Original Paper

Clinical Features of SARS-CoV-2 Infected Patients in a Large Population Cohort from the South-West Region of Romania

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ABSTRACT: SARS-CoV-2 infection was first detected in Wuhan City, Hubei Province, China, in the last months of 2019 as an atypical pneumonia, from where it rapidly spread worldwide causing the most severe pandemic of the 21st century. The disease had a complex symptomatology, with clinical signs of pulmonary impairment, frequently accompanied by digestive, renal, cardiovascular or nervous signs. In the present study, we aimed at analyzing a group of 5649 patients, aged between 3 and 104 years old, diagnosed with Covid-19 and hospitalized within the Clinical Hospital of Infectious Diseases in Craiova between 2020-2022. In Romania, the first cases of COVID-19 started in the first quarter of 2020. Our study revealed that, in the first year of the pandemic, 1404 (24.85%) patients were hospitalized; in 2021, 3670 (64.97%) patients were hospitalized, and in 2022, as a result of prophylaxis measures and the introduction of the anti-COVID-19 vaccination, the number of hospitalized patients decreased to 575 (10.18%). SARS-CoV-2 infection affected all age groups, from children younger than 5 years of age to people over 100 years of age, but most patients (3060 patients, representing 54.17% of the whole investigated group) were aged between 55 and 75 years old. Regarding sex, we found that the disease affected both sexes equally. The most common clinical signs were: cough and temperature change, each present in 62% of the total group of patients and dyspnea present in 29% of patients. The most common comorbidities were cardiovascular disease (39%), diabetes mellitus (9%) and chronic lung disease (10.21%).

KEYWORDS: *COVID-19, SARS-CoV-2, inflammation, respiratory symptoms, non-respiratory symptoms, sex distribution.*

Introduction

At the end of 2019, an infectious disease with a severe, often fatal course, predominantly affecting the respiratory tract, causing severe pneumonia, was detected in Wuhan city, Hubei province, China.

Subsequent studies showed that the disease was caused by a new virus of unknown origin, a beta coronavirus variant, which had 80% genomic identity with SARS-CoV-1 and 50% genomic identity with the Middle East respiratory syndrome coronavirus called MERS-CoV.

This new virus was named SARS-CoV-2 as it caused a severe acute respiratory syndrome in infected humans and COVID-19 [1-3].

The new virus was shown to be highly contagious, with COVID-19 disease spreading rapidly around the world with significant morbidity and mortality [4-6].

The rapid transmission of the disease and the development of severe forms not only caused huge strains on public health systems, but severely disrupted financial markets, society as a whole and the global economy.

All this compelled the World Health Organization (WHO) to declare COVID-19 a global pandemic on March 11th 2020.

SARS-CoV-2 virus has an increased ability to replicate in airway epithelial cells and pneumocytes, causing pneumonic outbreaks and, in severe cases, acute respiratory distress syndrome (ARDS) [3,8,9].

Virus entry into cells is mediated by angiotensin converting enzyme 2 (ACE2), which serves as a cellular receptor for the virus [10,11].

After the virus entry into cells, a local inflammatory reaction is triggered and ACE2 detaches from the cell membrane, increasing serum angiotensin II concentrations,

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exacerbating inflammation, vasoconstriction and vascular thrombosis [12].

The clinical manifestations of Covid-19 disease are numerous and vary significantly from one person to another. Generally, they included fever, anosmia, chest pain, fatigue, myalgias, nasal congestion, etc. [13,14].

Clinical studies indicated that children and young adults infected with SARS-CoV-2 were often asymptomatic, whereas older individuals were presented with more severe forms of the disease. The presence of comorbidities increased the risk of death among people affected by COVID-19 [15].

Although this pathogen most commonly affects the respiratory system, symptoms can be polymorphic because SARS-CoV-2 can also affect other systems or organs, such as the gastrointestinal system, kidneys, pancreas, cardiovascular system or central nervous system (CNS).

AIM

This study aimed to highlight the key clinical aspects of SARS-CoV-2 infection in a large population sample from the South-West region of Romania.

