Human albumin administration is associated with increased in-hospital mortality in heart failure with hypoproteinaemia patients: analysis of MIMIC-III Database

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Abstract

Background: Heart failure (HF) is a growing health problem worldwide, especially in the senior. To overcome diuretic resistance in inpatients with HF and hypoproteinaemia, some doctors administer albumin combined with diuretics, though clinical studies on the use of albumin in patients with HF were rare. We aimed to clarify the effect on mortality of administering human albumin during management of HF inpatient especially with hypoproteinaemia.

Methods: We extracted 6094 HF patients from Medical Information Mart for Intensive Care III (MIMIC-III) database. Receiver operating characteristic (ROC) curve was used to elucidate the relationship between serum albumin content and in-hospital mortality. Multivariate logistic regression models、propensity score matching (PSM) and lowess smoother curve were employed to analyze the relationship between albumin administration and clinical outcomes. The clinical outcomes contained in-hospital mortality, output at 24-hour, ICU length of stay (LOS) and hospital LOS. In addition, Kaplan-Meier (KM) curve was used to assess 90-day survival in albumin administration and non-albumin administration subgroups before and after PSM.

Results: Patients with heart failure, serum albumin concentration is negatively correlated with risk of in-hospital death. Based on ROC curve, the optimal cut-off value for predicting the mortality were 2.9g/dl (area under curve (AUC)= 0.643). Albumin administration was significantly associated with increased mortality during hospitalization in the HF plus serum albumin≤2.9g/dl group ($p<0.001$), but no significant difference in serum albumin>2.9g/dl group ($p= 0.25$). After PSM in serum albumin≤2.9g/dl group, hospital LOS and ICU LOS were prolonged ($p<0.001$, $p<0.001$), output at 24-hour had no association with albumin infusion ($p= 0.229$), 90-day mortality was no significant difference between albumin administration and non-albumin administration patients with albumin≤2.9g/dl after PSM ($p= 0.12$).

Conclusion: Albumin administration was associated with increased risk of in-hospital mortality, as well as longer hospital LOS and ICU LOS among HF patients with hypoproteinaemia.

Introduction

Heart failure (HF) is the most frequent cause of hospitalization and rehospitalization among elderly and the cost is unacceptably high[1]. HF mortality is higher than most cancers[2]. Volume overload is a common problem in HF patients and physicians deal it with volume intake restriction and diuretic administration. While diuretic resistance can occur in terminally ill HF patients, in spite of continuous and intermittent diuretic administrations. Previous studies have indicated that plasma albumin as a biovehicle are bound to 95% of furosemide molecules, and furosemide efficacy is dependent on serum albumin concentration. This biovehicle furosemide complex arrives proximal tubular cells and interacts with an anion transporter, eventually, more urine is produced[3]. Otherwise, human plasma protein can reflect the healthy state of the human body[4]. Low Serum albumin is not only correlated with malnutrition

and inflammation but also cardiovascular and cerebrovascular diseases, including coronary artery disease (CAD) and heart failure (HF) [5]. Thus, some physicians overcome furosemide resistance in HF inpatients especially with hypoalbuminemic using human albumin infusion. However, albumin as a colloidal solution also increases the volume load and may further aggravate HF. Previous clinical studies on the use of albumin in patients with HF were rare. The effectiveness of albumin infusion in hospitalized HF patients with hypoproteinemia remains unknown. Furthermore, human albumin is very expensive and limited availability of the sources, it is vital that its usage should be restricted to the indications for which it has been displayed to be effective. To evaluate the effect on mortality of human albumin infusion in hospitalized HF with hypoalbuminemia patients, we administrated a large sample retrospective study based on MIMIC-III database.

Methods

Study design

The retrospective cohort study based on a large freely-available database called MIMIC-III between 2001 and 2012 [6]. It contains high-quality and comprehensive data from critical care unit of Beth Israel Deaconess Medical Center (BIDMC). We obtained access to the database and extract the data (certificate code: 32299459). The study abides by the statement of Reporting of Studies Conducted using Observational Routinely Collected Health Data (RECORD) [7].

