Synergistic effect of hypoalbuminaemia and hypotension in predicting in-hospital mortality and intensive care admission: a retrospective cohort study

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ABSTRACT

Objective Hypoalbuminaemia is an important prognostic factor. It may be associated with poor nutritional states, chronic heart and kidney disease, long-standing infection and cancer. Hypotension is a hallmark of circulatory failure. We evaluated hypoalbuminaemia and hypotension synergism as predictor of in-hospital mortality and intensive care unit (ICU) admission.

Design We retrospectively analysed emergency department (ED) visits from January 2011 to December 2019.

Setting Data were retrieved from five Mount Sinai health system hospitals, New York.

Participants We included consecutive ED patients ≥18 years with albumin measurements.

Primary and secondary outcome measures Clinical outcomes were in-hospital mortality and ICU admission. The rates of these outcomes were stratified by systolic blood pressure (SBP) (<90 vs ≥90 mm Hg) and albumin levels. Variables included demographics, presenting vital signs, comorbidities (measured as ICD codes) and other common blood tests. Multivariable logistic regression models analysed the adjusted OR of different levels of albumin and SBP for predicting ICU admission and in-hospital mortality. The models were adjusted for demographics, vital signs, comorbidities and common laboratory results. Patients with albumin 3.5–4.5 g/dL and SBP ≥90 mm Hg were used as reference.

Results The cohort included 402 123 ED arrivals (27.9% of total adult ED visits). The rates of in-hospital mortality, ICU admission and overall admission were 1.7%, 8.4% and 47.1%, respectively. For SBP <90 mm Hg and albumin <2.5 g/dL, mortality and ICU admission rates were 34.0% and 40.6%, respectively; for SBP <90 mm Hg and albumin ≥2.5 g/dL 8.2% and 24.1%, respectively; for SBP ≥90 mm Hg and albumin <2.5 g/dL 11.4% and 18.6%, respectively; for SBP ≥90 mm Hg and albumin 3.5–4.5 g/dL 0.5% and 6.4%, respectively. Multivariable analysis showed that in patients with hypotension and albumin <2.5 g/dL, the adjusted OR for in-hospital mortality was 37.1 (95% CI 32.3 to 42.6), and for ICU admission was 5.4 (95% CI 4.8 to 6.1).

Conclusion Co-occurrence of hypotension and hypoalbuminaemia is associated with poor hospital outcomes.

INTRODUCTION

Clinicians rely on clinical and laboratory biomarkers for decision making. Hypoalbuminaemia has been widely studied. It has been associated with increased morbidity and mortality in many clinical conditions. A recent study showed that low albumin on admission is linked with increased in-hospital mortality.1 Other studies investigated hypoalbuminaemia in acute myocardial infarction,2,3 heart failure,4 sepsis,5 stroke,6 burns7 and malignancies.8 It was demonstrated that marked hypoalbuminaemia was associated with 34%–80% mortality.17

Albumin has important physiological functions such as maintenance of normal osmotic pressure, microvascular permeability and regulation of platelet aggregation.9 The link between hypoalbuminaemia and increased mortality could be attributed to the fact that hypoalbuminaemia reflects the severity of the systemic state. Hydropsudinaemia is associated with poor nutritional status, frailty, severe hepatic or renal dysfunction, inflammation and late cancer states.9–12
Shock is defined as a circulatory failure with the hypoperfusion of tissues. Hypotension is a hallmark of circulatory failure. When it persists, it leads to shock.\textsuperscript{13–15}

Serum albumin and systolic blood pressure (SBP) are widely used clinical measurements. Therefore, it is important to explore the interaction between these two parameters in a large-scale study. We evaluated hypoalbuminaemia and hypotension synergism as a predictor of in-hospital mortality and the need for intensive care unit (ICU) admission.

