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ORIGINAL ARTICLE

Risk of venous thromboembolism and arterial events in patients with hypoalbuminemia: a comprehensive meta-analysis of more than 2 million patients

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Abstract

Background: Albumin has antiplatelet and anticoagulant functions. Hypoalbuminemia, as defined by serum values of <3.5 g/dL, is associated with arterial thrombosis; its impact on venous thromboembolism (VTE) is unclear.

Objectives: The objective of this meta-analysis is to assess the VTE risk in patients with hypoalbuminemia.

Methods: MEDLINE and EMBASE were searched up to January 2024 for observational studies and randomized trials reporting data of interest. Primary outcome was the risk of VTE, while secondary outcomes were myocardial infarction and stroke risk in patients with hypoalbuminemia versus those without hypoalbuminemia. The risk of bias was evaluated using Newcastle–Ottawa scale and Cochrane tool. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated in a random-effects model.

Results: Forty-three studies for a total of 2 531 091 patients (39 738 medical and 2 491 353 surgical) were included in primary analysis; 79.1% of the studies used 3.5 g/dL cut-off value for hypoalbuminemia definition. Follow-up duration was 30 days in 60.5% of studies. Patients with hypoalbuminemia had a higher risk of VTE (RR, 1.88; 95% CI, 1.66-2.13). RRs were similar in both medical (RR, 1.87; 95% CI, 1.53-2.27) and surgical patients (RR, 1.87; 95% CI, 1.61-2.16) and in patients with (RR, 1.86; 95% CI, 1.66-2.10) and without cancer (RR, 1.89; 95% CI, 1.47-2.44). Risk of myocardial infarction (RR, 1.88; 95% CI, 1.54-2.31) and stroke (RR, 1.77; 95% CI, 1.26-2.48) was higher in patients with hypoalbuminemia.

Conclusion: Hypoalbuminemia is a risk factor for VTE in both medical and surgical patients irrespective of cancer coexistence. Serum albumin analysis may represent a simple and cheap tool to identify patients at VTE risk.

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Emanuele Valeriani and Arianna Pannunzio share co-first authorship.

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KEYWORDS
cardiovascular diseases, hypoalbuminemia, meta-analysis, serum albumin, venous thromboembolism

1 | INTRODUCTION

Albumin is the most represented acute phase reactive protein in humans and it is responsible for several homeostatic functions (eg, substance transport, colloid osmotic pressure maintenance, and pH regulation) [1]. Albumin shares antioxidant, antiplatelet, and antithrombotic activities [2,3]. It is known that albumin scavenges free reactive oxygen and nitrogen species, inhibits platelet aggregation through a Nox2-related oxidative stress mechanism, and helps regulating vascular tone and maintaining endothelial permeability via interactions with intestinal matrix [3–7]. It also binds antithrombin, inhibits liver synthesis (factors V and VII), and enhances the neutralization of some coagulation factors (factor Xa) [3,8].

Previous studies reported an inverse association between serum albumin and cardiovascular diseases and, more recently, such association has been better substantiated by using <3.5 g/dL albumin serum levels as hypoalbuminemia definition [1,8–11]. Thus, a previous study showed an inverse and linear increase in arterial events (eg, ischemic heart disease and stroke) with the highest risk in patients with plasma albumin values of <3.5 g/dL [10]. Similarly, a nearly doubled risk of acute arterial events has been reported in a large cohort of patients with albumin values of <3.5 g/dL and ischemic stroke [11].

Data for venous thromboembolism (VTE) are promising but heterogeneous [8,12]. The reason for high between-studies heterogeneity could be explained since most of the available studies did not evaluate VTE as the primary outcome or did not identify a specific cut-off value of serum albumin. There is a previous meta-analysis of just 3 studies in which VTE was a secondary outcome and in which its risk was evaluated in patients with different tertiles of albumin [13]. For those reasons, several issues still remain unresolved and a better understanding of the VTE risk of hypoalbuminemia in different clinical settings is warranted.

The objectives of our systematic review and meta-analysis are to comprehensively evaluate the risk of VTE in patients with hypoalbuminemia compared to patients with normal albumin values and to identify those populations at highest risk. Furthermore, we aimed to confirm the association between hypoalbuminemia and acute myocardial infarction, and acute ischemic stroke in a large population.

2 | METHODS

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines and was registered in PROSPERO with the ID number CRD42024512099 [14].

2.1 | Data sources and searches and study selection

We systematically searched MEDLINE and EMBASE databases from inception up to January 2024 for observational studies (cohort, case-control, cross-sectional studies, and case series) and randomized controlled trials (RCTs) evaluating the role of hypoalbuminemia in cardiovascular diseases (ie, VTE, acute myocardial infarction, and acute ischemic stroke). We excluded studies that did not report the outcomes of interest and did not specifically use a cut-off for hypoalbuminemia definition, and case reports or case series of less than 10 patients to avoid misleading results due to the small sample size. The complete search strategy is reported in Supplementary Tables S1 and S2. Two authors (E.V. and A.P.) independently screened the title and abstract of the records identified by the search. Any disagreement was discussed between the 2 reviewers and solved by consensus or involvement of a third review author (I.M.P.).

2.2 | Data extraction and quality assessment

The following data were independently extracted by 2 reviewer authors (E.V. and A.P): characteristics of the studies (eg, study design, clinical setting, cut-off of albumin chosen, and duration of follow-up), characteristics of the population (eg, age, sex category, body mass index, VTE and cardiovascular risk factors, albumin level, and history of cancer or active cancer), and outcomes of interest (ie, VTE, acute myocardial infarction, and acute ischemic stroke). Any disagreement was discussed between the 2 review authors and solved by consensus or involvement of a third review author (I.M.P.). In a similar manner, the risk of bias was evaluated using the Newcastle–Ottawa scale for observational studies (scores of 7-9, 4-6, and <4 classified a study as having a low, moderate, or high risk of bias, respectively) and the Cochrane tool for RCTs [15,16].

The primary outcome was the risk of VTE development in patients with hypoalbuminemia versus those with normal albumin values. VTE included pulmonary embolism, thrombosis in a deep vein of the lower or upper limb, thrombosis in the splanchnic, intra-abdominal, or cerebral vein districts.

The secondary outcome was the risk of arterial events (ie, acute myocardial infarction and acute ischemic stroke) in patients with hypoalbuminemia versus those with normal albumin values.

2.3 | Data synthesis and analysis

Categorical variables were described as counts and percentages, and continuous variables were presented as median or mean as

appropriate. For meta-analytical purposes, pooled risk ratios (RRs) with corresponding 95% confidence intervals (CIs) were calculated in a random-effects model through the inverse variance method, and DerSimonian-Laird method was used for $\tau 2$ estimation. Pooled prevalence with corresponding 95% CIs was calculated in a random-effects model through the inverse variance method, and DerSimonian–Laird method was used for $\tau 2$ estimation. We decided a priori not to use a continuity correction of 0.5 for studies with zero events. Heterogeneity was classified as follows: (i) 0% to 40% I^2 values indicate an heterogeneity that might not be important; (ii) 30% to 60% I^2 values may represent moderate heterogeneity, (iii) 50% to 90% I^2 values may represent substantial heterogeneity, and (iv) 75% to 100% I^2 values indicate a considerable heterogeneity [16]. The between-study heterogeneity was also evaluated by visual inspection of forest plots. A subgroup analysis was planned to evaluate the frequency of the outcomes of interest according to different settings of the population (ie, medical and surgical patients) and according to main clinical characteristics (eg, with or without cancer). Post-hoc sensitivity analysis for the primary outcome included studies using a cut-off value of 3.5 g/dL for hypoalbuminemia definition and studies at low risk of bias. The presence of publication bias was assessed by funnel plot of logit-transformed proportion versus standard error for the primary outcome. Statistical analyses were performed using R studio version 2023.12.0+369 ("meta" and "forest" packages).

