

# Association Between Hypoalbuminemia and Mortality in Critically Ill Non-Surgical Adult Patients: A Systematic Review and Meta-Analysis

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## Abstract

**Purpose:** The aim of this meta-analysis was to assess if hypoalbuminemia can predict mortality in critically ill non-surgical adult patients. **Methods:** We searched on Public Access to Medline (PubMed), Europe PubMed Central (Europe PMC) and ScienceDirect databases for relevant articles published from 1 January 2018 to 31 December 2024. We included observational studies of critically ill non-surgical adult patients in European hospitals. We performed the meta-analysis on Review Manager (RevMan Web by Cochrane

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Collaboration). The adjusted Odds Ratio (OR) for the association between hypoalbuminemia and mortality was extracted from included articles and pooled with 95% confidence intervals (CI). A random effect model was used. Sensitivity analysis was performed on RevMan. **Results:** We included a total of 9 observational studies with 6846 participants. Hypoalbuminemia was significantly associated with high mortality among critically ill non-surgical adult patients. The pooled OR was: 1.93 95% CI: 1.45, 2.56. Heterogeneity ( $I^2$ ) = 93%  $P < 0.00001$ . Sensitivity analysis showed that no study had an undue influence on the results of the study, as the effect size remained statistically significant to the exclusion of any study. **Conclusion:** The meta-analysis found that Hypoalbuminemia is a significant predictor of mortality for critically ill non-surgical adult patients. Our results may suggest that great attention should be paid for critically ill non-surgical adult patients with hypoalbuminemia to reduce the bad outcome. Health policies and procedures should include the albumin test for better outcomes.

## Keywords

Hypoalbuminemia, Mortality, Severe Non-Surgical Adult Patients, Meta-Analysis

## 1. Introduction

Albumin, the major serum protein, has multiple physiological functions including maintenance of colloidal osmotic pressure, binding of a wide variety of compounds, and provision of the bulk of plasma antioxidant activity. About 40% of albumin is intravascular. Albumin has a median half-life of approximately 18 to 19 days and is synthesized exclusively by the liver [1]-[4]. Albumin excretion in the urine is normally  $<20$  mg/day [5] [6]. Hypoalbuminemia is characterized by a decrease in serum albumin levels below 34 g/L [7] [8]. Three methods can be used in the laboratory to measure albuminemia. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) and immunoassays like enzyme-linked immunosorbent assay (ELISA) were determined to be a rigorous and suitable method to test for extreme albumin deficiency. There are also two dye-binding methods: bromocresol green (BCG) and bromocresol purple (BCP). The average difference between BCG methods and other methods is usually 0.5 - 0.6 g/dl. It is strongly recommended that authors in research studies disclose the type of methods used for future standardization of the cutoff between laboratory mean values for each age and sex groups [9] [10].

Hypoalbuminemia may result from an imbalance between albumin loss and albumin production [11]. An increase in albumin loss can occur in the gastrointestinal tract during protein-losing enteropathy, or in the kidneys during nephrotic syndrome, or by increased capillary permeability [12]. This increase in capillary permeability is due to biological mediators [7] produced in inflammatory pro-

cesses, which is a universal reaction related to trauma, serious illnesses, chronic diseases, life events, multiple or isolated organ failure, and cancer [12] [13]. Decreased production in the liver may result from liver failure such as in cases of liver cirrhosis [14]. Hypoalbuminemia can be seen in patients who are malnourished [15] or in patients with anorexia nervosa [12] [16]. In case of inflammation, the decrease in liver production of albumin is due to a prioritization of the production of pro-inflammatory mediators such as CRP [7]. The mass of serum albumin is also influenced by the half-life of serum albumin. This has been found in hypertension, acromegaly, nephrotic syndrome, and protein-losing enteropathy [12] [17]-[21]. Finally, an increase in albumin catabolism may also progress to hypoalbuminemia, which may occur in critically ill patients [22]. Socio demographic factors and life style influences the level of serum albumin and cause hypoalbuminemia, including age, smoking, a low-salt diet, being on social support, having fair or poor teeth or edentulism, and being a critically ill hospitalized patient. Hypoalbuminemia and lower serum albumin were independently associated with two or more limitations in activities of daily living and residence in a nursing home [23]-[29].

