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ORIGINAL ARTICLE

Differences in clinical and laboratory characteristics in patients infected with COVID-19 during different epidemic waves

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Summary

Introduction/Aim: So far, the COVID-19 pandemic has seen four major epidemic waves that have affected more than 753 million people. Epidemiological studies have confirmed variability of clinical presentation of SARS-CoV-2 infection in these epidemic waves. During this period, virus mutations have contributed to greater challenges regarding treatment and prevention. The aim of the study is to determine the differences in clinical presentation, laboratory parameters, as well as the treatment outcome of patients suffering from COVID-19 during four different epidemic waves caused by different genotypic and phenotypic variants of SARS-CoV-2.

Material and Methods: We conducted retrospective study in which data were collected from hospitalized patients at the University Clinical Centre of Serbia Clinic for Infectious and Tropical Diseases in the period between March 1, 2020 and December 1, 2021. Statistical analyses, socio-epidemiological, clinical, radiographic and laboratory characteristics of patients through different epidemic waves of COVID-19 were compared.

Results: The study included 523 patients. Elevated body temperature was the first and the most common symptom of COVID-19 infection in all 4 epidemic waves, whereas cough and malaise were most common symptoms in the fourth wave. Cough was second most common symptom in third wave ($p<0.05$), following elevated body temperature, whereas malaise was second most common in the second wave. Diarrhea and nausea were significantly more common in the fourth wave compared to the previous waves ($p=0.04$ and $p=0.02$).

Conclusion: Highest values of inflammatory biomarkers were found in the second and the fourth wave. The fourth wave was characterized by the largest number of hospitalized patients, and it represented the peak of the pandemic. Treatment options varied through the waves, and corticosteroid use was most common during the fourth epidemic wave in hospital conditions.

Keywords: COVID-19, pandemic, SARS-CoV-2, clinical presentation

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INTRODUCTION

Since the beginning of the pandemic caused by a new strain of the corona virus, *SARS-CoV-2*, more than 753 million people have tested positive for the disease caused by this virus (COVID-19), with 6.8 million people having died worldwide (1). Ori et al. (2) concluded that the omicron variant was less virulent than the delta variant, which was highly infectious and first identified in 2020 (3), having lower hospitalization rate and a lower rate of severe forms of disease. Clinical presentation of COVID-19 can be mild, moderate, severe, and very severe depending on several factors such as genetic predisposition, comorbidities, duration of infection, and the immune system (4). Epidemiological data have shown that the characteristics of the clinical presentation of *SARS-CoV-2* varied during different epidemic waves. The most common symptoms were fever, dry cough, shortness of breath, malaise, loss of sense of smell and taste, myalgia, and weakness, caused by an attack on the alveolar epithelial cells in the lungs (4,5). Consequently, variations in clinical presentation in different epidemic waves were accompanied by changes in laboratory parameters and radiographic findings. Rehan et al. (6) concluded that significant availability of antigen tests aided in rapid diagnosis and subsequent isolation, while severe cases and mortality rates were lower than in previous epidemic waves. The most likely reasons for these variations in clinical presentation, disease severity, laboratory and radiographic findings are the vaccine against *SARS-CoV-2* that was launched after the third wave (7,8), weakened viral virulence, a certain collective and personal immunity achieved through a contact with the virus during the first epidemic waves. Besides, it is important to mention the availability of new antiviral therapy that came into use later on during the pandemic, as well as the application and introduction of corticosteroid and biological therapy into global and national protocols for the treatment of COVID-19 infection (9).

Literature data indicate that patients hospitalized due to complications, with a peak in the third wave (10), had a high mortality rate (26%) and that about 17% of patients admitted to hospital treatment required respiratory support and intensive care. The hospital course of treatment was often additionally complicated by hospital infections such as enterocolitis caused by *Clostridium difficile* bacteria, urinary tract infections, bacterial infections of the respiratory tract, but also by non-infectious conditions such as pulmonary embolism, cardiac arrhythmia and renal insufficiency (11).

