Systematic Review and Meta-Analysis

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Hypoalbuminemia and colorectal cancer patients: Any correlation?

A systematic review and meta-analysis

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Abstract

Background: In malnourished patients with colorectal cancer, hypoalbuminemia is common and was proposed to determine the postoperative outcome of colorectal surgery. Mounting articles published but have not been evaluated. We aim to assess the predictive value of preoperative hypoalbuminemia in patients undergoing colorectal surgery.

Methods: We performed a literature search from PubMed, Euro PMC, and Cochrane with the terms serum albumin, hypoalbuminemia, prognosis, outcome, colorectal cancer, and neoplasm. We also hand-searched and included any relevant papers. Hypoalbuminemia is defined as plasma albumin level < 3.5 mg/dL. We restricted the included studies to English language and adults undergoing colectomy, laparotomy, laparoscopy, or abdominoperineal resection. Any types of articles were included, except an abstract-only publication and those that did not report the key exposure or outcome of interest. The key exposures were mortality, hospitalization time, and morbid conditions (thrombosis, surgical site infection, sepsis, and wound events). We pooled the odds ratio from each included literature as effect size. The Newcastle Ottawa scale and GRADE were used to determine the quality of each included study.

Results: Hereof 7 observational studies (236,480 individuals) were included. Our meta-analysis found that preoperative hypoalbuminemia can predict the postoperative outcome in colorectal cancer patients. Individuals with hypoalbuminemia were not associated with 30-day mortality (risk ratio [RR] 2.05 [0.72, 5.86], $P = .18$, $I^2 = 99\%$) but were associated with morbidity (RR 2.28 [1.78, 2.93], $P < .00001$, $I^2 = 87.5\%$), surgical complication (RR 1.69 [1.34, 2.13], $P < .00001$, $I^2 = 98\%$), and hospitalization (RR 2.21 [1.93, 2.52], $P < .00001$, $I^2 = 0\%$). According to newcastle ottawa scale, the included studies are of moderate to sound quality.

Conclusions: The current systematic review and meta-analysis showed that preoperative hypoalbuminemia was significantly associated with morbidity, length of stay, and surgical complication but not mortality.

Abbreviations: BSA = basal serum albumin, CRC = colorectal cancer, NOS = newcastle ottawa scale, RR = risk ratio.

Keywords: colorectal cancer, hypoalbuminemia, outcome, postoperative

1. Introduction

The third leading cause of cancer-related deaths worldwide is colorectal cancer (CRC).[1] The incidence and death of CRC show significant geographic variation, with relatively similar regional trends in men and women.[1,2] The best curative choice for patients with localized CRC is generally accepted to be aggressive surgery, despite significant regional variations in screening programs and treatment methods. Even though new treatments have increased survival, over 45% of CRC cases will pass away due to the tumor.[2]

Regional differences in the prognosis of CRC patients have been reported frequently; however, neither the tumor-node-metastasis categorization nor the currently accepted prognostic variables can fully account for these disparities. To increase our understanding of the issue and raise the standard of care in CRC, we must have a greater understanding of these aspects and how they interact, including how they relate to patients, healthcare professionals, treatments, or institutions.[3] It is becoming more common to link hematologic, immunological, and nutritional measures with cancer prognosis. Serum albumin is a valuable biomarker for many illnesses. It has been

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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linked to several acute, chronic, and neoplastic disorders, as well as healthy populations, as a significant prognostic indicator.[4–8]

Many predictive models use baseline serum albumin (BSA) to define or improve therapies in particular contexts. In the context of CRC, BSA has been characterized as a prognostic factor linked with survival and a predictor of surgical morbidity and death.[6,9,10]

BSA measurement is simple, affordable, accurate, and trustworthy, frequently used to determine patients general state with many types of medical conditions. Consequently, we aimed to evaluate the predictive value of preoperative hypoalbuminemia in patients undergoing colorectal surgery.

2. Methods

The authors performed a literature search from PubMed, Euro PMC, and Cochrane with the terms serum albumin, hypoalbuminemia, prognosis, outcome, colorectal cancer, and neoplasm. A detailed search strategy can be seen in Table 1. An initial search and title and abstract screening for pertinent papers were carried out independently by the 2 authors. We settled disagreements through discussion. After eliminating duplicates, we applied inclusion and exclusion criteria to the prospective full-texts for evaluation. We also hand-searched and included any relevant papers. All authors completed the literature search on December 20, 2022. This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses guideline.[11] We registered our systematic review to the PROSPERO (CRD42023388595).

