Systematic Review and Meta-Analysis

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Prognostic role of albumin level in heart failure

A systematic review and meta-analysis

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Abstract

Background: Hypoalbuminemia (HA) is common in HF, however, its pathophysiology and clinical implications are poorly understood. While multiple studies have been published in the past decade investigating the role of serum albumin in HF, there is still no consensus on the prognostic value of this widely available measure. The objective of this study is to assess the prognostic role of albumin in heart failure (HF) patient

Methods: Unrestricted searches of MEDLINE, EMBASE, Cochrane databases were performed. The results were screened for relevance and eligibility criteria. Relevant data were extracted and analyzed using Comprehensive Meta-Analysis software. The Begg and Mazumdar rank correlation test was utilized to evaluate for publication bias.

Results: A total of 48 studies examining 44,048 patients with HF were analyzed. HA was found in 32% (95% confidence interval [CI] 28.4%–37.4%) HF patients with marked heterogeneity (I^2 = 98%). In 10 studies evaluating acute HF, in-hospital mortality was almost 4 times more likely in HA with an odds ratios (OR) of 3.77 (95% CI 1.96–7.23). HA was also associated with a significant increase in long-term mortality (OR: 1.5; 95% CI: 1.36–1.64) especially at 1-year post-discharge (OR: 2.44; 95% CI: 2.05–2.91; I^2 = 11%). Pooled area under the curve (AUC 0.73; 95% CI 0.67–0.78) was comparable to serum brain natriuretic peptide (BNP) in predicting mortality in HF patients.

Conclusion: Our results suggest that HA is associated with significantly higher in-hospital mortality as well as long-term mortality with a predictive accuracy comparable to that reported for serum BNP. These findings suggest that serum albumin may be useful in determining high-risk patients.

Abbreviations: ADHF = acute decompensated heart failure, AUC = area under the curve, BNP = brain natriuretic peptide, CI = confidence interval, HA = hypoalbuminemia, HF = heart failure, HR = hazard ratio, LOS = length of hospital stay, LVAD = left ventricular assist devices, OR = odds ratio, SA = serum albumin, sST2 = soluble ST2.

Keywords: heart failure, hypoalbuminemia, in-hospital mortality, length of hospital stay, long-term mortality, prevalence, prognosis, rehospitalization, serum albumin

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Heart failure (HF) is associated with increased frequency of hospitalization, morbidity, and mortality. Disease burden is on the rise. By 2030, 1 in every 33 people in the United States are projected to suffer from HF.[1] To optimize disease management through medication dose titration, cardiac resynchronization, or ventricular-assist-devices, risk-stratification of patients has become increasingly compelling. Brain natriuretic peptide (BNP) and N-terminal pro-BNP have been increasingly used for prognostication in acute decompensated heart failure (ADHF).[2] Novel prognostic markers have been recently suggested.[3] The 2017 American College of Cardiology focused update on guidelines for the management of HF hinted toward possible future role of these markers[4]; such as admission cardiac troponin level in ADHF, soluble ST2 (sST2) in chronic HF, and other myocardial fibrosis markers for prediction of hospitalization and mortality. However, many of these biomarkers require expensive assays which aren't readily available. Albumin is synthesized in the liver and represents >50% of total serum proteins. Serum level depends on rate of albumin synthesis, distribution, degradation and excretion.[5–7] Hypoalbuminemia (HA) is linked to poor prognosis in multiple conditions, including left ventricular assist device (LVAD),[8] and acute kidney injury.[9] We found a vast amount of literature published in the past decade investigating the role of serum albumin (SA) as a

prognostic indicator in patients with HF. Considering the ease and wide availability of this test, we performed a systematic review and meta-analysis to evaluate the prognostic role of SA in HF.

2. Methods

2.1. Search strategies

This review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10] Unrestricted searches of MEDLINE, EMBASE, CINAHL, Cochrane bibliographic databases were performed using the terms "albumin" and "heart failure" from inception to January-2019. In addition, the reference lists of all selected publications were checked to retrieve relevant studies not identified by the search.

2.2. Study selection and eligibility criteria

Two reviewers (ME and BE) independently screened studies for inclusion based on pre-specified eligibility criteria: studies prospectively or retrospectively enrolled patients diagnosed with HF. Studies clearly reported the associations of SA and one or more outcomes of interest; all-cause mortality including in-hospital, long-term mortality, rehospitalization, or composite outcome of rehospitalization/mortality, providing a relevant hazard ratio (HR)/odds ratio (OR) and its 95% confidence interval (CI), or sufficient data to estimate them. Long-term mortality was defined as post-discharge mortality in patients admitted with acute HF and all-cause mortality in patients with chronic HF, articles published in languages other than English and conference abstracts were excluded.

