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Original Article

What are the main factors affecting the outcome of tocilizumab therapy in COVID-19-induced cytokine release syndrome?

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Abstract

Objective: Recommendations for the treatment of cytokine release syndrome/macrophage activation syndrome (MAS) associated with coronavirus disease-2019 (COVID-19) are still of poor quality. IL-6 is an important therapeutic target as a main mediator of cytokine storm. The aim of our study was to evaluate the tocilizumab (TCZ) efficacy and factors affecting the therapy outcome.

Methods: This retrospective study included 27 patients treated with TCZ for COVID-19-MAS. All patients in this study were treated with TCZ (intravenously, at a dose of 8 mg kg^{-1}) in addition to standard therapy. Clinical improvement (survival and decreased oxygen demand) on the 10-14th days and secondary infection rate were assessed.

Results: In our 27 treated patients, 14 (51.8%) received TCZ in the intensive care unit (ICU) and seven (25.9%) were need to invasive mechanical ventilation (IMV). Fifteen (55.6%) of these patients revealed a good clinical response (four patients discharge from the ICU and 11 patients who followed-up in non-ICU beds showed a decrease in oxygen demand). TCZ was significantly less effective in patients having high Murray lung injury score, low PO_2/FiO_2 ratio, IMV, and ICU admission ($P < .05$). Severity of hypoxemia was found as a single independent risk factor in the multivariable analysis ($P < .05$). Secondary bacterial infections rate was significantly higher in intubated patients ($P < .01$) or treated in the ICU ($P = .01$).

Conclusion: TCZ was showed limited efficacy for COVID-19-related MAS. The most important predictive indicator for therapy outcome was found as the severity of hypoxemia. In addition, IMV and/or ICU was associated with the poor outcome and high side effect. So, controlled trials are still needed to confirm the indications and timing of TCZ therapy.

Keywords: COVID-19, macrophage activation syndrome, interleukin-6, tocilizumab, cytokine release syndrome

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Introduction

Coronavirus disease-2019 (COVID-19) is a respiratory infection caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which is defined as a new member of the coronavirus family. The clinical presentation of COVID-19 is highly heterogeneous; it usually begins with an initial phase of viral replication and could be followed by a second phase of viral pneumonia, lung damage, and acute respiratory distress syndrome (ARDS).[1–3] It has been suggested that the host immune response increases concurrently with the second phase and could exaggerated in a small group of patients, resulting in tissue injury, cytokine release syndrome/macrophage activation syndrome (MAS), and mortality.[4,5]

MAS refers to an acute devastating inflammation that occurs as a result of excessive proinflammatory cytokines secretion (interleukin-6 (IL-6), IL-8, IL-10, IL-12, IL-18, Tumor necrosis factor-a (TNF), interferons (INF), etc.), and it is characterized by fever, cytopenia, liver dysfunction, and coagulopathy. Secondary form of MAS is a life-threatening complication of various viral infections and rheumatic diseases. The most common described viral etiologies are the following: herpes viruses, influenza (H1N1), and corona (SARS) viruses.[6,7] During the COVID-19 outbreak, observations revealed that excessive proinflammatory cytokines and increase acute phase reactants occurred in both active viral replication and pneumonia phases of SARS-CoV-2 infection. Additionally, uncontrolled inflammation was continuously observed after the end of viral replication and has been a cause of ARDS and MAS in some patients.[8,9]

IL-6 is thought to be one of the key mediators of the hyperinflammatory syndrome associated with SARS-CoV-2 infection. Many studies have reported that high IL-6 levels were correlated with disease severity and mortality as well.[10,11] Unfortunately, there is no clear treatment protocol for MAS related to COVID-19. However, cytokine-targeted biological therapies have been thought to be effective, due to the cytokines' important role in MAS pathophysiology. Tocilizumab (TCZ), a humanized monoclonal antibody against the IL-6 receptor, has become one of the therapeutic agents used in COVID-19-associated MAS. It was observed that this agent has positive effects in both clinical and radiological findings.[12,13] However, large-scale-controlled studies are required, due to the small number of patients in current studies and the presence of confounding factors. In our study, we have planned to assess the efficacy of TCZ treatment on SARS-CoV-2-induced MAS and its factors affecting the treatment response in our patients.