An observational retrospective study was carried out to analyze changes in albumin levels in hospitalized patients and found that, at the time of admission, hypoalbuminemia was present in more than half of the sample, with no sex differences. The serum albumin level decreases with age, with chronic conditions such as kidney disease, hypertension; appearing from 50 years and progressive worsening thereafter. Mild hypoalbuminemia was more prevalent in patients over 65 years of age. Hypoalbuminemia should be considered a dangerous condition in itself and a serious public health problem. Serum albumin levels are strongly associated with the morbidity, prognosis, and mortality rates of patients with hypoalbuminemia, which is a frequent problem during hospitalization [30]-[32]. Several studies had concluded that serum albumin is a good predictor of mortality in acutely ill medical patients [33]-[39].

In their meta-analysis, Christian J Wiedermann and coworkers had set out that they had found an association between hypoalbuminemia and development of acute kidney injury (AKI), and subsequent morbidity/mortality. This robust association is consistently evident in a wealth of observational studies conducted across a wide range of clinical settings and involving tens of thousands of patients, and may be interpreted as an indication of a causal link [40]. But it remains uncertain whether the effect of hypoalbuminemia on outcome is a cause-effect relationship or whether hypoalbuminemia is rather a marker of serious disease [41].

Our study published in 2015 based on data collected in a European ICU had highlighted the low predictive value of serum albumin on ICU mortality, which was even lower when albumin solutions were infused [42]. The result of this study raises the question of what would happen to a larger sample of patients with the most identical characteristics possible in this European ICU? Or what is the predictive value of hypoalbuminemia on mortality in severe patients? In such a study,



“hypoalbuminemia and mortality”. Grey literatures were explored and some relevant authors have been contacted. The search results were exported to EndNote, and after being pooled, they were deduplicated and screened by title and abstract. We used the PICO (Patient, Intervention, Comparison, Outcome) to improve search strategy [47]-[49].

Relevant articles were selected and download and their full texts submitted to the inclusion criteria. Inclusion factors are presented in **Table 2**. For studies carried out in the same center, we consider the one that has more patients and that has relevant outcomes.

### 2.1. Data Collection Process

The following variables has been extracted from individual articles by the two reviewers: article author name, year of publication, countries, participants characteristics (quantity and quality), level of albuminemia (independent variable), characteristics of patients, survivors versus non survivors, age, sex ratio or gender of patients, comorbidities, length of stay in the ICU and mortality (outcome or dependent variable). Adjusted Odds ratio (aOR) are the estimates of effects sizes that have been extracted from individual articles.

A first reviewer fills in an excel file with data extracted from the articles, a second reviewer reviews the procedure and confirms data and discrepancies have been sorted out by the third reviewer.

The Newcastle Ottawa Scale (NOS) was used to assess quality and the risk of bias of included studies. This scale includes 3 assessment domains. The maximum score is between 0 and 9. The NOS  $\geq$  score 6 is considered high-quality literature [50].

