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FROM TIMISOARA
FACULTY OF MEDICINE
DEPARTMENT IX SURGERY I**

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PhD THESIS

**THE ASSOCIATION BETWEEN BIOLOGICAL
PARAMETERS AND IMAGING STUDIES WITH SEVERE
FORMS OF SARS-COV-2 INFECTION**

- A B S T R A C T -

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**Timișoara
2023**

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CHAPTER 1. INDIVIDUAL CHARACTERISTICS AS PROGNOSTIC FACTORS OF THE EVOLUTION OF HOSPITALIZED COVID-19 ROMANIAN PATIENTS: A COMPARATIVE OBSERVATIONAL STUDY BETWEEN THE FIRST AND SECOND WAVES BASED ON GAUSSIAN GRAPHICAL MODELS AND STRUCTURAL EQUATION MODELING

BACKGROUND

The COVID-19 pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was first reported in Wuhan, China in late 2019 and quickly spread worldwide, leading to a public health emergency. Coronaviruses are a group of RNA viruses that cause respiratory infections in humans, ranging from mild to severe forms. SARS-CoV2 has been isolated from various bodily fluids and tissues and is associated with a range of biological markers that indicate disease severity. The aim of this study is to investigate how hospitalized COVID-19 patients recover based on individual characteristics, disease form, comorbidities, and treatment methods. The study will explore epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and outcomes of hospitalized COVID-19 patients. The study will use a modern methodology based on network analysis through Gaussian graphical models and structural equation modeling to provide new evidence on how patient evolution can be improved through comprehensive approaches tailored to individual features and treatment methods. Despite improvements in treatment, the second wave of the pandemic has shown a more aggressive virus with higher mortality and more severe cases. This study aims to provide robust evidence for a two-fold research endeavor, combining clinical/medical observations of COVID-19 patients with a complex econometric assessment of the interlinkages between patient evolution, personal traits, and treatment methods applied.

RESULTS

In the first wave of infection, 145 patients were analyzed, while in the second wave of SARS-COV2 infection we examined 129 patients. Symptomatology at the onset of SARS-COV2 infection and during hospitalization are summarized in a comparative approach between the two waves of infection. Patients in the first wave of COVID-19 infections were treated with: antivirals (25.65% of them with lopinavir + ritonavir), 24.58% with darunavir + cobicistat, 41.13% with darunavir + ritonavir, and 28.96% with hydroxychloroquine), antibiotic therapy (azithromycin—35.17%, vancomycin—2.78%), corticotherapy—31%, anticoagulant—21.37%. The second wave, much more aggressive, brought some changes in the therapeutic behavior of patients. In addition to the antivirals used in the first batch, lopinavir + ritonavir, darunavir + cobicistat, darunavir + ritonavir were used, for the medium to severe forms that amounted to 31% remdesivir was used and for the medium forms of the disease (12.50%) favipiravir was used as an antiviral, depending on their availability. These antivirals were used in combination with immunomodulators: Anakinra—4.65% and tocilizumab—15.50% and corticotherapy—77.51%.

In case of the first wave of COVID-19 infection, GGM results entail that there is a strong positive correlation between the evolution of the patients (EP) and the COVID-19 disease form (DF) developed by the hospitalized patients, which is further positively correlated with the Rezolsta treatment scheme and inversely correlated with DRV + RTV treatment method. Further positive linkages are with age and gender of the patients (a positive connection but with a lower intensity). The evolution of the patients is strongly and inversely correlated with the symptomatology and the ICU hospitalization. Moreover, the disease form is strongly and inversely correlated with DRV + RTV treatment and further negatively correlated with oxygen saturation (SPO2) and the residence of patients (U/R, urban/rural). The symptomatology at first appearance also strongly depends on the age of the patients (positive correlation) and of the fact that the patient is a smoker or non-smoker (S/NS) and has other comorbidities (CMD).