Methods

Twenty-seven patients, treated with TCZ for COVID-19-related MAS and hospitalized at Florence Nightingale Hospitals between March and May 2020, were included in this retrospective observational study. Due to classical MAS, diagnostic criteria are not useful for the identification of MAS induced by COVID-19; MAS was determined as refractory fever, progressive increase in C-reactive protein (CRP), d-dimer, ferritin levels, and the presence of lymphopenia/thrombocytopenia in this study. TCZ treatment indications were the following: >18 years of age, progressive deterioration of respiratory parameters with continuous increase in inflammatory and coagulopathy factors (CRP, ferritin, and d-dimer), and decrease in lymphocyte and/or platelet values. TCZ was administered to eligible patients [without treatment contraindications such as neutropenia (<500 μL^{-1}), thrombocytopenia (<50,000 μL^{-1}), concomitant bacterial infection, or active diverticulitis] intravenously at a dose of 8 mg kg^{-1} (maximum 800 mg), per 24 hours as two divided doses. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Medical Faculty of the Demiroglu Bilim University (12.05.2020/2020.08.02 ethics approval number).

Main Points

- The fact that plays a critical role of IL-6 in COVID-19 induced cytokine release syndrome has led to the widespread use of Tocilizumab.
- Tocilizumab treatment has been found to effective in almost half of the patients.
- The most important predictive indicator for treatment outcome was the severity of hypoxemia.

Demographic and laboratory parameters were recorded before and on the 10-14th days of TCZ treatment. Conventional X-ray and computed tomography (CT) imaging of the lungs were examined by two radiologists. The primary endpoints of this study were a clinical improvement (survival and decreased oxygen demand) rate and the determination of factors affecting treatment outcome on the 10-14th days, while the secondary endpoint was the detection of treatment-related secondary infection rates.

Hypoxemic respiratory failure was defined as arterial oxygen saturation (SO_2) below 90% or arterial oxygen pressure (PaO_2) below 60 mm Hg. ARDS was categorized by the severity of hypoxia (mild: PaO_2/FiO_2, 200-300 mm Hg and positive end-expiratory pressure (PEEP) $\geq$ 5 cm H_2O; moderate: PaO_2/FiO_2, 100 to $\leq$200 mm Hg and PEEP $\geq$ 5 cm H_2O; severe: PaO_2/FiO_2, $\leq$100 mm Hg and PEEP $\geq$ 5 cm H_2O).[14]

Acute pulmonary damage was evaluated by using "Murray lung injury score."[15] The scoring system includes four different respiratory and radiographic items [hypoxemia (PaO_2/FiO_2 from <100 to $\geq$300 mm Hg; points 0-4), lung conventional radiographic score (number of quadrants with alveolar consolidation; points 0-4), PEEP levels (from <5 to $\geq$15 cm H_2O; points 0-4) and respiratory system compliance (between $\geq$80 and $\leq$19 mL cm^{-1} H_2O; points 0-4)], low score (0.1-2.5) designates mild-to-moderate lung injury, and score over 2.5 refers to ARDS.

Thorax CT images were evaluated according to the presence and extent of ground glass pattern, consolidation, and fibrosis. Lung lobes (left upper, left lower, right upper, right middle, and right lower lobes) were scored by the percentage of each lobes' involvement (0% score 0; <5% score 1; 5-25% score 2; 25-50% score 3; 50-75% score 4; >75% score 5), and the total CT score (maximum score of 25) was calculated.[16]

Statistical analysis

Parametric variables were expressed as mean ± standard deviation (SD), and nonparametric variables as median (IQR). Discontinuous variables are given as (%) numbers. The paired t test was used for the comparison of normally distributed variables, and the Wilcoxon test was used for the comparison of variables that did not show normal distribution. Kappa analysis was used for the compatibility test between the two radiologists. The Fischer exact test, univariate regression, and multivariate logistic regression analyses were used to reveal independent risk factors (age, gender, lung patient score, degree of hypoxemia, Thorax CT score, etc.) for the TCZ treatment outcome. We considered *P* value score less than .05 to be statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp.; Armonk, NY, USA).

