„CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCUREȘTI
DOCTORAL SCHOOL
PHYSIOPATHOLOGY

PhD THESIS
SUMMARY

PhD Coordinator:
PROF. UNIV. DR. DANIELA ADRIANA ION

PhD Student:
LAURENȚIU – MIHĂIȚĂ STRATAN

2024

„CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCUREŞTI
DOCTORAL SCHOOL
PHYSIOPATHOLOGY

INFLAMMATORY SYNDROME AND COAGULOPATHY ASSOCIATED WITH SARS - COV -2 INFECTION. CLINICAL, PARACLINICAL AND IMAGING CORRELATIONS AND THERAPEUTIC IMPLICATIONS

Conducător de doctorat:
PROF. UNIV. DR. DANIELA ADRIANA ION

Student-doctorand:
LAURENȚIU – MIHĂIȚĂ STRATAN

TABLE OF CONTENTS

LIST OF RESEARCH PAPERS

Published research

1. COVID-19 associated coagulopathy is correlated with increased age and markers of inflammation response
Autori: Laurențiu Stratan, Cătălin Tilișcan, Victoria Aramă, Mihai Lazăr, Angelica Vișan, Oana Ganea, Maria I. Trifonescu, Sorin S. Aramă, Daniela Ion
Published in Revista Română de Medicină de Laborator Vol. 29, Nr. 4, October, 2021, pag. 387 - 394
ISI Thomson-Reuters cu IF = 0.5
ISSN online: 2284-5623
ISSN-L: 1841-6624
Rejection rate (2020): 75%
Link: https://www.rrml.ro/articole/2021/2021_4_4.pdf

2. Real-life comparison of tocilizumab and anakinra associated with corticosteroid use in a cohort of hospitalized patients with SARS – COV - 2 infection
Autori: Laurențiu - Mihăiță Stratan, Cătălin Tilișcan, Mihai Lazăr, Constanța Angelica Vișan, Sorin Ștefan Aramă, Nicoleta Mihai, Oana Ganea, Victoria Aramă, Andreea Letiția Arsene, Daniela Adriana Ion
Web of Science Core Collection, JCR® Impact Factor – 1,6 for 2022
ISSN: 2065-0019 (for the On-Line Edition)
ISSN: 0014-8237 (for the Printed Edition)
Published in Farmacia, 2022, Vol. 70, Nr. 1
Link:https://farmaciajournal.com/wp-content/uploads/art-03-Stratan_Tiliscan_Ion_17-22.pdf

INTRODUCTION

COVID-19 is an infectious disease caused by a new coronavirus called SARS-CoV-2. Apparently different from other previously known members of the genus Coronavirinae, SARS – CoV – 2 was first identified in Wuhan, a city located in China's Hubei province. The first cases of pneumonia suspected to be caused by the new coronavirus occurred on December 8 and were subsequently reported to WHO on December 31, 2019.

In February 2020, the World Health Organization (WHO) named the disease COVID-19, short for Coronavirus Disease 2019 (1). The Coronaviridae Study Group of the International Committee on Taxonomy of Viruses proposed that this virus should be named SARS - CoV – 2, short for Severe Acute Respiratory Syndrome Coronavirus 2 (2).

Due to its high rate of transmission, the virus spread quickly, leading to COVID-19 being declared pandemic by the World Health Organization on March 11, 2020. In May 2023, WHO declared the cessation of the public health emergency of international concern caused by COVID - 19, more than three years after its emergence. By that time, the pandemic had claimed 6.9 million lives. However, the rate of new cases is still relatively high (3).

Since the beginning of the pandemic, there have been multiple theories and speculations about the pathophysiology of SARS-CoV-2 infection, with direct consequences for the initial evaluation of patients, the importance of comorbidities, the difficulty in establishing a prognosis, the discrepancies between the clinical picture of patients and the pulmonary involvement evidenced by imaging.

In light of these questions, I chose to study the inflammatory syndrome and coagulopathy associated with SARS - CoV - 2 infection and its clinical, lab, imaging and therapeutic implications. The objectives of this research were to establish correlations between the clinical picture (with emphasis on comorbidities), paraclinical results (pulmonary involvement assessed by computed tomography) and

the severity of COVID -19 and the various treatment regimens used, especially regarding the length of hospital stay.

We retrospectively followed 2 different groups of patients, from two distinct periods of the COVID - 19 pandemic, one during the initial wave (106 patients), the other during the period of dominance of the Delta variant (393 patients), the particularity being that I was directly involvement in the assessment, monitoring and therapeutic management of each patient included.

I chose these two pandemic periods, the first one due to the novelty of the disease and the decisional dynamics involved and the second one due to the impressive number of cases, their severity and the newly acquired access to various therapeutic regimens, including immunomodulators.

Briefly, the first study showed that an important proportion of patients with moderate and severe forms of COVID - 19 - had coagulopathy, that was closely related to their inflammatory profile and age. The second study showed that the age of the patients and the treatment used had a significant impact on the duration of hospitalization, but not the comorbidities most frequently cited in the literature. Also, the use of a specific immunomodulator (tocilizumab) reduced the length of hospital stay, but no other.

In regard to the limitations of the research, it should be mentioned the retrospective nature of the study, the relatively small number of patients included and the lack of patients from the Omicron variant period, as well as the exclusion of patients with critical COVID - 19, that required orotracheal intubation and mechanical ventilation. As far as the duration of hospital stay is involved, it is not possible to make an eloquent comparison between the two included groups, because in the early period of the pandemic, hospital discharge was frequently dictated by the negative result of two RT - PCR tests, which could artificially prolong the length of the hospital stay.