Participants selection

Patients in the MIMIC-III who has HF were eligible for inclusion. HF patients were extract from MIMIC-III by the International Classification of Diseases 9th Edition (ICD-9) code and admitting diagnosis. We first extracted 10436 patients with HF. Due to high mortality from acute myocardial infarction and acute pulmonary embolism, as well as the severity of heart failure determined by the location and area of infarct, we excluded 9711 patients with acute myocardial infarction and 166 patients with acute pulmonary embolism. We excluded 3451 patients who were hospitalized for less than 24 hours and younger than the age of 18 as well as repeated admissions and pregnant women. Finally, a total of 6094 patients with HF were included in our study. In addition, if there were more than once ICU stay, we analyzed only the first one.

Variable extraction

Structured query language (SQL) was used to collect baseline characteristics after ICU admission, Baseline characteristics included age, sex and Sequential Organ Failure Assessment (SOFA) score. Human albumin administration was also recorded. Laboratory variables including Initial albumin content, white blood cell (WBC) count, platelet counts, glucose levels, potassium, creatinine, blood urea nitrogen,

sodium and hematocrit were extracted from the database. Time of admission and discharge, as well as in and out of ICU time were recorded. According to the recorded ICD-9 codes, comorbidities including hypertension, diabetes, coronary disease and chronic obstructive pulmonary disease (COPD) were also analyzed.

Outcomes

The primary outcome in the study was in-hospital mortality with or without albumin administration. Secondary outcomes included hospital length of stay, ICU length of stay, output at 24-hour and 90-day survival.

Statistical analysis

StataSE12.0 and IBM SPSS Statistics 25 software were performed to analyze the data. Continuous variables values are presented as the means (standard deviations) or medians. Categorical variables values are presented as total numbers and percentages. Comparisons between groups were performed according Student's t-test. Wilcoxon rank-sum or Kruskal-Wallis tests were used if variables were continuous. Categorical variables were served by $\chi 2$ test or Fisher's exact test as appropriate. ROC curves were used to predict in-hospital mortality across different levels of serum albumin concentration and obtained the cut-off value. Multivariate logistic regression grouped by the cut-off value were used to estimate the relationship between hospital mortality and baseline variables that were considered clinically relevant or that presented a univariate relevance with the outcome ($p< 0.05$). Propensity score matching (PSM)was also served to the adjustment of covariates to ensure the robust results[8]. One-to-one nearest neighbor matching with a caliper width of 0.05 was applied in our study. Outcomes were generated from the matched cohort. the lowess smoothing algorithm was used to show the rough relationship between the amount of albumin infusion and hospital mortality. All analyses were two sided and significance level was 0.05 level.

Results

Baseline characteristics

Excluding patients with acute myocardial infarction and pulmonary embolism, a total of 6094 patients had their serum albumin concentration measured in hospital. Survivors and non-survivors were 4951 and 1143 respectively, with a hospital mortality of 9.8%. The baseline characteristics of survivors and non-survivor groups for the study cohort is outlined in Table 1. Patients in the survivors group were younger (71.5±3.6 vs. 75.1±12.8 years $p<0.001$). SOFA scores were significantly higher in non-survivor cohort (6(4 to 9) vs. 4(3 to 7) $p<0.001$). In addition, non-survivors group reached lower initial serum albumin levels (2.8(2.3 to 3.2) vs. 3.1(2.7 to 3.6) g/dl $p<0.001$). With the exception of gender, maximal potassium and COPD, all other baseline factors were significant difference between survivors and non-survivors.

