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Inflammatory Marker Trajectories in Pulmonary COVID-19: An Analysis of IL-6, hsCRP, and IFN-γ

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ABSTRACT

Introduction: Multiple inflammatory markers, including high sensitivity C-reactive protein (hsCRP), procalcitonin, interleukin-6 (IL-6), D-dimer, lactate dehydrogenase (LDH), and ferritin, have demonstrated significant sensitivity as predictors of COVID-19 severity. However, there is a paucity of research investigating the association of IL-6, CRP, and interferon-gamma (IFN-γ) with day of illness in confirmed mild and moderate pulmonary COVID-19 cases in Indonesia.

Methods: This retrospective analytic study utilised secondary data extracted from the medical records. The study was conducted over a nine-month period, from December 2020 to October 2021, and included a total of 80 subjects. These subjects were categorised into 60 mild and 20 moderate COVID-19 cases.

Results: Analysis revealed a statistically significant difference in median IL-6 levels, with moderate cases exhibiting higher levels than mild cases (4.50 pg/mL vs. 2.87 pg/mL, difference = 1.63 pg/mL; p=0.008). Similarly, median hsCRP levels were significantly elevated in moderate cases compared to mild cases (3.85 mg/L vs. 0.90 mg/L, difference = 2.95 mg/L; p=0.001). Conversely, IFN-γ levels did not demonstrate a significant difference between moderate and mild cases (0.23 pg/mL vs. 0.28 pg/mL; p=0.907). Regarding temporal trends, IL-6 levels tended to increase until the fourth day of illness before declining on the fifth day. hsCRP levels were elevated on the first and fourth days but decreased by the fifth day, while IFN-γ concentrations peaked on the first and third days.

Conclusion: This study demonstrates a significant elevation in IL-6 and hsCRP levels in patients with confirmed moderate COVID-19, compared to those with mild disease. However, no significant difference was observed in IFN-γ levels between these two groups. Peak levels of IL-6 and hsCRP were recorded on day 1 and day 4 of illness, respectively.

Keywords: COVID-19, day of illness, IL-6, hsCRP, IFN-γ.
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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), commonly known as the novel coronavirus, emerged in December 2019 as the causative agent of Coronavirus Disease 2019 (COVID-19).[1] Evidence suggests that patients experiencing severe COVID-19 symptoms often exhibit impaired immune responses.[2] Therefore, it is crucial to examine laboratory parameters for markers of hyperinflammation to potentially reduce mortality. This is because a robust inflammatory response can paradoxically weaken the adaptive immune response, leading to overall immune dysfunction.[3] Consequently, circulating biomarkers reflecting inflammatory status hold promise as potential predictors of COVID-19 patient prognosis.[3]

A meta-analysis conducted in 2020 identified several inflammatory markers, including C-reactive protein (CRP), procalcitonin, interleukin-6 (IL-6), D-dimer, lactate dehydrogenase (LDH), and ferritin, as highly sensitive predictors of COVID-19 severity.[1,4] Previous research indicates that IL-6, a key cytokine produced during tissue damage, activates the inflammatory cascade and stimulates CRP production.[5,6] Conversely, interferon-gamma (IFN-γ) directly inhibits viral replication and acts as an immunomodulator against viral infections, stimulating the adaptive immune system to produce antibodies.[7,8]

An overrepresentation of interferons (IFNs) in the lower airways of severe COVID-19 patients is associated with the upregulation of gene pathways linked to increased apoptosis and decreased cellular proliferation (CELL 2021). Inhibiting IFN-γ and TNF-α was shown to reduce mortality in sepsis resulting from COVID-19 infection.[2] An earlier study

observed a decrease in IFN-γ among severe cases, yet it lacked a clear distinction between mild and moderate disease.

A cohort study investigating inflammatory cytokine levels found that fluctuations in cytokine levels in patients with mild COVID-19 were not significant compared to those with severe disease.[2] Most of these inflammatory cytokines typically peak 3-6 days after disease onset.[2] The day of illness is a critical variable when assessing inflammatory cytokine levels due to its direct relevance to the immune response and disease pathophysiology.[2] There is a paucity of research investigating the association of IL-6, hsCRP, and interferon-gamma (IFN-γ) with day of illness in COVID-19 cases in Indonesia. This study aimed to evaluate the association of IL-6, hsCRP, and IFN- γ with day of illness in confirmed mild and moderate pulmonary COVID-19 cases.

