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Efficacy of blood urea nitrogen-to-albumin ratio for predicting prognostic outcomes of inpatients with COVID-19

A meta-analysis

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Abstract

Background: The associations between blood urea nitrogen (BUN)/albumin ratio and poor prognosis in patients with diagnosis of coronavirus disease 2019 (COVID-19) remain to be clarified.

Methods: A search based on 4 electronic databases (i.e., EMBASE, Google scholar, MEDLINE, and Cochrane Library) was performed on June 23, 2022. The association of BUN/Albumin ratio with poor prognostic outcomes, defined as patients with mortality/severe illnesses, were analyzed.

Results: Results from analysis of 7 cohort studies (3600 individuals with COVID-19) published between 2020 and 2022 showed a higher BUN/Albumin ratio in the poor-prognosis group (Mean difference: = 2.838, 95% confidence interval: 2.015–3.66, $P < .001$, $I^2 = 92.5\%$) than the good-prognosis group. Additional investigation into the connection between BUN/Albumin ratio as a binary variable (i.e., high or low) and the risk of poor outcome also supported an association between a higher BUN/Albumin ratio and a poor prognostic risk (odd ratio = 3.009, 95% confidence interval: 1.565–5.783, $P = .001$, $I^2 = 93.7\%$, 5 studies). Merged analysis of poor prognosis produced a sensitivity of 0.76, specificity of 0.72, and area under curve of 0.81.

Conclusion: This meta-analysis demonstrated a positive correlation between BUN/albumin ratio and poor outcome in patients with COVID-19. Additional large-scale prospective studies are needed to verify our findings.

Abbreviations: AUC = area under curve, BUN = blood urea nitrogen, CI = confidence interval, COVID-19 = coronavirus disease 2019, OR = odds ratio, sROC = summary receiver operating characteristic.

Keywords: blood urea nitrogen/albumin ratio, coronavirus disease 2019, laboratory, mortality, prognosis

1. Introduction

The coronavirus disease 2019 (COVID-19) outbreak is an unprecedented global event that has not only claimed millions of lives but also imposed tremendous burdens on healthcare systems worldwide.[1] Notwithstanding the mild symptoms in some who contracted the disease, others may develop into fulminant illness such as acute respiratory distress syndrome and require intensive care.[2,3] Besides, multiple organ failure is not uncommon and the overall mortality of COVID-19 is still around 5% among those diagnosed with the disease.[4,5] In addition to well-known risk factors for disease progression such as male gender, advanced age, and comorbidities,[4–6] the use of a biomarker as an early predictor of prognosis has also been widely investigated.[7–10]

Blood urea nitrogen (BUN), which serves as an indicator of renal function, has a normal range of 6 to 20 mg/dL.

K-CH, Y-YL, F-SC, and C-KS contributed equally to this work.

The authors have no conflicts of interest to disclose.

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

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The manuscript is a systematic review and meta-analysis and as such data study reporting on published material. Therefore, no Ethics approval is required.

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While an increase in BUN is usually associated with high-protein diet, hypovolemia, gastrointestinal hemorrhage, increased catabolism, and a reduction in glomerular filtration rate, its concentration may decrease in individuals with syndrome of inappropriate antidiuretic hormone, severe liver disease, as well as those in an anabolic state.[11,12] Albumin, which is the most abundant (i.e., over 50%) plasma protein synthesized by hepatocytes, has a normal concentration between 3.5 g/dL and 5 g/dL. In addition to its role as a major modulator of plasma oncotic pressure, it acts as a transporter of endogenous (e.g., metabolites) and exogenous (i.e., drugs) ligands.[13] In clinical practice, its concentration is widely used to reflect an individual nutritional status.[13,14]

Instead of relying on a single marker, previous studies have demonstrated a superior accuracy of using a combination of different indices in prediction of prognosis for patients contracting COVID.[15,16] The results of a previous meta-analysis on 4659 patients diagnosed with COVID-19 showed that nonsurvivors had significantly lower albumin and higher BUN levels, suggesting their potential use as a combined predictor of mortality in this patient population.[17] In fact, BUN/albumin ratio has been previously reported to be a predictor of poor prognosis and mortality in patients with community-acquired pneumonia.[18,19] Recently, several studies have also identified BUN/albumin ratio as an indicator for prognostic outcomes in patients with COVID-19.[20–22] Nevertheless, its efficacy for predicting in-hospital mortality based on ROC analysis varied in different observational studies with a reported area under the curve (AUC) ranging from 0.733 to 0.809.[20,23] Together with the limitation of being single-center studies in previous reports, the level of evidence supporting its clinical predictive value remains controversial. Therefore, through reviewing currently available published data, the current systematic review and meta-analysis attempted to generate pooled evidence to test the validity of its use in prediction of disease severity and mortality among adult patients with COVID-19.

2. Materials and methods

In the current meta-analysis, we followed the preferred reporting items for systematic reviews and meta-analyses guidelines when we conducted the research (CRD42022341673). Study screening, data collection, and risk of bias evaluation were independently conducted by 2 reviewers. The disagreements were all resolved through a process of discussion. The study protocol and procedures for current study have also been described in our previous reports.[24,25] This study is a meta-analysis of data based on published reports. Therefore, no ethical approval was required.

