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Original Scientific Paper

ELEVATED SERUM C-REACTIVE PROTEIN LEVELS IN COVID-19 PATIENTS WITH SCIATICA: IMPLICATIONS FOR PROGNOSIS AND TREATMENT STRATEGIES

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SUMMARY – To the best of our knowledge, no previous study has reported characteristics of C-reactive protein (CRP) levels in COVID-19 patients with comorbidities such as sciatica and lumbar syndrome. The objective of this study was to examine whether CRP levels rose significantly in COVID-19 patients with acute sciatica as compared to COVID-19 patients without it. This prospective study was performed on 147 patients previously diagnosed with COVID-19 infection who were admitted to the COVID hospital. Myalgia (p=0.00008) and lower back pain (p=0.00001) occurred much more frequently in the study group than in the control group. There was a high probability that patients with a previous history of sciatica may experience it again during their stay in COVID-19 hospital and that patients without it would not (p=0.00001). There was a significant correlation between the severity of sciatica and CRP levels (r=0.19, p=0.0174). Our results suggest that serum CRP levels are significantly higher in COVID-19 patients with concomitant sciatica in comparison to patients without sciatic pain, indicating a connection between the increased systemic inflammation in COVID-19 and sciatica. Given that the occurrence of COVID-19 in patients with sciatica is not rare, the knowledge about this matter is of high medical relevance.

Key words: *COVID-19; Sciatica; COVID-19 vaccines; C-reactive protein*

Introduction

The COVID-19 pandemic made an undoubtful impact on global mortality and morbidity, influencing world politics, economy, as well as all kinds of social interactions, and people's way of living. Apart from pneumonia, during corona virus infection many chronic diseases amplify their symptomatology often leading to prolonging and diverting the course of illness and complicating patient treatment[1].

Neurological manifestations of COVID-19 such as cerebrovascular disease, encephalopathy, Guillain-Barré syndrome, and seizure have been widely reported in medical journals during the recent few years. Moreover, neurological disorders were detected in 13.5% of patients with COVID-19 in a large prospective study of hospitalized patients with COVID-19[2].

Low back pain and sciatica are the comorbidities that are rarely analyzed as health problems in COVID-19 patients, usually as some case reports[3]. The most common cause of sciatica is disc herniation,

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when the prolapsed or extruded intervertebral disc irritates the spinal nerve root. This degenerative illness is accompanied by a local inflammatory reaction, where cytokines play a significant role.

C-reactive protein (CRP) serum concentrations present an unspecific reflection of the presence of overall body inflammatory conditions. High serum CRP concentrations are undoubtful markers of the intensity of immune response to COVID-19 infection[4,5], but there also are some studies the results of which suggest that serum CRP concentrations rise in acute lumbar syndrome, and even can correlate with the degree of intervertebral disc degeneration[6,7].

As far as we are aware, there are no previous studies reporting on the characteristics of CRP levels in COVID-19 patients with comorbidities such as sciatica and lumbar syndrome. Therefore, this study aimed to investigate whether CRP levels rose significantly in COVID-19 patients with acute sciatica as compared to COVID-19 patients without it. As the rise of CRP usually happens within the first 48 hours from the onset of inflammation, its levels could be misinterpreted as a prognostic factor in COVID-19 patients with ongoing sciatica[4]. Since the occurrence of COVID-19 in patients with acute lumbar syndrome and sciatica is not rare[8], the knowledge about this matter is of high medical relevance.

Materials and Methods

This prospective study was conducted in hospitalized COVID-19 patients from April 2021 until April 2022. The study followed the principles of the Declaration of Helsinki from 2013 (seventh revision) and the Ethics Committee of the Clinical Center approved the study (no. 9882/5 as of April 2, 2021).

A total of 147 patients with the diagnosis of COVID-19 infection were enrolled and were hospitalized due to the severity of clinical presentation. Fifty of them had acute sciatica symptomatology during their hospital stay in COVID-19 hospital (study group), and the remaining 97 patients were without it (control group).