2.3. Data extraction and quality assessment

Two reviewers (ME and BE) independently extracted the following details from each study: publication year; country; study design; number of centers involved; acute or chronic HF; type of HF (reduced vs preserved ejection fraction); HA cut-off point; HA prevalence; sample size; mean age; inclusion and exclusion criteria for each study; reported outcomes; follow-up period; HR and/or OR with corresponding 95% CIs and adjusted variables. When multiple studies analyzed data form the same clinical trial, we elected to include only the study which either directly evaluated the role of SA or the one with the largest sample size in our qualitative analysis. To evaluate the quality of evidence, studies were assessed by the method proposed by

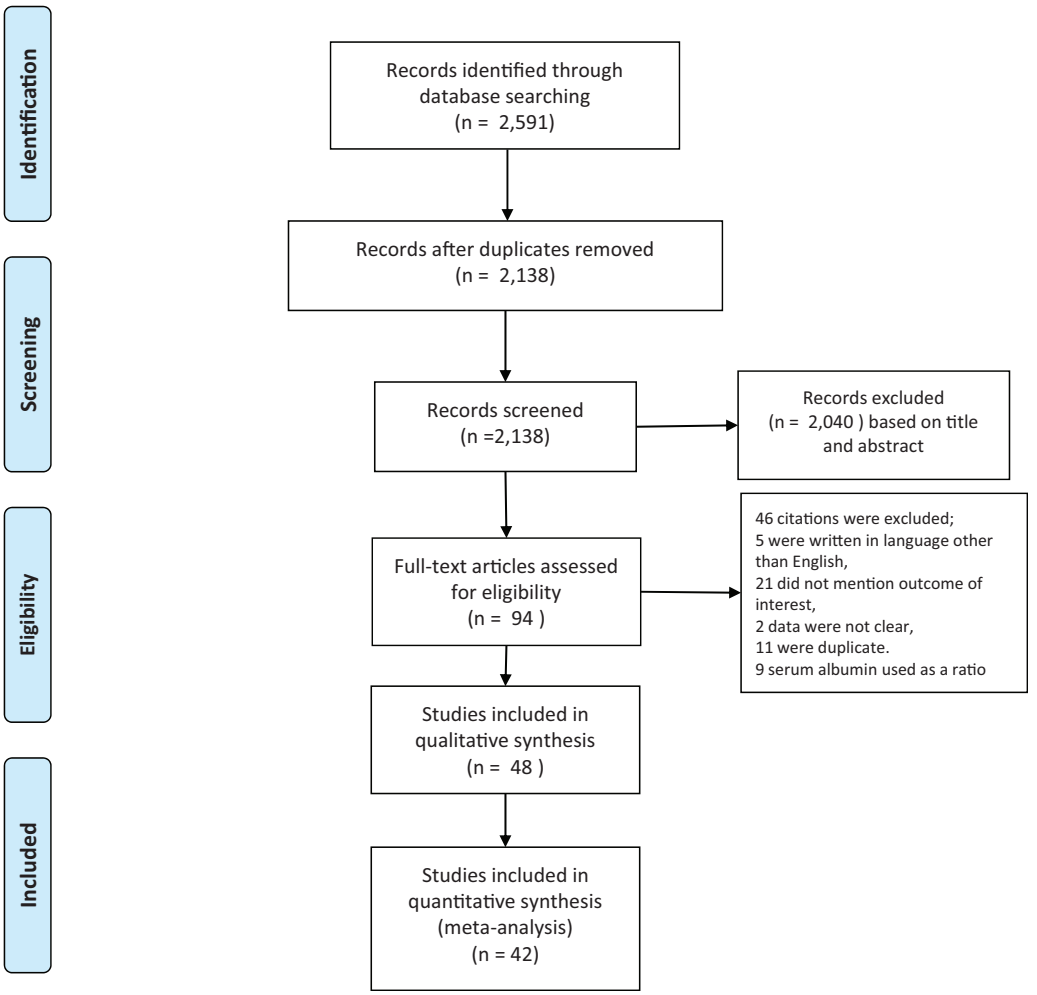


Figure 1. Flow diagram of record allocation.

Hayden et al[11] in systematic reviews of prognostic studies. Studies which failed to include all of the following: age, sex, body mass index (BMI), liver function tests, and renal function tests in multivariate analysis were considered at high risk of confounding bias.

2.4. Statistical analyses

OR or HR was either extracted or calculated from individual papers. Though defined differently, OR and HR have been shown to be similar theoretically as well as empirically.[9,12] Hence, throughout this systematic review, we used the term OR to denote both OR and HR. Cumulative OR with 95% confidence interval (CI) was calculated using random effects model. Heterogeneity was assessed for using the I^2 measure and the Cochran Q-statistic. We further stratified studies into subgroups based on type of analysis used (univariate vs multivariate) and follow up duration for each study. The Begg and Mazumdar rank correlation test was utilized to evaluate for publication bias. Statistical analyses were performed using the Comprehensive Meta-Analysis software version 3.3.070 (Biostat; Englewood, NJ). *P*-value <.05 was considered significant.

3. Results

3.1. Record allocation

Of the 2591 citations in the initial literature search, conference abstracts, review papers, letters to the editor, comments, and duplications were excluded. One hundred twenty five studies remained and were screened for eligibility criteria. A total of 48 studies were considered eligible and included in the analysis (Fig. 1). Six studies were included in the qualitative analysis, but not the quantitative analysis.

3.2. Study characteristics

Fourty eight studies examining 44,043 HF patients were included in this review (Table 1). Study characteristics are outlined in the supplementary table, http://links.lww.com/MD/F819.