Although the WHO has declared the cessation of the public health emergency of international concern caused by COVID-19, there is still a large burden of cases, including deaths caused by the SARS – CoV -2 infection, and research in this field will continue. There is a need to study new therapeutic options and to monitor the

long-term effects of SARS - CoV - 2 infection, particularly in people with multiple distinct episodes of illness. I therefore expect to continue my research in this area.

8. The relationship between COVID - 19 associated coagulopathy and clinical features, lab tests and imaging results in a group of romanian patients at the onset of COVID - 19 pandemic

8. Methods

In the framework of my PhD research, I conducted an observational, cross-sectional, retrospective study including all patients confirmed with SARS – COV - 2 infection, original strain (previous to variant B.1.1.7), treated in a hospital ward of the National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Bucharest, Romania, between 1st of March and 30th of September, 2020. All patients were confirmed with SARS - CoV - 2 infection by RT - PCR assay from nasopharyngeal swab. The study protocol was approved by the Ethics Committee of the National Institute for Infectious Diseases "Prof. Dr. Matei Balș", after the study documentation was analyzed and it was confirmed that it meets the necessary conditions according to the legislation and regulations in force, including GDPR (opinion no. CO408/2020). We enrolled all patients over 14 years of age, who signed informed consent to hospitalization (in person or through legal guardians) and I recorded the following information from observation files and electronic registers - age, sex, body mass index (BMI), clinical history, COVID-19 associated signs and symptoms, oxygen therapy requirements, markers of inflammation, serum fibrinogen (Fg) and C-reactive protein, serum alanine aminotransferase - ALT/TGP and aspartate aminotransferase - AST/TGO, serum lactate dehydrogenase (LDH), serum myoglobin, creatine kinases (CK and CK-MB), inactive precursor of B-type natriuretic peptide (NT-proBNP), CBC with leukocyte count (Le), neutrophil (Ne), lymphocytes (Ly), neutrophil to lymphocyte ratio (Ne/Ly), platelets (TR), hemoglobin, monocyte distribution width (MDW), coagulation balance with activated partial thromboplastin time (aPTT), prothrombin time QUICK (PT/INR), prothrombin concentration (CP), D-Dimers.

In the study, we used the following score to assess the magnitude of lung damage:

- 1 point for each lung segment involved
- 3 points for bilateral lesions
- 3 points for alveolar lesions
- 2 points for pleural or pericardial effusion

Table 8.2. Severity score of pneumonia

Severity of COVID – 19 associated pneumonia	Scoring system
Mild COVID – 19 related pneumonia	< 9 puncte
Moderate COVID – 19 related pneumonia	9 – 18 puncte
Severe COVID – 19 related pneumonia	> 18 puncte

Statistical analysis

SPSS® (Statistical Package for the Social Sciences) version 22.0, New York, USA, and Microsoft Excel, part of the Microsoft Office 2019 suite, were used for the statistical analysis of the collected data.

Results

The study included 106 patients confirmed with SARS-COV-2 infection, original strain, 50 males (47.2%) and 56 females (52.8%), admitted to a hospital ward at the Institute of Infectious Diseases "Prof. Dr. Matei Balș", Bucharest.

Of these, 53 (50%) had a known epidemiologic link (direct contact with a person subsequently confirmed with SARS - CoV - 2 infection).

The age range for the whole group was 14 - 91 years, with a mean age of 49.6 years (46.1 for males and 52.7 for females, p = 0.03). Further breakdown by usual age

groups and sex of patients shows the heterogeneity of the group, with a small number of patients in the extreme age ranges of 14 - 18 and 89 - 93 years, respectively.

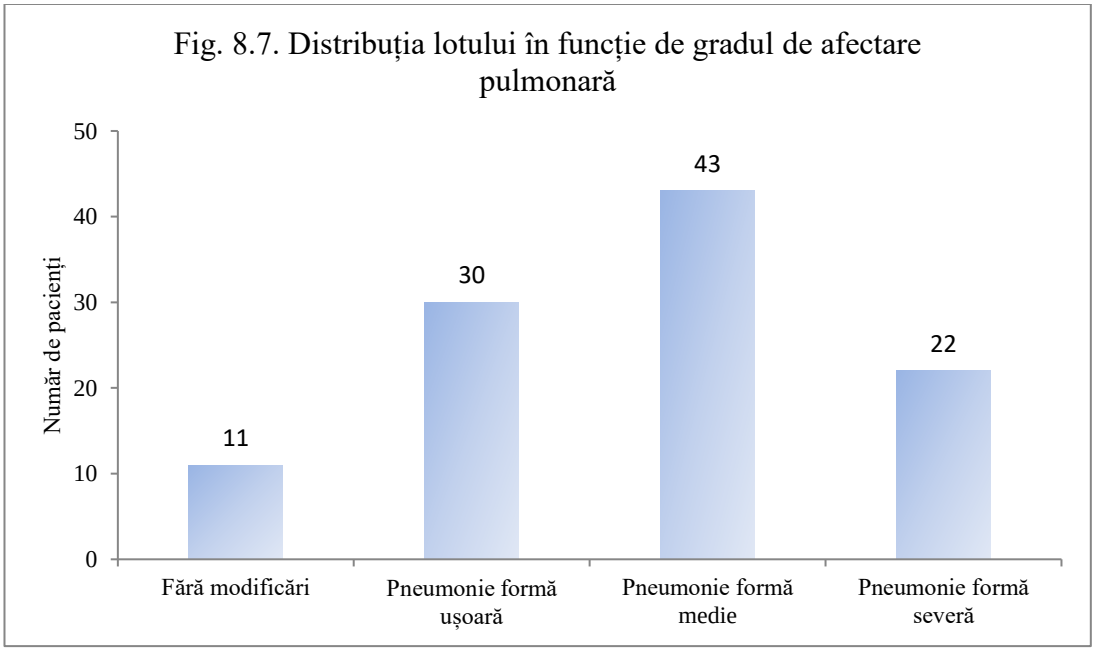
Of the total of 106, 14 patients (13.2%) were asymptomatic and 92 (86.7%) had various signs and symptoms of varying degrees of severity, from nasal obstruction to severe respiratory failure. It should be noted that not all patients who presented with respiratory failure (36, 33.94%) also presented with dyspnea (29, 27.35%).

