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The Role of ApOE, PSEN1, And Tnf-α as Predictor of COVID-19 Severity Evaluated Using Serial Thorax Radiograph

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Abstract: The high number of Covid-19 incidents is the main problem currently being faced, so how to reduce the number of incidents is a significant concern at this time. It is hoped that the risk factors and causes of mortality and how to detect the severity of Covid-19 can be a solution to reduce the morbidity of Covid-19 infection. This research is an analytical observational using the ApoE, Presenilin 1 (PSEN1), and TNF-α from the blood sample of Covid-19 patients; moreover, the thorax serial radiographs were evaluated by CARE score and were also used to determine the prognosis. All of the three indicators were examined using the ELISA Kit. Furthermore, the variables were analyzed using the SPSS 16.0 Ver. with Pearson and Spearman Rho data analysis. There is no correlation between ApoE, PSEN1, and TNF-α as Covid-19 severity predictors in this research regarding factors such as fewer geriatric samples, steroid usage as therapy, and fewer patients with comorbidities.

Keywords: apolipoprotein E, presenilin 1, TNF-α, COVID-19, severity, predictors.

载脂蛋白乙、早老素-1 和肿瘤坏死因子-一种作为新冠肺炎严重程度预测因子的作用，使用连续胸片评估

摘要：新冠肺炎事件的大量发生是当前面临的主要问题，因此如何减少事件数量是此时的一个重要问题。希望死亡的风险因素和原因以及如何检测新冠肺炎的严重程度可以成为降低新冠肺炎感染发病率的解决方案。这项研究是使用新冠肺炎患者血液样本中的载脂蛋白乙、早老素1和肿瘤坏死因子-
一种进行的分析观察；此外，胸部系列射线照片片通过心脏麻醉风险评估评分进行评估，也用于判断预后。使用酶联免疫吸附测定试剂盒检查所有三个指标。此外，使用社会科学统计包16.0对变量进行分析。使用皮尔逊和斯皮尔曼罗数据分析。在本研究中，载脂蛋白乙、早

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老素1和肿瘤坏死因子-
一种作为新冠肺炎严重程度预测因子与老年人样本较少、使用类固醇治疗和合并症患者较少等因素之间没有相关性。

关键词：载脂蛋白乙、早老素1、肿瘤坏死因子-
一种、新冠肺炎、严重程度、预测因子。

1. Introduction

SARS-CoV2, more popularly known as Coronavirus Disease 2019 (Covid-19), is a significant health problem that causes mortality, especially for the elderly. World Health Organization (WHO) has declared the Covid-19 as a pandemic on 11 March 2020, in which more than 1.8 million people were positive for Covid-19; moreover, there were more than 114.000 deaths globally [1].

The mortality for Covid-19 ARDS ranged between 26% and 61.5% if he had been treated in critical care. If he had received treatment using mechanical ventilation, the mortality could increase by about 65.7% to 94%(2). Several risk factors could worsen the Covid-19 patients, which consist of older ages, comorbidity such as hypertension, diabetes, cardiovascular-related disease, kidney injury, lower lymphocyte counts, and raise D-dimer levels. Furthermore, 53% of deaths regarding Covid-19 ARDS were attributed to respiratory failure, 33% were caused by respiratory failure, combined with cardiac failure. In comparison, 7% of deaths were caused by myocardial damage and circulatory failure by unspecified causes [2].

In the brain and lungs infected with SARS-CoV2, an immune reaction occurs, which results in the activation of gold cells and the release of previously formed and newly formed mediators in the brain. This process then continues with the activation of glial cells, which causes neurons' degeneration when a cytokine storm occurs in the lungs, reaching the brain via the blood-brain barrier, possibly exacerbating neurological complications. In these circumstances, patients with previous neurological disorders (ADRD, PD, stroke, NMD) have a higher risk of developing comorbidities. Special attention and medical support systems are needed in these circumstances [3].

Adipocytes, hepatocytes, brain astrocytes, and arterial wall macrophages synthesize ApoE, which functions in lipids' transport, which plays a role in the brain, immune and vascular functions [4]. Compared with homozygous ApoE3, homozygous ApoE4 is 2.2 times the risk of positivity for Covid-19 and 4.3 times as much as death cases after Covid-19 [5], [6]. Covid-19 under linear dose dependence was associated with heterozygosity (ε3/ε4), whereas dementia, hypertension, coronary heart disease (CHD) or type II diabetes did not reduce the strong association for the association between ε4 / ε4 and Covid-19 [4].

Cytokine storms play a central role in severity and mortality in SARS-CoV2 infection with increased plasma levels of IL-1β, IL-7, IL-8, IL-9, IL-10, G-CSF, GM-CSF, IFNγ, IP- 10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF in both ICU and non-ICU patients. Furthermore, patients with severe pneumonia who became ARDS admitted to the ICU and required oxygen compared to non-ICU patients with ARDS pneumonia found higher plasma levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and TNF-α [7].