The studies were published between 2006 and 2018, while 1 was published in 1992. Sample-size ranged from 33 to 8246. Mean-age of study populations ranged from 55 to 93 years. Percentage of male patients ranged from 13% to 100%. Nine studies were prospective, 25 retrospective, and 14 were secondary analyses of data collected in randomized controlled trials. Four[13–16] out of the 14 studies used data of population from a single trial[17] and 2 studies[18,19] used data from another trial.[20]

3.3. Quality of evidence evaluation

The overall risk of internal bias for included studies was rated as moderate. No publication bias was found in any of the analyzed outcomes using Begg and Mazumdar test. Twenty seven out of 48 of the included studies were not designed to assess the prognostic role of SA. On the other hand, 90% of the included studies used multivariate analysis to examine the prognostic role of studied parameters independently and decrease the risk of bias. The domains at low risk of bias were: population description/ selection, attrition, description of statistical analysis, and outcome definition and measurement. Fourteen of the included studies used composite outcomes of rehospitalization or mortality after discharge or during follow up. In respect to prognostic factor assessment, HA was clearly defined only in 26 studies. Furthermore, techniques of albumin measurement and other laboratory parameters were not clearly described in 46% and 48% (Q3b, and Q3c), respectively. Studies which failed to include all of the following: age, sex, body mass index, liver function tests, and renal function tests in multivariate analysis were considered at high risk of confounding bias, this was the case in 50% of the included studies. Thus, the overall risk of bias in this category (Q5b) was considered to be moderate (Fig. 2).

3.4. Pooled prevalence of hypoalbuminemia in HF

Twenty two studies reported HA prevalence[13,21–29,29–40] ranging between 28% and 37%. Pooled prevalence was 32% (95% CI 28.4%–37.4%) with marked heterogeneity (I^2=98%) (Fig. 3). Subgroup analysis showed that hypoalbuminemia is more prevalent in acute HF 38.5% (95% CI 34.6%–42.5%) than in chronic 19.7% (95% CI 15.2%–25.1%).

3.5. Hypoalbuminemia in HF and association to mortality

In 10 studies evaluating acute HF patients[13,21,23,30,31,34,41–44] mortality was approximately 4 times more likely in HA (OR 3.77 [95% CI 1.96–7.23] [Fig. 4A]). Further stratification by type of analysis revealed a pooled OR 5.62 (95% CI 1.86–16.95) in 5 studies performing univariate analysis compared with OR 3.05 (95% CI 1.36–6.82) in the 5 studies[13,21,30,42,43] which performed a multivariate analysis accounting for confounders such as age, sex, BMI, serum creatinine, BNP level, C-reactive peptide level, systolic blood pressure, and left ventricular ejection fraction (LVEF). OR for mortality at 3 months[26–28] was 2.12

Table 1

Study characteristics.

Characteristics	Number of studies	Total sample size
Study design, no		
Prospective	9 (19%)	9987 (23%)
Retrospective	25 (52%)	20,060 (45%)
Secondary analysis of randomized controlled trials	14 (29%)	13,996 (32%)
Research country		
North America	12 (24%)	11,348 (26%)
Europe	9 (19%)	1951 (4%)
Asia	15 (31%)	16,079 (36%)
Africa	1 (2%)	120 (0.2%)
Australia	2 (4%)	7789 (18%)
Inter-continent	9 (19%)	6756 (15%)
Number of hospitals		
Single center	33 (69%)	15,293 (35%)
Multicenter	15 (31%)	28,750 (65%)
Sample size		
>1000	16 (33%)	30,379 (69%)
<1000	32 (66%)	13,664 (31%)
Mean age		
50–69	20 (42%)	12,476 (28%)
70–80	16 (33%)	16,159 (36%)
80–95	8 (17%)	8998 (20%)
NA	4 (8%)	6468 (15%)
Acute vs chronic		
Acute	42 (87%)	34,962 (79%)
Chronic	6 (13%)	9081 (21%)