3 | RESULTS

3.1 | Studies identification and selection

The initial search as well as the manual screening of relevant citations identified 1566 potentially relevant items (467 from MEDLINE and 1099 from EMBASE). After removal of duplicate records (95 items), 1471 items were screened based on titles and abstracts, and 119 were assessed for eligibility based of full-text analysis. Of the latter, 55 items were excluded as data of interest could not be extracted from full-text articles, 11 did not meet the inclusion criteria, and 4 were duplicates of other studies. In total, we included 49 studies of which 43 [8,17–58] included 2 531 091 patients for the primary outcome and 31 [8,17,18,20,23,27,28,30,33,36,37,39,41–46,48–52,54,56,59–64] included 2 467 949 patients for the secondary outcome (Figure 1).

3.2 | Characteristics of included studies

The main characteristics of the included studies addressing the primary outcome are reported in Table 1 [8,17–58]. Overall, 1 study was a post-hoc analysis of a RCT, 9 had a prospective design, and 33 had a retrospective design. Sample sizes ranged from 74 to 887 248 patients. Eleven studies included 39 738 medical patients (29 434 outpatients and 10 304 hospitalized), while 32 studies 2 491 353 hospitalized surgical patients. Twenty-three studies evaluated both venous and arterial events and 20 studies evaluated only venous events. VTE was primary outcome in 93.0% of studies and 18.6% of studies reported if the outcome was objectively reported. Most of the included studies (79.1%) used a cut-off value for hypoalbuminemia of 3.5 g/dL. Follow-up duration was 30 days in 60.5% of studies, while 9.3% of the studies used a longer follow-up. Tables 2 and Supplementary Figures S1–S6 reported the incidence of VTE and arterial events in patients with hypoalbuminemia and in patients with normal albumin values. Table 3 and Supplementary Figure S7 report the prevalence of hypoalbuminemia in different clinical settings. Supplementary Table S3 reports the characteristic of included studies evaluating the secondary outcomes.

The quality of the included studies is reported in Supplementary Figure S8 and Supplementary Tables S4 and S5 and varied from low to high. The results of publication bias are reported in Supplementary Figure S9.

3.3 | Characteristics of included patients

Mean age was 66 years in patients with hypoalbuminemia and it was 63 years in patients without hypoalbuminemia (26 studies), while 42.0% and 33.8% of patients (29 studies), respectively, were male. Mean body mass index values were 28.9 kg/m^2 and 29.4 kg/m^2 in patients with and without hypoalbuminemia (17 studies), respectively, while 25.5% versus 16.2% (14 studies) had cancer and 2.9% vs 2.9% (4 studies) had previous VTE as risk factors for event development.

3.4 | Primary outcome

Overall (Figure 2 and Supplementary Figure S10), patients with hypoalbuminemia had a higher risk of VTE than patients with normal albumin values (RR, 1.88; 95% CI, 1.66-2.13; 2 531 091 patients). RRs were similar in both medical (RR, 1.87; 95% CI, 1.53-2.27) and surgical patients (RR, 1.87; 95% CI, 1.61-2.16). Results were also similar when the analysis was restricted to those studies using a cut-off value of 3.5 g/dL for hypoalbuminemia definition (Supplementary Figure S11) or studies at low risk of bias (Supplementary Figure S12).

The risk of VTE associated with hypoalbuminemia remained significantly increased in both patients with (RR, 1.86; 95% CI, 1.66-2.10; 132 823 patients) and without cancer (RR, 1.89; 95% CI, 1.47-2.44; 900 992 patients; Supplementary Figures S13 and S14).

3.5 | Secondary outcomes

Overall (Figure 3 and Supplementary Figures S15 and S16), patients with hypoalbuminemia had a higher risk of acute myocardial infarction (RR, 1.88; 95% CI, 1.54-2.31; 2 480 202 patients) and acute ischemic stroke (RR, 1.77; 95% CI, 1.26-2.48; 1 942 091 patients) with similar RRs in both medical and surgical patients.