The aim of the study is to determine differences in the clinical presentation, radiographic findings, laboratory parameters, applied therapy and the outcome of treatment in patients suffering from COVID-19 during four different epidemic waves caused by different genotypic and phenotypic variants of the *SARS-CoV-2* virus in the period between March 1st 2020 and December 1st 2021.

MATERIAL AND METHODS

Study group

A retrospective study was conducted at the Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia, the Department of Clinical Pharmacotherapy. Data were collected from patients who were hospitalized in this department due *to SARS-CoV-2* infection in the period between March 1st 2020 and December 1st 2021. Patients who met the following criteria were included in the study: I) positive PCR or Ag test for *SARS-CoV-2* before admission and II) age ≥18 years. The following data were collected from the medical history: (I) socio-epidemiological data, (II) laboratory analyses on admission and during hospital stay, (III) radiological analyses on admission and during hospital stay, (IV) data on clinical presentation on admission and during hospital stay, (V) therapy before admission and during hospital stay, (VI) data on the course and complication of the disease, and (VII) treatment outcome.

All patients were divided into 4 groups depending on the period of hospitalization:

I group (alpha strain SARS-CoV2) – the first epidemic wave from March 2020 to May 2020 (34 patients);

II group (alpha strain SARS-CoV2) – the second epidemic wave from July 2020 to August 2020 (61 patients);

III group (delta strain SARS-CoV2) – the third epidemic wave from September 2020 to February 2021 (180 patients);

IV group (omikron strain SARS-CoV2) – the fourth epidemic wave from August 2021 to December 2021 (248 patients).

Patients were divided into groups according to the waves defined by the World Health Organization (WHO). Patient data collection and retrospective study were performed in accordance with the Helsinki Declaration on the Protection of Patients' Rights.

Statistical analysis

Statistical analysis was used to compare the obtained laboratory, clinical and radiological variables through 4 different waves of the COVID-19 pandemic. Chi-square and Fisher's test were used to compare categorical variables, Mann-Whitney U test was used for ordinal and numerical data that deviated from normal distribution, while Student's T-test was used for numerical data with normal distribution. Some of the variables were described during different waves of COVID-19 pandemic using value prediction. Variables with normal distribution are described by the mean and standard, while variables outside the normal distribution are described by the median with maximum and minimum values. The values of certain categories are represented by percentages and numbers. Statistical Package for the Social Sciences (SPSS) version

23 was used to analyze patient data (SPSS Statistics, IBM Corp, Armonk, NY). The significance level of $p<0.05$ was established for all statistical tests.

RESULTS

Socioepidemiological data

A total of 523 patients who met the inclusion criteria were included in the study. Of the total number of patients, 59.1% (309/523) were men, with the average age of 56.7 years. More than half of the patients (62.1%) had at least one chronic disease, the most common of which was hypertension found in 43.4% of patients (227/523), obesity in 26.4% (138/523), diabetes in 13.4% (70/523) and atrial fibrillation in 7.6% (40/523) of patients. Vaccination in our country started on January 19, 2021 and comprised a quarter of patients (25.6%, 138/523), of which in the fourth wave, as many as 83.6% (112/138) were vaccinated with all three doses of vaccines **(Table 1 and Table 2)**.

