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CERVICOBRACHIAL SYNDROME: PREVALENCE AND CLINICAL CORRELATION WITH CORONAVIRUS 2019 DISEASE AMONG HOSPITALIZED PATIENTS

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There are currently emerging concerns about the multisystem involvement of the coronavirus disease 2019 (COVID-19) infection as well as potential long-term complications. The aim of our study was to examine the prevalence and clinical characteristics of cervicobrachial syndrome among hospitalized patients with COVID-19. The research was conducted as a prospective study on 147 patients with previously confirmed COVID-19 infection by using a Real-Time Polymerase Chain Reaction assay for SARS-Cov-2. After neurological assessment and meticulous patient history-taking, the patients were divided into a group with and a group without a previous history of cervicobrachialgia. The pain intensity was self-assessed by patients using a numerical scale ranging from 0 to 10, while routine laboratory analyzes related to COVID-19 were performed from venous blood samples. Our data demonstrate a statistically significant association between previous history and recurrence of cervicobrachialgia (LR = 28.655; p = 0.000). Moreover, the pain intensity assessment in patients with a previous history of cervicobrachialgia statistically significantly correlates with the current degree of cervicobrachialgia during hospitalization (p = 0.000). Furthermore, a weak positive correlation (r = 0.168; p = 0.046) was noted between the current degree of cervicobrachiialgia and the neutrophil to lymphocyte ratio. The present study demonstrates a statistically significant association between the previous history of cervicobrachial syndrome and its recurrence, as well as pain intensity assessment in hospitalized patients due to COVID-19. The neutrophil-to-lymphocyte ratio positively correlates with the degree of cervicobrachialgia and may indicate an increase in the local inflammatory response in cervicobrachial syndrome.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and there are currently emerging concerns about the multisystem involvement of the COVID-19 infection as well as potential long-term complications (1, 2). The pandemic has indisputably exerted a profound influence on the health domain, notably in terms of both morbidity and mortality outcomes, since the numerous diagnostic and therapeutic measures for other diseases were postponed (1).

Individuals infected with COVID-19 exhibit a wide spectrum of clinical manifestations, while the most frequently encountered symptoms include fever, myalgia, fatigue, non-productive cough, productive cough, pharyngitis, headache, ageusia, anosmia, nausea, fever, dyspnea, diarrhoea, vomiting (3). Moreover, neurological symptomatology can encompass not only headache, anosmia and ageusia, but there is also a growing body of evidence to suggest that infection can induce the emergence of stroke, Guillain–Barré syndrome, syncope and convulsions, and in the most severe cases, cause toxic metabolic encephalopathy (4).

Cervicobrachial syndrome represents pain in the neck and arms, which may be caused by cervical radiculopathy due to disc herniation and is clinically manifested as discomfort, numbness or

tingling in the arm and accompanying headache (5). Some other etiologic factors that may cause cervicobrachialgia in patients without neurological deficits could encompass facet joint pain, fibromyalgia with associated trigger points and inflamed nerve tissue, while there are also potential non-somatic referral patterns (5, 6).

Considering the profound impact of the COVID-19 pandemic, there has been a significant reduction in the scope of diagnostic and therapeutic procedures on the cervical spine (7, 8). Furthermore, there is no data in the relevant scientific literature about cervicobrachial syndrome in hospitalized COVID-19 patients. Therefore, the aim of our study was to examine the prevalence and characteristics of cervicobrachial syndrome in hospitalized COVID-19 patients.

Patients and methods

The authors conducted this prospective study on patients during the treatment in a COVID-19 hospital in the period from April 2021 to May 2022, after obtaining the consent of the referent ethics committee. The study followed the principles of the Declaration of Helsinki from 2013 (seventh revision) while the ethics committee approved the study (Number 9882/5 on April 2, 2021). Upon obtaining the informed consent as well, the research was conducted on 147 patients with a previously confirmed COVID-19 infection with a Real-Time Polymerase Chain Reaction assay for SARS-Cov-2 by using the Bioer LineGene 9600 Plus Real Time Thermalcycler PCR Systems (Biosynex, Illkirch- Graffenstaden, France).