We restricted the included studies to English language and adults undergoing colectomy, laparotomy, laparoscopy, or abdominoperineal resection. Any types of articles were included, except an abstract-only publication and those that did not report the key exposure or outcome of interest.

The authors (N.M. and J.H.) separately extracted data from each included study on the information: Author, year, research design, age, gender, albumin level, mortality, morbidity, length of stay, surgical complications, such as surgical site infection, thrombosis event, sepsis, and wound event, and other outcomes of interests. We recorded all data on standardized forms. We defined hypoalbuminemia as plasma albumin level < 3.5 mg/dL. We described the mortality rate as deaths from all causes within 30 days or during the hospitalization for the index procedure.

The primary outcome of the current study is mortality. Secondary outcomes were hospitalization time, thrombosis, surgical site infection, sepsis, and wound events.

The possibility of bias in each included publication was evaluated using the Newcastle Ottawa scale (NOS), which is used to rate the quality of non-randomized research in meta-analyses. It has been suggested that the NOS be used while reviewing observational studies. For cohort studies, the NOS has 3 domains – selection, comparability, and outcome – and 8 elements. A study with a score of 7 to 9 is considered high quality; studies with scores of 4 to 6 have a significant risk of bias, and studies with scores of 0 to 3 have an extremely high risk of bias. The maximum possible score is 9.

We used Review Manager 5.4 (Cochrane Collaboration) to conduct the meta-analysis. We calculated the risk ratios (RRs) for dichotomous variables using the Mantel-Haenszel algorithm, and their 95% confidence intervals are provided. Despite the heterogeneity, We utilized a random-effects model for the calculation. In this investigation, the threshold for statistical significance was set at .05, and all *P* values were 2-tailed. The likelihood of publication bias was assessed using an inverted funnel-plot approach.

3. Results

From 3 unique medical electronic databases, we extracted a total of 20,626 studies. After omitting duplicates and using a filter from each database, we were left with 19,152 studies. After screening the titles and abstracts, we excluded a total of 19,106 literature. After evaluating 48 full-text articles for eligibility, we excluded 41 of them because conference abstracts (n = 4), not English literature (n = 2), colorectal surgeries, but not colorectal carcinoma (n = 4), and did not report key interest (n = 31). A detailed literature saturation process can be seen in Figure 1. Overall, there were 236,460 patients from 7 studies.[12–18] The characteristics of the included studies are displayed in Table 2

Our meta-analysis found that preoperative hypoalbuminemia can predict the postoperative outcome in CRC patients. Individuals with hypoalbuminemia were not associated with 30-day mortality (RR 2.05 [0.72, 5.86], $P = .18$, $I^2 = 99\%$) but were associated with morbidity (RR 2.28 [1.78, 2.93], $P < .00001$, $I^2 = 87.5\%$), surgical complication (RR 1.69 [1.34, 2.13], $P < .00001$, $I^2 = 98\%$), and hospitalization (RR 2.21 [1.93, 2.52], $P < .00001$, $I^2 = 0\%$). The

Table 1

Search query used at different search engine.

Scientific database	Search terms
PubMed	("albumin s"[All Fields] OR "albumine"[All Fields] OR "albumines"[All Fields] OR "albumins"[MeSH Terms] OR "albumins"[All Fields] OR "albumin"[All Fields] OR ("serum albumin"[MeSH Terms] OR ("serum"[All Fields] AND "albumin"[All Fields]) OR "serum albumin"[All Fields]) OR ("hypoalbuminaemia"[All Fields] OR "hypoalbuminemia"[MeSH Terms] OR "hypoalbuminemia"[All Fields])) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields] OR ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]) OR ("outcome"[All Fields] OR "outcomes"[All Fields]) OR ("prognostic"[All Fields] OR "prognostical"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognosticated"[All Fields] OR "prognosticates"[All Fields] OR "prognosticating"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticator"[All Fields] OR "prognosticators"[All Fields] OR "prognostics"[All Fields])) AND ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields] OR ("colonic neoplasms"[MeSH Terms] OR ("colonic"[All Fields] AND "neoplasms"[All Fields]) OR "colonic neoplasms"[All Fields] OR ("colon"[All Fields] AND "cancer"[All Fields]) OR "colon cancer"[All Fields]) OR ("rectal neoplasms"[MeSH Terms] OR ("rectal"[All Fields] AND "neoplasms"[All Fields]) OR "rectal neoplasms"[All Fields] OR ("rectal"[All Fields] AND "cancer"[All Fields]) OR "rectal cancer"[All Fields]) OR ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]))
Europe PMC	albumin OR serum albumin OR hypoalbuminemia AND prognosis OR survival OR outcome OR prognostic AND colorectal cancer OR colon cancer OR rectal cancer OR neoplasm
Cochrane	albumin OR serum albumin OR hypoalbuminemia AND prognosis OR survival OR outcome OR prognostic AND colorectal cancer OR colon cancer OR rectal cancer OR neoplasm

