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ORIGINAL ARTICLE

The Relationship Between Serum Endocan Levels and Macrophage Activation Syndrome in COVID-19 Patients

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Abstract

Background: Endothelial cell-specific molecule-1 (ESM-1), also known as endocan, is a biomarker associated with endothelial dysfunction. It is synthesised primarily by vascular endothelial cells, epithelial cells lining the distal renal tubules, and submucosal glands of the bronchi and lungs. The objectives of this study were to investigate the relationship between this molecule, which is known to play a role in inflammatory processes, and macrophage activation syndrome (MAS) associated with COVID-19; and to evaluate whether serum endocan levels are a predictive marker of mortality and clinical severity in COVID-19 patients.

Methods: A total of 90 patients diagnosed with COVID-19 were included in the study. Serum samples were collected to determine endocan levels, which were measured using the enzyme-linked immunosorbent assay (ELISA) method. Patients were divided into two groups based on the COVID-19-associated hyperinflammatory syndrome (cHIS) score: Group 1 (cHIS score ≥2/ low-grade hyperinflammation) and Group 2 (cHIS score <2).

Results: There was no statistically significant difference in serum endocan levels between the two groups. However, Group 1 showed significantly lower lymphocyte counts (p=0.007) and significantly higher levels of ferritin, CRP, IL-6, D-dimer, neutrophil/lymphocyte ratio, LDH, and glucose (all p<0.001) compared to Group 2. Hospital stay duration was positively correlated with the neutrophil/lymphocyte ratio (p<0.001, r=0.464), D-dimer (p=0.014, r=0.277), LDH (p=0.001, r=0.364), and AST (p=0.005, r=0.312).

Conclusion: No significant association was found between serum endocan levels and COVID-19-related hyperinflammatory states. Considering the multiple mechanisms that may influence endocan expression, long-term, multicenter, and controlled studies are required to better understand the clinical significance of this biomarker.

Keywords: Macrophage activation syndrome, cytokine storm, endocan.

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INTRODUCTION

COVID-19 is a highly contagious infectious disease caused by SARS-CoV-2 virus, transmitted by respiratory droplets and declared a global pandemic in 2020 (1,2). The main route of transmission is the respiratory tract; faecal-oral transmission is supported by limited evidence (3).

In severe cases, acute respiratory distress syndrome (ARDS), cardiac arrhythmias, thromboembolism, encephalopathy and secondary infections may be observed (4). Increased markers including D-dimer, CRP, LDH, ferritin, troponin and lymphocytopenia are typical in laboratory findings (5).

Although RT-PCR is accepted as the gold standard in the diagnosis, its sensitivity is limited; therefore, it is recommended to be supported by thorax CT and serological tests (6).

There is no specific treatment for the disease yet. While mild cases are followed up symptomatically, dexamethasone, oxygen support and some antiviral/immunomodulatory drugs are used in severe cases (7).

Macrophage activation syndrome (MAS), also known as haemophagocytic lymphohistiocytosis (HLH), is a severe hyperinflammatory syndrome that occurs with excessive activation of the immune system and may lead to high mortality (8).

Macrophage activation syndrome (MAS) is an important hyperinflammatory picture that is common in severe forms of COVID-19 and increases mortality.

Since lymphopenia, neutrophilia and high fibrinogen levels, which are common in COVID-19 patients, do not overlap with classical MAS diagnostic systems (HLH-2004, H-Score), the cHIS scoring system was developed by Webb et al. This system includes six criteria and a score of ≥2 increases mortality and the need for mechanical ventilation (9).

Immunosuppressive agents are at the forefront in treatment. While high-dose corticosteroids constitute the basic approach, IL-1 inhibitor anakinra and IL-6 inhibitor tocilizumab are effective options in severe cases (10).

Endothelial cell-specific molecule-1 (ESM-1) or endocan is a new biomarker related with endothelial damage, which was defined in 1996 (11). It is synthesised mainly in vascular endothelial cells, bronchial and lung submucosal glands and renal distal tubule epithelia. Endocan, which is found at low levels in the circulation, plays a role in regulating cellular adhesion during inflammation and tumour development (12).