Material and Methods

All patients diagnosed with COVID-19 and hospitalized at the Clinical Hospital for Infectious Diseases in Craiova between 2020 and 2022 were included in the study. The cohort consisted of 5,649 patients, aged between 3 and 104 years.

Patients presented with mild, moderate, and severe forms of the disease, or were asymptomatic but tested positive via real-time reverse transcriptase polymerase chain reaction (RT-PCR). Patients with mild symptoms or asymptomatic cases were hospitalized as a precautionary measure to prevent the spread of SARS-CoV-2, in accordance with Decision No. 3 of 28.02.2020 issued by the Romanian National Committee for Special Emergency Situations on managing infections with the novel coronavirus. The study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova (no 177/14.09.2003).

All medical data were obtained from the clinical observation sheets of hospitalized patients. Data were initially recorded in plain text format, processed using MATLAB (MathWorks, USA), and subsequently exported to Microsoft Excel for statistical analysis. Since all data were categorical, the chi-square test was employed for statistical comparisons. A p-value of <0.05 was considered statistically significant.

Results

In Romania, the COVID-19 pandemic began in the spring of 2020, and the number of SARS-CoV-2 positive and hospitalized patients increased towards the end of the year.

In 2020, 1404 (24.85%) patients were hospitalized in the Infectious Diseases Hospital of Craiova, COVID-19 department.

In 2021, 3670 (64.97%) patients were hospitalized, and in 2022, as a result of prophylaxis measures and the introduction of anti-COVID-19 vaccination, the number of hospitalized patients was reduced to 575 (10.18%) (Figure 1).

Also, from Figure 1, it can be seen that the distribution of hospitalized patients by gender was almost equal during each year of the study.

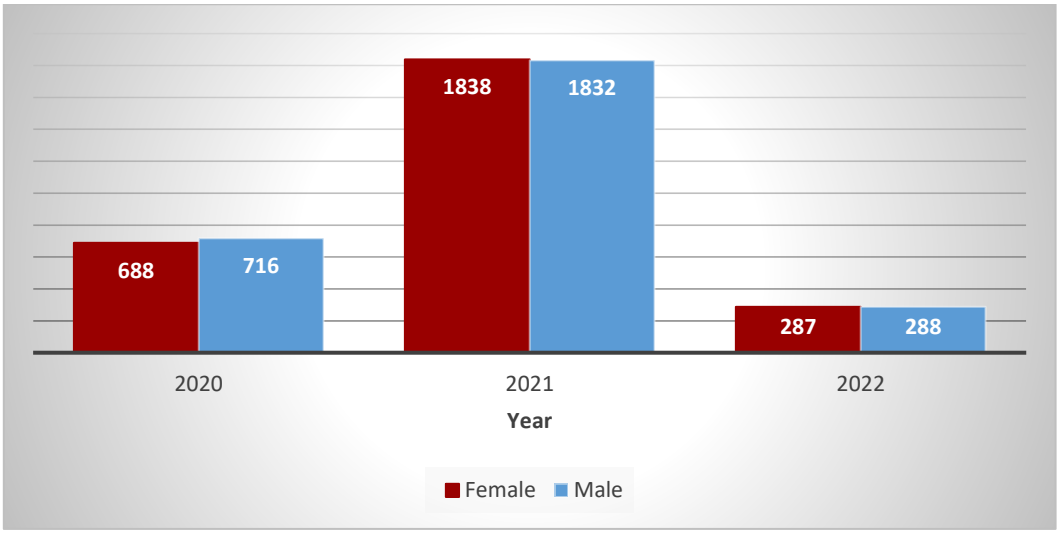

Figure 1. Yearly Distribution of SARS-CoV-2 Hospital Admissions.
The chi-square statistic is 0.4763. The p-value is 788078. The result is not significant at p<05.

An essential aspect that we investigated was the distribution of the group of patients infected with SARS-CoV-2, depending on age, given that the immune defense decreases with age, and viral infections predominantly affect those with a low immune defense system. The data we obtained showed that SARS-CoV-2 infection affected all age groups, from children under 5 years old to people over 100 years old.

