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ORIGINAL RESEARCH ARTICLE

Serum albumin level and hospital mortality in acute non-ischemic heart failure

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Abstract

Aims Hypoalbuminemia is common in heart failure (HF), especially in elderly patients. It is associated with an increased risk of death. The present study sought to examine the prognostic significance of serum albumin level in the prediction of hospital mortality in patients admitted for acute non-ischemic HF.

Methods and results We examined the association between albumin and hospital mortality in a cohort of 546 patients admitted for acute non-ischemic HF. None of the patients had infectious disease, severe arrhythmias (atrial fibrillation, ventricular tachycardia, ventricular fibrillation), required invasive ventilation, or presented with acute coronary syndrome or primary valvular disease. Thirty-six patients (7%) died during the hospital stay. These patients were significantly older (78 ± 9 vs. 72 ± 12 years; $P = 0.006$), had higher heart rate ($P < 0.0001$), increased creatinine level ($P = 0.01$), lower systolic and diastolic blood pressures ($P < 0.05$), elevated leucocyte count ($P = 0.001$), and lower albumin levels (31.3 ± 5.6 g/L vs. 36.9 ± 4.1 g/L; $P < 0.001$). With multivariable analysis, age ($P = 0.01$), heart rate ($P < 0.0003$), diastolic blood pressure ($P < 0.01$), leukocyte count ($P = 0.009$), and serum albumin level ($P < 0.0001$) emerged as independent predictors of hospital mortality. Hypoalbuminemia (<34 g/L) yielded the best sensitivity (78.8%) and specificity (75%) for predicting hospital death.

Conclusions Serum albumin level measured at admission can serve as a simple prognostic factor in acute non-ischemic HF. Hypoalbuminemia is associated with increased risk of hospital mortality, especially in elderly patients.

Keywords Heart failure; Albumin; Hospital mortality; Outcome

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Introduction

Acute heart failure (HF) is a common and growing medical problem associated with major morbidity and mortality.[1] Options for the management of these patients remain limited with high in-hospital mortality rates. Accurate individual risk stratification can thus help physicians to choose the intensity of care needed and promote tailored medical decision-making.[2]

Hypoalbuminemia is common in patients with HF,[3] especially in the elderly likely in relation with the increasing rate of frailty.[4] In HF, hypoalbuminemia may be a marker of comorbidity burden, inflammatory state, malnutrition, and cachexia.[5] Low serum albumin levels are associated with increased risk of HF onset and progression. Indeed, hypoalbuminemia may promote pulmonary congestion (according to Starling's law),[6] myocardial edema and subsequently worsening of myocardial dysfunction,[7] diuretic resistance and fluid retention,[8] and a decrease in antioxidant functions and anti-inflammatory properties.[9]

Several authors have demonstrated an association between low serum albumin and increased cardiovascular morbidity and mortality in patients with chronic HF.[4,10–12] Conversely, very few studies have examined the impact of hypoalbuminemia in the acute HF setting.[10,13] In elderly patients (>80 years)[14,15] and nonagenarians[16] with acute HF,

severe hypoalbuminemia represents a potential predictor of adverse in-hospital outcome. To our knowledge, the clinical relevance of hypoalbuminemia has not yet been fully evaluated in this clinical setting. The aim of the present study was to examine the prognostic significance of serum albumin level in the prediction of hospital mortality in patients admitted for acute non-ischemic HF in a Belgian community hospital.

