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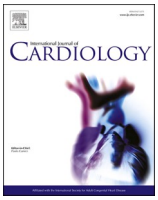

Hypoalbuminemia as predictor of thrombotic events in patients with community-acquired pneumonia

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ABSTRACT

Background: Hypoalbuminemia complicates acute diseases and infections and is associated with a worst prognosis. The aim is to evaluate whether hypoalbuminemia is associated with higher incidence and risk of thrombotic events in community-acquired pneumonia.

Methods: We retrospectively collected data from a prospective study investigating the incidence of thrombotic events in community-acquired pneumonia hospitalized patients from 2011 to 2016 at University-Hospital Policlinico Umberto I. Baseline characteristics and outcomes were collected. Incidence of outcomes were calculated. Kaplan-Meier curves were created, Cox model used to identify predictors for the outcomes, and competing risk analysis performed.

Results: From a total of 231 patients, 130 (56.3%) and 101 (43.7%) had or not hypoalbuminemia. Age, proportion of female, BMI, major comorbidities, and severity of pneumonia were similar between two subgroups. A less proportion of patients with hypoalbuminemia received antithrombotic and statin therapy. Median hospital stay was 11 days in both subgroups. Patients with hypoalbuminemia had higher D-dimer and high- sensitivity C-reactive-protein values with an inverse relation between albumin values and these markers. Incidence of thrombotic events was 26 and 11 per 1000 patient-days in patient with and without hypoalbuminemia. At Cox model, hypoalbuminemia was associated with thrombotic events development in univariable (hazard ratio; 2.67, 95% confidence intervals, 1.30–5.40) and multivariable (hazard ratio 3.19; 95% confidence intervals, 1.48–6.89) analysis.

Conclusions: More than a half of patients with community acquired pneumonia had hypoalbuminemia that is associated with a doubled incidence and a three-fold increased risk of thrombotic events. The inverse relation between baseline albumin and D-dimer values confirms this association.

1. Introduction

Albumin is the most represented plasmatic protein in humans and is synthesized by the liver through intestinal absorption derived or protein muscle catabolism derived amino acids. [1] Along with several homeostatic (e.g., colloid osmotic pressure and pH regulation, substances transportation) and antioxidant (e.g., oxygen free radicals scavenging) properties, albumin share a relevant antithrombotic role though antithrombin binding, platelet aggregation inhibition, and factor Xa neutralization. [1,2]

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Hypoalbuminemia is defined as a serum concentration < 3.5 g/dL and may develop in several clinical scenario characterized by an impaired production (e.g., acute liver failure or cirrhosis, nutritional deficiencies) or elimination (e.g., nephrotic syndrome, extensive burns). [1,3] Hypoalbuminemia often complicates acute diseases and has been associated with worst intra-hospital and long-term outcomes, including all-cause mortality and cardiovascular events. [2,4–7] Patients with serum albumin levels <3.4 g/dL, indeed, had an increased incidence and a roughly doubled risk of thrombotic events than patients with higher values. [2] Whether hypoalbuminemia share a similar predictive role in less severe or localized infection is of clinical and therapeutic interest. [8] Community-acquired pneumonia, the most common cause of hospitalization and mortality among infectious disease other than sepsis, present a relevant prothrombotic state that translate to an increased incidence of intra-hospital thrombotic, mostly arterial complications (10% of patients). [9–12] Even if several pathogenetic mechanisms have been identified (e.g., increased platelet activation, coagulation factor abnormalities, low grade endotoxemia and gut permeability alteration), the effect of hypoalbuminemia has not yet been investigated. [9,11,12] Therefore, the aims of this study are to stratify the incidences of thrombotic events by baseline albumin values and to evaluate the role of hypoalbuminemia in predicting the risk of thrombotic events in hospitalized patients with community-acquired pneumonia.