There was a positive correlation between the number of Covid-19 cases and the age of the patients, with most Covid-19 cases (3060 patients, representing 54.17% of the entire investigated group) being registered in the decades between 55 and 75 years old (Figure 2).

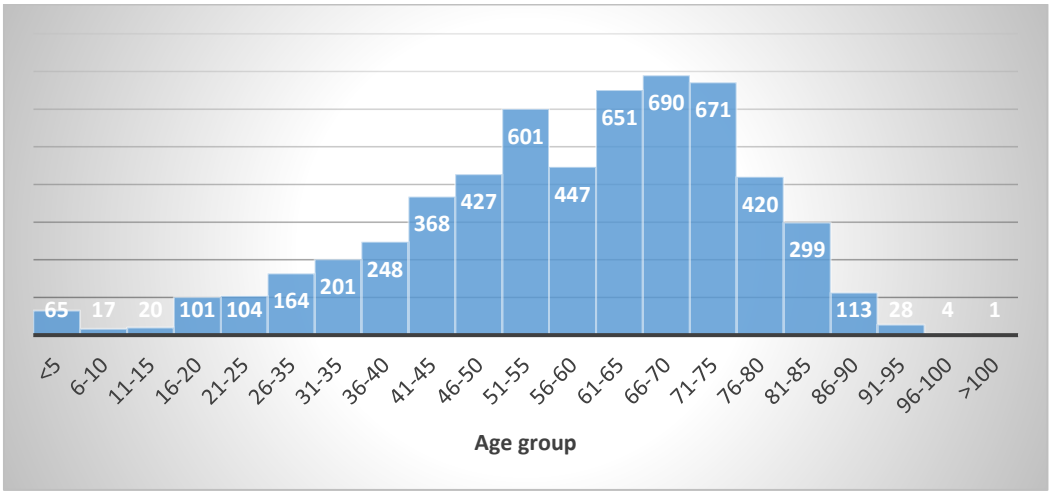

Figure 2. Age Group Distribution of SARS-CoV-2 Patients.

Regarding the distribution of the patient group by gender, our study highlighted that SARS-CoV-2 infection affected both sexes and age groups in approximately equal proportions (Figures 3 and 4), statistically insignificant (chi square test p-value=0.788078).

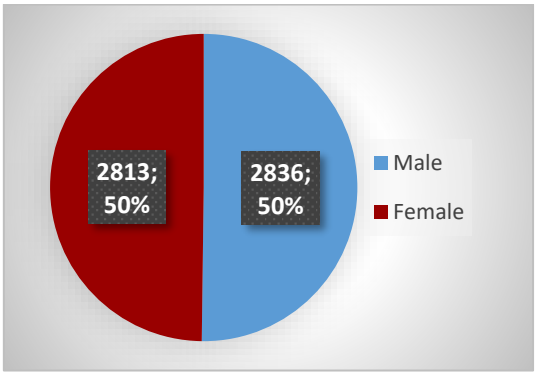

Figure 3. Gender Distribution of COVID-19 Patients.