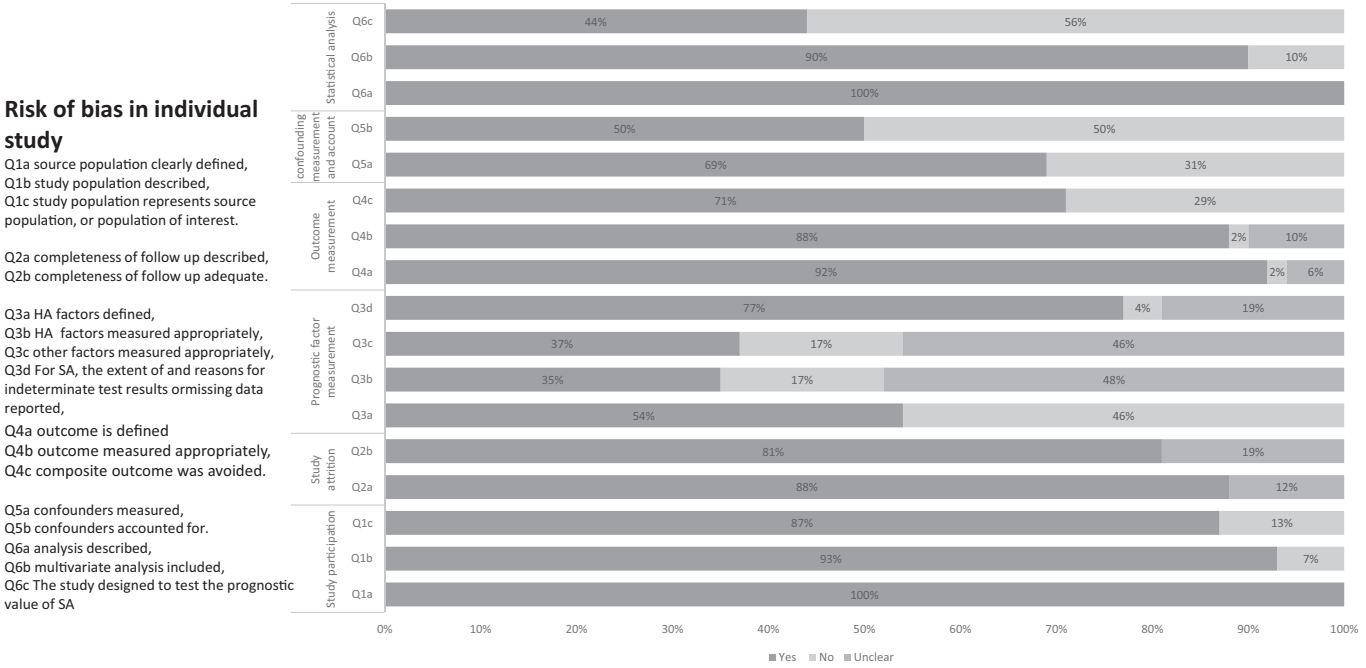


Figure 2. Risk of bias assessment.

(95% CI: 1.19–3.37), at 6 months[13,36,38,45–47] was 1.16 (95% CI: 1.03–1.36), and at 12 months[22,24,25,48–51] was 2.44 (95% CI 2.05–2.91) (Fig. 4B). HA was associated with a significant increase in long-term mortality (OR: 1.5; 95% CI: 1.36–1.64). The association was most strikingly demonstrated at 1-year follow-up (OR: 2.44; 95% CI: 2.05–2.91; $I^2 = 11\%$).

Seven studies[23,25,30,42,43,50,52] evaluated the diagnostic accuracy of HA in predicting mortality in HF (pooled area under the

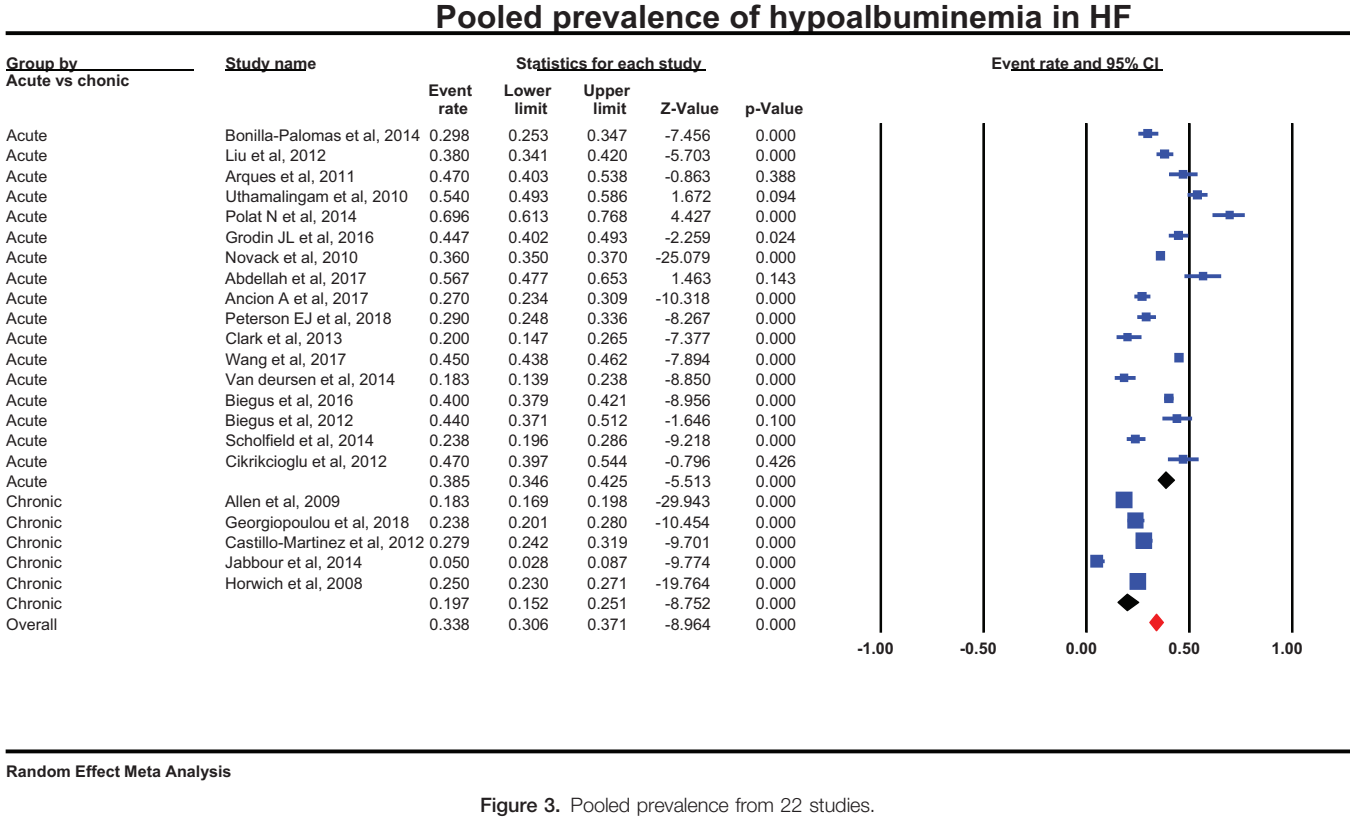


Figure 3. Pooled prevalence from 22 studies.

