ORIGINAL ARTICLE

CONTENTS

Systemic inflammation and quality of life in patients with coronavirus disease: interrelation features

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ABSTRACT

Aim: To characterize the features of the interrelation of systemic inflammation with the quality of life of patients with coronary virus disease.

Materials and Methods: 30 patients were examined 1 month after inpatient treatment for COVID-19. Quality of life (QoL) of patients was determined according to the questionnaire Medical Outcomes Study – 36-item Short Form (SF-36). The glucose level, circulating immune complexes (CICs), concentration of immunoglobulin (Ig) A, interleukin (IL)-8 and IL-33 levels were determined in the blood serum of patients.

Results: QoL of patients after coronavirus disease is significantly deteriorated: patients note a significant limitation in physical functioning, pain perception, vitality, role-physical and social functioning and mental health. The increase in glycemia and glycated hemoglobin levels in post-COVID-19 patients was significantly associated with the deterioration of patients` general health (GH) ($r = -0,228$; ($p=0,040$) and ($r = -0,280$; ($p=0,014$), respectively). The IL-33 concentration in such patients correlated directly with role-physical functioning (RP) ($r = 0,385$; $p=0,029$). The CICs level decline was associated with deterioration of RP ($r = 0,227$; $p=0,042$) and GH ($r = 0,227$; $p=0,041$).

Conclusions: The study of clinical-functional, biochemical, immunological and psychological indicators, quality of life, and their mutual influences should be included in the development of the program for the diagnosis, treatment, and rehabilitation of patients after the transfer of COVID-19 at the outpatient stage of treatment by doctors of general practice-family medicine.

KEY WORDS: systemic inflammation, quality of life, coronavirus disease, interrelation features

Wiad Lek. 2024;77(5):992-997. doi: 10.36740/WLek202405118 DOI

INTRODUCTION

COVID-19 is an acute respiratory infection caused by the acute respiratory syndrome virus SARS-CoV-2. The severity of this condition is determined by such risk factors as age, male gender, concomitant chronic diseases and aberrant metabolic status [1, 2].

Numerous randomized studies and meta-analyses have shown [1, 2] a long-term inflammation with profound synthesis of cytokines (interleukins IL-1β, IL-6) at COVID-19, which is a prognostic factor for type 2 diabetes mellitus development [3, 4]. Chronic mild inflammation leads to the progression of atherosclerosis through tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) [4].

Chronic mild inflammation leads to the progression of atherosclerosis through interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-α) [4]. C. Huang et al. [5] and N. Lelapi et al. [6] reported that COVID-19-associated coagulopathy culminates in deep vein thrombosis, pulmonary embolism, and stroke, which increases the risk of adverse cardiovascular events.

S. Gando and T. Wada [7] demonstrated three main pathophysiological mechanisms of COVID-19-associated coagulopathy: angiotensin (Ang)-II-induced coagulopathy, hyperfibrinolysis due to coagulation factor XII (FXII) and kallikrein/kinin system (KKS) activation, and disseminated intravascular coagulation (DIC) syndrome, provoking systemic inflammation, coagulation and fibrinolysis activation associated with organ dysfunction, bleeding and poor prognosis. Thrombin, plasmin, and inflammation control is a major goal in ameliorating COVID-19-associated coagulopathy [7]. But at the same time, S. Gando and T. Wada [7] emphasized that the expediency of fibrinolytic and antifibrinolytic therapy for COVID-19 is still unknown. Based on the study of well-defined molecular mechanisms of COVID-19-associated coagulopathy, further research is needed to create reliable strategies for its prevention and treatment [7].

A new promising strategy for COVID-19 treatment is the combination of anticoagulants and antidepressants (selective serotonin reuptake inhibitors – SSRIs) [1].

In the treatment of SARS-CoV-2, SSRIs are used, which leads to a decrease in the release of cytokines [8]. M. Szilveszter et al. [1] reported that inflammation/infection-triggered cytokine storm, vasculopathy, obesity, hyperglycemia and advanced age are significant risk factors for COVID-19 severe complications and the cause of reduced quality of life (QoL) for these patients.

AIM

To evaluate the features of the interrelation of systemic inflammation with the quality of life of patients with coronary virus disease.