In the second wave of COVID-19 infection, these interlinkages seem to be less intense overall and strongly relate the treatment schemes (kaletra, DRV + RTV and rezolsta) with the age of the patients as a major criterion in the evolution of the patients. Kaletra and DRV + RTV are inversely correlated with age, while rezolsta is positively correlated with the age of hospitalized COVID-19 patients. Remdesivir was also introduced in the treatment of COVID-19 patients in the second wave according to the adopted protocol, being less correlated with age and negatively connected with gender and the fact that the patient is a smoker or non-smoker and has other comorbidities. Remdesivir is also positively related with kaletra and rezolsta treatment and also with the oxygen saturation. As expected, there is a positive link between the number of hospitalized days and the number of tests until the patient is negative, as well as an inverse correlation between hospitalized days and the evolution of the patient, disease form, symptomatology and oxygen saturation.

The EBICglasso method of estimation allowed us to extract and highlight only the fundamental linkages between considered variables, in a comparative approach between the two waves. Hence, in the first wave, the disease form (DF) was essentially placed in the center of the network between the evolution of the patient (EP) (positive), comorbidities (CMD) (positive), symptomatology (SFA) (positive), DRV + RTV (negative) and rezolsta (positive) treatment, ICU hospitalization (negative), oxygen saturation (SPO2) (negative) and age (positive). In the second wave, the network was configured having the evolution of the patient (EP) in the center and surrounded by disease form (DF) (positive), age (positive), ICU (negative), and oxygen saturation (negative), symptomatology (negative).

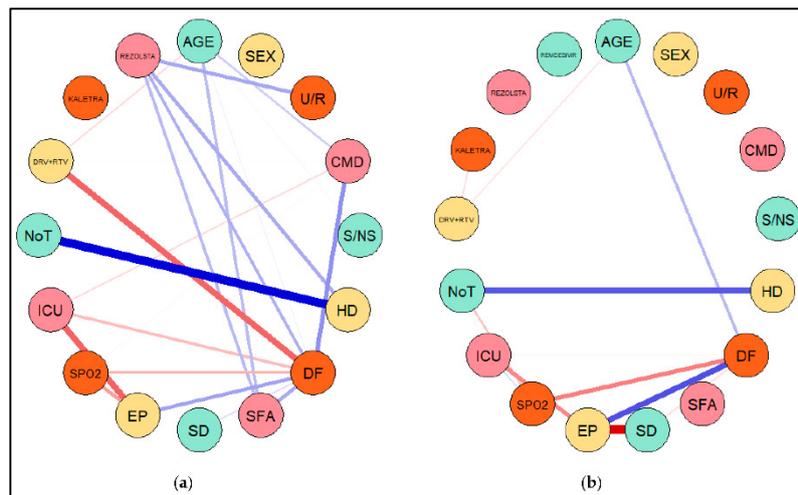


Figure 1. GGMs configuration through the EBIC with graphical lasso method and the associated results.

SEM results bring additional empirical evidence to attest that age, gender, disease form and treatment schemes/protocol significantly shape the evolution of the COVID-19 patients. By analyzing SEM results we note that in the first wave of infection the treatment schemes tend to have an inverse impact on the evolution of the patient (negative estimated coefficients of -0.034 for DRV-RTV, -0.015 for kaletra, and -0.048 for rezolsta, significant at 1% and 5% thresholds. The positive estimated coefficients of 0.072 for DRV + RTV, 0.046 for kaletra, 0.101 for rezolsta and 0.006 for remdesivir—introduced to hospitalized patients considered in our analysis as a treatment protocol in only in the second wave of infection). At the same time, in the case of both waves (both samples) age and gender positively shape the evolution of hospitalized. The form of disease was also positively associated in a causal relationship with the evolution of the patients in both waves of infection (positive estimated coefficients of 0.041 in the first wave. The fact that patients needed ICU hospitalization negatively impacted the evolution of the patient in both waves, as expected (negative estimated coefficients of -0.488 in the first wave. We allowed for a correlation between ICU hospitalization, oxygen saturation disease form and the age of the patients in a further impact

upon the evolution of the patients and the results brought additional evidence of the interlinkages between these credentials (both positive and negative). All considered variables had a notable impact on the evolution of the COVID-19 hospitalized patients in the case of both waves of infection. These results reinforce previous GGM estimations, as well as the detailed clinical/medical observation and the medical investigations of the patients.