2. Methods

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement for observational studies, was conducted according to the principles stated in the Declaration of Helsinki, and was approved by the local ethics committee. [13]

2.1. Study and patients' characteristics

For this analysis we retrospectively collected data from a prospective observational study investigating the incidence of thrombotic events in hospitalized patients with community-acquired pneumonia (study ID: NCT01773863). Patients were consecutively included from October 2011 to January 2016 at the Departments of Internal Medicine and Medical Specialties, Clinical Medicine, and Public Health and Infectious Diseases of the University-Hospital Policlinico Umberto I, Sapienza University of Rome - Italy - if they were aged ≥18 years, had an acute illness with ≥ two signs or symptoms of community-acquired pneumonia (i.e., fever, tachycardia, chills, dyspnea, cough, and chest pain, presence of typical pulmonary findings - rales, rhonchi, bronchial breath sounds, dullness, increased fremitus and egophony -), [14] presented a new consolidation(s) on chest X-ray, and fulfilled all criteria for community-acquired pneumonia. [15] Exclusion criteria were: (i) radiographic evidence of pre-existing infiltrates, (ii) presence of immunosuppression (human immunodeficiency virus infection, chemotherapy, high dose of immunosuppressive agents to prevent the rejection of transplanted organs and tissues or to treat autoimmune diseases), (iii) presence of malignancy, (iv) pregnancy or breast feeding, (v) documented severe allergy to antibiotics, (vi) health care-associated pneumonia. [15]

The following data were extracted from medical records onto an electronic dataset: demographic, clinical, and cardiovascular risk factors (e.g., age, sex category, body mass index – BMI – history of hypertension, diabetes mellitus, smoking habit), laboratory values at hospital admission (e.g., complete blood count, high sensitivity C reactive protein – hs-CRP –, D-dimer, albumin), concomitant therapy (e.g., antiplatelets or anticoagulants, statins), severity index (e.g., CURB-65, pneumonia severity index – PSI –), [16] and outcomes of interest.

2.2. Clinical outcomes

Arterial thrombotic events comprehended acute myocardial infarction (diagnosed on electrocardiographic findings associated with elevation of serum markers of myocardial necrosis), acute ischemic stroke (identified by observing the onset of new focal neurological signs and symptoms and confirmed with magnetic resonance imaging or computed tomography imaging), and acute limb ischemia. Venous thromboembolism comprehended objectively documented pulmonary embolism and superficial and deep vein thrombosis of the lower limbs or atypical site thrombosis (e.g., splanchnic vein thrombosis, cerebral vein thrombosis). All diagnostic procedures were performed upon attending physician's requests. Cardiovascular death included fatal myocardial infarction or stroke, sudden death, death due to cardiogenic shock in patients with heart failure, due to pulmonary embolism, to a rupture or dissection of aneurysm, death related to cardiovascular investigation/procedure/operation, death due to other specified cardiovascular causes.

All patients were followed-up until hospital discharge or in-hospital death whichever came first.

2.3. Statistical analysis

Baseline characteristics of the enrolled population are reported as descriptive statistics. Continuous variables were expressed as mean (standard deviation) or median (interquartile range – IQR –) values, according to data distribution after applying the Wilk-Shapiro test. Categorical variables were expressed as counts and percentages. Continuous variables were compared using the Student's *t*-test or the Mann-Whitney *U* test, and categorical variables were compared using the chi-squared or Fisher's exact tests, as appropriate. In the analysis, patients were sorted by albumin values (i.e., < 3.5 g/dL and ≥ 3.5 g/dL). Follow-up time (patient-days) was calculated from the hospitalization until the occurrence of one of the events of interest, whichever came first. Kaplan-Meier curves were created to estimate the overall incidence of thrombotic events and compared using the log-rank test. A Cox proportional hazards model with stepwise (both backward and forward) elimination by the Akaike's information criterion was used to identify potential predictors for thrombotic events. The following variables were included in the model: age, female sex, hs-CRP, albumin values (i.e., < 3.5 g/dL and ≥ 3.5 g/dL), comorbidities leading to hypoalbuminemia (e.g., diabetes mellitus, chronic kidney disease) and antiplatelet, anticoagulant, and statin administration. Arterial and venous thrombotic events were further analyzed in competing risk analysis, considering intrahospital non-cardiovascular death as a competing event. [17] The Gray's test was used to compare the curves. Statistical significance was set at 0.05. RStudio (version 2023.09.1 + 494, R Core Development Team, Vienna, Austria) was used for the analysis. [18] E.V. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

3. Results

3.1. Baseline patients' characteristics

A total of 231 out of 523 initially evaluated patients had baseline albumin values and were included in this analysis. More than 50% (130 out of 231) of included patients had hypoalbuminemia. The baseline characteristics of the overall cohort and of patients sorted by their albumin values are shown in Table 1. Median age (79 years vs 76 years, $p = 0.139$), female sex (31.5% vs 35.6%, $p = 0.606$), and BMI (27 kg/m^2 vs 27 kg/m^2, $p = 0.979$) were similar between the two groups, as well all as the evaluated cardiovascular risk factors and underlying comorbidities. A lower proportion of patients with hypoalbuminemia received anticoagulant (12.6% vs 24.0%, $p = 0.039$), antiplatelet (37.8% vs 52.0%, $p = 0.045$), and statin therapies (26.8% vs 46.0%, $p = 0.004$).