Methods

Patients

The present study collected detailed hospitalization data from computerised medical records of patients presenting with acute HF at CHU of Liège, Belgium, between 2010 and 2012. Patients (n = 1611) were eligible for the first round of selection if they were >18 years of age, had a suspected diagnosis of HF, and were alive 24–36 h after admission. After a second round of selection, 899 patients with ≥1 following criteria were disqualified: respiratory support, cardiogenic shock, acute coronary syndrome, inotropic support, primary valvular heart disease, permanent pacemaker pacing, severe arrhythmias (atrial fibrillation, ventricular tachycardia, ventricular fibrillation), infectious/inflammatory disease (C-reactive protein >10 mg/L), end-stage renal failure requiring dialysis, liver failure, and cancer. The following clinical data were available from electronic hospital records: demographic information, the use of beta-blockers or angiotensin-converting enzyme (ACE) inhibitor at admission, medical history, prior myocardial infarction, prior hear failure hospitalization, laboratory findings (albumin, hemoglobin, sodium, creatinine, NT-proBNP, cholesterol, glucose, calcium, leukocytes), heart rate and blood pressure, left ventricular ejection fraction, and in-hospital mortality. The impact of heart rate was already reported in this population.[17] At the end of the selection process, we kept 546 patients with a measure of serum albumin level available. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Data collection

The following clinical data were abstracted from hospital records: demographic information, the use of beta-blocker or angiotensin-converting enzyme (ACE) inhibitor at admission, medical history, prior myocardial infarction, prior HF hospitalization, laboratory findings (hemoglobin, sodium, creatinine, NT-proBNP and albumin), heart rate, blood pressure, left ventricular ejection fraction, and hospital mortality. Serum albumin levels were analyzed using a bromocresol purple dye-binding method. The in-house reference range for this albumin assay is 38 to 49 g/L, with total imprecision <2.5%. All other blood tests were performed using standard routine techniques.

Statistical methods

Data are reported as mean ± standard deviation for continuous variables or percentages of patients for categorical variables. Quantitative variables were tested for distribution normality with the Shapiro–Wilk test. Group comparisons for categorical variables were obtained with chi-square test and for continuous variables with Mann–Whitney–Wilcoxon test, as they were not normally distributed. We made a forward selection and introduced variables significantly different between groups ($P < 0.05$) in a logistic model according to their level of significance. An exception to this rule was done for age (P = 0.006), which was introduced first in the model because of its prognostic relevance. We performed a likelihood ratio test (LRT) on these tested models to select the significant predictors (LRT $P < 0.05$) of in hospital mortality. To deal with missing data in this multivariable analysis, we imputed the missing quantitative variables by use of multiple imputation (N = 50) that we obtained with the MICE package (https://cran.r-project.org/web/packages/mice/mice.pdf). All statistical analyses were performed with R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Sensitivity and specificity for prediction of hospital mortality were determined for various cut-off values of the selected predictors using receiver operating characteristic (ROC) curves. The critical cut-off values for these variables were defined as those given the higher sensitivity–specificity product. The critical value observed for age and albumin were then used as categorical variable in the logistic regression model described above. We also compared the distribution of either categorical or quantitative variables between the tertiles of albumin by a chi-square or a Kruskal–Wallis test, respectively. The authors had full access to and take full responsibility for the integrity of the data.

All authors have read and agree to the manuscript as written.

Results

Patients' characteristics

Among the 546 patients included (72 ± 12 years, 59% of male), 48% had hypertension, 20% were diabetics, 20% previously experienced myocardial infarction, 43% had ischemic heart disease, and 45% had prior cardiac decompensation diagnosis (*Table 1*). Left ventricular systolic dysfunction (ejection fraction < 40%) was identified in 242 (44%) patients. Mildly reduced ejection fraction (40–49%) was observed in