Results

A total of 27 COVID-19-related MAS patients (20 males and seven females) treated with TCZ were included in this study. The mean age of the patients was 62 ± 15.6 years. The most common symptoms were fever (24 patients) and dyspnea (23 patients). Eighty-one percent of the patients had at least one comorbidity [17 patients were being treated for arterial hypertension (angiotensin-converting-enzyme inhibitors - one, angiotensin receptor blockers - seven, and other antihypertensives - 15) and seven patients were being treated for diabetes mellitus (oral antidiabetic drugs - six and insulin - two)]. Only one patient was using an immunosuppressive agent (tacrolimus); none of the patients was taking systemic steroids. The demographic characteristics of the patients are summarized in Table 1.

COVID-19 was confirmed by a positive reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA on nasopharyngeal swab (in 25 patients) and/or by computed tomographic (CT) with highly suggestive findings for COVID-19 (in all patients). Thorax CT findings were the following: ground glass opacity (24 patients), fine reticular lines (five patients), and consolidation (three patients). Both radiologists' agreements on radiologic findings were found to be very high (κ: 0.94).

All patients in the study were treated with both TCZ and standard supportive therapy (supplemental oxygen), hydroxychloroquine (400 mg twice daily loading dose followed by 200 mg twice daily maintenance), and antiviral drugs [favipiravir 1,600 mg twice daily loading dose followed by 600 mg twice daily maintenance - 24 cases and/or other antiviral agents (oseltamivir 150 mg day^{-1} for 22 cases and/or darunavir 800 mg day^{-1} for 14 cases)]. None of the patients were treated with high-dose corticosteroids. According to surviving sepsis campaign 2020 guidelines for critically ill

Table 1. Demographics and Clinical Characteristics of the Patients

	Total (n = 27)	Improved (n = 15)	Worsened (n = 12)
Gender (M/F)	20/7	12/3	8/4
Age (year) (mean ± SD)	62 ± 15.6	57 ± 17.7	68 ± 10
Comorbidity, n (%)	22 (81)	11 (73)	11 (92)
Arterial hypertension, n (%)	17 (63)	8 (53)	9 (75)
Diabetes mellitus, n (%)	7 (26)	3 (20)	4 (33)
Cardiovascular disease, n (%)	7 (26)	3 (20)	4 (33)
COPD, n (%)	3 (11)	1 (7)	2 (17)
Malignancy, n (%)	1 (4)	1 (7)	0
Chronic kidney disease, n (%)	2 (7)	2 (13)	0
Thyroid disease, n (%)	2 (7)	1 (7)	1 (8)
Symptoms			
Fever, n (%)	24 (89)	14 (93)	10 (83)
Dyspnea, n (%)	23 (85)	11 (73)	12 (100)
Cough, n (%)	18 (67)	10 (67)	8 (67)
Diarrhea, n (%)	2 (7.4)	2 (13)	0
Sore throat, n (%)	1 (3.7)	1 (7)	0
Headache, n (%)	1 (3.7)	1 (7)	0
MAS emergence time (day) (mean ± SD)	8.48 ± 1.3	8.67 ± 1.49	8.25 ± 1
PaO_2/FiO_2^* (mm Hg) (mean ± SD)	185 ± 89	245.67 ± 66.75	110 ± 42
Murray lung injury score* (mean ± SD)	2 ± 1	1.4 ± 0.6	3 ± 0.7
Thorax CT score (mean ± SD)	14.7 ± 5	13.7 ± 5	15 ± 4.8
IL-6 level (pg mL^{-1}) median (IQR)	105 (44.5-168.5)	98 (44.3-699)	106 (67.5-359.5)

COPD, chronic obstructive pulmonary disease; MAS, macrophage activation syndrome; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; CT, computed tomography; IL-6, interleukin-6.
Data were expressed as number (%), mean ± SD, or median (IQR).
*$P < .01$.