Table 1. Characteristics of patients treated for COVID-19

Characteristics of patients (n=523)	**N (%)**
Gender (male)	309 (59,0)
Age	56,7 ± 16,0
Comorbidities	**325 (62,1)**
Hypertension	227 (43,4)
Obesity	138 (26,4)
Diabetes	70 (13,4)
Atrial fibrillation	40 (7,6)
Coronary disease	39 (7,5)
Solid tumors	42 (8,0)
Metastasis	11 (26,2)
COPD	31 (5,9)
Connective tissue disease	30 (5,7)
Neurological disease	23 (4,4)
Leukemia/Lymphoma	20 (3,8)
Cardiomyopathy	19 (3,6)
Paralysis	15 (2,9)
Hashimoto thyroiditis	10 (1,9)
Liver disease	10 (1,9)
Chronic kidney disease	9 (1,7)
Congestive heart failure	8 (1,5)
Dementia	6 (1,1)
HIV	4 (0,8)
Peptic ulcer	4 (0,8)
Intrahospital infections	**22 (4,0)**
Bacterial	16 (72,7)
UTI*	10 (45,4)
SMI**	3 (13,6)
Clostridium difficile	2 (9,0)
Syphilis	1 (4,5)
Viral/Fungal	6 (27,2)
Vaccinated	**134 (25,6)**
Sinopharm	102 (76,1)
Sputnik	14 (10,4)
Pfizer	10 (7,5)
Other	5 (3,7)
Astra Zeneca	3 (2,2)
Number of doses	
1 dose	7 (5,2)
2 doses	15 (11,2)
3 doses	112 (83,6)
Primary treatment during hospitalization	
Immunosuppressive	31 (6,0)
Biological	4 (0,8)
Antiviral	53 (10,1)
Corticosteroid	86 (16,4)
Symptomatic	17 (3,3)
No treatment	143 (27,3)
Antibiotics	304 (58,1)
Macrolides	139 (45,7)
Cephalosporins	127 (41,8)
Fluoroquinolones	121 (39,8)
Penicillin	16 (5,3)
Other	16 (5,3)
Metronidazole	5 (1,6)

COPD – chronic obstructive pulmonary disease; HIV – human immunodeficiency virus; *UTI – urinary tract infection; **SIM – skin and mucosa infection

Clinical presentation on admission and during hospital stay

Cough stood out as the leading symptom with an upward trend from the first to the fourth wave (R^2=0.998, p=0.001), followed by nausea (R^2=0.969, p=0.02) and diarrhea (R^2=0.917, p=0.04) which were significantly more often present in the later waves. Malaise showed a positive but not statistically significant frequency trend (R^2=0.762, p=0.13) **(Table 3)**.

Laboratory findings upon admission to hospital and during hospital stay

Observing the mean values of laboratory findings on admission, none of the parameters was statistically significant. Sodium had lower values in hospitalized patients (R^2=0.898, p=0.05) in all the waves. In addition to sodium, several other findings showed a positive trend of increasing values across waves (p=0.05), including fibrinogen (R^2=0.885, p=0.06), CRP (R^2=0.762, p=0.13), LDH (R^2=0.525, p=0.28) and CK (R^2=0.706, p=0.16), although none of them has shown to be statistically significant **(Table 4)**.

Table 2. Comorbidities identified in patients with COVID-19 in different epidemic waves

Comorbidities	Trend equalization	R^2	P
Total	y = -0,19x + 63,2	0,003	0,94
Hypertension	y = 3,25x + 33,2	0,772	0,12
Obesity	y = 6,41x + 6,6	0,548	0,26
Diabetes	y = 1,32x + 9,4	0,416	0,36
Atrial fibrillation	y = 0,15x + 7,4	0,013	0,89
Coronary disease	y = 1,99x + 0,9	0,574	0,24
Solid tumor	y = -1,06x + 9,3	0,823	0,09
COPD	y = -0,04x + 6,0	0,001	0,96
Connective tissue disease	y = 1,21x + 1,9	0,914	**0,04**
Neurological diseases	y = 1,2x + 0,5	0,535	0,27
Leukemia/Lymphoma	y = 0,02x + 3,9	0	0,99
Cardiomyopathy	y = 0,49x + 1,9	0,284	0,47
Paralysis	y = -0,68x + 4,9	0,189	0,57
Hashimoto thyroiditis	y = 0,88x – 1,0	0,637	0,20
Liver disease	y = -0,55x + 3,8	0,691	0,17
Chronic kidney disease	y = 0,38x + 0,7	0,123	0,65
Congestive heart failure	y = 0,42x + 0,2	0,341	0,42
Dementia	y = -0,68x + 3,3	0,896	0,05
HIV	y = -0,51x + 2,3	0,23	0,52
Peptic ulcer	y = 0,29x – 0,2	0,216	0,54

COPD – chronic obstructive pulmonary disease; HIV – human immunodeficiency virus; R^2– coefficient of determination; statistically significant values (p < 0,05) are bolded

Table 3. Comparison of symptoms in patients with COVID-19 in different epidemic waves