curve [AUC] 0.73; 95% CI 0.67–0.78). While pooled AUC for 1-year mortality was 0.69 (95% CI 0.61–0.79) from 2 studies,[25,50] pooled AUC for in-hospital mortality was 0.79 (95% CI 0.76–0.81) from 3 studies.[23,30,42] (Fig. 4C).

3.6. Serum albumin relation to length of hospital stay (LOS) and readmission rates in heart failure patients

Six studies evaluated the relationship between HA and LOS in patients admitted with ADHF. Five studies[14,18,23,41,53] showed that HA was associated with longer hospital stay. Multivariate analysis[14,23,53] was used in 3 publications, demonstrating that SA was an independent predictor of LOS. The reporting of LOS in median (interquartile range) form hindered our ability to perform a meaningful meta-analysis of HA effect on LOS.

Four studies[26,29,52,54] reported on the association between HA and rehospitalization showing an insignificant increase in rehospitalization in the HA group (OR 1.22; 95% CI: 0.96–1.55). Four other studies[14,33,36,55] reported a significant increase in a composite outcome of rehospitalization or cardiac death in the HA group an (OR 1.17; 95% CI: 1.06–1.30) (Fig. 5A).

3.7. Mortality is negatively correlated to SA

Five studies reported the effect of decreasing levels of SA on mortality.[13,24,26,36,56] Mortality increased as SA decreased with OR 1.64 (95% CI 1.08–2.50) for each 1 g/L decrement in SA (Fig. 5B).

4. Discussion

While multiple risk-stratification models and prognostic scores for HF have been proposed and validated, none of them investigated the role of SA.[57,58] In a recent meta-analysis, Peng et al[59] studied HA and mortality in HF, however, in our study we aimed to summarize the increasingly available evidence on the overall prognostic role of HA in HF in inpatient and outpatient mortality, LOS, and rehospitalization. Vincent et al[12] found HA to be an independent prognostic factor in all patients acutely admitted to the hospital. In this review we show this holds true for patients with acute HF. We note HA was present in one-third of HF patients and associated with increased HF mortality in the inpatient (OR 3.77, 95% CI 1.96–7.23) and outpatient (OR 2.44; 95% CI: 2.05–2.91) setting. This observation was preserved after excluding studies which only conducted univariate analysis indicating the independent effects of HA on mortality in HF. Similarly, Peng et al[59] showed in their meta-analysis that HA was associated with increased mortality in heart failure. We also found mortality to be negatively correlated to SA. Although SA is not a specific cardiac marker, admission HA had a pooled AUC of 0.79 (95% CI 0.76–0.81) in predicting in-hospital mortality which is comparable to that reported for elevated BNP