2.1. Data sources and searches

Using relevant keywords and MeSH terms, we focused on observational studies reporting the relationship between the prognostic outcomes and BUN/albumin ratio in adults with a confirmed diagnosis of COVID-19 from the following electronic databases on June 23, 2022: Medline, Cochrane Library, and Embase. In addition, search was performed manually on the Google scholar website for retrieving other relevant studies. The keywords used are shown below: ("severe acute respiratory syndrome" or "coronavirus 2" or "coronavirus" or "corona virus" or "covid-19" or "nCoV" or "2019nCoV" or "Wuhan virus" or "2019-nCoV" or "SARS-CoV-2 Infection*") and ("blood urea nitrogen/albumin ratio" or "blood urea nitrogen-to-albumin ratio" or "blood urea nitrogen to serum albumin ratio" or "BUN to albumin" or "BUN/albumin"). To maximize the scope of our search, no restriction was applied on language, number of patients, publication year, and location. Moreover, we scrutinized the details of the relevant studies and meta-analyses for further identifying potentially qualified reports.

2.2. Study selection and data collection

Observational studies were collected if they met the following criteria: Original reports adopting case control, cross-sectional, and cohort designs; Available BUN/albumin ratio at hospital admission; Individuals who were admitted to hospital because of COVID-19 infection; Investigation of the association of BUN/albumin ratio with mortality or disease severity or, and; Reports which provide information regarding BUN/albumin ratio, odds ratio (OR), sensitivity and specificity. We excluded studies that were review, case series, case report, letter to editor, and duplicated article as well as those that were conducted in the pediatric population or only in outpatients.

2.3. Data extraction

Two authors independently extracted the following details from the included studies: first author/publication year, type of publication, patient characteristics (e.g., age), country, total sample size, number of individuals in poor- and good-prognosis groups, BUN/albumin ratio, sensitivity/specificity. Differences in opinions between the 2 researchers were settled through consensus or discussion involving a third author. We sought to fill missing information in our included articles by contacting their authors.

2.4. Study outcomes and definitions

For the current study, all patients were divided into either the poor- or good-prognosis groups. The former referred to those with poor prognostic outcomes (i.e., mortality or severe disease), while the latter was defined as those without poor prognostic outcomes. Two approaches were applied to the investigation of the relationship between BUN/albumin ratio and prognostic outcomes. First, the baseline BUN/albumin ratio was assessed between the poor- and good-prognosis groups; second, the association of BUN/albumin ratio with the poor prognosis risk was assessed with the BUN/albumin ratio being a binary variable (i.e., high vs low). Our primary outcome aimed at investigating the mean difference in BUN/albumin ratio between patients with poor and good prognosis. For secondary outcomes, we included the risk of poor prognostic outcomes in COVID-19 patients with low and high BUN/albumin ratio as well as the efficacy of BUN/albumin ratio in prediction of outcomes. The classification of disease severity was according to that reported in each study. Examination into the correlations of other predictors (e.g., age and serum markers) with COVID-19 prognosis were not performed because of the limited number of available studies.

2.5. Assessment of quality of the included studies

The risk of bias of included studies was assessed by 2 independent reviewers according to the 6 domains described in the quality in prognostic studies tool, including "study participation," "outcome measurement," "study attrition," "prognostic factor measurement," "adjustment for other prognostic factors," and "statistical analysis and reporting."[26] The risk of a study for each domain was recorded as low, unclear, or high. The overall risk of bias of a study was regarded as low if the risks in all domains were considered low in that study.[25]

2.6. Data synthesis and analysis

Effect sizes on continuous variables are reported as mean differences (SDs) and 95% confidence intervals (CIs), while

categorical variables are expressed as ORs using the random-effects model (DerSimonian–Laird method). I^2 statistics was used for heterogeneity assessment with an I^2 over 50% being defined as substantial heterogeneity.[27] Sensitivity analysis was performed through removing 1 study each time to evaluate the reliability and robustness of the obtained evidence.[28] For a outcome described in 10 or more studies, the possibility of publication bias was examined by the inspection of a funnel plot and the results of Egger tests.[29] We conducted all statistical analyses with the comprehensive meta-analysis V3 software (Biostat, Englewood, NJ). To investigate the accuracy of BUN/albumin ratio for poor-prognosis prediction, we calculated the pooled estimates of sensitivity and specificity based on the bivariate model.[30] The AUC, which was derived from a hierarchical summary receiver operating characteristic curve, was used to determine the diagnostic performance of the BUN/albumin ratio according to the summary receiver operating characteristic (sROC) curve. Forest plots on pooled sensitivity/specificity, sROC curve, and Deeks funnel plot for evaluating publication bias were created with the software of MIDAS command in Stata 15 (StataCorp LLC., College Station, TX). A probability value of < 0.05 was regarded as statistically significant.