Table 2. Follow-Up Data of the Laboratory Findings

	Total (n = 27)			Improved (n = 15)			Worsened (n = 12)		
	Pre-TCZ	Post-TCZ	*P*	Pre-TCZ	Post-TCZ	*P*	Pre-TCZ	Post-TCZ	*P*
Leukocyte ($\times 10^3$ μL)	7.4 ± 3.3	13 ± 8.7	**<.01**	6.7 ± 2.4	8.5 ± 4.6	.2		20.4 ± 8.5	**<.01**
Lymphocyte ($\times 10^3$ μL)	0.78 ± 0.5	1.3 ± 0.83	**<.01**	0.92 ± 0.6	1.6 ± 0.9	**<.01**	0.61 ± 0.17	0.97 ± 0.5	.06
Hemoglobin (g dL^{-1})	12.5 ± 1.9	12.3 ± 2.3	.7	12.8 ± 1.7	13.5 ± 1.9	**<.01**	12.1 ± 2.1	10.7 ± 1.7	.03
Platelets ($\times 10^3$ μL)	230 ± 81	220 ± 92	.8	216 ± 92	250 ± 97	.2	246 ± 67	176 ± 67	**<.01**
C-reactive protein (mg L^{-1})	157.9 ± 91	7.6 ± 10.8	**<.01**	131 ± 84.7	2.9 ± 4.7	**<.01**	191.4 ± 90	14.4 ± 13	**<.01**
Ferritin (ng mL^{-1})	1,526 ± 1,232	801 ± 585	**<.01**	1,554 ± 1,238	724 ± 493	**<.01**	1,492 ± 1,279	905 ± 706	.05
D-dimer (μg L^{-1})	1,200 (733-1,580)	1,230 (513-3,760)	.8	995 (688-1,520)	912 (365-2,842)	.3	1,220 (828-2,088)	2,960 (928-10,420)	.2
Fibrinogen (mg dL^{-1})	555 ± 184	237 ± 100	**<.01**	546 ± 206	–	–	562 ± 178	231 ± 107	**<.01**
Pro-calcitonin	0.32 ± 0.5	0.17 ± 0.1	.2	0.32 ± 0.5	0.06 ± 0.03	.4	0.33 ± 0.46	0.26 ± 0.2	.4

TCZ, tocilizumab.
Data were expressed as mean ± SD or median (IQR).
Bold values indicate $P < .05$.

adults with COVID-19, a moderate dose of corticosteroid (0.5-1 mg kg^{-1} day^{-1} methylprednisolone) was administered only to patients treated for acute hypoxic respiratory failure in the intensive care unit (ICU).[17] Appropriate antibiotic (macrolide, cephalosporin, piperacillin/tazobactam, quinolone, or vancomycin) regimens were initiated in for patients with secondary bacterial infection.

High inflammatory response (CRP, ferritin, fibrinogen, and IL-6), severe lymphopenia, and coagulopathy (high D-dimers) were seen in all patients at the beginning of TCZ treatment. At day 6, a significant decline in post-TCZ treatment in CRP and ferritin levels and an improvement in lymphopenia were observed ($P < .01$) (Table 2).

All patients treated with TCZ had acute hypoxic respiratory failure (mild - 10, moderate - 11, and severe - 6), 14 (51.8%) patients were admitted to the ICU, and eight of them required ventilatory support [seven (25.9%) - invasive mechanical ventilation (IMV) and one - non-IMV]. On the 10-14th day after TCZ infusion, 15 (55.6%) patients showed clinical and respiratory improvements (four patients discharged from the ICU and 11 patients who followed-up in non-ICU beds showed a decrease in oxygen demand) compared to 12 (44.4%) who worsened [two were unresponsive and 10 died (acute hypoxemic respiratory failure - eight and septic shock - two)]. Good response was significantly higher in patients treated in the non-ICU beds [non-ICU: 11/13 (84.6%) vs ICU: 4/14 (28.5%), $P < .001$, OR: 13.7 (95% CI: 2.05-92)]. In addition, IMV was associated with worse outcome [good response: 1/7 (14.2%)-IMV vs 14/20 (70%)-non-IMV or low dose oxygen support, $P = .02$, OR: 14 (95% CI: 1.37-142.8)] (Figure 1).