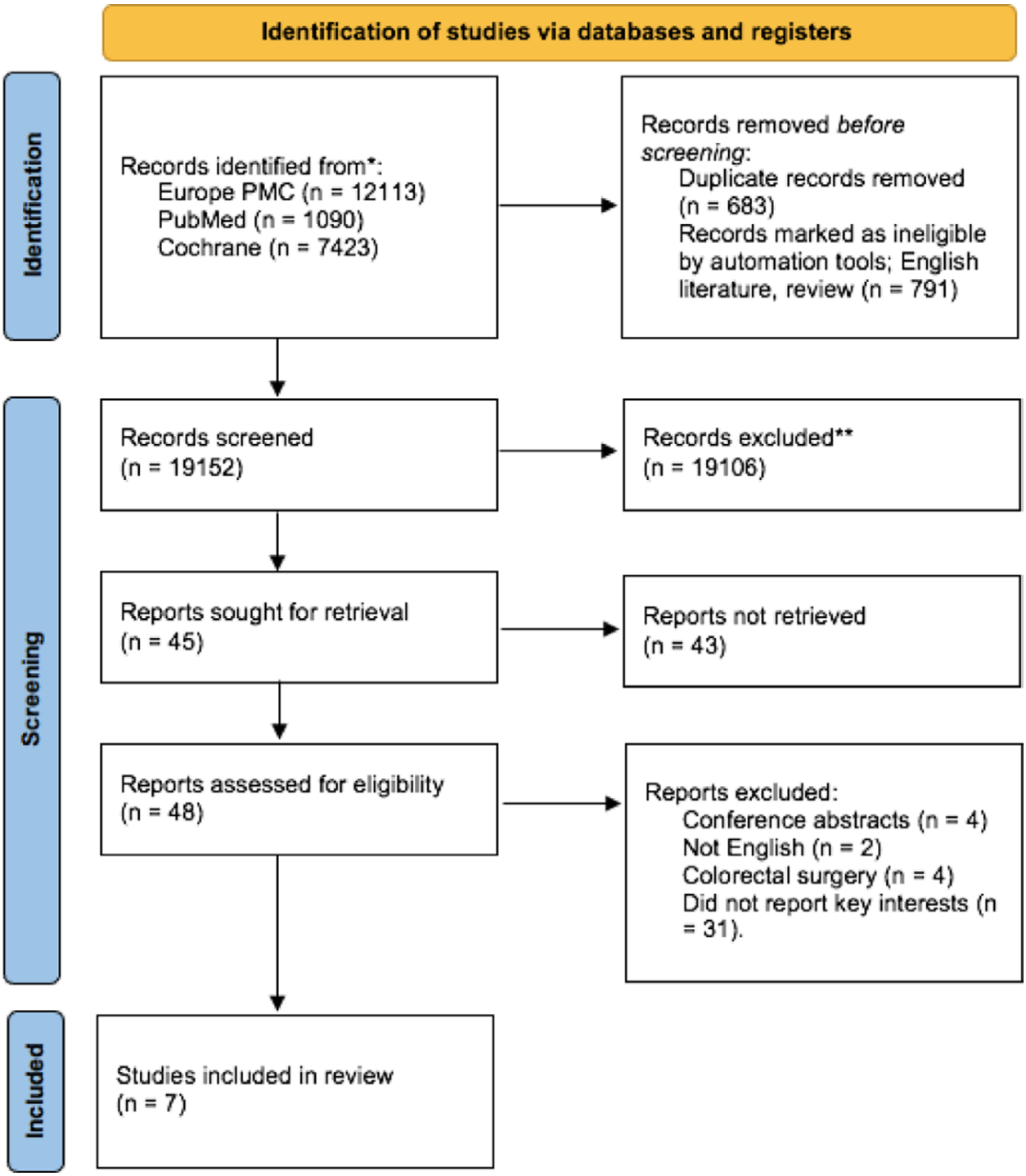

Figure 1. PRISMA flow diagram of current systematic review.

forest plot and funnel plot showing the correlation between hypoalbuminemia and mortality, morbidity, surgical complication, and length of stay were shown in Figures 2, 3, 4, and 5, respectively.