Exclusion criteria for patient enrolment in the study were respiratory unstable, intubated, unconscious and pregnant patients, and age younger than 21. In included patients, the minimal oxygen saturation (SpO2) was 90%.

Patients received standard treatment for their main morbidity in the COVID Center, as well as treatment for any other comorbidity identified during their hospital stay, based on specialist recommendations. During hospital treatment, sciatica was managed with conservative therapy, which included only paracetamol and dexamethasone because other non-steroidal anti-inflammatory drugs and depot corticosteroids were prohibited in the national guideline for the treatment of COVID-19 infection, while a small number of patients (n=11) underwent kinesitherapy.

The SARS-CoV-2 virus was detected with a real-time polymerase chain reaction (RT-PCR) test by using the Bioer LineGene 9600 Plus Real-Time Thermalcycler PCR Systems (Biosynex, Illkirch-Graffenstaden, France). Overall 400 μL of nasal and oral swab specimens was extracted using ExiPrep 96 Viral RNA Kit (Bioneer). RNA was extracted twice, along with subsequent elution with 100 μL each, then pooled and stored at -80 °C until analysis. Kits with an endogenous internal control were applied to validate the success of extraction, while the exogenous internal controls were not added to the extraction, and the PCR amplification process was monitored with the help of internal master mix controls. All the manufacturer's instructions and recommendations were respected in the preparation of the master mix, cycling protocol, thermocycler, and in the interpretation of the results. According to the manufacturer's recommendations, testing was repeated in cases of unreliable and invalid results.

A venous blood sample was obtained from each participant after an overnight fast. Complete blood count was determined by using a Celltac MEK-6510K automatic analyzer (Nihon Kohden, Tokyo, Japan). A regular serum tube with gel separator was used to collect blood for the rest of the analyses performed. CRP was determined immediately by using standard biochemical methods on an AU680 Clinical Chemistry Analyzer (Beckman Coulter, Brea, CA, USA). Serum CRP concentration was determined daily during hospital stay, however, for the study purpose we took into account its highest value. The levels of CRP were expressed in mg/L.

Pain intensity was measured by the visual analog scale (VAS) with the descriptor extremes "no pain at all" and "my pain is as bad as it could possibly be", numerically from 0 to 10. The measuring was completed by the patients themselves.

Vaccination status was determined based on the vaccination certificate from the state medical database.

The status was divided into unvaccinated (0 vaccines) and vaccinated (1 and more vaccines). The patients previously had the option to be vaccinated with the vaccines of their choice.

Medical data such as the presence of back pain and sciatica, stretch leg test results, motor weakness, and numbness were collected *via* classic clinical and neurological assessment.

Diagnosis of sciatica was established by neurological examination where sciatica was defined as pain that typically occurs in the distribution of a dermatome and goes below the knee to the foot with or without weakness or numbness.

Statistical analysis

Data were expressed as mean and standard deviation (SD) or interquartile range (IQR), while statistical significance was defined as $p<0.05$ in all comparisons. Statistical significance was analyzed using the χ^2-test for categorical variables, two-sample *t*-test for continuous variables, and Pearson correlation coefficient. The results are presented in tables as numeric values and percentages and graphically for the last statistical analysis. All statistical tests were run through SPSS 26.0 for Windows (SPSS Inc., USA).

Results

Our patients (N=147) experienced a high rate of myalgia (n=64; 43.54%), back pain (n=71; 48.30%), and sciatica (n=50; 34.01%). The mean age of our overall group was 54.10±13.76 years, and 58 (39.46%) of them were females (Table 1).

There were no statistically significant age differences between the study group and control group (p=0.0921). There was no significant difference in sex distribution between the two compared groups of COVID-19 patients (p=0.7954) either (Table 2).

