflammation and reduces oxidative damage, which are beneficial to reduce the damage of sepsis to various organs of the body.

The present study found that high serum albumin level was beneficial to shorten LOS of AHF patients, and the result could guide clinicians to reduce LOS of AHF patients by changing albumin levels. However, our study also has some limitations. Firstly, The maximum serum albumin_{initial} level included in our study was 5.1g/dl. When the albumin level is greater than 5.1g/dl, whether the relationship between serum albumin and LOS is still negative has not been studied. Secondly, the study was a single-center retrospective design, the numbers of patients included are not large, and the selected population is relatively limited. Finally, we might not adjust other potential confounding factors.

5. Conclusion

When serum albumin was less than 5.1g/dl, the negative association was presented between serum albumin level and LOS among patients with AHF, and this association is even closer in patients with sepsis, and it maybe guide clinical treatments and judge prognosis.

Abbreviations

LOS: length of stay

ICU: the intensive care unit

heart failure: HF

the medical information mart for intensive care IV: MIMIC-IV

systolic blood pressure: SBP

diastolic blood pressure: DBP

body mass index: BMI

confidence interval: CI

Declarations

Ethics approval: Ethics approval Laboratory for Computational Physiology at the Massachusetts Institute of Technology.

Patient consent Obtained.

Availability of data and materials The data of the present investigation were from MIMIC-IV database(<https://mimic.mit.edu/>)

Competing interests: None declared.

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Contributors: TL was mainly responsible for extraction of data and writing of the manuscript, LLW, XQL, ZHL, ZXT, HCX and CFW was responsible for data processing and collection; JHC was responsible for reviewing the literature; TDX and DYL contributed to their support and guidance in article design and writing.

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Figures

Figure 1

Flow chart of being included patients with acute heart failure.

Figure 2

The association between serum albumin with length of ICU stay. Each black point represents a patient with acute heart failure in ICU. The upper and lower blue dashed lines represent 95% CI of serum albumin. A continuous red line indicates the level of serum albumin. (A) and (B) showed the relationship between albumininitial and length of ICU stay. (C) and (D) showed the relationship between albuminmin and length of ICU stay. (E) and (F) showed the relationship between albuminmax and length of ICU stay. albumininitial, the first serum albumin level when entering the ICU; albuminmin, minimum albumin level during ICU; albuminmax, maximum albumin level during ICU; ICU, intensive care unit.

Supplementary Files

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- [AppendixTableA1.pdf](#)
- [AppendixTableA2.docx](#)
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