Procalcitonin Levels in Pregnant Women With or Without Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Infection

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Abstract

Background : Coronavirus Disease (Covid-19) can affects all levels of society, there is no exception for pregnant women. Physiological changes and modulate immune response occur during pregnancy as a form of tolerance to fetal-allogenic, as well as reserving the ability to fight against microorganism. Inflammatory response can be shown by circulating biomarkers that can represent inflammatory status like neutrophile, lymphocyte and procalcitonin. There has been a lot of research before, that indicate the biomarkers can be use as predictors to diagnosis and prognosis of Covid-19.
Objective : This study aims to determine whether there are differences in NLR, PLR, and procalcitonin of pregnant women and infected by SARS-CoV-2 at third trimester gestasional age
Methods : Prospective cross sectional study was conducted between January and March 2021 among 48 pregnant women with or without Covid-19 infection.
Results : This study analyze 24 pregnant women with no infection and 24 pregnant women with Covid-19 infection. There were patients with asymptomatic (n=14), mild symptom (n=8) and severe (n=2). Procalcitonin levels in non-infected and infected group were 156,29 (93,72–445,5) and 212,25 (111,8–650,5) respectively.
Conclusion : Procalcitonin value tends to be the same in non-infected and infected Covid-19 groups. Even in infected group based on severity disease there was no difference procalcitonin levels.

Keywords : Covid-19 in pregnancy, procalcitonin, inflammatory biomarker

1. Introduction

The emergence condition of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread rapidly throughout the world and caused a disease known as Coronavirus Disease 2019 (Covid-19). This virus is a new type of coronavirus not previously identified in humans, at least two types of similar viruses have been known to cause diseases with severe symptoms have emerged Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). First reported on 31 December 2019, identified as a new type of coronavirus on 7 January 2020 and declared as a pandemic condition on 11 March 2020 by WHO. (Li et al., 2020)

The course of the disease is very vary, making a diagnosis of Covid-19 is a bit difficult and clinical symptoms that appear change very quickly, early diagnosis and evaluation of disease severity through radiological images depends on the experience of the examiner (Wang et al., 2020). Appropriate indicators to predict disease suspicion and to assess disease severity are urgently necessary in order to significantly reduce the risk of transmission and mortality in patients with severe symptoms. Among all parameters, the blood

lymphocyte percentage is the most significant and consistent in reflecting the disease because has an important role in maintaining homeostasis and inflammatory responses throughout the body. (Tan et al., 2020)

A severe inflammatory response contributes to a weak adaptive immune response, resulting in an imbalanced immune response. This makes circulating markers able to represent inflammatory status and potential predictors for the prognosis of Covid-19 patients such as white blood cell count, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio and platelet to lymphocyte ratio (PLR) is widely used to predict the prognosis of patients with viral pneumonia (Yang et al., 2020). Another inflammatory biomarker that is thought to be used as a parameter is procalcitonin. In conditions infected of Covid-19 procalcitonin tends to be increase in severe symptoms. (Hu et al., 2020)

Procalcitonin is the amino acid polypeptide of the hormone calcitonin, is normally synthesised and produced by thyroid parafollicular C cells , metabolized to produce calcitonin hormone precursors that play a role in calcium hemostasis through osteoclasts in bone. Similar to C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and elevated white blood cell count are widely used in clinical practice for the diagnosis and management of infection (Lippi and Carvellin., 2018). In pregnant women procalcitonin levels remain normal until the third trimester of pregnancy. (Paccolat et al., 2011).

2. Materials and methods

This study is a cross-sectional study to assess differences of procalcitonin in third trimester pregnant women with or without Covid-19 infection. This research was conducted in delivery room at Dr. Soetomo Hospital Surabaya, which is a tertiary referral hospital in East Java since January–March 2021 and has approval by Ethics Committee of Soetomo Hospital Medical Sciences

The qualified research subjects will be treated the same by taking venous blood samples for examination of inflammatory biomarkers using the appropriate protocol. Research subjects in infected group obtained positive results for SARS-CoV-2 with laboratory examination using *Real Time Reverse Transcriptase Polymerase Chain Reaction* (RT-PCR) in the nasopharynx with Abbot m2000 reagent if RdRP or N-gene with CT (cycle threshold) < 40.