Mortality analysis by logistic regression

Furthermore, we used ROC curves to predict the relationship between initial serum albumin levels and in-hospital mortality, and the optimal cut-off value was 2.9g/dl (area under curve (AUC)=0.643) (Fig.1). According to the cut-off value, the cohort was divided into two subgroups, albumin>2.9g/dl and albumin≤2.9g/dl groups. And then, logistics regression was used to predict in-hospital mortality in the two subgroups according to the cutoff value respectively. Univariate logistic regression was used to preliminarily screen the influencing factors, and then P <0.05 was selected as the result variables for multivariate logistic regression. Forward likelihood method was employed to establish the final regression model with P<0.05. Variance inflation factor (VIF) was detected after multivariate logistic regression. We eliminated the variable of maximum sodium in albumin>2.9g/dl group, Because the VIF was 48.65, which means existence of strong multicollinearity. No significantly different effect of albumin administration in terms of in-hospital mortality when serum albumin>2.9g/dl (OR: 1.05, 95% CI 0.788 to 1.403, p=0.733). If serum albumin concentration ≤ 2.9g/dl, albumin administration was associated with decreased mortality by univariate logistic regression analyses, but had adverse result by multivariate logistic regression analyses (OR: 0.68, 95% CI 0.47 to 0.89, p□0.001; OR: 1.62, 95% CI 1.29 to 2.04, p□0.001) (Table.2, Table.3).

Primary and secondary outcomes after PSM

We minimized the imbalance in the covariates between the albumin administration and non-albumin administration groups by means of PSM (Fig.2). We matched all other baseline variables except gender, maximum potassium and chronic obstructive pulmonary disease age. After PSM, primary and secondary outcomes were analyzed in 1221 patients when albumin≤2.9g/dl. We found that albumin administration in serum albumin≤2.9g/dl group was related to higher in-hospital mortality, longer hospital LOS and ICU LOS (p<0.001, p<0.001, p<0.001). However, albumin infusion was not associated with output at 24-hour (p=0.229) (Table. 4). Furthermore, we investigated rough relationship between the amount of human albumin infusion within 24 hours and in-hospital mortality in HF group and HF plus albumin≤2.9g/dl group respectively. The elevated amount of albumin infusion significantly relevant to higher rates of hospital mortality in the two groups (Fig. 3). We also performed KM curve to analyze 90-day mortality between albumin administration and non-albumin administration in the herd of albumin level ≤2.9g/dl before and after PSM. The result showed that albumin administration was association with increased mortality at 90-day before PSM (p<0.001), while had no significant relevance after PSM (p= 0.12) (Fig. 4).

Discussion

Our study demonstrated that human albumin administration was associated with higher risk-adjusted in-hospital mortality as well as longer hospital and ICU LOS, while had no association with output at 24-hour in HF patients with serum albumin level ≤ 2.9g/dl than non-albumin administration for the first time.

Serum albumin synthesized by liver is provide a variety of physiological functions. It accounts for 80% total plasma colloid oncotic pressure in the plasma, as well as maintains capillary membrane integrity. Therefore, it keep the balance across the capillary wall[5]. Previous studies demonstrated that albumin promote the effects of anticoagulant and antiplatelet [9–12]. It is also have suppressive effects on inflammation response by proinflammatory mediators[13]. As an anti-inflammatory agent, it can selectively inhibit cytokine stimulate endothelial activation, which is known to be a critical initiating pathway in atherosclerosis[14]. The concentration of serum albumin can be attributed to synthesis rates, degradation, and distribution inside and outside of the vascular compartments. Serum albumin concentration associated with a reliable prognostic value for cardiovascular disease(CVD) since a serendipitous result in 1989[15]. HF is a complex systemic clinical syndrome characterized by cardiocirculatory injuries, complex interplay of neurohormonal and biochemical disorders and organ failure. Albumin synthesis is reduced in patients with heart failure due to intestinal wall edema, liver congestion, or even congestive cirrhosis. Hypoalbuminemia is common occurs in HF patients and represents a powerful independent predictor of adverse outcomes and worse survival of the patients[16]. In addition, low albumin level is associated with incidence of preserved ejection fraction HF (HFpEF)[17, 18]. In our study, we analyzed the relationship between initial serum albumin levels and in-hospital mortality using ROC curves. In line with previous studies, we found hypoalbuminaemia serves as predictor of all-cause mortality in HF patients in hospital. The optimal cut-off value was 2.9g/dl.