Table 1
Baseline patients' characteristics sorted by serum albumin values.

Variables	Overall $N = 231$	Albumin < 3.5 g/dL $N = 130$	Albumin ≥ 3.5 g/dL $N = 101$	p-values
Mean age, years (SD)	78 (11.1)	79 (10.6)	76 (11.7)	0.139
Female sex, n (%)	77 (33.3)	41 (31.5)	36 (35.6)	0.606
Mean BMI, kg/m^2 (SD)	27 (6.8)	27 (8.4)	27 (4.0)	0.979
Cardiovascular risk factors, comorbidities and antithrombotic therapy				
Diabetes mellitus, n (%)	76 (32.9)	37 (28.5)	39 (38.6)	0.137
Dyslipidemia, n (%)	78 (35.0)	37 (29.6)	41 (41.8)	0.078
Actual smoker, n (%)	41 (18.6)	24 (19.2)	17 (17.7)	0.914
Former smoker, n (%)	95 (41.3)	51 (39.2)	44 (44.0)	0.553
Coronary heart disease, n (%)	84 (36.4)	40 (30.8)	44 (43.6)	0.062
Cerebrovascular disease, n (%)	33 (14.6)	18 (14.2)	15 (15.2)	0.987
Liver cirrhosis, n (%)	4 (1.7)	2 (1.5)	2 (2.0)	1.000
Chronic kidney disease, n (%)	46 (19.9)	27 (20.8)	19 (18.8)	0.839
COPD, n (%)	85 (36.8)	48 (36.9)	37 (36.6)	1.000
Peripheral artery disease, n (%)	28 (12.1)	14 (10.8)	14 (13.9)	0.609
Heart failure, n (%)	61 (26.4)	28 (21.5)	33 (32.7)	0.079
Anticoagulant therapy, n (%)	***40 (17.6)***	***16 (12.6)***	***24 (24.0)***	***0.039***
Antiplatelet therapy, n (%)	***100 (44.1)***	***48 (37.8)***	***52 (52.0)***	***0.045***
Statin therapy, n (%)	***80 (35.2)***	***34 (26.8)***	***46 (46.0)***	***0.004***
Severity indexes and lab values				
PSI, median [IQR]	110 [85, 131]	115 [90, 132]	103 [83, 129]	0.087
CURB-65, median [IQR]	2 [1, 3]	2 [1, 3]	2 [1, 3]	0.649
Median albumin, g/dL (SD)	***3.5 (0.5)***	***3.1 (0.3)***	***3.9 (0.2)***	***<0.001***
Median D-dimer, ng/mL [IQR]	***1320 [626, 2520]***	***1518 [946, 3233]***	***736 [550, 1371]***	***<0.001***
Median hs-CRP, mg/L [IQR]	***49.8 [16.8, 108.5]***	***76.5 [32.0, 156.4]***	***26.3 [12.8, 69.0]***	***<0.001***
Median creatinine, mg/dl [IQR]	1.00 [0.80, 1.50]	1.00 [0.80, 1.75]	1.05 [0.80, 1.31]	0.346
Median white blood cells, N/ul [IQR]	11,028 [8,620, 13,515]	11,028 [8937, 13,615]	10,110 [8460, 13,300]	0.162
Median platelet, Nx10^3/ul [IQR]	209 [143, 280]	212 [143, 299]	206 [145, 269]	0.331
Clinical outcomes				
NSTEMI, n (%)	32 (14.0)	25 (19.2)	7 (7.1)	0.015
STEMI, n (%)	2 (0.9)	2 (1.5)	0 (0.0)	0.601
Acute ischemic stroke, n (%)	7 (3.1)	4 (3.1)	3 (3.0)	1.000
Venous thromboembolism, n (%)	0	0	0	NA
Cardiovascular death, n (%)	8 (3.5)	7 (5.4)	1 (1.0)	0.155
Non cardiovascular death, n (%)	3 (1.3)	0	3 (3.0)	0.164
Overall death, n (%)	11 (4.8)	7 (5.4)	4 (4.0)	0.847

hs-CRP, high sensitivity C-reactive protein; IQR, interquartile range; NSTEMI, non ST-elevation myocardial infarction; SD, standard deviation; STEMI, ST-elevation myocardial infarction; PSI, pneumonia severity index.