Symptoms	Equalizing trend	R^2	*p*
Temperature	y = 2,55x + 81,0	0,365	0,40
Cough	y = 11,66x + 31,9	**0,998**	**0,001**
Fatigue	y = 12,74x + 28,4	0,762	0,13
Dyspnea	y = -2,68x + 32,4	0,628	0,21
Myalgia	y = -0,54x + 24,6	0,006	0,93
Diarrhea	y = 3,96x + 6,6	**0,917**	**0,04**
Nausea	y = 6,0x – 1,9	**0,969**	**0,02**
Anosmia	y = 3,09x + 4,6	0,482	0,31
Headache	y = 1,51x + 8,5	0,269	0,48
Loss of taste	y = 2,69x + 4,3	0,288	0,46
Throat pain	y = -0,39x + 10,6	0,039	0,80
Chest pain	y = 3,95x – 4,1	0,485	0,30
Runny nose	y = 0,9x + 4,3	0,6	0,23
Vomiting	y = 2,33x – 0,8	0,724	0,15
Altered consciousness	y = 0,34x + 1,7	0,15	0,61
Coughing of blood	y = 0,44x + 0,7	0,175	0,58
Vertigo	y = 0,13x + 1,3	0,013	0,89
Skin changes	y = 0,2x + 1,1	0,036	0,81

R2 – coefficient of determination; statistically significant values (p < 0.05) are bolded

Table 4. Trend analysis of laboratory test values in patients with COVID-19

Laboratory values	Trend equalization	R^2	*P*
Hgb	y = 4,95x + 173	0,540	0,30
PLT	y = -2,15x + 146	0,495	0,27
CRP	y = 15,945x – 6,6	0,762	0,13
IL-6	y = 9,82x – 1,125	0,834	0,09
Urea	y = -0,15x + 6,1	0,600	0,23
Creatinine	y = 1,5x + 84,5	0,495	0,30
AST	y = 0,15x + 32,75	0,012	0,89
ALT	y = 43,75	0,000	1,00
GGT	y = 0,55x + 38,5	0,032	0,82
ALP	y = -1,35x + 67,25	0,377	0,39
LDH	y = 9,8x + 208,5	0,525	0,28
CK	y = 10,7x + 69,5	0,706	0,16
Fe	y = -0,93x + 7,75	0,788	0,11
Na	y = -2,55x + 146,25	0,898	**0,05**
K	y = 0,045x + 3,925	0,600	0,23
D-dimer	y = 0,036x + 0,53	0,158	0,60
Fibrinogen	y = 0,58x + 2,15	0,885	0,06

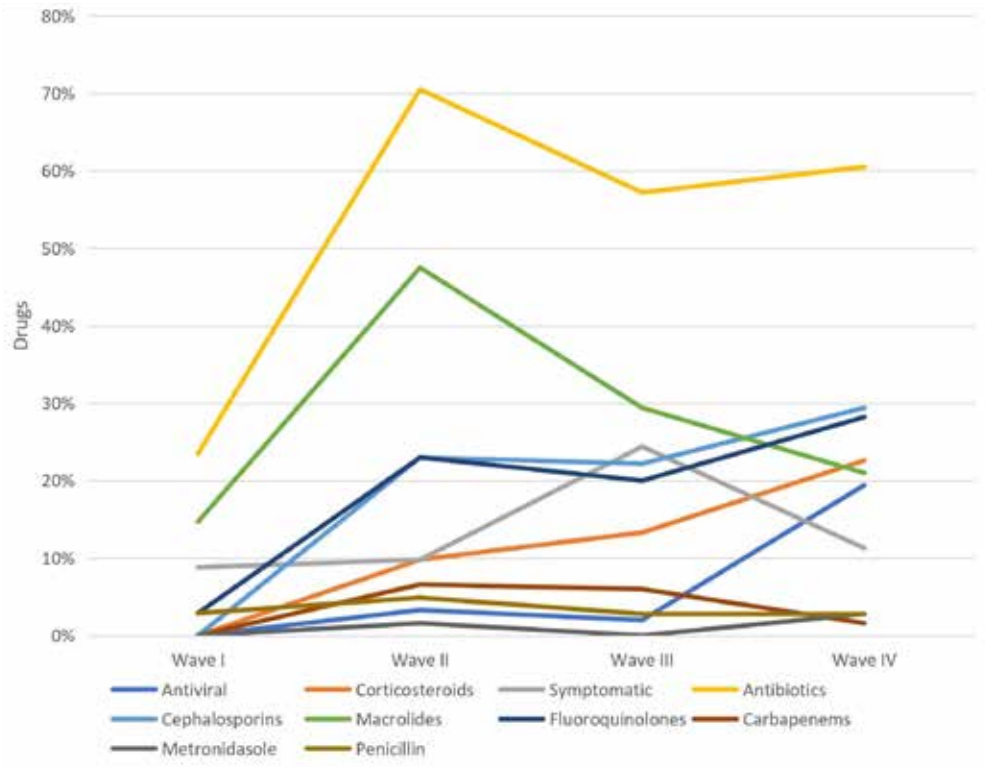
Hgb- hemoglobin; PLT- platelets; CRP- C-reactive protein; IL-6- interleukin-6; AST- aspartate aminotransferase; ALT- alanine aminotransferase; GGT- gamma glutamyl transferase; ALP- alkaline phosphatase; LDH- lactate dehydrogenase; CK- creatin kinase; Fe- iron; Na- sodium; K- potassium. R^2- coefficient of determination; statistically significant values (p < 0.05) are bolded