**MATERIALS AND METHODS**

**Study setting and data source**

We identified all consecutive admissions to five emergency departments (EDs) in the Mount Sinai health system (MSHS), New York, USA (Mount Sinai Hospital, Mount Sinai Brooklyn, Mount Sinai Queens, Mount Sinai Morningside and Mount Sinai West). Electronic health record (EHR) data were extracted from EPIC (Epic Systems, Verona, Wisconsin, USA). The study time frame was from 1 January 2011 to 31 December 2019.

The MSHS is a large, diverse health system. All included EDs in the study were co-located with a hospital. The approximate total numbers of yearly ED visits are 50 000–1 00 000 per hospital. The approximate admission rate in the MSHS is 17%.

**Study design**

**Population**

Patients were included in the analyses if they had an ED visit for any reason during the study period. We excluded patients younger than 18, patients with records that were erroneously created, and visits without albumin measurements at admission. We also excluded patients with missing data regarding laboratory and vital signs.

**Variables**

The primary outcomes were all-cause in-hospital mortality and ICU admission. Covariates of interest included: age, sex, comorbidities (coded using International Classification of Diseases-10 Clinical Modification (ICD-10-CM) and grouped using the diagnostic clinical classification software: congestive heart failure (CHF), coronary artery disease (CAD), diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and known cancer), first vital signs (SBP, diastolic blood pressure, heart rate, temperature, pulse oximetry, respiratory rate), and first commonly used laboratory test results in the ED (albumin, haemoglobin (HB), white blood cells (WBC), blood urea nitrogen (BUN), creatinine (CR), sodium, chloride, potassium).

ICD-10-CM codes were retrieved for each patient from the MSHS Epic EHR. All codes were limited to those registered prior to the index ED visit.

**Albumin and blood pressure groups selection**

Similar to previous publication,\textsuperscript{1} patients were clustered into five groups based on albumin levels at admission: albumin < 2.5 g/dL, albumin ≥ 2.5 g/dL and <3.5 g/dL, albumin ≥3.5 g/dL and <4.5 g/dL and albumin ≥ 4.5 g/dL. Patients were also defined as hypotensive (SBP <90 mm Hg) based on their SBP at admission.

**Statistical analysis**

Descriptive statistics were reported for all patient characteristics using means and SD or medians with IQR for continuous variables and counts with percentages for categorical variables. Continuous variables were compared using either the unpaired t-test for two variables or one-way analysis of variance (ANOVA) for more than two variables. Categorical variables were compared using the $\chi^2$ test.

Patients were stratified according to the admission SBP (low <90 mm Hg and ≥90 mm Hg) and the admission serum albumin (low <2.5 g/dL, 2.5–3.0 g/dL, 3.0–3.5 g/dL, 3.5–4.5 g/dL, and >4.5 g/dL).

We estimated the predictive value of albumin for in-hospital mortality and ICU admission in hypotensive patients. For this, receiver operator curves (ROC) were plotted, and the area under the ROC (AUC) were computed. For informational basis, albumin AUCs were compared with the AUCs of other common clinical variables in the ED (age, HR, WBC, HGB, BUN, CR).

Two multivariable logistic regression models compared rates of outcomes between subgroups of patients stratified by albumin and SBP at admission levels: one model for in-hospital mortality prediction and one model for ICU admission. In each model there were ten combined albumin and SBP groups. Each albumin/SBP group represented a combination of one albumin level (<2.5, 2.5–3.5, 3.5–4.5, 4.5 g/dL) and one SBP at admission level (<90 or ≥90 mm Hg). In each model, patients that had both albumin 3.5–4.5 g/dL and SBP at admission ≥90 mm Hg constituted the reference group. The models were adjusted for important clinical variables in the ED. These included demographics (age, sex), vital signs (TEMP, HR, RR), comorbidities (CHF, CAD, DM, HTN, CKD, COPD, cancer) and laboratory results (WBC, HB, BUN, CR).

We have also analysed albumin and SBP at admission as continuous variables. We have thus built multivariable logistic regression models using the same outcomes and covariates, with albumin and SBP at admission as continuous variables.
A correlation matrix was constructed to assess the possible collinearity between covariates. All covariate correlations were below 0.7. Adjusted OR with 95% CIs were reported.