3. Results

3.1. Study selection

Of a total of 42 citations identified through our electronic database search, 12 were duplicate reports. After further title and abstract screening, 13 articles were excluded. Of the remaining 17 articles subjected to full-text review, 10 were excluded for being letters (n = 2) or lack of relevant information (n = 8) (Fig. 1). Finally, a quantitative synthesis was conducted on 7 studies involving 3600 patients that were published between 2020 and 2021.[20–23,31–33]

3.2. Study characteristics and quality of studies

An overview of the characteristics of the observational reports can be found in Table 1. Studies were conducted in 4 countries throughout the world, including the following: Turkey (3 studies),[21,23,31] China (2 studies),[22,32] India (1 study),[33] and Iran (1 study).[20] Six studies recruited inpatients without mention the units to which they were admitted,[20,22,23,31–33] while 1 study exclusively investigated intensive care unit (ICU) patients.[21] The exclusion criteria for participants are summarized in Table S1, Supplemental Digital Content, http://links.lww.com/MD/I496. Patients with renal function impairment were excluded in 5 studies,[20–23,33] while this information was not available in the other 2 studies.[31,32] The age of participants ranged from 37 to 75 years with the proportion of males between 42.3% and 61.5%. The number of patients ranged from 97 to 1370. Regarding the diagnostic efficacy of BUN/albumin ratio for the prediction of poor prognosis, the AUC ranged from 0.695 to 0.823, while 1 study did not provide relevant detail.[32] Four studies focused on the association between the BUN/albumin ratio and the risk of mortality,[20,21,23,33] while 3 studies investigated its relationship with the risk of severe disease.[22,31,32]

Based on the quality in prognostic studies tool, the risk of bias of study participation in all studies was deemed unclear due to the significant differences in age and gender distribution between the 2 groups (Fig. 2). In addition, the risk in the domain of adjustment for other prognostic factors was considered unclear in all studies because of their retrospective study design that could not take into account the unpredicted confounders during the course of study.

3.3. Data analysis

The merged results based on 7 studies revealed a higher mean BUN/albumin ratio in the poor-prognosis group (Mean difference: 2.838, 95% CI: 2.015–3.66, $P < .001$, $I^2 = 92.5\%$, 7 studies) than the good-prognosis group (Fig. 3).[20–23,31–33] Sensitivity analysis reinforced the robustness of the result by showing no significant impact of the finding from a single study on the overall outcome. Publication bias was not investigated because only 7 studies were available.

A review of the data from 5 studies that examined the correlation between BUN/albumin ratios as binary variables (i.e., high vs low) and the risk of poor prognosis also indicated that there was an association between a higher BUN/albumin ratio and a higher risk (OR: 3.009, 95% CI: 1.565–5.783, $P = .001$, $I^2 = 93.7\%$) (Fig. 4).[21–23,31,33] Sensitivity analysis supported consistency of the result on this outcome.

The pooled sensitivity and specificity of using BUN/albumin ratio for the prediction of poor-prognosis were 0.76 (95% CI = 0.68–0.82; $I^2 = 70.59\%$) and 0.72 (95% CI = 0.63–0. 8; $I^2 = 95.79\%$), respectively (Fig. 5).[20–23,31,33] Linear regression analysis of sROC generated from mathematical computation of true and false positivity (1-specificity) of each study showed an AUC of 0.81 (95% CI = 0.77–0.84) (Fig. 6).[20–23,31,33]

4. Discussion

Despite the importance of an accurate prediction of COVID-19 progression in guiding resource allocation and decision-making regarding the timing of implementing individualized treatment strategies,[34,35] the wide variation in symptoms has caused great difficulty in predicting mortality and disease severity based on clinical presentations.[36,37] Our results supported the utilization of BUN/albumin ratio to predict poor prognosis with a pooled sensitivity of 0.76 and specificity of 0.72 (AUC of sROC: 0.81) in inpatients diagnosed with COVID-19. The simplicity of its calculation highlighted the possibility of its being used as a cost-effective biomarker for medical resource allocation, which is of critical importance during the pandemic.

An elevated BUN level, which is an indicator of disease severity, has been found to be associated with increased mortality in patients with community-acquired pneumonia.[18,38] In patients with COVID-19, the level of BUN was also higher in those with a fatal outcome or a severe disease compared to those without.[21,22,31] Not only does serum albumin play a vital part in maintaining intravascular colloidal pressure but it is also an acute-phase reactant with antioxidant properties involved in the destruction of free oxygen radicals generated from oxidative stress[39,40] as in COVID-19.[41,42] Consistently, previous reports have revealed an association between a low serum albumin concentration and an unfavorable COVID-19 prognosis.[41,42] Researchers have recently reported a superior efficacy of BUN/albumin ratio for predicting poor prognosis of COVID-19 in comparison with the use of either BUN or albumin alone,[22,23] underscoring the usefulness of this indicator. In addition to COVID-19, a previous meta-analysis on 1900 patients has reported a link between a high BUN/albumin ratio and poor prognosis in those with community-acquired pneumonia.[38] Another large-scale retrospective study on 801 septic patients has also identified the BUN/albumin ratio as an independent predictor of mortality from sepsis by demonstrating its strong associations with both the Acute Physiology and Chronic Health Evaluation II and the Sepsis-related Organ Failure Assessment scores,[43] suggesting its versatility as a prognostic predictor in different clinical settings.

