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CLINIC OF RHEUMATOLOGY AT UMBAL "ST. MARINA" - EAD-VARNA

PAIN AS PART OF THE RHEUMATIC MANIFESTATIONS OF COVID-19 VIRAL INFECTION

SUMMARY

OF A DISSERTATION PAPER FOR OBTAINING THE EDUCATIONAL AND SCIENTIFIC DEGREE OF DOCTOR OF MEDICINE

SCIENTIFIC SUPERVISOR:

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The dissertation contains 167 pages including 55 tables, 20 figures and 9 graphs. 419 literary sources are cited.

The dissertation work has been discussed and proposed for defense to the departmental council of the Department of Propedeutics of Internal Diseases at the MU "Prof. Dr. Paraskev Stoyanov" - Varna on February 17, 2023.

The official defense of the dissertation work will take place on 01.06.23 at 13:00 in room 1301, at an open meeting of the scientific jury.

I INTRODUCTION

In the year 2020, humanity was forever marked by the appearance of a new, never-seen before disease. For the first time, modern mankind was faced with an infection that caused a global threat, classified as a pandemic by the World Health Organization (WHO) almost 3 years ago.

The new pandemic, the coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, began in Wuhan (China) in late 2019 and rapidly spread throughout the world (Li et al., 2020).

The concept of the disease, originally considered a flu-like illness, underwent a radical change. Currently, the disease is perceived as a polysyndromic inflammatory disease involving not only the respiratory system, but also the musculoskeletal system, the cardiovascular system, the skin, the urinary and nervous systems, and is accompanied by a number of hematological, gastrohepatoenterological and endocrine disorders. It became clear that the tissue damage was immune-mediated, resembling exacerbations of advanced rheumatological disease. Many pain syndromes are also present in the heterogeneous picture of the disease, with joint and muscle pain being one of the most common symptoms in patients with COVID-19.

II OBJECTIVE: In the response of the increasing needs to understand the nature of COVID-19, the purpose of this study is to determine factors predicting the manifestation and severity of musculoskeletal pain in patients with COVID-19, to be applied in clinical practice for clarify the understanding of these symptoms

III TASKS:

1. To assess the severity of myalgias and arthralgias in patients treated in clinical settings with COVID-19.

2. To analyze anxiety-depressive manifestations in patients treated in clinical settings with COVID-19.

3. To investigate the relationship between the severity of the pain syndrome and laboratory indicators of inflammation predicting the severity of the course of COVID-19.

4. To evaluate the relationship between the severity of the pain syndrome and the presence of anxiety and depressive symptoms in patients

5. To analyze the relative weight of both anxiety-depressive symptoms and inflammatory indicators for the presence and expressiveness of pain sensations

HYPOTHESES:

Musculoskeletal manifestations are present very often in the clinic of patients with COVID-19, and the most common are pain phenomena - myalgias and arthralgias. COVID-19 is a new disease of a pandemic nature, with very high contagiousness, relatively high mortality and disability, and all these data undoubtedly lead to changes in the mood and emotions of the sick. In this regard, a significant part of pain syndromes, such as symptoms of COVID-19, are associated with the presence or worsened by the presence of anxiety and depressive symptoms. On the other hand, pain, in addition to the presence of inflammation, is significantly influenced by the age and gender of the patient.

IV MATERIALS AND METHODS

1. SUBJECT OF RESEARCH

Investigating the pain and psychoemotional health in hospitalized patients with moderate to severe COVID-19 and inflammatory joint diseases on anticytokine therapy, analysis of associations between them and their interaction.

2. OBJECT OF RESEARCH

The study was conducted at the Rheumatology Clinic, at the "St. Marina" after approval by the Scientific Ethics Committee of the Medical University-Varna with protocol No. 116/28.04.2022. (KENIMUV), in accordance with the requirements of the Declaration of Helsinki, the patients are informed in detail about the aims and methodology of the planned study, about the possible inconveniences during inclusion (traumatic experience when taking blood, additional time for conducting a clinical examination, conversation and providing the available medical documentation). Participants sign informed consent declarations by hand.

A single-center, observational, one-stage analysis of case/control patients included patients with moderate to severe COVID-19, as well as those with inflammatory joint disease on anticyticine therapy.

364 patients over 18 years of age were included in the study. 234 of them with proven COVID-19 and new-onset musculoskeletal pain during the acute phase of COVID-19 and a control group of 130 patients with chronic pain with inflammatory joint diseases (IJD) who were on long-term anticytokine drug therapy.

Patients with COVID-19 are hospitalized in the UMBAL "St. Marina" - Varna (Clinic of Rheumatology - COVID sector) during the period 29.04.2022 to 31.12. 2022. The control group of patients with inflammatory joint diseases are patients who are undergoing anti-cytokine therapy and are dispensary to the diagnostic-consultative rheumatology office at UMBAL "St. Marina" - Varna.

Before signing informed consent, the purpose and tasks of the study were explained in detail to all patients, they were given sufficient time and all questions related to the benefit and lack of risks of their participation in the study were answered.

After a handwritten signature certifying consent, a complete and detailed history was taken of the onset of the disease, the duration of the complaints, the presence or

absence of muscle and joint pain. With a positive result regarding muscle-joint pain, the patients were included in the analysis.

All patients (COVID-19 and IJD) were thoroughly examined by a rheumatologist and information was collected regarding the demographic characteristics of the examined patients.

In all hospitalized patients with COVID-19, the etiology of the disease - SARS-CoV-2 was accepted when a positive polymerase chain reaction (PCR) or rapid antigen test for SARS-COV-2 was available.

Visual analogue scales (VAS) were used to assess pain intensity (muscular and joint) and Zung self-report scales for depression (SDS) and anxiety (SAS). Laboratory acute phase indicators and thrombotic biomarkers were investigated, chest imaging was performed in all patients.

Inclusion/exclusion criteria for COVID-19 patients in the study

Table 1

Inclusion criteria in the study
1. Patients aged 18 and over;
2. Patients hospitalized at the University Hospital "St. Marina Hospital due to COVID-19
3. Patients testing positive for SARS-CoV-2 with: a. Polymerase chain reaction (PCR) b. Rapid antigen test for SARS-CoV-2.
4. New-onset musculoskeletal pain during the acute phase of COVID-19
5. Allo- and autopsychotically oriented patients able to read, understand and sign the informed consent form on their own;
6. Patients who expressed their willingness to participate in the study and subsequently signed an informed consent form.
Exclusion criteria in the study
1. Patients under 18 years of age;
2. Patients with a diagnosis of COVID-19 and a history of musculoskeletal pain that has not debuted during the acute phase of the disease and is due to

another disease (inflammatory, degenerative or metabolic joint diseases, as well as autoimmune vascular diseases for which patients are taking medications - non-steroidal, corticosteroids or disease-modifying agents).
3. Patients diagnosed with COVID-19 without present musculoskeletal pain
4. Patients with a proven mental illness - recurrent depressive disorder, anxiety disorder, schizophrenia, bipolar affective disorder
5. Illiterate, alto- and autopsychically disoriented, unable to read, understand and sign their own handwritten informed consent;
6. Patients with pulmonary and/or other diseases negative for SARS-CoV-2 and presenting musculoskeletal pain

In the study population, patients had a detailed history of the onset and duration of complaints and were thoroughly examined by a rheumatologist.

Selection criteria for a control group of chronic pain patients

In the control group of patients with chronic pain were included 130 patients with inflammatory joint disease wich underwent 42 outpatient procedures as part of the requirements for treatment with anticytokin medications. Patients in the control group were diagnosed with rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis with the generally accepted disease criteria.

Inclusion/exclusion criteria for patients in the control group

Table 2

Inclusion criteria for the control group
1. Older then 18 years of age;
2. Patients with inflammatory joint disease (IJD): a. Rheumatoid arthritis b. Ankylosing spondylitis c. Psoriatic arthritis;
d. Patients with IJD undergoing long-term therapy with anticytokine medications e. Anti TNFα

f. Anti IL6 g. Anti IL17
3. Literate, allo- and auto-psychically oriented individuals capable of reading, understanding and signing an informed consent form on their own;
4. Persons who have expressed their willingness to participate in the study and have signed an informed consent form by hand.
Exclusion criteria for the control group
1. Patients under 18 years of age;; 2. Patients without IJD;
3. Patients with IJD who are not on anticytokine therapy
4. Illiterate and/or alto- and autopsychically disoriented persons unable to read, understand and sign an informed consent form in their own handwriting;
5. Patients who did not consent to participate in the study

3. METHODS

3.1 Sociodemographic and clinical indicators

The following groups of characteristics were analyzed: demographics, pulmonary involvement (for COVID-19 patients), degree of inflammation, musculoskeletal pain - presence and severity, psychoemotional status - presence and degree of anxiety and depression.

Table 3 Clinical and demographic indicators analysed in the study

Sociodemographic characteristics including:
1. Age;
2. Gender;
Clinical indicators
3. Presence of musculoskeletal symptoms
4. Duration of musculoskeletal symptoms
Specific indicators
5. Pulmonary involvement with chest imaging

6. Inflammatory joint disease
Psycho-emotional state
7. Anxiety assessment 8. Assessment of depression
Indicators of inflammation
9. Erythrocyte sedimentation rate (ESR)
10. C reactive protein (CRP)

3.2 Standard laboratory tests

All patients with COVID-19 had a detailed history and physical status taken by a rheumatologist at the time of hospitalization in the Rheumatology Clinic, which was transformed into the COVID-19 sector.

Biochemical and imaging investigations were ordered and performed. Blood was collected in 3 vacutainers on one occasion, which is part of the routine procedure for hospitalization. Acute phase markers of inflammation were tested including:

- Erythrocyte sedimentation rate (ESR),
- C reactive protein (CRP),
- Fibrinogen,
- Ferritin,
- Lactate dehydrogenase (LDH),
- Thrombotic biomarkers (D-dimer) as a specific end product of fibrinolysis.

In the control group of patients with IJD, acute phase markers of inflammation including

- Erythrocyte sedimentation rate (ESR),
- C reactive protein (CRP),
- Fibrinogen

The laboratory parameters were examined in the Medical Diagnostic Laboratories of the University Hospital "St. Marina" with SIEMENS - ADVIA 1800 Chemistry system and ALIFAX - Roller 20PN.

3.3 Standard instrumental tests

All patients with COVID-19 underwent chest radiographic imaging, which included conventional chest radiography and/or chest computer tomography (CT) to demonstrate pulmonary involvement.

3.4 Pain assessment

Pain assessment based on a visual analogue scale (VAS) was performed by all patients reflecting on a pre-prepared form, designed for self- self-administration by the respondent. The patient is asked to indicate the severity of the pain he feels (joint or muscle) by marking with a cross or a line on the scale, at a place that corresponds to his condition, with an indication "No pain at all" to the left of the "0" mark and "Pain is as bad as it could be" to the right of the "100" mark. For the purposes of this study, the scale was coded with VAS-m for muscle pain and VAS-a for joint pain.

Depending on the assessment given by the patient, according to the intensity the pain can be defined as mild, moderate and severe pain, respectively:

- Mild pain with VAS of 5-44 mm,
- Moderate pain with VAS of 45-74 mm
- Severe pain at VAS of 75-100 mm.

3.5 Mood and emotion assessment

Assessment of the psychoemotional state of both COVID-19 and IJD patients was performed by examining the degree of anxiety and depression. For this purpose, two independent scales were used to assess mood disorders. The intensity of depression and anxiety were assessed with self-report scales. In order to avoid treatment interference, the anxiety and depression grade surveys in COVID-19 patients were performed on the day of hospitalization, before treatment initiation. In the group of IJD patients the assessment of mood and emotions was performed during visit for extension of treatment with anticytokine medication.

For the purposes of this dissertation were used Zung's self-report scales for depression (SDS) and for anxiety (SAS) (Rush, AJ et al., 2008; Guy, W., 1976). Both Zung's self-report scales (SAS and SDS) were developed in 1971 and are used as a screening method for mood disorders (Dunstan DAet al., 2017). They are not a tool that can be used to make a clinical diagnosis of depression or anxiety. Rather, their use in clinical practice may indicate the presence of depressive attitudes or anxiety, which may be a reason to refer the patient to seek specialist psychiatric help.

The Zung Depression Self-rating Scale (SDS) is a brief self-administered questionnaire used to quantify the depressive state of patients (Zung WWK., 1965). It can also be used as a screening method to detect mood disorders. The scale has 20 subscales that assess the four common characteristics of depression: the pervasive effect, physiological equivalents, other disturbances, and psychomotor activities. There are ten positively worded questions assessing positive experiences or feelings and ten negatively worded questions assessing negative feelings. The patient rates on a scale of 1 to 4 for each item, according to frequency of occurrence, over a time span of one week prior to the assessment (7 days prior to the examination). Options include the responses: never or rarely, sometimes, often, very often, or always (Romera, I et al., 2008). Higher scores indicate higher severity of depressive symptoms (Lam, R et al., 2005). In contrast, for questions describing a positive experience, so-called reverse questions, scoring is reversed (Dunstan, DA et al., 2017). Once determined, scores on individual items are added together to generate a raw score ranging from 20-80 (Dunstan, DA et al., 2019). The resulting scale score can then be multiplied by 1.25 to convert to a so-called index score (SDS Index) of 100. An index score of 50 or more or a raw score greater than 40 is required to identify patients with depressive disorder. Therefore, according to the obtained score (SDS Index), mild, moderate and severe depression are identified (Jokelainen, J et al., 2019).

- 20-49 normal range
- 50-59 mild depression
- 60-69 moderate depression
- >70 severe depression

The other self-report anxiety scale used is the Zung Anxiety Scale, or SAS, which is a scale for measuring the level of generalized anxiety in patients. The scale includes a

total of 20 items, and it measures anxiety levels based on scoring in 4 groups of manifestations: cognitive, autonomic, motor, and central nervous system symptoms (Zung WWK., 1971). Responding to the statements, the person must indicate how much each statement applies to him or her within one week (7 days) before completing the test. Each question is scored on a scale of 1-4, with the possible answers being: never or rarely, sometimes, often, very often, or always. Some questions are phrased in the negative to avoid the problem with the answer given. The overall assessment is done by total score. The resulting total score points range from 20-80. (Zung, W. W., 1973). The resulting scale score can then be multiplied by 1.25 to convert to an index score of 100. A score above 45 indicates increased anxiety and requires medical intervention (Zung, W. W. et al.,1990). Therefore, according to the score obtained are identified mild, moderate-severe, severe and extreme anxiety:

- 20-44 normal range
- 45-59 mild to moderate anxiety
- 60-74 severe anxiety
- >75 extreme anxiety.