Summarizing, main finding of our research entail that patients in the first wave of infections had a mild form of the disease, with minor symptoms, few of them requiring oxygen therapy. At the same time, patients belonging to the second wave had a much more aggressive form of the disease, with many complications (inaugural diabetes mellitus, hypertension, hematomas located in different areas, pulmonary thromboembolism), many of them had an oxygen saturation at admission into the hospital less than 93% and at discharge a relatively high number of the patients needed O2 concentrator at home. Patients who had severe form of pneumonia remained with pulmonary fibrosis.

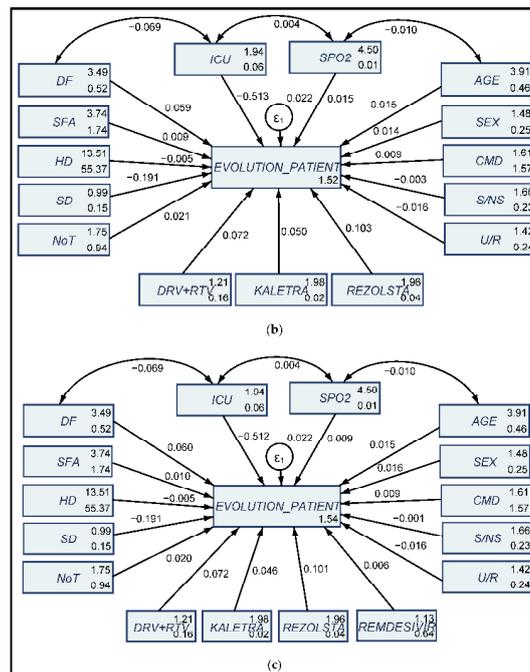


Figure 2. SEM results obtained through the maximum likelihood estimation method.

CONCLUSIONS

The research therefore brings new evidence to strengthen the knowledge in this field and presents a comprehensive two-fold assessment (medical observation/investigation and econometric modeling through GGMs and SEM) of the evolution of COVID-19 patients in a particular setting, predefined framework, as largely detailed within the paper. Both advanced methods to modeling longitudinal data, GGMs and SEM, have provided important insights on the specific ways in which the individual features of the patients and the specific treatment methods applied can positively influence the evolution of COVID-19 patients. These complex and modern research methods are complementary, hence combined in such a way as to enhance the qualities of each other, each trying to discard the other's limits, so that the final estimations are accurate, robust, and correctly interpreted and support the conclusions drawn. In case of the first wave of COVID-19 infection, GGM results entail that there is a strong positive correlation between the evolution of the patients and the COVID-19 disease form, which is further positively correlated with the treatment scheme.

CHAPTER 2. A RETROSPECTIVE ASSESSMENT OF LABORATORY FINDINGS AND CYTOKINE MARKERS IN SEVERE SARS-COV-2 INFECTION AMONG PATIENTS OF ROMA POPULATION

BACKGROUND

COVID-19 has had a devastating impact on communities worldwide, but some groups have been disproportionately affected by the disease. The Roma community is one such group that has experienced severe consequences due to the pandemic. Previous research has shown that the Roma population is one of the most underprivileged and undeveloped minority groups in Europe, with worse health outcomes compared to the general population. From a syndemic perspective, their health outcomes are influenced by a combination of genetic differences, lifestyle factors, and social underdevelopment. Studies have also indicated higher rates of substance use among Roma populations, and they are more susceptible to contagious illnesses such as hepatitis, tuberculosis, and measles. In addition, some racial and ethnic groups appear to be more prone to comorbidities that predispose them to worse COVID-19 outcomes. The Roma community, in particular, faces various socio-economic challenges that make them more vulnerable to infectious diseases. Limited access to healthcare services, inadequate housing conditions, and poverty contribute to a higher rate of transmission and worse clinical outcomes. These factors, coupled with the lack of data on the dynamics of SARS-CoV-2 viral manifestations in the Roma community, have led to concerns that the Roma population may experience more severe symptoms and worse clinical outcomes than other communities.