When the relevant literature was examined, it was observed that studies examining endocan levels in patients diagnosed with COVID-19 were limited. In this study, it was aimed to examine the endocan level of patients diagnosed with COVID-19. For this purpose, patients were divided into two groups as cHIS≥2 and cHIS<2 according to their cHIS scores and it was examined whether endocan levels differed according to the groups. The importance of this study is that it provides direction for future research.

MATERIALS AND METHODS

This study was approved by the Health Sciences University (SBU) Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee with decision number 488 on 29.12.2020. The study is an observational prospective research and was conducted using the Human Endocan-1 ELISA kit. The kit was provided by the hospital in accordance with the decision of the Medical Speciality Education Board (TUEK) dated 26.11.2020, Meeting No: 52.

The study was started on 1 January 2021 and the study period was planned as one month. Detailed information about the study was given to the patient and control group individuals participating in the study, and written informed consent was obtained from all participants.

A total of 90 volunteer COVID-19 patients who were hospitalised in the Internal Medicine and COVID-19 wards of the University of Health Sciences Prof. Dr. Cemil Taşcıoğlu City Hospital and actively followed up during the research period were included in the study. Participants were included in the study if they met the conditions of having a positive COVID-19 PCR test, being over 18 years of age, not being pregnant, and voluntarily participating in the study.

Participants were scored according to the cHIS scoring system and divided into two groups. Patients with a cHIS score ≥2 constituted Group 1; patients with a cHIS score <2 constituted Group 2, which was defined as the

control group. The cHIS score assessment and serum endocan measurements were performed on the same day for each participant to ensure temporal consistency between clinical and biochemical data.

Exclusion criteria were applied in the same way for both groups. Accordingly, individuals under 18 years of age, volunteers who did not want to participate in the study, pregnant women, patients with negative COVID-19 PCR test, patients with a diagnosis of chronic kidney disease with glomerular filtration rate (GFR) <30 ml/min/1.73 m², patients with a history of active malignancy, patients with chronic inflammatory disease (e.g. rheumatoid arthritis, SLE), coronary artery or peripheral artery disease, and patients with diagnosed diabetes mellitus were excluded from the study. These comprehensive exclusion criteria were determined to control for other inflammatory or vascular diseases that might affect endocan levels.

One venous blood sample was collected in a biochemistry tube from each patient and control group to measure endocan-1 levels. The samples were centrifuged and the supernatant was separated and transferred to Eppendorf tubes and stored at -80°C. These samples were analysed in Gelişim Medical Laboratory.

Age, gender, height and weight information of the patients were recorded. Comorbidities, medications used were questioned and physical examinations were performed. The duration of hospitalisation and clinical outcomes (discharge, need for intensive care, excitus) were also recorded. Liver function tests, haemogram, glucose, coagulation tests, ferritin, D-dimer, fibrinogen, procalcitonin, LDH, SO_2, IL-6 and C-reactive protein (CRP) levels, which are frequently used in COVID-19 follow-up, were scanned from the hospital information system.

In line with these parameters, the cHIS scoring system was applied for patients diagnosed with COVID-19 (See Table 5). Individuals with cHIS ≥ 2 according to the scoring were included in Group 1, and individuals with cHIS < 2 were included in Group 2, which was defined as the control group. In accordance with the data obtained, the relationship between endocan-1 levels in these two groups was analysed statistically.

The scoring system used in the evaluation of COVID-19-related hyperinflammatory syndrome (cHIS) is based on six main clinical and laboratory parameters. In this system, each criterion is evaluated on a 1-point scale. The first criterion is fever and body temperature above ≥38 °C is included in the scoring. A ferritin level of ≥700 μg/L reflecting macrophage activation is the second criterion. A D-dimer level of ≥1.5 μg/mL as a sign of coagulopathy and LDH ≥400 U/L or AST ≥100 U/L as an indicator of liver damage are considered. IL-6 ≥15 pg/mL, triglyceride ≥150 mg/dL or CRP ≥15 mg/dL are considered valid for cytokinemia evaluation. Finally, the haematological dysfunction parameter is scored if the neutrophil/lymphocyte ratio is ≥10, haemoglobin concentration ≤9.2 g/dL or platelet count ≤110 × 10^9/L.

Statistical Analysis

SPSS Statistics 25 software was used for statistical analyses. Power analysis was performed with the computer-aided G*Power statistical programme. Based on previous endocan studies in the literature, the minimum sample size to represent the population was calculated as 33 with an effect size of 0.62, a Type I margin of error (α) of 0.05 and 80% power (Type II margin of error: 20%).