Table 1 Univariable analysis: predictors of hospital mortality

Variables	Whole cohort (n = 546)	Survivors (n = 510, 93%)	Death (n = 36, 7%)	P
Age, years	72 ± 12	72 ± 12	78 ± 9	0.006
Male gender, *n* (%)	323 (59)	297 (58)	26 (72)	0.14
Heart rate, bpm	80 ± 19	79 ± 18	93 ± 21	<0.0001
Systolic blood pressure, mmHg	122 ± 21	123 ± 21	112 ± 20	0.004
Diastolic blood pressure, mmHg	68 ± 12	69 ± 12	61 ± 10	0.0009
Left ventricular ejection fraction, %	45 ± 16	45 ± 16	46 ± 15	0.48
Left ventricular ejection fraction <40%, *n* (%)	242 (44)	227 (45)	15 (42)	0.81
Medical history				
Hypertension, *n* (%)	261 (48)	246 (48)	15 (42)	0.23
Diabetes, *n* (%)	110 (20)	97 (19)	13 (36)	0.06
COPD, *n* (%)	136 (25)	126 (25)	10 (28)	0.99
Ischemic cardiomyopathy, *n* (%)	236 (43)	214 (42)	22 (61)	0.04
Prior heart failure, *n* (%)	248 (45)	227 (45)	21 (58)	0.15
Prior myocardial infarction, *n* (%)	109 (20)	98 (19)	11 (31)	0.15
Medications				
ACE-inhibitor	178 (33)	171 (34)	7 (19)	0.12
Beta-blockers	195 (36)	187 (37)	8 (22)	0.12
Laboratory findings				
Total cholesterol, mg/dL	140 ± 40	140 ± 41	132 ± 52	0.39
Glucose, g/L	1.2 ± 0.5	1.2 ± 0.5	1.3 ± 0.6	0.21
Hemoglobin, g/L	12.1 ± 2.2	12.1 ± 2.2	12.4 ± 2.3	0.80
Hematocrite, %	37 ± 6	37 ± 6	38 ± 7	0.87
Leukocytes count, 10^3 cells/mm^3	8.5 ± 4.2	8.3 ± 3.9	11.4 ± 6.3	0.001
Albumin, g/L	36.5 ± 4.5	36.9 ± 4.1	31.3 ± 5.6	<0.0001
Total protein, g/L	64.5 ± 6.8	64.8 ± 6.3	60.6 ± 10.3	0.03
NT-proBNP, pg/mLl	9370 ± 12 928	8354 ± 10 673	23 726 ± 28 399	0.15
Calcium, mmol/L	2.2 ± 0.2	2.2 ± 0.1	2.1 ± 0.2	0.08
Sodium, mmol/L	140.7 ± 4.5	140.7 ± 4.3	140.7 ± 6.3	0.68
Creatinine, mg/dl	14.7 ± 11.6	14.4 ± 10.8	18.7 ± 18.3	0.01
Estimated GFR, mL/min/mm^3	57.7 ± 27.9	58.4 ± 28.0	48.5 ± 25.4	0.03
Aspartate aminotransferase, UI/L	49.9 ± 165.9	42.6 ± 129.4	142.7 ± 399.0	0.06
Alanine aminotransferase, UI/L	47.0 ± 148.8	40.9 ± 121.1	123.4 ± 336.3	0.23

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease.

52 patients (9.5%). Angiotensin-converting enzyme (ACE)-inhibitor and beta-blocker were taken at the time of admission by 178 (32%) and 195 (35%) patients, respectively.

Association of albumin levels with clinical and biological variables

Mean albumin level was 36.5 ± 4.5 g/L (median 37.15 g/L, range: 13.4–47.6 g/L, *Table 1*). According to albumin level tertile (first tertile: 13.4–35 g/L, second tertile: 35.1–38.6 g/L and third g/L, 38.7–47.6 g/L), patients with a lower albumin level were often older and have lower hematocrit and hemoglobin levels (*Table 2*). As regards the proportion of patients treated with either beta-blocker or ACE-inhibitor, we only detected a slight increase in patients treated with ACE-inhibitor in the third tertile whereas the renal function was better in this tertile.

Hospital mortality

Thirty-six patients (7%) died during the hospital stay. The comparisons between patients with hospital death and survivors for clinical and biologic data are reported in *Table 1*. Hospital survivors were significantly younger and had better renal parameters. Conversely, in-hospital death patients frequently displayed a medical history of prior ischemic cardiomyopathy and had lower systolic and diastolic blood pressures and higher heart rate at 24–36 h after admission. Of note, there was no significant difference between in-hospital death and survival regarding diabetes, chronic obstructive disease, prior myocardial infarction, and history of HF. The proportion of patients taking an ACE-inhibitor or beta-blocker at the time of admission did not significantly differ between survivors and patients who died. Interestingly, patients were really at high risk of death if they had lower albumin level and in a less extent, if they had a higher leukocyte count.