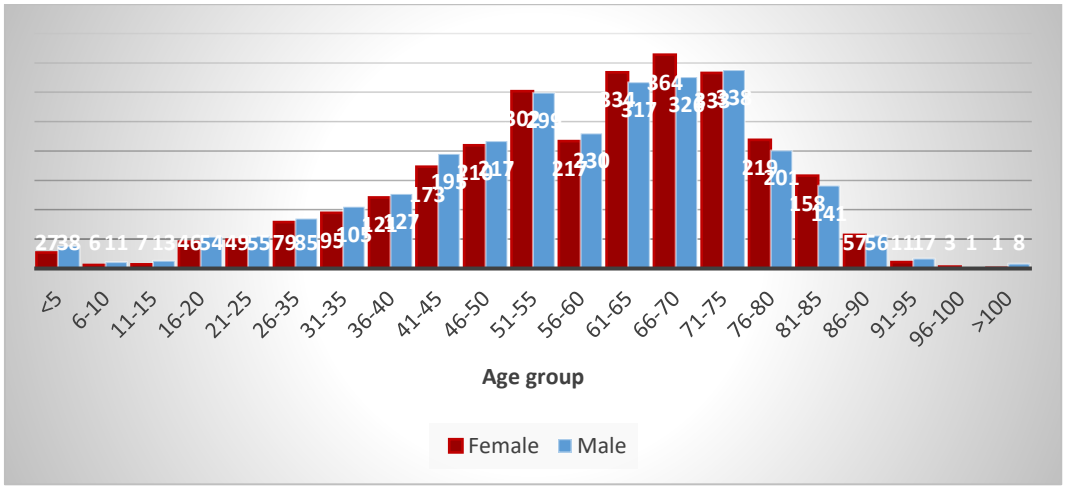

Figure 4. Age and Gender Distribution of COVID-19 Patients.

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The clinical symptoms and signs of patients infected with SARS-CoV-2 and hospitalized in the Clinical Hospital of Infectious Diseases in Craiova were complex, with most patients presenting a multisystemic involvement including a plethora of non-respiratory symptoms. After the clinical predominance of symptoms, the respiratory system was most frequently affected, with over 67% of cases.

Most often, the disease began as rhinitis or nasopharyngitis, with a slightly altered general condition, which led many patients to seek late medical attention and thus favoring the dissemination of the virus in the environment, but also the progression of the infection towards the lower respiratory tract.

The most frequent clinical signs indicating respiratory tract involvement were: cough and temperature changes (low fever, fever) present in 62% of the total group of patients (Figures 5 and 6).

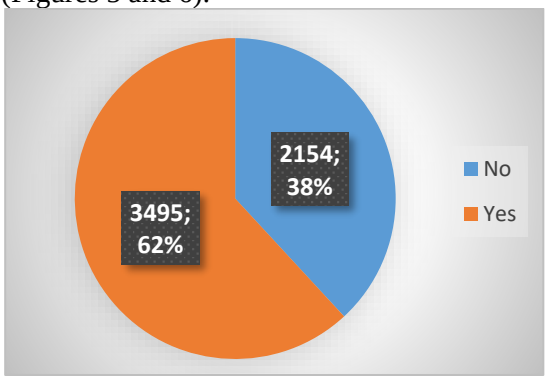

Figure 5. Cough as the Most Common Symptom in COVID-19 Patients.

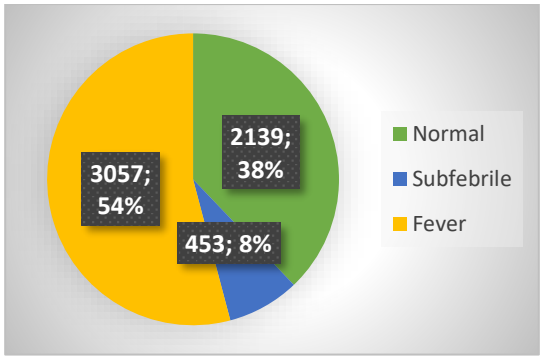

Figure 6. Temperature Changes (Fever and Subfebrile) in COVID-19 Patients.

Most patients presented a dry, irritating or mucous cough. Other clinical signs indicating respiratory tract damage were: dyspnea present in 1653 (29%) patients (Figure 7), polypnea present in only 65 (1%) patients, chills present in 1502 (27%) patients (Figure 8), sweating present in 637 (11%) patients (Figure 9), chest pain-present in 403 (7%) patients.

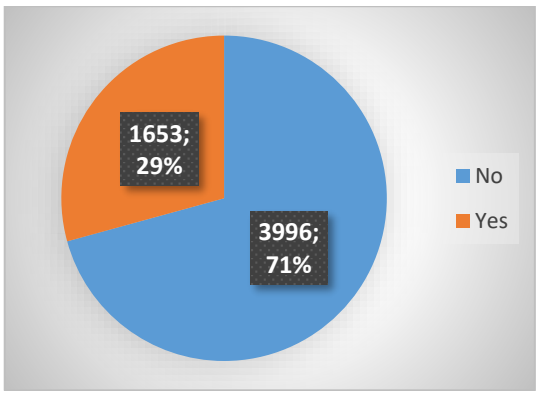

Figure 7. Incidence of Dyspnea in COVID-19 Patients.