Radiological findings on admission and during hospital stay

The majority of patients (82.6%; 432/523) had a pathological finding on radiography of the lungs, of which 29.2% were described as spotty shadows, while 20.2% were described as undoubtable pneumonia (inhomogeneous diffuse shadows). As for the patients who underwent lung imaging with computerized tomography (CT) scan, the findings in 33.3% of cases indicated diffuse shadows, while in 18.7% the CT findings were described as diffuse consolidations. A significantly higher CT score of changes in the lungs, i.e., a more severe form of pneumonia, was registered in obese patients compared to patients with normal weight (p=0.008). Other characteristics did not prove to be statistically significant predictors of severe pneumonia (gender, comorbidities, hypertension, coronary heart disease, COPD).

Therapy before admission and during hospital stay

More than half of the admitted patients (58.1%, 304/523) used antibiotics before admission to hospital. A statistically significant, positive trend across waves was obtained for the use of corticosteroids in the treatment of patients with COVID-19 (R^2=0.972, p=0.01). The trend of antibiotic use before admission to hospital decreased signifi-



Graph 1. Distribution of drug use in four different waves of COVID-1

cantly through the waves, because of the introduction of antivirals, but was not statistically significant (R^2=0.382, p=0.38) despite a significant positive trend, both overall and especially in the two antibiotic groups administered during hospital stay – cephalosporins (R^2=0.772, p=0.12) and fluoroquinolones (R^2=0.738, p=0.14). During hospitalization, patients were treated with anticoagulant therapy in 90.4% of cases. During hospitalization, patients aged ≥66 years were more often treated with antibiotic therapy compared to patients aged 18-30 years, who were more often treated with antibiotic therapy before hospitalization **(Graph 1)**.

Complications of the disease

Complications of COVID-19 pneumonia were observed in 81/523 (15.5%) patients, the most common of which was respiratory failure in 27/523 (5.2%) patients. Intrahospital infections were recorded in 17/523 (3.2%) patients, of which urinary tract infections were most common (11/523, 64.7%). Other complications were rare, including pulmonary embolism (9/523, 1.7%), hyperglycemia (6/523, 1.1%), and new-onset cardiac arrhythmia (5/523, 1%). Complication trend analysis showed a statistically significant positive trend for the overall complication rate from the first to the fourth wave (R^2=0.915, p=0.04), especially for respiratory failure (R^2=0.944, p=0.03). No other complication showed a consistent positive or negative trend in occurrence **(Graph 2, Table 5)**.