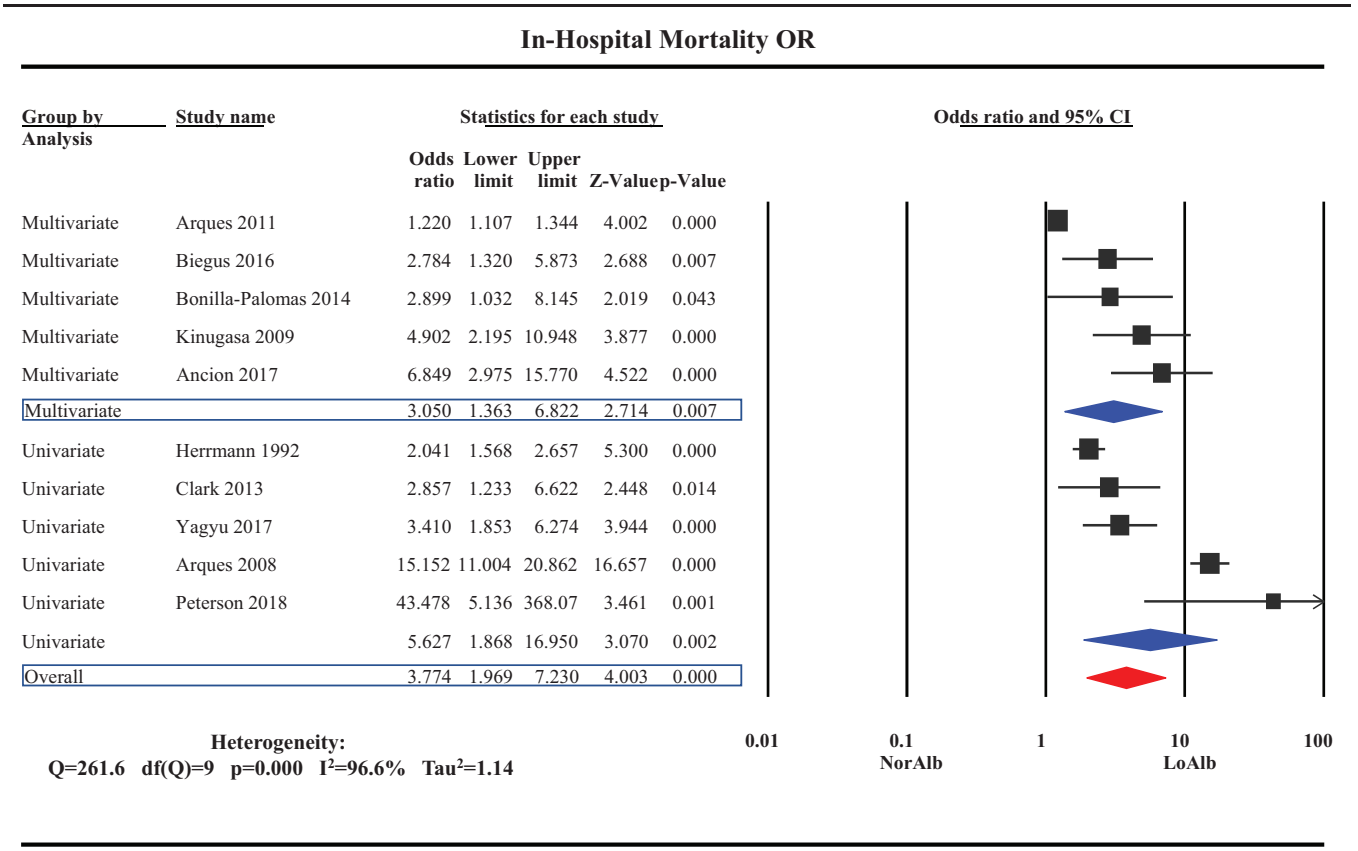
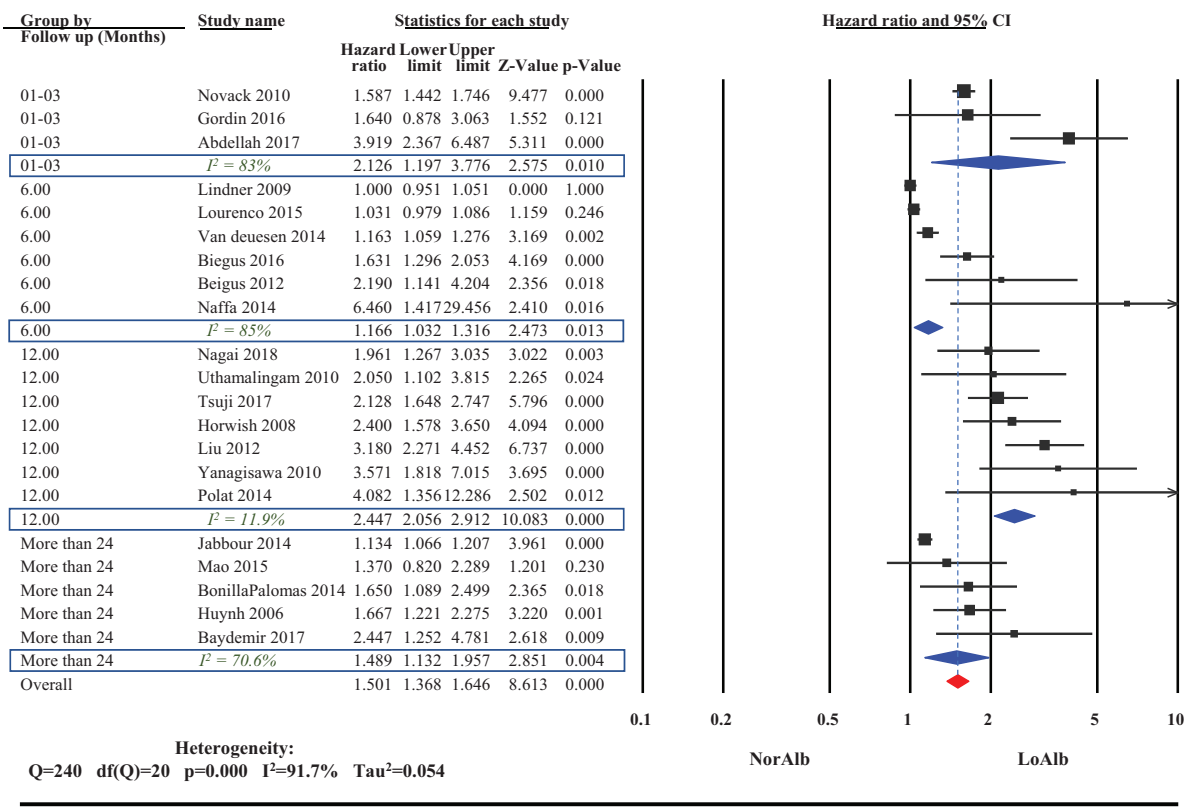
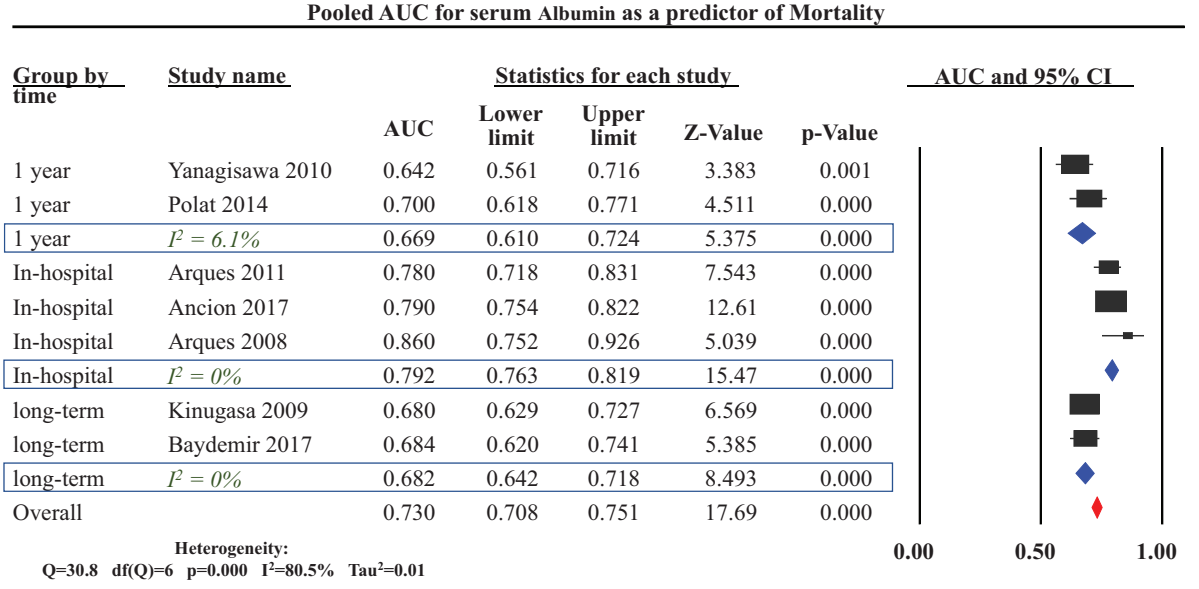


