ORIGINAL PAPER

Evaluation of the Effectiveness of Coronavirus Disease (COVID-19) Therapeutic Protocols Using Inflammatory Markers

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ABSTRACT

Background: The pathophysiology and therapy of coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), are a dilemma for scientists and health professionals, and the fact that patients show different symptoms and severity of the clinical picture also contributes to that. **Objective:** This paper aims to evaluate the effectiveness of therapeutic protocols (the use of immunomodulators) in the treatment of COVID-19 patients of various severity of the clinical picture by monitoring inflammatory markers (ESR and CRP), as well as the impact of the type and number of comorbidities patients had on these markers. **Methods:** A total of 200 patients with a mild (n=76), moderate (n=70) or severe (n=54) clinical picture was included. Inflammatory markers [ESR (erythrocyte sedimentation rate), CRP (C-reactive protein)] were examined on three occasions: twice during hospitalization and once after hospital discharge. Immunomodulators used intrahospital were corticosteroids (methylprednisolone, dexamethasone, methylprednisolone + dexamethasone), tocilizumab or metenkefalin/tridecactide. Posthospital, patients were taking either methylprednisolone or did not use any immunomodulators. For statistical analysis, SPSS 26.0 and Microsoft Excel 2019 were used, with a level of significance of α=0.05. Nonparametric tests (Kruskal-Wallis and Wilcoxon Signed-Rank) were applied and effect size (ES) was calculated. **Results:** Three corticosteroid therapies used intrahospital caused a significant decrease in both inflammatory markers, especially in patients with a severe clinical picture, but the ES was the biggest with methylprednisolone + dexamethasone, then dexamethasone, and lastly methylprednisolone. Posthospital, methylprednisolone caused a significant decrease in both inflammatory markers, especially in patients with a severe clinical picture. The most common comorbidity in all patients, as well as in patients with a severe clinical picture, was hypertension. There was no statistically significant impact of the number of comorbidities patients had on ESR and CRP, but the highest number of comorbidities was in patients with a severe clinical picture. **Conclusion:** The use of immunomodulators, especially methylprednisolone + dexamethasone intrahospital and methylprednisolone posthospital, is justified in most COVID-19 cases as there is a significant correlation between this disease's pathophysiology and the immune response. There is also a positive correlation between the number of comorbidities patients have and the severity of the clinical picture.

Keywords: COVID-19, inflammatory markers, immunomodulators, comorbidities.

1. BACKGROUND

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease-19 (COVID-19), characterized by a dysregulation of the immune response, which leads to a more intense release of proinflammatory cytokines (1). In COVID-19 patients, inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually modified. These markers correlate with the severity of the clinical picture. ESR increases, especially in patients with a severe clinical picture and pneumonia (2). Elevated levels of CRP (>150 mg/L) are associated with an increased risk of severe pneumonia and death in these patients (3).