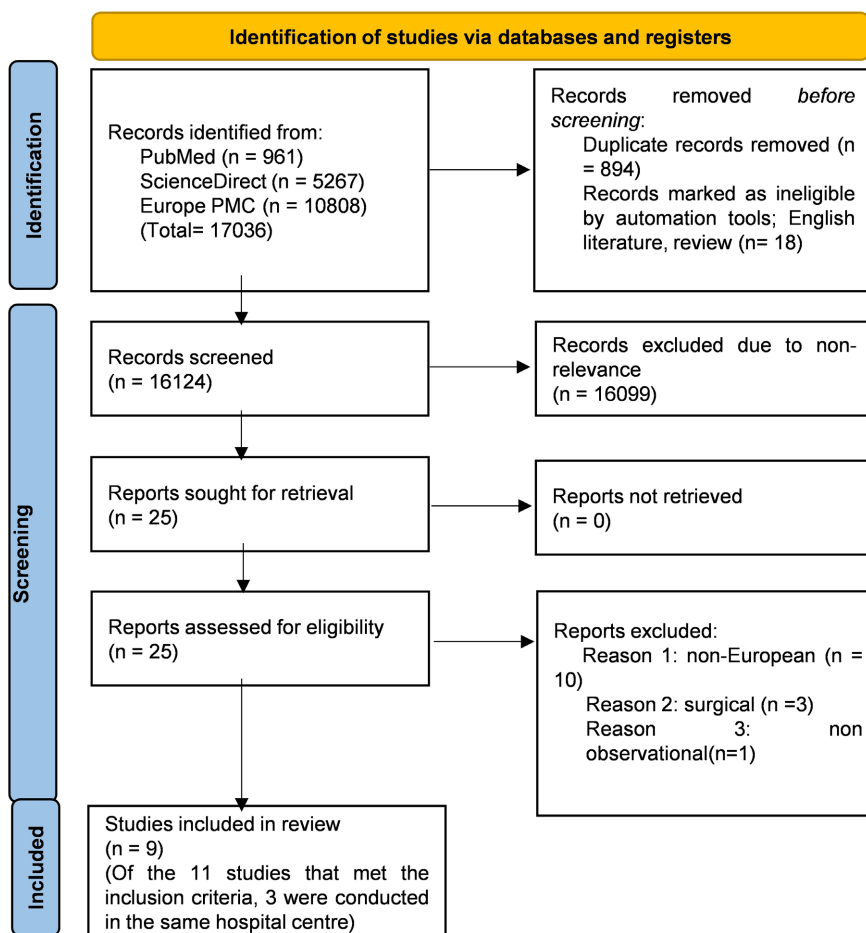
### 2.2. Statistical Analysis

We performed the meta-analysis on Review Manager (RevMan Web by Cochrane Collaboration) [51]-[56]. The aOR extracted from included studies were used to calculate pooled OR with 95% confidence intervals (CI). We used random-effects model. Inter-study heterogeneity was assessed by the  $I^2$  statistic.  $I^2 = 0\% - 40\%$  meant limited,  $40\% - 60\%$  meant moderate,  $60\% - 80\%$  meant substantial and  $80\% - 100\%$  meant considerable heterogeneity. Forest Plot has been performed to explore and to synthesize outcome. Due to the limited number of included studies ( $n = 9$ ), we did not perform a funnel plot or formal asymmetry tests. According to methodological recommendations, such analyzes are not reliable with a small number of studies and may lead to misleading interpretations of publication bias [57]. Sensitivity analysis was performed to examine the influence of each study on the review results. Each article was removed one by one and the pooled effect was recalculated for the remaining articles. All authors have read and agree to the manuscript as written.

## 3. Results

The outcomes of the selection process are presented in **Figure 1**. Out of the 17036 articles collected in the databases, 16124 were screened. Of the 16124 screened and

16099 were excluded for non-relevance. Twenty-five articles were downloaded and their full-texts were analyzed. Eleven fulfilled the inclusion criteria. Among them, 3 were from the same center and we retained the one with a large number of patients. So, nine studies were included in the review.



**Figure 1.** PRISMA flow chart for the association between hypoalbuminemia and mortality in Europe.

The characteristics of the included studies are presented in **Table 3**. All studies were observational cohort studies. All studies were published between 2018 and 2024. All studies had a NOS between 7 and 9. Those made in the countries of the European Union have a New Castle Ottawa Scale (NOS > 7) greater than those made in countries outside the European Union (NOS = 7). The total number of patients is 6846. All patients are non-surgical and treated in European hospitals. The mean age of included patients was more than 59 years. Male gender ranged from 46% to 74% of all patients in all included studies.

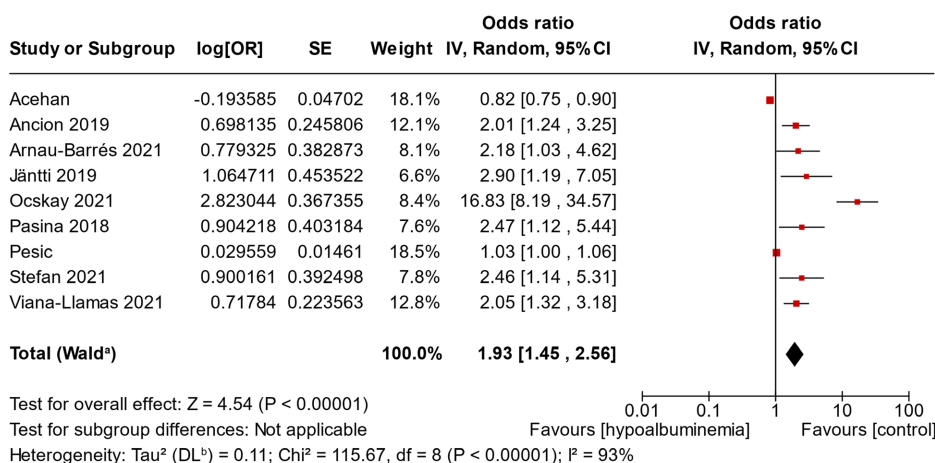
For the meta-analysis, here is the clinical setting of the included studies: acute cholangitis [58], acute heart failure [59], COVID-19 [60], cardiogenic shock [61], acute pancreatitis [62], non-oncologic elderly in-patients with multi-morbidities, receiving multiple drugs [63], acute kidney injury [64], COVID-19 [65], COVID-19 [66].