The time from the onset of first COVID - 19 specific symptoms to hospitalization averaged 5.6 days and ranged from 0 to 15 days. Of the total 106 patients, 33 (31.1%) were obese (BMI ≥ 30). The mean BMI of the entire group was 28.2, higher in males at 29.39.

The BMI value did not vary with age, both for females (R2 = 0.003) and males (R2 = 0.002). The group also presented extreme values, 5 underweight females (BMI ≤ 18.5), 4 females and 5 males respectively with morbid obesity (BMI ≥ 40).

According to chest CT imaging evaluation, 11 patients (10.3%) showed no lung lesions, 30 (28.8%) had mild interstitial pneumonia, 43 (40.5%) had moderate and had 22 (20.7%) had severe interstitial pneumonia.

Fig. 8.7. Distribuția lotului în funcție de gradul de afectare pulmonară



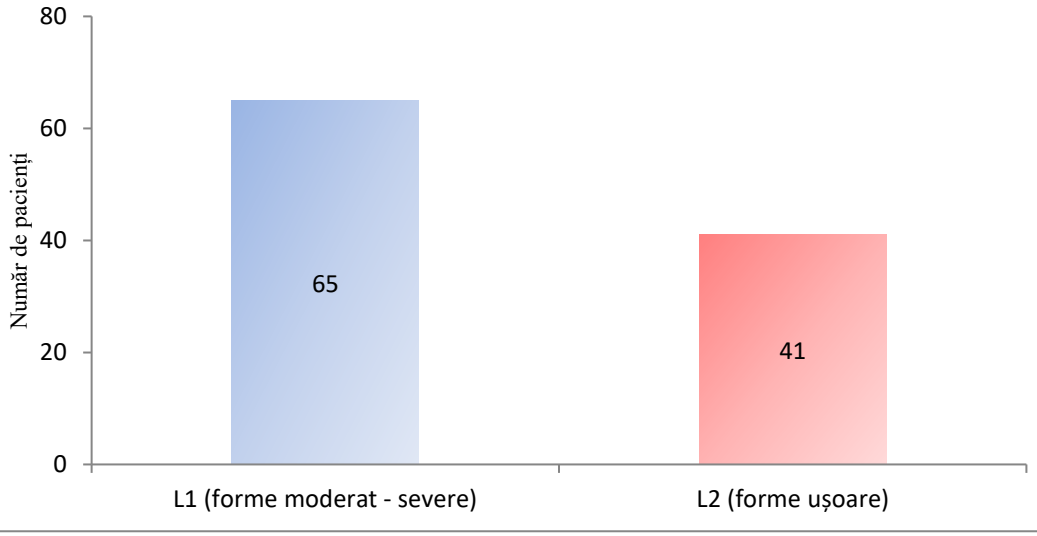
Regarding the whole group, the most frequent comorbidities were essential hypertension (HT), obesity, diabetes (17 patients with diabetes mellitus on diet or oral antidiabetic treatment, 2 patients were on insulin), mixed dyslipidemia, chronic liver disease (chronic hepatitis B, C and steatohepatitis). The most frequent association of two comorbidities was between hypertension and diabetes (15 patients), hypertension and dyslipidemia (15 patients), hypertension and obesity (14 patients). The most frequent association of three comorbidities was between hypertension, diabetes and obesity (9 patients).

All patients received anticoagulation therapy since hospitalization with LMWM (nadroparin calcium). The choice of the drug used was given by availability in the hospital pharmacy and not by other factors. DOAC was discontinued and was replaced with LMWM in equivalent doses. 71 received nadroparin in therapeutic dosage and 35 received nadroparin in prophylactic dosage. No events leading to discontinuation of anticoagulant therapy were reported. Doses were adjusted during hospitalization due to declining eGFR, worsening of the patients' condition, or increased d-dimer values.

Across the whole group, the most commonly used classes of drugs were β-blockers (24 patients), diuretics (18 patients), statins (17 patients), oral antidiabetic drugs (ADO - 10 patients), antiplatelet medication (AAG - 9 patients), angiotensin-converting enzyme inhibitors (ACEIs - 8 patients). The most frequent association was β-blockers with diuretics (12 patients) and statins (10 patients). The most frequent combination of 3 different classes of drugs was between β-blockers, diuretics and statins (5 patients).

In the doctoral research, in order to further characterize and analyze the group and the clinical course of the patients, the group was divided into two subunits, L1, comprising of patients with moderate to severe forms of the disease and moderate or severe lung involvement and L2, comprising of patients with mild forms of the disease with minimal lung involvement or no CT-detected lesions. After I applied the lung involvement score mentioned above, mild to moderate forms were interpreted as moderate and moderate to severe forms were interpreted as severe.

Fig. 8.10. Subloturile generate de gradul de severitate al COVID-19



From L1, 22 patients had severe interstitial pneumonia and 43 had moderate interstitial pneumonia. All patients with severe form of pneumonia had acute hypoxemic respiratory failure requiring oxygen therapy. However, the moderate form of interstitial pneumonia was also associated in some cases with respiratory failure requiring oxygen therapy (14 out of 43, 32.5%).