Data are expressed as medians (interquartile range) for numeric variables. Continuos variables with a normal distribution are expressed as mean (standard deviation). Categorical variables are summarised as counts (percentages). Kolmogorov-Smirnov one sample normality test to see the distribution of the data. Continued by using parametric test (T-test) or non-parametric test (Mann-Whitney test). All analyses were performed with IBM SPSS Statistics v23. A p-value <0.05 was considered statistically significant.

3. Results

A total of 48 patients were included in the study, consist of 24 pregnant women infected with Covid-19 and 24 pregnant women not infected have been qualified. According to their severity of pneumonia on admission to hospital, they were classified into three groups as follows asymptomatic (n=14), mild (n=8), and severe (n=2). There was a different feature of symptoms that appeared, the most common symptomps in the mild group were fever (3/8; 37.5%), cough (6/8; 75%), and anosmia (5/8; 62.5%), while in the severe group is

always accompanied by shortness of breath that worsen very quickly and death occurs. There was no history of other diseases in these patients. Differences in maternal characteristics and laboratory parameters can be seen in table 1. Procalcitonin levels in infected and non-infected group described in figure 1.

Table 1. Maternal characteristics and laboratory parameters

|	Not infected n = 24	Infected n = 24	p value
Maternal Characteristics			
Maternal age	31,04± 5,7	29,96± 4,9	0,441
Gestational age	36,13± 1,92	36,5± 2,3	1,000
Parity			0,002
Nullipara	3 (12,5%)	13 (54,2%)	
Multipara	21 (87,5%)	11 (45,8%)	
Laboratory Parameters			
Leucocytes (× 103/μL)	11,54 (5,6-22,8)	11,81 (5,9-21,7)	0,578
Neutrophils (× 103/μL)	8,75 (3,6-19,4)	8,99 (4,5-18,7)	0,845
Lymphocytes (× 103/μL)	1,69 ± 0,57	1,51 ± 0,68	0,315
Platelets (× 103/μL)	271,5 (148-392)	295,0 (135-631)	0,445
NLR	5,62 (1,9-21,1)	6,01 (2,3-27,9)	0,421
PLR	156,29 (93,7-445,5)	212,25 (111,8-650,5)	0,048
Procalcitonin	0,09 (0,01-0,41)	0,14 (0,01-2,52)	0,185
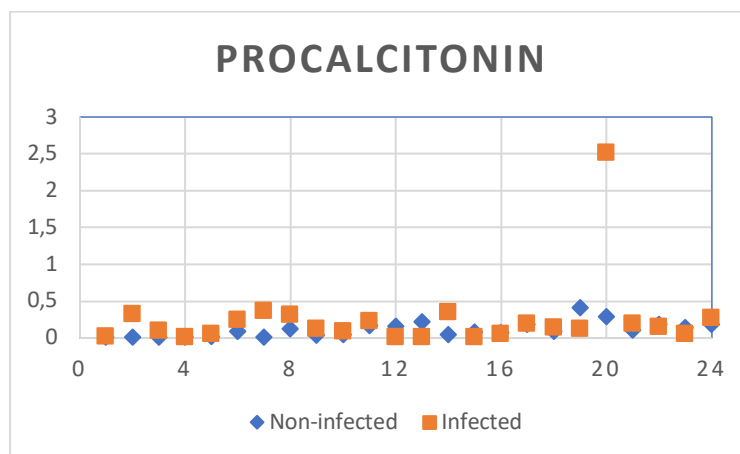
Figure 1. Difference of procalcitonin levels

4. Discussion

This study showed procalcitonin levels in almost whole patients (infected or non-infected) was <0,5μg/L. Of 24 patients with laboratory confirmed SARS-CoV-2 infection, two patients died. One patient presented with severe symptoms in respiratory failure and acidosis, procalcitonin value was 2,52 μg/L, normal chest X-

ray, and no history of infectious disease before the onset symptoms of shortness of breath and had no comorbidities. The patient complained of shortness of breath two days before admission that worsened very rapidly and died after four days of treatment and termination of pregnancy.