One study reported an adjusted hazard ratio (aHR), the authors contacted gave the value of the aOR [65]. Two studies did not specify whether there was adjustment for OR and the authors contacted did not respond [58] [64].

**Table 3.** Overview of included studies and synthesis table illustrating key characteristics of studies, outcomes and analysis methods, sorted alphabetically.

Studies	NOS	Number of patients	Data collection country	Age, yrs: mean ± SD or median (IQR)	Sex: M	Clinical Setting	Design	Analysis	Collection period	Odds Ratio
1 Acehan 2023 [58]	7	309	Turkey	77.2 ± 8	0.482	Acute cholangitis	RCS	LRA	02/2019-08/2022	OR (0.751 - 0.903)
2 Ancion 2019 [59]	9	509	Belgium	72 ± 12	0.58	Acute heart failure	RCSCS	MRA	2010-2012	aOR (1.24 - 3.25)
3 Arnau-Barrés 2021 [60]	9	405	Spain	79 ± 8.6	0.46	Elders with Covid	RCSCS	MRA	03/20-05/20	aOR (1.03 - 4.62)
4 Jäntti 2019 [61]	9	178	Finland	66 ± 12	0.74	Cardiogenic shock	PCMCS	MRA	2010-2012	aOR (1.2 - 7.1)
5 Ocskay 2021 [62]	8	2461	Hungary	59.7 ± 18.0	0.57	Acute pancreatitis	PCMCS	MRA	31/12/19-	aOR (8.323 - 35.129)
6 Pasina 2018 [63]	9	2058	Italia	79.1 ± 7.6	0.468	Elders non-oncologic with multi morbidities	PCMCS	LRA	2008-2016	aOR (1.12 - 5.44)
7 Pesic 2022 [64]	7	280	Serbia	67.8 ± 13.8	0.504	Acute kidney injury	RCSCS	BLRA	2017-2022	OR (1.001 - 1.060)
8 Stefan 2021 [65]	9	37	Romania	64 (55 - 71)	0.51	Hemodialysis for COVID-19	RCSCS	MRA	24/03/20-22/05/20	aHR (1.14 - 5.31)
9 Viana-Llamas 2021 [66]	9	609	Spain	71 (58 - 82)	0.603	COVID-19	RCSCS	MRA	03/20-05/20	aOR (1.323 - 3.178)

RCS, retrospective cohort study; RCSCS, retrospective cohort single-center study; PCMCS, prospective, cohort, multi-center study; MRA, multivariate regression analysis; LRA, logistic regression analysis; BLRA, binary logistic regression, NOS, New Castle Ottawa Scale.



**Footnotes**

<sup>a</sup>CI calculated by Wald-type method.  
<sup>b</sup>Tau<sup>2</sup> calculated by DerSimonian and Laird method.

**Figure 2.** Meta-analysis (forest plot) of the association between hypoalbuminemia and mortality in critically ill non-surgical adult patients in Europe.

**Figure 2** shows that hypoalbuminemia was significantly associated with an increased mortality among critically ill non-surgical adult patients. OR = 1.93 95% CI: 1.45, 2.56  $I^2 = 93\%$   $P < 0.00001$  (**Figure 2**).

The results of the sensitivity analysis are shown in **Table 4**. No study showed undue influence on the study results, as the effect size remained statistically significant after exclusion of any study.