Figure 4. Mortality and hypoalbuminemia in patient with HF. (A) Overall odds ratio for in-hospital mortality in patient with heart failure sub-grouped according to the type of analysis conduct. (B) Long-term mortality in hypoalbuminemia group categorized by duration of follow up. (C) Pooled area under the curve for serum albumin in sub-groups based on duration of follow up. HF = heart failure.



B

Figure 4. Continued



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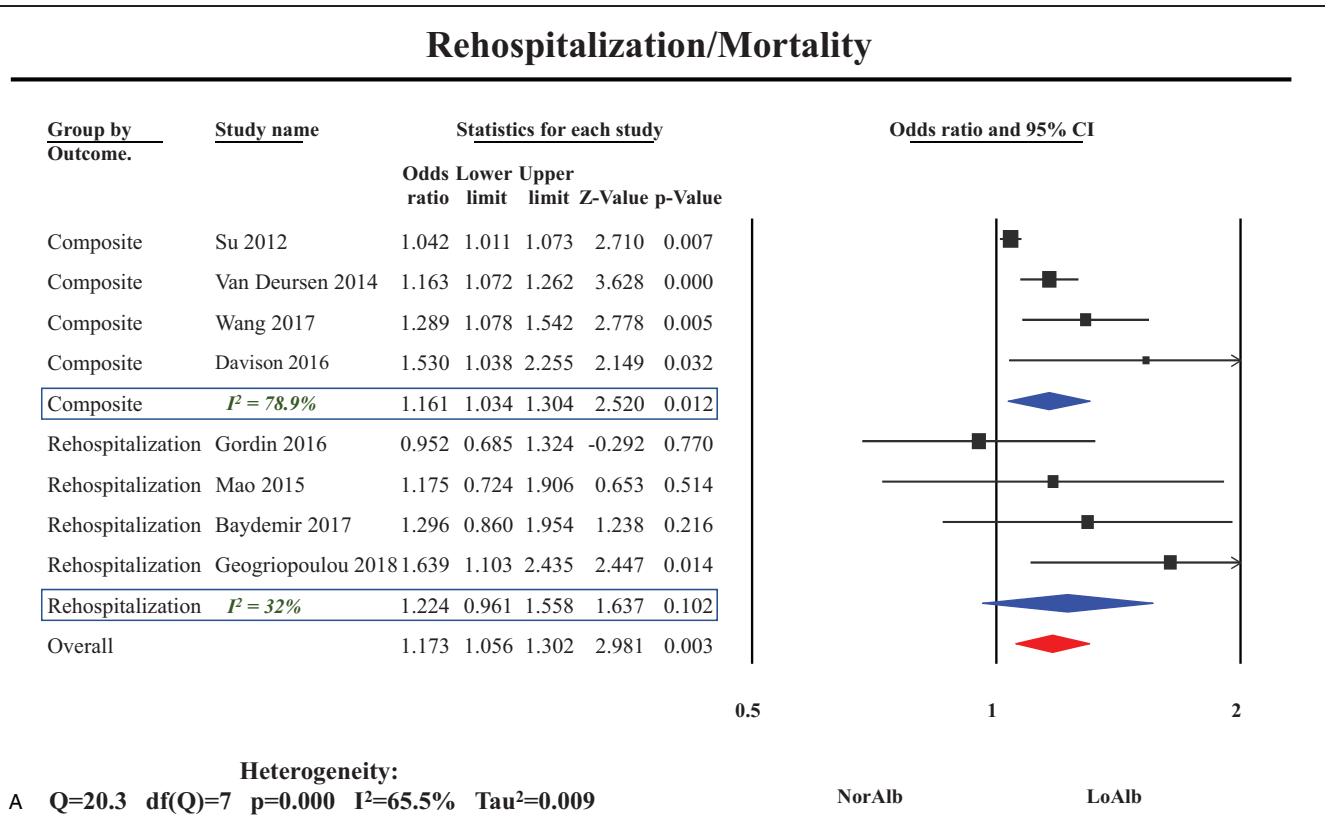