Previous studies have shown that pa-

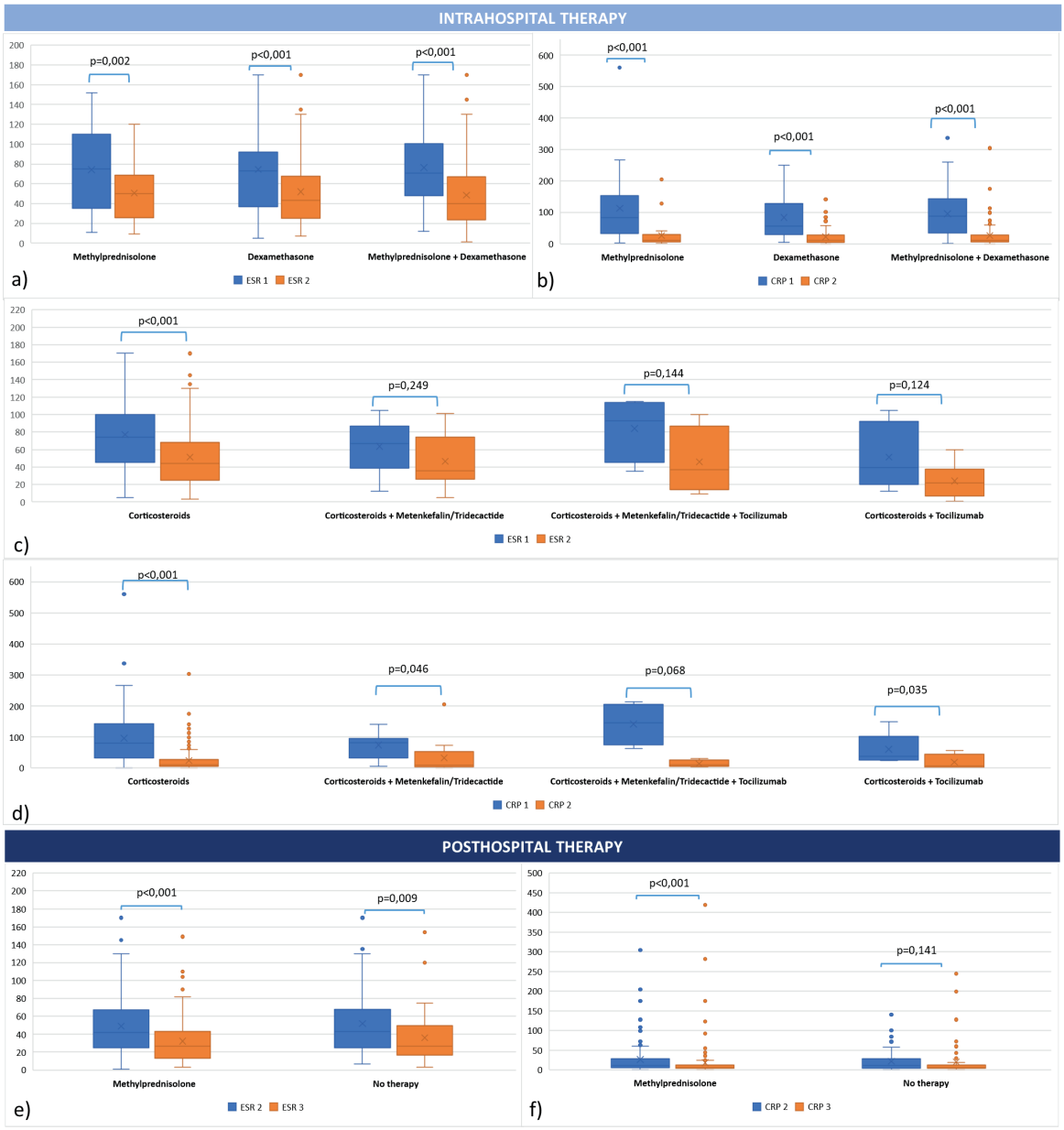

Figure 1. Impact of immunomodulators on inflammatory markers

tients with the following comorbidities and conditions have a higher risk of developing a severe clinical picture after contracting COVID-19: cancer, cardiovascular diseases, diabetes mellitus, diseases of the lungs, kidneys and liver and some mental diseases (4).

2. OBJECTIVE

This paper aims to evaluate the effectiveness of therapeutic protocols (the use of immunomodulators) in the treatment of COVID-19 patients of various severity of the clinical picture by monitoring inflammatory markers (ESR and CRP), as well as the impact of the type and number of comorbidities patients had on these markers.

3. MATERIAL AND METHODS

This study was designed as a single-centre retrospective-prospective study. Data were obtained from medical records, discharge summaries and other medical documentation of patients hospitalized in General Hospital Tešanj in the period July 2020 – November 2021.