The diagnostic efficacy for poor outcomes in patients with COVID-19 varies among different biomarkers. Compared with CURB-65,[44] which is a severity score for pneumonia, the diagnostic efficacy was more favorable for the BUN/albumin ratio (AUC = 0.821) than that for the former (AUC = 0.744).[22]

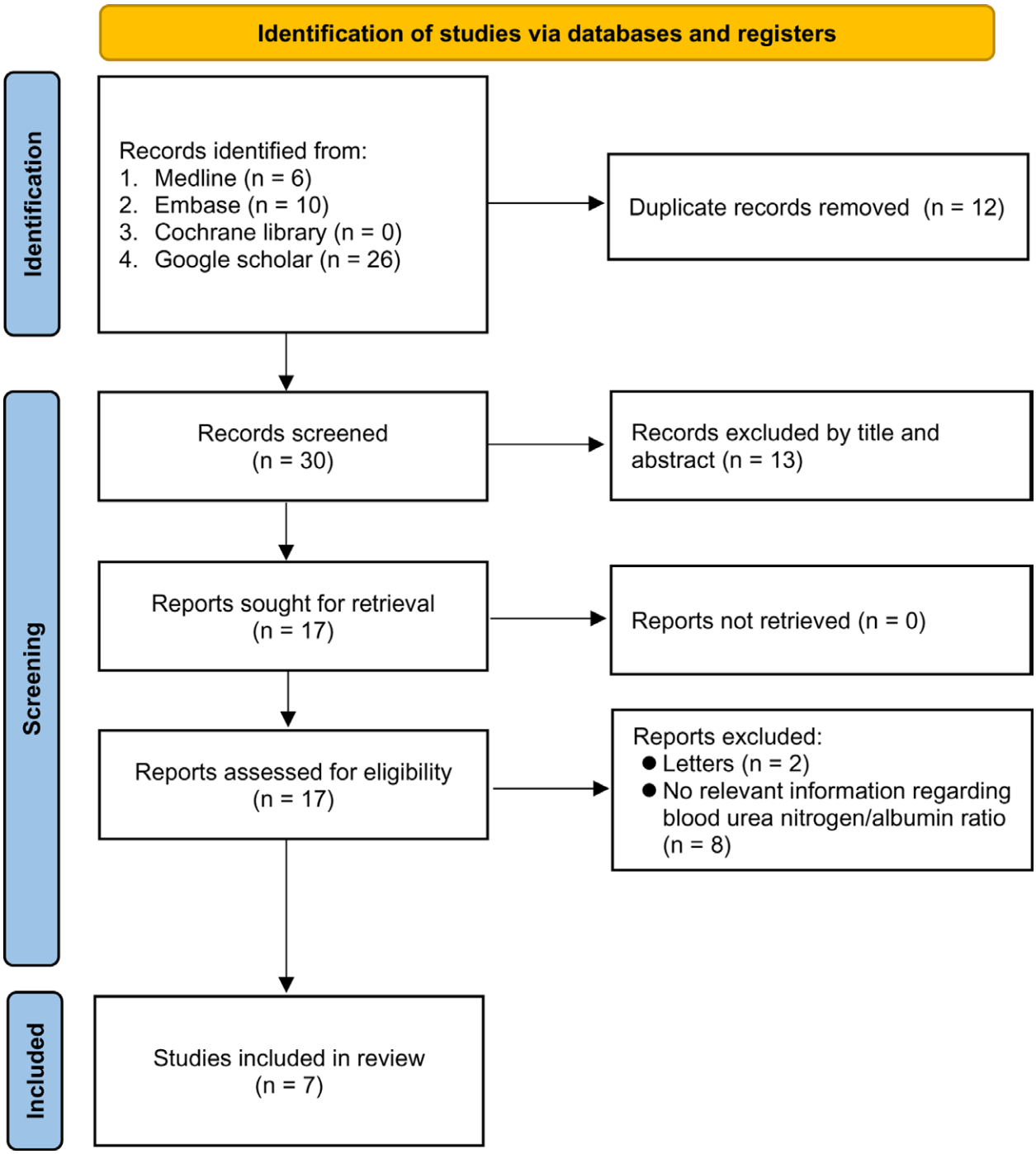

Figure 1. Flow chart showing the process of inclusion and exclusion.

Neutrophil-to-lymphocyte ratio is another useful prognostic predictor in patients with COVID-19.[45] One of our included studies reported a potentially superior diagnostic efficacy of the BUN/albumin ratio (AUC = 0.823) compared with that of the neutrophil-to-lymphocyte ratio (AUC = 0.749).[21] In concert with that finding, another study, which investigated the diagnostic efficacy of 11 biochemical parameters including neutrophil-to-lymphocyte ratio for the severity of disease on 609 patients diagnosed with COVID-19, reported that BUN/albumin ratio (AUC = 0.795) and neutrophil/albumin ratios (AUC = 0.759) may be better predictors than others.[31] These findings suggested that BUN/albumin ratio may be a favorable indicator for prognosis prediction in clinical practice. Despite the promising diagnostic efficacy of BUN/albumin ratio reported in several studies,[21,22,31] 1 study reported that the diagnostic efficacy of BUN/albumin ratio was not superior to that of albumin alone.[33] Through incorporating the results from 7 studies, our pooled analysis of the predictive value of BUN/albumin ratio for poor prognostic outcomes generated a sensitivity of 0.76, specificity of 0.72, and AUC of 0.81. Taking into consideration that an AUC over 0.9 denotes a high accuracy, 0.7 to 0.9 represents moderate accuracy, 0.5 to 0.7 signifies a low accuracy, and 0.5 indicates a chance result (i.e., a toss-up),[46] our finding may provide useful guidance for decision-making.