Figure 5. . Rehospitalization and hypoalbuminemia in patient with HF. (A) Odds ratios of rehospitalization and hypoalbuminemia sub-grouped by type of outcome (composite vs rehospitalization). (B) Odds ratios of rehospitalization/mortality composite outcome per drop in serum albumin. HF = heart failure.

on admission (AUC of 0.79).[60] This suggests SA might be a potential marker for mortality in HF.

A downward trend in SA was associated with worse prognosis in acute[13,31,61,62] and chronic HF.[32] Jabbour et al[32] followed 212 patients with chronic systolic HF for over 2 years and found that a drop in SA from baseline was associated with higher mortality compared with retained baseline SA. A study by Biegus et al[13] showed that a downward trend in SA during the first 4 days of hospitalization was associated with, increased 6-month mortality, the risk was proportional to the extent of albumin decrement. Moreover, an upward trend in SA was associated with a drop in cardiovascular and heart failure related mortality

as well as all-cause mortality in ADHF.[61] The pathophysiology behind this association is not clear. However, ineffective diuresis and fluid overload might have a dilutional effect on SA and a subsequent worsening of outcome.[13] Accentuated inflammatory reaction has also been suggested.[31] These results suggest that a downward trend in SA might assist in longitudinal prognostication of HF patients over time.

SA can be affected by nutrition, inflammation, hepatorenal conditions, and volume-status of HF patients (Fig. 5). Reports have linked HA in HF to ongoing inflammation reflected by its strong correlation to C-reactive protein (CRP),[21,25,52] and serum total cholesterol[24,30] levels. Moreover, SA has been used as a marker for malnutrition and wasting syndrome in HF.[21,25] Another cause of HA can be hepatic dysfunction due to venous congestion and ischemic injury.[38] Other mechanisms include renal dysfunction,[22] protein-losing enteropathy secondary to gastrointestinal congestion[49] and hemodilution.[55] The effect of HA on HF is not completely understood. However, HA has been used as an indicator of inflammation, cachexia, and malnutrition[21,25] in patients with HF. Moreover, diuretic resistance, and pulmonary edema are more pronounced in patients with severe hypoalbuminemia.[25] This might explain the higher risk of mortality associated with HA.

Despite the findings above, no specific therapy targeting HA in HF has been studied. The only available data on rectifying HA in HF is derived from studies on LVAD outcomes. Two studies followed patients with HF who received LVAD. Longitudinal trend of SA in this population showed a progressive rise,[63,64] and even normalization of SA within 6 months.[63] Furthermore, a study found that patients with resolution of HA after LVAD had improved overall outcome.[65] This might be related to enhanced liver perfusion, decreased hepatic congestion and improved fluid status.[63] Although the co-administration of albumin and diuretics has been studied in nephrotic syndrome, and liver cirrhosis,[66] data are lacking on this treatment in HF. Future studies are needed to explore the role of this treatment strategy in HF.

4.1. Limitations

This study has the following limitations: only 9 out of the 48 studies used prospective design, half of the included studies did not adequately address relevant confounders in their multivariate analysis. Moreover, we observed significant heterogeneity between included studies. This might be related to the large variation between sample size, age, sex, and study design among the included studies. In addition, only 44% of the included papers were designed to evaluate the effect of HA on HF outcomes. Furthermore, we have used OR to denote both OR and HR, which might have introduced some bias. Despite these limitations, our findings provide valuable insights into the significance of SA in HF prognostication. Our results emphasize the need for population-based studies which longitudinally follow SA in HF patients to validate its prognostic utility.

4.2. Future direction

In Conclusion, SA is an independent predictor of mortality in HF especially in ADHF. Therefore, SA might be an additional marker for the identification of patients at high-risk of complications and mortality, who would require a higher level of monitoring, and earlier, intensive treatment. Our finding needs to be validated in controlled trial to assess whether an earlier intervention in ADHF patients with HA would change the outcome.

5. Conclusion

In summary, we found that HA in HF is associated with increased mortality rates and increased LOS. A downward trend in SA might indicate worse outcome. HA is a strong predictor of mortality in acute HF with AUC of 0.79 comparable to that reported for established factors like BNP. As such, SA level, which is a broadly available and affordable test, might provide a simple method to identify patients with increased risk of mortality.

Author contributions

Conceptualization: Mahmoud El Iskandarani, Bara El Kurdi, Timir K. Paul, Marwan M. Refaat.
Data curation: Mahmoud El Iskandarani, Bara El Kurdi, Ghulam Murtaza.
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Writing – original draft: Mahmoud El Iskandarani, Bara El Kurdi, Ghulam Murtaza, Timir K. Paul.
Writing – review & editing: Timir K. Paul, Marwan M. Refaat.

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