Since serum albumin is so important to the body, is there any benefit to infusing albumin in patients with hypoproteinemia? Albumin administration may improve organ function in hypoalbuminemic critically ill patients[19]. Caraceni et al. demonstrate that albumin infusion group overall 18-month survival was significantly higher in decompensated cirrhosis patients [20]. But, the latest randomized controlled trial shows that, albumin administration increase the albumin level to a target of 30 g per liter or more had no good for hospitalized patients with decompensated cirrhosis[21]. Although previous studies presented conflicting results concerning the impact of albumin administration on hypoproteinemia, human albumin has been widely used for hypoproteinemia therapy. We analyzed the data from MIMIC-III and found albumin administration was associated with decreased mortality by univariate logistic regression analyses, but had adverse result by multivariate logistic regression analyses in HF with albumin level ≤ 2.9g/dl. After adjustment for confounding factors, albumin administration in HF plus hypoalbuminemic patients were relevant to higher in-hospital mortality and tended to longer hospital and ICU LOS than non-albumin administration subgroups. Furthermore, we investigated rough relationship between the amount of human albumin infusion at 24 hours and hospital mortality, and found that the elevated amount of albumin infusion is related to higher rates of hospital mortality.

Volume overload, a common problem in HF patients, treated with volume restriction and diuretic usage. However, furosemide resistance is a big problem in HF. Decreased amount of drug transferred to the target site is one of the vital mechanisms result in diuretic resistance[22]. Albumin as a biovehicle, can transported drugs to target organ[3, 23]. Hypoalbuminemia can reduce diuretic agent secretion to tubular

lumen[24, 25]. Previous clinical study revealed that intravenous injection of furosemide bound to albumin can rapidly increase the urine volume of hypoproteinemia patients who present obvious resistance to this diuretic[26]. Furosemide plus albumin for acute lung injury/acute respiratory distress syndrome patients with hypoproteinemic therapy significantly improved oxygenation, net negative fluid balance and hemodynamic stability than furosemide therapy[27]. Chalasani et al. demonstrated that the parameters, including urinary, sodium excretion and urinary furosemide excretion, are similar between the furosemide group and furosemide plus albumin group in cirrhotic patients with ascites[28]. Currently, there is no direct evidence about benefits of albumin infusion in heart failure. But some physicians use human albumin infusion to overcome furosemide resistance in HF inpatients especially with hypoalbuminemic. In the present study, we found the volume of 24-hour output had no relevance to albumin injection. Besides, albumin as a colloidal solution also increases the volume load and may further aggravate the symptom of HF. Because of retrospective study with limitation data sets, we abandoned central venous pressure (CVP) measurement. Whether the CVP was decreased need to be further explored.

Our trial was the first study exploring albumin therapy in HF with hypoalbuminemic and did not found clinically important effect in hospitalized patients. On the contrary, we demonstrated that albumin administration in HF with hypoalbuminemic was relevant to increased hospitalized mortality, longer hospital and ICU LOS. There are several interpretations for the results. Firstly, albumin as a colloidal solution, can increase the volume load and further aggravate adverse outcomes of HF. While albumin may reduce resistance to diuretics and increase urine production, the increased volume load overweight increased urine amount. Secondly, albumin physiological functions concerning suppressive effects on inflammation response, anticoagulant and antiplatelet takes longer time to kick in. The maximum duration of our study was 90-day and we found in-hospital mortality is increased and 90-day mortality have not changed after albumin infusion. The mortality might be decreased at longer follow-up time. Patients who would benefit from albumin infusion in the long-term need be further investigated. Lastly, albumin modifications contain reversible oxidized albumin form human nonmercaptalbumin1(HNA1) and irreversible oxidized albumin form HNA2[29]. We could pay more attention to the ratio of HNA1 to HNA2 than the amount of serum albumin alone and focus on the conversion of HNA1 into human mercaptalbumin[30].