The severity of infection was similar between the two groups as reported by the CURB-65 (2 vs 2, $p = 0.649$) and the PSI (115 vs 103, $p = 0.087$) scores. Median length of stay was 11 (8 to 14) days in both subgroup of patients.

3.2. Hypoalbuminemia and thrombotic and inflammatory markers

Patients with hypoalbuminemia had higher values of D-Dimer (1518 ng/mL vs 736 ng/mL, $p < 0.001$) and hs-CRP (76.5 mg/L vs 26.3 mg/L, $p < 0.001$) (Figs. S1 and S2) with an inverse relation between albumin values and that of D-dimer and hs-CRP (Figs. S3 and S4).

3.3. Thrombotic events

During a total of 2162 patient-days of follow-up the incidence of thrombotic events was 20 per 1000 patient-days overall and 26 per 1000 patient-days and 11 per 1000 patient-days in patients with and without hypoalbuminemia, respectively. Among 41 thrombotic events, 32 were non-ST- and two ST-elevation myocardial infarction, and 7 an acute ischemic stroke. Of these events 6 occurred during anticoagulant and 18 during antiplatelet therapy while 19 during statin therapy. No venous thromboembolism occurred during follow-up.

A total of 11 patients died due to a cardiovascular (8 patients) or a non-cardiovascular cause (3 patients).

3.4. Survival and competing risk analysis

Kaplan-Meier curves reported higher cumulative thrombotic events during follow-up (Fig. 1) as well as the probability of thrombotic events in the competing risk of non-cardiovascular death was higher in patients with than without hypoalbuminemia (Fig. 2).

Table 2 and Fig. 3 reported the results of Cox proportional hazard model. The presence of hypoalbuminemia remained a strong predictor of thrombotic events in both univariable (hazard ratio; 2.67, 95% confidence intervals, 1.30 to 5.40) and multivariable (hazard ratio; 3.19, 95% confidence intervals, 1.48 to 6.89) analysis.

4. Discussion

The results of this study showed that hypoalbuminemia, as defined by albumin values <3.5 g/dL, characterized more than half of our cohort of patients with community acquired pneumonia and is associated with an increased incidence and risk of thrombotic events even if corrected for other relevant variables (e.g., age, sex category, relevant comorbidities, antithrombotic or statin therapies). The inverse relation between albumin values and D-dimer helps explaining this increased thrombotic risk.

Albumin levels can rapidly fall during acute infections (within hours) even in patients with a normal nutritional status probably due to the increased capillary filtration-related loss from the vascular space. [2,19,20] A reduced rate of albumin mRNA transcription and synthesis has also been observed in the acute-phase response to infection or inflammation. [21] So, hypoalbuminemia is present in a variable proportion of patients with acute diseases (from 20% to 50%) and data from previous publication confirmed its association with the risk of both thrombotic events and mortality. [2,22] In a large cohort of patients hospitalized for acute illness hypoalbuminemia was associated with increased length of stay, re-hospitalization, and all-cause death. [20] Hypoalbuminemia also predicted short- (28-day) and long-term mortality (up to 1-year) in intensive care units hospitalized septic patients with a mortality risk that progressively increase with the severity of hypoalbuminemia but that appear not to be affected by albumin administration. [4–7] The presence of specific comorbidities (e.g., chronic kidney failure, liver cirrhosis) or malnutrition may further increase the severity of hypoalbuminemia. [2] In a large cohort derived from the POliterapie SIMI Register, patients hospitalized for acute illness with albumin values <3.4 g/dL were older, frailer, had more comorbidities, and were most frequently underweight than those with higher albumin values. [2] The above mentioned subgroup of patients also had a higher chance of dying and a higher likelihood of experiencing ischemic events even when these risks were corrected by age, sex category, and comorbidities index. [2] Data from previous studies are sound but included population that are heterogeneous in terms of baseline characteristics and type and severity of illness. [2] Whether hypoalbuminemia share a similar prognostic value in more specific subgroup of infections at increased thrombotic burden is a matter of debate.