Statistical methods for processing the results

Statistical methods included SPSS v 23 for iOS, Microsoft Excel for Mac, Biorender - online graphic solution. To present the obtained results were used graphical and tabular methods. Statistical significance level of $p < 0.01$ was predefined. Frequency and descriptive statistics, non-parametric analysis of variance of quantitative variables - mean, standard deviation (SD) were used. Paired Samples t-test was applied to compare means and relative proportions assuming significance level for $p<0.01$, Pearson correlation analysis, multivariate classical regression analysis assuming significance level for $F<0.05$, TwoStep Cluster analysis - Bayesian information criterion (BIC).

V RESULTS AND DISCUSSION

DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

For the purposes of this dissertation were included 364 patients - 234 patients with moderate to severe COVID-19 (64.3%) and 130 patients (control group of IJD) (35.7%) with chronic pain, on anticytokine treatment.

Comparative analysis of the patients

Of all evaluated patients (n=364), those with COVID-19 represented a significantly higher proportion compared with those with IJD (64/3% vs 35.7%) (Table 4).

Table №.4 Comparison of the two groups of patients

	Number	Rate (%)
Patients with COVID-19	234	64.3
Patients with IJD	130	35.7
Total	364	100.0

1.1 AGE

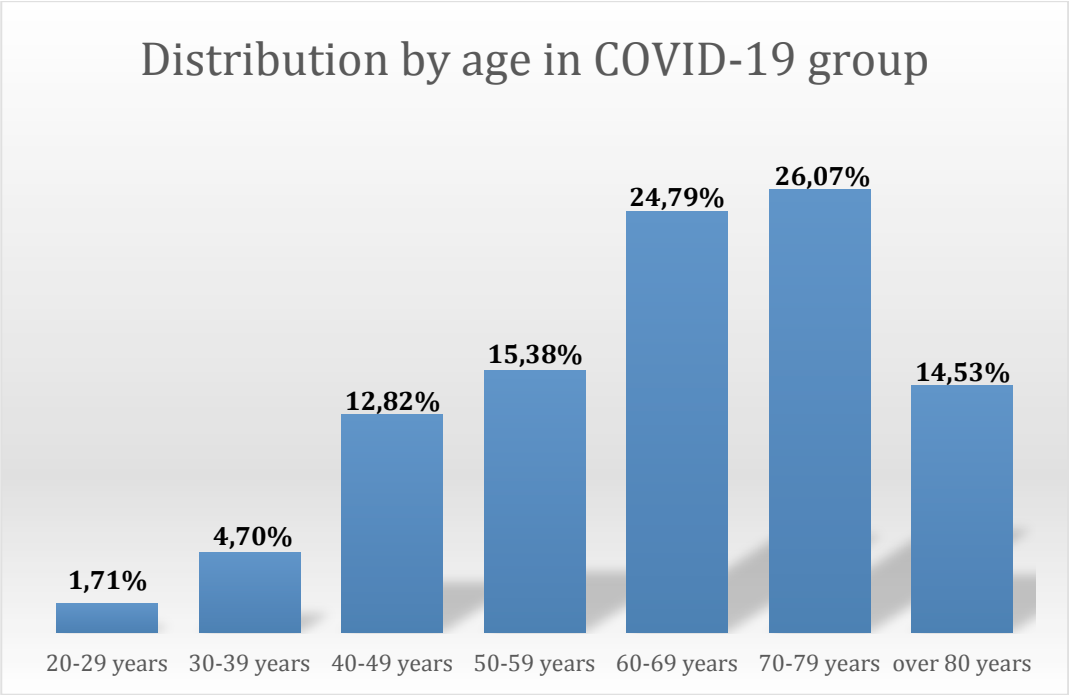
The age profile of the COVID-19 group included patients from 26 to 91 years, with a mean age of 63.7 years (± SD 14.457) (Table 5).

Table 5 Distribution of COVID-19 patients by age

	Number	Minimum	Maximum	Mean	St.deviation
Age	234	26	91	63.74	14.457
a. Group = COVID-19 patients					

The distribution by age group showed that a significant proportion of the studied group of COVID-19 patients were over 60 years of age, (n-153, 65.38% of all COVID-19 patients (Figure 1).

Chart №.1 Distribution of COVID-19 patients by age



Group of patients with IJD

The group of patients with chronic pain included patients with IJD from 21 to 76 years, with a mean age of 56.4 years (Table 6).

Table 6 Distribution of chronic pain patients by age

	Number	Minimum	Maximum	Mean	St.deviatiom
Age	130	21	76	56.37	9.834

a. Group = Patients with IJD

Table №.7 Proportion of patients over 60 years of age

Total	COVID-19	IJD	p value	95%CI

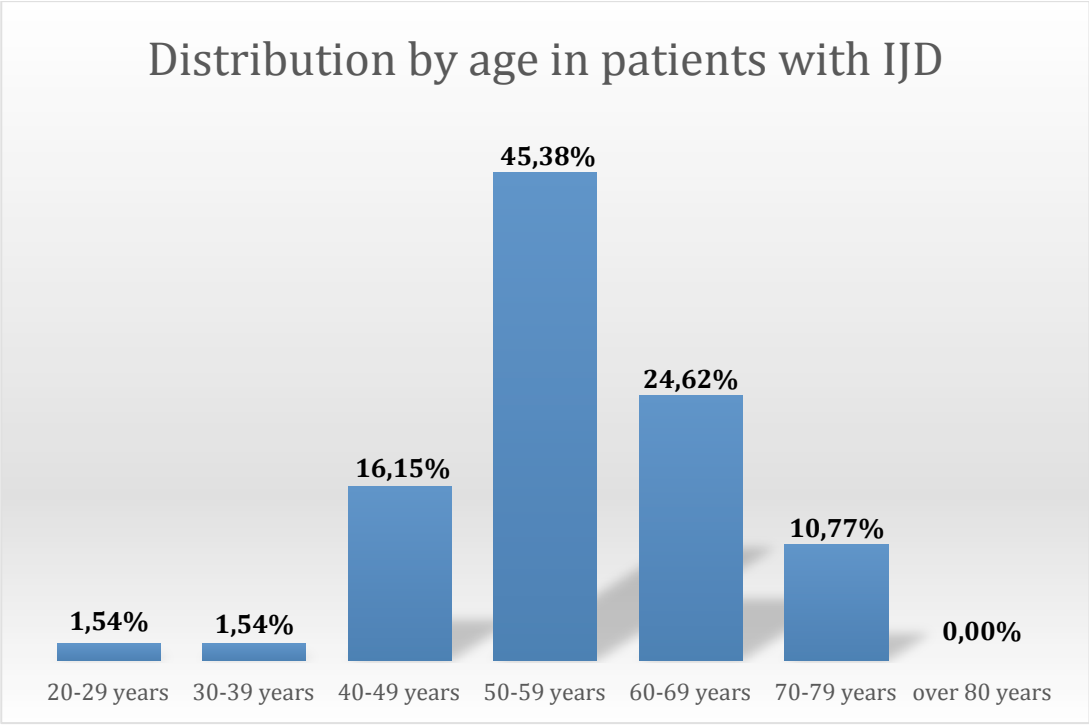
patients n=364	n=234		n=130			
> 60 years	153	65.38	76	33.85	<0.001	14.81-45.61

*Legend:*COVID-19 - Coronavirus Disease 2019, IJD - Inflammatory Joint Diseases

The distribution by age groups showed that the proportion of patients over 60 years of age in COVID-19 group was significantly higher compared to that in IJD group. (65,38% vs 33,85%, p<0,001) (tabl.7).

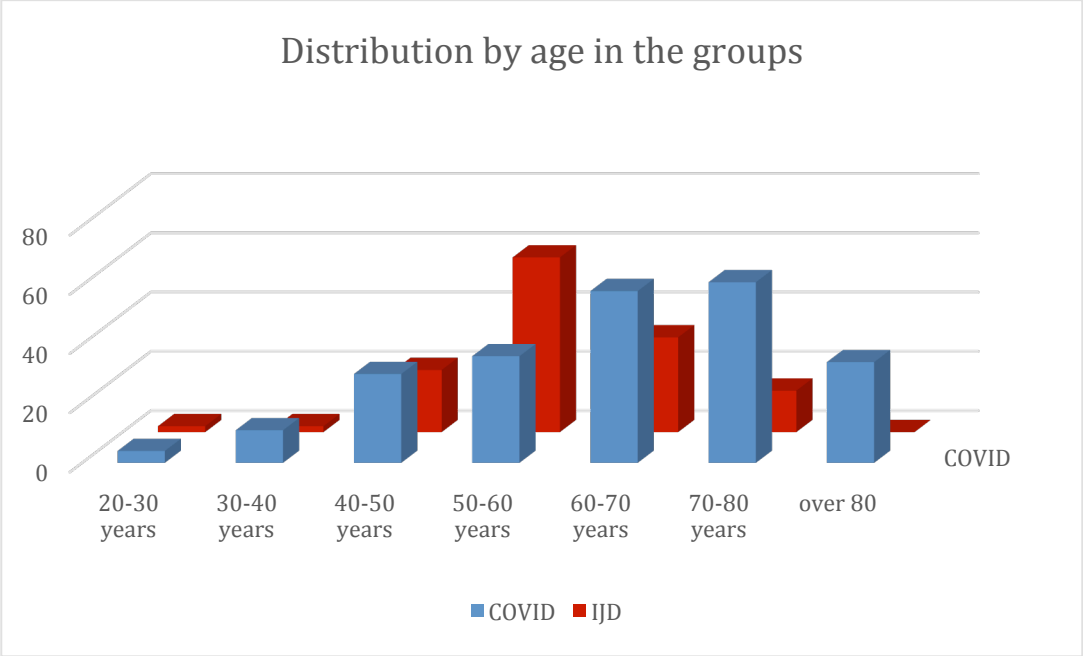
The mean age of patients with IJD and the proportion of patients aged over 60 years were significantly lower compared to patients with COVID-19

Chart №2 Distribution by age of patients with IJD



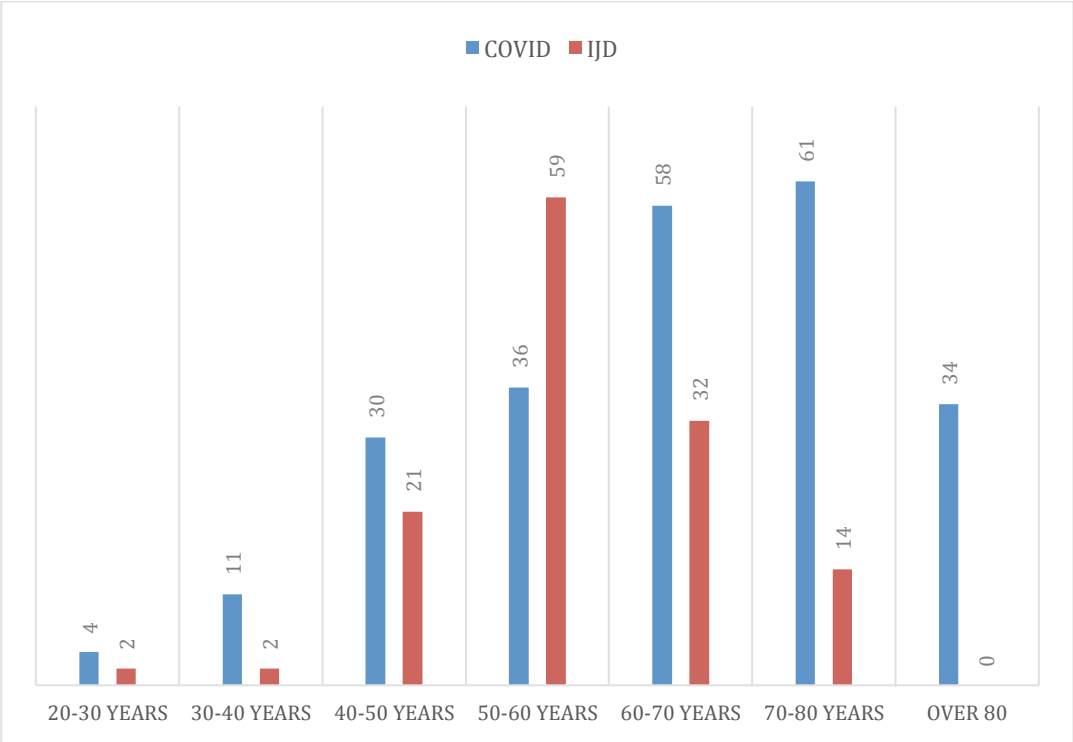
The distribution of the two groups (Figure 3) shows a different age structure which is related to the disease characteristics of the groups (COVID-19 and IJD)

Chart №3 Comparison by age groups between patients with COVID-19 and IJD



These data correlate with known data so far. According to medical records, the median age of inpatients from COVID-19 was 69 (58-77) years, and 74.5% of hospitalized patients were ≥50 years of age (Garg S et al., 2020).

Chart №4 Comparison by age groups between patients with COVID-19 and those with VJD



1.2 GENDER

The gender distribution shows that in the group of COVID-19 patients, males represented 54.7% (n=128) of the investigated population, while females represented 45.3% (n=106) (Table 8). In the group of patients with IJD, males represent 58.46% (n=76) , while females were 41.44% (n=74) of the group.

Table №.8 Distribution of patients according to disease and gender

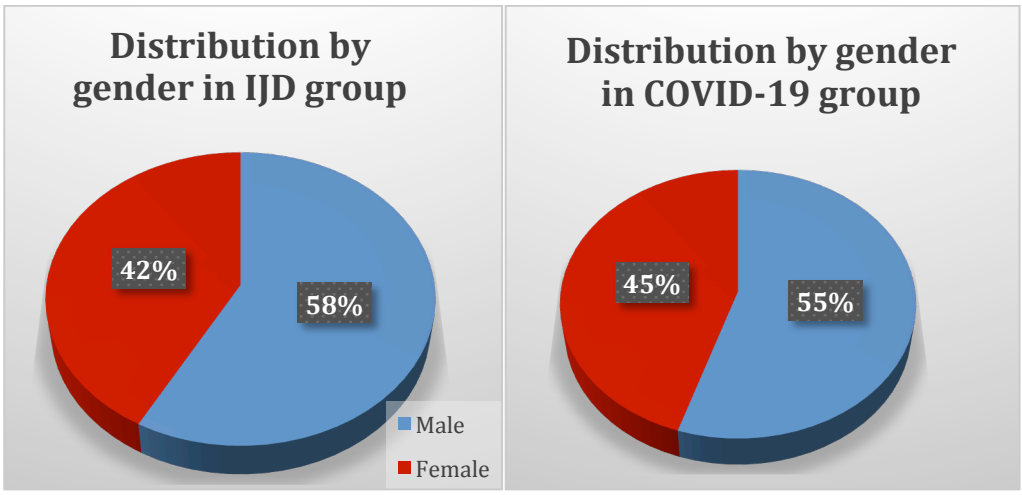
Total patients n=364	COVID-19 [1]		p value	IJD [2]		p value	p value 1,2	95%CI
	n=234	100%		n=130	100.00%			
Male(n=204)	128	54.7	NS	76	58.46		NS	-10.23-17.28

*Legend:*COVID-19 - Coronavirus Disease 2019, IJD - Inflammatory Joint Diseases

Gender distribution (males and females) in the two investigated groups - patients with COVID-19 and patients with IJD was comparable (Fig. 1) (54.70% vs 58.46%, p>0.05).