The median CRP level in the study and control group was 80.8 (IQR 44.5-100.8) and 47.8 (IQR 33.5-60.2), respectively. CRP levels were significantly higher in the study group (p=0.0049) (Table 2).

Myalgia occurred in both the study group and control group, i.e., in 66% (n=33) and 31.96% (n=31), respectively. In the study group, myalgia occurred much more frequently than in the control group (p=0.00008). Back pain also occurred in the two groups, in 70% (n=35) and 26.80% (n=26), respectively. In the study group, back pain occurred significantly more frequently than in the control group (p=0.00001). In the study group, 39 (78.00%) patients had a previous history of sciatica and 11 (22.00%) were without a previous history of sciatica. In the control group, 17 (17.52%) had sciatica earlier in life and 80 (82.48%) did not. There was a high probability that patients with a history of sciatica may experience it again during their stay in COVID-19 hospital and that patients without it would not (p=0.00001). COVID-19 patients with acute sciatica had significantly more often a history of back pain than COVID-19 patients without acute sciatica (p=0.00001). There were 129 (87.75%) unvaccinated and 18 (12.25%) vaccinated patients. Only eight (16%) study group patients and ten (10.31%) control group patients were vaccinated. There was no connection between vaccinal status and presence of sciatica in COVID-19 patients (p=0.3186) (Table 2).

Among all patients (N=147), 38.10% (n =56) had a history of sciatica before getting COVID-19 infection. In the study group, 15 (38.46%) out of 39 patients described their symptomatology as more severe than ever before, 5 (12.82%) patients as severe as before, and the rest experienced modest symptomology.

In the study group, neurological motor deficit was present in 42% (n=21), paresis of peroneal nerve in 22% (n=11), paresis of tibial nerve in 16% (n=7), and femoral weakness in 4% (n=2) of patients. Lazarevics (straight leg raising) test was positive in 78% (n=39), while leg hypesthesia was present in 82% (n=41) of patients. Sphincter disturbance did not occur in any of the patients, although 3 patients already had it due to reasons other than degenerative spine disease (Table 3).

In the study group, there were 3 patients with normal CRP levels, 20 with modestly elevated CRP (5-40), 19 with very high CRP (40-200), and 8 with extreme CRP levels (>200). Furthermore, in the control group, there were 18 patients with normal CRP levels, 35 with modestly elevated CRP (5-40), 40 with very high CRP (40-200), and 4 with extreme CRP levels (>200) (Table 4). There were significant differences in the subgroups of CRP levels between COVID-19 patients with and without sciatica (χ^2=9.56; p=0.022). Serum CRP concentrations measured in patients ranged from 1.9 to up to 443 as the highest, and the mean serum CRP concentration was 63.41±75.34. There were 97 patients without sciatica, and their intensity of sciatica was marked as 0. There was a significant correlation between the severity of sciatica and CRP levels (r=0.19, p=0.0174) (Fig. 1).

Table 1. Demographic and clinical characteristics of the patients

Patient characteristic	n ± SD
Age (years), mean (SD)	54.10±13.76
Female (%)	58 (39.46%)
C-reactive protein (mg/L), mean (SD)	63.41±75.34
D-dimer (ng/mL), mean (SD)	1017.10±174.35
Lymphocytes (%),mean (SD)	14.86±9.56
Neutrophils (%), mean (SD)	77.12±12.67
Myalgia	64 (43.54%)
Back pain	71 (48.30%)
Sciatica	50 (34.01%)
History of anti-COVID vaccine	18 (39.46%)

SD = standard deviation

Table 2. Comparison of the parameters between the study group and control group patients