AUCs, also known as C-statistics, were calculated for each multivariable model. Bootstrapping validations (1000 bootstrap resamples) were used to calculate 95% CIs for all metrics.

All analyses were conducted with Python (Python software foundation, V.3.6.5). Statistical significance was established at a two-sided p<0.05.

**Patient and public involvement**

No patients were involved in the formulation of the study.

**RESULTS**

Our final cohort comprised 407 492 patients ≥18 years old who had albumin measured in the ED and had complete vital signs (27.9% of the adult ED population). Figure 1 presents the study inclusion flow chart. The median age in the cohort was 55 (IQR 37–71) years, and 222 768 (55.4%) patients were females (table 1). Of the

**Table 1**  
Table shows the demographic, clinical and biochemical characteristics of adult patients presenting in the ED, stratified by admission albumin level

| Albumin <2.5 g/dL (n=17 153, 4.3%) | Albumin ≥2.5 g/dL and <3.0 g/dL (n=27 867, 6.9%) | Albumin ≥3.0 g/dL and <3.5 g/dL (n=63 683, 15.8%) | Albumin ≥3.5 g/dL and <4.5 g/dL (n=247 432, 61.5%) | Albumin ≥4.5 g/dL (n=45 988, 11.4%) | P value† |
|-----------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------|
| Demographics                      |                                               |                                               |                                               |                                               |         |
| Age, median (IQR), year           | 64 (54–76)                                    | 66 (54–79)                                    | 65 (51–78)                                    | 53 (37–68)                                    | 36 (27–53) | <0.001  |
| Female, N (%)                     | 8126 (47.4)                                   | 14 242 (51.1)                                 | 36 164 (56.8)                                 | 143 746 (58.1)                                | 20 490 (44.6) | <0.001 |
| SBP, median (IQR), mm Hg          | 120 (104–138)                                 | 126 (110–146)                                 | 132 (116–151)                                 | 134 (119–152)                                 | 134 (121–150) | <0.001  |
| SBP <90 mm Hg, N (%)              | 1548 (9.0)                                    | 1270 (4.6)                                    | 1595 (2.5)                                    | 2204 (0.9)                                    | 194 (0.4) | <0.001 |
| DBP, median (IQR), mm Hg          | 66 (57–77)                                    | 69 (60–79)                                    | 72 (64–82)                                    | 77 (68–86)                                    | 79 (70–88) | <0.001  |
| Heart rate, median (IQR), b/min   | 92 (79–107)                                   | 89 (76–104)                                   | 87 (75–100)                                   | 84 (73–97)                                    | 86 (74–99) | <0.001  |
| Temperature, median (IQR), Celsius| 36.7 (36.2–37.1)                              | 36.7 (36.3–37.1)                              | 36.7 (36.3–37.0)                              | 36.7 (36.3–36.9)                              | 36.6 (36.2–36.9) | <0.001 |
| Respiratory rate, median (IQR), breath/min | 18 (18–20)                                   | 18 (18–20)                                   | 18 (18–20)                                   | 18 (18–20)                                   | 18 (18–20) | <0.001  |
| O2 saturation, median (IQR)%      | 98 (96–99)                                    | 98 (96–99)                                    | 98 (96–99)                                    | 98 (97–99)                                    | 98 (97–100) | <0.001  |
| Pain scale, median (IQR), (0–10)  | 0 (0–7)                                       | 0 (0–7)                                       | 3 (0–7)                                       | 5 (0–8)                                       | 6 (0–8) | <0.001  |
| Comorbidities                     |                                               |                                               |                                               |                                               |         |