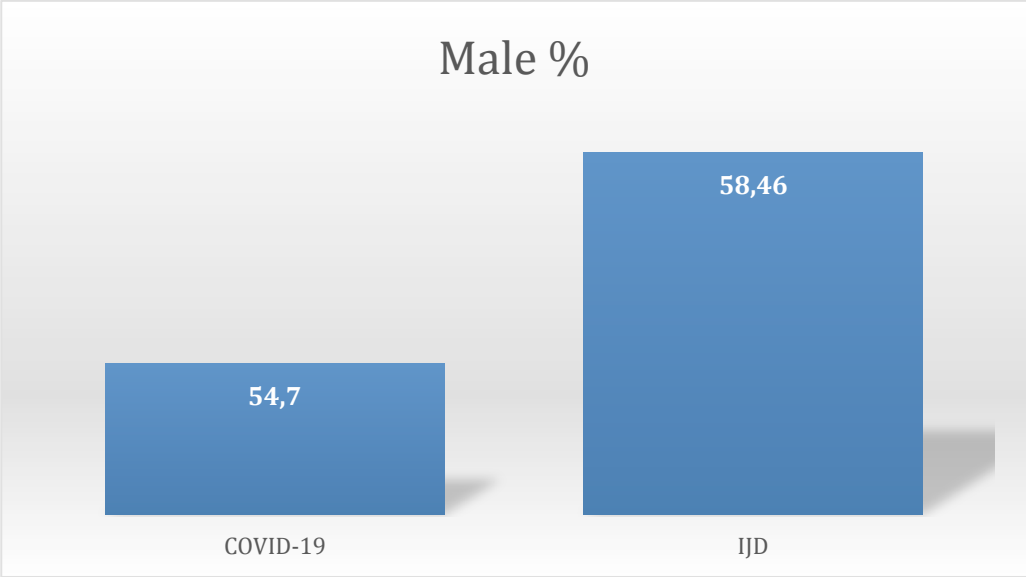
The obtained data for gender distribution are compatible with those from available registries (Garg S et al., 2020). Male gender was associated with more frequent hospitalization (Chow N et al., 2020)

Figure 1 Distribution of patients by disease and gender



The gender distribution also shows that the male gender has a numerical superiority (prevails) in both groups of patients, the difference in proportions is not significant (Table 8, Fig. 2).

Figure 2 Proportion of men in the two disease groups



*Legend:*COVID-19 - Coronavirus Disease 2019, IJD - Inflammatory Joint Diseases

2. LABORATORY TESTS AND SELF-ASSESSMENT SCALES

2.1 Patients with COVID-19

The values of examinated inflammation and thrombogenic biomarkers are summarized on the attached table (Table 9).

COVID-19 patients presented with high values of ESR, CRP, LDH, ferritin and fibrinogen and high thrombogenic biomarkers measured with the specific degradation products of fibrinolysis, D-dimer.

The analyses were performed on a group of patients with COVID-19 who had moderate or severe disease requiring hospital admission for specific treatment. This explains the high mean values of all inflammatory and thrombogenic parameters studied. These patients are in the risk group of patients where the disease often leads to complications (Yu, B. et al., 2020). The results of our analysis correlate with those

reported in the database (Chen L et al., 2020; Hanny Al-Samkari et al., 2020, Statsenko Y et al., 2021). High levels of inflammation and thrombogenic biomarkers correlate with a more severe course of COVID-19 (Ghahramani, S., Tabrizi, R., Lankarani, K.B. et al., 2020).

Table 9 Results of inflammatory indices and thrombogenic biomarkers in COVID-19 patients

Indicator	Minimum	Maximum	Mean	SD
ESR (mm/h)	2	120	78.78	30.16
CRP (mg/l)	0.40	492.70	96.81	78.04
Fibrinogen (g/l)	2.18	9.63	5.82	1.75
Ferritin (ng/mL)	11.52	35040.00	1159.41	2521.41
LDH (U/I)	1.955	6868.00	688.76	520.99
D-dimer (mcg/mL)	0	1333	7.26	87.11

a. Group = COVID-19 patients

Mean serum CRP concentration in COVID-19 patients over 19 times the upper reference range (96.81 mg/l vs 5.0 mg/l).

The risk of developing severe adverse events increases by 5% for each one-unit increase in CRP concentration in COVID-19 patients (Wang G et al., 2020).

Analysing D-dimer in COVID-19 patients aims to detect a bleeding disorder. SARS-CoV-2 infection is known to impair coagulation and is associated with a higher risk of thrombosis (pulmonary and deep venous). Coagulation disorders are the predominant cause of death from COVID-19. Together with other parameters that constitute the risk profile for severe COVID-19 evolution, the determination of D-dimers on admission to hospital has proven to be extremely useful in the management of COVID-19 (Baroiu L et al., 2022).

In our cohort of hospitalized moderate-to-severe COVID-19 patients, mean D-dimer values were significantly higher than the upper reference limit (7.26±87.11 mcg/mL

vs ≤0.5 mcg/mL). We did not set out to determine both the proportion of patients with high values of this indicator, the degree of respiratory failure in them, and to follow its values in dynamics, as this is not the subject of the present work. The data presented in the studies are aimed to express the severity of the disease in the studied patients hospitalized in Rheumatology clinic - COVID-19 sector.

2.2 Patients with IJD

The results of the inflamatory markers in patients with IJD are presented in Table №. 10.

The mean values for ESR were 30.94 mm/h, for CRP 8.39 mg/L and for fibrinogen 2.93 g/L. These results are slightly above the upper reference limit only for the CRP, while the mean values for EST and fibrinogen are in the normal range. All patients with IJD who were included in the analysis were on active treatment with biologic medication. On the background of this treatment, the patients showed varying degrees of inflammation response as expressed by the examined inflamatory markers. Achievement and maintenance of low disease activity, or remission of inflammatory joint disease, is estimated by complex composite scores that differ between different nosological entities of this group of diseases. Determination of the proportion of patients achieving low activity or remission of IBD is not the subject of the present study. These results are useful for understanding the association between the inflammatory response scores, the presence and severity of muscle and joint pain, and the extent of changes in patients' psycho-emotional status.

Table. №.10 Results of inflammatory markers of patients with

Patients (n=130)	Minimum	Maximum	Mean	SD
ESR (mm/h)	2	120	30.94	27.29
CRP (mh/L)	0.12	117.60	8.38	21.06
Fibrinogen (g/L)	0.63	5.80	2.93	1.177

3. PAIN ASSESSMENT

3.1 Patients with COVID-19

The results obtained from the joint and muscle pain rating scales (VAS) in COVID-19 patients are summarized in Table 11.

COVID-19 patients presented joint and muscle pain severity with similar mean values according to VAS, respectively (a= 42.36 mm vs m= 43.0 mm, p>0.05), with a slight predominance for muscle pain.

When the values of joint and muscle pain were analyzed according to gender, it was found that female patients with COVID-19 experienced more pain, both joint and muscle. The mean VAS value for joint pain (VAS-a) for males was 37.6, while for females it was 48.1 (p=0.019). The same correlation was found for muscle pain. COVID-19 female patients scored higher VAS values for muscle pain expression compared to COVID-19 male patients (49.32 vs 37.77, p=0.021) (Table 11, Table 12).

Table №.11 Joint and muscle pain severity according to gender in hospitalized patients with moderate to severe COVID-19

COVID-19 patients (n=234)	**VAS a (мм)**	**VAS m (мм)**
Mean (mean±SD)	42.36±27.99	43.00±28.32
Men (n= 128; mean±SD)	37.6±27.59	37.77±28.32
Women (n=106; mean±SD)	48.10±27.52	49.32±27.12

Legend: COVID-19 – Coronavirus Disease 2019

Table №.12 Comparative analysis of Visual Analogue Scales (VAS) results by gender - COVID-19 patients

	Paired Differences				t	Sig. (2-tailed)
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Joint pain (male)–Joint pain (female)	-9.39	40.40	-17.17	-1.60	-2.39	**.019**
Muscle pain (male)–Muscle pain (female)	-9.32	41.06	-17.22	-1.41	-2.34	**.021**

Proportions of COVID-19 patients according to the severity of pain symptomatology as measured by the visual analogue scale scores for muscle and joint pain are presented in Table 1. 9 and Table 10. 2.6% of all COVID-19 patients had no joint pain and 5.1% had no muscle pain, while the remaining patients had varying degrees of joint and/or muscle pain - mild, moderate and severe (Table 13 and Table 14).

Table №.13 Distribution of COVID-19 patients according to the level of joint pain

Level of joint pain			
	Incidence	Rate	Cumulative rate

No pain	6	2.6	2.6
Mild pain	125	53.4	56.0
Moderate pain	61	26.1	82.1
Severe pain	42	17.9	100.0
Total	234	100.0	

Table №.14 Proportion of COVID-19 patients according to the level of muscle pain

Level of muscle pain			
	Incidence	Rate	Cumulative rate
No pain	12	5.1	5.1
Mild pain	119	50.9	56.0
Moderate pain	58	24.8	80.8
Severe pain	45	19.2	100.0
Total	234	100.0	

A very small proportion of patients (2.6% for joint pain and 5.1% for muscle pain) responded that they did not have one of the two types of pain assessed. About half of the patients rated their pain as mild (53.4% for joint pain and 50.9% for muscle pain). The remaining patients rated pain as moderate or severe. A significantly higher proportion of male COVID-19 patients experienced mild joint pain compared to females (60.2% vs 45.3%, p=0.0023). Significantly fewer COVID-19 male patients experienced severe joint pain compared to females (13.3% vs 23.6%, p=0.041). The results are presented in table and graph (Table 15, Figure 3).

Table №.15 Distribution of COVID-19 patients according to joint pain and gender

Level of joint pain

	Incidence	Rate	Cumulative rate
No pain	4	3.1	3.1
Mild pain	77	60.2	63.3
Moderate pain	30	23.4	86.7
Severe pain	17	13.3	100.0
Total male	**128**	**100.0**	
No pain	2	1.9	1.9
Mild pain	48	45.3	47.2
Moderate pain	31	29.2	76.4
Severe pain	25	23.6	100.0
Total female	**106**	**100.0**	

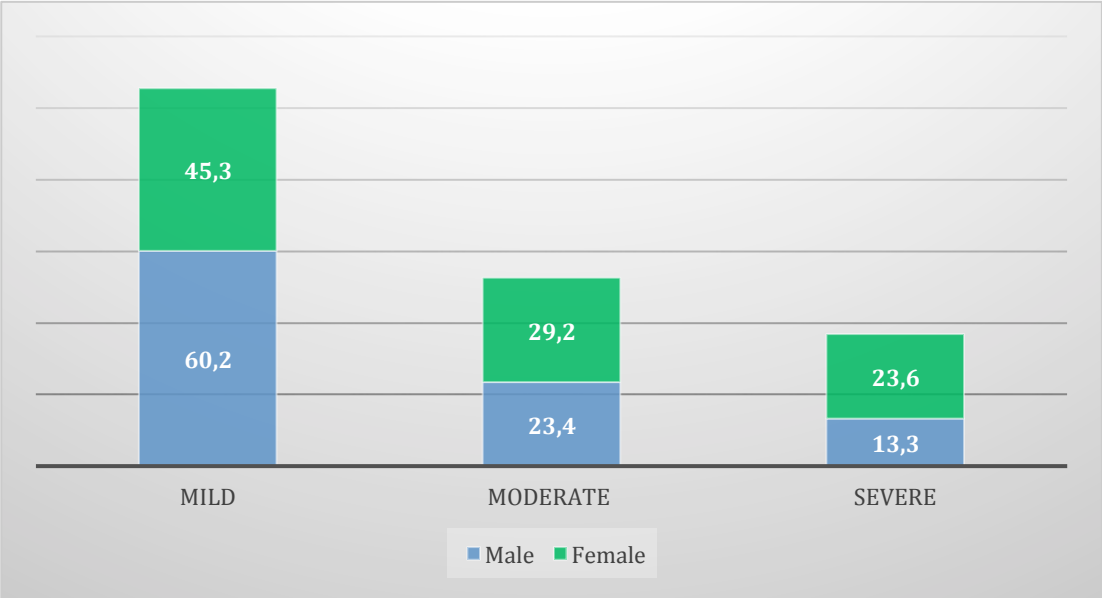


Figure 3 Distribution of COVID-19 patients according to joint pain severity and gender

Muscle, like joint pain, shows a gender dependence. Women who experience muscle pain (mild, moderate and severe) compared to men have a numerical superiority

(97.9% vs 92.3%). The difference of 5.6% was not significant (p>0.05) (Table 16). Moderate to severe muscle pain was found in significantly more women with COVID-19 compared to men (56.3% vs 36%, p=0.0019) (figure 4).