Table 8.3. Corelation between patients age and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 19 (L2)	p
Nr.	106	65	41	-
Age (years)	49,6 ± 17.8	53,3 ± 15.4	43,7 ± 19.7	**0,00069**

Table 8.4. Corelation between gender and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 1**9** (L2)	p
Nr.	106	65	41	-
Male gender	50	33	17	0,4255

Table 8.5. Corelation between obesity and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 1**9** (L2)	p
Nr.	106	65	41	-
Obese patients	33	28	5	**0,0011**

Table 8.6. Corelation between BMI and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 1**9** (L2)	p
Nr.	106	65	41	
IMC (kg/m^2)	28,2 ± 6.7	29 ± 7.2	25.5 ± 4.6	**0,00001**

Table 8.7. Corelation between hipertension and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 19 (L2)	p
Nr.	106	65	41	-
HT	35	28	7	**0,0061**

Table 8.8. Corelation between diabetes and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 19 (L2)	p
Nr.	106	65	41	-
DM	19	17	2	**0,0018**

Table 8.9. Corelation between dyslipidemia and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 19 (L2)	p
Nr.	106	65	41	
Dyslipidemia	18	18	4	**0,029**

Table 8.10. Corelation between medication and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 19 (L2)	p
Nr.	106	65	41	-
ACE inhibitors	8	5	3	1
Anti platelet medication	9	7	2	0.48

Statins	17	13	4	0.28
B-blockers	24	19	5	0.15

Table 8.11. Corelation between lab results and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 1**9** (L2)	U	Z-score	p
Nr.	106	65	41	-	-	-
Leucocytes	6991 ± 2.72k	7360 ± 0.29k	6391 ± 2.2k	1055.5	1.61	0,10
Neutrophils	4861 ± 2.33k	5346 ± 2.51k	4086 ± 1.79k	913	2.44	**0.014**
Limfocytes	1529 ± 0.89k	1433 ± 1.02k	1682 ± 0.62k	800.5	-3	**0.0026**
Trombocytes	222913 ± 91k	225306 ± 96k	219084 ± 83k	1122	-0.93	0.35
Ne/Ly	3	3.7	2.2	749.5	3.45	**0.00056**
Hemoglobin	13,9 ± 1.5	13,94 ± 1.5	13,8 ± 1.6	1241	0.12	0.89
MDW	23 ± 3.7	24.5 ± 3.4	20.7 ± 2.9	439	4.54	< **0.00001**

Table 8.12. . Corelation between lab results regarding coagulation and inflammation and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 1**9** (L2)	U	Z-score	p
Nr.	106	65	41	-	-	-
Fibrinogen	453 ± 163	522.67 ± 163.9	343.1 ± 83.5	328.5	6.29	<**0 .00001**
Coef. D - dimers (xLSN)	1.19 ± 1.47	1.45 ± 1.76	0.76 ± 0.63	716	3.43	**0.00058**
aPTT (s)	33.1±7.7	33.5 ± 8,5	32 ± 6.1	558.5	0.33	0.72
CP	85 ± 15.8	86.2 ± 16.2	87.9 ± 15.3	1155.5	- 0.23	0.81
CRP	15.8	31.7	1.9	390	5.62	< **0.00001**

LDH	293.45 ± 123.09	324.86 ± 128.03	215.74 ± 77.04	394.5	5.11	< **0.00001**

Table 8.13. Corelation between biochem. lab results and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 1**9** (L2)	U	Z-score	p
Nr.	106	65	41	-	-	-
Urea	37,3 ± 15.1	39,7 ± 16.6	33,6 ± 11.6	1059.5	1.35	0.17
Creatinine	0,7 ± 0.2	0,8 ± 0.2	0,7 ± 0.2	1033.5	1.41	0.15
Glycaemia	118 ± 55.1	132 ± 65.9	97,23 ± 17.1	485.5	4.89	**0.00**
Na+	138,1 ± 2.6	137,5 ± 2.8	139,03 ± 2	802.5	-2.99	**0.0027**
K+	4,1 ± 0.4	4,2 ± 0.5	4 ± 0.3	1012	1.55	0.11
ALT	29	32,5	25	908	2.37	**0.017**
AST	33,5	37	30	780	3.24	**0.0012**
GGT	57.97 ± 61.74	68.8 ± 65.25	40.9 ± 52.08	716.5	3.67	**0.0002**
ALKP	71.25 ± 31.27	70.19 ± 28.67	72.87 ± 35.18	1200.5	0.13	0.89
DB	0.23 ± 0.19	0.27 ± 0.22	0.16±0.11	674.5	3.39	**0.0007**
IB	0.41 ± 0.21	0.43 ± 0.23	0.38 ± 0.19	972.5	1.21	0.22
Lipase	220.4 ± 293.03	297.33 ± 356.52	150 ± 112.5	297	1.84	0.065

Tabelul 8.14. . Corelation between cardiac marker results and COVID – 19 severity

	Initial group	Moderate to severe COVID - 19 (L1)	Mild COVID - 1**9** (L2)	U	Z-score	p
Nr.	106	65	41	-	-	-
CK	126.41 + 148	132.22 ± 156.13	116.83 ± 135.04	1124.5	0.02	0.97
CK-MB	9,5	9	9,5	945.5	-0.88	0.37
Myoglobin	68	89,4	44,8	448	2.31	**0.0208**
Troponin	0,04	0,05	0,03	661.5	0.39	0.68
NT-proBNP	23,5	28	15	461	1.59	0.1

In the analysis, the comorbidities that showed statistically significant differences between the two groups of patients were age, obesity, body mass index, hypertension, dyslipidemia and diabetes mellitus.

There was no statistical significance in the male gender distribution in the two groups. Background treatment of patients with ACEIs, statins, β-blockers or antiplatelet agents was also not statistically significant.