Patient characteristic	Study group (n=50)	Control group (n=97)	p value
Age (years), median (IQR)	50.5 (43-61)	52 (43-64)	0.0921
Female, n (%)	19 (38%)	39 (40.21%)	0.7954
CRP (mg/L), median (IQR)	80.8 (44.5-100.8)	47.8 (33.5-60.2)	**0.0049***
D-dimer (ng/mL), median (IQR)	598.5 (93-691.5)	363 (185.5–548.5)	0.2216
Lymphocytes (%), median (IQR)	12 (7.9-19.9)	10.5 (8.9-19.4)	0.4760
Neutrophils (%), median (IQR)	78.8 (71.0-85.0)	81.6 (72.2-85.6)	0.3079
Myalgia	33 (66%)	31 (31.96%)	**0.00008***
Back pain	35 (70%)	26 (26.80%)	**0.00001***
History of sciatica	39 (78%)	17 (17,52%)	**0.00001***
History of back pain	36 (72%)	34 (35.05%)	**0.00001***
History of anti-COVID vaccine	8 (16%)	10 (10.31%)	0.3816

CRP = C-reactive protein; IQR = interquartile range; *statistically significant

Table 3. Neurological characteristics associated with sciatica in the study group

Sciatica characteristic	n	%
Straight leg raising test	39	78
Neurological motor deficit	21	42
Hypesthesia	41	82
Acute sphincter disturbance	0	0

Table 4. Comparison of CRP levels between the study and control group patients

Patient group	CRP <5	CRP 5-40	CRP 40-200	CRP >200	Σ
Study group	3 (6%)	20 (40%)	19 (38%)	8 (16%)	50 (100%)
Control group	18 (18.55%)	35 (36.08%)	40 (41.23%)	4 (4.12%)	97 (100%)

CRP = C-reactive protein

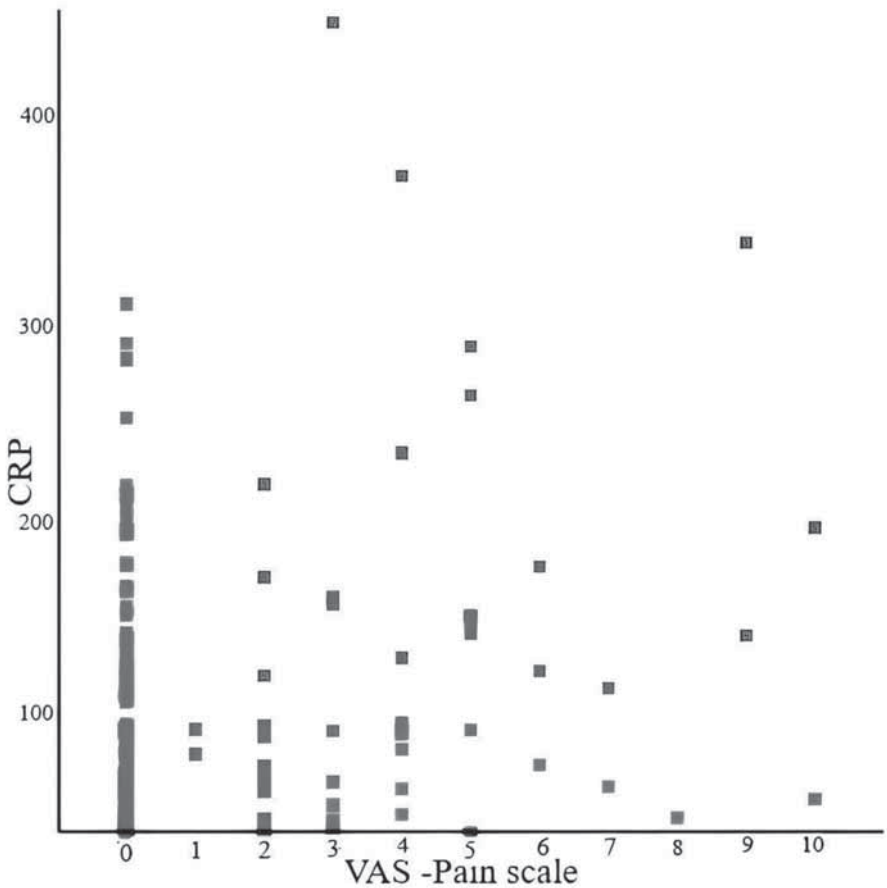

Fig. 1. Correlation between CRP values and VAS pain score in COVID-19 patients.