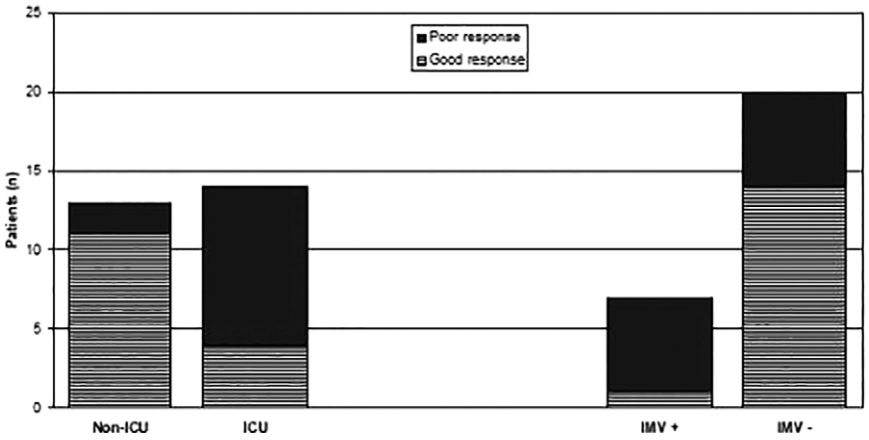

Figure 1. Clinical response rates of the patients. ICU: intensive care unit; IMV: invasive mechanical ventilation.

Table 3. Factors Affecting Tocilizumab Treatment Response

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Age	–	.09	–	
Gender	–	NS		
Comorbidity	–	NS	–	
ICU	13.7 (2.05-92)	<.01	–	
IMV	14 (1.4-142.8)	.02	–	
Thorax CT score	–	NS	–	
Murray lung injury score	21.5 (2.2-203.3)	.01	–	
PaO_2/FiO_2	0.9 (0.9-0.99)	.01	0.94 (0.9-0.99)	.01
Lymphocyte (pretreatment)	–	NS	–	
CRP (pretreatment)	–	.09	–	
Ferritin (pretreatment)	–	NS	–	
D-dimer (pretreatment)	–	NS	–	
IL-6 (pretreatment)	–	NS	–	

ICU, intensive care unit; IMV, invasive mechanical ventilation; CT, computed tomography; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; CRP, C-reactive protein; IL-6, interleukin-6; NS, not significant.

The univariate analysis showed that high Murray lung injury score, low PO_2/FiO_2 ratio, IMV, and ICU admission had a significantly poor outcome with TCZ treatment ($P < .05$). On the other hand, severity of hypoxemia was seen as a single independent factor in the multivariable analysis ($P < .05$) (Table 3).

We observed significantly higher secondary bacterial infections in patients treated in the ICU [ICU: nine (64%) vs non-ICU: two (15%) cases, $P = .01$, OR: 9.9 (95% CI: 1.5-63.6)] and placed on IMV [six (86%) vs five (25%) cases, $P < .01$, OR: 18 (95% CI: 1.7-188)].

Discussion

MAS can occur as a complication of excessive and uncontrolled release of proinflammatory cytokines in COVID-19. IL-6 is one of the important mediators that plays a critical role in the development and severity of SARS-CoV-2-mediated ARDS and MAS. For this reason, TCZ has thought to be a good treatment option against COVID-19-induced MAS.[10,11,18] However, data on the efficacy of TCZ treatment are limited to small observational studies conducted with poor quality. According to our study, which evaluated clinical efficacy of TCZ in severe COVID-19, we found approximately 55% of the patients had a good response.

The first and highly promising study on TCZ treatment in SARS-CoV-2 infection was conducted in a single center of China and revealed the TCZ was successful in approximately 90% out of 21 patients.[12] In the following period, treatment results were evaluated with other larger case series and reported that an average of 69-87% of patients had a good response (clinical improvement and stable course).[19–22] However, our study results were not as good as that studies, and adding TCZ to standard treatments was effective in almost half of the patients. On the other hand, later published systematic review and a randomized placebo-controlled trial had disappointing results showing no significant effect of TCZ treatment on the risk of intubation or death.[23,24] These conflicting results are thought to be associated with having different disease severity of the patients in the trials and the lack of clear protocols for optimal timing and indications for TCZ therapy. For example, one of the randomized controlled study included only moderately ill patients who did not require IMV, while 62.9% of our patients had moderate to severe respiratory failure and 25.9% required respiratory support with IMV.[24] In addition, methodologically, the risk of bias is seen at high levels due to the fact that most studies have a retrospective design, including small number of patients treated with TCZ and mostly not having a control group.[25] After these controversial results, newly published large controlled randomized trial (RECOVERY) was reported that adding TCZ to standard care had beneficial effect to reduce mortality (31% vs 35%, *P*

< .05). In addition, the meta-analysis of all randomized controlled trials, included in this paper, had shown that TCZ improved survival in hospitalized COVID-19 patients (75% vs 72%, $P < .05$). On the other hand, subgroup analyses of RECOVERY trial showed that TCZ had significant good effect to clinical outcome only in patients who had not need ventilatory support or followed with non-IMV. However, TCZ had not found to have additional beneficial effect in patients who needed IMV at baseline.[26] These findings support to our study results.