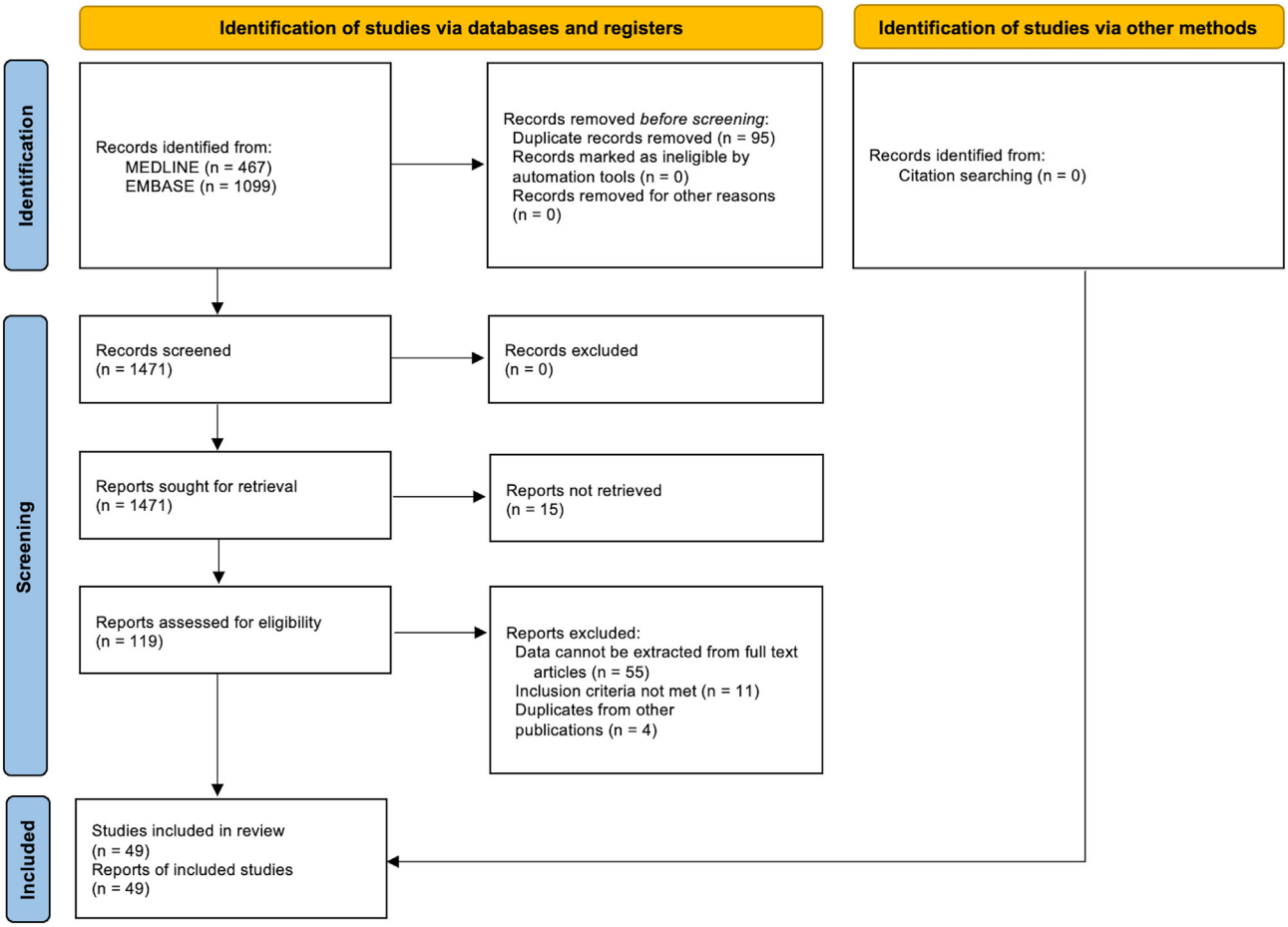

FIGURE 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses.

4 | DISCUSSION

The results of our study show that the presence of hypoalbuminemia confers a roughly 2-fold increased risk of VTE in a population of more than 2 million individuals. This risk persists in both medical and surgical patients as well as in those with and without cancer. We also confirmed in the largest available reported population that hypoalbuminemia was associated with an increased risk of acute myocardial infarction and acute ischemic stroke.

During the last years, a great scientific effort has been made to identify those subgroups of patients who share the highest risk of thrombotic complications and that may benefit from a proper medical and/or mechanical thromboprophylaxis. Some data recently questioned the clinical usefulness of the most widely used scores for VTE prediction (eg, Khorana score, Padua Prediction Score, IMPROVE score) [65–70]. Their impact on outcomes reduction has not been extensively evaluated and it seems that they do not completely fit with specific patients' populations [65–69]. Thus, clinical judgment often remains the preferred method for risk assessment [69]. The inclusion of feasible biomarkers may increase the power of these scores. Knowing that albumin shares antioxidant, antiplatelet, and antithrombotic properties, a relevant role in cardiovascular disease may be hypothesized [2,71]. A further strength of hypoalbuminemia is that it often complicates the course of several acute diseases and that the presence of specific comorbidities (eg, chronic kidney failure, liver cirrhosis, and cancer) or malnutrition may increase its severity [8]. In this regard, the ADA score, which considers age, D-dimer, and albumin, has been recently introduced in clinical practice for the identification of thrombotic risk of SARS-CoV-2 patients and validated in acutely ill hospitalized medical patients showing a modest superiority over the IMPROVE score [72]. Whether the ADA score is useful in other specific patient populations or clinical setting (eg, atrial fibrillation) is of clinical interest and has to be evaluated in future studies. Even if it has been demonstrated that hypoalbuminemia surely increases the risk of cardiovascular complications, no available risk assessment model for arterial event development (eg, CHA_2DS_2-VASc score and ABC score) still includes it [73].

The relevance of our results is that they comprehensively evaluated the role of hypoalbuminemia in predicting VTE and that allowed a better understanding of the usefulness of albumin measurement in daily clinical practice. Different from a previous meta-analysis, the inclusion of a large population allowed us to perform subgroup analysis on the type of clinical setting (ie, medical or surgical) and on the presence of cancer [13]. We also classified studies by different VTE

TABLE 1 Characteristics of included studies for primary outcome.

Study	Design	Type of VTE	Detection of VTE	VTE as primary outcome	Hypoalbuminemia events	Number of patients with hypoalbuminemia	Normal albumin values (events)	Normal albumin values (number of patients)	Clinical setting	Major comorbidity	Albumin cut-off, g/dL	Duration of follow-up
Adogwa et al., 2014 [17]	Retrospective	Usual type VTE	Not reported	Yes	1	14	0	60	Hospitalized surgical	Neurosurgery	3.5	Not reported
Aldebeyan et al., 2017 [18]	Retrospective	Usual type VTE	Not reported	Yes	60	4703	86	5414	Hospitalized surgical	Orthopedic	3.5	30 d
Ali and Parkash, 2023 [19]	Retrospective	Portal vein thrombosis	Objectively detected	No	74	318	9	62	Ambulatory	Hepatocellular carcinoma	3.5	Not reported
Caras et al., 2017 [20]	Retrospective	Usual type VTE	Not reported	Yes	70	2564	223	15 241	Hospitalized surgical	Cancer	3.5	30 d
Carr and Guerra, 2017 [21]	Retrospective	Portal vein thrombosis	Objectively detected	No	603	1889	349	2250	Ambulatory	Hepatocellular carcinoma	3.5	Not reported
Chi et al., 2018 [22]	Randomized trial	Usual type VTE	Objectively detected	Yes	110	1490	215	4270	Hospitalized medical	Mixed	3.5	77 d
Chung et al., 2018 [23]	Retrospective	Usual type VTE	Not reported	Yes	123	5867	108	6506	Hospitalized surgical	Orthopedic	3.5	30 d
Dasenbrock et al., 2017 [24]	Prospective	Usual type VTE	Not reported	Yes	55	1107	174	4715	Hospitalized surgical	Neurosurgery	3.5	30 d
Folsom et al., 2010 [25]	Prospective	Usual type VTE	Not reported	Yes	104	2908	358	12 392	Ambulatory	General population	3.6	16.9 y
Garcia et al., 2016 [26]	Retrospective	Usual type VTE	Not reported	Yes	10	128	12	1553	Hospitalized surgical	Orthopedic	3.5	30 d
Gelfand et al., 2021 [27]	Retrospective	Usual type VTE	Not reported	Yes	32	253	34	448	Hospitalized surgical	Cancer	3.5	30 d
Gupta et al., 2019 [28]	Retrospective	Usual type VTE	Not reported	Yes	30	785	17	1194	Hospitalized surgical	Vertebral fracture	3.5	30 d
Gyamlani et al., 2017 [29]	Prospective	Mixed type of VTE	Not reported	Yes	34	920	124	6117	Ambulatory	Nephrotic syndrome	3.0	Not reported
Hu et al., 2019 [30]	Retrospective	Usual type VTE	Not reported	Yes	169	4305	189	8610	Hospitalized surgical	Colorectal cancer	3.5	30 d
Isaacs et al, 2020 [31]	Retrospective	Usual type VTE	Not reported	Yes	12	36	10	126	Ambulatory	Vasculitis	3.0	Not reported
Johnson et al., 1999 [32]	Prospective	Usual type VTE	Objectively detected	Yes	76	120	38	91	Hospitalized medical	Cancer	3.5	Not reported
Kamath et al., 2017 [33]	Retrospective	Usual type VTE	Not reported	Yes	17	715	58	3838	Hospitalized surgical	Orthopedic	3.5	Not reported
Khawaja et al., 2023 [34]	Retrospective	Usual type VTE	Not reported	Yes	2	384	7	6831	Hospitalized surgical	Not reported	3.5	30 d
Kheir et al., 2021 [35]	Retrospective	Usual type VTE	Not reported	Yes	10	109	1	72	Hospitalized medical	COVID-19	3.3	Not reported
Kishawi et al., 2020 [36]	Retrospective	Usual type VTE	Not reported	Yes	124	9749	1321	125 270	Hospitalized surgical	Orthopedic	3.5	30 d
Lee et al., 2022 [37]	Retrospective	Usual type VTE	Not reported	No	1	174	1	1037	Hospitalized surgical	Maxillofacial fracture	3.5	30 d
Lee et al., 2017 [38]	Retrospective	Usual type VTE	Not reported	Yes	10	265	15	1308	Hospitalized surgical	Orthopedic	3.5	30 d
Lemdani et al., 2022 [39]	Retrospective	Usual type VTE	Not reported	Yes	2	77	2	241	Hospitalized surgical	Not reported	3.5	30 d
Liu et al., 2019 [40]	Retrospective	Usual type VTE	Not reported	Yes	11	50	23	233	Ambulatory	Cancer	3.5	Not reported
Meyer et al., 2017 [41]	Prospective	Usual type VTE	Not reported	Yes	1073	35 922	2506	168 897	Hospitalized surgical	Mixed	3.5	30 d