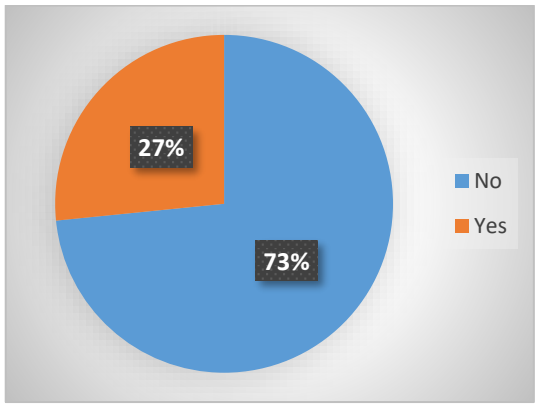

Figure 8. Incidence of Chills in COVID-19 Patients.

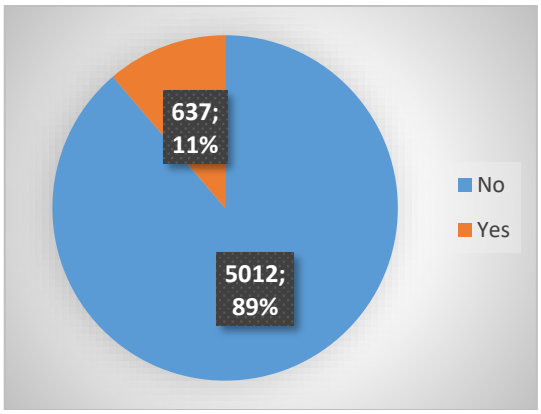

Figure 9. Incidence of Excessive Sweating in COVID-19 Patients.

The positive diagnosis of pulmonary damage was based on the positive reaction in RT-PCR, on oximetry through which we measured oxygen saturation in the blood (Figure 10) and on the x-ray or computed tomography (CT) examination.

Oximetry and imaging examinations provided interesting data regarding the degree of lung damage.

In the present study, a number of 440 (8%) patients presented low oximetry values upon admission (Figure 10).

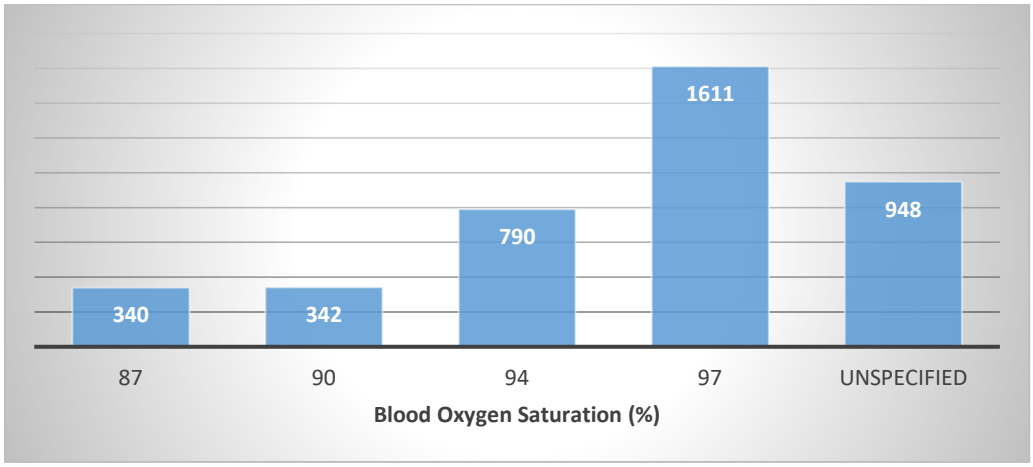

Figure 10. Blood Oxygen Saturation on Admission.