MATERIALS AND METHODS

30 patients were examined 1 month after inpatient treatment for COVID-19 based on the Municipal Non-Profit Enterprises "Primary Medical and Sanitary Care Center" No. 1 and No. 3 of Sviatoshyn district of Kyiv. We diagnose COVID-19 based on the Order of the Ministry of Health of Ukraine No. 762 dated April 2, 2020 «Protocol of providing medical assistance in the treatment of coronavirus disease (COVID-19)» [9], the clinical guideline "Clinical management of COVID-19" [10], Order of the Ministry of Health of Ukraine No. 771 dated 04.20.2021 "Protocol of providing rehabilitation assistance for patients with coronavirus disease (COVID-19) and convalescents [11]. In our study, ethical principles were applied, taking into account GIP-SH and the Declaration of Helsinki [12]. The written informed consent of all participants was obtained, and all bioethical conditions were met and agreed with the ethics committee.

Thirty patients aged (mean ± standard error [M ± m]) 57,17±1,33 years, 22 men and 8 women, were examined. The enrolled patients were examined by the Order of the Ministry of Health of Ukraine dated April 20, 2021, No. 771 «Protocol for the provision of rehabilitation care for patients with coronavirus disease (COVID-19) and convalescents» [11]. QoL of patients was determined according to the Medical Outcomes Study – 36-item Short Form (SF-36) [13] during a visit to a family doctor. We studied general (GH) and mental health (MH); physical (PF); role-physical (RP), role-emotional (RE) and social (SF) functioning; pain (BP), and viability (VT).

The blood glucose level of patients was measured by the enzymatic colorimetric method. The glycated hemoglobin concentration was measured by the ion exchange chromatography on immunoenzymatic photometer [14]. The level of circulating immune complexes (CIC) (mainly C1q-binding immunoglobulins G) was measured by the precipitation methodology on an immunoenzymatic photometer. The concentration of immunoglobulin A (IgA) was determined by the methodology of solid-phase immunoenzyme assay on an immunoenzymatic photometer [15]. The interleukin (IL)-8 and IL-33 levels were determined by the «sandwich» methodology of indirect non-competitive heterogeneous enzyme immunoassay [16].

Mathematical statistics methods were used for the mathematical processing of study results [17]. We used the computer program «Statistica 7.0 for Windows». The studied indicators had a distribution close to normal. Average values of indicators (M), and their errors (m) were calculated. A correlation analysis with the measurement of Pearson`s correlation coefficient (r) was performed. The critical level of statistical significance was $p<0,05$.

RESULTS

In previous studies, we reported a significant decrease in patients` QoL after coronavirus disease: severe limitation of physical functioning, pain perception, vitality, role-physical and social functioning, and mental health. Even a month after treatment, patients noted significant fatigue, memory disorders and dizziness, shortness of breath and cough, sleep and heart rhythm disturbances, and vascular thrombosis. Almost a third of the examined patients noted significant limitations in physical activity due to pain and deterioration of well-being without its improvement in self-assessment, and about half had psychological problems, and noted hyper-anxiety or depression [18].

O.-Z. Akácsos-Szász et al. [19] hypothesized that COVID-19-induced coagulopathy in the presence of metabolic syndrome and type 2 diabetes mellitus. Thus COVID-19 is characterized by coagulopathy and hemostatic imbalance [19].

Despite that the glucose level in the examined patients was at the upper limit of reference, it was correlated inversely with GH ($r= -0,228$; $p=0,040$) (Fig. 1A). In addition, we revealed an inverse correlation of glycated hemoglobin with GH ($r= -0,280$; $p=0,014$) (Fig. 1B).

R. Ker et al. [20] found that cytokines disturb normal hemostasis in humans and are probably one of the key factors in the thrombotic potential of SARS-CoV-19, contributing to an imbalance in prothrombotic and intrinsic anticoagulant pathways, such as loss tissue factor pathway inhibitor activity, downregulation of thrombomodulin expression on endothelial cells, and decreased antithrombin III levels in blood serum [21].