Whether the numerical variables in the data set were normally distributed or not was evaluated by Kolmogorov-Smirnov test. In descriptive statistics, mean, standard deviation, median, 25%-75% percentile values were used for numerical data; frequency and percentage (%) were used for categorical variables.

In comparisons between groups:

- Independent Samples t test for variables with parametric distribution,
- Mann-Whitney U test for variables with nonparametric distribution,
- Pearson Chi-square test was used for categorical variables.

In case of a significant difference when more than two groups were compared, post-hoc analysis was performed to determine between which groups the difference was between. Since the distribution of numerical variables did not meet the parametric test conditions, correlation analyses were performed with the non-parametric Spearman's correlation test. All statistical results were evaluated at 95% confidence interval and $p < 0.05$ was accepted as the limit of statistical significance.

RESULTS

In our study, patients diagnosed with COVID-19 hospitalised in our wards were divided into two groups according to cHIS scoring. Patients with cHIS scores 2-3-4-5-6 were assigned to group 1 (n=60), and patients with cHIS scores 0-1 were assigned to group 2 (n=30). According to cHIS scoring, there were 8 patients with 0 points, 22 patients with 1 point, 12 patients with 2 points, 14 patients with 3 points, 12 patients with 4 points, 14 patients with 5 points, and 8 patients with 6 points. Group 1 (cHIS score≥ 2) patients were treated with pulse steroid for 3 days, while group 2 (cHIS score <2) patients were treated with 40 mg methylprednisolone daily.

A total of 90 patients were included in the study and these patients were divided into two groups as Group 1 (n = 60) with cHIS score ≥ 2 and Group 2 (n = 30) with cHIS score < 2. There was no significant difference in mean age between the groups (Group 1: 62.7 ± 11.5 years; Group 2: 58.6 ± 16.3 years; p = 0.227). Body mass index (BMI) was similar between the groups and no statistically significant difference was found (Group 1: 29.6 ± 3.7 kg/m²; Group 2: 28.5 ± 5.05 kg/m²; p = 0.225).

However, a significant difference was found between the groups in terms of gender distribution. The proportion of males was significantly higher in Group 1, 73.4% of the cases were males and 26.6% were females. In contrast, the proportion of females was higher in Group 2 (63.3% females, 36.7% males; p = 0.001). 44 of the patients with a cHIS score ≥ 2 were male and 16 were female, while 19 females and 11 males were included in the group with a score < 2. These findings suggest that male gender may be associated with higher cHIS score.

Lymphocytes in group 1 (p:0.007) were significantly lower than in group 2. Procalcitonin (p:0.026) was significantly higher in group 1 compared to group 2. Platelet and fibrinogen values were similar in both groups (Table 1).

Table 1. Comparison of laboratory parameters between group 1 and group 2

		Group 1 (n:60)	Group 2 (n:30)	p value*
PLT ($10^3/\mu L$)	mean	281.8	316	p;0.171
	SD	102.3	126.1	
LYM ($10^3/\mu L$)	mean	5.9	12.9	p;0.007
	SD	11.9	10.3	
PRC ($\mu g/L$)	mean	0.11	0.08	p;0.026
	SD	0.07	0.04	
FIBRINOGEN (mg/dL)	mean	605.6	520.7	p;0.061
	SD	210.9	176.2	

*Calculated with Independent T-Test.
Abbreviations
PLT: Platelet, LYM: Lymphocyte, CRP: C reactive protein, PRC: Procalcitonin, SD: Standard deviation. Group 1 (cHIS score≥ 2) and group 2 (cHIS score <2)
Abbreviations LDH: Lactate dehydrogenase, IL-6: Interleukin-6,
NEU/LYM: Neutrophil/lymphocyte ratio, CRP: C Reactive Protein.
Group 1 (cHIS score ≥ 2) and group 2 (cHIS score<2)

These ratios are shown in Table 2. Ferritin (p<0.001), CRP (p<0.001) IL-6 (p:0.01), D-Dimer (p<0.001), Neutrophil/Lymphocyte ratio (p<0.001), LDH (p<0.001), glucose (p:0.008) were found significantly higher in group 1 compared to group 2. Saturation (SO2 ,(p<0.001) was significantly lower in group 1 than in group 2 (Table 2).