METHODS

This was a retrospective analytical study, which utilised data from the RHEA-COVID-19 research that were conducted at two primary COVID-19 treatment centers in Indonesia: RSUP Dr. Hasan Sadikin Bandung and the Wisma Athletes Emergency Hospital for COVID-19 handling in Jakarta. Subject recruitment occurred between December 2020 and October 2021, encompassing patients who met predefined inclusion and exclusion criteria. Total sampling was used in this study.

Inclusion criteria for participants were adults aged 18 to 50 years who had pulmonary COVID-19 confirmed by PCR testing, presenting with either mild or moderate disease severity. Exclusion criteria comprised individuals who were pregnant or lactating, diagnosed with comorbidities such as: cardiovascular disease, cardiac arrhythmia, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, neurological disease, a history of autoimmune diseases, cancer, or HIV/AIDS; using steroids, either acutely (3 to 14 days) or long-term (>14 days), and had secondary bacterial infection. The study protocol received approval from the Health Research Ethics Committee of RSUP Dr. Hasan Sadikin Bandung (ethic approval number: LB.02.01/X.6.5/202/2022). Data collection from the RHEA-COVID-19 study's medical records took place in July and August 2022. Only confirmed pulmonary COVID-19 patients who fulfilled both the inclusion and exclusion criteria were enrolled as subjects.

Statistical analysis

Numerical data underwent normality testing using the Kolmogorov-Smirnov statistical test. Data were considered normally distributed if the p-value exceeded 0.05. Comparative analysis was performed using the Mann-Whitney U test, with statistical significance defined as a p-value less than 0.05.

Inflammatory marker analysis

Sampling of inflammatory marker parameters was conducted on the first day of the subjects' treatment, without subsequent daily follow-up. Inflammatory markers were examined using ELISA and immunoturbidimetry methods. High-sensitivity C-reactive protein (hsCRP) was specifically utilised in this study due to its enhanced sensitivity for quantification, particularly to evaluate mild and moderate cases. Analysis across illness days was decribed narratively.

RESULTS

The study comprised a total of 80 subjects, with an average age of 31 years (SD: 9 years). The cohort was equally distributed by gender, with 50% male and 50% female participants. The median day of illness at the time of assessment was 2 days, ranging from 1 to 9 days, as detailed in **Table 1**.

IL-6 levels generally showed an upward trend, peaking on the fourth day of illness before declining by the fifth day. In contrast, hsCRP levels were notably elevated on the first day, subsequently decreasing until the third day, then rising again on the fourth day, only to decrease once more by the fifth day of illness. IFN-γ levels exhibited fluctuations from the first to the third day, followed by a decrease on both the fourth and fifth days of illness. These trends are visually represented in **Table 2** and **Figure 1**.

Table 3 presents the differences in IL-6, hsCRP, and IFN-γ levels categorised by disease severity. The median IL-6 concentration in moderate cases was significantly higher than in mild cases, with a difference of 1.63 pg/mL (4.50 pg/mL vs. 2.87 pg/mL, p=0.008). Similarly, median hsCRP levels were also significantly elevated in moderate cases compared to mild cases, showing a difference of 2.95 mg/L (3.85 mg/L vs. 0.90 mg/L, p=0.001). Conversely, IFN-γ levels did not exhibit a statistically significant difference between moderate and mild disease (0.23 pg/mL vs. 0.28 pg/mL, p=0.907).

Analysis based on disease severity revealed that IL-6 and hsCRP levels were elevated in moderate cases compared to mild cases, while IFN-γ levels remained largely comparable between the two groups. In subjects with mild disease, IL-6 levels typically rose until the third day of illness, subsequently decreasing on the fourth and fifth days. Similarly, hsCRP and IFN-γ levels in this group also increased until the fourth day, followed by a decline on the fifth day of illness. Conversely, in subjects with moderate disease, IL-6, hsCRP, and IFN-γ levels were already high on the first day. IL-6 and IFN-γ levels in this group tended to decrease until the third day, but then increased again on the fourth day of illness. hsCRP, however, showed an initial decrease on the second day before increasing again until the fourth day of illness. These patterns are further illustrated in **Table 4, Figures 2, 3,** and **4**.