Table №.16 Distribution of COVID-19 patients according to level of muscle pain and gender

Level of muscule pain [a]			
	Incidence	Rate	Cumulative rate
Male			
No pain	10	7.8	7.8
Mild pain	72	56.3	64.1
Moderate pain	28	21.9	85.9
Severe pain	18	14.1	100.0
Total	128	100.0	
Female			
No pain	2	1.9	1.9
Mild pain	7	4 .3	46.2
Moderate pain	30	28.3	74.5
Severe pain	27	25.5	100.0
Total	106	100.0	

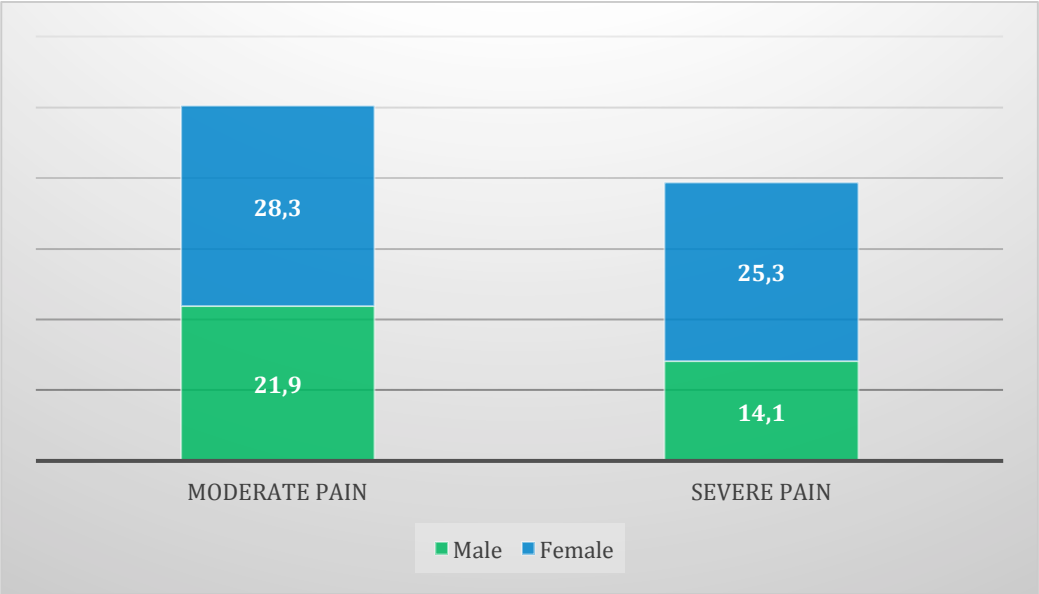


Figure №.4 Distribution of COVID-19 patients according to degree of muscle pain and gender

Comparative analysis between pain severity (joint and muscle) and gender found that the difference was significant at a significance level of $p<0.05$ ($p=0.019$ for joint pain and $p=0.021$ for muscle pain) (Table 12).

The results from our study show a similar trend to those described in the literature so far. There is a large amount of literature indicating that gender is an important factor influencing both the perception and severity of pain (Bernardes SF et al., 2008) and the effects of treatment with analgesic medication. (Hurley RW Adams MC, 2008, Bartley E. J et al., 2013).

Sex hormones and the distribution of their receptors in areas of the peripheral and central nervous system that are associated with nociceptive transmission influence patients' sensitivity to pain, with pain threshold and pain tolerance in women varying according to estrogen levels and the stage of the menstrual cycle. Reduced androgen concentrations are associated with the presence of chronic pain (Niesters M, Dahan A, Kest B, et al., 2010), with women more likely to report pain (Gerdle B, Bjork J, Coster L, Henriksson K, Henriksson C, Bengtsson A., 2008) and they are also more likely to suffer from chronic pain (Fillingim RB, et al., 2009). The data about whether women are more sensitive to pain, i.e. whether there is a difference in the interpretation of pain severity still remain contradictory at this stage. A meta-analysis

of the records of >11,000 patients who reported new-onset pain indicated that women rated their pain higher than men (Ruau D et al., 2012).

3.2 Patients with IJD

The results obtained from the pain assessment scales (VAS) in joints and muscles in patients with IJF are summarized in Table.17.

IJD patients presented joint and muscle pain severity with mean values according to VAS-a= 42.43 mm vs VAS-m= 35.32 mm, respectively. It can be said that IJD patients on anticytokine therapy experience mostly joint pain, and less muscle pain. This is a significant difference compared to COVID-19 patients. The latter reported muscle and joint pain of similar severity, with a nonsignificant predominance of muscle pain.

Table №.17 Mean values of muscle and joint pain measured by VAS in patients with IJD on anticytokine therapy

Patients with IJD (n=130)	Minimum	Maximum	Mean	SD
Joint pain (mm)	5.0	80.0	42.43	21.37
Muscle pain (mm)	2.0	80.0	35.32	21.42

In the group of patients with IJD, females again reported higher scores for joint pain but not for muscle pain (where the values were very similar) (table.18).

Males with IJD experience more joint pain than muscle pain (39.55 vs 35.82).

Females with IJD experienced more joint pain than muscle pain (46.48 vs 34.63, p = 0.0014).

Table №.18 Mean values of muscle and joint pain evaluated by VAS in patients with IJD on anticytokine therapy according to gender

Pain severity in IJD patients on anticytokine therapy					
Patients (n=76)	Incidence	Minimum	Maximum	Mean	SD

Pain severity in IJD patients on anticytokine therapy					
Patients (n=76)	Incidence	Minimum	Maximum	Mean	SD
Male (n=76)					
Joint pain	76	5.0	80.0	39.55	23.07
Muscle pain	76	3.0	80.0	35.82	22.86
Female (n=54)					
Joint pain	54	17.0	80.0	46.48	18.15
Muscle pain	54	2.0	75.0	34.63	19.41

Table №.19 Comparative analysis of pain severity (joint and muscle) in IJD patients according to gender.

	Paired Differences					
			95% CI of the Difference			
VAS (mm)	Mean	SD	Lower	Upper	t	P value
Joint pain (Male)/Joint pain (Female)	-6.07	32.59	-14.97	-1.60	-1.36	**0.177**
Muscle pain (Male)/Muscle pain(Female)	1.42	28.79	-6.43	-1.41	.36	**0.717**

In contrary to the COVID-19 patients, where there was a significant difference (at the significance level $p<0.05$) in the joint and muscle pain scores between the two genders (females scored higher than males), there was no significant difference in the muscle and joint pain scores between the two genders in the IJD group ($p=0.717$ and $p=0.177$, respectively) (Table 19).

4. ASSESSMENT OF MOOD AND EMOTIONS

4.1 Patients with COVID-19

The results of Zung's self-report scales for anxiety and depression are summarized in Table 20. The mean value of Zung's depression scale was 61.82 and the mean value of the anxiety scale was 56.38.

Table №.20 Anxiety and depression levels in COVID-19 patients

	Patients	Minimum	Maximum	Mean	St. deviation
Depression Scale	234	30	93	61.82	14.79
Anxiety Scale	234	26	84	56.38	13.14

a. Group = COVID-19 patients

Again, the results for both males and females were examined and compared.

Values from the two mood disorders rating scales for males averaged 59.16 points for the depression scale and 53.17 points for the anxiety scale (Table 21).

Table. № 21 Results from the anxiety and sepression scales by gender for male - COVID-19 patients [a]

	Incidence	Minimum	Maximum	Mean	St. deviation
Depression scale	128	30	93	59.16	15.114

Anxiety scale	128	28	84	53.17	13.005
Valid N (listwise)	128				

a. Gender = Male (COVID-19 patients)

Respectively, the scores for the two scales in females were 51.91 for the depression scale and 47.56 for the anxiety scale (Table 22). It is evident that females scored higher in both self-reported mood disorder scales - anxiety and depression.

Table №.22 Results of the anxiety and depression scales by gender for females - COVID-19 patients [a]

	Incidence	Мinimum	Maximum	Mean	St. deviation
Depression scale	106	35	90	65.05	13.78
Anxiety scale	106	26	83	59.60	12.62
Valid N (listwise)	106				

a. Gender = Female (COVID-19 patients)

In relation to the reported differences in anxiety and depression scores, the results for men and women were again examined and compared. Anxiety and depression scores were again significantly different for males and females in the COVID-19 group

(p=0.008 for depression and p=0.002 for anxiety), with females rating higher (Table 23)

Table № 23 T test on scores of the anxiety and depression scales by gender for women - COVID-19 patients [a]

	Paired Differences				t	Sig. (2-tailed)
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Depression scale (Male) – Depression scale (Female)	-5.472	20.92	-9.50	-1.44	-2.69	**.008**
Anxiety scale (Male) – Anxiety scale (Female)	-5.594	18.39	-9.137	-2.05	-3.13	**.002**

a. Group = COVID-19 patients

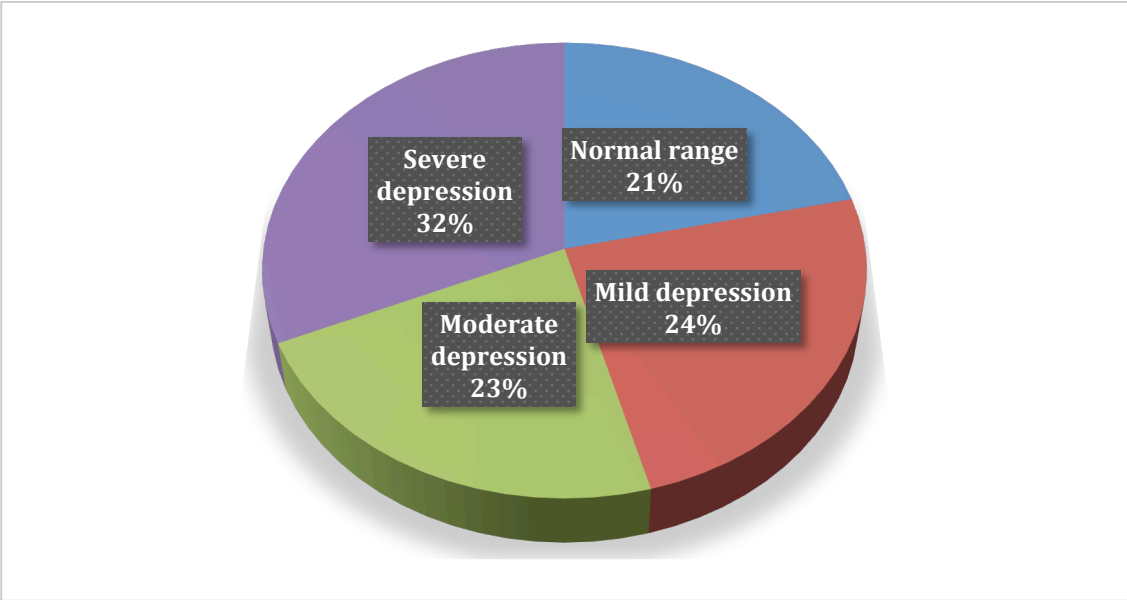
The interpretation of the results obtained in the assessment of anxiety and depressive scales allows to identify patients with and without psycho-emotional manifestations and to evaluate those with such manifestations according to their severity. COVID-19 patients, according to the index score obtained from Zung's self-report scales, were divided into those without depressive disorders (normal range), those with mild depression, those with moderate depression, and those with severe depression (21.4%, 24.4%, 22.6%, and 31.6%, respectively) (Table 24).

Table №. 24 Distribution of depressive symptoms severity in COVID-19 Patients

Depressive symptom severity			
	Incidence	Rate	Cumulative rate
Normal range	50	21.4	21.4
Mild depression	57	24.4	45.7
Moderate depression	53	22.6	68.4
Severe depression	74	31.6	100.0
Total	234	100.0	

The graphical distribution of patients in the COVID-19 group according to severity of depressive symptoms is shown in Fig. 14, with defined subgroups according to SDS Index score. Various depression severity was found in a significantly large proportion of the COVID-19 patients (79 %) (fig. 5).

Figure №.5 Distribution of depressive symptoms severity in patients with COVID-19



Even when using conservative norms to determine the severity of depressive symptoms, according to the instrument author, 54.2% of COVID-19 patients had

moderate to severe depression. With such severity of symptoms we can speak of clinically marked depression that requires treatment (Zung WWK. A, 1965). We performed the distribution of the severity of depressive symptoms according to gender in the group of COVID-19 patients (Table 25 and Table 26).

Table №.25 Distribution of depressive symptoms severity in patients with COVID-19-male

Depressive symptom severity - male			
	Incidence	Rate	Cumulative rate
Normal range	34	26.6	26.6
Mild depression	34	26.6	53.1
Moderate depression	25	19.5	72.7
Severe depression	35	27.3	100.0
Total	128	100.0	

Table №.26 Distribution of depressive symptoms severity in patients with COVID-19-female

Depressive symptom severity - female			
	Incidence	Rate	Cumulative rate
Normal range	16	15.1	15.1
Mild depression	23	21.7	36.8
Moderate depression	28	26.4	63.2
Severe depression	39	36.8	100.0
Total	106	100.0	

Separating the two genders, the results for female patients were even more alarming - 63.2% of them had moderate to severe depression. For men, this rate was significantly lower at 46.8%. Our results are similar to those described in the literature.

According to literature, women are more likely than men to experience depression (Albert PR., 2015, Baxter AJ et al., 2014). Some studies suggest that one third of women will experience a major depressive episode in their lifetime (Cyranowski JM et al., 2000). Evidence from registries suggests that women have the illness 1.7 times more often than men and that it is more severe (Whiteford HA et al., 2013). It has been suggested that the high incidence of depression in women is due to changes (fluctuations) in sex hormones. Estrogen levels appear to be of significant importance, as a decrease in estrogen may increase the risk of depression.

In COVID-19 patients, women also report depressive symptoms more frequently. Reports from various authors indicate that female COVID-19 patients report more pronounced anxiety and depression (Özdin S et al., 2020, Effati-Daryani F et al., 2020, Durankuş F et al., 2022). This was also echoed in patients who required hospitalization (Dai LL et al., 2020).

COVID-19 patients according to the obtained index score of the self-reported Zsung scales were divided into patients without anxiety disorders (normal range), with mild to moderate anxiety, with severe anxiety and those with extreme anxiety (18.8%, 42.3%, 27.44%, 11.5% respectively) (Table 27).