Predictors of hospital mortality

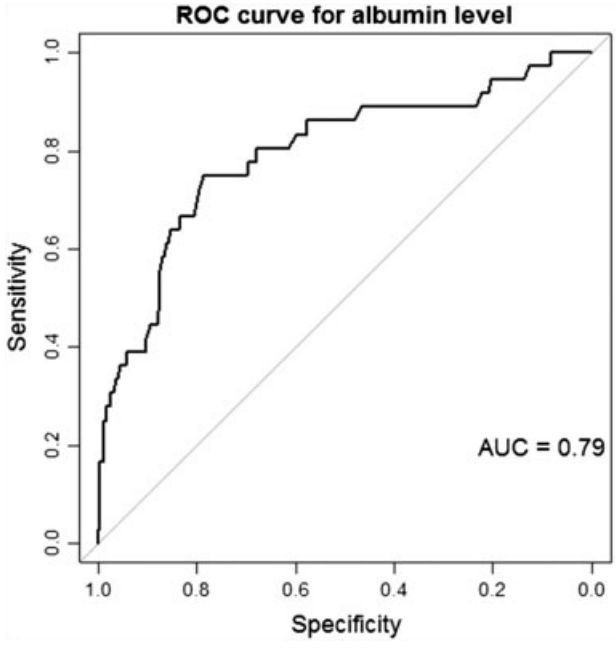
Based on results from the likelihood ratio tests, there was a significant relationship between age, albumin level, heart rate, arterial diastolic blood pressure, and hospital mortality. Using ROC curves analyses, the best cut-off value to predict hospital mortality was 78 years for age (area under the curve

Table 2 Cofactors associated with albumin level tertiles

Variables	First tertile (n = 181)	Second tertile (n = 173)	Third tertile (n = 192)	P
Age, years	75 ± 11	72 ± 13	70 ± 12	0.001
Male gender, *n* (%)	103 (57)	104 (60)	116 (60)	0.75
Heart rate, bpm	82 ± 20	78 ± 18	79 ± 17	0.1
Systolic blood pressure, mmHg	120 ± 19	124 ± 23	122 ± 21	0.25
Diastolic blood pressure, mmHg	67 ± 12	69 ± 13	69 ± 13	0.15
Left ventricular ejection fraction, %	46 ± 16	45 ± 15	43 ± 18	0.44
Left ventricular ejection fraction <40%, *n* (%)	77 (43)	73 (42)	92 (48)	0.37
Medical history				
Hypertension, *n* (%)	85 (47)	79 (46)	97 (51)	0.28
Diabetes, *n* (%)	40 (22)	39 (23)	31 (16)	0.34
COPD, *n* (%)	45 (25)	42 (24)	49 (26)	0.85
Ischemic cardiomyopathy, *n* (%)	75 (41)	71 (41)	90 (47)	0.45
Prior heart failure, *n* (%)	81 (45)	81 (47)	86 (45)	0.9
Prior myocardial infarction, *n* (%)	38 (21)	34 (20)	37 (19)	0.91
Medications				
ACE-inhibitor	48 (27)	54 (31)	76 (40)	0.02
Beta-blockers	54 (30)	62 (36)	79 (41)	0.07
Laboratory findings				
Total cholesterol, mg/dL	130 ± 40	151 ± 42	154 ± 43	0.03
Glucose, g/L	1.2 ± 0.6	1.1 ± 0.4	1.2 ± 0.4	0.12
Hemoglobin, g/L	11.7 ± 2.2	12.1 ± 2.1	12.7 ± 2.1	<0.0001
Hematocrite, %	36 ± 6	37 ± 6	39 ± 6	0.0008
Leukocyte count, 10^3 cells/mm^3	8.9 ± 4.3	8.2 ± 3.2	8.3 ± 4.9	0.44
NT-proBNP, pg/ml	10 854 ± 10 098	9270 ± 13 842	8199 ± 14 233	0.07
Calcium, mmol/L	2.1 ± 0.2	2.2 ± 0.1	2.2 ± 0.1	<0.0001
Sodium, mmol/L	141.2 ± 4.7	140.4 ± 4.6	140.6 ± 4.1	0.4
Creatinine, mg/dL	16.1 ± 12.4	15.5 ± 14	12.2 ± 6.5	0.007
Estimated GFR, mL/min/mm^3	54 ± 29.6	56.1 ± 26.9	63.5 ± 26.2	0.001
Aspartate aminotransferase, UI/L	62.9 ± 188.4	44.1 ± 194.6	40.5 ± 85.2	0.02
Alanine aminotransferase, UI/L	54.3 ± 161.4	42.8 ± 174.9	42.8 ± 95.1	0.04