DISCUSSION

COVID-19 patients exhibit elevated levels of several pro-inflammatory cytokines, such as IL-1β, IL-6, TNF, IL-12, IFN-γ, and IL-17, with these increases correlating with greater disease severity and higher mortality rates.[2] The findings of this study largely align with those reported by Liu et al., which demonstrated significant differences in inflammatory marker levels between mild and severe COVID-19 cases.[9] Our results indicated that IL-6 levels typically rose until the fourth day of illness before declining by the fifth day. High-sensitivity C-reactive protein (hsCRP) was observed to be elevated on the first day, subsequently decreasing until the third day, increasing again on the fourth day, and then declining by the fifth day of

Table 1. Baseline Characteristics of the Patients

Characteristics	Total n=80
Age (years)[a]	31 ± 9
Gender[c]	
Female	40 (50.0)
Male	40 (50.0)
Day of ilness[b]	2 (1 – 9)
Day of illness, n (%)	
1	26 (32.5)
2	29 (36.3)
3	12 (15.0)
4	7 (8.8)
5 or more	6 (7.5)

Note: [a]Mean±SD; [b]Median (Min-Maks);

illness. Interferon-gamma (IFN-γ) levels tended to fluctuate between the first and third days, followed by a decrease on both the fourth and fifth days. Longitudinal analysis conducted by Liu et al. similarly found that elevated IL-6 and CRP levels peaked on the third day of illness, although an increase in IFN-γ levels was exclusively noted in severe case.[9] Further analysis revealed elevated levels of IL-6, IL-10, IL-2, and IFN-γ in the peripheral blood of severe cases compared to mild cases. In severe COVID-19 patients who recovered, cytokine levels gradually normalised to levels comparable to those observed in mild cases at later time points.[9]

The observed elevations in IL-6 and hsCRP levels are consistent with their established roles in the inflammatory cascade. Following local tissue injury, IL-6 is rapidly released into the bloodstream, stimulating the liver to produce acute phase proteins, including CRP.[10] The circulating concentration of CRP is largely determined by its synthesis rate.[10] While the liver is the primary site of CRP synthesis, its mRNA has been detected in various other tissues, such as adipose tissue, lungs, renal cortical tubular epithelial cells, atherosclerotic lesions, macrophages, lymphocytes, and smooth muscle cells.[11] During the initial phase of infection, lymphocytes and macrophages are the dominant leukocyte cells.[12] The synthesis of CRP on the first day of illness is associated with the high activity of these cells, which can produce CRP independently, thus not requiring

Table 2. Distribution of IL-6, hsCRP, and IFN-γ Levels by Day of Illness

Day of Illness	n	IL-6 (pg/mL) Median (IQR)	hsCRP (mg/L) Median (IQR)	IFN-γ (pg/mL) Median (IQR)
1	26	2.95 (2.37 - 4.57)	2.50 (0.45 - 4.75)	0.36 (0.15 - 0.87)
2	29	3.06 (2.31 - 3.96)	1.20 (0.35 - 6.70)	0.21 (0.15 - 0.84)
3	12	3.69 (2.88 - 5.93)	0.95 (0.40 - 2.18)	0.30 (0.17 - 1.08)
4	7	3.84 (1.93 - 13.36)	2.10 (0.60 - 21.60)	0.24 (0.15 - 1.26)
≥5	6	2.38 (2.11 - 3.06)	0.50 (0.25 - 1.93)	0.16 (0.14 - 0.53)

Note: IQR: Interquartile Range

Table 3. Differences in IL-6, hsCRP, and IFN-γ Levels based on the Severity of Illness

Variable	Mild n=60 Median (IQR)	Moderate n=20 Median (IQR)	Median Difference (95% CI)	p-value
IL-6 (pg/mL)	2.87 (1.27 – 19.53)	4.50 (1.45 – 14.17)	1.63 (0.39 – 2.45)	**0.008***
hsCRP (mg/L)	0.90 (0.05 – 32.30)	3.85 (0.40 – 42.60)	2.95 (0.70 – 4.40)	**0.001***
IFN-γ (pg/mL)	0.28 (0.09 – 9.72)	0.23 (0.09 – 5.33)	-0.05 (-0.13 – 0.11)	0.907