| CAD, N (%)                        | 3167 (18.5)                                   | 14 428 (22.7)                                 | 32 079 (13.0)                                 | 2240 (4.9)                                    | <0.001  |
| CHF, N (%)                        | 4032 (23.5)                                   | 14 722 (23.1)                                 | 23 756 (9.6)                                  | 1466 (3.1)                                    | <0.001  |
| DM, N (%)                         | 6877 (40.1)                                   | 23 563 (37.0)                                 | 58 244 (23.5)                                 | 5849 (12.7)                                   | <0.001  |
| HTN, N (%)                        | 8251 (48.1)                                   | 31 679 (49.7)                                 | 78 625 (31.8)                                 | 7223 (15.7)                                   | <0.001  |
| CKD, N (%)                        | 4011 (23.4)                                   | 12 528 (19.7)                                 | 19 962 (8.1)                                  | 1464 (3.2)                                    | <0.001  |
| COPD, N (%)                       | 1944 (11.3)                                   | 8804 (13.8)                                   | 18 092 (7.3)                                  | 1264 (2.7)                                    | <0.001  |
| Cancer, N (%)                     | 6821 (39.8)                                   | 17 788 (27.9)                                 | 41 605 (16.8)                                 | 4355 (9.5)                                    | <0.001  |
| Laboratory results                |                                               |                                               |                                               |                                               |         |
| WBC, median (IQR), x10 3/uL       | 9.4 (6.2–14.2)                                 | 8.4 (6.2–11.3)                                | 8.1 (6.3–10.5)                                | 8.8 (6.9–11.5)                                 | <0.001  |
| NEUT, median (IQR), x10 3/uL      | 7.2 (4.3–11.8)                                 | 5.9 (4.0–8.6)                                 | 5.4 (3.8–7.7)                                 | 6.1 (4.3–8.9)                                  | <0.001  |
| HGB, median (IQR), g/dL           | 9.6 (8.2–11.1)                                 | 10.5 (9.0–12.0)                               | 11.6 (10.2–12.9)                              | 13.1 (11.9–14.2)                               | 14.4 (13.3–15.4) | <0.001 |
| BUN, median (IQR), mg/dL          | 22.0 (13.0–39.0)                               | 20.0 (13.0–35.0)                              | 17.0 (12.0–28.0)                              | 14.0 (11.0–19.0)                               | 13.0 (10.0–17.0) | <0.001 |
| Cr, median (IQR), mg/dL           | 1.1 (0.8–2.1)                                  | 0.9 (0.7–1.4)                                 | 0.8 (0.7–1.0)                                 | 0.8 (0.7–1.0)                                  | <0.001  |
| Na, median (IQR), mEq/L           | 135 (132–139)                                  | 137 (135–140)                                 | 139 (136–140)                                 | 139 (137–141)                                  | <0.001  |
| K, median (IQR), mEq/L            | 4.1 (3.6–4.8)                                  | 4.2 (3.7–4.7)                                 | 4.1 (3.7–4.6)                                 | 4.0 (3.7–4.3)                                  | <0.001  |
| Admission                         |                                               |                                               |                                               |                                               |         |
| Hospital admission                | 14 633 (85.3)                                  | 21 764 (78.1)                                 | 40 953 (64.3)                                 | 96 682 (39.1)                                  | 15 176 (33.0) |        |