(AUC) = 0.64), 34 g/L for albumin level (AUC = 0.79, *Figure 1*), 91 beats per minute for heart rate (AUC = 0.72), and 64 mmHg for diastolic blood pressure (AUC = 0.7) (*Table 3*).

Figure 1 Receiver operating characteristic curve for albumin levels.



After adjustment for age, the risk of in-hospital death for patients with <34 g/L of albumin was increased by nine-fold as compared to patients with levels above this critical value. Moreover, patients older than 78 years had a three-fold increased risk of in-hospital death. We then adapted our logistic regression model by introducing the critical values measured for age (78 years) and albumin (34 g/L). Based on this new model, we found the previously unrevealed significant relationship between leukocyte count with in-hospital mortality (*Table 4*). The best cut-off value for leukocyte count to predict in-hospital mortality was 9×10^3 cells/mm^3 (AUC = 0.67) (*Table 3*).

Effect of age and albumin level on hospital mortality

We assigned our 546 individuals to four categories based on age and albumin level as follows: individuals of <78 years old with an albumin level > 34 g/L (category 1), individuals of ≥78 years old with an albumin level >34 g/L (category 2), individuals of <78 years old with an albumin level ≤34 g/L (category 3), individuals of ≥78 years old with an albumin level ≤34 g/L (category 4). The proportion of survivors and deaths in these categories are reported in *Table 5*. We compared the proportion of death between these four

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Table 3 Cut-off values from receiver operating characteristic curves analysis for variables associated with hospital mortality

Variable	Threshold	Specificity (%)	Sensibility (%)	AUC
Albumin, g/L	34	78.8	75.0	0.79
Age, years	78	65.7	58.3	0.64
Heart rate, bpm	91	78.2	58.3	0.72
Arterial diastolic blood pressure, mmHg	64	56.3	79.2	0.70
Leukocyte count, 10^3 cells/mm^3	9	71.1	60.6	0.67

Table 4 Mutivariable analysis: predictors of hospital mortality

Variables	Odds-ratio	95% Confidence interval	*p*
Age ≥78 years	1.89	0.87–4.1	0.01
Albumin ≤ 34 g/L	6.87	2.99–15.8	<0.0001
Heart rate, per bpm	1.03	1.02–1.05	0.0003
Diastolic blood pressure, per mmHg	0.95	0.91–0.99	0.01
Leukocyte count, 10^3 cells/mm^3	1.09	1.02–1.16	0.009

Table 5 Contingency table for the proportion of survivors and deaths in the four categories defined by age and albumin level

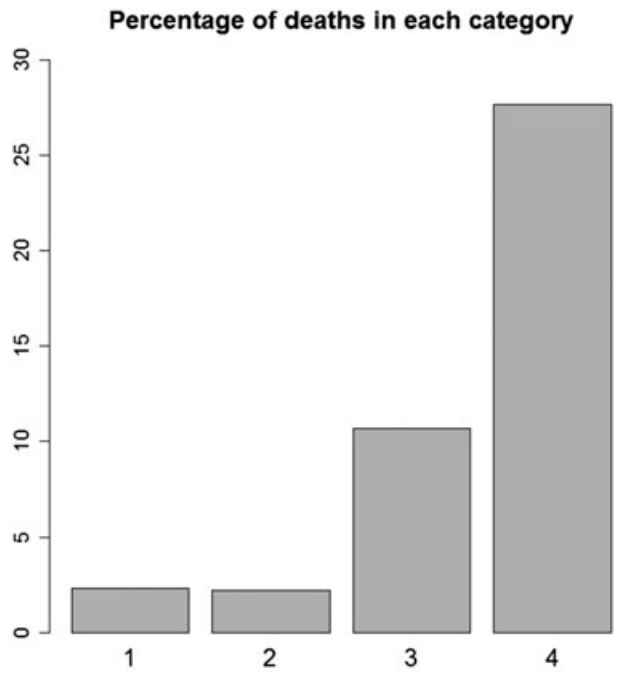
Category	0	1
1	253 (97.7)	6 (2.3)
2	135 (97.8)	3 (2.2)
3	75 (89.3)	9 (10.7)
4	47 (72.3)	18 (27.7)