The inverted funnel plot demonstrated a qualitatively asymmetrical shape for mortality and surgical complication but not for morbidity and hospital stay duration. According to NOS, all studies were of good quality.

4. Discussions

Patients with cancer, including those with colon cancer, frequently struggle with malnutrition, which renders them helpless. Malnutrition in colon cancer patients can be brought on by increased metabolic rates brought on by the disease, decreased food intake, problems with hepatic protein synthesis, blood loss, etc.[19,20] Serum albumin level is frequently utilized, even though it cannot comprehensively represent the nutritional state of individuals.[20,21] It is commonly acknowledged that hypoalbuminemia is a reliable sign of malnutrition.[22] The current study showed that preoperative hypoalbuminemia was significantly associated with poor postoperative outcomes.

In several published studies, it has been discussed how comorbidities and hypoalbuminemia are correlated. Hospitalized patients with mild hypoalbuminemia (albumin 25–35 g/L) had

Table 2

Characteristics of each cohort from eligible studies (n = 236,460).

Study ID, NOS, country details	Age (yr, mean ± SD)	Male (n)	Tumor location (n)			Albumin level (mg/dL)	30-d mortality rate (n)		SSI		Sepsis		Thrombotic events (n)		Wound events (n)	
			Right	Left	Oth-ers		No	HA	No	HA	No	HA	No	HA	No	HA
Lai 2010, 7, China	62.5 ± 13.6	1968	1449	2283	-	-	17	28							57	33
Hu 2019, 7, US	66.2 ± 13.8	13,897	-	-	-	-	248	196	1713	543	715	245	474	253	259	85
Egenvall 2018, 8, Sweden	68.8 ± 10.9	229	121	80	180	-	-	-	-	-	-	-	-	-	-	-
González-Trejo 2017, 8, US	59.1 ± 14.9	782	96	203	1166	3.42 ± 0.59	-	-	-	-	-	-	-	-	-	-
Haskins 2017, 7, US	68 ± 2.7	2585	-	-	-	3.95 ± 0.51	35	19	-	-	127	36	63	17	381	89
Chiang 2015, 8, China	-	-	-	-	-	-										
Larson 2020, 7, US	-	40,278	-	-	-	-	711	310	780	7209	2882	503	1063	200	91	723

HA = hypoalbuminemia, No = normal, NOS = newcastle ottawa scale, SD = standard deviation, SSI = surgical site infection, US = United States.