In Table 3, no significant difference was found between the groups in terms of serum endocan level (p:0.934).

Table 2. Comparison of laboratory parameters between group 1 and group 2

		Group 1 (n:60)	Group 2 (n:30)	p value*
D-Dimer(ng/ml)	Mean/Median	1.61/1.09	0.41/0.31	p <0.001
	(%25-%75)	(0.41-2.07)	(0.23-0.63)	
Crp(mg/L)	Mean/Median	81.94/67.15	27.87/13.2	p <0.001
	(%25-%75)	(33.32-132.61)	(5.1-40.57)	
Ferritin (μg/L)	Mean/Median	1435/957	316/271	p <0.001
	(%25-%75)	(723-1408)	(115-468)	
Ldh(U/L)	Mean/Median	481/436	273/287	p <0.001
	(%25-%75)	(342-585)	(233-330)	
Glucose (mg/dl)	Mean/Median	148/142	126/104	p:0.008
	(%25-%75)	(111-181)	(90-123)	
Il-6(pg/mL)	Mean/Median	38.61/25.1	16.05/10.54	p:0.010
	(%25-%75)	(12.32-54.52)	(5.18-23.37)	
Neu/Lym (10^3/μl)	Mean/Median	20.25/14.3	2.15/0.84	p <0.001
	(%25-%75)	(1.68-24.04)	(0.26-2.38)	
SO^2(%)	Mean/Median	83.5/86.75	90.03/89.5	p <0.001
	(%25-%75)	(83.02-89.27)	(88-92)	

*Calculated with the Mann Whitney U test.
Abbreviations LDH: Lactate dehydrogenase, IL-6: Interleukin-6,
NEU/LYM: Neutrophil/lymphocyte ratio, CRP: C Reactive Protein, SO^2: saturation O2 .
Group 1 (cHIS score≥ 2) and group 2 (cHIS score<2)

Table 3. Comparison of serum endocan levels between group 1 and group 2

		Group 1 (n:60)	Group 2 (n:30)	p value*
END OCAN	Mean	223,3	221,5	0.934
	SD	80,2	124,6	

*Calculated with Independent T-Test.
Abbreviations SD: Standard deviation
Group 1 (cHIS score≥2) and group 2 (cHIS score<2)

According to Sperman's correlation test in table 4, a significant positive correlation was observed between LDH (p:0.018, r:0.249) and serum endocan (figure 1), while no signif icant statistical difference was found between neutrophil/lymphocyte ratio, D-Dimer, ferritin, CRP, SO2, glucose values.