Therefore, this study aims to investigate the clinical progression of severely infected Roma patients with SARS-CoV-2. By analyzing laboratory results and inflammatory markers, we hope to determine whether the Roma community experiences more severe symptoms of COVID-19 and worse clinical outcomes than other communities. We also seek to identify specific markers associated with severe COVID-19 in the Roma population. Insights gained from this study may help to identify underlying mechanisms that contribute to the severity of COVID-19 in the Roma population. With this information, public health officials can develop targeted interventions to prevent and manage the spread of the disease among the Roma community. In conclusion, this study is an important step towards addressing the disparities in health outcomes faced by the Roma population during the COVID-19 pandemic.

RESULTS

A total of 319 patients with severe SARS-CoV-2 infection were included in the study, where 83 of them were of Roma ethnicity, and the other 236 were Romanians. It was observed that the age groups were significantly different since admitted Roma patients with severe COVID-19 were younger than the patients in the control group (38.6% older than 65 years vs. 48.3% in the other group, p -value = 0.019). There were significantly more overweight patients in the Roma group than in the control group (57.8% vs. 40.7%, p -value = 0.023). Other significant changes were the area of residence and occupation, where there were more unemployed Roma patients, and most of them lived in the rural region (55.4%). It was also observed that high blood pressure and diabetes mellitus were significantly more prevalent in the group of Roma patients (44.6% vs. 32.2%, p -value = 0.042), respectively 38.6% vs. 22.9% (p -value = 0.005).

There were no obvious differences in the prevalence of signs and symptoms between study groups, as well as there was no difference in the treatment approach during the hospital admission of the cohort of patients included in this study. However, it was observed that the mean duration of hospitalization was significantly longer in the group of Roma patients (18.1 days vs. 16.3 days, p -value = 0.016). There were also more ICU admissions and requirements of oxygen supplementation in patients of Roma ethnicity with severe SARS-CoV-2 infection (44.6% vs. 31.8%, p -value = 0.035), respectively 75.9% vs. 64.0% (p -value = 0.046). Finally,

the mortality rate was not significantly influenced when comparing the two groups. It was observed that the complete blood count was generally altered but without statistically significant differences between the two groups of patients with severe SARS-CoV-2 infection. Regarding liver function, we observed that fasting glucose levels were significantly more elevated in the group of Roma patients, with 43.4% of patients having higher than normal glucose levels, compared with 28.8% in the control group (p-value = 0.014).

Creatinine levels at admission were also higher in the Roma population (39.8% values outside the normal range), as well as cholesterol levels were more altered (38.6% vs. 25.4%, p-value = 0.023). Similarly, the median values of laboratory findings between the comparison groups showed significant differences between the fasting glucose levels, creatinine, and cholesterol levels. IL-6 and CRP levels were significantly more elevated during admission in the group of Roma patients (43.4% vs. 28.4%, p-value = 0.012), respectively 63.9% vs. 50.0% (p-value = 0.029), as presented in Figure 5. However, it was observed that at discharge (Figure 6) that the IL-6 levels normalized when comparing the two study groups, although CRP levels remained significantly higher in the group of Roma patients (47.6% vs. 32.8%, p-value = 0.033). ESR levels were also more elevated in the Roma patient group versus the general population, with 54.0% of patients having out-of-range ESR values, compared to 38.9% (p-value = 0.034).