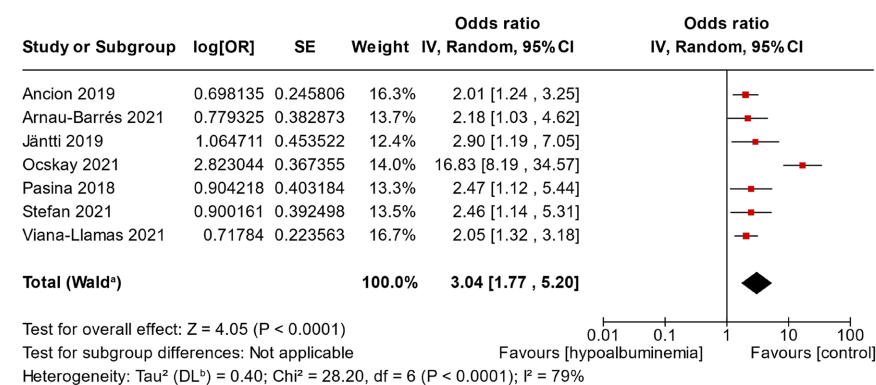
**Table 4.** Sensibility analysis.

Excluded study	Odds ratio
Acehan, F., <i>et al.</i> (2023) [54]	2.61 95% CI: 1.44, 4.73 $I^2 = 92\%$ $P = 0.002$
Ancion, A., <i>et al.</i> (2019) [55]	1.91 95% CI: 1.42, 2.58 $I^2 = 94\%$ $P < 0.0001$
Arnau-Barrés, I., <i>et al.</i> (2021) [56]	1.90 95% CI: 1.42, 2.56 $I^2 = 94\%$ $P < 0.0001$
Jäntti, T., <i>et al.</i> (2019) [57]	1.87 95% CI: 1.40, 2.49 $I^2 = 94\%$ $P < 0.0001$
Ocskay, K., <i>et al.</i> (2021) [58]	1.44 95% CI: 1.15, 1.81 $I^2 = 88\%$ $P = 0.002$
Pasina, L., <i>et al.</i> (2018) [59]	1.88 95% CI: 1.41, 2.53 $I^2 = 94\%$ $P < 0.0001$
Pesic, S., <i>et al.</i> (2022) [60]	2.55 95% CI: 1.29, 5.02 $I^2 = 94\%$ $P = 0.007$
Stefan, G., <i>et al.</i> (2021) [61]	1.88 95% CI: 1.41, 2.52 $I^2 = 94\%$ $P < 0.0001$
Viana-Llamas, M., <i>et al.</i> (2021) [62]	1.90 95% CI: 1.41, 2.56 $I^2 = 93\%$ $P < 0.0001$

**Table 5.** Meta-regression findings.

Variable	OR (95% CI)	P-value
Age, per year,	0.93 (0.86, 1.00)	0.056
COVID-19	1.18 (0.13, 11.0)	0.89
Study year	0.97 (0.88, 1.06)	0.478
GI-related	1.68 (0.15, 19.3)	
Other	0.77 (0.07, 8.82)	

GI = gastro-intestinal.

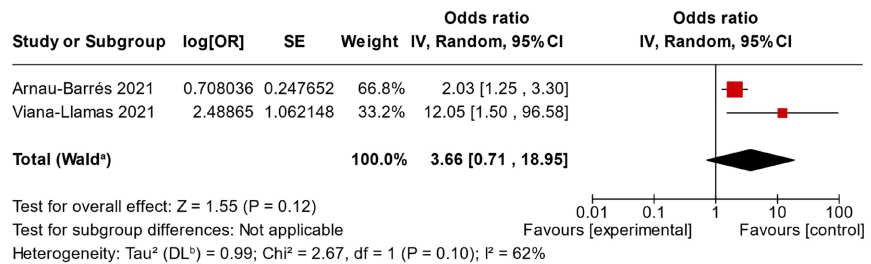


**Footnotes**

<sup>a</sup>CI calculated by Wald-type method.

<sup>b</sup> $Tau^2$  calculated by DerSimonian and Laird method.

(a)



**Footnotes**

<sup>a</sup>CI calculated by Wald-type method.  
<sup>b</sup>Tau<sup>2</sup> calculated by DerSimonian and Laird method.

(b)

**Figure 3.** Subgroups analysis. (a) Meta-analysis of the association between hypoalbuminemia and mortality in critically ill non-surgical adult patients in countries of European Union; (b) Association between C Reactive Protein and mortality in critically ill non-surgical adult patients in countries of European Union.

Results of the meta-regression analysis are presented in **Table 5**. We noted that variables age, COVID-19 and study years had no statically significant influence on the effect size.

The subgroup analysis is presented in **Figure 3**.