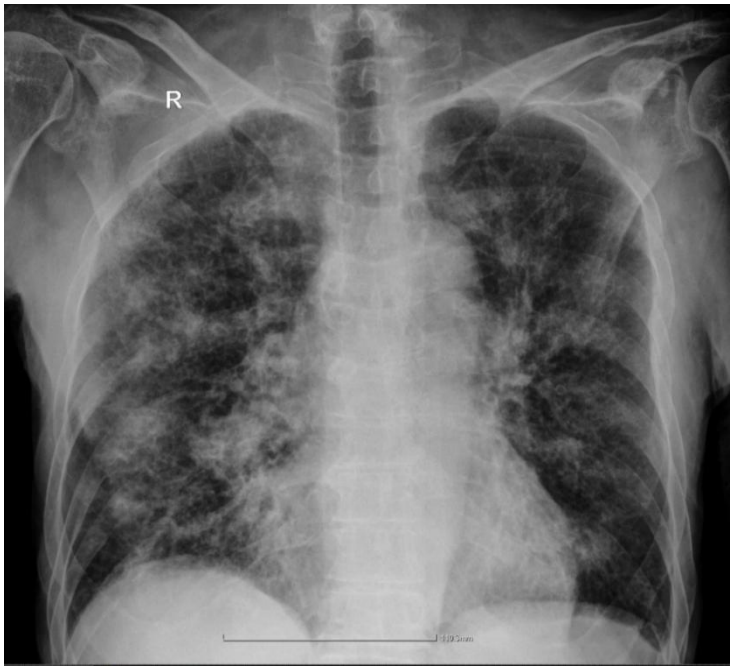

Figure 11. Mediastinal-pulmonary radiological image, containing several heterogenous pulmonary condensations with a "ground glass" aspect disseminated across both lung areas.

The x-ray examination in moderate or severe forms of the disease showed unsystematic pulmonary condensations with a "ground glass" aspect (Figure 11).

In mild forms of the disease, only CT revealed small areas of pulmonary condensation.

A second group of patients consisting of 2453 people, representing 43% of the entire study group, also presented various clinical signs of digestive impairment (abdominal pain, loss of appetite, dysphagia, vomiting, nausea, postprandial bloating, diarrheal stools, epigastralgia, etc.) (Figure 12).

Neurological signs (headache, anosmia, dizziness, asthenia, dysphonia, anxiety) were identified in a number of 810 (14%) patients (Figure 13).

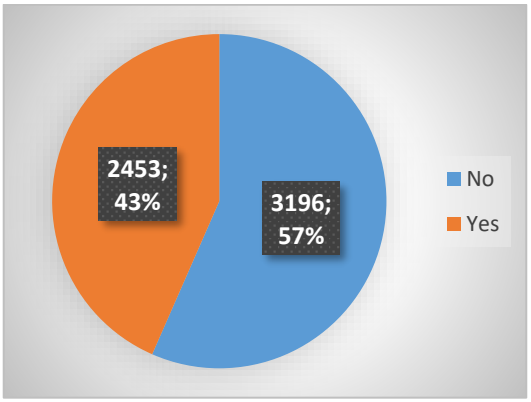

Figure 12. Incidence of Digestive Symptoms in COVID-19 Patients (Abdominal Pain, Loss of Appetite, Dysphagia, Vomiting, Nausea, Bloating, Diarrhea, Epigastralgia).

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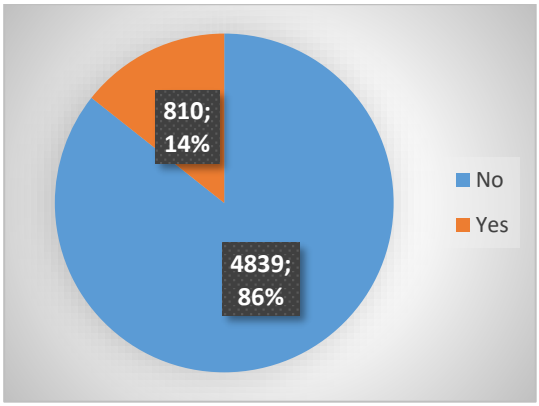

Figure 13. Neurological Symptoms in COVID-19 Patients (Headache, Anosmia, Dizziness, Asthenia, Dysphonia, Anxiety).