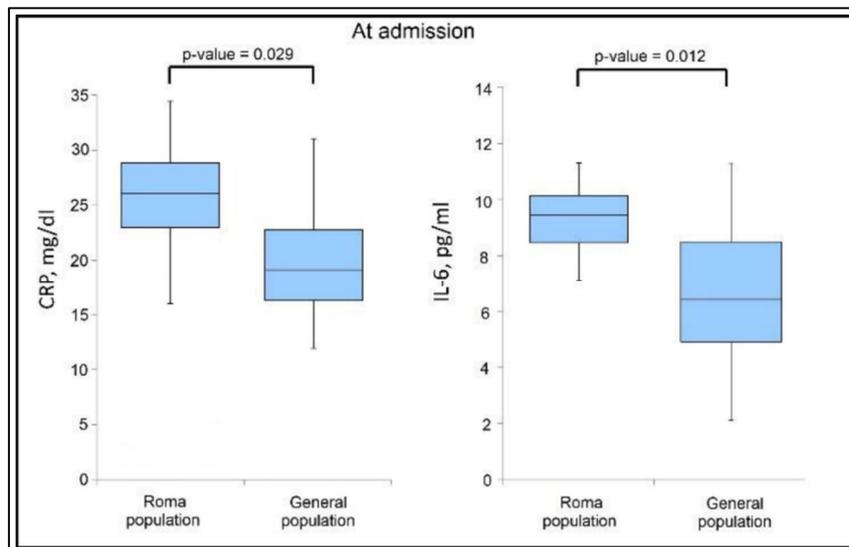


Figure 3. Boxplot of significant findings in biological parameters.

CONCLUSIONS

This study determined that being from the Roma ethnic group determines a higher likelihood of severe complications necessitating ICU admission during SARS-CoV-2 infection. IL-6 and CRP levels were significantly more elevated during admission in the Roma group, which might correlate with the higher proportion of patients being sent to the ICU. Remarkably, ICU admissions were significantly more frequent among Roma patients with severe COVID-19, but the mortality rate was not significantly higher than in the control group representing the general population with severe COVID-19. Among survivors, IL-6 levels normalized at discharge, but ESR remained elevated and significantly higher than the control group. Although several inflammatory markers were more elevated than in the general population of patients with severe COVID-19, people of the Roma minority suffer from a higher prevalence of associated comorbidities that can contribute to these negative outcomes and higher ICU admissions. Efforts should prioritize expanding access to health services and health information and be carried out in an equitable, culturally sensitive, and non-discriminatory manner utilizing evidence-based strategies such as dedicated services, health worker outreach, and specialist roles for community leaders.

CHAPTER 3. LABORATORY FINDINGS AND CLINICAL OUTCOMES OF ICU-ADMITTED COVID-19 PATIENTS: A RETROSPECTIVE ASSESSMENT OF PARTICULARITIES IDENTIFIED AMONG ROMANIAN MINORITIES

BACKGROUND

SARS-CoV-2 typically causes no or mild symptoms in most patients, but those with multiple comorbidities or who are elderly may develop severe forms of the disease and immune overactivation. Common symptoms include fever, fatigue, and a dry cough, while severe cases may lead to interstitial pneumonia, thromboembolic events, and acute respiratory distress syndrome. Excessive inflammation, driven by cytokine storms, is a defining characteristic of severe COVID-19. Researchers have investigated various pharmacotherapeutic treatments, including anti-inflammatory drugs and antivirals, with limited success. Early treatment with immunomodulators, corticosteroids, and cytokine antagonists may reduce mortality and intensive care admissions in patients with cytokine storms. Studies suggest that the Roma community may be at a higher risk of SARS-CoV-2 infection, with potential social, psychological, and economic repercussions. Some racial and ethnic groups may be predisposed to comorbidities that lead to poorer COVID-19 outcomes, and the genetic profiles of these groups may contribute to the severity of infection. However, there is a lack of data on the dynamics of SARS-CoV-2 in the Roma population. This study aims to investigate the clinical development of COVID-19 in Roma patients, including laboratory findings and inflammatory markers, in order to provide insight into the disease progression in this population.

RESULTS

A total of 71 cases were included in the analysis, and 213 controls with a 1:3 ratio and case-matched by age and COVID-19 vaccination status. The majority of patients were at retirement age, over 65 years old (>47%), being represented more often by the male gender (>54%). The body mass index of patients was statistically significantly higher among Roma patients, with more than 57% being overweight, compared with 40.7% in the control group. Other background characteristics of the study participants identified a higher prevalence of Roma patients residing in the rural regions of Romania, with significantly more of them being unemployed (38.0% vs. 25.8%, p-value = 0.049). Frequent smoking was also more prevalent in patients of Roma ethnicity (38.0% vs. 24.9%, p-value = 0.032). Another important finding was that Roma patients admitted to the ICU had more comorbidities, with 53.5% having three or more comorbid conditions, compared with 34.7% in the control group (p-value = 0.017). Moreover, 12.7% of cases vs. 12.2% of controls were immunized with COVID-19 vaccines).