*Total number included in the cohort 407 492.
†Way analysis of variance estimated statistical difference between the different albumin groups.
BUN, blood urea nitrogen; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CR, creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; ED, emergency department; HGB, haemoglobin; HTN, hypertension; K, potassium; Na, sodium; NEUT, absolute neutrophil count; SBP, systolic blood pressure; WBC, white blood cells.
ED visits, 189,208 (47.1%) were admitted to the hospital. The overall in-hospital mortality rate was 1.7% (n=6729). The ICU admission rate was 8.4% (n=33,780).

**Albumin and SBP**

The albumin distribution was left-skewed (figure 2), with a median of 3.8 g/dL (IQR 3.4–4.2). Hypoalbuminaemia (<3.5 g/dL) was found in 27.0% of the cohort; 11.2% had albumin <3.0 g/dL and 4.3% had albumin <2.5 g/dL. SBP at admission showed a median of 132 (IQR 118–151) (figure 3). 1.7% of the cohort had SBP <90 mm Hg at admission.

Patients with hypoalbuminaemia had significantly more comorbidities (cancer 31.7% in patients with hypoalbuminaemia vs 15.7% without hypoalbuminaemia; cardiovascular disease 33.9% in patients with hypoalbuminaemia vs 15.9% without hypoalbuminaemia). These patients also had lower HGB, with a median HGB of 9.6 in the <2.5 g/dL albumin group (table 1).

Compared with common clinical and laboratory markers measured on ED admission, albumin was the best predictor of both in-hospital mortality and ICU admission (figure 4A,B). In the hypotensive group, albumin showed an AUC of 0.77 (95% CI 0.75 to 0.78) for predicting in-hospital mortality. It also established an AUC of 0.64 (95% CI 0.63 to 0.65) for predicting ICU admission.

**Multivariable models**

The rates of outcomes were significantly associated with SBP at admission and albumin synergism (figure 5A,B). The co-occurrence of SBP at admission <90 mm Hg and albumin <2.5 g/dL was associated with 34.0% in-hospital mortality and 40.6% ICU admission rates. In comparison, in patients with SBP at admission <90 mm Hg but albumin ≥2.5 g/dL, an in-hospital mortality rate of 8.2%, and ICU admission rates of 24.1% were observed. In patients with albumin <2.5 g/dL but SBP at admission ≥90 mm Hg, an in-hospital mortality rate of 11.4% and ICU admission rates of 18.6% were observed.

The multivariable logistic regression models adjusting for demographics, vital signs, comorbidities and blood test results had C-statistics of 0.89 (95% CI 0.89 to 0.90) for in-hospital mortality and 0.75 (95% CI 0.74 to 0.75) for ICU admittance. The adjusted ORs of all the features
in the models are presented in online supplemental tables 1,2. Adjusted aORs were similar to the crude rates (tables 2 and 3). The aORs for in-hospital mortality in patients with albumin <2.5 g/dL and hypotension was 37.1 (95% CI 32.3 to 42.6). The aOR for ICU admission in this group was 5.4 (95% CI 4.8 to 6.1).

In the multivariable logistic regression models, using albumin and SBP at admission as continuous variables, the adjusted OR of albumin for in-hospital mortality was 0.3 (95% CI 0.3 to 0.3) and the adjusted OR of SBP at admission was 0.9 (95% CI 0.9 to 0.9). For ICU admission, the adjusted OR of albumin was 0.6 (95% CI 0.6 to 0.6) and the adjusted OR of SBP at admission was 1.0 (95% CI 1.0 to 1.0). Online supplemental tables 3 and 4 present the adjusted ORs of all covariates in these models.

**DISCUSSION**

Both albumin and SBP are important clinical markers. Abnormalities in these indices may signify severe outcomes. Thus, it is important to elucidate the interaction between these two parameters. We found that in ED patients, the combination of hypoalbuminaemia and hypotension showed a strong synergistic effect for in-hospital mortality and ICU admission.

Several previous studies evaluated the significance of albumin levels in shock and preshock states. Holder et al analysed 582 ED patients with sepsis without organ failure or shock. They found that albumin below 3.5 g/dL was an indicator for progression to severe sepsis or shock.16 This study excluded patients with SBP <90 mm Hg at admission. Another study analysed 561 patients admitted to the ED with sepsis. In this study, admission albumin levels were associated with 28-day mortality.17 Arteo et al analysed 112 patients with septic shock or severe sepsis. They showed that hypoalbuminaemia was the most important prognostic factor in community-acquired bloodstream infection with severe sepsis.18 It was recently demonstrated that hypoalbuminaemia is an important prognostic marker in cardiogenic shock.19

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**Table 2**

| Albumin | Crude in-hospital mortality rates | Adjusted OR for in-hospital mortality |
|---------|---------------------------------|-------------------------------------|
| <2.5 g/dL | SBP <90 mm Hg (527/1548) (34.0%) | SBP <90 mm Hg (37.1 (95% CI 32.3 to 42.6) p<0.001 |
| >2.5 and <3.0 g/dL | 212/1270 (16.7%) | 12.9 (95% CI 11.8 to 14.1) p<0.001 |
| >3.0 and <3.5 g/dL | 132/1595 (8.3%) | 5.9 (95% CI 5.4 to 6.5) p<0.001 |
| >3.5 g/dL | 85/2204 (3.9%) | 2.7 (95% CI 2.5 to 2.9) p<0.001 |
| >4.5 g/dL | 4/194 (2.1%) | 1 (Reference) p<0.001 |