Despite the previous identification of age, especially those over 70 years, as a prognostic factor for predicting mortality,[47,48] a previous meta-analysis covering thirteen European countries demonstrated no difference in COVID-19-related ICU

Table 1

Characteristics of studies (n = 7).

Studies (yr)	Age§(yr)‖	Male (%)‖	N (4401)	AUC	Sensitivity/Specificity (%)	BUN/albumin ratio cut off point (mg/g)	Outcomes	Country
Alirezaei (2022)	72 vs 56	63 vs 60	433	0.733	75.8/70.8	4.94	Mortality	Iran
Ata (2021)†	66 vs 48	44 vs 39	358	0.823	74.5/75.6	3.4	Mortality	Turkey
Gemcioglu (2021)	68 vs 46	56 vs 57	609	0.795	63.37/84.89	4.83	Severity	Turkey
Huang (2021)	67 vs 54	62 vs 44	1370	0.821	69/78.6	3.79	Severity	China
Kucukceran (2021)	75 vs 60	66 vs 49	602	0.809	87.5/59.9	3.9	Mortality	Turkey
Nie (2020)	58 vs 37	52 vs 29	97	NA	NA	NA	Severity	China
Singh (2022)	56 vs 53	31 vs 69	131	0.695	79/54	6.23	Mortality	India

AUC = area under curve, BUN = blood urea nitrogen, NA = not available.

† patients admitted to the intensive care unit;

§median or mean age according to individual studies;

‖presented as poor- vs good-prognosis groups.