Comorbidities were recorded in patients infected with SARS-CoV-2. In our study, the most common chronic conditions (comorbidities) recorded in patients with COVID-19 were:

- cardiovascular diseases; out of the entire group of 5649 patients, 2228 (39%) of them were known to have a cardiovascular disease (heart failure, hypertension, ischemic cardiopathy, cardiomyopathy, atrial fibrillation, bundle branch block, myocardial infarction) (Figure 14);
- diabetes mellitus was present in 484 (9%) patients (Figure 15);
- chronic lung diseases-10.21% (bronchial asthma-177 (3.23%) patients; COPD-135 (2%) patients; pulmonary emphysema 104 (2%) patients, TB 87 (2%) patients; pulmonary fibrosis-74 (1%) patients;
- neurological diseases 230 (4%) patients
- liver diseases-222 (4%) patients;
- chronic digestive diseases (gastritis, rectocolitis, Chron's disease)-59 (1%) patients;
- chronic kidney diseases-58 (1%) patients.

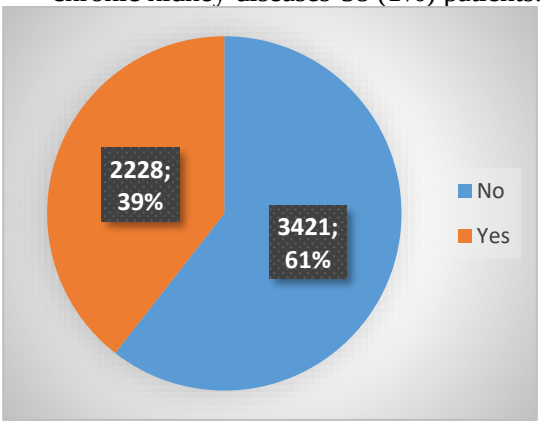

Figure 14. Cardiovascular Comorbidities in COVID-19 Patients (Hypertension, Ischemic Heart Disease, Cardiomyopathy, Atrial Fibrillation, Bundle Branch Block, Myocardial Infarction)

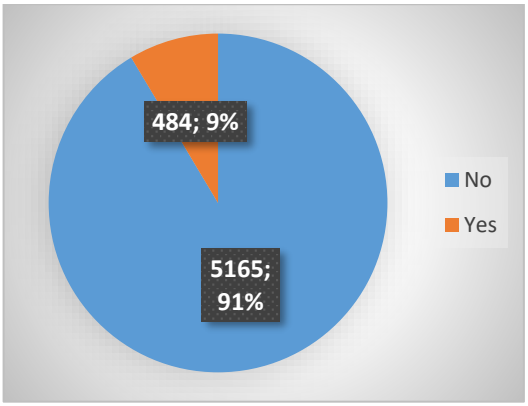

Figure 15. Diabetes as the Second Most Common Comorbidity in COVID-19 Patients.

Discussions

As a global pandemic, COVID-19 has also spread rapidly in Romania, resulting in 5,649 hospitalizations in a single medical center in Craiova between 2020 and 2022. The large number of hospitalized patients caused an intense pressure on the Romanian healthcare system, which prioritized COVID-19 over other conditions. As in other regions of the world, the disease predominantly affected the respiratory system, but often affected multiple systems (digestive, cardiovascular, urinary, nervous), sometimes presenting polymorphic symptoms [16-18].

In our study, the disease had complex symptoms and signs, with clinical signs of pulmonary involvement frequently accompanied by digestive signs. It is believed that the systemic involvement is largely due to an intense inflammatory response, which manifests itself not only in the respiratory system, but also has profound effects on the cardiovascular, digestive, renal, and neurological systems [19,20].

In the vast majority of cases, the disease began as a moderate inflammatory process of the upper respiratory tract, with clinical signs similar to influenza (fever, cough, altered general condition, difficulty in breathing), dyspnea or polypnea, chest tightness, subsequently affecting the lower respiratory tract or other systems and organs [21,22].