Table 6 *P*-values from pairwise comparison for the proportion of death between the four categories defined by age and albumin level

Category	1	2	3
2	1	—	—
3	0.012	0.042	—
4	<0.0001	<0.0001	0.042

groups using a chi-squared test. *P*-values were adjusted for multiple testing using Holm's method and are reported in *Table 6*. We found that the proportion of deaths was not significantly different between category 1 and 2 in which all patients had an albumin level >34 g/L irrespective of their age (< or ≥78 years old) (*Figure 2*). However, the proportion of deaths was significantly higher in category 3 and 4 (in which albumin level was <34 g/L) as compared to category 1 or 2 ($P_{cat1–3}$ = 0.01, $P_{cat1–4}$ < 0.0001 and $P_{cat2–3}$ = 0.04, $P_{cat2–4}$ < 0.0001, *Table* 5). Moreover, when albumin level was low, age became critical as the proportion of death between category 4 and categories 1 or 2 was more significant than the difference between category 3 and the two same categories.

Figure 2 Percentage of deaths in the four categories defined by age and albumin level.



Discussion

In patients hospitalized with acute HF, hypoalbuminemia is frequent (27%) and is associated with increased risk of hospital mortality. Low serum albumin levels carry additional risk prediction of hospital outcome independent of conventional risk markers such clinical (age), hemodynamic (diastolic blood pressure, heart rate), and biological (leucocyte count) factors.

Predictors of hospital mortality in acute HF

The continued high mortality rate for patients hospitalized with acute HF provides a compelling indication for accurate risk stratification to potentially improve individual management and hospital outcome.[18] In acute HF, risk of hospital mortality is known to increase with age, higher heart rate at admission, and lower diastolic blood pressure.[17,18]

Elderly HF patients are likely to have multiple cardiovascular and non-cardiovascular comorbidities that influence prognosis. Whilst it is noteworthy that our population (72 $\pm$ 12 years) was relatively young, the rate of hospital death was still high (7%), which remains close to previous registries with similar rate of comorbidities.[17–19]

As previously shown, heart rates exceeding 91 bpm predicted higher in-hospital mortality while lower thresholds portended better hospital prognosis.[17] Several pathophysiological mechanisms, including increased myocardial oxygen consumption, reduced diastolic filling times, compromised coronary perfusion with induction of myocardial ischemia, and precipitation of rhythm disturbances have been proposed to explain this association.[20–22]

A diastolic blood pressure lower than 64 mmHg, close to previously reported threshold, emerged as the best cut-off to indicate higher mortality risk.[23] The mechanisms of this association are unclear, but may be linked to the compromised coronary perfusion.

Elevated leukocyte count ($>9 \times 10^3/mm^3$) also emerged as an independent risk predictor. Leukocytes are the main producers of cytokines that promote the development of HF.[24] There is evidence to suggest an association between leukocytes and HF development and outcome.[25] In apparently healthy subjects, leukocyte count has been associated with incident HF.[26] Elevated leukocyte level has been recently identified as a potential predictor of early mortality in patients with acute ischemic HF[27] and of long term-survival in patients with dilated cardiomyopathy.[28]

Few recent studies conducted in acute and chronic HF have shown that albumin predict in-hospital outcome and survival up to 1 year after measurement.[14] This finding has been mainly derived from special populations including octogenarian and nonagenarian patients hospitalized for HF.[15,16] Our results confirm and extend these previous observations showing that the risk of hospital death of patients with low serum albumin levels ($<$34 g/L) is markedly increased. Risk prediction is independent of age, but remains important in the elderly. The number of deaths is multiplied by about 3 in case of low serum albumin ($<$34 g/L), and significantly amplified by about 9 if they are also older than 78 years.