(Continues)

TABLE 1 (Continued)

Study	Design	Type of VTE	Detection of VTE	VTE as primary outcome	Hypoalbuminemia events	Number of patients with hypoalbuminemia	Normal albumin values (events)	Normal albumin values (number of patients)	Clinical setting	Major comorbidity	Albumin cut-off, g/dL	Duration of follow-up
Moghadamyeghaneh et al., 2015 [42]	Retrospective	Usual type VTE	Not reported	Yes	380	16 962	735	71 495	Hospitalized surgical	Not reported	3.5	30 d
Newman et al., 2020 [43]	Prospective	Usual type VTE	Not reported	Yes	9	569	20	1098	Hospitalized surgical	Orthopedic	3.5	30 d
Nguyen et al., 2019 [44]	Prospective	Usual type VTE	Not reported	Yes	209	4523	117	6390	Hospitalized surgical	Inflammatory bowel disease	3.5	30 d
Nipper et al., 2022 [45]	Retrospective	Usual type VTE	Not reported	Yes	5999	148 478	10 220	694 194	Hospitalized surgical	Mixed	3.4	30 d
Peacock et al., 2017 [46]	Retrospective	Usual type VTE	Not reported	Yes	31	2327	39	2783	Hospitalized surgical	Not reported	3.5	39 d
Phan et al., 2019 [47]	Retrospective	Usual type VTE	Not reported	Yes	3	159	29	2251	Hospitalized surgical	Orthopedic	3.5	30 d
Raad et al., 2022 [48]	Retrospective	Usual type VTE	Not reported	Yes	5	357	21	3980	Hospitalized surgical	Orthopedic	3.5	30 d
Soloff et al., 2021 [49]	Retrospective	Usual type VTE	Not reported	Yes	27	4055	623	195 365	Hospitalized surgical	Not reported	3.5	30 d
Uppal et al., 2013 [50]	Prospective	Usual type VTE	Not reported	Yes	14	279	32	1831	Hospitalized surgical	Cancer	3.5	30 d
Violi et al., 2023 [8]	Retrospective	Usual type VTE	Not reported	Yes	30	2193	5	1959	Hospitalized medical	Mixed	3.4	12 mo
Vora et al., 2020 [51]	Retrospective	Usual type VTE	Not reported	Yes	4	290	10	626	Hospitalized surgical	Orthopedic	3.5	30 d
Walls et al., 2015 [52]	Prospective	Usual type VTE	Not reported	Yes	12	1122	177	23 116	Hospitalized surgical	Orthopedic	3.5	30 d
Wang et al., 2022 [53]	Retrospective	Usual type VTE	Objectively detected	Yes	66	376	39	479	Hospitalized surgical	Orthopedic	3.3	Not reported
Wilson et al., 2019 [54]	Retrospective	Usual type VTE	Not reported	Yes	2	292	1	1697	Hospitalized surgical	Orthopedic	3.5	30 d
Xiong et al., 2023 [55]	Retrospective	Usual type VTE	Objectively detected	Yes	62	798	48	1335	Ambulatory	Osteoarthritis	3.7	Not reported
Ying et al., 2024 [56]	Retrospective	Usual type VTE	Not reported	Yes	236	49 845	2388	837 403	Hospitalized surgical	Not reported	3.5	30 d
Zhu et al., 2021 [57]	Retrospective	Usual type VTE	Objectively detected	Yes	17	67	4	191	Hospitalized surgical	Orthopedic	3.4	Not reported
Zuo et al., 2020 [58]	Retrospective	Usual type VTE	Objectively detected	Yes	83	373	33	205	Hospitalized surgical	Orthopedic	3.5	Not reported

VTE, venous thromboembolism.

TABLE 2 Pooled incidence of venous thromboembolism in patients with hypoalbuminemia and with normal albumin values.

	Venous thromboembolism		Acute myocardial infarction		Acute ischemic stroke	
Type of patients	Hypoalbuminemia	Normal albumin values	Hypoalbuminemia	Normal albumin values	Hypoalbuminemia	Normal albumin values
Outpatients medical, % (95% CI)	13 (5-30)	6 (3-13)	5 (1-21)	2 (0-36)	3 (1-16)	2 (0-10)
Hospitalized medical, % (95% CI)	11 (2-43)	4 (1-21)	3 (1-12)	1 (0-1)	5 (0-62)	3 (0-31)
Hospitalized surgical, % (95% CI)	3 (2-4)	1 (1-2)	1 (1-1)	0 (0-1)	0 (0-1)	0 (0-0)

risk factors and types of surgical interventions (Figure 2). Of note, hypoalbuminemia maintained its predictive role in all evaluated populations. A further strength of our analysis is that most of the included studies considered the same cut-off value to identify the presence of hypoalbuminemia (ie, <3.5 g/dL). This latter aspect is of utmost importance as a more precise definition of the condition may guide researchers for future studies and clinicians for patient management. Secondly, our data also confirmed the role of hypoalbuminemia in prediction of arterial events and complete previous data showing a similar risk in different clinical settings (ie, medical or surgical patients).

Even if some antithrombotic functions of albumin has been identified, a wide comprehension of its interaction with cardiovascular system is still lacking and new mechanisms may be hypothesized [3]. In mice models, albumin administration significantly reduces the TLR4 mRNA expression, possibly interfering with the recently elucidated mechanism of lipopolysaccharide-associated thrombosis [7,74,75]. Furthermore, albumin infusion reduces D-dimer values in patients with SARS-CoV2 infection, thus dampening the hypercoagulability state related to infection and inflammation [76]. Hypoalbuminemia may also interfere with the efficacy of antithrombotic treatments. It has been demonstrated in patients with diabetes mellitus that aspirin efficacy varies according to albumin levels due to an impaired COX-1 inhibition [77]. Similarly, some anticoagulants have a reduced efficacy in preventing VTE in patients with hypoalbuminemia [22]. If confirmed, all these data may suggest possible future therapeutic interventions in specific subgroups of patients.