Another case of death in this study was a patient with shortness of breath then laboratory confirmed Covid-19 three days later and respiratory failure at admission, chest x-ray results bilateral pneumonia and procalcitonin value 0,32 μg/L. After ten days of treatment since the symptoms were appeared, evaluation of procalcitonin examination was carried out with result was 16,96 μg/L and chest X-ray with severe bilateral pneumonia. This case shows that procalcitonin value is not suitable to be used as inflammatory marker in Covid-19 infection and cannot be used to assess severity disease caused by Covid-19 infection, but serial procalcitonin measurements may be useful for predicting the prognosis or severity disease when the secondary infection occured. Elevated procalcitonin levels have been reported to be associated with the severity of Covid-19.

A recent study using procalcitonin as an inflammatory marker to assess the severity of Covid-19 infection was carried out on 95 patients with positive RT-PCR swab results were grouped into mild symptoms, severe symptoms and critical symptoms. The study demonstrates that there was an increase in procalcitonin levels on 3 days measurement after admission, during treatment and 7 days before discharged with significance value of $p<0,05$. Procalcitonin levels increase as well as the disease progresses. The average value of procalcitonin in severe symptom group was 4 times higher than mild symptom group and about 8 times higher in critical symptoms group than mild symptoms group. (Hu et al., 2020)

A meta-analysis showed that elevated procalcitonin levels had a five-fold higher risk of becoming infected with SARS-CoV-2. Laboratory data from Tongji Medical College in Wuhan China on 62 patients with moderate symptoms and 21 patients with severe disease showed that procalcitonin levels increased with disease severity ($p < 0.05$). Of the 38 patients recovered, procalcitonin levels decreased during treatment, significant difference from levels at first measurement. (Hu et al., 2020)

Procalcitonin produced and released into the circulation from extra-thyroid is very large during bacterial infection actively maintained by increasing the concentration of IL-1β, TNF-α and IL-6. However, this biomarker can be inhibited by increasing IFN-γ during viral infection. It is not surprising that procalcitonin levels remain within normal limits in some patients with uncomplicated SARS-CoV-2 infection, but a substantial increase would reflect the presence of secondary infection that develops in severe disease conditions. (Lippi and Plebani., 2020)

In sepsis condition, procalcitonin can also be released from liver and peripheral blood mononuclear cells mediated by IL-6, IL-1β and TNF-α. Most studies accepted procalcitonin as diagnostic marker of the inflammatory process and guidelines antibiotic prescribing, especially in respiratory disease (Rhodes et al., 2017). During severe inflammation or sepsis, procalcitonin levels increase rapidly than CRP and peaks within very short time. While in pregnancy, procalcitonin is not relevant to be used as the maternal infection marker because procalcitonin is expressed very low by decidual cells and hormonal-immune conditions in pregnancy which cause rejection of lipopolysaccharide activation. (Mangogna et al., 2019)

This study uses subjects with specific population the pregnant women, during the outbreaks research about inflammatory markers has been carried out in general population only. Best our knowledge, this is the first study distinguish inflammatory markers in a group of pregnant women. Several notable limitations existed in this study. First, procalcitonin measurement only carried out once when the patient admitted. This causes appraisal of procalcitonin biomarkers cannot be used as a parameter to determine disease prognosis or the occurrence of secondary infection by Covid-19. In addition, the unmatched sample selection between control group and case group could also affect the results study, and gestational age used in this study was limited on third trimester.

5. Conclusion

This study showed that there was no difference in procalcitonin levels in pregnant women infected with Covid-19 and those who were not infected. Serial procalcitonin measurements may be useful in predicting the prognosis and requiring further research.

Conflicts of Interest

The authors declare there are no conflicts of interest

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