Serum albumin is an abundant plasma protein with multiple physiological properties, including colloid osmotic effect, antioxidant and anti-inflammatory functions, and binding capacity for many molecules and drugs.[29] In HF, low-level albumin can reflect reduced protein intake (malnutrition), decreased hepatic synthesis, increased vascular permeability (increased hydrostatic venous pressure), and enteric or renal losses (splanchnic congestion).[30] Growing evidence suggests that hypoalbuminaemia represents a risk factor exerting adverse pleiotropic effects on many organs and neurohumoral systems that are involved in the clinical syndrome of HF. In our study, lower levels of albumin were related to aging, lower hemoglobin (multifactorial cause) and cholesterol (malnutrition/inflammation) levels, impaired renal and hepatic function, lower rate of beta-blockers and ACE inhibitors use, but not to leukocyte count, or to left ventricular ejection fraction. Hence, hypoalbuminemia can also serve as a risk marker identifying the sickest patients independent of the degree of left ventricular systolic dysfunction.[12]

Clinical implications

The unbalance between protein/energy demands and its availability secondary to hypoalbuminemia predicts ominous hospital HF outcome. Patients with low serum albumin levels should thus receive more aggressive therapeutic support while targeting its causes. For example, depletion treatments with diuretics have managed to reduce the trans-capillary escape rate of albumin[30] and correct hypoalbuminemia after the resolution of splanchnic congestion.[31] Attenuating inflammatory responses associated with HF may potentially represent another drug target (e.g. by use of angiotensin II receptor blocker, ω-3 polyunsaturated acids).[32,33] The randomized PICNIC study is currently evaluating the impact of nutritional intervention on morbidity and mortality in malnourished hospitalized HF patients with and without hypoalbuminemia.[34] Whether albumin administration in patients with HF would likely be beneficial as in sepsis, brain trauma, or lung injury is unknown.[35–38] In these conditions, the use of albumin is likely necessary to expand the volume and maintain the circulation. In HF, fluid retention is key and treatment strategies are used to minimize signs of hypervolemia. Furthermore, the use of albumin in acute HF setting is not usually recommended. Experimental data in dogs have recently demonstrated the potential ability to prevent pulmonary edema by increasing plasma oncotic pressure with albumin administration.[38] So, the clinical relevance of albumin administration in patients with chronic HF and low serum albumin level needs to be investigated.

Limitations

Our study has several limitations related to its retrospective nature that are worth noting. They do not pertain to all patients presenting with acute HF. Anthropometric data (weight, height, and body mass index), white blood cell components (neutrophils, lymphocytes, monocytes),

nutritional status, and information about the use of additional HF treatment (mineralocorticoid receptor antagonist) were missing. However, the hyperhydration state of our HF patients makes the interpretation of anthropometric measurements very difficult. Specific inflammatory biomarkers (high sensitivity C-reactive protein, interleukins, tumor necrosis factor-α) were also not available. The potential association between albumin level and inflammatory status needs additional exploration. Before 2012, NT-proBNP was not routinely measured, resulting in small number of patients with these data available. NT-proBNP was then not included in the mutltivariable model. However, when available, blood concentrations of these biomarkers were confirmed to be significantly increased in both worsening and *de novo* HF patients. The prognostic impact of albumin in these patients remains to be determined in further studies.

Conclusions

Serum albumin level detected at admission can serve as a simple prognostic factor in acute non-ischemic HF. Hypoalbuminemia is associated with increased risk of hospital mortality, especially in elderly patients. Lower diastolic blood pressure, higher heart rate, and elevated leukocytes count are additional predictive factors. Although they need to be confirmed, our data raise the issue of underlying potential therapeutic implications, which merit further investigations.

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Conflict of interest

None declared.

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