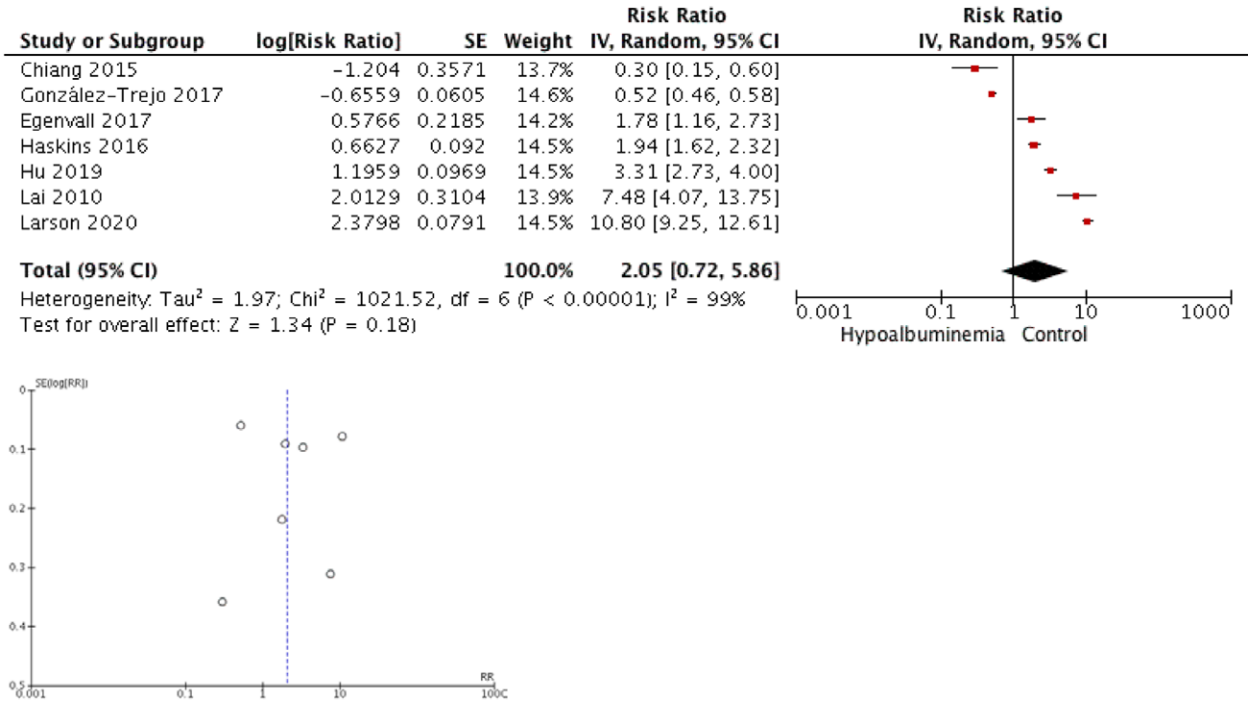

Figure 2. Meta-analysis showing correlation between hypoalbuminemia and mortality.

lower body mass indices, were older and had higher rates of hypertension, congestive heart failure, and chronic renal failure than patients with normal albumin levels.[23] Acute renal failure was strongly associated with severe hypoalbuminemia, which was found in 4% of chronic obstructive pulmonary disease patients.[24] In individuals with chronic heart failure, the prevalence of hypoalbuminemia ranged from 20% to 25% to 90% in frail, elderly patients with acute heart failure.[25] Here, we found that hypoalbuminemia was correlated with a wide range of comorbidities in patients with colorectal cancer. Early detection of malnutrition in individuals with multiple comorbidities is advised because even minor hypoalbuminemia carries a higher postoperative risk.

4.1. Key results and interpretation

There were some notable findings from the current study. Firstly, we wanted to stress that in the subset analysis of morbidity, we found that hypoalbuminemia is associated with thromboembolic events. Folsom et al[26] found that low serum albumin was a minor predictor of an elevated risk of venous thromboembolism. In the data from their 2 cohorts, the adjusted hazard ratio for albumin below the fifth percentile was 1.28 and 1.8. In colon and rectal surgery, deep vein thrombosis has been linked to hypoalbuminemia (serum albumin level 35 mg/L).[27] A comparable outcome in cancer patients was also seen. It is unclear how hypoalbuminemia and VTE