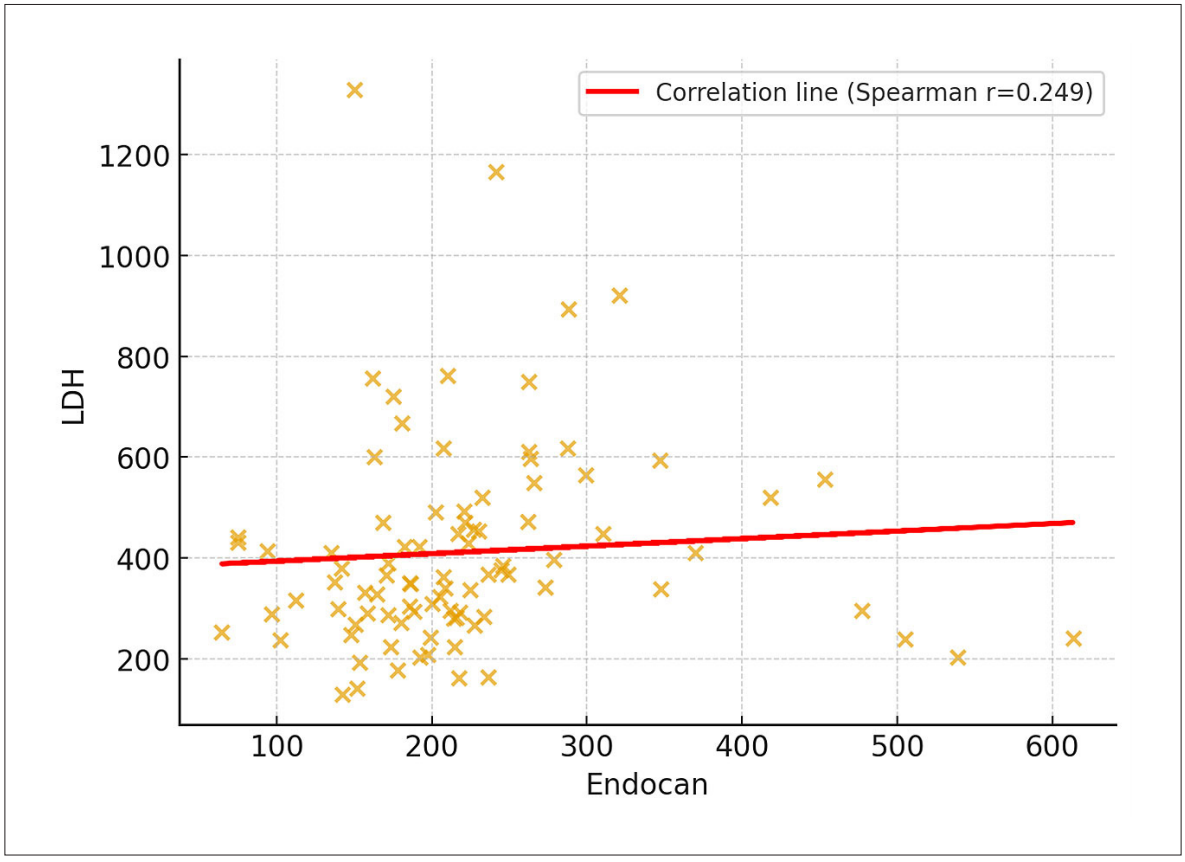

Figure 1: Correlation graph between endocan and LDH (Spearman's)

Table 4. Comparison of serum endocan with laboratory parameters (Spearman's)

*	IL-6 (pg mL)	Neu/Lym ($10^3/\mu l$)	D-Dimer (ng/ml)	Ferritin ($\mu g/L$)	CRP (mg/L)	So2 (%)	Glucose (mg/dl)	LDH (U/L)
r	-0.049	0.090	0.023	0.034	0.111	-0.015	0.071	0.249
p	0.648	0.400	0.830	0.750	0.299	0.886	0.506	0.018

* Calculated by Spearman's correlation test
Abbreviations:
CRP: C reactive protein, IL-6: Interleukin-6, LDH: Lactate dehydrogenase
NEU/LYM: Neutrophil/lymphocyte ratio

DISCUSSION

COVID-19 is a viral respiratory tract disease that triggers systemic inflammation with symptoms including cough, headache, muscle pain and fever. As the disease progresses, an increase in inflammatory markers including D-dimer, ferritin, LDH and lymphocytopenia are among the common laboratory findings (13). Conditions such as respiratory failure, thromboembolic complications and macrophage activation syndrome (MAS) that may develop during the course of the disease increase the risk of mortality. Hyperinflammatory pictures such as secondary haemophagocytic lymphohistiocytosis and cytokine storm are especially prominent in cases with a fatal course (14).

Scoring systems such as classical HLH-2004 and H-Score have been shown to be inadequate due to the rarity of splenomegaly with normal triglyceride and high fibrinogen levels frequently observed in COVID-19 patients. In this context, the cHIS (COVID-19 associated hyperinflammatory syndrome) scoring system based on parameters such as fever, haematological dysfunction, liver damage, cytokinaemia, coagulopathy and macrophage activation has been proposed (9).

In COVID-19 infection, endothelial damage progresses in parallel with hyperinflammation and is associated with the severity of the disease. Endocan, which is released from endothelial cells and reflects vascular dysfunction, is an important biomarker in this respect. Endocan levels have been shown to increase in conditions including coronary artery disease, malignancies and severe infections (15). Although it is known that proinflammatory cytokines such as TNF-α and IL-1β stimulate endocan production (12), interferon-γ has been found to inhibit this effect (16).

In this study, COVID-19 patients were divided into two groups with <2 and ≥2 points according to the cHIS score and serum endocan levels were compared. Although there are a limited number of studies in the literature evaluating the relationship between the hyperinflammatory response due to COVID-19 and endocan, Medetalibeyoğlu et al. reported that endocan levels increased significantly in patients with severe COVID-19 (17). However, no significant difference was found between the two groups in terms of serum endocan levels in this study.