The study found no statistically significant differences in signs, symptoms, and treatment for COVID-19 between the study groups. However, patients of Roma ethnicity had a significantly higher proportion of severe imaging features at admission and longer hospitalization by 1.8 days. The viral clearance had a significantly longer duration in the Roma ethnicity group, confirming the longer mean duration of hospitalization. Although not statistically significant, the median duration from symptom onset to hospital admission was shorter in the Roma group. The SOFA score and proportion of severe in-hospital complications did not differ significantly. However, the median duration of ICU stay was significantly longer in the Roma group, while the proportion of intubated patients and mortality did not differ significantly. The study found that ESR and CRP levels were significantly increased in the Roma patient group at hospital admission. Additionally, at the moment of ICU admission, the inflammatory markers worsened, increasing in a majority of patients. Lastly, the Kaplan-Meier probability curve of mortality after ICU admission between patients of Roma ethnicity and the general population showed similar risks in both groups, with no significant differences.

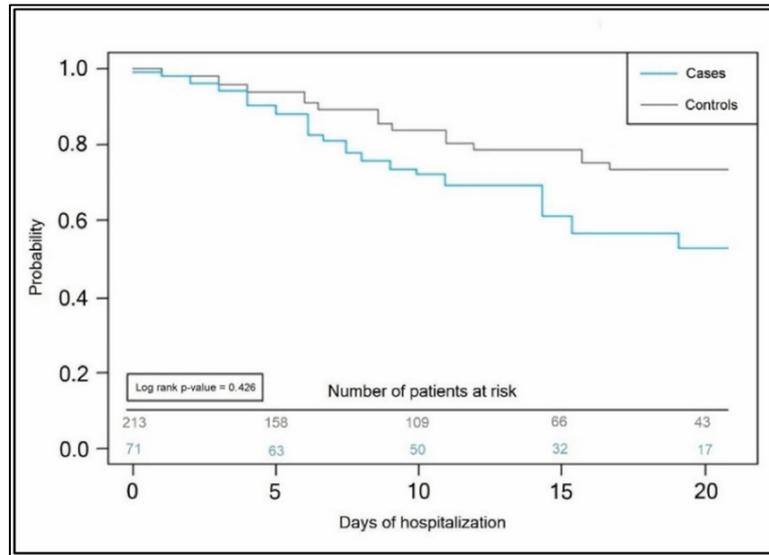


Figure 4. Kaplan–Meier probability curve of survival after ICU admission between patients of Roma ethnicity and the general population.

A multivariate regression analysis was performed to determine the influence of patients' ethnicity for elevated inflammatory markers at hospital admission. The control group from the general population was considered as the reference group for risk analysis, while CRP, ESR, and IL-6 were considered the dependent variables potentially influenced by the ethnicity of the patients. Only these inflammatory markers were considered for inclusion in the regression analysis after previously determining a statistically significant difference between the cases and control groups regarding these three serum markers. The regression was performed using a threshold for the dependent variables as the upper value of the normal range, and two times the upper value of the normal range. It was observed that the general population did not influence significantly the variation of inflammatory markers above the normal range or two times above the normal range. On the other hand, Roma ethnicity did not have a significant influence on these markers elevated one time above the normal range; however, at two times the normal range, it was shown that it influenced significantly the CRP ($\beta = 1.93$, p-value = 0.020) and IL-6 ($\beta = 1.85$, p-value = 0.044).

CONCLUSIONS

We believe that patients of Roma ethnicity exhibit particular population-specific features that manifest differently when facing a disease such as COVID-19. This study showed that Roma patients admitted to the ICU did not have more frequent first symptoms than the general population, such as fever, shortness of breath, and cough. However, they had more risk factors for mortality after intubation, which is likely to be influenced by a higher proportion of comorbid conditions and unhealthy behavior such as smoking, in this particular population. Some inflammatory markers such as ESR, CRP, and IL-6 were significantly more elevated in some of the cases, which could potentially increase the mortality rates. However, in reality, we did not observe a significantly higher rate of Roma patients being intubated or a higher mortality, which can be attributed to good, individualized treatment and management in the ICU. Additional prospective studies must be conducted in order to address more specific laboratory markers of the infected individuals that are highly correlated with a severe SARS-CoV-2 infection and to find the most effective therapy methods.