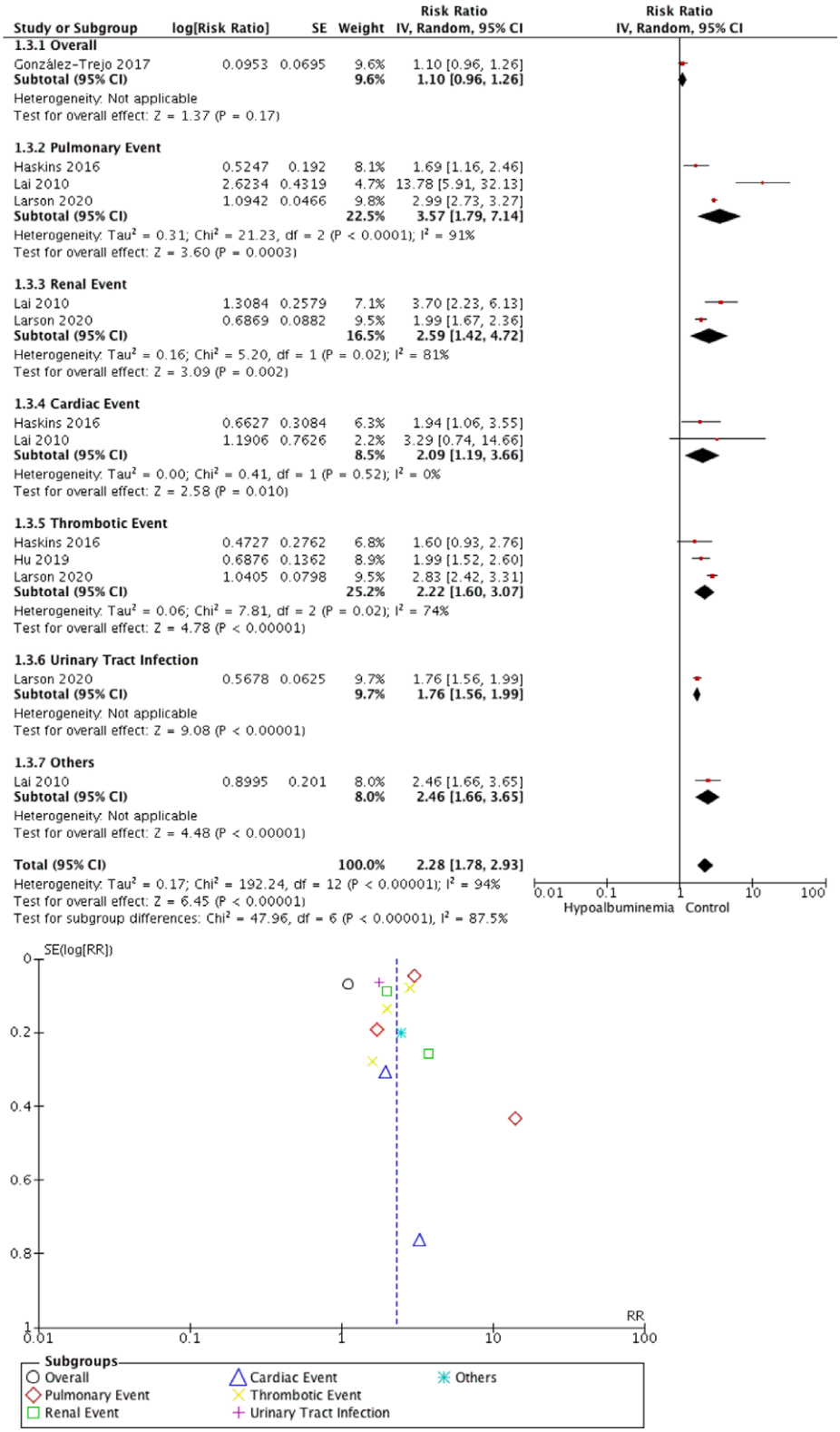

Figure 3. Meta-analysis showing correlation between hypoalbuminemia and morbidity.

are related, but hyperinflammatory or hypercoagulable conditions may cause them.

Preoperative hypoalbuminemia (serum albumin 30 g/L) was an independent predictor of the development of superficial and deep surgical site infections and an extended hospital stay after gastrointestinal surgery in a multi-institutional study.[28] Other operational methods also reported the associations.[29,30] According to the meta-analysis, a slight drop in serum albumin substantially impacted the length of the hospital stay, surgical site infection, and other comorbidities.[8,31] Low serum albumin was a good indicator of malnutrition, linked to slow infection and wound healing. Albumin has an immunomodulatory function, and hypoalbuminemia mice had abnormal macrophage activation and granuloma development.[32,33] A negative