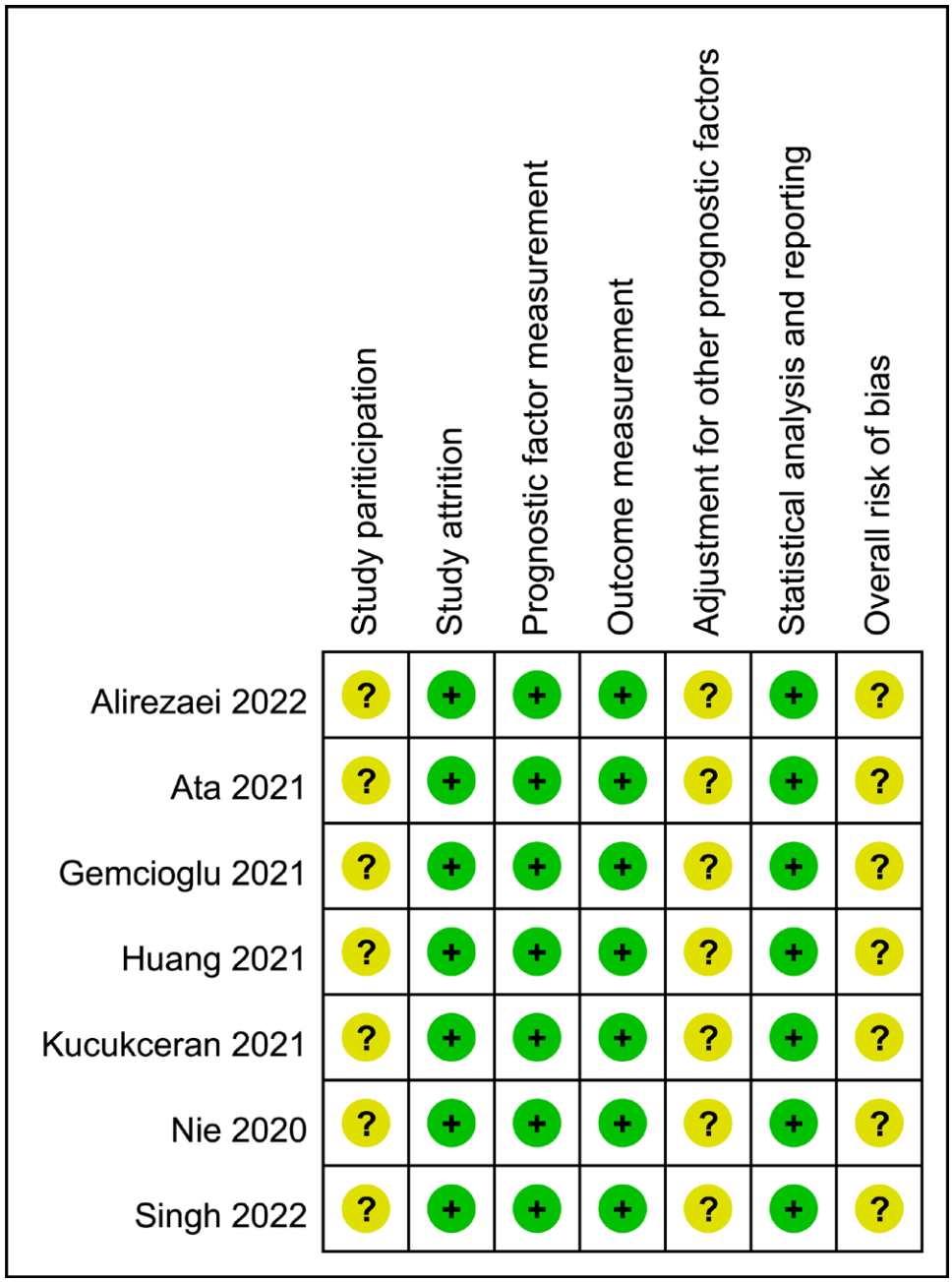

Figure 2. Quality of studies assessed based on the quality in prognostic studies (QUIPS) tool.

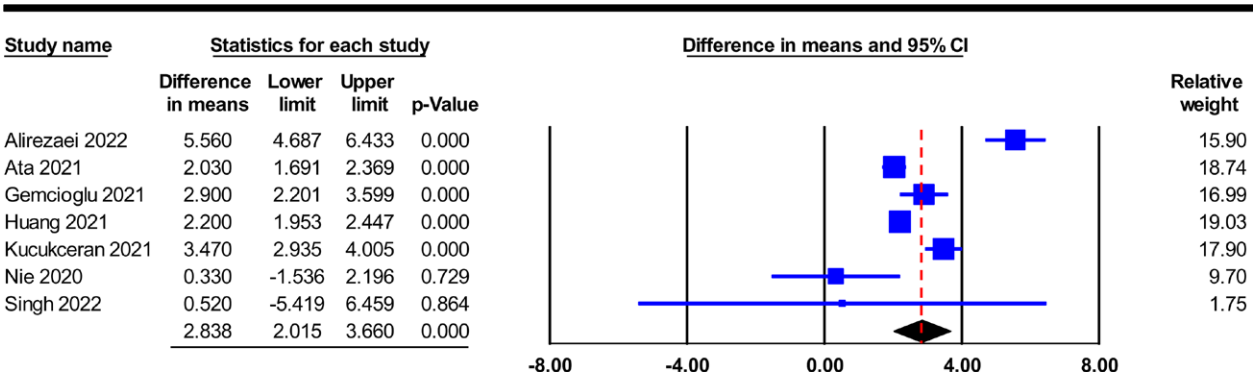

Figure 3. Forest plot comparing the blood urea nitrogen to albumin ratio (BUN/Albumin ratio) between patients with poor and good prognosis, showing a higher mean BUN/Albumin ratio in the former group compared to the latter group (MD: 2.838, 95% CI: 2.015 to 3.66, $P < .001$, I2 = 92.5%). BUN = blood urea nitrogen, CI = confidence interval, MD = mean difference.

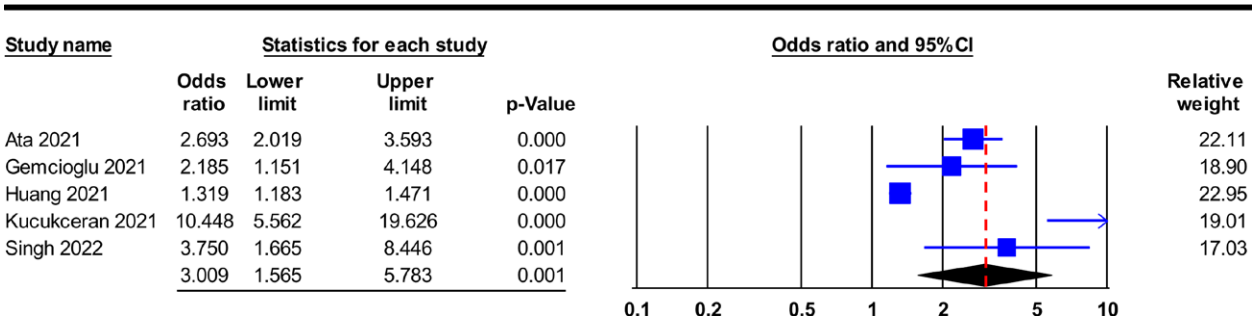

Figure 4. Forest plot revealing a positive association between risk of poor prognosis and BUN/Albumin ratio as as a binary parameter (odds ratio: 3.009, 95% CI: 1.565 to 5.783, $P < .001$, I2 = 93.7%). BUN = blood urea nitrogen, CI = confidence interval.

admission between the 2 age groups (i.e., 40–69 years vs ≥ 70 years: 52.6% vs 41.8 %) although mortality did increase with age (i.e., 40–69 years vs ≥ 70 years: 13% vs 86.6%).[48] The findings, therefore, suggested comparable prevalence of contracting a severe disease between the 2 age groups. Consistently, The Canadian Geriatrics Society recommended that decisions on access to critical care or mechanical ventilation should be individualized, but not based on age alone.[49] In addition to age, hypertension, chronic renal failure, type 2 diabetes mellitus, obesity, and asthma were also independent risk factors of ICU admission.[50] Our finding demonstrated that a high BUN/albumin ratio was associated with a 3-fold increased risk of poor prognosis in COVID-19 inpatients with a diagnostic efficacy based on AUC being up to 81. Taking into account the intermingling factors involved in COVID-19 progression, a simple prognostic index obtainable through laboratory routines may be vital for guiding effective allocation of medical resources particularly in countries where health-care resources are limited.