Cytokine IL-6 is a mediator of inflammation and a stimulus of the acute phase response. The role of IL-6

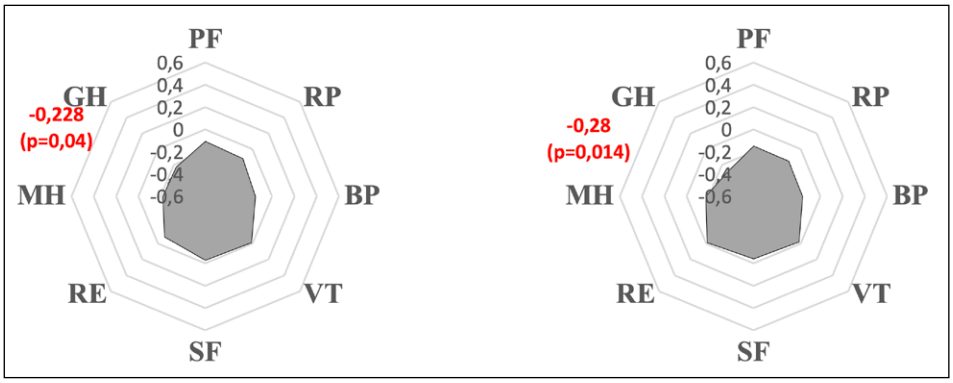

Fig. 1. The correlations of glucose (A) and glycated hemoglobin (B) levels with QoL parameters (n=30).

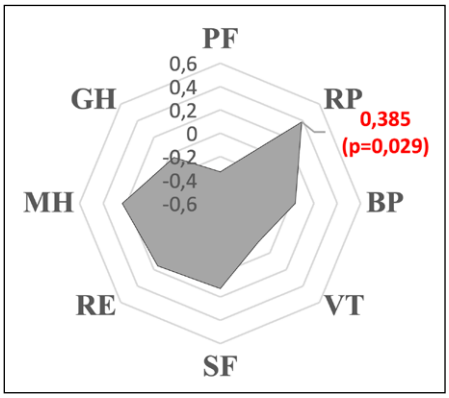

Fig. 2. The correlations of IL-33 level with QoL parameters (n=30).

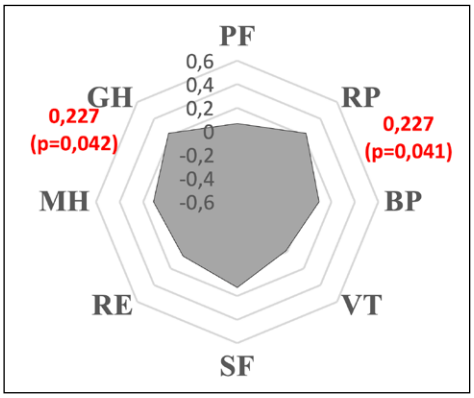

Fig. 3. The correlations of CIC level with QoL parameters (n=30).

in the pathological inflammatory response that causes severe COVID-19 is important. IL-10 is one of the most important regulatory cytokines that largely determine the direction of the immune response: under IL-10 activity the cellular response (regulated by Th1) is suppressed and the humoral response (Th2) is stimulated. It belongs to anti-inflammatory cytokines [22]. In our previous studies, IL-6 and IL-10 levels in patients after coronavirus disease were (median, interquartile range [Me, IQR]) 4,3 (2,4-5,8) pg/ml and 3,0 (0,9-3,9) pg/ml, respectively [23].

We did not observe any significant correlations of IL-8 with QoL parameters. At the same time, IL-33 in post-COVID patients related to RP (r=0,385; p=0,029) (Fig. 2).

A great important has synergism between IgA and mechanisms of nonspecific defense – complement, lysozyme, phagocytosed cells and their enzymes. This contributes to the implementation of antibacterial protection, increasing its overall effectiveness. In examined COVID-19 patients the level of IgA was (Me [IQR]) 1,6 (1,3-1,95) pg/ml [23].

One of the most important biological functions of immunoglobulins is the antigen-binding and the formation of circulating immune complexes (CIC), which is a physiological process that is aimed at maintaining the stability of its internal environment. The CIC formation is one of the components of the physiological immune response. The most important function of CIC is the ability to activate the complement system, which determines its role in the inflammation process and regulation of the immune system's functional activity. All patients with COVID-19 had a CIC of (Me [IQR]) 0,037 (0,025-0,047) IU/ml [23].

The level of CIC was associated with RP (r=0,227; p=0,041) and GH (r=0,227; p=0,042) (Fig. 3). On the contrary, we did not reveal any significant correlations of IgA level concentration and QoL parameters.