Concerning laboratory tests, those that showed statistically significant differences between the two groups were neutrophil and lymphocyte counts (implicitly also their ratio, Ne/Ly index), MDW, D-dimers, fibrinogen, CRP, LDH, blood glucose levels, natremia, liver enzymes, direct bilirubin, GGT and myoglobin.

The following laboratory tests did not show statistically significant differences between the groups: total leukocyte count, platelet count and hemoglobin value, prothrombin and aPTT concentration, blood urea nitrogen, creatinine, glycemia, potassium, alkaline phosphatase, indirect bilirubin, lipase, CK, CK-MB, troponin, NT-proBNP.

Patients included in group L1, with moderate and severe forms of COVID - 19. were older (53.3 vs. 43.7 years, p = 0.00), more frequently obese (43% vs. 12. 2%), thus also with a higher body mass index (29.8 vs. 25.5 kg/m2), had hypertension (40% vs. 17%) and diabetes mellitus, (24.6% vs. 2.4%, p = 0.01), compared to patients in group 2 with mild forms of COVID - 19.

In terms of laboratory workup, it was observed that group L1, with patients with moderate and severe forms of COVID - 19, showed statistically significant higher values of neutrophils (5346 ± 2. 51k versus 4086 ± 1.79k), lymphocytes (1433 ± 1.02k versus 1682 ± 0.62k), Ne/Ly ratio (3.7 versus 2.2), MDW (24.5 ± 3.4 versus 20.7 ± 2.9), D-dimers (coef. 1.45 ± 1.76 versus 0.76 ± 0.63), fibrinogen (522. 67 ± 163.9 vs. 341.1 ± 83.5), CRP (31.7 vs. 1.9), LDH (324.86 ± 128.03 vs. 215.74 ± 77.04), blood glucose (132 ± 65.9 vs. 97.23 ± 17.1), natremia (137.5 ± 2.8 vs. 139.09 ± 2), TGP (32. 5 versus 25), TGO (37 versus 30), direct bilirubin (0.27 ± 0.22 versus 0.16 ± 0.11), GGT (68.8 ± 65.25 versus 40.9 ± 52.08), LDH (324.86 ± 128.03 versus 215.74 ± 77.04), myoglobin (89.4 versus 44.8).

An elevated D-dimer level was observed in 52% of all patients, and the presence of an abnormal D-dimer level was significantly associated with moderate/severe

disease, with a hazard ratio of 2.38 (1.4 - 4.05, with confidence interval set at 95%, p = 0.00). There was no correlation between abnormal D-dimer values and patient sex, but patients with coagulopathy were significantly older (57.2±17.6 versus 41.3±13.7, p = 0.00) compared to those with normal D-dimer values. Multiple linear regression analysis was performed to highlight the association of variables that could predict the level of D-dimer.

In univariate linear models, the following variables were significantly correlated and predicted D-dimer values: age (r = 0.28, p = 0.00) and fibrinogen (r = 0.2, p = 0.04). Independent variables with a p-value less than 0.1 in the univariate analysis were included in the multivariate regression models. These were represented by lymphocyte count (R = 0.18, p = 0.06), CRP (R = 0.18, p = 0.07) and LDH (R = 0.16, p = 0.1).

Multivariate regression that optimally predicted D-dimer levels required three variables - age, lymphocyte count and LDH (R = 0.42, r = 0.18, p = 0.00).

Results related to this PhD research study were published in October 2021.

8.5. Conclusions

The study provides an architypal description of a relatively small group of patients hospitalized with COVID-19 in an usual hospital ward at the Institute of Infectious Diseases "Prof. Dr. Matei Balș" Bucharest", regarding COVID-19 associated coagulopathy and the presence of systemic inflammation. A significant proportion of patients with moderate and severe disease had coagulation abnormalities and these were associated with inflammation and old age.

9. Influence of single and combined immunomodulatory therapy on the length of hospital stay

9.2. Methods

We conducted an retrospective cross-sectional study that included all patients confirmed with SARS-COV-2 infection, Delta variant (variant B.1.617.2) treated on a hospital ward of the National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Bucharest, Romania, from February 1st, 2021 to May 31st, 2021. Thus, we

included of 394 patients. In the doctoral research, the initial cohort was 330 patients and was subsequently expanded.

All patients were confirmed with SARS - CoV -2 infection by RT-PCR from nasopharyngeal swabs. We excluded patients with confirmed SARS - COV -2 infection who required orotracheal intubation and invasive mechanical ventilation at admission.

The study protocol was approved by the Ethics Committee of the National Institute of Infectious Diseases Prof. Dr. Matei Balș, after the study documentation was analyzed and it was confirmed that it met the necessary conditions according to the laws and regulations in force, including GDPR (opinion no. CO409/2020).

I enrolled all patients aged 18 years or older, who signed informed consent to hospitalization (in person or through legal guardians) and recorded the following data from the observation sheets and electronic registers - age, sex, body mass index (BMI), clinical history (hypertension, diabetes mellitus, pre-existing chronic lung disease, chronic kidney injury, chronic liver disease), signs and symptoms associated with COVID-19, oxygen therapy requirements, treatment received during hospitalization, duration of hospital stay.

All enrolled patients underwent imaging evaluation by computed tomography to assess the severity of pulmonary involvement. Imaging acquisitions were performed by spiral CT (deep inspiral, when possible, depending on the patient's condition), with a pitch of 1.2, with CARE Dose4D and CARE kV enabled to reduce the radiation dose received by the patient, with collimation at 1.2 mm and reconstruction at 3 mm, with B31f image filter in the mediastinal window and B80f ultra sharp image filter for the pulmonary window.

Statistical analysis

SPSS® (Statistical Package for the Social Sciences) version 22.0, New York, USA, and Microsoft Excel, part of the Microsoft Office 2019 suite, were used for the statistical analysis of the collected data.