Community-acquired pneumonia represents the second most common cause of hospitalization and mortality other than sepsis with rates

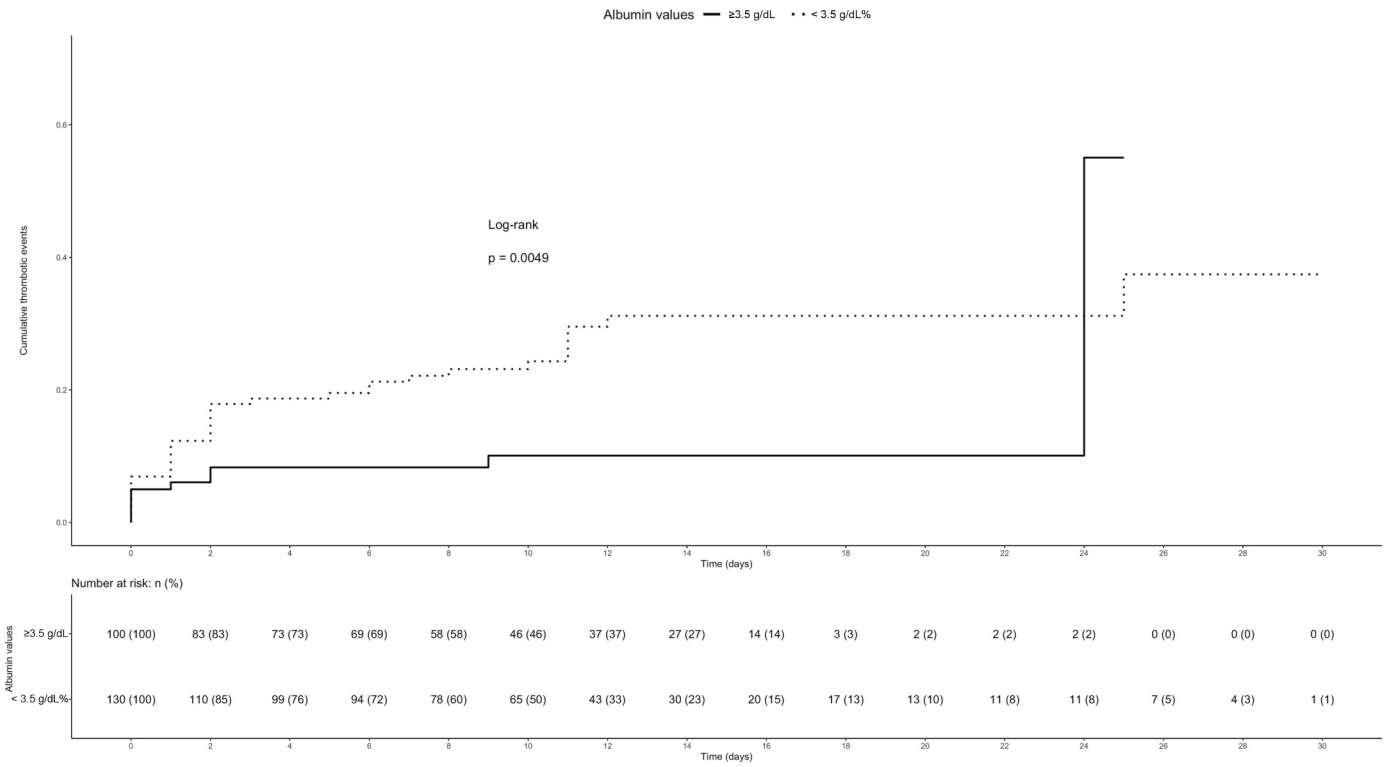

Fig. 1. Kaplan-Meier curves for intrahospital cardiovascular events (i.e., STEMI, NSTEMI, acute ischemic stroke, cardiovascular death).
NSTEMI, non ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