Furthermore, all the participants involved were individuals, older than 18 years, with a mild clinical presentation and absence of significant comorbidities (their SpO2 value exceeded 90%). Our patients were hospitalized for a minimum of 7 days and were under constant supervision by medical staff, which included regular assessment of body temperature, oxygen saturation, breathing rate and diuresis. Vaccination status was determined based on the vaccination certificate from the state medical database. On the basis of vaccination status, patients were divided into the unvaccinated group, the group vaccinated with one dose, and the group vaccinated with 2 or more doses, while the patients previously had the option to be vaccinated with the vaccines of their choice.

The confirmation of the diagnosis of cervicobrachial syndrome was achieved through anamnestic data, as well as by neurological assessment of the patients with manual muscle testing, upper limb reflex evaluation, Spurling's Test, shoulder abduction test and upper limb tension tests.

According to the presence of cervicobrachialgia, the patients were categorized into group I, which was comprised of patients with a documented history of cervicobrachial syndrome, as well as Group II, which encompassed patients experiencing cervicobrachialgia for the first time, without any prior occurrences.

The intensity of cervicobrachial pain was self-evaluated by the patients with a numerical scale ranging from 0 (indicating no pain) to 10 (representing the most severe pain imaginable). Throughout the patient's hospitalization, cervicobrachialgia was treated with conservative therapy that included only paracetamol and dexamethasone, since other nonsteroidal anti-inflammatory drugs and depot corticosteroids were not recommended by the National guidelines for the treatment of COVID-19 infection, while a small number of patients underwent kinesitherapy. Additional diagnostic and therapeutic procedures for cervicobrachial syndrome were postponed until patients had recovered from the COVID-19 infection.

Statistical data processing

Data entry and statistical processing were performed using the SPSS software package (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Among the basic descriptive statistical parameters, standard statistical methods were used for qualitative and quantitative assessment of the results: absolute numbers, relative numbers (%), arithmetic mean ($\bar{x}$), standard deviation (SD), and minimum and maximum values. The normality of the distribution of individual values was examined by Kolmogorov–Smirnov test. The χ^2 test was used to test the statistical significance and interpret the relationship between two categorical variables. The statistical hypothesis was tested at the level of significance for the risk of $\alpha = 0.05$, i.e. the difference between the samples was considered significant if $p < 0.05$.

We applied the Mann–Whitney U test as a nonparametric test to compare outcomes between two independent groups. One-way ANOVA (Analysis of Variance) was employed as a statistical test to analyze the difference between the means of more than two groups. Binary logistic regression analysis was used to estimate the probability or likelihood of the cervicobrachialgia occurring based on the values of the predictor variables, as a regression model where the target variable is binary.

Results

There was no statistically significant association between the incidence of cervicobrachial syndrome among genders (Chi-square statistic was 0.848 and $p = 0.357$). There was no statistically significant difference in the age of the patients (Table 1) regarding the presence of cervicobrachialgia (Z-score was -0.803 and $p = 0.422$). The average age of the patients in our study was 66.35 years (min 29, max 89), while the gender structure consisted of 88 (59.86%)

male and 59 female (40.13%) patients. Out of a total of 147 patients from our study, 127 patients (86.39%) were not vaccinated, 14 patients (9.52%) were vaccinated with two doses of vaccine, while 6 patients (4.08%) were vaccinated with one dose of vaccine (Table 2).

The results of our research indicate that a total of 27 patients (64.28%) with a previous history of cervicobrachialgia had a recurrence of this syndrome (Table 3). However, 19 patients (18.09%) who had never experienced cervicobrachialgia before suffered from this syndrome for the first time during the hospitalization. Our data demonstrated a statistically significant association between previous history and recurrence of cervicobrachialgia (LR = 28.655; p = 0.000) (Table 3). Moreover, the pain intensity assessment in patients with a previous history of cervicobrachialgia statistically significantly correlated with the current degree of cervicobrachialgia during hospitalization (p = 0.000) (Table 4).

Furthermore, a weak positive correlation (r = 0.168; p = 0.046) was noted between the current degree of cervicobrachialgia and the neutrophil-to-lymphocyte ratio (Table 4). Additionally, no statistically significant correlation was found between the inflammatory parameters and the degree of pain (Table 4). Moreover, the vaccination status of the patients was also not statistically significantly associated (F = 0.328; p = 0.895) with the cervicobrachial syndrome (Table 4.).

Various other symptoms and signs of COVID-19 infection, which we considered during our research did not show statistically significant associations with the occurrence of cervicobrachialgia (Table 5).