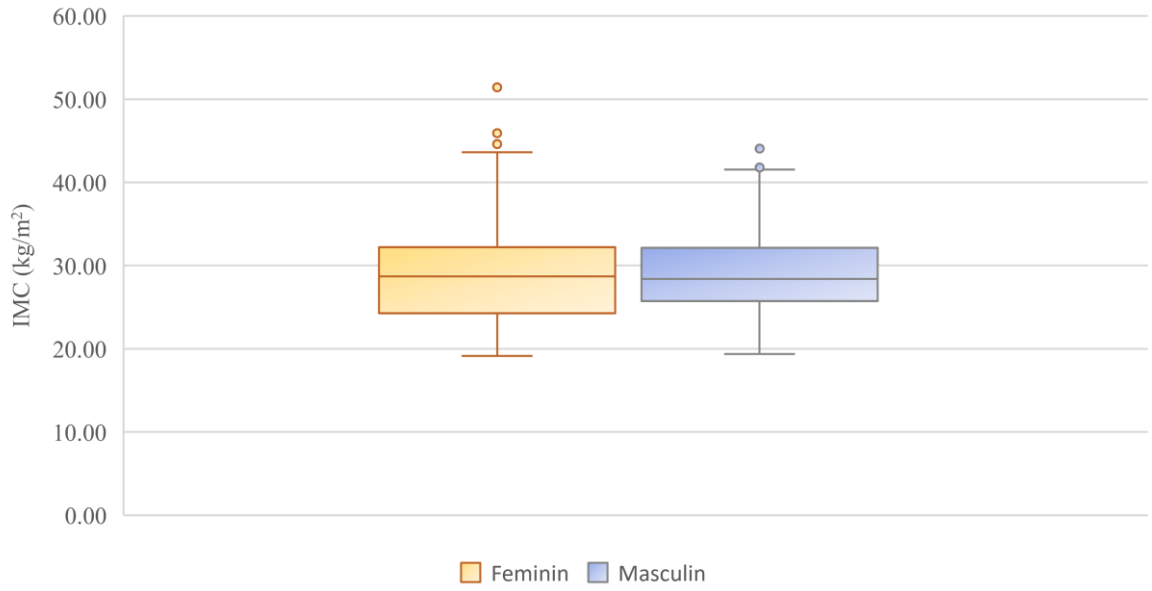
9.3. Results

We excluded 5 patients who required orotracheal intubation after admission and 4 patients who died. Thus, the final cohort included 393 patients, of whom 248 were male (63.1%) and 145 female (36.9%).

The age range for the entire group was 21 - 92 years, with a mean age of 58.38 years (56.56 years for males and 61.5 years for females, p=0.00054). A further breakdown by the usual age groups and sex of the patients shows the heterogeneity of the group, with a small number of patients in the extreme age ranges of 19 - 28 and 84 - 93 years, respectively.

Of the total number of patients, 133 (33.84%) had a known epidemiologic link (direct contact with a person subsequently confirmed with SARS - CoV - 2 infection). Only 2 patients were asymptomatic, admitted due to comorbidity (chronic kidney disease stage IIIb and chronic lymphocytic leukemia). Patients presented a variety of signs and symptoms, the most common being cough, respiratory failure (with varying degrees of severity), physical asthenia, fever, myalgia, dyspnea, headache. It is worth mentioning that not all patients who presented with respiratory failure (255, 64.88%) also had dyspnea (176, 35.12%).

Fig. 9.4. Distribuția IMC în funcție de sex

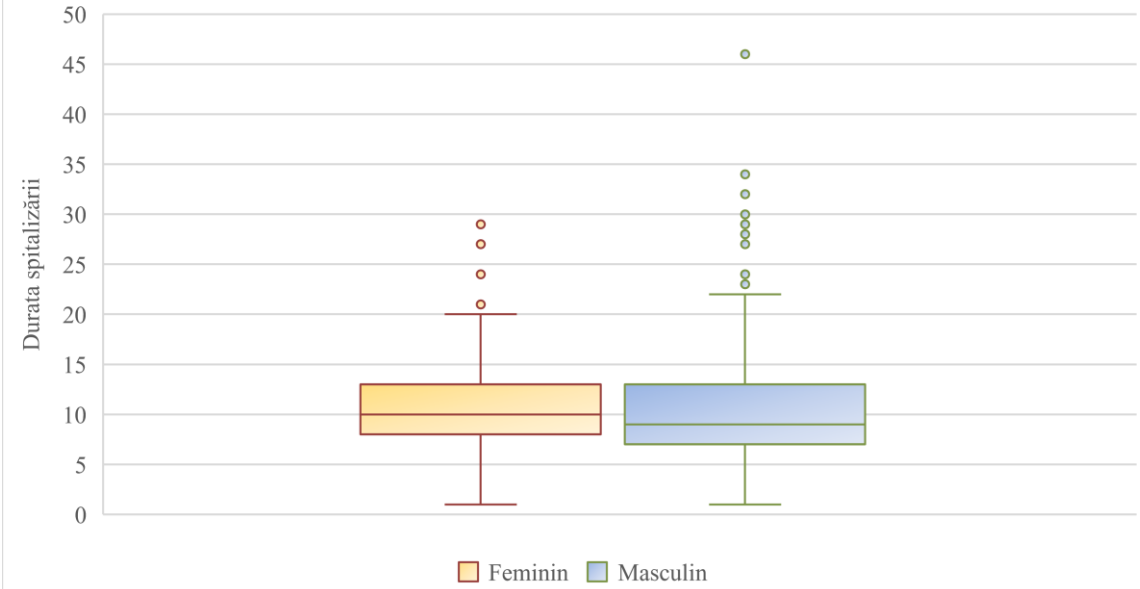


Out of 393 patients, 153 (38.9%) were obese (BMI ≥ 30). The mean BMI of the entire group was 29.14, higher in males at 29.25. BMI did not vary with age, both for

female (R2 =0.0069) and male (R2=0.0381). The group also presented extreme values, 8 females respectively 9 males with morbid obesity (BMI ≥ 40).