Note: IQR: Interquartile Range, *p<0.05 is considered significant

Table 4. Distribution of IL-6, hsCRP, and IFN-γ Levels based on Severity and Days of Illness

Day of illness	Severity	n	IL-6 (pg/mL) Median (IQR)	hsCRP (mg/L) Median (IQR)	IFN-γ (pg/mL) Median (IQR)
1	Mild	19	0.95 (0.38 - 2.83)	2.53 (2.20 - 3.58)	0.30 (0.15 - 0.56)
2	Mild	23	1.10 (0.10 - 2.40)	2.87 (2.24 - 3.90)	0.28 (0.15 - 0.92)
3	Mild	9	1.30 (0.40 - 5.90)	3.13 (2.63 - 5.12)	0.41 (0.19 - 1.02)
4	Mild	3	0.60 (0.40 - 3.20)	3.84 (2.16 - 4.75)	1.10 (0.14 - 1.26)
≥5	Mild	6	0.50 (0.25 - 1.93)	2.38 (2.11 - 3.06)	0.16 (0.14 - 0.53)
1	Moderate	7	4.80 (3.50 - 15.10)	4.53 (3.46 - 5.06)	0.42 (0.34 - 2.58)
2	Moderate	6	3.60 (1.95 - 19.58)	3.99 (2.94 - 9.02)	0.17 (0.14 - 1.49)
3	Moderate	3	0.44 (0.40 - 2.10)	5.98 (3.19 - 6.99)	0.13 (0.12 - 1.85)
4	Moderate	4	11.85 (1.13 - 27.53)	7.65 (1.89 - 13.97)	0.22 (0.16 - 1.84)
≥5	Moderate	-	-	-	-

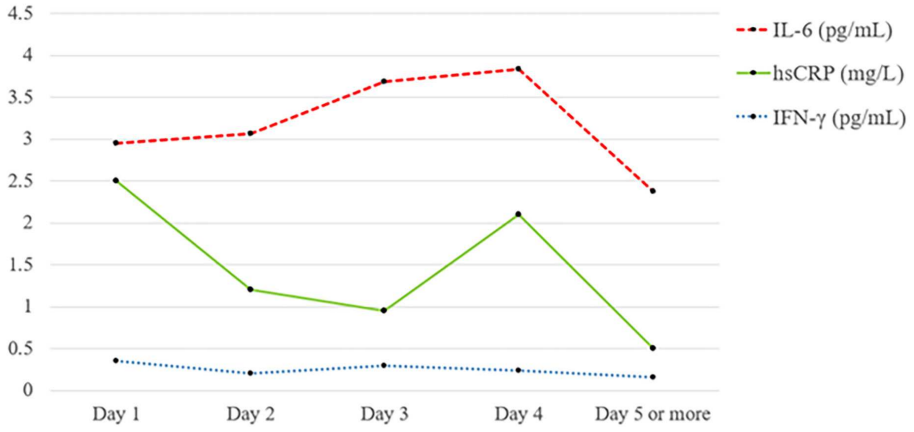

Figure 1. IL-6, hsCRP and IFN-γ levels by day of illness

IL-6 stimulation.[12] A study conducted by Hu et al. demonstrated significant increase of CRP levels between moderate and severe COVID-19 patients.[13] This finding is consistent with our results, which demonstrated elevated hsCRP levels in the moderate case group compared to the mild case group.

Interferon-gamma plays a crucial role in both innate and adaptive immune responses.[8] It functions as an effector for various immune mechanisms, including the activation of cell-mediated immunity through natural killer (NK) cells, cytotoxic immunity via the interaction of T cells and antigen-presenting cells (APCs), and macrophage activation.[8,14] The coordinated action of IL-12 and IFN-γ is vital for pathogen recognition by the innate immune system and the induction of specific immunity by augmenting the Th1 response.[14] In COVID-19 infection, IFN-γ can enhance the expression of ACE2 (the SARS-CoV-2 receptor) on airway epithelial cells, suggesting a potential proviral effect that counterbalances its antiviral action.[13] However, studies show conflicting results regarding IFN-γ levels and disease severity.[15] Some report increased IFN-γ in severe cases, while others link decreased levels to lung fibrosis or find robust IFN-γ responses in asymptomatic individuals, suggesting immunotolerance.[15]