Our work had some limitations that warrant discussion. First, the included patients were heterogeneous in their underlying characteristics resulting in a high between-studies heterogeneity that possibly affects the external validity of the results. The overall size of the included population and the availability of some specific characteristics allowed performing subgroup analysis that partly explained this heterogeneity but left the risk for residual confounding. Second, the evaluation of data on a study-level basis represents an intrinsic limitation of our meta-analysis and hampered an in-depth evaluation of the role of specific characteristics (eg, VTE risk factors, methods for outcome assessment, and the use of anticoagulants or antiplatelets) on the outcomes of interest. Data on the use of anticoagulants (7 studies) [8,22,29,53,55,56,58] or antiplatelets (3 studies) [22,55,58] were sparely reported without any further information on the indication, dose, or duration of these therapies. This lack of data did not allow us to evaluate the effect of specific treatments on the outcomes of interest nor whether hypoalbuminemia predicts the risk of cardiovascular events despite appropriate antithrombotic treatment. Furthermore, we cannot correct the analysis for specific confounding factors that may lead to hypoalbuminemia (eg, liver or kidney diseases, malnutrition, and chronic inflammation) and affect the outcomes. Subgroup analyses were performed by clinical setting and presence of cancer confirming the overall results. Furthermore, sorting studies by underlying VTE risk factors and types of surgical intervention help reducing the visual heterogeneity of the results. We also acknowledge the fact that a little number of studies used a slightly different cut-off for hypoalbuminemia and evaluated VTE as a secondary outcome. Third, all included studies were at some risk of bias potentially limiting the external validity of the results and there was evidence of significant publication bias. This latter finding is consistent with the possibility that small studies with large effect size were not published. However, it is unlikely that the latter were missed by our comprehensive and systematic database search. Even if several data have been published so far, the above limitations suggest an urgent need of further ad-hoc studies to identify those subgroup of patients in which albumin value measurement may be of utmost clinical relevance in cardiovascular outcome prediction.

TABLE 3 Pooled prevalence of hypoalbuminemia in different clinical setting.

Type of patients	Hypoalbuminemia
Outpatients medical, % (95% CI)	33 (22-45)
Hospitalized medical, % (95% CI)	44 (30-59)
Hospitalized surgical, % (95% CI)	19 (15-24)

5 | CONCLUSION

Hypoalbuminemia is a relevant risk factor for VTE in both medical and surgical patients. This risk persists irrespective of the presence or absence of cancer. Hypoalbuminemia is also associated with an increased risk of acute myocardial infarction and acute ischemic stroke. Serum albumin analysis may represent a simple and cheap tool to identify patients at VTE risk.

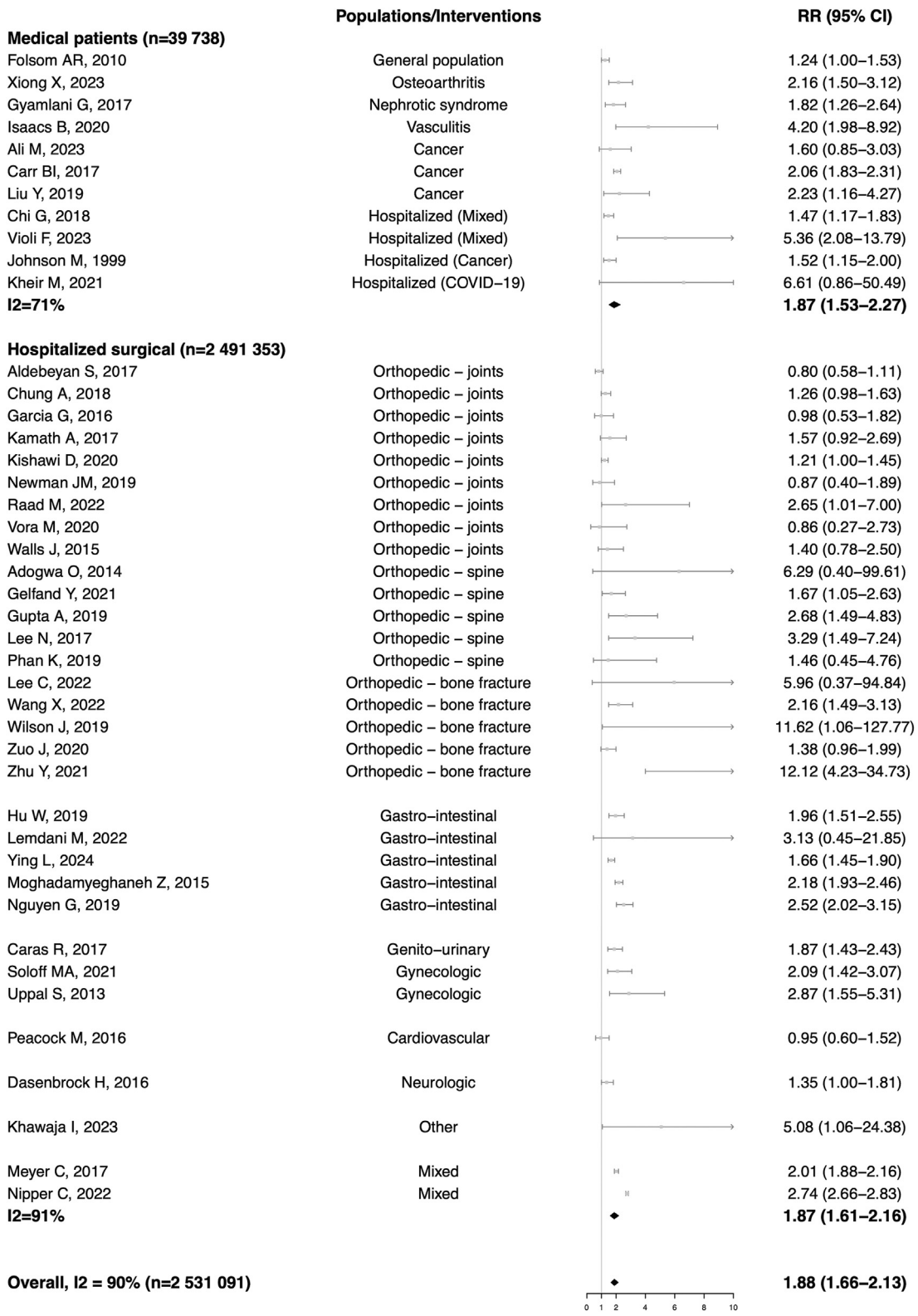

FIGURE 2 Risk of venous thromboembolism in patients with hypoalbuminemia versus those without hypoalbuminemia. CI, confidence interval; RR, risk ratio.