Patients were discharged after a mean length of hospital stay (LOS) of 10.7 ± 5.47 days, 10.84 for females and 10.74 for males (p=0.28). The individual length of hospitalization ranged from 1 to 46 days.

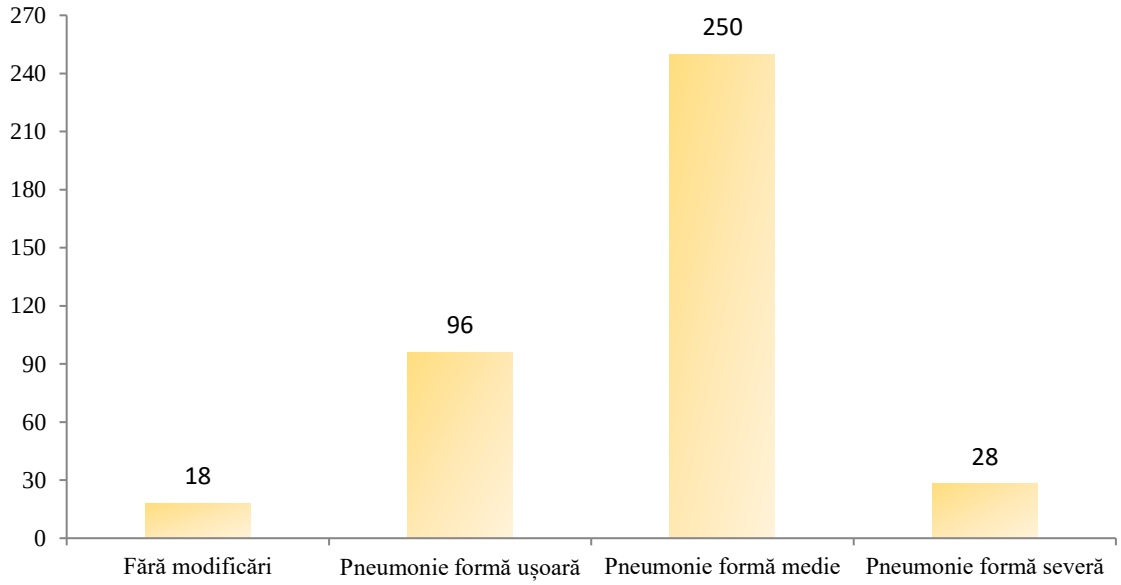
Fig. 9.7. Durata de spitalizare în funcție de sexul pacienților



Of the 393 patients, 255 (44.2%) had hypoxemic acute respiratory failure and required oxygen therapy on admission. Of the total 138 (29.1%) patients without acute respiratory failure on admission, 57 subsequently developed it during hospitalization and also required oxygen therapy.

As assessed by chest CT imaging, 18 patients (4.58%) had no lung injury, 96 (24.42%) had mild interstitial pneumonia, 250 (63.61%) had moderate and 28 (7.12%) had severe interstitial pneumonia. One patient was not evaluated by imaging, as she was with progressing pregnancy.

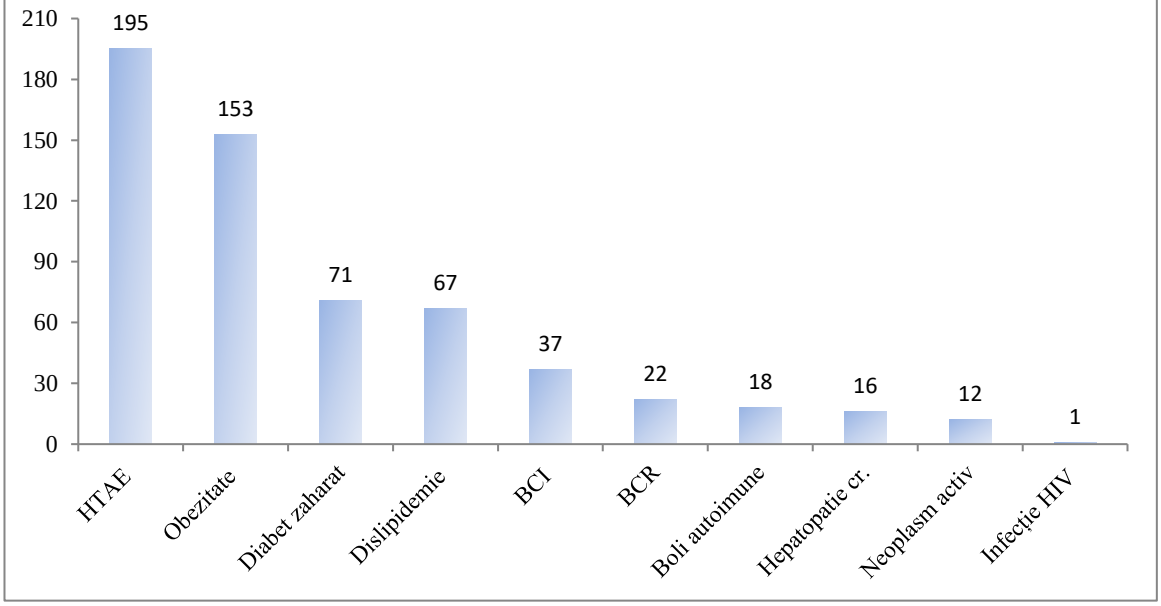
Fig. 9.8. Distribuția lotului în funcție de gradul de afectare pulmonară



Across the whole group, the most frequent comorbidities were essential hypertension (HT), obesity, diabetes mellitus (18 patients with diabetes mellitus on diet or oral antidiabetic treatment, 2 patients with insulin), mixed dyslipidemia, chronic liver disease (chronic hepatitis HBV, HCV, steatohepatitis).