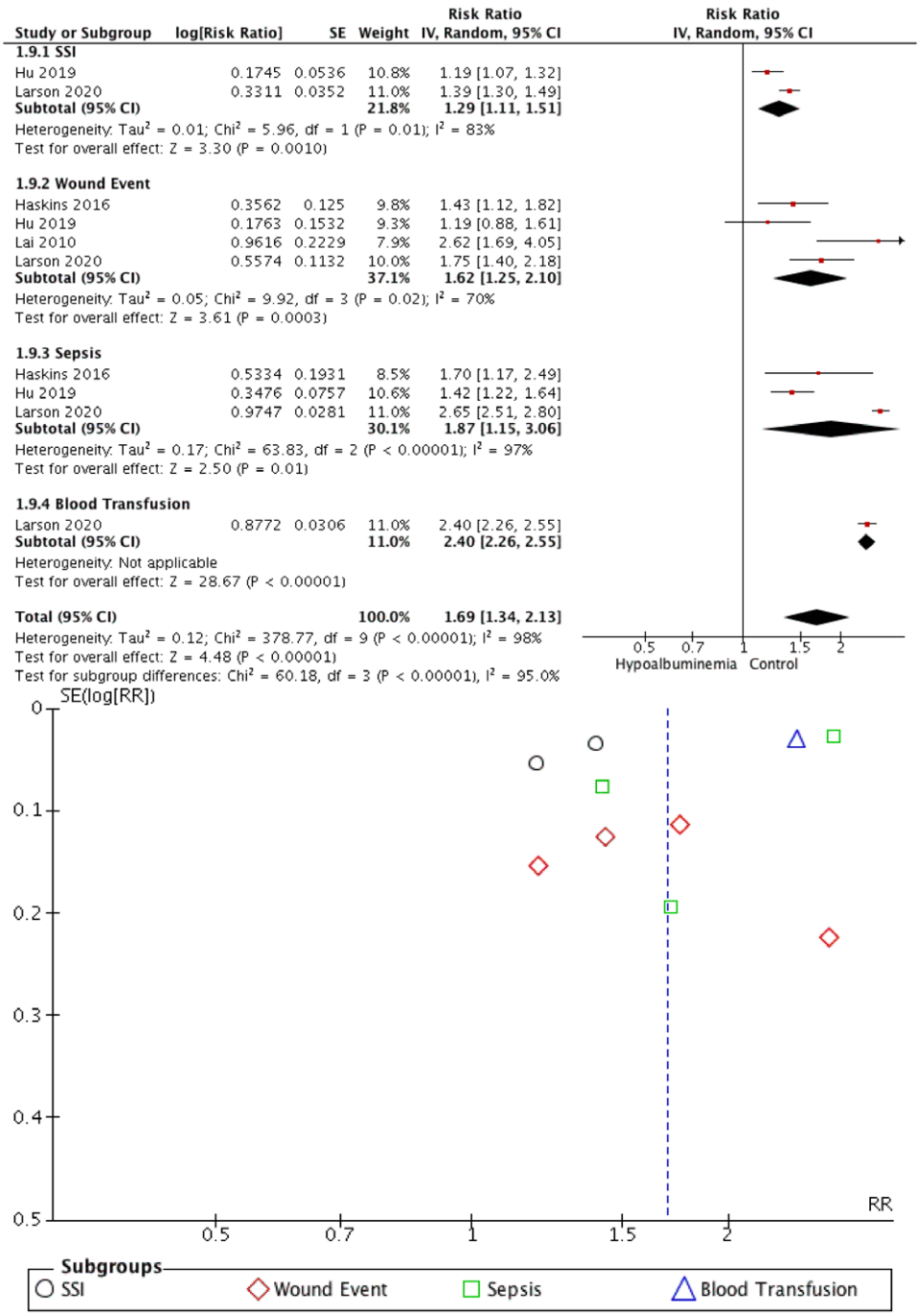

Figure 4. Meta-analysis showing correlation between hypoalbuminemia and surgical complication.

acute-phase protein during an inflammatory response to bacterial infection is serum albumin.

4.2. Implications in daily practice

Serum albumin is a negative acute-phase protein that expresses less and loses more when there is inflammation or when a person is underweight. Therefore, hypoalbuminemia in both acutely and chronically ill people is a sign of malnutrition.[34,35] According to several research, hypoalbuminemia doesn't become clinically important until levels lower than 25 g/L. The influence of preoperative hypoalbuminemia on subsequent colon cancer metastasis is unknown, though. As a result, we needed to conduct additional research.

4.3. Limitations

The potential for publication bias, as is illustrated by the asymmetrical funnel plot, is the limitation of this systematic review and meta-analysis. Most of this research used an observational, retrospective methodology. Last, the current systematic review and meta-analysis needed to match better. The present systematic review and meta-analysis included 8 studies, which is insufficient to conduct meta-regression. As a result, the outcome could be affected by several confounders.