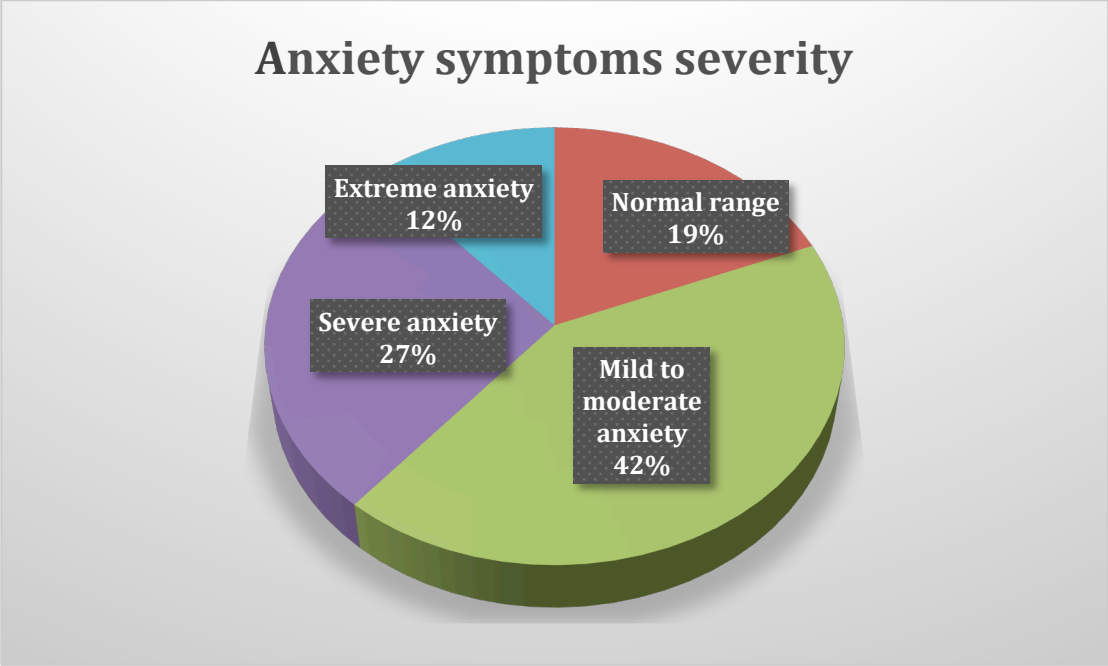
Table №. 27 Distribution of anxiety symptoms severity in patients with COVID-19

Anxiety symptom severity			
	Incidence	Rate	Cumulative rate
Normal range	44	18.8	18.8
Mild to moderate anxiety	99	42.3	61.1
Severe anxiety	64	27.4	88.5
Extreme anxiety	27	11.5	100.0
Total	234	100.0	

The graphical distribution of patients in the COVID-19 group according to the severity of anxiety symptoms is shown in Fig. 15, with defined subgroups according to the SAS Index score.

Anxiety of varying severity was found in a significantly large proportion of the COVID-19 patients (81,2 %) (fig.6).

Figure №.6 Distribution of anxiety symptoms severity in patients with COVID-19



Even when using conservative norms to determine the severity of anxiety symptoms, according to the instrument author, 39% of COVID-19 patients had severe and extreme anxiety. When the patients are separated by gender, it is evident that this rate reaches 46.2% in women. With such severity of symptoms we can speak of clinically marked anxiety that requires treatment (Zung WWK. A, 1965). We made distribution of the anxiety symptom severity according to gender in the group of COVID-19 patients (Table 28 and Table 29).

Table №.28 Distribution of anxiety symptoms severity in patients with COVID-19-male

Anxiety symptoms severity-male			
	Incidence	Rate	Cumulative rate
Normal range	36	28.1	28.1
Mild to moderate anxiety	50	39.1	67.2
Severe anxiety	31	24.2	91.4
Extreme anxiety	11	8.6	100.0
Total	128	100.0	

Таблица №.29 Distribution of anxiety symptoms severity in patients with COVID-19-female

Anxiety symptoms severity-female			
	Incidence	Rate	Cumulative rate
Normal range	8	7.5	7.5
Mild to moderate anxiety	49	46.2	53.8
Severe anxiety	33	31.1	84.9
Extreme anxiety	16	15.1	100.0
Total	106	100.0	

1.2 Patients with IJD

The results of the self-rated depression and anxiety scales are summarized in Table 30. The mean scores for depression and anxiety were similar. There was no significant difference between the values of the two scorers (46.34 vs 45.32, $p>0.05$).

It can be said that the degree of anxiety and depression have similar manifestation in patients of VCD on anticytokine therapy.

Table №.30 Mean scores of anxiety and depression scales in patients with IJD

IJD	N=130	Minimum	Maximum	Mean	SD
Depression scale	130	30	66	46.34	9.27
Anxiety scale	130	29	65	45.32	8.59

Legend: IJD – inflammatory joint disease

Considering the significant differences in depression and anxiety rating scales between males and females in the COVID-19 group, we investigatetd for a similar pattern here.

The results are summarized in Table 31. The mean Zung scale score for depression in males was 42.97 points and for anxiety was 43.03 points (Table 31).

Table №.31 Mean scores of anxiety and depression scales in patients with IJD by gender

	Incidence	Minimum	Maximum	Mealn	SD
Мъже (n=76)					
Depression scale	76	30	60	42.97	8.39
Abxiety scale	76	29	65	43.03	8.37
Female (n=54)					
Depression scale	54	31	66	51.0	8.41
Anxiety scale	54	33	64	48.56	7.89

Females with IJD reported higher scores on the depression scale compared to males with IBD (51.07 vs 42.97).

Females with IJD, as well as COVID-19 patients, scored higher on the anxiety and depression scales (Table 32).I

t can be noted that females with IJD on anticytokine therapy scored higher on the anxiety and depression scales compared to males in the same group.

Table №.32 Mean variation of anxiety and depression scores in patients with IJD according to gender.

	Paired Differences				t	P value
	Mean diffrenc e	Std. Deviation	95% CI of the Difference			
			Lower	Upper		
Depression scale (Male/Female)	-8.48	10.44	-11.33	-5.63	-5.97	**0.000**
Anxiety scale (Male/Female)	-5.31	10.68	-8.23	-2.39	-3.66	**0.001**

These results correlate well with available literature data. Mood disorders are more common in women with IJD (Barnabe C et al., 2012. Studies have been done in patients with RA (Bilberg A et al., 2018), and in patients with PsA (McDonough E et al., 2014), women report depression and anxiety more frequently than men.

COMPARATIVE STATISTICS OF PATIENTS IN THE STUDY

The results obtained in the two groups of patients were compared – COVID-19 and IJD.

The results are presented in a table and graph. COVID-19 patients had significantly higher values of acute phase indices. The mean values of ESR in the studied patients were almost three times higher in COVID-19 patients compared to patients from the VUS on anticytokine therapy and more than 10 times higher for CRP (Table 6 and Table 7).

High mean CRP values in the study group of patients hospitalized with COVID-19 demonstrated the severity of the disease. Patients can be defined as having a severe course of COVID-19 and a poor prognosis in terms of survival (Parimoo A et al., 2021).

In patients with IJD, the mean values of both CRP and ESR were slightly above the upper reference limit. Prolonged treatment with biologic drugs targeting key target proinflammatory cytokines (TNFα, IL6, IL17) has a beneficial effect on the inflammatory response in IJD, suppressing the level of inflammation. Patients with an

adequate response had normal values of acute phase parameters, in particular CRP. They have a favorable prognosis in terms of quality of life.

There are few cases of COVID-19 patients who required hospitalization and lacked joint or muscle pain. Majority of them had different severity of muscle or joint symptomatology, which for joint pain was comparable to that in patients with IJD undergoing adectal anticytokine therapy (44.68 vs 42.43, $p>0.05$).

There was a low linear correlation between joint pain severity and CRP values, both in COVID-19 inpatients and in the IJD group on anticytokine therapy (Table 33, Table 34). Joint pain in these two groups of patients was significantly determined by factors other than the degree of inflammation.

Table №.33 Correlation between CRP and pain in COVID-19 patients

		CRP	Joint pain	Muscle pain
CRP	Pearson Correlation	1	.142*	.176**
	Sig. (2-tailed)		.029	.007
	N	234	234	234
Join pain	Pearson Correlation	.142*	1	.863**
	Sig. (2-tailed)	.029		.000
	N	234	234	234

Muscle pain	Pearson Correlation	.176**	.863**	1
	Sig. (2-tailed)	.007	.000	
	N	234	234	234

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table №.34 Correlation between CRP and pain in IJD patients

		CRP	Join pain	Muscle pain
CRP	Pearson Correlation	1	.239**	.243**
	Sig. (2-tailed)		.006	.005
	N	130	130	130
Join pain	Pearson Correlation	.239**	1	.672**
	Sig. (2-tailed)	.006		.000
	N	130	130	130
Muscle pain	Pearson Correlation	.243**	.672**	1

	Sig. (2-tailed)	.005	.000	
	N	130	130	130

**. Correlation is significant at the 0.01 level (2-tailed).

Table №. 34a Comparison of the data between the two groups in the study

Comparative statistics between groups			
	COVID-19 (n=234)	IJD (n=130)	P value
ESR (mean± SD)	78.78±30.16	30.94±27.29	<0.001
CRP (mean± SD)	96.81±78.04	8.38±21.06	<0.001
Fibrinogen (mean± SD)	5.82±1.75	2.93±1.12	<0.001
Joint pain (mean± SD)	42.36±27.99	42.43±21.37	NS
Muscle paia (mean± SD)	43.00±28.32	35.32±21.42	<0.001
Anxiety scale	65.38±13.14	45.32±8.59	<0.001
Depression scale	61.82±14.79	46.34±9.27	<0.001

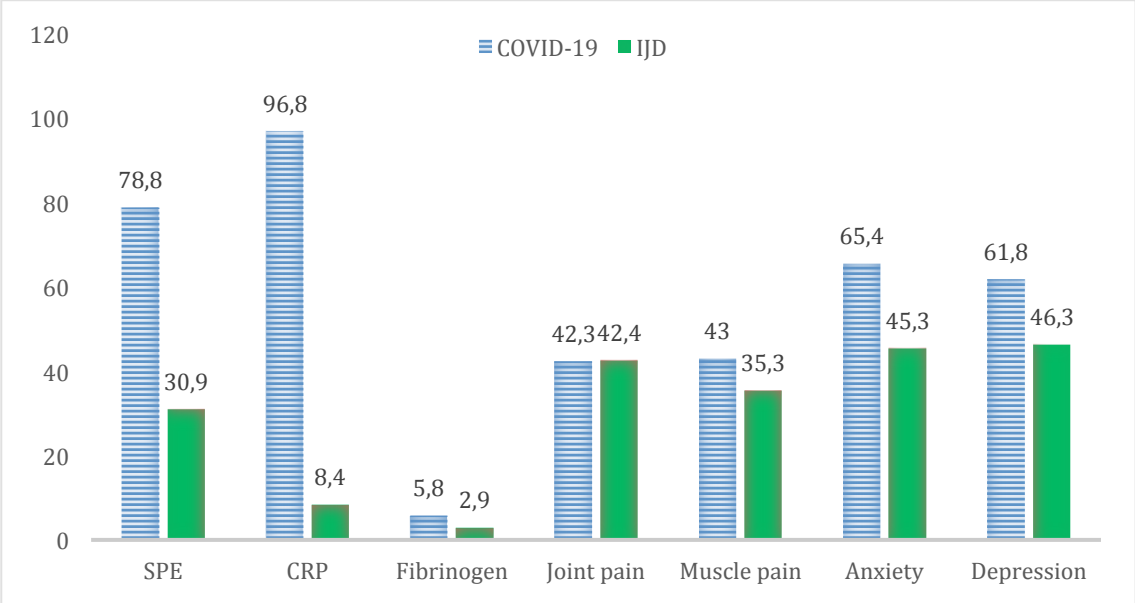


Figure 7 Mean values of indices in COVID-19 and IJD patients - comparative presentation.

We found a significant difference in VAS-m values between the two groups, with COVID-19 patients sharing significantly more muscle pain than those with IJD (43.00 vs 35.32, $p<0.001$) (Table 34a and Figure 7).

Patients with IJD on anticytokine therapy have predominantly joint pain, while patients with moderate to severe COVID-19 have predominantly muscle pain. This difference is significant and understandable because the two groups of diseases are heterogenic and have differences in their pathogenetic mechanism.

In the two groups of patients we investigated (the first with acute pain due to severe SARS CoV-2 viral infection and the other with chronic pain due to IJD), there was a linear correlation between muscle pain severity on the one hand and CRP values on the other (Table 33, Table 34). The severity of muscle pain as measured by self-reported VAS in these two groups of patients is probably determined by other factors beyond the degree of inflammation expressed by CRP.

According to Zung's scale, mean depressive symptom scores were significantly higher among hospitalized COVID-19 patients compared with IJD patients on anticytokine therapy. There was a significant difference between the mean SDS scores of COVID-19 patients and IJD patients (63.93 vs 46.34, $p<0.001$).

These values correspond with moderate depression (60 to 69) according to the scales used. The findings allow to assume that patients of moderate to severe course and requiring hospitalization COVID-19 are more depressed compared to those of IJD treated with anticytokine medication.

The same patterns are found for the anxiety (SAS). COVID-19 patients were significantly more anxious than those with IJD (58.83 vs 45.32, $p<0.001$).

A correlation was found between patients' age and scores on self-rating scales in COVID-19 patients. The linear correlation is moderate (Table 35) between age on the one hand and the VAS assessment of muscle and joint pain and with the scales assessing anxiety and depression. Older COVID-19 patients were more likely to have more severe joint and muscle pain, to be more anxious and more tend to be depressed.

Considering the high mean age (63.74, respectively) of the COVID-19 patients studied, it is possible that this is one of the factors that lead to high scores on all self-assessment instruments, for pain and for mood disorders. According to the available literature, depression and anxiety scores also trend to increase with aging (Akincigil A et al., 2011) and patients with diagnosed mood disorder are more likely to report the presence of chronic pain (Dersh J et al., 2002)

Table №.35 Correlation between patients' age and self-assessment instruments in COVID-19 patients

		Age	Depression scale	Anxiety scale	Joint pain	Muscle pain
Age	Pearson Correlation	1	0.525**	0.394**	0.371**	0.345**
	P value		0.000	0.000	0.000	0.000
	N	234	234	234	234	234

**. Correlation is significant at the 0.01 level (2-tailed).

The highest positive correlations with anxiety were the scores from the depression scale (SDS) and the anxiety scale (SAS). The correlation between age and pain was similarly moderately positive with psycho-emotional mood disorders. Patient age was more strongly associated with anxiety and depresson compared with pain experiences in hospitalized COVID-19 patients. These reults are consistent with those known in the literature. More recent research has found that COVID-19 is associated with poorer mental health across all age groups, with some evidence of stronger associations in people aged 50 years and older. These findings could be interpreted as the possibility that older people may be more likely to suffer from more severe forms of COVID-19 and potentially also suffer greater anxiety about infection due to their age and greater likelihood of existing health problems (Thompson EJ et al., 2022).

COVID-19 patients with depressive symptoms experience more severe joint and muscle pain. There was a linear correlation between the degree of depressive mood and the severity of joint and muscle pain, which was present in COVID-19 patients ($r=0.692$, $r=0.665$ respectively, $p<0.001$). A linear correlation between the level of anxiety and the severity of joint and muscle pain was present in COVID-19 patients ($r=0.677$, $r=0.647$ respectively $p<0.001$) (Table 36).