In COVID-19 patients, elevated IL-6 levels lead to a significant depletion of crucial immune cells—specifically CD4+ T cells, CD8+ T cells, and natural killer cells—thereby compromising the overall immune response.[16] A study conducted by Ghaffarpour et al. demonstrated that across all COVID-19 subgroups, TNF-α, IL-6, IL-2, IL-8, and IL-18 exhibited significantly elevated concentrations when compared to the control group.[2] Across all study time points, interleukin-6 (IL-6) production was markedly increased in the moderate, severe, and critical subgroups when contrasted with the mild group. Additionally, the moderate case group consistently exhibited higher IL-6 levels than the critical case group throughout the study duration.[2] IFN-γ levels did not show a significant difference among the study groups.[2] This finding aligns with our results, which similarly demonstrated no significant difference in IFN-γ levels between mild and moderate cases.

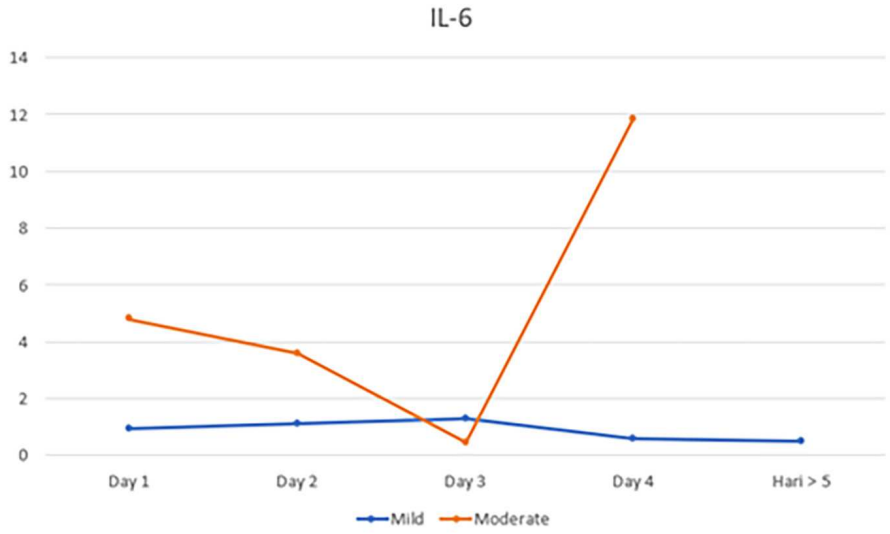

Figure 2. IL-6 Levels based on Severity and Days of Illness

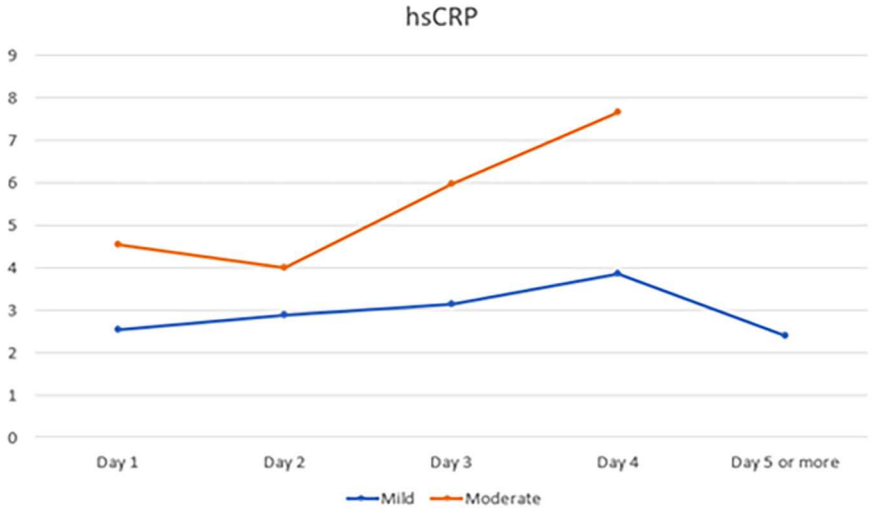

Figure 3. hsCRP Levels based on Severity and Days of Illness

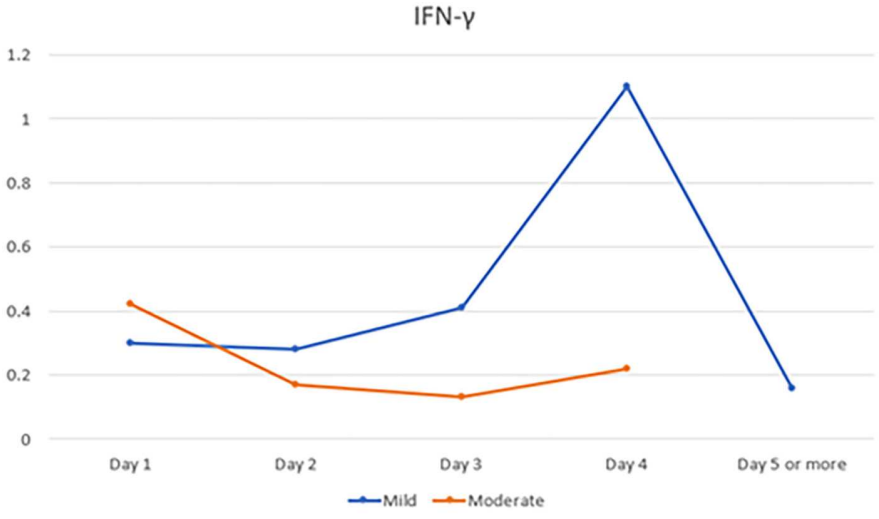

Figure 4. IFN-γ Levels based on Severity and Days of Illness

A study by Gadotti et al. identified IFN-γ as an independent risk factor for mortality in patients with moderate and severe COVID-19 infection.[17] Their findings indicated an effective Th1 response followed by the development of an adaptive Th2 immune response.[17] IFN-γ possesses antiviral properties but can also contribute to fibrosis development following viral infection, a phenomenon not observed in mild and moderate COVID-19 cases.[13,17] A study conducted by Hu et al. found there was no difference in the IFN-γ levels between moderate and severe COVID-19 patients.[13] At discharge, 46 (60.5%) patients had lung fibrosis, and their plasma IFN-γ levels were twofold lower than those without fibrosis.[13] For every 1-SD (standard deviation) increase in basal IFN-γ, the fibrotic volume decreased by 0.070% at discharge.[13] This suggests that decreased circulating IFN-γ is a risk factor for lung fibrosis in COVID-19.[13] Given that the subjects in the current study were aged 18-50 years and presented with mild to moderate COVID-19, these risk factors for fibrosis were not present.