**Figure 3(a)** shows that hypoalbuminemia was significantly associated with an increased mortality among critically ill non-surgical adult patients in studies carried out in the countries of the European Union. OR = 3.04 95% CI: 1.77, 5.20 I<sup>2</sup> = 79% P < 0.0001. **Figure 3(b)** shows that CRP does not significantly influence mortality (P = 0.12).

## 4. Discussion

### 4.1. Key Results and Interpretation

In our meta-analysis, hypoalbuminemia was significantly associated with an increased mortality. Pooled adjusted OR of 1.93 reveals that hypoalbuminemia is associated with a 93% increased risk of mortality among critically ill non-surgical adult patients. Other studies before us have also found an association between hypoalbuminemia and high mortality for specific patient types. This is the case of the studies carried out by Bonilla-Palomas for heart failure patients [67]. and Watanabe for patients with Takotsubo syndrome [68]. As well as the meta-analyses carried out by Wang X. *et al.* in 2023 for patients undergoing continuous renal replacement therapy [69] and Peng W. *et al.* in 2019 for patients with heart failure [70]. In our meta-analysis, we pooled the adjusted OR to reduce the effect of confounding factors on the overall result, and thus constitute a direct relationship between hypoalbuminemia and mortality, this to reduce the effect of other upstream factors such as inflammation and malnutrition. This direct association between hypoalbuminemia and high mortality is favorable for a positive effect of an albumin infusion replacement treatment. This is what J.L. Vincent stipulates in relation to the controversy over the direct contribution of hypoalbuminemia on poor outcomes, in which case albumin replacement therapy might bestow ben-

efit, or merely serves as a marker for other “upstream” pathologic processes such as malnutrition or inflammation, in which case exogenous albumin might be ineffective in altering the clinical course of the patient [7]. This association between hypoalbuminemia and high mortality would be due to the fact that serum albumin has several functions in the body and its decrease leads to deleterious consequences [1]. While malnutrition and inflammation are important confounding factors in the deleterious effects of hypoalbuminemia, Vincent JL *et al.* had found that poor outcome in case of hypoalbuminemia persisted after adjustment for body mass index and other measures of nutritional status. They found also that the effects of hypoalbuminemia on outcome to be independent of CRP, as well as other markers of inflammation [7]. Such observations make plain that inflammation, at least as manifested by altered levels of currently identified inflammatory markers, may contribute to reduced serum albumin levels but nevertheless cannot fully account for the association between hypoalbuminemia and poor outcome. To prevent hypoalbuminemia from being just an epiphenomenon, we took into account the confounding factors that could influence mortality. For this reason, we first excluded all surgical patients from our meta-analysis. Indeed, as said in the introduction, a trauma in general, or during surgery in particular, there is a release of inflammatory mediators including CRP leading to an increase in capillary permeability with the passage of albumin from the intravascular environment to the interstitial environment leading to hypoalbuminemia. Surgery also directly influences mortality. We did a meta-regression in which we analyzed a limited number of variables due to the scarcity of reporting of basic variables such as mean albumin levels at admission, patient BMI, etc., as well as the limited number of studies. Meta-regression did not show an association between age, genre male, study year, COVID-19 and outcome. Even after accounting for certain variables in the model, heterogeneity remains present. The considerable heterogeneity could be attributed to the difference in variables between the 9 studies as well as to within-study sampling variability. In addition to meta-regression, we investigated heterogeneity by subgroup analysis which revealed that hypoalbuminemia is associated with high mortality in the subgroup of European Union countries and that heterogeneity is substantial as it was considerable for the meta-analysis on the 9 studies. This may be due to the fact that the countries of the European Union have similar health laws, particularly in the prescription and use of albumin as an infusion. Pooling of the OR of the association between CRP and mortality for the subgroup of studies for which CRP data were available (1014 COVID-19 patients) revealed that CRP does not influence the outcome (mortality). The meta-regression shows, like the subgroup analysis, that COVID-19 (=infectious and inflammatory disease) does not influence mortality. In the study by Jäntti and coworkers, although hypoalbuminemia was associated with high CRP, the association between hypoalbuminemia and mortality was adjusted for CRP. In the Ocskay study, an increase in dose-dependent C-reactive protein (CRP) ( $P < 0.001$ ) and procalcitonin (PCT) ( $P < 0.001$ ) was observed in the lower albumin groups. However, this is explained physiologically by the high CRP which increases the