Table 5. Comparison of complications of COVID-19 in patients hospitalized in different epidemic waves

Complications	Trend equation	R^2	*p*
Total	y = 4,05x + 0,35	0,915	**0,04**
DVT	y = 0,11x - 3E-18	0,067	0,74
PE	y = 0,69x – 0,6	0,328	0,43
HAI	y= - 0,91x + 5,75	0,358	0,40
Respiratory insufficiency	y = 2,25x – 2,0	0,944	**0,03**
Pericarditis	y = 0,87x – 0,35	0,279	0,47
Hyperglycemia	y = 0,72x – 1,2	0,600	0,23

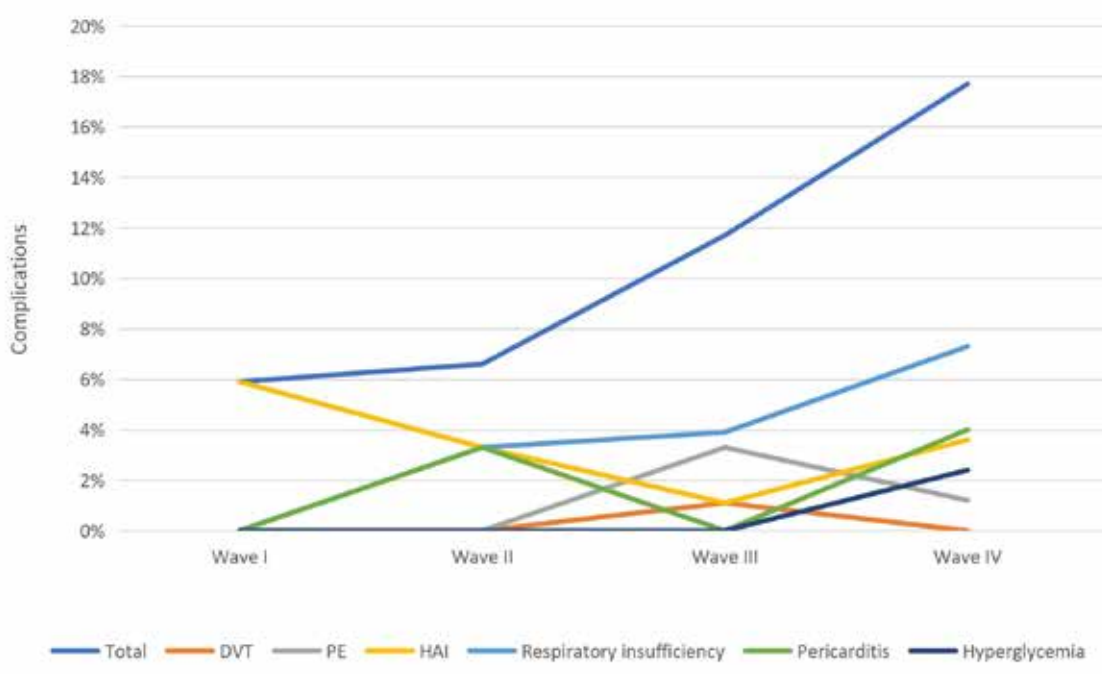
R^2 – degree of certainty; statistically significant values ($p < 0.05$) are marked in bold; DVT- deep vein thrombosis; PE- pulmonary embolism; HAI- hospitalization associated infection

Treatment outcome

As many as 91% (476/523) of patients were discharged from hospital cured, while 3.8% (20/523) of patients were transferred to the intensive care unit due to the development of disease complications. Only 3 deaths were recorded (0.6%).

Comparison of different comorbidities in COVID-19 epidemic waves

The distribution of the most common comorbidities was similar in all waves (R^2=0.003, p=0.94), with connective tissue diseases being the only chronic condition that showed a statistically significant positive trend in occurrence (R^2=0.914, p=0.04) and hypertension, which showed a positive but not statistically significant trend



DVT- deep veins thrombosis; PE- pulmonary embolism; HAI-hospitalization associated infections

Graph 2. Distribution of complications of COVID-19 in hospitalized patients in four different waves

(R^2=0.772, p=0.12). Other comorbidities, including obesity (R^2=0.548, p=0.26) and diabetes (R^2=0.416, p=0.36) did not show a statistically significant trend of occurrence from the first to the fourth wave of the pandemic.