CHAPTER 4. ANGIOCATHETER DECOMPRESSION ON A COVID-19 PATIENT WITH SEVERE PNEUMONIA, PNEUMOTHORAX, AND SUBCUTANEOUS EMPHYSEMA

BACKGROUND

Between February 2020 and November 2021, a total of 5,193 SARS-CoV2 patients were hospitalized at Clinical Hospital of Infectious Diseases and Pneumology "Victor Babes" in Timisoara, with 559 deaths, comprising 2,785 men and 2,405 women. Only a small percentage of patients developed subcutaneous emphysema (1.4%), pneumothorax (0.4%), and pneumomediastinum (0.1%), with only 14 patients (0.2%) having all three complications simultaneously. In this study, we present the case of a 45-year-old man who developed these complications without mechanical ventilation, making a full recovery. While the literature suggests barotrauma during mechanical ventilation as the cause of such complications, this case is unique as the patient did not require mechanical ventilation. The patient also experienced extensive subcutaneous emphysema and required percutaneous angiocatheters to stabilize him, with full resolution in less than 24 hours. We believe that this case report is significant in adding to the existing discussions and theories about COVID-19 developments and interventions. The medical community has faced significant challenges due to severe COVID-19 pneumonia, and it is important to make such case reports public to deepen our understanding of the occurrence and management of these complications.

CASE REPORT

A 45-year-old man with grade 1 essential hypertension under treatment with a beta-blocker, Sartan, and Hydrochlorothiazide; grade 1 obesity (weighting 115 kg/182 cm height), arrived on of February 8, 2021, at the Emergency Unit Clinical Hospital of Infectious Diseases and Pneumophtisiology "Victor Babes" Timisoara with mild temperature, general weakness, and cough. The suspicion of SARS-CoV-2 infection was raised, which is why nasal and pharyngeal swabs were performed. The results came back positive for COVID-19 disease. At the onset of the disease, the patient was un-vaccinated against SARS-CoV-2.

Biological analysis and pulmonary X-ray were performed, which showed ground glass condensation. Finally, the patient was sent home with the recommendation to continue the treatment for COVID-19, containing supportive therapies (vitamin C, D3, and Zinc) and the anticoagulant drug Apixaban 2.5 mg twice daily (brand name Eliquis).

In the following days, the patient continued to have a fever and cough associated with dyspnea. On the 7th day of illness, the patient came back to the Emergency Unit, where he was hospitalized. At the admission, the patient had blood pressure (BP) = 121/82 mmHg, heart rate - 81 BPM, oxygen saturation (SpO2) = 89%, which increased to 96% - 97% after which he was administered oxygen on the mask with a flow of 9 L/minutes. He was agitated, with pale, sweaty skin and marked fatigue. The blood test results are presented in Table 1. Chest CT showed moderate pneumonia affecting approximately 50% of the lung surface. Antiviral treatment was initiated with Favipiravir 1,600 mg twice daily on day 1 of treatment, then 800 mg twice daily on day 2, corticotherapy (Dexamethasone 8 mg/2 mL 1 doze every 12 hours), Moxifloxacin 400 mg/day, gastric protector (Pantoprazole 40 mg, 1 tablet/day), Nadro-parinum 0.9 mL subcutaneous injection twice a day for 18 days, Vitamin C 2 g/day, Vitamin D3 4,000 units/ day, Zinc 15 mg/day, liver protector (Vitamin B6 and Romanian medicine Silimatina, synonym Legalon), and oxygen therapy with the mask with a tank flow of 9 L/minute.