permeability of the vascular limb with albumin leakage from the intravascular environment, as well as an effect of CRP on the liver stimulating it to prioritize the production of inflammatory cytokines to the detriment of albumin. Ancon and coworkers excluded from their study patients who had a C-reactive protein > 10 mg/L. Thus, in their study, mortality had not been influenced by infectious and inflammatory diseases. In Stefan's study, the association between CRP and mortality was not statistically significant ( $P = 0.1$ ). From the above, we can therefore see that the inflammation quantified by CRP in the different studies included in our meta-analysis does not influence the outcome (mortality). Unfortunately, little anthropometric data could be collected from the studies included in our meta-analysis due to their unavailability: only one had obesity as a covariate, 2 provided the BMI of the patients enrolled in their study, and BMI was adjusted in the study by Jäntti and coworkers. This is insufficient for the purposes of the analysis. Although in our meta-analysis CRP does not influence mortality, other studies have shown that several daily doses of CRP taken over several days allow the monitoring of the severity of acute patients.

#### **4.2. Implications in Daily Practice**

Our results may suggest that non-surgical adult patients with low albumin levels should be prioritized and treated to reduce adverse outcomes. The dosage of serum albumin during hospitalization is a routine practice and an easy-to-access process. Albumin can be considered as a low-cost marker to stratify patients by risk during hospitalization [31]. A good prognostic value of albuminemia could be used in disadvantaged settings for the follow-up of non-surgical critically ill ICU patients, since the dosage of serum albumin is less expensive. And even in the most developed and wealthy health facilities, studies carried out in different types of severe adult patients have demonstrated the clinical interest of taking into account hypoalbuminemia. In some cases, its underlying cause may require treatment but mostly it is just a parameter to be monitored and used as one measure of clinical progress or deterioration [71]. The strength of the study is that the 9 studies have been published in the last 5 years, which brings contemporary evidence. We worked on the adjusted OR to avoid the influence of confounding factors on the outcome. We excluded from our meta-analysis major confounders, such as surgery. One of the 9 studies excluded infectious/inflammatory patients [59] and another excluded oncology patients [63].

#### **4.3. Limitations**

We have performed a meta-analysis of observational studies to establish whether or not hypoalbuminemia is a risk factor for mortality among critically ill non-surgical adult patients. However, we did not correlate the period of onset of this hypoalbuminemia with mortality, depending on whether albuminemia was measured at admission or during hospitalization. The dose-response correlation between level of hypoalbuminemia and mortality has also not been established. We agree that performing dose-response analysis to explore the relationship between

the severity of hypoalbuminemia and the risk of mortality could provide meaningful insights to inform clinical decision-making. Unfortunately, the data we have on hand does not contain sufficient information to perform this analysis robustly. Nor can we say that correcting hypoalbuminemia with an albumin infusion will improve the outcome of this type of patient, this conclusion would require a meta-analysis of the outcome of controlled trials evaluating the effects of hypoalbuminemia correction on morbidity. Nine studies included in the meta-analysis are observational studies with the disadvantages of precision compared to clinical trials. Several variables may influence the association between hypoalbuminemia and mortality. We reduced this bias by constituting the pool of adjusted OR in our meta-analysis but we cannot exclude the possibility of the existence of ignored or unknown unadjusted confounding factors. Some authors contacted to give the OR value for the association between hypoalbuminemia and mortality did not respond.

#### 4.4. Future

In the future, it would be necessary to explore the effects of alternative solutions in reducing the influence of hypoalbuminemia on mortality. It would also be interesting to analyze the results of controlled trials evaluating the effects of correcting hypoalbuminemia by alternatives on morbidity. Our current meta-analysis did not take account hospital structures restricting the therapeutic use of albumin infusion. We therefore recommend in future a multicenter cohort study involving many more patients in countries not using albumin infusion for the normalization of albuminemia in cases of hypoalbuminemia.

#### 5. Conclusion

The current meta-analysis found that hypoalbuminemia is an important predictor of mortality in critically ill non-surgical adult patients. These results may suggest that critically ill non-surgical adult patients with hypoalbuminemia should be treated first to reduce adverse effects. Given the limited number of studies conducted in our meta-analysis, we recommend that in the future a meta-analysis be performed to analyze many more cohort studies and patients than ours.

#### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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