Comparison of symptoms and clinical variables across different epidemic waves of the SARS-CoV-2

Cough had the most significant positive trend of occurrence from the first to the fourth wave of the pandemic, with the peak frequency in the fourth wave (p=0.001). An increase in the symptoms of fatigue and weakness was most significant from the first to the second wave, as well as from the third to the fourth wave, but statistical significance was not proven. Diarrhea (p=0.04) and nausea (p=0.02) had a significant upward trend during the pandemic, with a marked gradual increase in occurrence and peak in the fourth epidemic wave. Elevated body temperature, as the most common symptom, did not show oscillations in occurrence during waves (p=0.4).

Comparison of laboratory parameters in different epidemic waves of SARS-CoV-2

Laboratory parameters such as hemoglobin (Hgb), sodium (Na+), D-dimer and iron (Fe) did not change across epidemic waves. Sodium level was elevated in the laboratory results in all waves; also, a significant downward trend was present from the first to the fourth wave, but no statistical significance was shown.

Comparison of outcomes across different epidemic waves of SARS-CoV-2

At the end of all four waves, 3 deaths were recorded. The duration of hospital stay as well as the stay in intensive care units (ICU) were shorter in the last wave due to the less severe clinical presentation of patients in that period, compared to previous waves, but without statistical significance. In case of patients who were transferred from the clinical department to the ICU, the further course of the disease was not monitored, but only the outcome of the disease was recorded, therefore no information is available on the number of days spent in the ICU **(Table 6)**.

DISCUSSION

SARS-CoV-2 pandemic that began in March 2020 affected health and economy of the entire world population (12). Clinical, laboratory and radiographic picture of COVID-19 changed through epidemic waves.

In our study, we found that the most common comorbidity in patients with COVID-19 was hypertension, followed by obesity and COPD. According to literature, apart from obesity, frequent comorbidities were atrial fibrillation, coronary heart disease and solid tumors (12). In other studies, liver insufficiency was highlighted as an important comorbidity, apart from cardiovascular diseases, which were the most common comorbidity (12). In our study, liver failure was a rare comorbidity. In the group of vaccinated patients in our study, the largest number of patients with COVID-19 infection were ≥66 years of age, who were treated for at least one chronic disease.

Table 6. Complications and outcomes of treatment of COVID-19 in patients hospitalized in different epidemic waves of the *SARS-CoV2*

Patient characteristics (n=523)	**N (%)**
Complications	81 (15,5)
Respiratory insufficiency	27 (5,2)
Intrahospital infections	17 (3,2)
Urinary tract infections	11 (64,7)
Clostridium difficile infection	4 (23,5)
Pulmonary embolism	9 (1,7)
Hyperglycemia	6 (1,1)
Cardiac arrhythmia	5 (1,0)
Altered conscious	4 (0,8)
Pericarditis	2 (0,4)
Neutropenia	2 (0,4)
Deep venous thrombosis	2 (0,4)
Liver insufficiency	1 (0,2)
Acute pancreatitis	1 (0,2)
Acute myocardial infarction	1 (0,2)
Outcome	
Recovered	476 (91,0)
Transferred to ICU	20 (3,8)
Transferred to other hospital	19 (3,6)
Died	3 (0,6)
Dismissed at personal request	5 (1,0)

ICU- intensive care unit

In the first wave, mostly patients who belonged to younger population were hospitalized, with oxygen saturation <90% upon admission, and these were slightly more often female patients (13). In a study conducted by Alfonso et al. (14) the most common symptoms were fever, cough and dyspnea. In our study, the most common symptom was cough, while diarrhea and nausea were in the second and third place, respectively.

Anticoagulant therapy was administered to hospitalized patients in 90.4% of cases in our study. When comparing the waves, anticoagulant therapy was less commonly administrated in the first wave, while it was part of routine treatment in the second, third, and fourth wave. The reason for this was the positive outcome of patients treated with corticosteroids and anticoagulant therapy in later waves, whereas in the first wave, there was no experience or published data on this topic, so doctors rarely chose to treat patients with anticoagulant therapy. Same was the case with corticosteroid therapy, which was less commonly administered in the first wave, while it became part of routine treatment for COVID-19 in the later waves, based on the previous experiences of positive outcomes. At the same time, this was the reason for our group's low mortality rate, as appropriate corticosteroid and anticoagulant treatment was administered on time.