The study included 200 patients with a mild (n=76), moderate (n=70) or severe (n=54) clinical picture. The inclusion criteria were: age over 18, both genders; diagnosis of COVID-19 [according to International Classification of Diseases-10 (ICD-10): U07.1 and U07.2], confirmed either by polymerase chain reaction (PCR) or antigen test; hospitalization period of at least two weeks; patients with a mild, moderate or severe clinical picture; signed informed consent. People below 18 years of age, pregnant and nursing women, asymptomatic and patients in critical condition, as well as exitus letalis cases, were not included in the study.

Upon admission of patients to the hospital, before prescribing therapy, the following inflammatory markers were analyzed: ESR and CRP. Analyzes of these markers at the second point were performed intrahospital, within two weeks of patients' admission to the hospital, after prescribing therapy. Analyzes of these markers at the third point were performed posthospital, when patients arrived for control check, approximately one to two months after hospital discharge. Mentioned markers were indicators of the effectiveness of im-

PARAMETER	GROUP	THERAPY								
		1	2	3	4	5	6	7	8	9
ESR	All patients	0.225	0.303	0.379	0.489	/	/	/	0.324	0.193
	Mild clinical picture	0.162	0.243	0.267	0.350	/	/	/	0.318	0.243
	Moderate clinical picture	0.204	0.259	0.293	0.392	/	/	/	0.330	0.260
	Severe clinical picture	0.315	0.350	0.538	0.694	/	/	/	0.616	0.415
CRP	All patients	0.274	0.421	0.502	0.661	0.155	0.146	/	0.306	/
	Mild clinical picture	0.222	0.337	0.352	0.567	/	/	/	0.468	0.337
	Moderate clinical picture	0.250	0.391	0.514	0.590	/	/	/	0.567	0.404
	Severe clinical picture	0.333	0.404	0.554	0.726	0.276	/	/	0.600	0.464

Table 1. ES of immunomodulatory therapies on the values of ESR and CRP in all patients and regarding the severity of the clinical picture. 1 – methylprednisolone intrahospital; 2 – dexamethasone; 3 – methylprednisolone + dexamethasone; 4 – all corticorticosteroids; 5 – corticosteroids + tocilizumab; 6 – corticosteroids + metenkefalin/tridecactide; 7 – corticosteroids + tocilizumab + metenkefalin/tridecactide; 8 – methylprednisolone posthospital; 9 – no posthospital therapy; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein

munomodulators used in the treatment of these patients and therapeutic outcomes were evaluated by monitoring them at all three points.

Corticosteroids used intrahospital were methylprednisolone, dexamethasone and methylprednisolone + dexamethasone. Methylprednisolone was administered intravenously in doses of 50, 100, 200 or 400 mg once daily. Dexamethasone was administered intravenously in the following dosage regimens: 16+0+0, 8+6+8, 8+0+8, 8+0+4, 8+0+0, 6+6+0, 6+0+6, 6+0+4, 6+0+0, 4+0+4 or 4+0+0. Tocilizumab was administered intravenously in doses of 400, 560, 600, 640 or 800 mg once daily (for one day). Metenkefalin/tridecactide was administered subcutaneously in doses of 5+1 mg once daily (until the hospital discharge). Posthospital, patients were taking either methylprednisolone orally in the following dosage regimens: 16+8+0, 16+0+0, 8+8+0, 8+4+0, 8+0+0, 4+4+0 or 4+0+0 or did not use any immunomodulators.

The type and number of comorbidities patients had were also analyzed and their impact on the severity of the clinical picture and inflammatory markers was evaluated. Patients were divided into three groups based on the number of comorbidities: 1. no comorbidities; 2. one or two comorbidities; 3. more than two comorbidities.

For statistical analysis, SPSS 26.0 and Microsoft Excel 2019 were used, with a level of significance of α=0.05. Nonparametric tests (Kruskal-Wallis and Wilcoxon Signed-Rank) were applied. Effect size (ES) (5) was considered small if 0.2-0.49, medium if 0.5-0.79 and large if ≥0.8.