5. Conclusions

The current systematic review and meta-analysis showed that preoperative hypoalbuminemia was significantly associated

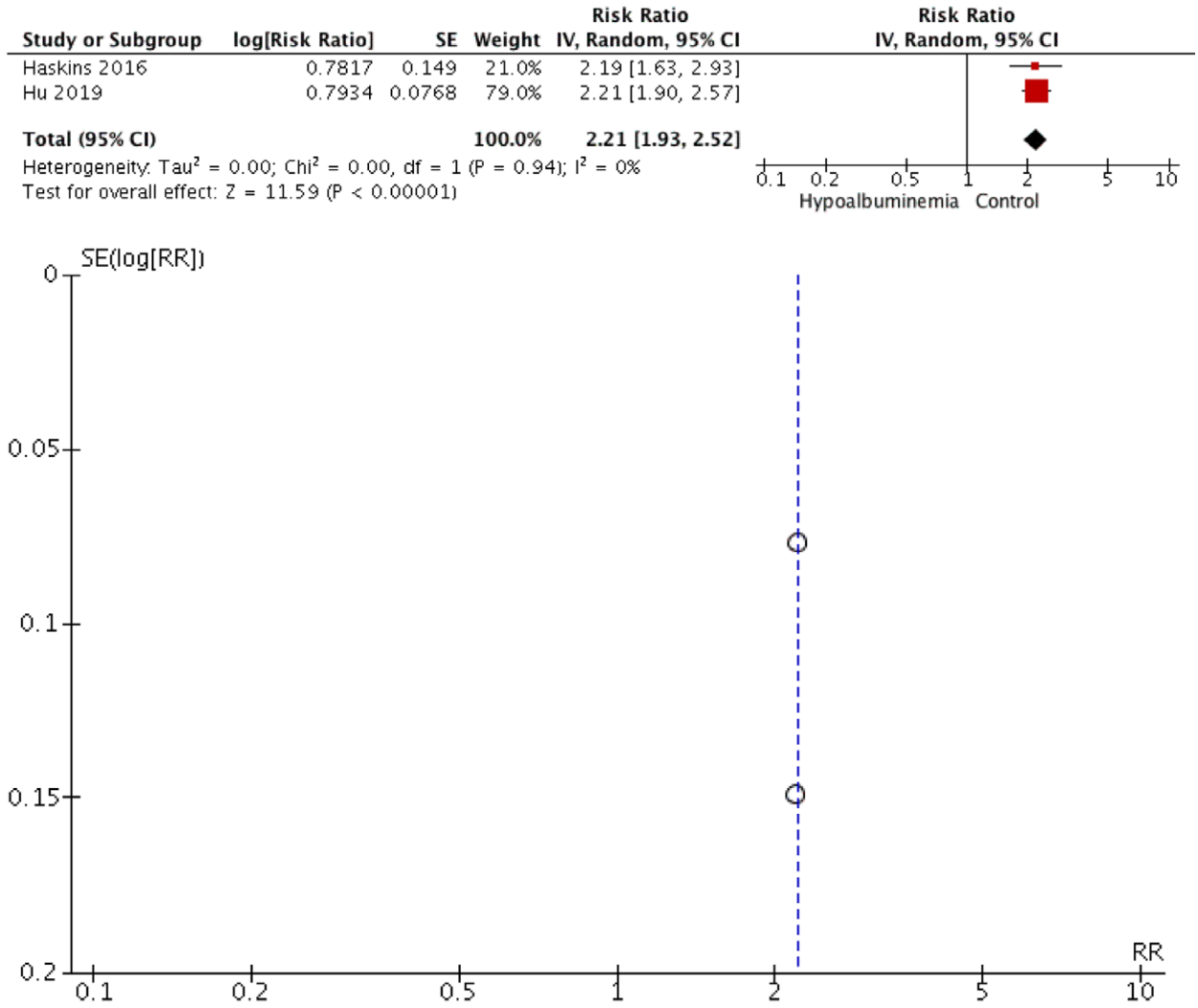

Figure 5. Meta-analysis showing correlation between hypoalbuminemia and length of stay.

with morbidity, length of stay, and surgical complication but not mortality. More studies still need to be conducted to see any possible confounding variables affecting hypoalbuminemia in predicting the outcome in patients with colorectal cancer.

Corrections

This article was originally published with incorrect affiliations for Teddy Tjahyanto, Jason Gunawan Lie, Daniel Octavianus, Johanes Andrew, Yusuf Damar Jatinugroho, and Christian Shiady. Their affiliations have been changed to Department of Medicine, Universitas Tarumanagara, Jakarta, Indonesia in the online version. These authors also originally had incorrect degrees listed. Their degrees have been changed from MD to BSc in the online version.

Author contribution

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