Although our results showed robust evidence of a positive association between BUN/albumin ratio and poor prognostic outcomes, there are still a number of issues that need to be clarified. First, because malnutrition as reflected by a low serum albumin concentration may be a modifiable predictor, the effects of nutrition supplementation on outcomes in COVID-19 patients requires further elucidation. Second, there was no information in our included studies pertinent to the implementation of any COVID-19 vaccination program, which may mitigate disease severity and mortality regardless of BUN and serum albumin levels. In addition to vaccination, a gender impact on the overall mortality related to COVID-19 has also been reported with the mortality rate of males being 2.3-fold higher than that in females. Nevertheless, due to the inclusion of both males and females in all of our included studies, the effect of gender on our study outcome could not be clarified. Moreover, ethnicity is also a significant concern as Asians have a lower incidence of disease severity and mortality than other groups of people.[51,52] Variations in mortality rates with differences in countries and phases of the pandemic[5] suggested that our results, which were derived mainly from China and Turkey, may not be extrapolated to populations of other ethnic or geographical backgrounds. Therefore, further large-scale clinical studies are warranted to address these issues.

Several limitations in the current study need to be taken into consideration. First, the retrospective design of all our included observational studies precluded precise patient grouping based on age, gender, and comorbidities that are all reported factors related to outcomes in population contracting COVID-19. Second, only data on patient admission were analyzed because information about BUN and serum albumin concentrations during hospitalization was unavailable. Therefore, whether changes in the BUN/albumin ratio during the course of treatment could dynamically reflect a patient prognosis remain unclear. Besides, despite the exclusion of patients with renal function impairment in 5 of the included studies, the unavailability of relevant information in the other 2 studies could not rule out the possibility of recruiting those with end-stage renal disease whose BUN may fluctuate with dialysis. Third, our results may be influenced by variations in the definition of illness severity and cutoff value of BUN/albumin ratio for prognosis prediction among our included studies. Fourth, our sample size was small compared with the staggering number of patients contracting COVID-19 worldwide. Finally, because our study outcomes were mortality and disease severity during hospitalization, whether the BUN/albumin ratio could also reflect long-term outcomes (e.g., delayed mortality or sequelae) remains to be elucidated.