Another issue under the discussion is which markers can be used as a reliable item to assess TCZ efficacy. IL-6 is one of the main mediators in the acute phase response, and the reduction of CRP levels is independent of its efficacy. Therefore, it may be misleading to determine the treatment outcome by the acute phase responses' alone. Hence, in our study, high levels of CRP, ferritin, d-dimer, IL-6, and severe lymphopenia have been improved after TCZ treatment, similar to the other data in the literature.[27,28] Unlike classical MAS, the lungs are the predominantly affected organ in COVID-19.[9] Therefore, respiratory parameters can be more reliable than acute phase reactants and other inflammatory markers in determining the treatment response.

Although most of the studies focused on efficacy, there is not clear conclusion about which factors have influence on the treatment outcome of TCZ in the literature. In our study, analysis of the impact according the patients' demographic and clinical characteristics on treatment revealed that patients followed in the ICU and/or IMV having a high Murray lung injury score or severe hypoxemia have a poor outcome. These results seem to be compatible with some data in the literature.[29–31] In the multivariate analysis of our study, the severity of hypoxemia was found to be a single independent risk factor for clinical response. Our result supports newly published prospective TOCIVID-19 trial that reported as older age and lower PaO_2/FiO_2 ratio negatively affected survival.[32] However, unlike the results of some uncontrolled studies, we did not find any correlation between CT score and treatment outcome. Such differences are thought to be due to our small number of patients in the analysis.

Safety issue is another concern when TCZ is used for patients with severe COVID-19. Elevated hepatic enzymes, neutropenia, thrombocytopenia, gastrointestinal perforation, and secondary bacterial or fungal infections are the main side effects reported within different rates in patients.[20,33] Although we have not seen neutropenia and elevated transaminases, secondary bacterial infection was detected in 40.7% of our groups, and superinfection risk was higher in intubated patients and treated in ICU. Similar to these results, there are data supporting bacterial superinfection that was increased in patients receiving TCZ treatment (42.9%), and it was as an independent risk factor for secondary infection (up to 75% of cases in ICU).[19,34,35] Otherwise, some small uncontrolled studies have reported that these side effects were not increase after TCZ therapy, including secondary infections.[36,37] However, considering various interventional procedures done in the ICU and with IMV cases, it should be kept in mind that many other possible factors may play a role in the development of an infection.

In summary, TCZ treatment has been found to be effective in almost half of the patients, and the most important factor affecting treatment response was the severity of hypoxemia. In addition, treatment outcomes were worse in patients treated in the ICU and/or IMV, and secondary infections were more frequent in these groups. These results suggest that initiation of TCZ therapy before requirement of IMV could be more effective and less harmful. However, our study has several limitations, such as the small number of patients and the absence of a control group, which deserves a separate discussion for a better interpretation of the findings. In light of these reasons, large-scale randomized controlled studies need to be conducted for definitive conclusions on supporting the effectiveness of TCZ treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Demiroglu Bilim University Medical Faculty (Approval number: 12.05.2020/2020.08.02).

Informed Consent: Informed consent was not obtained due to the nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.A., N.Y.; Design - C.A., N.Y.; Supervision - N.Y.; Materials - C.A., N.Y.; Data Collection and/or Processing - C.A., S.G.G., İ.H.S., S.K.D., E.C., E.E., Z.G., Y.C., N.Y.; Analysis and/or Interpretation - C.A., S.G.G., İ.H.S., S.K.D., E.C., E.E., Z.G., Y.C., N.Y.; Literature Review - C.A., N.Y.; Writing - C.A., N.Y.; Critical Review - N.Y.

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