European Review for Medical and Pharmacological Sciences 2021; 25: 3879-3885

The association between serum prealbumin and poor outcome in COVID-19 – Systematic review and meta-analysis

M.R. AKBAR[1], R. PRANATA[1,2], A. WIBOWO[1], M.A. LIM[2], T.A. SIHITE, J.W. MARTHA

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine Universitas Padjadjaran, Rumah Sakit Umum Pusat Hasan Sadikin, Bandung, Indonesia
[2]Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

Abstract. – OBJECTIVE: This systematic review and meta-analysis aimed to evaluate the association between the prealbumin and severity and mortality in COVID-19.

MATERIALS AND METHODS: We performed a systematic literature search from PubMed, Embase, and Scopus databases up until 2 February 2021. The primary outcome was the poor outcome, a composite of mortality and severity. Severe COVID-19 was defined as COVID-19 that fulfill the criteria for severe pneumonia or patients with acute respiratory distress syndrome/disease progression/need for intensive care unit or mechanical ventilation. The effect estimates were a mean difference between patients with and without a poor outcome in mg/dL and odds ratio (OR) per 1 mg/dL decrease in prealbumin level. The effect estimates were reported with their 95% confidence interval (95% CI).

RESULTS: Nine studies comprising of 2104 patients were included in this systematic review and meta-analysis. Patients with poor outcome have lower prealbumin level (mean difference -71.48 mg/dL [95% CI -93.74, -49.22], $p<0.001$; I^2: 85.9%). Every 1 mg/dL decrease in prealbumin level was associated with 1% increase in poor outcome (OR 0.992 [0.987, 0.997], $p=0.004$, I^2: 81.7%). Meta-regression analysis showed that the association between the prealbumin level and poor outcome varies with gender (male) (coefficient: 3.50, R^2: 100%, $p<0.001$), but not age, diabetes, hypertension, and chronic kidney disease.

CONCLUSIONS: Low serum prealbumin was associated with poor outcomes in patients with COVID-19.

Key Words:
Acute phase reactants, Coronavirus, Mortality, Severity, Transthyretin.

Introduction

To date, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 100 million people[1]. Without specific treatments and medications to fight the virus, identifying risk factors for poor outcomes is essential. Patients with older age and comorbidities have a poorer prognosis[2-4]. Such vulnerable individuals may experience a variety of serious and life-threatening complications, including acute respiratory distress syndrome (ARDS), sepsis, coagulopathy, disseminated intravascular coagulation (DIC), multiorgan dysfunction, and death[5].

Considering the growth of new COVID-19 cases, predicting the outcome of SARS-CoV-2 infection is essential in managing depleted medical resources and providing better medical care. A range of laboratory markers has been used in predicting the prognosis of infected patients, especially those indicating inflammatory parameters, such as C-reactive protein, lactate dehydrogenase, interleukin, D-dimer, prothrombin time, ferritin, and procalcitonin[6,7]. Serum prealbumin, also known as transthyretin, was generally lower in patients with severe clinical presentation[8,9]. This systematic review and meta-analysis aimed to evaluate the association between the prealbumin and severity and mortality in COVID-19.

Materials and Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Me-

Corresponding Author: Mohammad Rizki Akbar, MD, Ph.D; e-mail: m.r.akbar@unpad.ac.id

ta-Analyses (PRISMA) reporting guidelines and is registered in PROSPERO (CRD42021234805).

Eligibility Criteria

We included studies that fulfill the following criteria: (1) observational prospective and retrospective studies reporting COVID-19 patients, (2) reporting prealbumin levels, (3) reporting mortality/severity/ARDS/disease progression/need for intensive care unit or mechanical ventilation.

We excluded studies that fulfill one of the following criteria: (1) review articles, (2) preprints, (3) non-research letters, (4) editorials/commentaries/viewpoints, and (5) Non-English language articles.

Outcome

The primary outcome was the poor outcome, a composite of mortality and severity. Severe COVID-19 was defined as COVID-19 that fulfill the criteria for severe pneumonia[10] or patients with ARDS/disease progression/need for intensive care unit or mechanical ventilation.