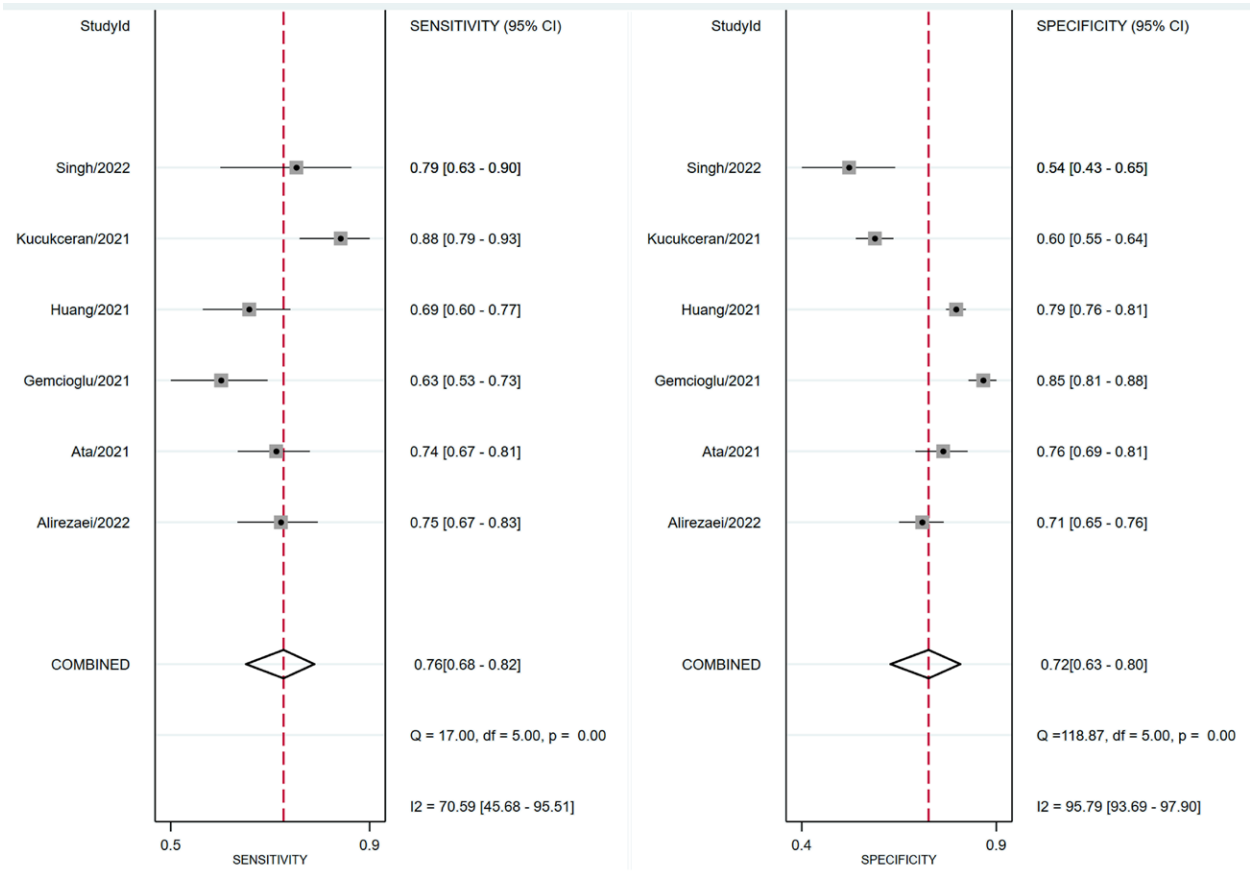

Figure 5. (A) Forest plots showing the sensitivity and specificity of using blood urea nigrogen to albumine ratio (BUN/Albumin ratio) for predicting poor outcomes in patients with COVID-19. BUN = blood urea nitrogen, COVID-19 = coronavirus disease 2019.

5. Conclusion

This meta-analysis on 3600 patients with COVID-19 demonstrated an over 3-fold increase in risk of poor prognostic outcomes among those with an elevated BUN to albumin ratio, thereby supporting its use as a promising index for predicting in-hospital prognosis with a reported optimal cutoff value ranging from 3.4 to 6.23 mg/g. Further large-scale studies are required to shed light on the potential benefits of its clinical use during the pandemic.

Author contributions

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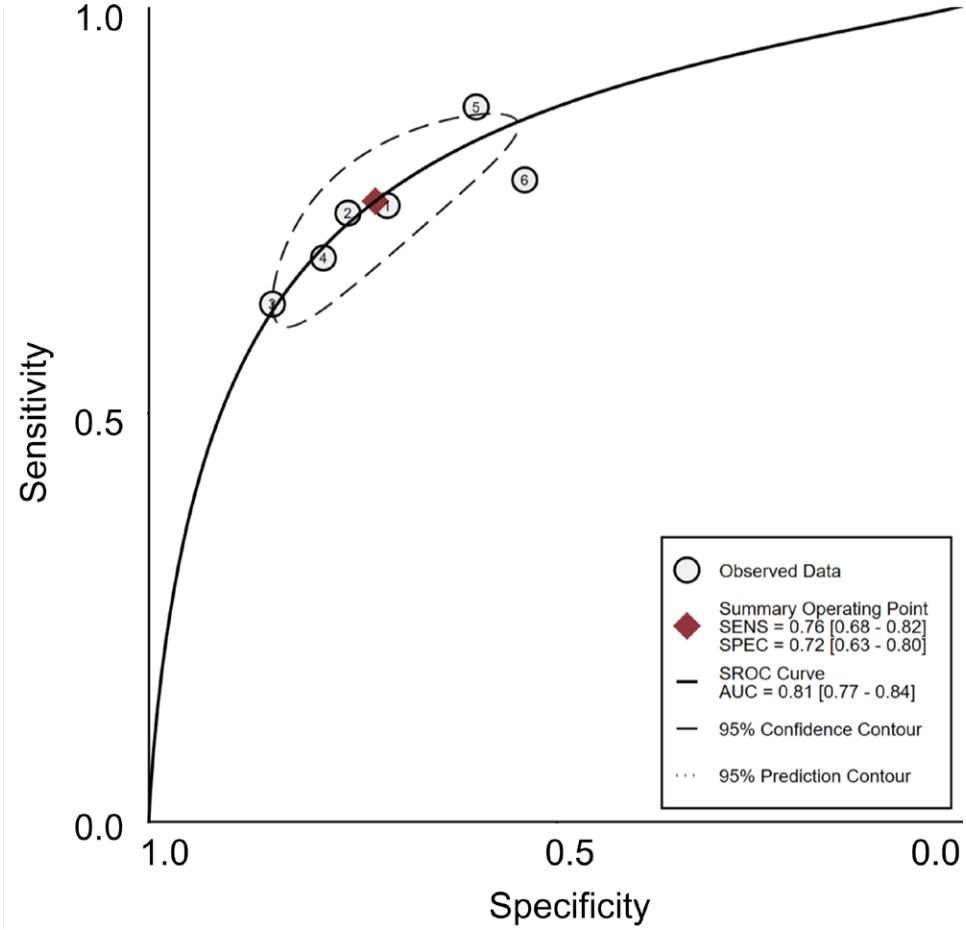

Figure 6. Hierarchical summary receiver operating characteristic (hsROC) curves showing the predictive efficacy of blood urea nigrogen to albumine ratio (BUN/Albumin ratio) on poor-prognosis in patients with COVID-19. AUC = Area under the curve, BUN = blood urea nitrogen, COVID-19 = coronavirus disease 2019, SENS = sensitivity, SPEC = specificity, SROC = summary receiver operating characteristic.

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