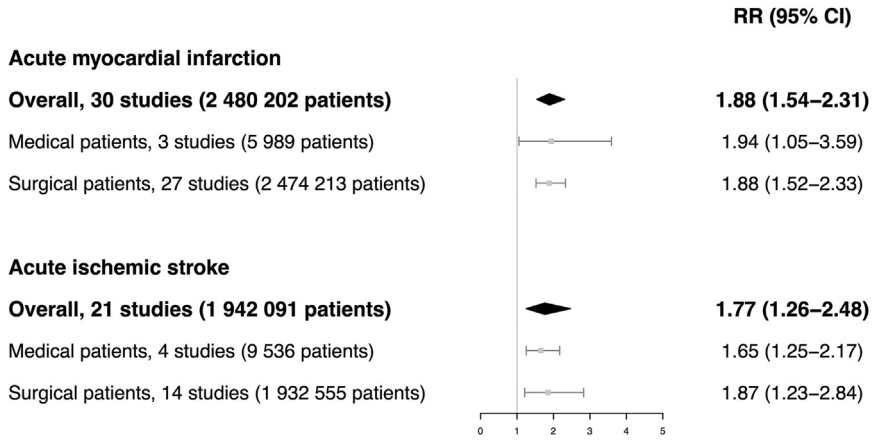

FIGURE 3 Risk of acute myocardial infarction and acute ischemic stroke in patients with hypoalbuminemia versus patients without hypoalbuminemia. CI, confidence intervals; RR, risk ratio.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

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

AUTHOR CONTRIBUTIONS

V.F. conceived and designed the study. V.E., P.A., and P.I.M. performed data acquisition. V.E. and V.F. performed statistical analysis. All authors contributed to data interpretation. V.E., P.A., and V.F. drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors gave final approval of the manuscript.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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REFERENCES

[1] Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. *Intern Emerg Med*. 2012;7:S193–9.

[2] Belinskaia DA, Voronina PA, Goncharov NV. Integrative role of albumin: evolutionary, biochemical and pathophysiological aspects. *J Evol Biochem Physiol*. 2021;57:1419–48.

[3] Basili S, Carnevale R, Nocella C, Bartimoccia S, Raparelli V, Talerico G, Stefanini L, Romiti GF, Perticone F, Corazza GR, Piscaglia F, Pietrangelo A, Violi F, Collaborators PL. Serum albumin is inversely associated with portal vein thrombosis in cirrhosis. *Hepatol Commun*. 2019;3:504–12.

[4] Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. *Mol Aspects Med*. 2012;33:209–90.

[5] Nelson JJ, Liao D, Sharrett AR, Folsom AR, Chambless LE, Shahar E, Szklo M, Eckfeldt J, Heiss G. Serum albumin level as a predictor of incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*. 2000;151:468–77.

[6] Garcia-Martinez R, Andreola F, Mehta G, Poulton K, Oria M, Jover M, Soeda J, Macnaughtan J, De Chiara F, Habtesion A, Mookerjee RP, Davies N, Jalan R. Immunomodulatory and antioxidant function of albumin stabilises the endothelium and improves survival in a rodent model of chronic liver failure. *J Hepatol*. 2015;62:799–806.

[7] Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol*. 2014;61:396–407.

[8] Violi F, Novella A, Pignatelli P, Castellani V, Tettamanti M, Mannucci PM, Nobili A, REPOSI (REgistro POliterapie SIMI, Società Italiana di Medicina Interna) Study Group. Low serum albumin is associated with mortality and arterial and venous ischemic events in acutely ill medical patients. Results of a retrospective observational study. *Thromb Res*. 2023;225:1–10.

[9] Akirov A, Masri-Iraqi H, Atamna A, Shimon I. Low albumin levels are associated with mortality risk in hospitalized patients. *Am J Med*. 2017;130:1465.e11–9.

[10] Ronit A, Kirkegaard-Klitbo DM, Dohlmann TL, Lundgren J, Sabin CA, Phillips AN, Nordestgaard BG, Afzal S. Plasma albumin and incident cardiovascular disease: results from the CGPS and an updated meta-analysis. *Arterioscler Thromb Vasc Biol*. 2020;40:473–82.

[11] Bucci T, Pastori D, Pignatelli P, Ntaios G, Abdul-Rahim AH, Violi F, Lip GYH. Albumin levels and risk of early cardiovascular complications after ischemic stroke: a propensity-matched analysis of a global federated health network. *Stroke*. 2024;55:604–12.

[12] Violi F, Pignatelli P, Vestri AR, Spagnoli A, Cipollone F, Ceccarelli G, Oliva A, Amitrano M, Pirro M, Taliani G, Cangemi R, Lichtner M, Pugliese F, Falcone M, D'Ardes D, Venditti M, Mastroianni CM, Loffredo L, Ada G. The ADA (Age-D-Dimer-Albumin) Score to predict thrombosis in SARS-CoV-2. *Thromb Haemost*. 2022;122:1567–72.

[13] Seidu S, Kunutsor SK, Khunti K. Serum albumin, cardiometabolic and other adverse outcomes: systematic review and meta-analyses of 48 published observational cohort studies involving 1,492,237 participants. *Scand Cardiovasc J*. 2020;54:280–93.

[14] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hrobjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.

[15] Wells GA, Shea B, O'Connel D, Peterson J, Welch V, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses; 2012. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [accessed January 10, 2023].

[16] Deeks J, Higgins J, Altma ND. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T,