Thus, the increase in both glycemia and glycated hemoglobin levels in COVID-19 patients was significantly associated with the deterioration of patients` GH. Moreover, the IL-33 level was directly correlated with RP. Finally, a decline in CICs level was associated with the deterioration of RP and GH.

DISCUSSION

S. Gando and T. Wada [7] emphasize that thromboplasmatic coagulopathy in COVID-19 consists of Ang II-induced coagulopathy, activated FXIIa and KKS-enhanced fibrinolysis, and DIC syndrome. All of these conditions induce systemic inflammation via each pathomechanism-developed production of inflammatory cytokines. Coronavirus disease upregulates angiotensin-converting enzyme and leads to increase of Ang II levels. Ang II-induced coagulopathy affects platelet activation, thrombin generation, expression

of plasminogen activator inhibitor-1, and endothelial damage and thrombosis 1 [7].

L. Giubelan et al. [24] found differences in inflammatory biomarkers in patients with moderate or severe COVID-19: patients with obesity or diabetes mellitus had significantly higher levels of leukocytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimers and serum glucose concentrations. A. Mureşan et al. [25] showed that elevated inflammatory markers are independent predictors of adverse prognosis for all patients with SARS-CoV-2.

D. Sun et al. [26] demonstrated that some cytokines (IL-6, IL-2, IFN-γ, TNF-α, MIP (macrophage inflammatory protein), and MCP-1 (monocyte chemoattractant protein 1) present in critically ill patients. Angiotensin II (AngII) triggers the nuclear factor kappa-B (NF-κB) activation, resulting in hyperinflammation, mainly via enhanced synthesis of IL-1β and IL-6. With a severe course of COVID-19, these interleukins increase significantly [27].

J. Gómez-Mesa et al. [28] determined that IL-6 and IL-1α play an important role in inflammatory response and blood coagulation system conjunction; at inflammation macrophages release tissue factor in response to IL-6. IL-6 is also involved in the production of fibrinogen and factor VIII. In addition, IL-6 acts on the endothelium, enhancing the vascular endothelial growth factor synthesis, and resulting in vascular hyperpermeability and hypotension [29]. Conversely, TNF-α and IL-1 are the most important mediators of endogenous coagulation cascade inhibition [28], which is crucial in the development of COVID-19 complications and essentially worsens the QoL in such patients.

Even a month after COVID treatment, patients complained of shortness of breath and cough, arrhythmia, vascular thrombosis, memory disorders, muscle disorders, fatigue, hair loss [23]. Our findings are comparable to a meta-analysis of 12 studies, including 4,828 patients with persistent symptoms six months after infection [30]. Impaired QoL on the visual analog scale (EQ-VAS) reached 59 % in the complete sample; and with severe coronavirus disease and complaints of fatigue during examination, QoL indicators deteriorate even more [30]. R. Meys et al. [31] showed that the QoL value in such patients is lower than the average population data even three months after treatment, which is consistent with our data.

CONCLUSIONS

1. The QoL of patients after coronavirus disease has significantly deteriorated: patients note a significant limitation in physical functioning, pain perception, vitality, role-physical and social functioning, and mental health. Almost a third of the surveyed needs indicate significant problems with physical and emotional activity, social and role functioning; about half have psychological problems and report increased anxiety or depression.
2. The increase in glycemia and glycated hemoglobin levels in post-COVID-19 patients were significantly associated with the deterioration of patients` GH. The IL-33 concentration in such patients correlated directly with RP. The CICs level decline was associated with the deterioration of RP and GH.
3. The study of clinical-functional, biochemical, immunological and psychological indicators, quality of life, and their mutual influences should be included in the program of diagnosis and rehabilitation of patients after the COVID-19 at the outpatient stage of treatment by doctors of general practice-family medicine.

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The results of the study were obtained by the authors during the research work of the Department of Family Medicine of Shupyk National University of Health of Ukraine on the topic «Development and Justification of Programs For the Prevention and Treatment of Patients With Comorbid Pathology of Organs and Systems» (state registration number 0122U-002416; term: 2022-2026 years).

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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RECEIVED: 15.12.2023
ACCEPTED: 24.04.2024