In our study, comorbidities including hypertension, diabetes and coronary disease were associated with decreased in-hospital mortality by logistic regression analyses. This might be because physicians payed more attention to the exacerbation of heart failure in these patients and therefore took more notice to medication and volume restriction.

Our results simply reflect the true effect of albumin administration in real-world clinical practice and did not show benefit effects in HF patients with hypoalbuminemia. These findings argue against the clinical utilization of albumin therapy strategy. The results can be probably extrapolated to other hypoproteinemia, such as cirrhotic patients with ascites. Clinicians should not waive human albumin therapy but consider how to utilize human albumin in an appropriate way.

Several limitations in our study should be considered. First, the amount of N-terminal pro-brain-type natriuretic peptide (NT-proBNP) data extracted from MIMIC-III was about 2000. Due to too many missing values, we had to discard the variable of BNP. Hence, the definition of HF was based on ICD-9 and admitting diagnosis. In addition, we could not get a cardiac function grade from this database. Second, our study was a retrospective single-center cohort study based on MIMIC-III database which ranged from 2001 to 2015, and the results might have only reflected local practices during the period. Third, some variables, such as 24-hour input amount, body mass index (BMI) and the use of diuretics in our study, which had over 50% missing values, were eliminated. Some other unmeasured confounders such as different haemodynamic monitoring techniques usage, including central venous pressure measurement and transthoracic echocardiography were uncertain. These confounding factors and variables could affect our results. Forth, there were multiple factors that influence the initial CVP levels, including the rate of albumin infusion, as well as other solution, were difficult to adjust in a retrospective observational study. Besides, we did not investigate the effect of protein concentration on the results in the further research. Finally, the causal relationship between human albumin administration and mortality was not explored thoroughly, and the LOS longer in HF cohort in our study might have nothing to do with albumin administration, as LOS was related with complex clinical practice. A randomized study comparing the effect of human albumin administration and non-human albumin administration is needed in the future.

Conclusion

In this study, hypoalbuminemia predicted all-cause mortality in HF hospitalized patients. Albumin administration associated with increased risk-adjusted in-hospital and 28-day mortality and longer hospital LOS and ICU LOS in HF and hypoalbuminemia patients. Besides, Albumin infusion had no relevance to output at 24-hour, but had no significantly different change in 90-day mortality after albumin infusion. Mortality might be decreased at longer follow-up time. Physicians should be prudent before albumin administration in HF plus hypoproteinaemia patients.

Abbreviations

HF Heart failure, MIMIC-III Medical Information Mart for Intensive Care III, ROC receiver operating characteristic, PSM propensity score matching, ICU intensive care unit, LOS length of stay, KM Kaplan-Meier, AUC area under curve, CAD coronary artery disease, BIDMC Beth Israel Deaconess Medical Center, RECORD Reporting of Studies Conducted using Observational Routinely Collected Health Data, ICD-9 International Classification of Diseases 9th Edition, SQL Structured query language, WBC white blood cell, SOFA Sequential Organ Failure Assessment, COPD chronic obstructive pulmonary disease, VIF variance inflation factor, HFpEF preserved ejection fraction HF, CVP central venous pressure, HNA human nonmercaptalbumin□NT-proBNP N-terminal pro-brain-type natriuretic peptide

Declarations

Acknowledgements

None

Authors' contribution

Yan Lai and Xuebo Liu conceptualized the research aims, planned the analyses and guided the literature review. Tongqing Yao: responsible for data analysis and writing of the manuscript. Jun Qian and Fei Chen: responsible for data analysis. Jun Qian: responsible for study data extraction. Hao Lin and Fei Chen: responsible for data validation. All authors have read, revised and approved the final manuscript.

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Availability of data and materials

The datasets in the study are available in the MIMIC III database (https://physionet.org/works/MIMICIIIClinicalDatabase/files/).