Table 1. Demographic characteristics of the examined patients

Variable	Patients with cervicobrachial syndrome	Patients without cervicobrachial syndrome	p‡
	Number (Percentage)	Number (Percentage)	
Gender			
Male	25 (54.35%)	63 (62.37%)	
Female	21 (45.65%)	38 (37.62%)	p = 0.357
Age (years) †	65.60 ± 14.03	66.34 ± 13.93	p = 0.422

† Mean ± standard deviation, ‡ Chi−squared test, ‖ Mann−Whitney U-test

Table 2. Vaccination status of the hospitalized patients

Variable	Frequency	Percent
No vaccines	127	86.39
Pfizer−BioNTech COVID-19 Vaccine 1 dose	1	0.68
Sinopharm [Vero Cell]- Inactivated 1 dose	2	1.36
Sinopharm [Vero Cell]- Inactivated 2 doses	14	9.52
The Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine) COVID-19 vaccine—1 dose	3	2.04
Total	147	100

Table 3. The presence of cervicobrachial syndrome in comparison to the patient's prior medical history

Variable	**Patients with cervicobrachial syndrome**	**Patients without cervicobrachial syndrome**	**p‡**
	Number (Percentage)	Number (Percentage)	
Previous history of cervicobrachial syndrome	27 (64.28%)	15 (35.71%)	
The patient has never had cervicobrachial syndrome	19 (18.09%)	86 (81.91%)	**p = 0.000**

‡Chi-squared test

Table 4. Relationship between the degree of cervicobrachialgia, vaccination status, hospitalization and laboratory parameters

Variables	Current degree of cervicobrachialgia	
	Pearson Correlation	p
Hospitalization in patients with previous history of cervicobrachialgia	0.579	**0.000**
Fever	-0.085	0.306
Creatine kinase	0.080	0.768
Interleukin 6	-0.150	0.465
Lymphocyte count	-0.045	0.601
Lymphocyte percentage	0.101	0.336
Neutrophil count	0.043	0.627
Neutrophil percentage	-0.005	0.964
Neutrophil to lymphocyte ratio	0.168	**0.046**
Vaccination status	0.328†	0.895
D-dimer	-0.116	0.450
C-reactive protein	-0.064	0.442

†F—a value on the F distribution in the ANOVA test

Table 5. The influence of the tested parameters on the development of cervicobrachial syndrome (Binary logistic regression)

Variable	OR	95% CI	p
Myalgia	0.446	0.146–1.364	0.157
Fatigue	0.975	0.231–4.117	0.973
Nonproductive cough	1.254	0.413–3.812	0.690
Productive cough	0.373	0.100–1.384	0.140
Pharyngitis	1.440	0.321–6.456	0.690
Headache	1.241	0.341–4.514	0.743
Dysgeusia	7.645	0.008–7295.427	0.561
Anosmia	0.495	0.001–441.843	0.839
Nausea	1.817	0.491–6.718	0.371
Fever	0.665	0.170–2.601	0.557
Dyspnea	0.476	0.114–1.990	0.309
Diarrhoea	0.455	0.077–2.698	0.386
Vomiting	2.487	0.214–28.859	0.466

Discussion

Based on the available relevant scientific data and empirical evidence from referent databases (MEDLINE, PubMed, Embase, ClinicalTrials.gov, Cochrane databases, EBSCO, Redalyc) and to the best of our knowledge, this is the only study that has investigated and reported the frequency and characteristics of cervicobrachialgia in hospitalized COVID-19 patients.

With the implementation of immunization strategies against COVID-19, the pandemic trajectory was reversed, but on the other hand, numerous side effects were recorded. One study conducted in Mexico showed that the most common neurological side effects after vaccination were headache, transient sensory symptoms and weakness, while epileptic seizures, Guillain–Barré syndrome and transverse myelitis were documented solely in a couple of cases (9). On the other hand, Göbel et al. recorded that although the headache occurred often, it was transient in duration (18.0 ± 27.0 h after vaccination and lasted 14.2 ± 21.3 h) (10). It has been assumed that the vaccination against SARS-CoV-2 can lead to the development of transverse myelitis as a serious complication due to inflammatory and immune reactions, and be clinically manifested by motor, sensory and autonomic dysfunctions, which has been recorded in extremely rare cases (11, 12, 13). The results of our research indicate that there was no statistically significant association between the vaccination status of the patients ($F = 0.328$; $p = 0.895$) and the cervicobrachial syndrome. Among numerous studies examining the effects of vaccination against COVID-19, no association between vaccination status and the frequency of cervicobrachialgia has been examined and reported.