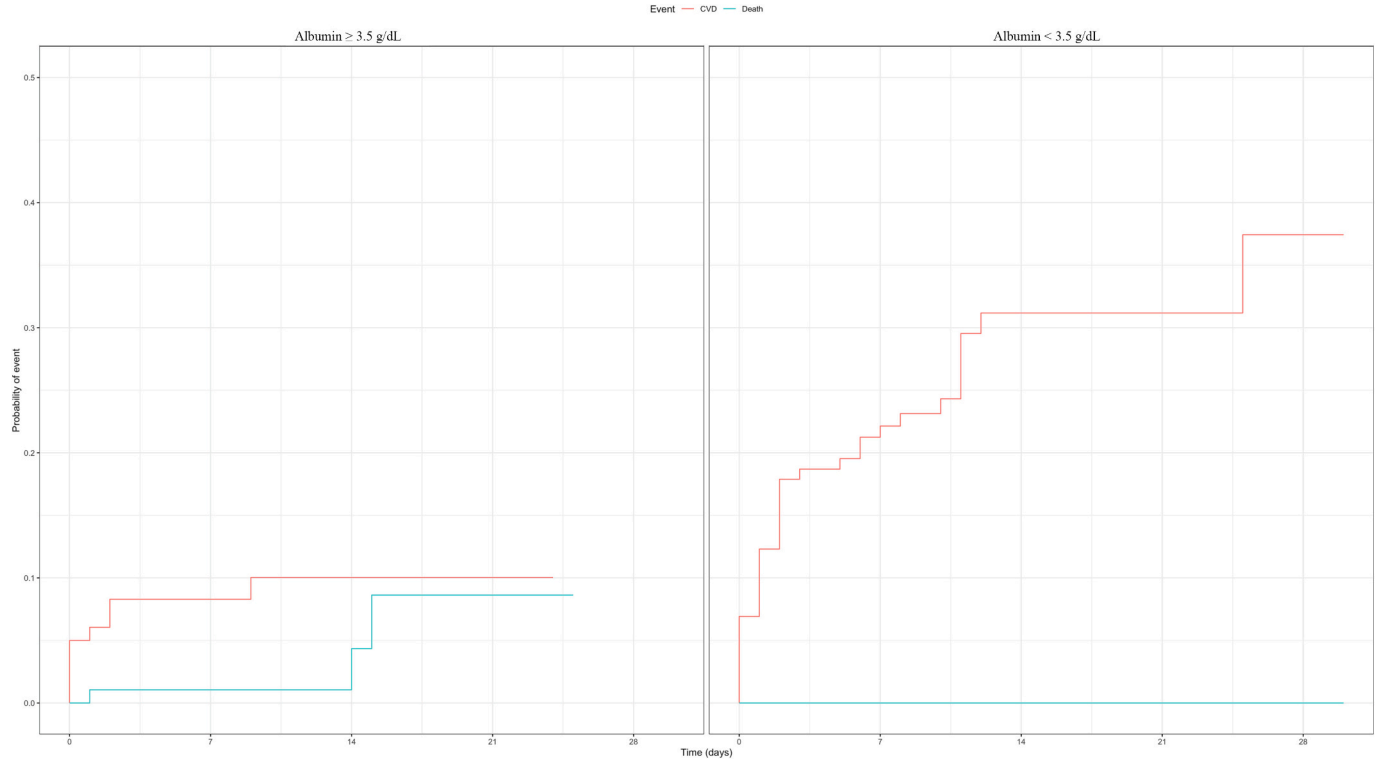

Fig. 2. Competing risk analysis – intrahospital cardiovascular events (i.e., STEMI, NSTEMI, acute ischemic stroke, cardiovascular death) and non-cardiovascular deaths.
CVD, Cardiovascular event; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 2
Univariable and Multivariable Cox regression hazard model for intrahospital cardiovascular events (i.e., STEMI, NSTEMI, acute ischemic stroke, cardiovascular death).