4. RESULTS

In the group of patients with a mild clinical picture, 38 (50%) were men and 38 (50%) women; seven (9.21%) were from 19 to 39, 21 (27.63%) from 40 to 59, and 48 (63.16%) above 60 years of age. In the group of patients with a moderate clinical picture, 49 (70%) were men and 21 (30%) women; six (8.58%) were from 19 to 39, 25 (35.71%) from 40 to 59, and 39 (55.71%) above 60 years of age. In the group of patients with a severe clinical picture, 21 (38.89%) were men and 33 (61.11%) women; 11 (20.37%) were from 40 to 59, and 43 (79.63%) above 60 years of age.

The first and third measurements of ESR (p=0.001; p=0.019, respectively) and CRP (p<0.001; p=0.001, respectively) showed a significant difference between patients of various severity of the clinical picture. Patients with a severe clinical picture had the highest value of ESR and CRP at the beginning, but the decrease in these values was also the biggest in patients with this clinical picture (ESR: from 90.81 to 39.37; CRP: from 131.17 to 19.89).

MARKER	CLINICAL PICTURE	COMORBIDITIES – GROUPS	$\bar{x}$	H	p
ESR	Mild	1	46	0.035	0.983
		2	55		
		3	64		
	Moderate	1	59.5	1.915	0.384
		2	75		
		3	80		
	Severe	1	72	0.670	0.715
		2	82		
		3	85.5		
CRP	Mild	1	30	1.457	0.480
		2	41		
		3	48		
	Moderate	1	53	1.838	0.399
		2	69		
		3	98		
	Severe	1	98	0.486	0.784
		2	131		
		3	138		

Table 2. The impact of the number of comorbidities patients had on inflammatory markers. ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; 1 – no comorbidities; 2 – one or two comorbidities; 3 – more than two comorbidities

Figure 1 a) and b) presents that three corticosteroid therapies used intrahospital (methylprednisolone, dexamethasone, methylprednisolone + dexamethasone) caused a significant decrease in both inflammatory markers [ESR (p=0.002; p<0.001; p<0.001, respectively); CRP (p<0.001 all)], but the ES was the biggest with methylprednisolone + dexamethasone, then dexamethasone, and lastly methylprednisolone. Regarding the severity of the clinical picture, methylprednisolone + dexamethasone caused the biggest decrease in both inflammatory markers in patients with a severe clinical picture (ΔESR=45.52; ΔCRP=76.21), then moderate (ΔESR=22.28; ΔCRP=72.47), and lastly mild (ΔESR=17.53; ΔCRP=55.72).

The impact of corticosteroids alone was compared to their combinations with tocilizumab or metenkefalin/tridecactide or tocilizumab + metenkefalin/tridecactide [Figure 1 c) and d)]. Only corticosteroids alone caused a significant decrease in ESR (p<0.001), while corticosteroids + tocilizumab, corticosteroids + metenkefalin/tridecactide and corticosteroids + tocilizumab + metenkefalin/tridecactide did not (p=0.124; p=0.249; p=0.144, respectively). Cor-

ticosteroids, corticosteroids + tocilizumab and corticosteroids + metenkefalin/tridecactide caused a significant decrease in CRP (p<0.001; p=0.035; p=0.046, respectively), while corticosteroids + tocilizumab + metenkefalin/tridecactide did not (p=0.068). Regarding the severity of the clinical picture, corticosteroids caused the biggest decrease in both inflammatory markers in patients with a severe clinical picture (ΔESR=44.14; ΔCRP=106.30), then moderate (ΔESR=18.92; ΔCRP=65.83), and lastly mild (ΔESR=16.63; ΔCRP=50.02).