Table №.36 Correlation between patient age and self-assessment instruments in the COVID-19 patients

		Age	Depression scale	Anxiety scale	Joint pain	Muscle pain
Age	Pearson Correlation	1	0.525**	0.394**	.371**	.345**
	P value		0.000	0.000	0.000	0.000
	N	234	234	234	234	234
Depression scale	Pearson Correlation	0.525**	1	0.876**	0.692**	0.665**
	P value	.000		.000	.000	.000
	N	234	234	234	234	234
Anxiety scale	Pearson Correlation	.394**	.876**	1	0.677**	0.647**
	P value	0.000	0.000		0.000	0.000
	N	234	234	234	234	234
Joint pain	Pearson Correlation	.371**	.692**	.677**	1	.863**
	P value	.000	.000	.000		.000
	N	234	234	234	234	234
Muscle pain	Pearson Correlation	.345**	.665**	.647**	.863**	1
	P value	.000	.000	.000	.000	
	N	234	234	234	234	234

**. Correlation is significant at the 0.01 level (2-tailed).

In the COVID-19 patients investigated in this study, a significant moderate to strong linear correlation was found between the level of depression and anxiety on the one hand and the pain severity for the two pain phenomena investigated, myalgias and arthralgias, on the other (r=0.692; 0.665 respectively, p<0.001) (Table 37).

Table №. 37 Correlation between SDS and SAS scores and VAS for muscle and joint pain in the COVID-19 group

		Depression scale	Anxiety scale	VAS – Joint pain	VAS – Muscle pain
Depression scale	Pearson Correlation	1	0.876**	0.692**	0.665**
	Sig. (2-tailed)		.000	.000	.000
	N	234	234	234	234
Anxiety scale	Pearson Correlation	.876**	1	.677**	.647**
	Sig. (2-tailed)	.000		.000	.000
	N	234	234	234	234

VAS – Joint pain	Pearson Correlation	.692**	0.677**	1	0.863**
	Sig. (2-tailed)	.000	.000		.000
	N	234	234	234	234
VAS – Muscle pain	Pearson Correlation	.665**	.647**	.863**	1
	Sig. (2-tailed)	.000	.000	.000	
	N	234	234	234	234

**. Correlation is significant at the 0.01 level (2-tailed).

Depression and anxiety scores (SDS and SAS) predicted half the variance of the joint pain score, R square 50.0% (Table 39), and almost half the variation of the muscle pain score, R square 46.0%, in COVID-19 patients (Table 41).

Table №.38 Regression analysis of SDS and SAS scores and VAS for joint pain in the COVID-19 patients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-43.880	5.842		-7.511	.000
	Depression scale	1.008	.229	.425	4.407	.000
	Anxiety scale	.811	.257	.304	3.151	.002

a. Dependent Variable: Joint pain

Table №.39 Regression analysis of SDS and SAS scores and VAS for joint pain in the COVID-19 patients

Joint pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.707[a]	0.500	0.496	19.8775

a. Predictors: (Constant), Anxiety scale, Depression scale

Table №.40 Regression analysis of SDS and SAS scores and VAS for muscle pain in COVID-19 patients

Model	Unstandardized Coefficients	Standardized Coefficients	t	Sig.

		B	Std. Error	Beta		
1	(Constant)	-40.561	6.143		-6.603	.000
	Depression scale	1.006	0.241	0.419	4.180	.000
	Anxiety scale	0.754	0.271	0.280	2.787	.006

a. Dependent Variable: Muscle pain

Table №.41 Regression analysis of SDS and SAS scores and VAS for muscle pain in COVID-19 patients

Muscle pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.678[a]	.460	.455	20.9016

a. Predictors: (Constant), Anxiety scale, Depression scale

On the other hand, in patients with SARS-CoV-2, we did not find a significant correlation (at new significance level $p<0.01$) of the two investigated pain phenomena, arthralgias and myalgias, with either inflammation parameters or with the thrombogenic markers (Table 42 and Table 44).

Table №.42 Regression analysis of inflammation indices and VAS thrombogenic markers for joint pain in COVID-19 patients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	39.066	3.489		11.196	.000
	CRP	.052	.025	.146	2.059	.041
	Fibrinogen	-.371	1.051	-.023	-.353	.724
	Ferritin	.001	.001	.059	.861	.390
	Lactate dehydrogenase	-.002	.004	-.046	-.663	.508
	D-dimer	-.024	.022	-.075	-1.119	.264

a. Dependent Variable: Joint pain

Respectively, all these indicators (predictors) determine only about 4% of the variation of the two pain parameters - for joint pain - unadjusted R square 3.5%,

adjusted 1.4% (Table 43) for muscle pain - unadjusted R square 4.4%, adjusted 2.3% (Table 45).

Table №.43 Regression analysis of inflammation and thrombogenic markers and VAS for joint pain in COVID-19 patients

Joint pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.188[a]	.035	.014	27.7952

a. Predictors: (Constant), D-dimer, Fibrinogen, Lactate dehydrogenase, Ferritin, CRP

Table №.44 Regression analysis of inflammation and thrombogenic markers and VAS for muscle pain in COVID-19 patients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	37.623	3.514		10.707	.000
	CRP	.062	.026	.172	2.437	.016
	Fibrinogen	-.098	1.063	-.006	-.092	.927
	Ferritin	.001	.001	.045	.658	.511
	Lactate dehydrogenase	-.001	.004	-.010	-.147	.883
	D-dimer	-.021	.022	-.066	-.981	.327

a. Dependent Variable: Muscle pain

Table №.45 Regression analysis of inflammation and thrombogenic markers and VAS for muscle pain in COVID-19 patients

Muscle pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.210[a]	.044	.023	27.9899

a. Predictors: (Constant), D-dimer, Fibrinogen, Lactate dehydrogenase, Ferritin, CRP

4.1 Patients with IJD

The same analyses of the association between SDS and SAS scores and data from inflammatory markers on the one hand and muscle and joint pain (VAS) scores on the

other hand showed different results in patients with inflammatory joint disease and chronic pain (Table 46). These results are subject to different analyses.

Table №. 46 Correlation between SDS and SAS scores and VAS for muscle and joint pain (in patients with IJD)

Correlation

		Depression scale	Anxiety scale	Joint pain	Muscle pain
Depression scale	Pearson Correlation	1	.693**	.349**	.231**
	Sig. (2-tailed)		.000	.000	.008
	N	130	130	130	130
Anxiety scale	Pearson Correlation	.693**	1	.248**	.189
	Sig. (2-tailed)	.000		.004	.031
	N	130	130	130	130
Joint pain	Pearson Correlation	.349**	.248**	1	.672**
	Sig. (2-tailed)	.000	.004		.000
	N	130	130	130	130
Muscle pain	Pearson Correlation	.231**	.189	.672**	1
	Sig. (2-tailed)	.008	.031	.000	
	N	130	130	130	130

**. Correlation is significant at the 0.01 level (2-tailed).

Self-assessed depression scale (SDS) showed a significant moderate correlation with joint pain and at the same time a weak correlation with muscle pain severity (Table 46). Anxiety scale (SAS) showed a significant but weak correlation with joint pain and no correlation with muscle pain (Table 46).

Only between 12.2% and 10.8% of the variations in joint pain severity could be explained by alterations in anxiety and depressive symptoms in IJD patients on anticytokine therapy. A more significant fraction of the joint pain variations in these patients was due to other factors.

Таблица №. 47 Regression analysis of SDS and SAS scores and VAS for joint pain (in patients with IJD)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	4.907	10.078		.487	.627
	Depression scale	.980	.332	.341	2.954	.004
	Anxiety scale	.037	.359	.012	.102	.919

a. Dependent Variable: Joint pain

Table №.48 Regression analysis of SDS and SAS scores and VAS for joint pain (in patients with IJD)

Joint pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.349[a]	.122	.108	20.1834

a. Predictors: (Constant), Anxiety scale, Depression scale

Таблица №. 49 Regression analysis of SDS and SAS scores and VAS for muscle pain (in patients with IJD)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	8.551	10.479		.816	.416
	Depression scale	.554	.345	.192	1.607	.111
	Anxiety scale	.174	.373	.056	.466	.642

a. Dependent Variable: Muscle pain

Only about 4% of the variations in muscle pain severity in patients with IBS were due to alterations in anxiety and depressive symptoms. The remaining larger proportion of variations are explained by other facts in these patients.

Table №. 50 Regression analysis of SDS and SAS scores and VAS for muscle pain (in patients with IJD)

Muscle pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.234[a]	.055	.040	20.9865

a. Predictors: (Constant), Anxiety scale, Depression scale

The SDS and SAS scores accounted for much less of the variance in the joint pain (R square 12.2%) (Table 48) and muscle pain (R square 5.5%) (Table 50) scores compared with the COVID-19 group. For muscle pain, neither the SDS score nor the SAS score had significant predictive value (Table 49), and for joint pain, only the SDS score had significant predictive value (Table 47).

The inflammatory indices examined in the patients in the control group and their relationship to the muscle and joint pain scores are presented in a table: (Table 51 and Table 53)

Таблица №. 51 Regression analysis of inflammation markers and VAS for joint pain in patients with IJD

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	36.059	5.493		6.564	.000
	CRP	.151	.108	.149	1.398	.165
	Fibrinogen	.501	2.256	.028	.222	.825
	ESR	.118	.092	.150	1.285	.201

a. Dependent Variable: Joint pain

Table №.52 Regression analysis of inflammation markers and VAS for joint pain in patients with IJD

Joint pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.279[a]	.078	.056	20.7642

a. Predictors: (Constant), ESR, CRP, Fibrinogen

Таблица №.53 Regression analysis of inflammation markers and VAS for muscle pain in patients with IJD

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	41.117	5.498		7.479	.000
	CRP	.358	.108	.352	3.311	.001
	Fibrinogen	-2.527	2.258	-.139	-1.119	.265
	ESR	-.045	.092	-.057	-.489	.626

a. Dependent Variable: Muscle pain

Table №.54 Regression analysis of inflammation markers and VAS for muscle pain in patients with IJD

Muscle pain (VAS 100mm)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.284[a]	.081	.059	20.7802

a. Predictors: (Constant), ESR, CRP, Fibrinogen

The only significant predictor reported in this group was between CRP and self-reported muscle pain.

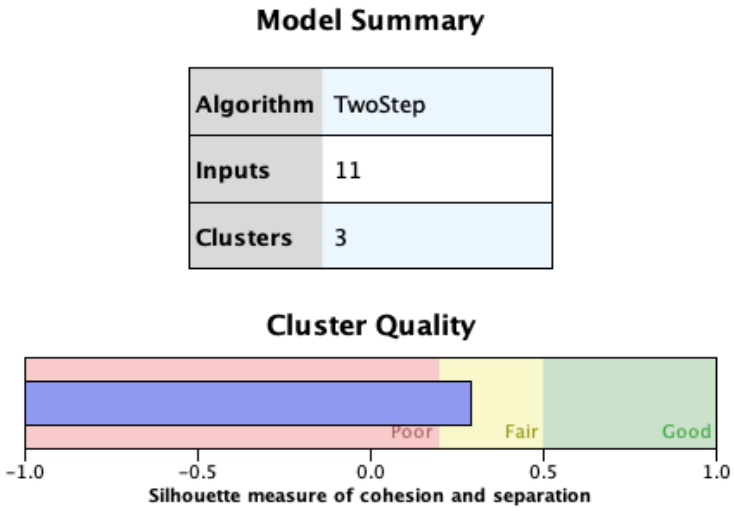
Correspondingly, inflammatory markers (predictors) determined about 8% of the variability of the two pain scores, R square 7.8% for joint pain (Table 52), R square 8.1% for muscle pain (Table 54).

This is about twice as much as in COVID-19 patients, but again the indexes are low. It should be reported that patients with IJD and chronic pain were receiving adequate, up-to-date treatment with biologics, and their overall pain scores were much lower than the COVID-19 group.

CLUSTER ANALYSIS OF THE PATIENTS IN COVID-19 GROUP

Grouping the scores from the self-assessment instruments according to severity and recommended norms allows the use of cluster analysis. With acceptable reliability according to cohesion and separation (Fig. 8), cluster analysis divided the COVID-19 patient group into three clusters (Fig. 9).

Figure №.8 Cluster analysis model (COVID-19 group)



In forming the clusters, all self-assessment instruments (joint pain and muscle pain severity and anxiety and depression severity), had the highest predictive value, while the patients' age and all inflammatory markers had a lower predictive value (chart 5).