The temperature decreased after receiving the medication, but the patient complained of insomnia, presented signs of anxiety, and increased dyspnea (SpO2 = 80%), requiring a higher oxygen flow on the mask with a tank flow of 15 L/minute. On the 9th day of the disease, immunomodulatory initiation therapy (Anakinra), antifungal (Fluconazole), Melatoninum, and Diazepam 10 mg/day was added to the existing treatment. The blood samples showed essential changes.

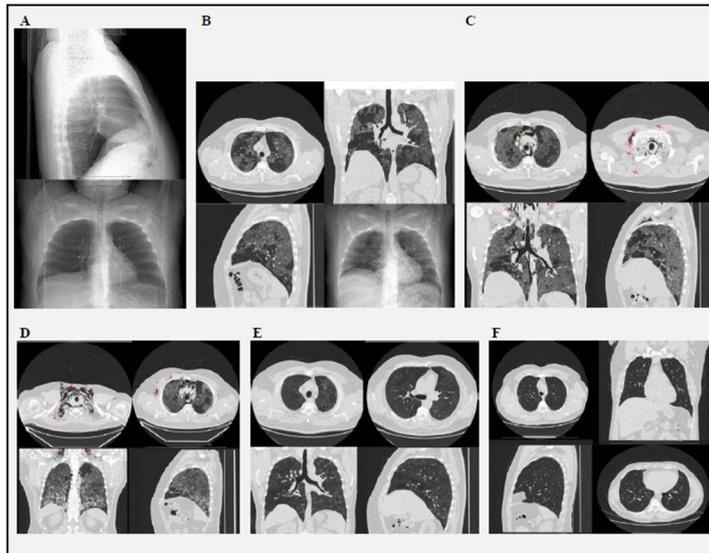


Figure 5. – X-ray and CT results of the patient, from the onset of the disease to 8 months after discharge.

On the 13th day of the disease, the patient developed subcutaneous pulmonary emphysema at the anterior thorax and bilateral lateral-cervical levels. The chest CT revealed that the lung lesions covered approximately 80% of the lung area, and there was a medium state of pneumomediastinum and light pneumothorax on the right side of the chest. The patient required thoracic surgery consultation, and on the 15th day of illness, the specialists placed angiocatheters into the chest wall. After 8 hours of the first placement, moderate decompression was noticed, and the angiocatheters were removed. A second angiocatheter placement was done 3 days later, with the patient presenting a full decompression 24 hours later. The patient's treatment was replaced by the 3rd generation of Cephalosporin (Ceftriaxone), the dose of Vitamin D3 was increased to 8,000 units/day, and Dexamethasone was replaced with Methylprednisolone.

Under this treatment course, the patient's evolution was favorable, with a decrease in the oxygen requirement on the mask and the remission of the subcutaneous pulmonary emphysema at the anterior thorax level and bilateral lateral-cervical level. CT scan was again performed on the 19th day of the disease, which highlighted the narrowing of the ground-glass areas, the appearance of peripheral peribronchial trabecular condensations (peribronchial cuffing), and the extension of the pneumomediastinum and subcutaneous pulmonary emphysema. On the 26th day of hospitalization, the patient tested negative for COVID-19 using the RT-PCR test. After two weeks, he was discharged, and the patient returned for medical evaluation at four months and eight months after hospital discharge. The long-term evolution was favorable, and the patient did not require any more oxygen therapy.

CONCLUSIONS

Our case report highlights a rare complication in a critically ill COVID-19 patient involving spontaneous pneumomediastinum, subcutaneous emphysema, and lung injury due to inflammatory reaction. The patient had underlying risk factors, including obesity, hypertension, and hyperglycemia, as well as high CRP and D-dimer levels, and lymphopenia. Pneumothorax and alveolar rupture are thought to result from diffuse alveolar damage, cystic and fibrotic changes, and increased intrathoracic pressure from continuous coughing and mechanical ventilation. Pneumomediastinum may arise from increased barotrauma and loss of lung compliance. Despite the severity of the disease, the patient fully recovered. This study contributes to the understanding of whether pneumothorax, pneumomediastinum, and subcutaneous emphysema could be predictive indicators for disease severity in COVID-19 patients without mechanical ventilation.