These results may be explained by the suppression of endocan production by some immunomodulatory effects. For example, all patients received corticosteroid treatment and the group with cHIS ≥2 received pulse steroid. It has been shown that cortisol may suppress endocan production, and it has been reported that metabolic changes induced by steroids, especially high insulin levels and hyperglycaemia, increase this suppressive effect (18). The finding of higher glucose levels in the cHIS ≥2 group in our study raises the possibility of endothelial inhibition due to hyperinsulinaemia. Endocan (also known as endothelial cell-specific molecule-1, ESM-1) is a soluble proteoglycan secreted by vascular endothelial cells. In adipocytes, endocan production is inhibited by insulin and cortisol, and circulating endocan levels have been found to be decreased in over-

weight and obese women with insulin resistance as well as in patients with type 2 diabetes (19, 20).

The effects of steroids to improve endothelial function may also indirectly decrease endocan levels. In the study by Gonzalez-Juanatey et al. it was shown that glucocorticoids improved endothelial functions with their anti-inflammatory effects (21). This is another mechanism explaining why the expected increase in endocan levels was not observed.

When the gender distribution was analysed, it was observed that male individuals were more common in the cHIS ≥2 group. This finding coincides with the results of Haitao et al., who reported that male gender was associated with poor prognosis (22).

This study has some limitations. Firstly, the sample size consisting of a single centre and a limited number of participants reduces the generalisability of the findings obtained. Especially in a disease with a heterogeneous clinical course such as COVID-19, these results should be confirmed by multicentre studies including larger and diverse populations.

Secondly, the fact that all patients in the study received corticosteroid treatment made it difficult to differentiate potential effects on endocan levels. Considering the ameliorative effect of corticosteroids on endothelial function and their role in suppressing endocan production, the extent to which endocan levels reflect the true burden of inflammation remains unclear. Therefore, evaluation of basal endocan levels obtained before the initiation of treatment may be an important recommendation for further studies.

Thirdly, endocan levels were measured at a single time point in the study and changes that may occur during the course of the disease could not be observed. However, since inflammatory biomarkers such as endocan may change dynamically over time, data obtained by serial measurements may provide more meaningful results in terms of clinical value.

Furthermore, some inflammatory markers (e.g. IL-6) were measured only in a limited number of patients, making it difficult to generalise the data to the whole population. Such missing data may lead to a loss of power and reduced statistical significance in further analyses.

Finally, although the cHIS score was used in the evaluation of hyperinflammation in the study, the validation of this scoring has been performed in a limited number of studies and needs to be tested in different clinical settings.

In conclusion, this study is one of the few studies comparing cHIS score with endocan levels in the evaluation of MAS like hyperinflammatory conditions in COVID-19 patients. The findings suggest that factors that suppress endocan production, such as corticosteroid treatment and hyperinsulinaemia, may be effective despite endothelial damage. The use of endocan levels alone as a marker of inflammation is complex, and multicentre and long-term follow-up studies with larger samples are needed in this field.

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Abbreviations List

ESM-1 : Endothelial cell-specific molecule-1
MAS : Macrophage activation syndrome
ELISA : Enzyme-linked immunosorbent assay
cHIS : COVID-19-associated hyperinflammatory syndrome
ARDS : Acute respiratory distress syndrome
HLH : Haemophagocytic lymphohistiocytosis

Ethical Approval and Consent To Participate

This study was approved by the Health Sciences University (SBU) Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee with decision number 488 on 29.12.2020. Written informed consent was obtained from all participants prior to surgery.

Consent for Publication

Written informed consent was obtained from all participants.

Availability of Data and Materials

Data related to the study is not stored digitally

Competing Interests

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Author Contributions

Idea/Concept: MAA, AB, MA, YA, TT Design: MAA, AB, UC, UY. Control/Supervision MAA, OKA, SS, MA. Data Collection And/or Processing: MAA, OKA, UC, UY. Analysis And/or Interpretation: MAA, MA, SS. Literature Review: MAA, UC, YA, TT. Writing The Article: MAA, BA, YA, TT Critical Review: MAA, OKA, UY, YA, TT.

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