Figure 1 e) and f) presents that posthospital, methylprednisolone caused a significant decrease in both inflammatory markers (p<0.001 all). In patients who did not take any immunomodulators, there was a significant decrease in ESR (p=0.009) but none in CRP (p=0.141). Regarding the severity of the clinical picture, methylprednisolone caused the biggest decrease in both inflammatory markers in patients with a severe clinical picture (ΔESR=26.67; ΔCRP=18.63), then moderate (ΔESR=14.82; ΔCRP=12.52), and lastly mild (ΔESR=6.93; ΔCRP=9.16).

Table 1. presents the ES of immunomodulatory therapies on the values of ESR and CRP in all patients and regarding the severity of the clinical picture.

In the group of patients with a mild clinical picture, 20 (26.32%) had no comorbidities, 39 (51.32%) had one or two comorbidities, and 17 (22.36%) had more than two comorbidities. In the group of patients with a moderate clinical picture, 26 (37.14%) had no comorbidities, 35 (50%) had one or two comorbidities, and nine (12.86%) had more than two comorbidities. In the group of patients with a severe clinical picture, nine (16.67%) had no comorbidities, 22 (40.74%) had one or two comorbidities, and 23 (42.59%) had more than two comorbidities. The highest number of comorbidities in one patient was 11, and that patient was a 70-year-old man with a severe clinical picture.

The most common comorbidity was hypertension, with 84 (42%) patients having that diagnosis. Next were type 2 diabetes mellitus (DMT2) [52 (26%)], chronic obstructive bronchitis [30 (15%)], chronic gastritis [27 (13.5%)], chronic cardiomyopathy [26 (13%)]. All of these comorbidities were the most prevalent in patients with a severe clinical picture [hypertension: 29 (53.7%); DMT2: 18 (33.33%); chronic obstructive bronchitis: 11 (20.37%); chronic gastritis: eight (14.81%); chronic cardiomyopathy: 11 (20.37%)].

Results showed that there was no statistically significant impact of the number of comorbidities patients had on ESR (H=0.895; p=0.639) and CRP (H=1.371; p=0.504) (first measurements). With regard to the number of comorbidities, there was also no statistically significant difference in ESR and CRP between patients of various severity of the clinical picture (Table 2).

5. DISCUSSION

In our study, 108 (54%) of patients were men, which correlates with the results of previous studies (6, 7), but more patients with a severe clinical picture were women [33 (61.11%)]. Also, 187 (93.5%) patients were older than 40. Interestingly, there were no patients under the age of 40 who had a severe clinical picture, suggesting that the severity of the clinical picture correlates with age, which is consistent with the results obtained in the study conducted by Zhang et al. (2021) (8). In the group of patients with a severe clinical picture, 79.63% of patients were older than 60, as the number of comorbidities is usually higher in older patients and represents the risk factor for developing a severe clinical picture.

Results of our study demonstrated that three corticosteroid therapies used intrahospital caused a significant decrease in both inflammatory markers, but ES was the biggest with methylprednisolone + dexamethasone. Both inflammatory markers were reduced the most in patients with a severe clinical picture. Patients were treated with corticosteroids from the beginning of the hospitalization. In a study conducted by Ho et al. (2021), out of 4313 hospitalized COVID-19 patients, 574 (13.31%) received corticosteroids (methylprednisolone, prednisone, dexamethasone or hydrocortisone). When administered within the first seven days from admission to the hospital, corticosteroids showed a significantly reduced intrahospital mortality rate (p=0.03) and the rate of admission to the ICU (p=0.02), which was mostly beneficial in patients younger than 65 and women. The effect of corticosteroids on CRP was statistically significant (p=0.03) (9).

In a retrospective cohort study conducted by Hyun et al. (2021), 22 COVID-19 patients with a severe clinical picture received corticosteroids. Out of them, 12 (55%) patients were treated within 10 days from diagnosis (early use group). In this group, the time from onset of symptoms to hospital discharge, the time from diagnosis to hospital discharge, as well as the duration of hospitalization, were significantly reduced (p= 0.03; p=0.024; p= 0.033, respectively). The overall mortality rate was 25%. In both groups, CRP improved over time (10).