Search Strategy and Study Selection

We performed a systematic literature search from PubMed, Embase, and Scopus databases with keywords "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "prealbumin" OR "pre-albumin" up until 2 February 2021. The PubMed (MEDLINE) search strategy was ((SARS-CoV-2) OR (2019-nCoV)) OR (COVID-19) AND ((prealbumin) OR (pre-albumin)). Two independent authors screened the titles and abstract after the removal of duplicate records. Potentially relevant articles were assessed for eligibility using the inclusion and exclusion criteria.

Data Extraction

Two authors extracted the data from eligible studies independently using the standardized extraction form comprising of author, publication year, study design, baseline characteristics such as age, male (gender), hypertension, diabetes, chronic kidney diseases, the primary outcome.

The main outcome was the poor outcome; the effect estimates were a mean difference between patients with and without poor outcomes in mg/dL and odds ratio (OR) per 1 mg/dL decrease in prealbumin level. The effect estimates were reported with their 95% confidence interval (95% CI).

Assessment of Methodology Criteria and Risk of Bias

Risk of bias assessment was performed by two independent authors using the Newcastle-Ottawa Scale (NOS). Arising discrepancies were resolved by discussion between the authors.

Statistical Analysis

STATA 16 (StataCorp LLC, Lakeway Drive College Station, TX, USA) was used to perform the meta-analysis. The pooled estimate of continuous variables was reported as mean difference (mg/dL). Both calculations for mean difference and ORs were performed using the restricted-maximum likelihood (REML) random-effects meta-analysis regardless of heterogeneity. *p*-values were considered as statistically significant if below 0.05. Heterogeneity was assessed using the I-squared (I^2) and Cochrane Q test; in which I^2 of >50% or *p*-value <0.10 indicates substantial heterogeneity. Egger's test and funnel-plot analysis were performed to assess publication bias.

Exploration of Heterogeneity

Meta-regression was performed to assess the influence of covariates (baseline characteristics) on the association between prealbumin and poor outcome.

Results

Nine studies comprising of 2104 patients[8,9,11-18]we collected the demographics and laboratory tests to predict whether the patient would progress to severe cases in hospitalization. Severe case was confirmed when one of the following criteria occurred: (a were included in this systematic review and meta-analysis [Figure 1]. The baseline characteristics of the included studies and their risk of bias based on NOS are displayed in in Table I.

Prealbumin and Poor Outcome

Patients with poor outcome have lower prealbumin level (mean difference -71.48 mg/dL [95% CI -93.74, -49.22], $p<0.001$; I^2: 85.9%, $p<0.001$) [Figure 2]. Every 1 mg/dL decrease in prealbumin level was associated with 1% increase in poor outcome (OR 0.992 [0.987, 0.997], $p=0.004$, I^2: 81.7%, $p=0.009$) [Figure 3].

Meta-Regression

Meta-regression analysis showed that the association between the prealbumin level and poor outcome varies with gender (male) (coefficient: 3.50, R^2: 100%, $p<0.001$), but not age (coefficient: -2.48, R^2: 29.1%, $p=0.090$), diabetes (co-