The most frequent association of two comorbidities was represented by HT and DM (15 patients), HT and dyslipidemia (15 patients), HT and obesity (14 patients). The most frequent association of three comorbidities was HT, DM and obesity (9 patients).

Fig. 9.9. Frecvența comorbidităților



Across the whole group, the most commonly used classes of drugs were β-blockers (24 patients), diuretics (18 patients), statins (17 patients), oral antidiabetic drugs (ADO - 10 patients), antiplatelet medication (AAG - 9 patients), angiotensin-converting enzyme inhibitors (ACEIs - 8 patients).

The most frequent association was β-blockers with diuretics (12 patients) and statins (10 patients). The most frequent combination of 3 different classes of drugs was β-blockers, diuretics and statins (5 patients).

In my research, in order to further characterize and analyze the group and the clinico-biological course of the patients, the group was divided into several subgroups:

L1No, the group of patients who did not require oxygen therapy on admission or during hospitalization

L1Lo, group of patients who required low-flow oxygen therapy (1 - 4 L/min)

L1Hi, group of patients requiring high-flow oxygen therapy (≥ 5 L/min)

L2NC, patients who did not receive corticosteroid therapy

L3C, group of patients who received oxygen therapy, corticosteroids, anticoagulants, no immunomodulators

L4CT, group of patients who received oxygen therapy, corticotherapy, anticoagulants + immunomodulators (Tocilizumab - TCZ)

L5CA, group of patients who received oxygen therapy, corticosteroid therapy, anticoagulants + immunomodulators (Anakinra - ANK)

L6CAT, group of patients who received oxygen therapy, corticosteroid therapy, anticoagulant + double immunomodulator treatment (Anakinra + Tocilizumab)

Table 9.2. Corelations between age, comorbidity and length of hospital stay

	Total	L2NC	L3C	L4CT	L5CA	L6CAT	p
No. of pacients (%)	393	53 (13.48 %)	189 (48.09%)	50 (12.72%)	71 (18.06%)	30 (7.63%)	
Median age (years)	58.38 ± 14.77	48.92 ± 15.39	60.13 ± 13.46	57.8 ± 14.64	60.45 ± 14.03	60.13 ± 16.83	**0.06**
Male gender (%)	248 (63.1%)	34 (64.15 %)	111 (58.73%)	35 (70%)	41 (57.74%)	27 (90%)	**0.00**
Obesity (%)	153 (38.93 %)	16 (30.18 %)	71 (37.56%)	18 (36%)	33 (46.47%)	15 (50%)	0.28
BMI (kg/m^2)	29.15 ± 5.32	27.97 ± 6.07	28.96 ± 5.17	29.24 ± 6.02	29.71 ± 4.53	30.90 ± 4.59	**0.03**
HT (%)	195 (49.61 %)	17 (32.07 %)	103 (54.49%)	20 (40%)	39 (54.92%)	16 (53.33%)	**0.04**

DM	71 (18.06 %)	9 (16.98 %)	32 (16.93%)	13 (26%)	10 (14.08%)	7 (23.33%)	0.41
Dyslipidemia	67 (17.04 %)	4 (7.54 %)	38 (20.1%)	5 (10%)	12 (16.9%)	6 (20%)	0.43
Length of hospital stay	10.77 ± 5.46	7.94 ± 4.2	10.08 ± 4.1	10.86 ± 4.83	12.35 ± 5.54	16.26 ± 9.46	**0.00**

Length of hospital stay was predicted by treatment group (r = 0.342, p = 0.00), older age (r = 0.331, p = 0.00), presence of hypertension (r = 0.215, p = 0.00), in univariate analysis.

In multivariate analysis, only treatment group and older age predicted length of hospital stay (r = 0.481, p = 0.00).

It was not influenced by body mass index (r = 0.004, p = 0.93), presence of obesity (r = 0.043, p = 0.44), diabetes mellitus (r = 0.09, p = 0.08), dyslipidemia, chronic kidney disease, autoimmune disease, chronic liver disease or active neoplasms.

In subgroup analysis, a statistically significant difference between the tocilizumab and anakinra treatment groups was observed only in HCO patients: 9.7±5.4 days for TCZ+CO (30 patients) versus 13.2±6.1 for ANK+CO (40 patients), p = 0.01.

For the L3C group, we did not observe significant differences: 8.6±2.3 days for TCZ-SC versus 10.1±3.1, p = 0.3.

9.5. Concluzii

In the patient cohort studied, length of hospital stay was significantly predicted by treatment group and older age. A significant difference in mean SD was observed between the group of patients who received tocilizumab and standard treatment (TCZ-CO) and the group of patients treated with anakinra and standard treatment

(ANK-CO). However, this difference was only seen in patients who required high-flow oxygen therapy of at least 5 L per minute.

Length of hospital stay was predicted by older age and was correlated with hypertension in univariate analysis, but was not associated with other significant comorbidities such as obesity, diabetes mellitus, dyslipidemia, chronic liver disease, chronic kidney disease or active neoplasms.

Results related to this PhD research study were published in January 2021,

References

1. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020.

2. Coronaviridae Study Group of the International Com. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS – CoV - 2. Nat Microbiol. 2020 Apr; 5(4): 536-544.

3. Stories UGpH. WHO chief declares end to COVID-19 as a global health emergency; 2023.