Corticosteroids caused a significant decrease in ESR and CRP, while corticosteroids + tocilizumab and corticosteroids + metenkefalin/tridecactide caused a significant decrease only in CRP. In one systematic review of literature on the association between the combination of corticosteroids and tocilizumab compared to corticosteroids alone on outcomes of COVID-19 patients, conducted by Alkofide et al. (2021), 17 studies were included. The mortality rate was lower in patients receiving the combination of corticosteroids and tocilizumab compared to corticosteroids alone (11). Tocilizumab was used for the management of elevated levels of CRP in COVID-19 patients with a severe clinical picture and was successful: p<0.001 (12). In our study, only 10 (5%) patients received tocilizumab, which can be the reason why our results showed that corticosteroids alone were more effective compared to the combination of corticosteroids and tocilizumab. A clinical trial on the use of metenkefalin/tridecactide in 120 COVID-19 patients was completed but to this day no results were posted on ClinicalTrials.gov (13).

Results of our study demonstrated that posthospital, methylprednisolone caused a significant decrease in both inflammatory markers, while in patients who did not take any immunomodulators, there was a significant decrease only in ESR. Both inflammatory markers were reduced the most in patients with a severe clinical picture. In a study conducted by Huang et al. (2022), 1164 COVID-19 patients received dexamethasone (6 mg/day) for less than 10 days during hospitalization. The mortality rate within 14 days from hospital discharge was 9.1% among patients who continued using dexamethasone (n=692) compared to 11.4% among patients who

did not (n=472). As the difference was not statistically significant, it is not recommended to routinely prescribe these medications to COVID-19 patients at hospital discharge (14). Continuous administration of corticosteroids may suppress the immune system and slow down viral clearance (15).

The risk of developing a severe clinical picture is much higher in COVID-19 patients with various medical conditions, including chronic kidney disease, diabetes mellitus, lung and liver disease, cardiovascular diseases, obesity, anxiety, immunodeficiency and mental illnesses (16). Compared to people without chronic conditions, the risk of death is 1.5 times higher for those with one comorbidity and 3.8 times higher for those with more than 10 comorbidities (17). Although the exact mechanisms by which existing chronic conditions influence the severity of the clinical picture in COVID-19 patients are not known, it is assumed that inflammatory and hormonal pathways are involved (18). In a study conducted by Tuna et al. (2022), CRP was compared in 38 comorbid COVID-19 patients and 31 patients without any comorbidities. Compared to patients without any comorbidities, comorbid patients had significantly higher CRP ($p<0.001$) (19). In our study, results showed that patients with a severe clinical picture were the least common in the group with no comorbidities and the most common in the group with more than two comorbidities. The most prevailing comorbidities in all patients, as well as in patients with a severe clinical picture, were hypertension, DMT2, chronic obstructive bronchitis, chronic gastritis and chronic cardiomyopathy, the diagnoses of which are proven risk factors for developing a severe clinical picture. Although there was no statistically significant impact of the number of comorbidities patients had on inflammatory markers in all patients and regarding the severity of the clinical picture, which differs from the results obtained in the study conducted by Tuna et al. (2022), the highest number of comorbidities was in patients with a severe clinical picture.

6. CONCLUSION

The use of immunomodulators, especially methylprednisolone + dexamethasone intrahospital and methylprednisolone posthospital, is justified in most COVID-19 cases as there is a significant correlation between this disease's pathophysiology and the immune response. There is also a positive correlation between the number of comorbidities patients have and the severity of the clinical picture.

- **Patient consent form:** All participants were informed about the subject of the study.
- **Author's contribution:** N.O.C. and S.S. gave substantial contributions to the conception or design of the work in the acquisition or interpretation of data. N.O.C. performed a statistical analysis of data. N.O.C. and S.S. had a part in the article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published.
- **Conflict of interest:** None declared.
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