Chart No.5 Predictor value of indicators in the cluster model

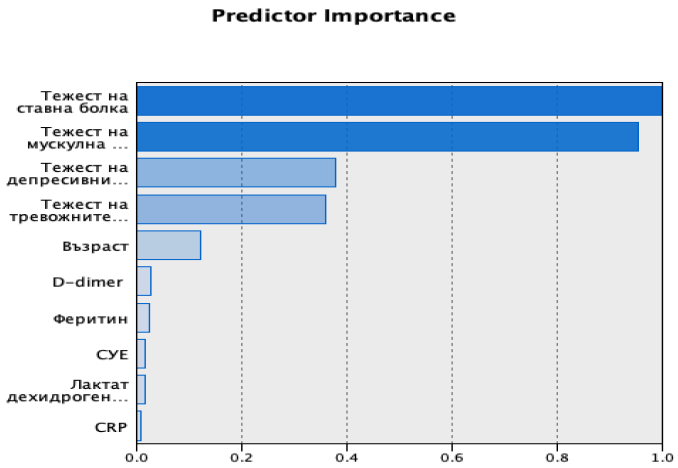
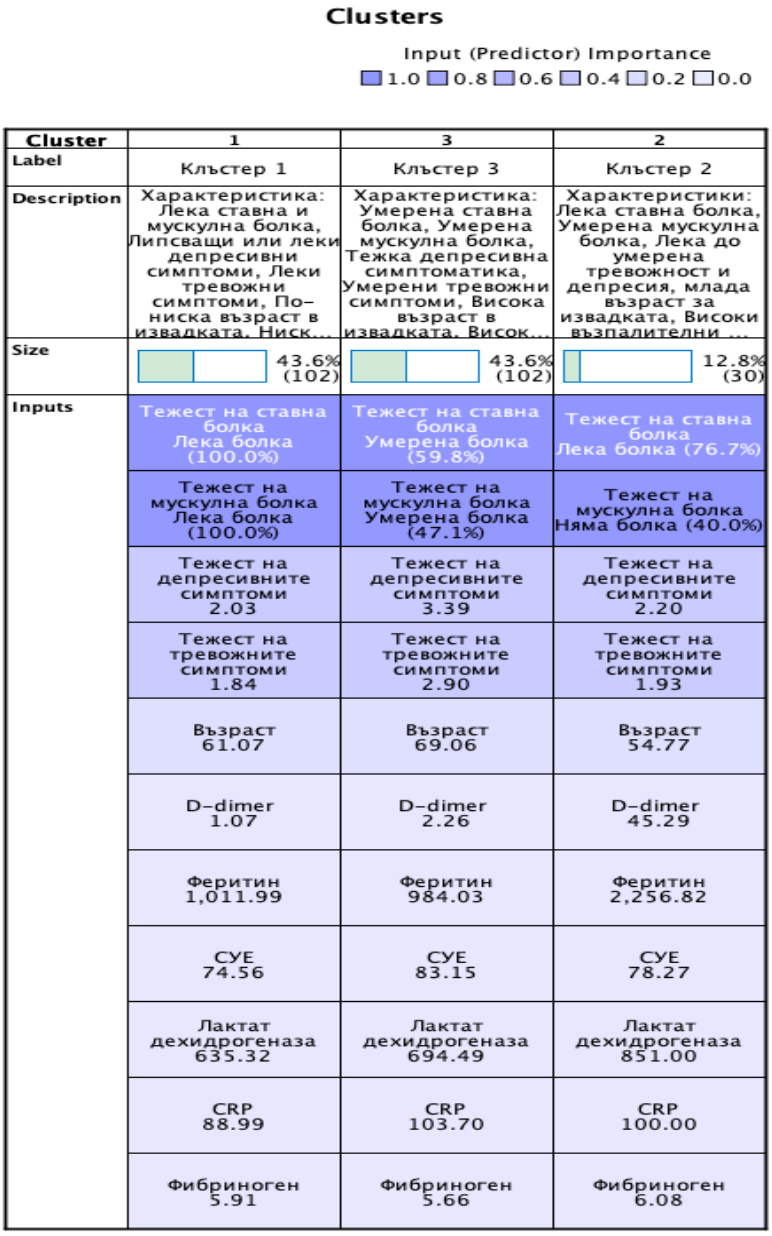


Figure 9 Clusters in the COVID-19 group



Cluster	1	3	2
Label	Клъстер 1	Клъстер 3	Клъстер 2
Description	Характеристика: Лека ставна и мускулна болка, Липсващи или леки депресивни симптоми, Леки тревожни симптоми, По-ниска възраст в извадката, Ниск...	Характеристика: Умерена ставна болка, Умерена мускулна болка, Тежка депресивна симптоматика, Умерени тревожни симптоми, Висока възраст в извадката, Висок...	Характеристики: Лека ставна болка, Умерена мускулна болка, Лека до умерена тревожност и депресия, млада възраст за извадката, Високи възпалителни ...
Size	43.6% (102)	43.6% (102)	12.8% (30)
Inputs	Тежест на ставна болка Лека болка (100.0%)	Тежест на ставна болка Умерена болка (59.8%)	Тежест на ставна болка Лека болка (76.7%)
	Тежест на мускулна болка Лека болка (100.0%)	Тежест на мускулна болка Умерена болка (47.1%)	Тежест на мускулна болка Няма болка (40.0%)
	Тежест на депресивните симптоми 2.03	Тежест на депресивните симптоми 3.39	Тежест на депресивните симптоми 2.20
	Тежест на тревожните симптоми 1.84	Тежест на тревожните симптоми 2.90	Тежест на тревожните симптоми 1.93
	Възраст 61.07	Възраст 69.06	Възраст 54.77
	D-dimer 1.07	D-dimer 2.26	D-dimer 45.29
	Феритин 1,011.99	Феритин 984.03	Феритин 2,256.82
	СУЕ 74.56	СУЕ 83.15	СУЕ 78.27
	Лактат дехидрогеназа 635.32	Лактат дехидрогеназа 694.49	Лактат дехидрогеназа 851.00
	CRP 88.99	CRP 103.70	CRP 100.00
	Фибриноген 5.91	Фибриноген 5.66	Фибриноген 6.08

Characteristics of the individual clusters:

1. Cluster 1 (43.6% of the group) is represented by:
    - Predominantly mild joint and muscle pain
    - Absent or mild depressive symptoms
    - Predominantly mild anxiety symptoms
    - Lower age in the sample (mean age of 61.07 years, group mean 63.74)

- Low inflammatory markers

2. Cluster 2 (12.8% of the group) is represented by:
    - Mild joint pain,
    - Mild to moderate muscle pain
    - Mild to moderate anxiety
    - Mild to moderate depression
    - Young age in the group (mean age of 54.77 years)
    - High inflammatory markers
3. Cluster 3 (43.6% of the group) is represented by:
    - Moderate to severe joint pain
    - Moderate to severe muscle pain
    - Severe depressive symptoms
    - Moderate anxiety symptoms
    - High age in the group (mean age of 69.06 years, group mean 63.74)
    - High inflammatory markers

Cluster analysis can have a strict practical application by allowing individual clusters to be considered as groups of patients in the COVID-19 cohort who have a different clinical presentation and would require a different approach in the therapeutic process.

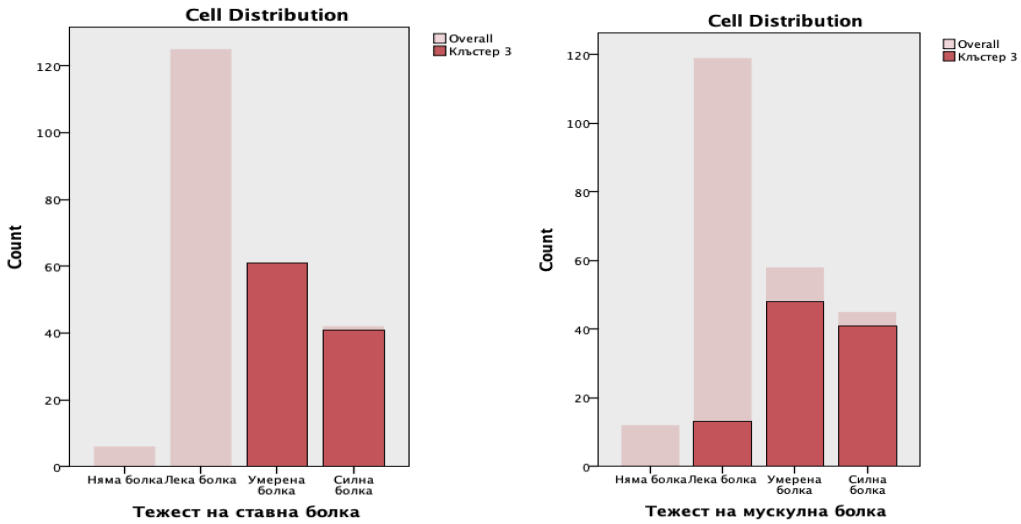
The first cluster, which is slightly less than half the actual COVID-19 group, are patients who have basically no pronounced findings, neither pain nor anxiety and depression, having moderate laboratory findings relative to the entire cohort. The original study design did not include the collecting of data on saturation and somatic complains, such as shortness of breath. For this reason, we can only speculate as to why these patients were treated in hospital in practice. Certainly the estimated relatively low scores of inflammatory parameters are low for the cohort, i.e. we are not talking about normal results (mean values for ESR - 74.6 and CRP - 88.7).

The second cluster was smaller - 30 patients, mean age 55 years, with very high inflammatory markers, a background of mild to moderate anxiety and depression, and moderate muscle pain. Patients were young for the cohort, with a pronounced viral infection who required somatic clinical or intensive monitoring and treatment.

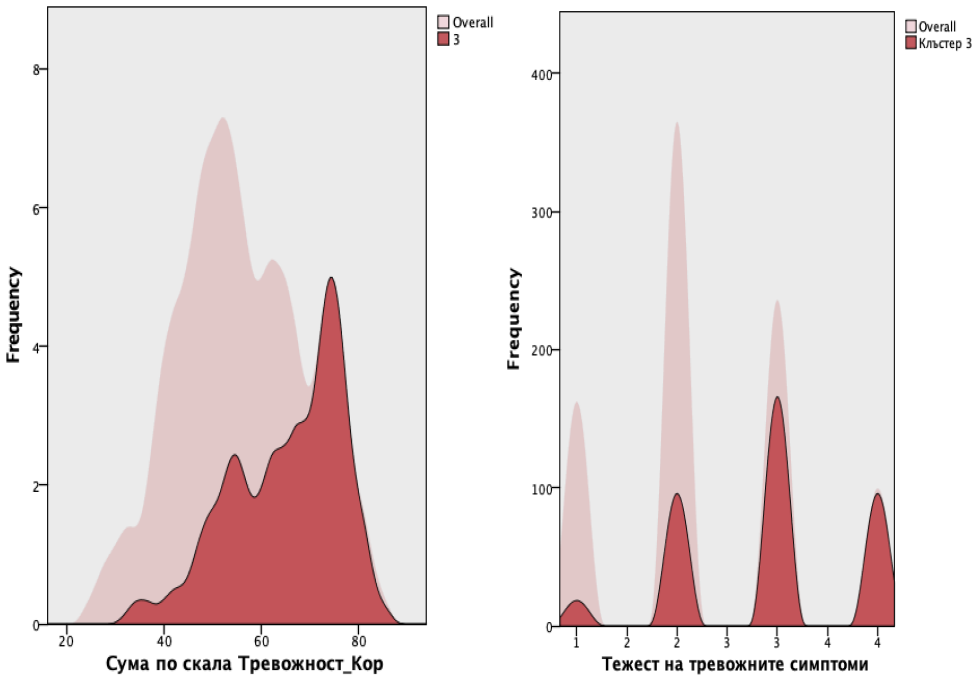
The third cluster is the most interesting finding within the study. It included almost half of the patients with COVID-19 (43.6%). These are patients with the highest mean age for the cohort, around 70 years, who share moderate to severe muscle and joint pain, alongside self-reported severe depressive and moderately severe anxiety symptoms. Inflammatory index values were not statistically significantly different from those of patients in Cluster 1. These are patients for which psychological interventions or psychiatric treatment should necessarily be conducted in clinical practice. Many studies have been conducted worldwide showing psychological attitudes in the general population in relation to the COVID-19 pandemic. However, very few studies have shown these attitudes and psychiatric symptoms in the clinical population of COVID-19 patients. High age, presence of comorbidity, marked anxiety and depression (associated with published data of high mortality in this age group) determine the severe course in patients in this cluster.

Cluster 3 - characteristics and distribution of individual indicators, compared to the whole group of patients with COVID-19:

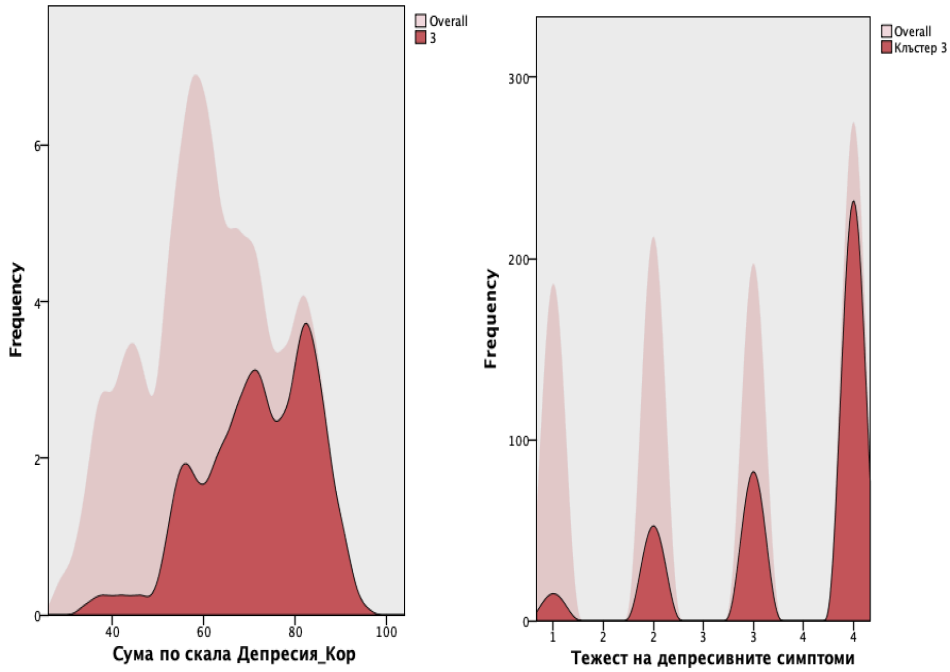
Graph №.6 Pain symptoms severity in Cluster 3 of the COVID-19 patient group



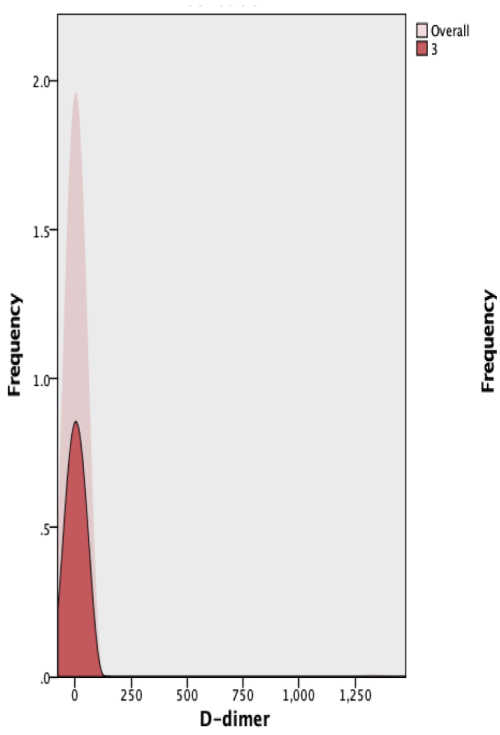
Graph №.7 Self-assessed anxiety symptoms in Cluster 3 of COVID-19 patients