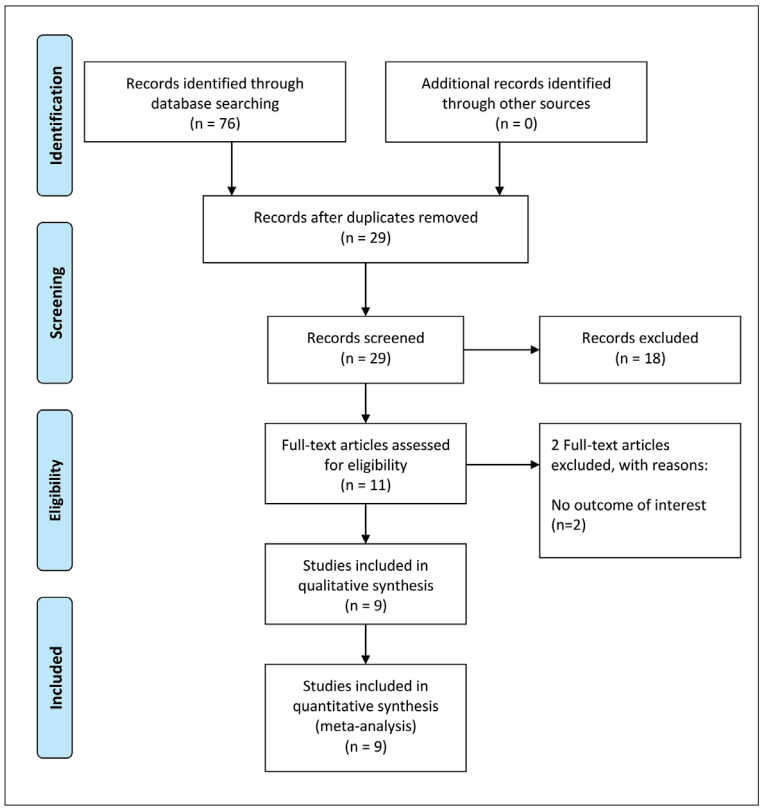

Figure 1. PRISMA flowchart.

efficient: -1.91, R^2: 0%, p=0.434), hypertension (coefficient: -0.95, R2: 0%, p=0.357), and chronic kidney disease (coefficient: -7.79, R^2: 10.9%, p=0.333).

Publication Bias

There is no indication of small-study effects (p=0.233), but the funnel-plot was asymmetrical [Figure 4].

Discussion

This pooled analysis indicates that serum prealbumin was lower in patients with poor outcomes, and every 1 mg/dL decrease in prealbumin was associated with 1% increase in poor outcomes.

Meta-regression analysis indicates that the association between prealbumin and poor out-

Table I. Baseline characteristics of the included studies.

First Author	Design	Sample	Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	CKD (%)	Outcome	NOS
Chen Z 2020	Retrospective	635	61	50	37.6	22.8	3.1	Severity	8
Duan J 2020	Retrospective	348	44.8	53	4.9	7.5	0.2	Severity	7
Ji M 2020	Retrospective	101	51	48	20	13	4	Severity	6
Li L 2020	Retrospective	72	45.9	NR	NR	NR	NR	Severity	5
Li T 2020	Retrospective	80	62	47.5	36.3	16.3	NR	Mortality	7
Ouyang S 2020	Retrospective	107	57.5	59.8	NR	NR	NR	Mortality	5
Wu C 2020	Retrospective	201	51	63.7	19.4	10.9	1	Severity	8
Xue G 2020	Retrospective	114	62	56.1	32.5	14.0	NR	Severity	8
Zuo P 2020	Retrospective	446	73	52.4	56.3	24.4	3	Mortality	7

CKD: Chronic Kidney Disease, ICU: Intensive Care Unit, NOS: Newcastle-Ottawa Scale, NR: Not Reported.

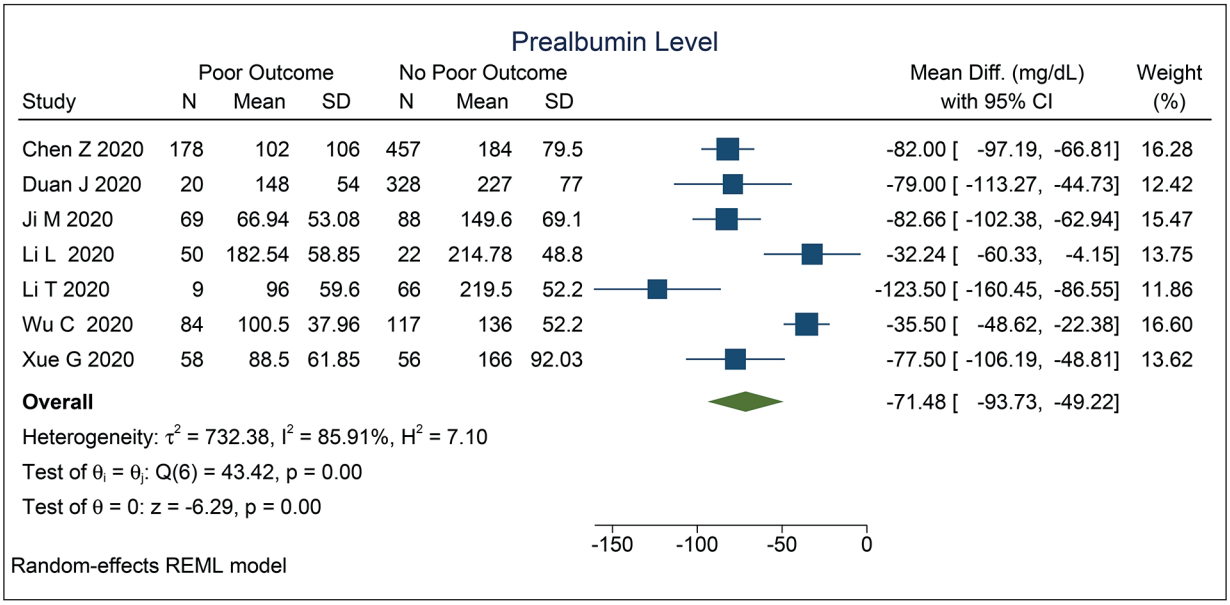

Figure 2. Prealbumin and poor outcome (mean difference).