The findings derived from our research demonstrated that in 64.28% of patients with a previous history of cervicobrachialgia a recurrence occurred, while 18.09% of patients encountered cervicobrachial pain for the first time in their lifetime during hospitalization. A potential explanation for the exacerbation of chronic pain such as cervicobrachial syndrome is that its multifactorial and multidimensional nature may be caused by both psychosocial factors and central sensitization, which we could associate with hospital treatment during the COVID-19 pandemic (5). Moreover, our results indicate a statistically significant association between previous history and recurrence of cervicobrachialgia ($LR = 28.655$; $p = 0.000$) while the degree of pain in patients with a previous history of cervicobrachialgia statistically significantly correlates with the current degree of cervicobrachialgia during the hospital treatment ($p = 0.000$). The findings obtained from one research have shown that degenerative spine diseases with

radicular pain distribution, such as lumbago and sciatica are statistically significantly more prone to relapse in hospitalized patients treated for COVID-19 (14). Moreover, the results we obtained could be explained by the fact that the locomotor system in hospitalized COVID-19 patients is minimally active for a significant time, and applied to all bed-rest-related illnesses, while the patients in our study were hospitalized for a minimum of 7 days. It is widely acknowledged that a low level of physical activity is a risk factor for worsening of degenerative spine disorders (14, 15).

Numerous hypotheses attempt to clarify the mechanism by which SARS-CoV-2 exerts its neurotropic effects on the central and peripheral nervous system. The effects on the nervous system are widely postulated to result from direct viral invasion of nervous tissue or indirectly through systemic hyperinflammation. Furthermore, proinflammatory mediators are released by excessive activation of the innate immune system, which serves as a distinctive hallmark of COVID-19 (16, 17).

The radicular distribution of pain in disc herniation and compression on the nerve root is attributed to mechanical pressure, as well as a local inflammatory response. Furthermore, in patients with disc herniation, a local increase in the concentration of inflammatory cytokines, such as interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin 21 (IL-21), interleukin 17 (IL-17) and cyclooxygenase-2 (COX-2), has been observed, while the high-sensitivity CRP increases in proportion to the extent of the herniation (18). As a result, the local concentration of chemokines around the compressed nerve root and disc herniation increases, and the cellular concentration and activation of macrophages, mast cells, T and B lymphocytes becomes greater (18).

Additionally, concentrations of IL-6 and IL-8 have been demonstrated to be significantly higher in polydiscopathy compared to single-segment disc disease (19). On the other hand, pro-inflammatory cytokines such as Interleukin 1 (IL-1α and IL-1β) increase following the occurrence of COVID-19 infection and damage to the respiratory tract epithelium, after which IL-6, TNF-α and IFN-γ increase their concentration in the blood, correlating with the degree of inflammation (20). Moreover, a comprehensive understanding of the underlying pathophysiological mechanisms of how the above-mentioned inflammatory mediators increase both in COVID-19 infection and cervical disc herniation remains elusive, and additional research is needed to provide a comprehensive explanation between the connection between cervicobrachial syndrome and COVID-19.

On the other hand, the results of our research showed that inflammation markers, apart from neutrophil-to-lymphocyte ratio (NLR), were not statistically significantly elevated in patients with cervicobrachialgia (Table 4). Furthermore, NLR can be determined by dividing the neutrophil and lymphocyte counts and has been recognized as a marker of different inflammatory diseases. The clinical condition and disease status in patients with inflammatory connective tissue diseases, rheumatoid arthritis and other rheumatic diseases, ulcerative colitis, infectious conditions as well as autoimmune diseases could be observed by an increase in NLR, as suggested by some authors (21, 22). Additionally, there is an increasing body of research that indicates that NLR could be the widely available and more economical replacement for markers of systemic inflammation, oncological diseases, as well as various neurological disorders (23, 24). On the other hand, Gelibter et al. obtained results indicating that NLR was not a reliable marker neither for the activity of demyelinating diseases nor a determinant for predicting disability in these patients (25). Parthasarathi et al. demonstrated in a systematic review that NLR could be useful in estimating the morbidity and mortality associated with COVID-19, while NLR values > 6.5 were correlated with a higher morbidity and worse disease outcome (26). In addition, the results of our research indicate a weak positive correlation ($r = 0.168$; $p = 0.046$) between the degree of cervicobrachial syndrome and the NLR values (Table 4). Although the data about the correlation between NLR and cervicobrachial syndrome remains scarce, we identify a potential explanation for our results in the fact that correlations between NLR and different neurological, inflammatory and rheumatic diseases have been shown in some previous research, while cervicobrachial syndrome comprises all of these conditions (21–26).