Covariates	Univariable, HR (95% CI)	Multivariable*, HR (95% CI)
Age	1.04 (1.00 to 1.10)	1.03 (1.00 to 1.10)
Female sex	1.28 (0.71 to 2.30)	1.34 (0.71 to 2.53)
hs-CRP	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)
Albumin < 3.5 g/dL	***2.67 (1.30 to 5.40)***	***3.19 (1.48 to 6.89)***
Diabetes mellitus	1.36 (0.75 to 2.50)	1.35 (0.73 to 2.51)
Chronic kidney disease	1.12 (0.55 to 2.30)	0.93 (0.45 to 1.96)
Anticoagulant therapy	0.67 (0.28 to 1.60)	0.66 (0.26 to 1.69)
Antiplatelet therapy	0.80 (0.44 to 1.40)	0.71 (0.36 to 1.39)
Statin therapy	1.31 (0.73 to 2.40)	1.70 (0.90 to 3.22)

CI, confidence interval; hs-CRP, high sensitivity C-reactive protein; HR, hazard ratio; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
* Likelihood ratio test, $p = 0.007$.

of cardiovascular events, mostly arterial, as high as 10%. [23] Our results extend these data showing a doubled incidence and a three-fold higher risk of thrombotic events in patients with hypoalbuminemia. Furthermore, our results confirm the pro-thrombotic role of hypoalbuminemia that may be added to the other mechanisms previously identified (e.g., increased oxidative stress, lipopolysaccharide-mediated platelet activation). [10,24,25] Previous studies showed as albumin share an heparin like activity enhancing the anti-factor Xa activity of antithrombin III and have an inhibitory effect on platelet aggregation by thromboxane A inactivation. [26–28] Albumin administration is also able to reduce platelet and coagulation activation in acute infection or severe liver disease. [29,30] A further explanation of this pro-thrombotic effect is that the presence of hypoalbuminemia may interfere with the efficacy of antithrombotic treatments. Thus, it has been demonstrated that the efficacy of aspirin varies according to albumin levels due to an impaired COX-1 inhibition in patients with diabetes mellitus. [31] Similarly, the efficacy of some anticoagulants in preventing venous thromboembolism is reduced in patients with hypoalbuminemia. [22] Even if our study may not establish any cause-effect relationship between hypoalbuminemia and thrombotic events development, the inverse relation between albumin and D-dimer values confirms and strengthens this association.

This study is of clinical relevance and of future therapeutic implications. While albumin values is mainly measured in the setting of sever liver disease to assess the oncotic pressure, its role in other clinical setting, as in acute infection, remains often underestimated. [1] Our study suggests the usefulness of baseline albumin values to stratify patients that may need a more intensive clinical and therapeutic management. The addition of albumin values may further increase the performance of validated severity indexes (e.g., CURB-65 and PSI). Whether therapeutic albumin administration may also improve antithrombotic treatment efficacy and patients' outcome is an intriguing