Page MJ, Welch VA, eds. *Cochrane handbook for systematic reviews of interventions version 6.1*. Cochrane; 2020 [accessed January 2023].
[17] Adogwa O, Martin JR, Huang K, Verla T, Fatemi P, Thompson P, Cheng J, Kuchibhatla M, Lad SP, Bagley CA, Gottfried ON. Preoperative serum albumin level as a predictor of postoperative complication after spine fusion. *Spine*. 2014;39:1513–9.
[18] Aldebeyan S, Nooh A, Aoude A, Weber MH, Harvey EJ. Hypoalbuminaemia—a marker of malnutrition and predictor of postoperative complications and mortality after hip fractures. *Injury*. 2017;48:436–40.
[19] Ali M, Parkash O. Serum albumin levels relation to tumor aggressiveness in patients with hepatocellular carcinoma from a tertiary care hospital in Pakistan. *Middle East J*. 2023;15:203–6.
[20] Caras RJ, Lustik MB, Kern SQ, McMann LP, Sterbis JR. Preoperative albumin is predictive of early postoperative morbidity and mortality in common urologic oncologic surgeries. *Clin Genitourin Cancer*. 2017;15:e255–62.
[21] Carr BI, Guerra V. Serum albumin levels in relation to tumor parameters in hepatocellular carcinoma patients. *Int J Biol Markers*. 2017;32:e391–6.
[22] Chi G, Gibson CM, Liu Y, Hernandez AF, Hull RD, Cohen AT, Harrington RA, Goldhaber SZ. Inverse relationship of serum albumin to the risk of venous thromboembolism among acutely ill hospitalized patients: analysis from the APEX trial. *Am J Hematol*. 2019;94:21–8.
[23] Chung AS, Hustedt JW, Walker R, Jones C, Lowe J, Russell GV. Increasing severity of malnutrition is associated with poorer 30-day outcomes in patients undergoing hip fracture surgery. *J Orthop Trauma*. 2018;32:155–60.
[24] Dasenbrock HH, Liu KX, Chavakula V, Devine CA, Gormley WB, Claus EB, Smith TR, Dunn IF. Body habitus, serum albumin, and the outcomes after craniotomy for tumor: a National Surgical Quality Improvement Program analysis. *J Neurosurg*. 2017;126:677–89.
[25] Folsom AR, Lutsey PL, Heckbert SR, Cushman M. Serum albumin and risk of venous thromboembolism. *Thromb Haemost*. 2010;104:100–4.
[26] Garcia GH, Fu MC, Dines DM, Craig EV, Gulotta LV. Malnutrition: a marker for increased complications, mortality, and length of stay after total shoulder arthroplasty. *J Shoulder Elbow Surg*. 2016;25:193–200.
[27] Gelfand Y, De la Garza Ramos R, Nakhla JP, Echt M, Yanamadala V, Yassari R. Predictive value of hypoalbuminemia and severe hypoalbuminemia in oncologic spine surgery. *Clin Neurol Neurosurg*. 2021;210:107009.
[28] Gupta A, Upadhyaya S, Cha T, Schwab J, Bono C, Hershman S. Serum albumin levels predict which patients are at increased risk for complications following surgical management of acute osteoporotic vertebral compression fractures. *Spine J*. 2019;19:1796–802.
[29] Gyamlani G, Molnar MZ, Lu JL, Sumida K, Kalantar-Zadeh K, Kovesdy CP. Association of serum albumin level and venous thromboembolic events in a large cohort of patients with nephrotic syndrome. *Nephrol Dial Transplant*. 2017;32:157–64.
[30] Hu WH, Eisenstein S, Parry L, Ramamoorthy S. Preoperative malnutrition with mild hypoalbuminemia associated with postoperative mortality and morbidity of colorectal cancer: a propensity score matching study. *Nutr J*. 2019;18:33.
[31] Isaacs B, Gapud EJ, Antiochos B, Seo P, Geetha D. Venous thrombotic events in ANCA-associated vasculitis: incidence and risk factors. *Kidney360*. 2020;1:258–62.
[32] Johnson MJ, Sproule MW, Paul J. The prevalence and associated variables of deep venous thrombosis in patients with advanced cancer. *Clin Oncol (R Coll Radiol)*. 1999;11:105–10.
[33] Kamath AF, Nelson CL, Elkassabany N, Guo Z, Liu J. Low albumin is a risk factor for complications after revision total knee arthroplasty. *J Knee Surg*. 2017;30:269–75.
[34] Khawaja IM, Randhawa A, Randhawa K, Aftab OM, Patel RV, Eloy JA, Fang CH. Effect of hypoalbuminemia in patients undergoing parathyroidectomy for primary hyperparathyroidism. *Laryngoscope*. 2023;133:2035–9.
[35] Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. *PLoS One*. 2021;16:e0248358.
[36] Kishawi D, Schwarzman G, Mejia A, Hussain AK, Gonzalez MH. Low preoperative albumin levels predict adverse outcomes after total joint arthroplasty. *J Bone Joint Surg Am*. 2020;102:889–95.
[37] Lee CC, Wang TT, Hunter WP, Peacock ZS. Is preoperative serum albumin predictive of adverse surgical outcomes in maxillofacial fracture repair? *J Oral Maxillofac Surg*. 2022;80:286–95.
[38] Lee NJ, Kothari P, Kim JS, Phan K, Di Capua J, Shin J, Cho SK. Nutritional status as an adjunct risk factor for early postoperative complications following posterior cervical fusion. *Spine (Phila Pa 1976)*. 2017;42:1367–74.
[39] Lemdani MS, Choudhry HS, Patel AM, Ahmad M, Patel R, Patel P, Eloy JA. Malnutrition and postoperative outcomes following transcervical Zenker diverticulectomy. *Laryngoscope*. 2023;133:1402–8.
[40] Liu Y, Gu Y, Yi F, Cao B. [Retrospective analysis of risk factors for venous thromboembolism in 283 patients with lung cancer during systemic therapy]. [Chinese]. *Zhongguo Fei Ai Za Zhi*. 2019;22:419–26.
[41] Meyer CP, Rios-Diaz AJ, Dalela D, Ravi P, Sood A, Hanske J, Chun FKH, Kibel AS, Lipsitz SR, Sun M, Trinh QD. The association of hypoalbuminemia with early perioperative outcomes—a comprehensive assessment across 16 major procedures. *Am J Surg*. 2017;214:871–83.
[42] Moghadamyeghaneh Z, Hwang G, Hanna MH, Phelan MJ, Carmichael JC, Mills SD, Pigazzi A, Dolich MO, Stamos MJ. Even modest hypoalbuminemia affects outcomes of colorectal surgery patients. *Am J Surg*. 2015;210:276–84.
[43] Newman JM, Sodhi N, Khlopas A, Piuzzi NS, Yakubek GA, Sultan AA, Klika AK, Higuera CA, Mont MA. Malnutrition increases the 30-day complication and re-operation rates in hip fracture patients treated with total hip arthroplasty. *Hip Int*. 2020;30:635–40.
[44] Nguyen GC, Du L, Chong RY, Jackson TD. *Hypoalbuminaemia and postoperative outcomes in inflammatory bowel disease: the NSQIP surgical cohort*. 13. 2019:1433–8.
[45] Nipper CA, Lim K, Riveros C, Hsu E, Ranganathan S, Xu J, Brooks M, Esnaola N, Klaassen Z, Jerath A, Arrington A, Wallis CJD, Satkunasivam R. The association between serum albumin and postoperative outcomes among patients undergoing common surgical procedures: an analysis of a multi-specialty surgical cohort from the National Surgical Quality Improvement Program (NSQIP). *J Clin Med*. 2022;11:6543.
[46] Peacock MR, Farber A, Eslami MH, Kalish JA, Rybin D, Doros G, Shah NK, Siracuse JJ. Hypoalbuminemia predicts perioperative morbidity and mortality after infrainguinal lower extremity bypass for critical limb ischemia. *Ann Vasc Surg*. 2017;41:169–75.e4.
[47] Phan K, Ranson W, White SJW, Cheung ZB, Kim J, Shin JI, Ukogu C, Lee NJ, Kothari P, Cho SK. Thirty-day perioperative complications, prolonged length of stay, and readmission following elective posterior lumbar fusion associated with poor nutritional status. *Glob Spine J*. 2019;9:417–23.
[48] Raad M, Best MJ, Rogers D, Bronheim R, Nayar SK, Puvanesarajah V, Marrache M, Srikumaran U. Hypoalbuminemia and the higher risk of perioperative sentinel adverse events in patients undergoing total shoulder arthroplasty: a propensity score matched analysis. *Arch Bone Jt Surg*. 2022;10:858–62.
[49] Soloff MA, Vargas MV, Wei C, Ohnona A, Tyan P, Gu A, Georgakopoulos B, Thomas CA, Quan T, Barishansky S, Moawad G. Malnutrition is associated with poor postoperative outcomes following laparoscopic hysterectomy. *JSLS*. 2021;25:e2020.00084.