Ethics approval and consent to participate

The MIMIC-III database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and we obtained the consent for the original data collection before the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Tables 1 to 4 are available in the Supplementary Files section

Figures

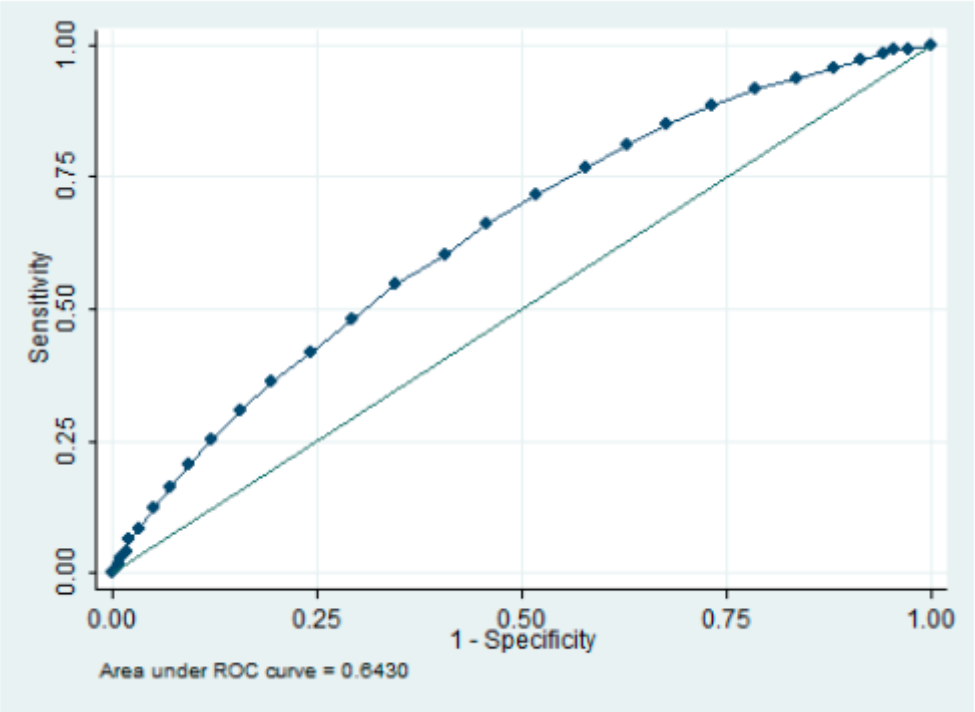

Figure 1

Performance in predicting in-hospital mortality using albumin concentration. Prediction performance was based on ROC. The area under curve was 0.643. The cutoff value was 2.9g/dl. ROC receiver operator curves.