come was affected by gender, in which the difference was wider in male patients and narrower in female patients. In patients with trauma, the prealbumin response differs among male and female patients, indicating a different physiological response[19]. Thus, it is possible that there is a gender-specific response in patients with COVID-19.

Prealbumin is a globular, non-glycosylated protein produced by the liver and complexed with a retinol-binding protein to transport retinol/vitamin A and thyroid hormones. Compared to albumin, prealbumin has a shorter half-life, a faster hepatic synthesis rate, and a predictable catabolic rate, and therefore, it may serve as a more sensitive indicator. Plasma prealbumin levels may decrease with age, inflammation, and nutritional deficiency. Low serum prealbumin concentrations have been used as an initial laboratory indicator of malnutrition or poor nutritional status. During inflammation, a

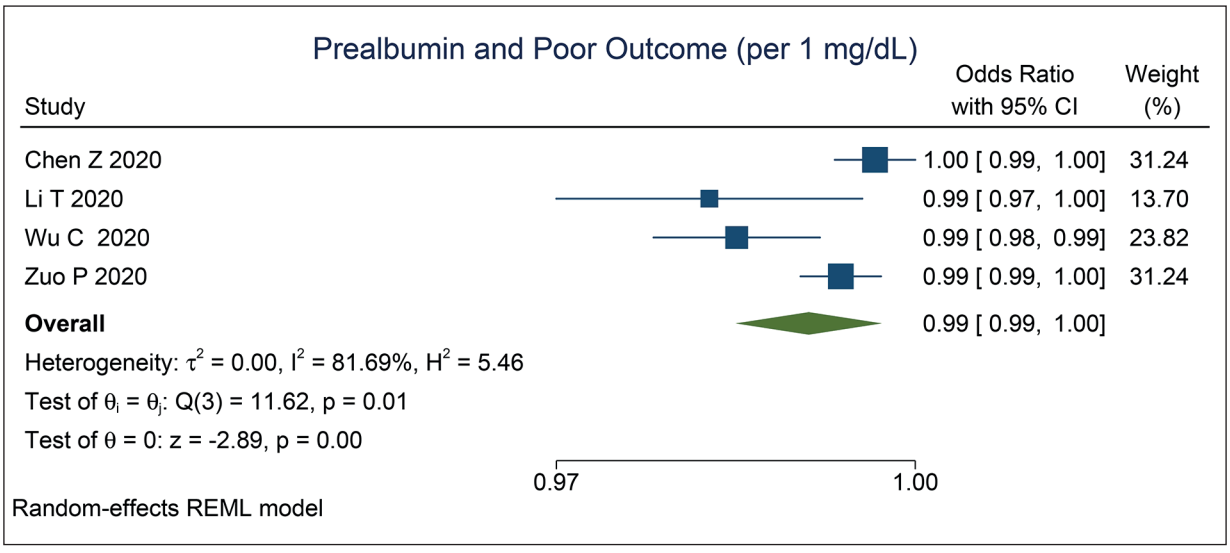

Figure 3. Prealbumin and poor outcome (per 1 mg/dL decrease).