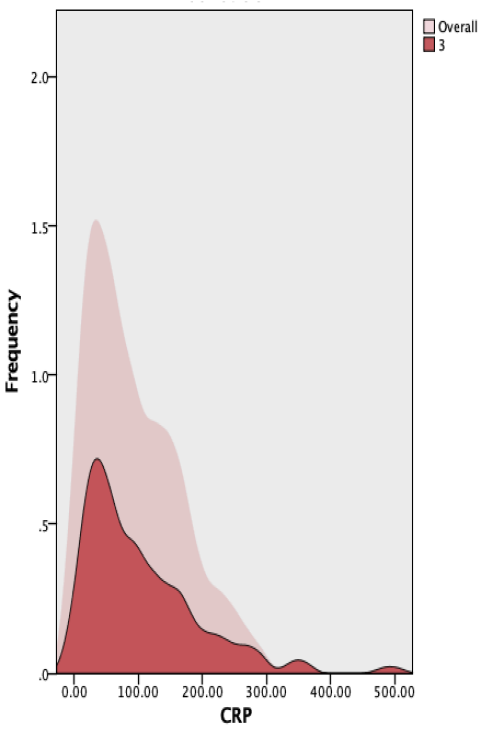


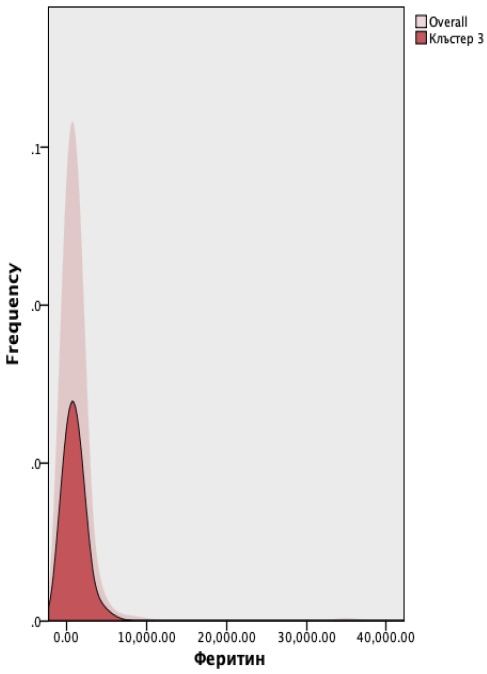
Graph №.8 Self-assessed depressive symptoms in Cluster 3 of COVID-19 patients

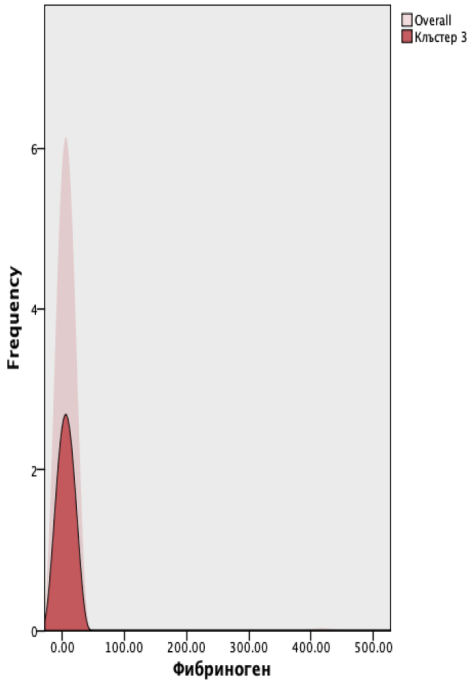


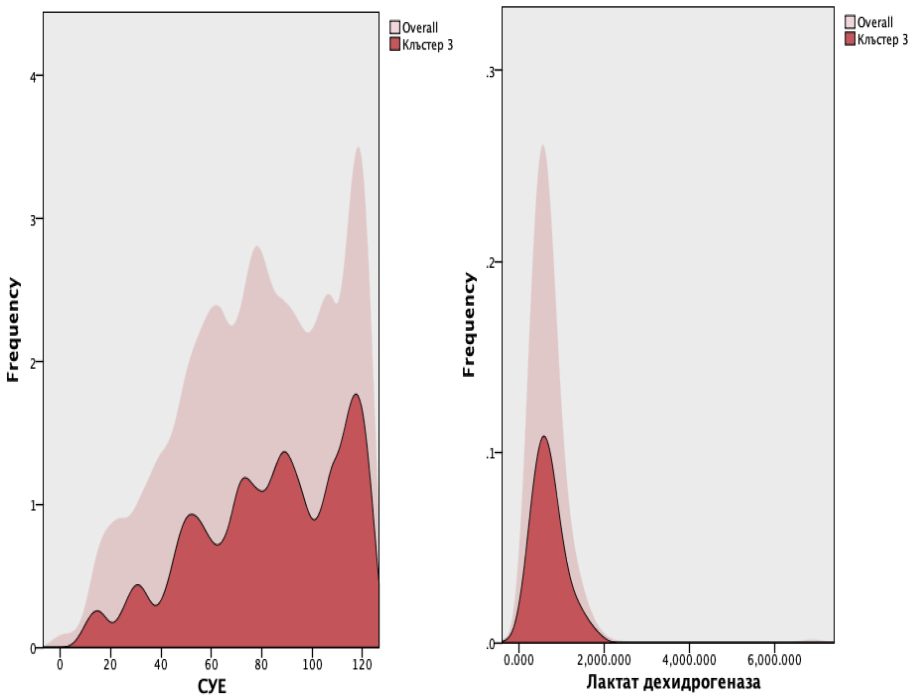
Graph №. 9 Laboratory parameter values in Cluster 3 of the COVID-19 group compared to the whole group


Overall
3
Frequency
2.0
1.5
1.0
.5
.0
0
250
500
750
1,000
1,250
D-dimer


Overall
3
Frequency
2.0
1.5
1.0
.5
.0
0.00
100.00
200.00
300.00
400.00
500.00
CRP


Overall
Клъстер 3
Frequency
.1
.0
.0
.0
0.00
10,000.00
20,000.00
30,000.00
40,000.00
Феритин


Overall
Клъстер 3
Frequency
6
4
2
0
0.00
100.00
200.00
300.00
400.00
500.00
Фибриноген



The results of cluster analysis can find a clinical implementation. The mood and pain disorders assessment can be applied as a screening method to patients in the so-called "risk group" - polymorbid, elderly, with a severe disease course, ensuring that these patients are referred early and in a timely manner to the appropriate specialist for subsequent psychological or psychiatric treatment. This would help to improve the quality of life for these patients.

V. DEBATE AND DISCUSSION

Musculoskeletal pain phenomena are one of the most common clinical manifestations in COVID-19. They can be observed as an individual manifestation of the disease or in the context of symptoms from other organs and systems. They are often one of the first manifestations of the disease. Pain is the cumulative result of complex biochemical processes and is influenced to varying degrees by biological, physiological and social factors. Pain perception is not always proportional to the intensity of tissue damage or to the unwanted stimulus.The latest studies have shown that the intensity of muscle pain does not correlate with the severity of COVID-19 in patients.

Pain can trigger psycho-emotional symptoms in patients, and acute pain is known to often evoke anxiety, while chronic pain is more likely to lead to depression. The

inverse relationship is also possible, depression in turn can cause abnormal pain perception and modulation, with an increased risk of developing chronic pain.

The results of the current study clearly show that patients with moderate to severe COVID-19 experience joint and muscle pain. The observed severity of muscle and joint pain, as measured by mean VAS values, is significantly above the generally accepted norm of up to 4 mm and can be defined as "moderate" pain. Musculoskeletal pain in COVID-19 patients is also significantly determined by the psycho-emotional attitudes of the patients, with the degree of anxiety (anxiiety) and depression directly and significantly correlated with pain severity. Combining the two indicators, anxiety and depression largely determined the variance of musculoskeletal pain, accounting for 50.8% of joint pain and 45.9% of muscle pain variance, respectively. These results are similar to existing investigations on the influence of mood disorders on pain intensity.

On the other hand, the severity of systemic inflammation is not always a reliable marker of the intensity of pain symptoms in patients with musculoskeletal involvement in COVID-19. Our results also showed no association between the inflammatory markers and the severity of musculoskeletal pain in patients with moderate or severe COVID-19.

Another significant factor affecting pain perception is the age of the patients. It is known that with advancing age, the risk of depression and anxiety increases, especially when associated with illness, which lowers the pain threshold and alters its perception. It should be noted that chronic pain occurs significantly more frequently in the older population, and we know that this group of patients is at higher risk of developing a severe form of COVID-19. When interpreting our results, it is necessary to keep in mind that patients older than 60 years of age represent a significantly higher proportion than younger patients in the study group (63.3%). This fact alone could explain the higher level of anxiety and depression, especially when adding the available COVID-19 disease.

An important factor is also gender difference, which influences both the perception and severity of pain and the impact of analgesic therapy. Although no gender predominance was found in the group of COVID-19 patients studied, women reported

significantly more pain than men. A significant difference was found between the mean VASm and VASa values in men and women (10.2 mm and 9.9 mm resp.).

Assessment of depressive and anxiety symptoms, joint and muscle pain scores, and age allowed for the formation of a subgroup of COVID-19 patients treated in inpatient settings who needed specific psychological interventions or psychiatric treatment. The presence of social support in this group further assists their treatment process. In the present study, the applied cluster analysis shows that such a subgroup of COVID-19 patients constitutes almost half of the total sample.

Assessment of mood disorders and pain can be applied as a screening method to patients in the "at risk group" - polymorbid, elderly, with severe ongoing illness, ensuring that these patients are referred early and in a timely manner to the appropriate specialist for further psychological or psychiatric management**.**

VI. CONCLUSIONS

1. The COVID-19 patients included in the study cohort had a mean age of 65 years or older, high infamatory markers, prominent pain symptoms, and extensive psychoemotional mood disorders - anxiety and depression.
   1.1. All COVID-19 patients enrolled in the study had joint or muscle pain. Pain assessment with VAS showed that only 2.6% of patients had no joint pain and 5.1% had no muscle pain. All other patients in the sample had both joint and muscle pain.
   1.2. In COVID-19 patients, muscle pain slightly outweighed joint pain (VAS-m= 43.0 mm vs. VAS-a= 42.36 mm). In the group of patients with IJD, joint pain was more severe than muscle pain (VAS-m=35.32 mm vs. VAS-a=42.43 mm)
   1.3. Pain perception in the investigated cohort of COVID-19 patients is associated with:
      - Age - as patients get older they evaluate pain sensations more intense;
      - Anxiety and depressive states - more anxious and depressed patients rate pain higher. Our results showed that anxious and depressive symptoms in COVID-19 patients determine basically half of the variation in pain perception;
      - Gender - all analyses performed in both groups show that women rate both pain and anxiety and depressive symptoms more severely than men;
   1.4. Pain of articular and muscular origin in the investigated group of patients did not correlate with:
      - The level of inflammatory indicators:
        - EST, CRP, fibrinogen, ferritin, LDH
      - Thrombotic biomarkers:
        - D-dimer

      According to the performed analyses, all these indicators determine only about 4% of the variation of the two pain parameters. For the group of patients with IJD, this rate was higher – all inflammatory and thrombotic predictors determined about 8% of the variation in pain.

1.5. The severity of joint and muscle pain in COVID-19 patients can be effectively used to form subgroups of SARS-CoV-2-infected patients for which is needed a specific therapeutic approach.

- Moderate to severe joint and muscle pain is associated with:
  - severe depressive and moderate anxiety symptoms;
  - higher age,
  - high D-dimer
  - value (mean) of CRP >100 mg/L
  - Necessity of psychological interventions

2. Changes in psychoemotional state should be kept in mind when interpreting VAS results in COVID-19 patients because they appear as an essential part of the subjective pain assessment;
3. The analyses allow us to identify a clinically relevant subgroup of patients with COVID-19 in whom a specific therapeutic approach is needed.
4. All the results confirm the original hypothesis of the study that pain syndromes are aggravated by the presence of anxiety and depressive symptoms on the one hand, and significantly influenced by the age and gender of the patients on the other.
5. Although they were used for comparison in the study, multiple data regarding pain and the severity of anxiety and depression were collected in patients in the IJD group. These data can be used for subsequent analyses and interrelation in future work.

VII. CONTRIBUTIONS

1. Original contributions

1. Patients with rheumatologic manifestations in COVID-19 - their demographic characteristics, assessment of laboratory and clinical disease activity and evaluation of psychoemotional state are reviewed and analyzed.
2. We analyzed the association of pain with inflammatory markers, thrombogenic biomarkers, and psycho-emotional state among hospitalized patients with COVID-19 and patients with IJD
3. Acute and chronic pain are considered in a comprehensive manner and in their assessment was taken a different approach, despite inflammatory activity.
4. We proposed guidelines (algorithm) to conduct successful screening of patients in the "at risk group" - polymorbid, elderly, with severe disease, ensuring that these patients are referred early and in a timely manner to the appropriate specialist for psychological or psychiatric counseling / treatment..

2. Definitive contributions

1. The association between infmammatory markers and the evaluation of the disease activity is confirmed
2. It is confirmed that the pain evaluation depends on the gender distribution
3. It is confirmed that age has a significant impact on pain assessment
4. It is confirmed that the psycho-emotional state of the patient directly influences and determines the intensity of musculoskeletal pain manifestations.

Disadvantages of the study

The study has its disadvantages. No data were analyzed on the comorbidities of COVID-19 in the study population. These could influence both the pain intensity and the psycho-emotional status of the patients. Differences in therapeutic algorithms to which patients are subjected are also not taken into account, as medications could also influence the psychosomatic status of patients (such as the administration of high

doses of corticosteroids). Another shortcoming that we report is that patients were assessed at one point in time, i.e., there was no follow-up after dehospitalization to ascertain the extent to which patients developed residual symptomatology (musculoskeletal and/or psychoemotional). Finally, the lack of quality of life assessment in these patients is reported as a drawback. All of these weaknesses of the present research work would warrant future researchers who would shed more light and provide greater clarity on the role of the psycho-emotional state and the perception of pain, as well as the various factors by which it is determined.

- **Publications related to the dissertation work**

- Мускулно-ставна болка при болни от COVID-19, Богданова-Петрова С., списание Ревматология XXX, бр.2, 2022г., 3-17

- Типове болка при COVID-19 и особености на патогенетичните молекулни механизми – литературен обзор, Богданова-Петрова С., Т. Шивачева, Цв. Георгиев, П. Петров, списание Ревматология XXX, бр.4, 2022г.

Scientific forums and participations related to the dissertation work

- POS1224 Rheumatic manifestations in COVID-19 patients - single-center experience amidst the pandemic, S. Bogdanova-Petrova, T. Georgiev, G. Gerganov, S. Hristova, S. Dimitrov, T. Shivacheva, Annals of the Rheumatic Diseases, 80 (Suppl 1), 2021, 869

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