Several noteworthy neuroprotective factors have been examined as potential predictors for peripheral and central nervous system damage caused by COVID-19 and include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4 and NT-5, NT-6, NT-7 and neurofilament light chain (NFLC) in the blood. Additionally, some of the functions of the previously mentioned neurotropic factors include roles in survival, homeostasis and development of neurons, while alterations in their values are associated with inflammatory, musculoskeletal and pain-sensitive diseases (27, 28). The authors of one study showed an association between lower levels of BDNF and neurological decline of the COVID patients (29). Moreover, according to the results of one research, the concentration of NFLC in the plasma of patients infected with COVID-19 was elevated during the first few days of hospitalization, and therefore NFLC has been proposed as a potential marker for the assessment of neurological involvement during the pandemic (28, 30). Therefore, further investigation is needed to examine the neurological consequences of the SARS-CoV-2 virus and biochemical markers, which would help in the early detection and prevention of neurological complications.

Conclusion

The present study demonstrates a statistically significant association between the previous history of cervicobrachial syndrome and its recurrence, as well as pain intensity assessment in hospitalized patients due to COVID-19. The neutrophil-to-lymphocyte ratio positively correlates with the degree of cervicobrachialgia and may indicate an increase in the local inflammatory response in cervicobrachial syndrome. Furthermore, the results have the potential to facilitate a more holistic approach towards managing the complications of COVID-19.

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CERVIKOBRAHIJALNI SINDROM: PREVALENCIJA I KLINIČKA KORELACIJA SA KORONAVIRUSNOM BOLEŠĆU 2019 KOD HOSPITALIZOVANIH BOLESNIKA

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Trenutno je prisutna zabrinutost zbog multisistemskih implikacija infekcije koronavirusnom bolešću 2019 (COVID-19), kao i zbog njenih potencijalnih dugoročnih komplikacija. Cilj našeg istraživanja bilo je ispitivanje prevalencije i kliničkih karakteristika cervikobrahijalnog sindroma kod hospitalizovanih bolesnika sa oboljenjem COVID-19. Prospektivnom studijom obuhvaćeno je 147 bolesnika kojima je, korišćenjem testa lančane reakcije polimeraze u realnom vremenu za SARS-Cov-2, prethodno potvrđena infekcija COVID-19. Nakon neurološke procene i pažljivog uzimanja anamneze, bolesnici su razvrstani u grupu bolesnika sa prethodnom istorijom cervikobrahialgije i grupu bolesnika bez prethodne istorije bolesti. Intenzitet bola procenjivali su sami bolesnici koristeći numeričku skalu u rasponu od 0 do 10. Rutinske laboratorijske analize u vezi sa koronavirusnom bolešću 2019 rađene su na osnovu uzoraka venske krvi. Naši podaci pokazuju statistički značajnu povezanost prethodne istorije cervikobrahialgije sa njenim recidivom (LR = 28,655; p = 0,000). Štaviše, procena intenziteta bola kod bolesnika sa prethodnom istorijom cervikobrahialgije statistički značajno korelira sa trenutnim stepenom cervikobrahialgije tokom hospitalizacije (p = 0,000). Takođe, zabeležena je slaba pozitivna korelacija (r = 0,168; p = 0,046) između trenutnog stepena cervikobrahialgije i odnosa neutrofila i limfocita. U ovoj studiji prikazane su statistički značajna povezanost prethodne istorije cervikobrahijalnog sindroma sa njegovim ponavljanjem i procena intenziteta bola kod hospitalizovanih bolesnika zbog COVID-19 infekcije. Odnos neutrofila i limfocita pozitivno korelira sa stepenom cervikobrahialgije i može ukazivati na povećanje lokalnog inflamatornog odgovora kod cervikobrahijalnog sindroma.

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***Ključne reči**: koronavirusna bolest 2019, bol u vratu, cervikobrahijalna neuralgija, vakcine protiv koronavirusne bolesti 2019, odnos neutrofila i limfocita*