When Covid-19 infection meets the 2012 ARDS Berlin diagnostic criteria, the patient can be diagnosed with Covid-19 ARDS, with the assessment criteria (i) acute hypoxemic respiratory failure, (ii) bad respiratory symptoms within one week, (iii) bilateral air space on radiographs not fully explained by effusion, lobar, pulmonary collapse or nodules, (iv) acute hypoxemic respiratory failure not caused by heart failure [4].

The findings (CT) may be more sensitive than reverse transcription PCR (RT-PCR); chest radiography can be applied as the primary tool for diagnosis and monitoring. GG and Co on chest radiographs did not investigate their contribution; thus, chest radiographic scores (CASE) was used based on GG and Co's extension, considering the two subscores separately and evaluating their role in predicting patient outcomes [8]. There are numerous studies regarding Covid-19 that discuss practical and efficient methods to determine this disease as early as possible. The previous studies have tried ApOE and TNF-α as Covid-19 predictors with different results; however, the PSEN1 has never been used as the Covid-19 predictor. Hence, this study attempts to combine the ApOE and TNF-α with the PSEN1 to determine whether these indicators could be a proper Covid-19 predictor. Furthermore, we hypothesize that ApOE, PSEN1, and TNF-α might be a severity predictor for Covid-19 infection.

2. Methods

This research is quantitative and is included in the analytical observational study. It had 64 samples which then turned into 56 samples regarding the exclusion criteria of the samples. The instruments were used Human PS1 (Presiniilin 1) ELISA Kit, TNF-α (Human)

ELISA Kit, Human ApoE (Apolipoprotein E) ELISA Kit, and patient's thorax serial radiographs. The sampling procedure was first asked for the patient's informed consent, and then the blood sampling was taken due to the ApoE, PSEN1, and TNF-α examination. Second, the thorax serial radiographs were collected and examined by two radiographers in their fields. Furthermore, the ApoE, PSEN1, and TNF-α examinations were done using the ELISA Kit.

Moreover, the collected samples were processed using the SPSS Ver.16.0 application with Spearman rho data analysis to determine the correlation between the dependent and independent variables. In addition, this research had accepted the ethical clearance before it was started by the Health Research Ethics Committee of Dr. Soetomo General and Academic Hospital.

3. Results

There are several characteristics of Covid-19 patients collected as well, as the sampling process was done.

Table 1 Demography data of COVID-19 patients

Category	n = 65
Age	
(Adults = 20-60 years old)	48
(Elderly = > 60 years old)	8
Sex	
(Male)	40
(Female)	16
Comorbidity	12
Steroid Therapy	17
Severity	
(Remain)	19
(Better)	23
(Worsen)	14
Outcome	
(Heal)	41
(Passed away)	15

The table describes several Covid-19 patients' demography, which consists of Age, Sex, Comorbidity, Steroid therapy, Severity degree, and the outcome during treatments. It could be seen that the adults and the male sex have dominated the sample at 85.7% and 71.4 %, respectively. Moreover, a small proportion of respondents had the previous comorbidity at 21.42%, and about 30.3% of patients have received steroid therapy. The better prognosis was dominated the Covid-19 patients at 41.1%, followed by the better outcome at 73.2%.

The ApoE, PSEN1, and TNF-α were examined and processed by SPSS Ver.16 with Spearman Rho data analysis with the basis of decision making such as there is a significant correlation between variables if the value is sig. <0.05 and if the value is sig. > 0.05, there is no significant correlation between variables. Interpretation of the coefficient correlation between variables ranges from 0.01 to 1.00 with the following description: almost no correlation with the range 0.00-0.20, low correlation range 0.21-0.40, moderate correlation range 0.41-0.60, high correlation range 0.61-0.80, and perfect correlation in the range 0.81-1.00.

Table 2 Correlation between ApOE, PSEN1, and TNF-α with the severity score

Category	p-value	Coeficien Correlation
ApOE and severity score	0.440	-0.105
PSEN1 and severity score	0.338	0.118
TNF-α	0.776	0.039

The relation between severity score, which was tested with ApOE, PSEN1, and TNF-α, is mentioned in the table above. It could be seen that there is no correlation between all of the three indicators and severity score regarding the p-values of ApOE, PSEN1, and TNF-α (p-value = 0.440, 0.338, and 0.776 respectively; $\alpha = 0.05$). Furthermore, the ascendency of the indicators and severity score was tenuous, which was then proven by the result. The ApOE had the opposite direction of work; hence, the value was negative.