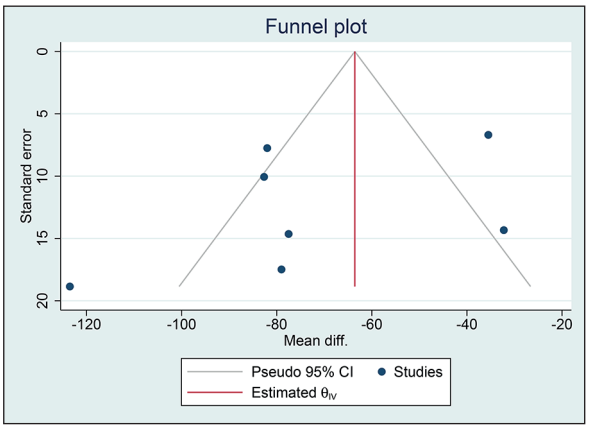

Figure 4. Funnel-plot analysis.

number of cytokines are released into the bloodstream, which downregulates plasma albumin and prealbumin levels. In COVID-19, cytokine storm has been postulated as one of the pathophysiology responsible for severe symptoms and serious complications. Therefore, serum prealbumin values can be used as a screening parameter for inflammation, including hyperinflammatory reactions that occur in COVID-19[8].

Aging, frailty, and chronic disorders are associated with decreased immunity which may also be exacerbated by poor nutritional status and immune dysregulation, leading to a poor prognosis[2,20,21]. Hence, elderly patients with COVID-19 often present with a more severe clinical presentation, elevated inflammatory parameters, and are more likely to experience critical illness and even death[8] 2020. Univariate and multivariate logistic regression models were employed to evaluate the correlation between prealbumin and in-hospital outcomes (in-hospital mortality, admission to the intensive care unit [ICU], and mechanical ventilation. Apart from nutritional status, serum prealbumin and albumin can partly reflect the patient's immune status. Immune insufficiency may contribute to higher viral replication, excessive inflammation, and extensive tissue damage, leading to poor outcomes. A low prealbumin level on admission may suggest a poor prognosis and the predictive value of prealbumin is superior to most routine laboratory parameters reflecting organ dysfunction or functional impairment for COVID-19 prognosis[9].

We assume that progressive decline of plasma prealbumin levels in COVID-19 patients may indicate disease progression and further deterioration of clinical status. Nutritional and immune status in the early stage of COVID-19 is likely to be crucial in predicting the course of the disease. Poor immunity may play a role in COVID-19-related complications and death. Although lymphopenia can indicate worse outcomes in COVID-19 patients, serum prealbumin may reflect the host's immune function better[22]. The single use of prealbumin could serve as a modest predictor of COVID-19 prognosis, but could yield better performance when combined with other laboratory parameters[9].

Clinical Implications

Serum prealbumin can be used for risk stratification in patients with COVID-19, and every 1 mg/dL decrease in prealbumin was associated with 1% increase in poor outcomes. Nevertheless, a single cut-off point will be more clinically relevant; this cannot be analyzed with the current data. Thus, future studies should evaluate the optimal cut-off point for risk prediction.

Limitations

The limitation of this systematic review includes the risk of publication bias, in which positive studies are more likely to be published. The investigations were mostly retrospective. There is no specific cut-off point for the prealbumin level, which is important for clinical relevance.

Conclusions

Shortly, low serum prealbumin was associated with poor outcomes in patients with COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

Not Applicable. Systematic review and meta-analysis contain data from published studies, not a primary data.

Informed Consent

Not Applicable. Systematic review and meta-analysis contain data from published studies, not a primary data.

Data Availability

Data are available on reasonable request.

Authors' Contribution

Mohammad Rizki Akbar: conceptualization, investigation, writing—review and editing, supervision. Raymond Pranata: conceptualization, methodology, software, data curation, formal analysis meta-analysis), investigation, validation, writing—original draft, writing—review and editing. Arief Wibowo: investigation, writing—original draft. Michael Anthonius Lim: data curation, investigation, writing—original draft. Teddy Arnold Sihite: investigation, writing—review and editing. Januar Wibawa Martha: investigation, writing—review and editing.

PROSPERO ID

CRD42021234805.