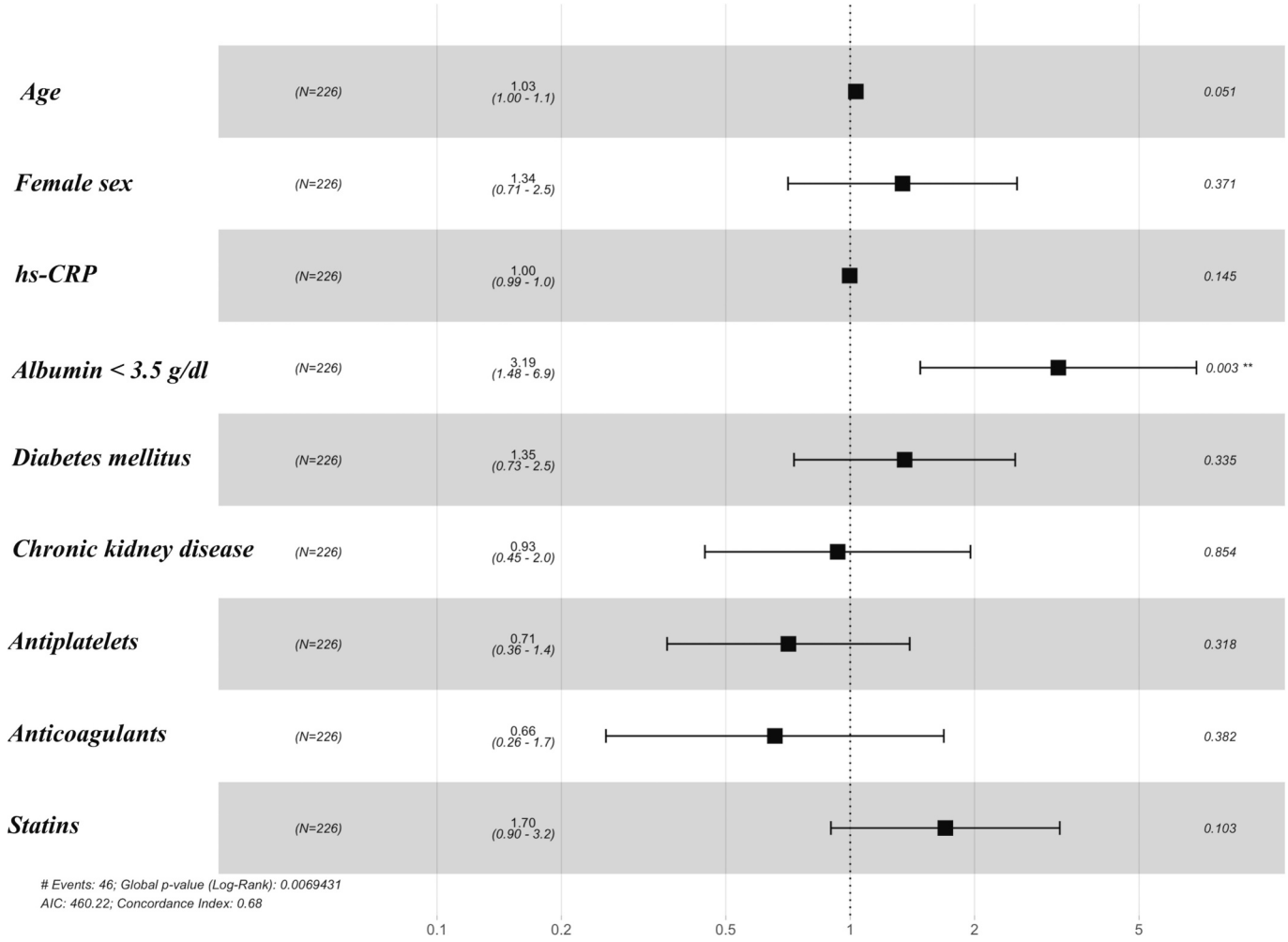

Fig. 3. Multivariable Cox regression hazard model for intrahospital cardiovascular events (i.e., STEMI, NSTEMI, acute ischemic stroke, cardiovascular death). hs-CRP, high sensitivity C-reactive protein; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
Legend of Graphical abstract: °*p*-values >0.05; *p-values <0.05.

hypothesis that have to be demonstrated in future studies.

The present study has some limitations that warrant discussion. First, data were retrospectively derived from a study designed for a different aim and some variables are not available for the overall initially included cohort (e.g., nutritional status of patients, presence of albuminuria). We also acknowledge that the exclusion of patients from the overall cohort due to the lack of albumin values may yield a selection bias. Furthermore, patients were evaluated at three department of a single Italian center, and this may affect the reproducibility in external cohorts. Second, no patients developed a venous event and we cannot evaluate the role of hypoalbuminemia in venous thromboembolism. Third, treatment decisions were entirely at the discretion of attending clinicians and no anti-thrombotic prophylactic algorithms were provided. Despite antithrombotic protocols were generally similar between our departments, we have no data about preadmission thromboprophylaxis dosages or changes on antithrombotic therapy during hospitalization. Furthermore, we do not have specific information about the clinical indication of antithrombotic therapy before the enrollment in this study. This may have partly affected the thrombotic rate but the correction of the model for potentially relevant covariates strengthens the role of hypoalbuminemia in predicting thrombotic events. Fourth, albumin values were checked at hospital admission and we cannot provide any information on potential change during the hospitalization and its effect on the outcomes.

5. Conclusions

More than a half of patients with community-acquired pneumonia had hypoalbuminemia that is associated with a doubled incidence and a three-fold increased risk of thrombotic events. The inverse relation between baseline albumin and D-dimer values confirms and strengthens the association between hypoalbuminemia and thrombotic complications.

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CRediT authorship contribution statement

Emanuele Valeriani: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roberto Carnevale:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Giulio Francesco Romiti:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Data curation. **Arianna Pannunzio:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Formal analysis. **Pasquale Pignatelli:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Formal analysis, Conceptualization. **Francesco Violi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

We did not use any artificial intelligence-assisted technology for this study.

Declaration of competing interest

All authors have read the journal's policy on disclosure of potential conflicts of interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131942.

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