Table 3 Correlation between ApoE, PSEN1, and TNF-α as the severity predictors of COVID-19

Category	p-value	Coeficien Correlation
ApOE and severity	0.06	- 0.253
PSEN1 and severity	0.730	0.047
TNF-α	0.183	0.180

The table describes the results of whether the ApoE, PSEN1, and TNF-α could become excellent severity predictors of Covid-19. It was found that neither the ApoE, PSEN1, nor TNF-α could become a Covid-19 severity predictor. There was no correlation between the three indicators as a Covid-19 severity predictor (p-value = 0.06, 0.730, and 0.183 respectively, which more than $\alpha = 0.05$). Each indicator had a poor relation as Covid-19 severity predictor; however, one thing that should be highlighted about the ApoE as the Covid-19 severity predictor is that it has controversy about whether the Variable ApoE increases the other variable will decrease.

4. Discussion

In previous studies, having one or two copies of ApoE4 predisposed the Severity of SARS-CoV2 disease, starting with a robust innate immune response, developing a cytokine storm, and ending with ARDS [9]. ApoE with e4e4 increases the risk of Severity of Covid-19 infection despite a pre-existing history of cardiovascular disease, type-2 diabetes, and dementia. Lipoprotein function and the pro-/anti-inflammatory macrophage phenotype were also influenced and moderated by ApOE e4. ACE2 and ApOE receptors are expressed in alveolar type II cells in the lungs, and as is known, SARS-CoV2 enters cells using ACE2 receptors. However, further study is needed to

understand better the biological mechanisms between the ApOE genotype and the Severity of Covid-19 [5].

Since the cytokines in this study consist of IL-6, IL-8, TNF-α, and IL-1β as a whole, we can predict the patient's life expectancy by examining the patients when they first arrived. After adjusting for demographics and comorbidities, each cytokine could predict overall survival independently. IL-6 and IL-8 levels were known to have a strong association with severity (moderate, severe, and severe with end-organ damage), taking into account lung imaging, creatinine clearance (CrCl), vasoactivity, and use of ventilation. However, TNF-a was found to be can differentiate between moderate and severe Covid-19 presentation, use of mechanical ventilation, and only increase with end-organ damage [10].

On the contrary, Presenilin 1 (PSEN1) has not been found yet regarding its correlation to predict the Covid-19 Severity. Hence, the PSEN1 in this research is relatively new.

This study found that ApoE, PSEN1, and TNF-α could not predict the severity of Covid-19 disease due to several reasons: the patient's age where the elderly in this study were minor, then the use of steroids by some patients, and comorbidities suffered by the patient.

The high mortality rate belonged to Elderly patients due to the increase of CFR and symptomatic infection rates. Some studies also say that a significant risk factor for death from Covid-19 is old age [11], [12], [13]. Hence, this research could not prove the three indicators as the good predictors of Covid-19 Severity regarding the less sample of elderly.

Furthermore, steroid usage as therapy could affect the study's result. The timing of corticosteroid therapy was associated with the death of Covid-19 patients at the hospital. Bahl et al. mentioned in their research that Corticosteroid initiation will be triggered at age onset> 7 days. Corticosteroid administration should be withheld for 48-72 hours without invasive mechanical ventilation and can be given if the patient remains in hospital. Hypoxia with supplemental oxygen therapy cannot be the standard for corticosteroid administration unless at the right time [14].

However, in the other study by Gibson, the adjunctive therapies most frequently used in typical ARDS are continuous neuromuscular blocking agents, high-dose corticosteroids, and recruitment maneuvers. In Covid-19 ARDS, corticosteroid administration is only recommended in patients with concomitant shock who are unresponsive to vasopressors, so evidence of systemic steroids is scarce. It is feared that the release of the virus and a higher mortality rate could occur due to steroid administration [15]. Additionally, administration of corticosteroid therapy is associated with delayed viral clearance in other Novel Coronavirus outbreaks. Corticosteroid therapy in pneumonia caused by the influenza virus has a poor outcome in patients' clinical work, including secondary bacterial infection and death [16].

In this research, 17 patients received the steroid therapy with results about three of 16 Covid-19 patients had worsened outcomes, and 5 of 15 patients who received the steroid were dead.

Factors that also influence this study are the comorbidities suffered by patients. It was found that 12 patients in this study had comorbidity that could exacerbate Covid-19 infections such as hypertension, type-2 diabetes mellitus, chronic kidney, and cardiovascular disease. Complementary conditions make it difficult for sufferers of SARS-CoV2 infection in a review with a broad scope, so patient management and proper medical care are essential steps to maintain patient survival [17]. Compared with the results of this study and previous research, there is an inequality in the results obtained, which may be due to the lack of sample size and time of the study and difficulties when collecting data with the Covid-19 situation is not flexible.

5. Conclusion

In this study, it was found that ApoE, PSEN1, and TNF-a were not good predictors for determining how severe the patient's Covid-19 infection was. This outcome is due to several factors that affect the results, such as the lack of a sample of the elderly, the use of steroid therapy, which still requires further research regarding the pros and cons of previous studies, and the small number of samples of patients who have comorbid that can exacerbate Covid-19 infection.

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