[50] Uppal S, Al-Niaimi A, Rice LW, Rose SL, Kushner DM, Spencer RJ, Hartenbach E. Preoperative hypoalbuminemia is an independent predictor of poor perioperative outcomes in women undergoing open surgery for gynecologic malignancies. *Gynecol Oncol*. 2013;131:416–22.
[51] Vora M, Sing DC, Yi PH, Cheah JW, Li X. Hypoalbuminemia is a risk factor for predicting early postoperative complications after proximal humerus fracture fixation. *J Orthop*. 2020;19:106–10.
[52] Walls JD, Abraham D, Nelson CL, Kamath AF, Elkassabany NM, Liu J. Hypoalbuminemia more than morbid obesity is an independent predictor of complications after total hip arthroplasty. *J Arthroplasty*. 2015;30:2290–5.
[53] Wang X, Jiang Z, Li Y, Gao K, Gao Y, He X, Zhou H, Zheng W. Prevalence of preoperative deep venous thrombosis (DVT) following elderly intertrochanteric fractures and development of a risk prediction model. *BMC Musculoskelet Disord*. 2022;23:417.
[54] Wilson JM, Holzgrefe RE, Staley CA, Schenker ML, Meals C. The effect of malnutrition on postoperative complications following surgery for distal radius fractures. *J Hand Surg Am*. 2019;44:742–50.
[55] Xiong X, Li T, Yu S, Lu X, Mao Q, Xiong Y. Association between low serum albumin and preoperative deep vein thrombosis in patients undergoing total joint arthroplasty: a retrospective study. *Clin Appl Thromb Hemost*. 2023;29:10760296231178547.
[56] Ying LD, Chao GF, Canner J, Graetz E, Ghiassi S, Schwartz JS, Zolfaghari EJ, Schneider EB, Gibbs KE. The degree of preoperative hypoalbuminemia is associated with risk of postoperative complications in metabolic and bariatric surgery patients. *Obes Surg*. 2024;34:51–70.
[57] Zhu Y, Meng H, Ma J, Zhang J, Li J, Zhao K, Zhang Y, Chen W. Prevalence of preoperative lower extremity deep vein thrombosis in bilateral calcaneal fractures. *J Foot Ankle Surg*. 2021;60:950–5.
[58] Zuo J, Hu Y. Admission deep venous thrombosis of lower extremity after intertrochanteric fracture in the elderly: a retrospective cohort study. *J Orthop Surg Res*. 2020;15:549.
[59] Montazerghaem H, Safaie N, Samiei Nezhad V. Body mass index or serum Albumin levels: which is further prognostic following cardiac surgery? *J Cardiovasc Thorac Res*. 2014;6:123–6.
[60] Oduncu V, Erkol A, Karabay CY, Kurt M, Akgun T, Bulut M, Pala S, Kirma C. The prognostic value of serum albumin levels on admission in patients with acute ST-segment elevation myocardial infarction undergoing a primary percutaneous coronary intervention. *Coron Artery Dis*. 2013;24:88–94.
[61] Rady MY, Ryan T, Starr NJ. *Clinical characteristics of preoperative hypoalbuminemia predict outcome of cardiovascular surgery*. 21. JPEN J Parenter Enteral Nutr; 1997:81–90.
[62] Westfall JC, Cheng TW, Farber A, Jones DW, Eslami MH, Kalish JA, Rybin D, Siracuse JJ. Hypoalbuminemia predicts increased readmission and emergency department visits after lower extremity bypass. *Vasc Endovasc Surg*. 2019;53:629–35.
[63] Zeng R, Li D, Deng L, He Y, Sun X, Wan Z, Nie H, Du X, Cao Y, Zeng Z. Hypoalbuminemia predicts clinical outcome in patients with type B acute aortic dissection after endovascular therapy. *Am J Emerg Med*. 2016;34:1369–72.
[64] Zhang Q, Lei YX, Wang Q, Jin YP, Fu RL, Geng HH, Huang LL, Wang XX, Wang PX. Serum albumin level is associated with the recurrence of acute ischemic stroke. *Am J Emerg Med*. 2016;34:1812–6.
[65] Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, De Bon E, Tormene D, Pagnan A, Prandoni P. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8:2450–7.
[66] Spyropoulos AC, Anderson FA Jr, FitzGerald G, Decousus H, Pini M, Chong BH, Zotz RB, Bergmann JF, Tapson V, Froehlich JB, Monreal M, Merli GJ, Pavanello R, Turpie AGG, Nakamura M, Piovella F, Kakkar AK, Spencer FA, IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest*. 2011;140:706–14.
[67] Darzi AJ, Repp AB, Spencer FA, Morsi RZ, Charide R, Etxeandia-Ikobaltzeta I, Bauer KA, Burnett AE, Cushman M, Dentali F, Kahn SR, Rezende SM, Zakai NA, Agarwal A, Karam SG, Lotfi T, Wiercioch W, Waziry R, Iorio A, Akl EA, et al. Risk-assessment models for VTE and bleeding in hospitalized medical patients: an overview of systematic reviews. *Blood Adv*. 2020;4:4929–44.
[68] van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahé I, Wilts IT, Twint DC, Porreca E, Arrieta O, Stepanian A, Smit K, De Tursi M, Bleker SM, Bossuyt PM, Nieuwland R, Kamphuisen PW, Buller HR. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. *Haematologica*. 2017;102:1494–501.
[69] Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, Lansing J, Balduzzi S, Darzi A, Morgano GP, Neumann I, Nieuwlaat R, Yepes-Nuñez JJ, Zhang Y, Wiercioch W. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2:3198–225.
[70] Di Nisio M, van Es N, Rotunno L, Anzoletti N, Falcone L, De Tursi M, Natoli C, Tinari N, Cavallo I, Valeriani E, Candeloro M, Guglielmi MD, Rutjes AWS, Porreca E. Long-term performance of risk scores for venous thromboembolism in ambulatory cancer patients. *J Thromb Thrombolysis*. 2019;48:125–33.
[71] Valeriani E, Cangemi R, Carnevale R, Romiti G, Pannunzio A, Pignatelli P, Violi F. Hypoalbuminemia as predictor of thrombotic events in patients with community-acquired pneumonia. *Int J Cardiol*. 2024;404:131942.
[72] Chi G, Violi F, Pignatelli P, Vestri A, Spagnoli A, Loffredo L, Hernandez AF, Hull RD, Cohen AT, Harrington RA, Goldhaber SZ, Gibson CM. External validation of the ADA score for predicting thrombosis among acutely ill hospitalized medical patients from the APEX Trial. *J Thromb Thrombolysis*. 2023;55:211–21.
[73] Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, Vicente V, Valdés M, Marín F, Lip GYH. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. *Thromb Haemost*. 2017;117:1848–58.
[74] Wang M, Wang Y, He J, Wei S, Zhang N, Liu F, Liu X, Kang Y, Yao X. Albumin induces neuroprotection against ischemic stroke by altering Toll-like receptor 4 and regulatory T cells in mice. *CNS Neurol Disord Drug Targets*. 2013;12:220–7.
[75] Violi F, Cammisotto V, Bartimoccia S, Pignatelli P, Carnevale R, Nocella C. Gut-derived low-grade endotoxaemia, atherothrombosis and cardiovascular disease. *Nat Rev Cardiol*. 2023;20:24–37.
[76] Violi F, Ceccarelli G, Loffredo L, Alessandri F, Cipollone F, D'Ardes D, D'Ettorre G, Pignatelli P, Venditti M, Mastroianni CM, Pugliese F. Albumin supplementation dampens hypercoagulability in COVID-19: a preliminary report. *Thromb Haemost*. 2021;121:102–5.
[77] Sciacqua A, Andreozzi F, Succurro E, Pastori D, Cammisotto V, Armentaro G, Mannino GC, Fiorentino TV, Pignatelli P, Angiolillo DJ, Sesti G, Violi F. Impaired clinical efficacy of aspirin in hypoalbuminemic patients with diabetes mellitus. *Front Pharmacol*. 2021;12:695961.

SUPPLEMENTARY MATERIAL

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