Adjusted ORs from multivariable logistic regression analyses adjusted for demographics, vital signs, comorbidities and blood test results. The table presents the crude rates and the multivariable-adjusted ORs.
In this study, hypoalbuminaemia patients had a higher in-hospital mortality rate (48% vs 28%).

It has been suggested that hypoalbuminaemia may play a direct role in poor reperfusion. The co-occurrence of hypoalbuminaemia and hypotension may reflect a decrease in blood flow to vital organs. Additionally, low albumin leads to colloid oncotic pressure which in turn leads to hypovolaemia and hypotension. Previous studies have suggested that hypoalbuminaemia is associated with pre-existing disease severity. It was also shown that a low albumin level is linked to frailty and impaired nutritional status. Thus, albumin expresses a poor performance status. Indeed, patients with hypoalbuminaemia had more comorbidities and lower HB levels. However, low albumin remained a significant prognostic predictor after adjustment for comorbidities.

Our research was a large multisite study. As expected in such a large cohort, all ANOVA p values were statistically significant (table 1).

It should be noted that the in-hospital mortality adjusted rates were pretty similar to the crude rates, highlighting fragility of the results. In other words, sicker patients have biased by including only patients who underwent albumin measurement in the ED. Future research should evaluate the clinical applicability of the results including the clinical value of albumin assessment in the ED and potential intervention.

In conclusion, the co-occurrence of hypotension and hypoalbuminaemia is an important ominous sign in the ED.

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**Table 3** ICU admission in adult patients presenting in the ED, stratified by admission albumin level and blood pressure

| Albumin <2.5 g/dL | Albumin ≥2.5 g/dL and <3.0 g/dL | Albumin ≥3.0 g/dL and <3.5 g/dL | Albumin ≥3.5 g/dL and <4.5 g/dL | Albumin ≥4.5 g/dL |
|-------------------|---------------------------------|---------------------------------|---------------------------------|-------------------|
| Crude ICU admission rates |
| SBP <90 mm Hg | 629/1548 (40.6%) | 435/1270 (34.3%) | 434/1595 (27.2%) | 382/2204 (17.3%) | 19/194 (9.8%) |
| SBP ≥90 mm Hg | 2915/15 605 (18.7%) | 4131/26 597 (15.5%) | 7464/62 088 (12.0%) | 15 763/245 228 (6.4%) | 1608/45 794 (3.5%) |
| Adjusted OR for ICU admission |
| SBP <90 mm Hg | 5.4 (95% CI 4.8 to 6.1) | 4.0 (95% CI 3.5 to 4.5) | 3.0 (95% CI 2.7 to 3.4) | 2.1 (95% CI 1.9 to 2.4) | 1.3 (95% CI 0.8 to 2.1) |
| SBP ≥90 mm Hg | 2.2 (95% CI 2.1 to 2.3) | 1.7 (95% CI 1.6 to 2.0) | 1.4 (95% CI 1.4 to 1.8) | 1.0 (Reference) | 0.7 (95% CI 0.7 to 1.0) |

Adjusted ORs from multivariable logistic regression analyses adjusted for demographics, vital signs, comorbidities and blood test results. The table presents the crude rates and the multivariable-adjusted ORs.

ED, emergency department; ICU, intensive care unit; SBP, systolic blood pressure.
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Contributors EK, SS, EZ, AZ, BSG, EG, DLR, RF and MAL developed the study concept and design. EK carried out the data analysis. EK and SS drafted the manuscript. EZ, AZ, BSG, EG, DLR, RF and MAL contributed to the interpretation of the results and critical review of the manuscript. EK is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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