CRP = C-reactive protein; VAS = visual analog scale

Discussion

Besides respiratory manifestations in COVID-19 patients, the symptoms and signs of extrapulmonary expression of viral activity on different organs is a matter of increasing interest to clinicians. One of the prominent symptoms is pain, and its pathophysiology is complex and yet to be thoroughly determined. It is composed of consequences of direct and indirect viral damage (through the actions of cytokines) together with the psychological status of patients.

Pain may persist chronically, even for 4 weeks after discharge from the hospital, unexpectedly frequently, manifesting as joint pain (27%), chest pain (22%), or myalgia (20%-30%)[9,10]. Very often, pain is accompanying the acute phase of COVID-19, where musculoskeletal pain may be present in 44% of patients[11]. Similarly, 34% of our group of COVID-19 patients developed sciatica, most of them additionally experiencing back pain. Our study showed that there was a high probability that patients with a history of sciatica may experience it again during their stay in COVID-19 hospital. The majority of our study group patients had a previous history of sciatica (78%), whereas only 22% experienced it for the first time. Similarly, in the study by Abdulateef, 68% of the COVID-19 patients with acute sciatica had a positive history of sciatica *versus* 32% of those that did not have such a history[8]. Also, our study showed that a history of back pain was a prognostic factor for its occurrence in COVID-19 patients. SARS-CoV-2 infection is associated with lumbar back pain, and moderate COVID-19 symptomatology is an independently associated factor of lumbar back pain[12].

Molecular mechanisms of pain genesis in COVID-19 patients are related to macrophage activation, direct viral damage, and cytokine-induced damage. The role of macrophages is fundamental in promoting the inflammatory processes, but also in the state of resolution. They enable sensory cell injury through stimulation of the production of inflammatory mediators (tumor necrosis factor [TNF], interleukin [IL]-6, IL-1β and bradykinins). This affects dorsal root ganglion sensory neurons, and through still incompletely defined processes of sensitization and activation, it can lead to hyperalgesia and pain[13]. On the other hand, the expression of angiotensin receptor type 2 (AT2R) in macrophages infiltrates the site of nerve injury but not in dorsal root ganglion[14], and this could be an explanation of macrophage activation in COVID-19-related pain.

The link between SARS-CoV-2, angiotensin converting enzyme type 2 (ACE2) host receptor, and Mas-mediated angiotensin (1-7) explains the genesis of acute pain in COVID-19 due to direct viral action. Imbalance of the ACE/Ang II/AT1R and the ACE2/Ang-(1-7)/MasR axes due to interaction between virus and ACE2 leads to sensory neuron injury, among others. Additionally, functional imbalance between cytokine systems characterized by impairment of the Ang (1-7) pathway (anti-nociceptive) could occur. This may be the reason for painful manifestations without intelligible evidence for viral invasion into nerve tissue[15].

The SARS-CoV-2 initiates pain through the activation of an extreme immune response. This immune-mediated inflammation is termed 'cytokine storm'. It is manifested as a high release of proinflammatory cytokines such as TNF-α, IL-6, IL-1β, IL-8 and IL-12, as well as IFN-γ inducible protein, macrophage inflammatory protein 1A, and monocyte chemoattractant protein 1[16].