References

1) World Health Organization. Weekly Epidemiological Update - 9 February 2021. 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update---9-february-2021
2) Pranata R, Henrina J, Lim MA, Lawrensia S, Yonas E, Vania R, Huang I, Lukito AA, Suastika K, Kuswardhani RAT, Setiati S. Clinical frailty scale and mortality in COVID-19: A systematic review and dose-response meta-analysis: clinical Frailty Scale in COVID-19. Arch Gerontol Geriatr 2021; 93: 104324.
3) Pranata R, Lim MA, Yonas E, Vania R, Lukito AA, Siswanto BB, Meyer M. Body mass index and outcome in patients with COVID-19: a dose-response meta-analysis. Diabetes Metab 2021; 47: 101178.
4) July J, Pranata R. Prevalence of dementia and its impact on mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. Geriatr Gerontol Int 2021; 21: 172-177.
5) Lim MA, Pranata R, Huang I, Yonas E, Soeroto AY, Supriyadi R. Multiorgan failure with emphasis on acute kidney injury and severity of COVID-19: systematic review and meta-analysis. Can J Kidney Heal Dis 2020; 7: 2054358120938573.
6) Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis 2020; 14: 1753466620937175.
7) Martha JW, Wibowo A, Pranata R. Prognostic value of elevated lactate dehydrogenase in patients with COVID-19: a systematic review and meta-analysis. Postgrad Med J 2021; postgradmedj-2020-139542. Doi: 10.1136/postgradmedj-2020-139542. Online ahead of print.
8) Zuo P, Tong S, Yan Q, Cheng L, Li Y, Song K, Chen Y, Dai Y, Gao H, Zhang C. Decreased prealbumin level is associated with increased risk for mortality in elderly hospitalized patients with COVID-19. Nutrition 2020; 78: 110930.
9) Luo Y, Xue Y, Mao L, Yuan X, Lin Q, Tang G, Song H, Wang F, Sun Z. Prealbumin as a predictor of prognosis in patients with coronavirus disease 2019. Front Med 2020; 7: 374.
10) Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2019; 200: e45-e67.
11) Duan J, Wang X, Chi J, Chen H, Bai L, Hu Q, Han X, Hu W, Zhu L, Wang X, Li Y, Zhou C, Mou H, Yan X, Guo S. Correlation between the variables collected at admission and progression to severe cases during hospitalization among patients with COVID-19 in Chongqing. J Med Virol 2020; 92: 2616-2622.
12) Ji M, Yuan L, Shen W, Lv J, Li Y, Li M, Lu X, Hu L, Dong W. Characteristics of disease progress in patients with coronavirus disease 2019 in Wuhan, China. Epidemiol Infect 2020; 148: e94.
13) Li L, Chen C. The contribution of acute phase reaction proteins to the diagnosis and treatment of 2019 novel coronavirus disease (COVID-19). Epidemiol Infect 2021; 148: e164.
14) Ouyang SM, Zhu HQ, Xie YN, Zou ZS, Zuo HM, Rao YW, Liu XY, Zhong B, Chen X. Temporal changes in laboratory markers of survivors and non-survivors of adult inpatients with COVID-19. BMC Infect Dis 2020; 20: 952.
15) Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; 180: 934-943.
16) Xue G, Gan X, Wu Z, Xie D, Xiong Y, Hua L, Zhou B, Zhou N, Xiang J, Li J. Novel serological biomarkers for inflammation in predicting disease severity in patients with COVID-19. Int Immunopharmacol 2020; 89(Pt A): 107065.
17) Chen Z, Zhang F, Hu W, Chen Q, Li C, Wu L, Zhang Z, Li B, Ye Q, Mei J, Yue J. Laboratory markers associated with COVID-19 progression in patients with or without comorbidity: a retrospective study. J Clin Lab Anal 2020; 35: e23644.
18) Li T, Guo Y, Zhuang X, Huang L, Zhang X, Wei F, Yang B. Abnormal liver-related biomarkers in COVID-19 patients and the role of prealbumin. Saudi J Gastroenterol 2020; 26: 272-278.
19) Houston-Bolze MS, Downing MT, Sayed AM, Meserve LA. Gender differences in the responses of serum insulin-like growth factor-1 and transthyretin (prealbumin) to trauma. Crit Care Med 1996; 24: 1982-1987.

20) Tuty Kuswardhani RA, Henrina J, Pranata R, Anthonius Lim M, Lawrensia S, Suastika K. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: a systematic review and meta-analysis. Diabetes Metab Syndr Clin Res Rev 2020; 14: 2103-2109.

21) Pranata R, Supriyadi R, Huang I, Permana H, Lim MA, Yonas E, Soetedjo NNM, Lukito AA. The association between chronic kidney disease and new onset renal replacement therapy on the outcome of COVID-19 patients: a meta-analysis. Clin Med Insights Circ Respirat Pulm Med 2020; 14: 1179548420959165.

22) Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): Systematic review and meta-analysis. J Intensive Care 2020; 8: 36.