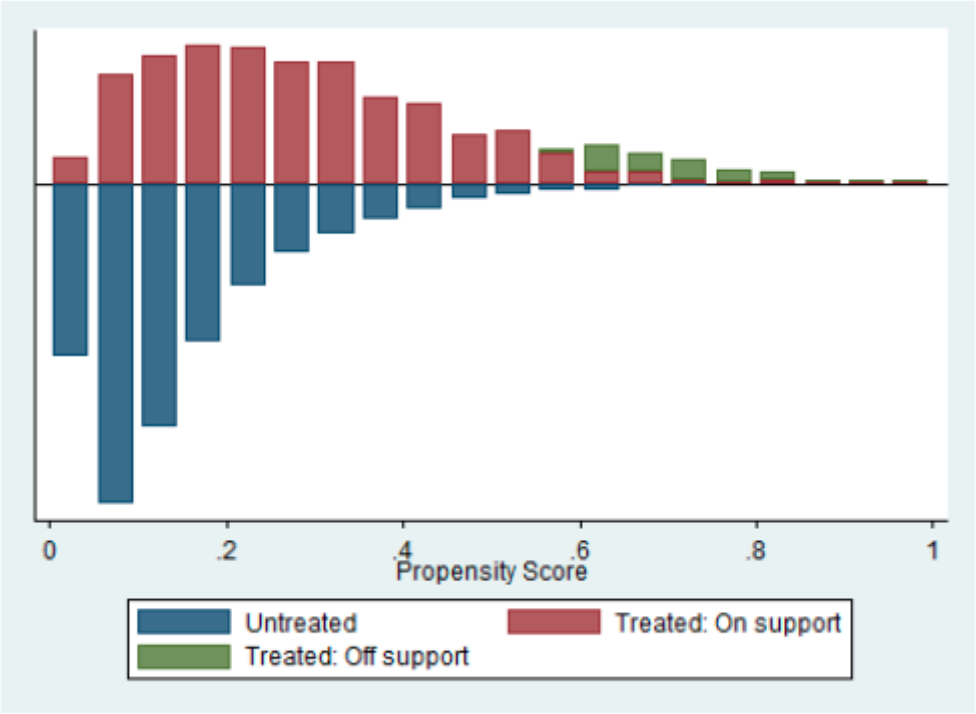

Figure 2

Covariate including age, initial albumin concentration, SOFA score, maximum white blood cell count, maximum blood platelet count, maximum glucose level, maximum creatinine level, maximum serum urea nitrogen level, maximum serum creatinine level, maximum serum sodium level, hypertension, coronary disease and diabetes were adjusted by propensity score matching (PSM) and the caliper was 0.05. After PSM, 1221 patients with albumin≤2.9g/dl were stayed.

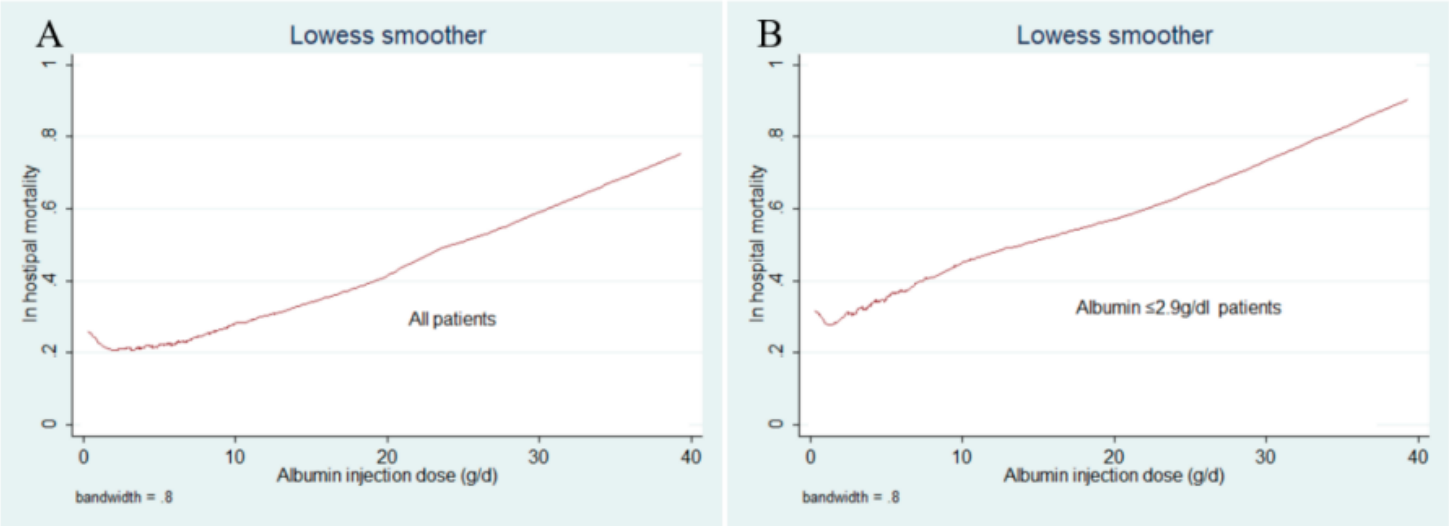

Figure 3

Rough relationship between the human albumin injection dose within 24 hours and in-hospital mortality in all HF patients (A) and in HF patients when serum albumin≤2.9g/dl (B). HF heart failure.

Supplementary Files

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- Tables.pdf