Sciatica is a manifestation of inflammatory processes due to compression or stretching of the specific lumbar nerve roots, usually after its contact with degenerated and herniated intervertebral disc. Also, other morphological changes in spine degenerative disease or sometimes tumors may cause nerve root injury and therefore specific inflammatory response. Interest in inflammatory etiologies of sciatica is focused on the cytokines such as TNF-α, IL-4, IL-6, IL-8, IL-1 α/β, IL-17, IL-10, interferon [IFN]-γ, chemokines, and prostaglandin (PGE)2, and it has shown the role of inflammatory cytokines in facilitating neuropathic pain[17-22]. It has been demonstrated that the expression of IL-1β and IL-1R is elevated in degenerated disc tissue[23], as well as in the surrounding tissues[24]. These cytokines have several common functions which include chemoattraction of neutrophils, induction of adhesion molecules on endothelial cells, and production of PGE2 by macrophages[25]. Nevertheless, some studies did not find significant difference in the concentration of serum markers associated with inflammation and angiogenesis between patients with and without sciatica[26,27].

C-reactive protein is a non-specific marker of acute inflammation, an annular (ring-shaped) pentameric

protein found in blood plasma. Macrophages and T-cells secret the cytokines such as IL-1 beta, IL-6, and TNF, which induce the synthesis of CRP by hepatocytes both *in vitro* and *in vivo*[28]. Therefore, CRP is elevated due to the same cytokine production in both COVID-19 infection and sciatica degenerated disc-related patients.

This knowledge led us to the idea to analyze the connection between two inflammatory entities in the same patients, for the first time. These two entities were COVID-19 infection and sciatica.

Pain is always a subjective phenomenon and its quantification by patients using VAS can be affected by different psychological variables such as patient mood, cultural learning, meaning of the situation, attention, etc.[29]. This could be the limitation of our study. Nevertheless, VAS is generally and broadly used when assessing pain intensity, and appropriate use in the study is confirmed by our results, i.e., the serum CRP level that correlated with the intensity of sciatica.

Conclusion

Our results suggest that serum CRP levels are significantly higher in COVID-19 patients that suffer from sciatica than in COVID-19 patients that are sciatica free. The levels of CRP which are of major importance in the prediction of treatment of COVID-19 infection combined with frequent comorbidity such as sciatica could mislead the prognosis of patient outcomes.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Sažetak

POVIŠENE RAZINE C-REAKTIVNOG PROTEINA U SERUMU KOD BOLESNIKA S COVID-19 I IŠIJASOM: IMPLIKACIJE ZA PROGNOZU I STRATEGIJE LIJEČENJA

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Prema našim saznanjima, niti jedna prethodna studija nije izvijestila o karakteristikama razina C-reaktivnog proteina (CRP) kod bolesnika s COVID-19 i popratnim bolestima kao što su išijas i lumbalni sindrom. Cilj ove studije bio je ispitati jesu li razine CRP-a značajno porasle kod bolesnika s COVID-19 i akutnim išijasom u usporedbi s bolesnicima s COVID-19 bez išijasa. Ova prospektivna studija provedena je na 147 bolesnika kojima je prethodno dijagnosticirana infekcija COVID-19 i koji su primljeni u COVID bolnicu. Mialgija (p=0,00008) i bol u donjem dijelu leđa (p=0,00001) javljale su se mnogo češće u ispitivanoj skupini nego u kontrolnoj skupini. Postojala je velika vjerojatnost da će bolesnici s prethodnom poviješću išijasa ponovno iskusiti išijas tijekom boravka u COVID bolnici, dok bolesnici bez njega neće (p=0,00001). Postojala je značajna korelacija između ozbiljnosti išijasa i razina CRP-a (r=0,19; p=0,0174). Naši rezultati ukazuju na to da su razine CRP-a u serumu značajno više kod bolesnika s COVID-19 koji imaju popratni išijas u usporedbi s bolesnicima bez išijasa, što upućuje na povezanost između povećane sistemske upale kod COVID-19 i išijasa. S obzirom na to da pojava COVID-19 kod bolesnika s išijasom nije rijetka, znanje o ovom pitanju od velike je medicinske važnosti.

Ključne riječi: *COVID-19;Išijas; Cjepiva protiv COVID-19; C-reaktivni protein*