The limitations of this study include: the inflammatory marker sampling was conducted on the second day of hospitalisation and lacked daily follow-up. Consequently, the complete temporal pattern of changes in inflammatory markers based on the day of illness could not be comprehensively observed. Furthermore, the reliance on patient history to determine the day of illness introduces the potential for recall bias, which could affect the accuracy of the results. Future research would benefit from a larger sample size and a more balanced distribution of mild and moderate cases, to enable statistically more robust comparisons.

CONCLUSION

A significant increase in IL-6 and hsCRP levels was observed in patients diagnosed with moderate COVID-19 compared to individuals with mild cases. However, no statistically significant difference in IFN-γ levels was found when comparing these two groups. The peak levels for IL-6 and hsCRP were identified on day 1 and day 4 of illness, respectively, suggesting these days may be optimal for assessing these specific inflammatory markers.

DISCLOSURES

ETHICAL APPROVAL

The study protocol received approval from the Health Research Ethics Committee of RSUP Dr. Hasan Sadikin Bandung (ethic approval number: LB.02.01/X.6.5/202/2022).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

PS and FR involved in conceptualization, designing, data curation, investigation, writing and supervising the manuscript. SC involved in conceptualization, investigation, writing, reviewing, and editing the manuscript. RS, AR, KL, and HB involved in data curation, investigation, reviewing and editing the manuscript. All authors prepare the manuscript and agree for this final version of manuscript to be submitted to this journal.

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