We believe, like other authors, that the predominant involvement of the respiratory system is due to the richness in receptors for SARS-CoV-2, namely the angiotensin-converting enzyme 2 (ACE2). ACE2, called the ACE2 “receptor”, is a cell surface protein that provides the entry point for the coronavirus into a wide range of human cells that it infects. The penetration of the virus into

cells causes direct viral damage and a dysregulated immune response [23,24].

ACE2 is abundantly expressed on the surface of cells in the respiratory tract (nasal and bronchial epithelial cells, goblet cells, ciliated cells) [25-28], but also in cells of the cardiovascular system, digestive tract, kidney, liver and central nervous system [29,30] which explains the diverse range of clinical signs and symptoms present in patients with COVID-19.

In addition to ACE2, there are other receptors or co-receptors (such as neuropilin-1 (NRP1) and transmembrane serine protease 2 (TMPRSS2),) that facilitate the entry of SARS-CoV-2 into host cells. Co-expression of these receptors in different tissues enhances the ability of the virus to infect multiple organ systems, further contributing to the systemic effects of the disease [31,32].

In our study, the most common clinical signs that indicated respiratory tract involvement were cough and temperature changes (subfebrile, fever) in 62% of SARS-CoV-2 infected patients. Other studies reported that the most common clinical symptoms reported were fever, dry cough, fatigue, dyspnea, anosmia, agueusia or a combination of these [8,33,34].

Regarding the sex of patients, in our study we found that both sexes were equally affected by SARS-CoV-2 infection, but other studies found differences related to sex. Thus, De Souza et al. (2020) in Brazil found more males infected with SARS-CoV-2 compared to females, while Gomes et al. (2024) also in Brazil found a higher proportion of females with COVID-19 compared to males [35,36].

In a study by Lai et al, (2019) the most common symptoms were fever (60.9%), myalgias or fatigue (60.0%), cough (56.4%), sore throat (50.0%) and muscle aches (45.5%) [37], while Nguyen et al. (2020) found that loss of smell or taste, fatigue, persistent cough, and loss of appetite predict COVID-19 positivity with high specificity using logistic regression and pre-test symptoms [38].

A particular aspect of the group of patients we studied was their age. It was found that young children and adolescents were less affected by SARS-CoV-2 infection compared to adults. More than half of the patients (54.17%) were aged between 55 and 75 years old. The increased incidence of COVID-19 disease with increasing age can be explained by longer exposure to risk factors, neglect of personal protective measures, accumulation of comorbidities that reduce immune defense. We also believe that the immune defense and reactivity of every individual organism had an influence on the severity of symptoms and the disease in general, as we had asymptomatic (oligosymptomatic), mild, moderate or severe cases in all age groups. The severity of symptoms of patients with COVID-19 is classified according to National Institutes of Health (NIH) criteria as asymptomatic, mild, moderate, severe, and critical or death [39,40].

In acute respiratory distress syndrome (ARDS), the clinical symptoms of COVID-19 often presented as flu-like symptoms with high fever, cough, shortness of breath, chest tightness, muscle aches and profound alterations in general health state [20].

Severe forms of the disease, including ARDS, resulted from a 'cytokine storm', characterized by an excessive release of inflammatory cytokines [41-43].

SARS-CoV-2 infection was shown to have an impact on innate immunity, typically triggering an increase in innate immune cells such as neutrophils and Natural Killer (NK) cells that result in an exaggerated immune response [44,45].

According to some studies, 'cytokine storms' and immune dysregulation are the primary causes of severe forms of COVID-19 [46,47].

Conclusions

Patients infected with SARS-CoV-2 exhibited complex and multifaceted symptomatology, highlighting the virus's tropism for multiple organ systems, including the respiratory, gastrointestinal, cardiovascular, renal, and central nervous systems.

In this study, the respiratory system was the most commonly affected, followed by the cardiovascular system, digestive, and nervous systems.

The infection impacted both men and women in approximately equal proportions.

SARS-CoV-2 infection affected individuals across all age groups, ranging from a 3-year-old child to individuals over 100 years of age, with infection incidence increasing with age.

The most prevalent comorbidities observed in patients with COVID-19 were cardiovascular diseases, diabetes, and chronic lung diseases.

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Conflict of interests

None to declare.

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