The results of laboratory results did not change significantly across the waves. The parameters that were most often above the referential values were CRP, fibrinogen, D-dimer, Na+, hemoglobin, platelets. Results of other studies are in accordance with our results, as elevated values of CRP, LDH, and accelerated erythrocyte sedimentation were highlighted in these studies as well (14).

Chest radiography represents an important diagnostic role in patients with suspected *SARS-CoV-2* infection, especially in settings where RT-PCR for *SARS-CoV-2* testing is not available or test results are delayed, as well as in patients with respiratory complaints or auscultatory verified pneumonia in which the RT-PCR test has been initially negative (15).

The most common COVID-19 complications are pneumonia (96%) and pulmonary thromboembolism (52%), as confirmed in our study, where 90.5% of patients were diagnosed with COVID-19 pneumonia. Only three lethal outcomes were observed in our study, all of which were patients transferred to the ICU unit who developed acute respiratory distress syndrome due to the COVID-19 cytokine storm and pneumonia, followed by multiorgan failure. None of our patients developed invasive fungal infections as a consequence of corticosteroid therapy.

During the COVID-19 pandemic, there has been a global increase in inappropriate use of antibiotics in the treatment of this viral infection (11). Antibiotics have been the most frequently used drugs during the pandemic. Our study showed that the younger population (33-45 years) used antibiotics more often in the treatment of COVID-19 compared to people ≥66 years. Despotovic et al. (11) showed that cephalosporins were the most frequently used antibiotics during the entire pandemic, which was also shown in our study in all waves. Along with cephalosporins, fluoroquinolones were the most commonly used drugs during all four epidemic waves of COVID-19.

Statistically, the most frequently used drugs in hospitalized patients during the *SARS-CoV-2* pandemic were corticosteroids, most likely due to their positive results in the treatment of complicated forms of COVID-19. Parrella and Marra (16) reported that the clinical use of corticosteroids in the treatment of patients with moderate to severe COVID-19 infection not only reduced the length of treatment and improved clinical outcome, but also significantly reduced mortality.

Complications of COVID-19 were recorded in 15.5% of patients and related to respiratory failure and intrahospital urinary infection. Prolonged duration of treatment in hospital conditions and the use of urinary catheter as a convenient location for urinary infections are the reason for most of these infections. Beatriz et al. (17) stated that the most common causes of urinary tract infections were *E. coli, E. faecalis and E. faecium*. In addition to urinary infections, literature data indicate that the leading co-infections that burdened healthcare in hospital conditions more than expected were central venous catheter infections and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia (18).

CONCLUSION

The highest values of inflammatory biomarkers were recorded in the second and the fourth wave. The fourth wave recorded the largest number of hospitalized patients and represented the peak of the pandemic. The choice of therapy changed across the waves, and significantly more frequent use of corticosteroids and antiviral therapy was shown in the fourth wave.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL

Since this is a retrospective observational study, the approval of the Ethics Committee of KCS was not required.

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RAZLIKE U KLINIČKIM I LABORATORIJSKIM KARAKTERISTIKAMA KOD PACIJENATA OBOLELIH OD KOVIDA 19 TOKOM RAZLIČITIH TALASA PANDEMIJE

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Sažetak

Uvod/Cilj rada: Od početka pandemije novim korona virusom (*SARS-CoV-2*), registrovana su četiri epidemijska talasa tokom kojih je obolelo više od 753 miliona ljudi. Karakteristike kliničke slike koju daje *SARS-CoV-2* varirale su tokom ova četiri talasa. Mutacije virusa su doprinele većem izazovu kada su u pitanju tok bolesti, lečenje i prevencija. Cilj studije je da se utvrde razlike u kliničkoj slici, laboratorijskim parametrima, kao i ishodu lečenja pacijenata obolelih od *COVID-19* tokom četiri različita talasa pandemije izazvanih različitim genotipskim i fenotipskim varijantama virusa *SARS-CoV-2*.

Materijal i metode: Sprovedena je retrospektivna studija tokom koje su prikupljeni i analizirani podaci hospitalizovanih pacijenata u Klinici za Infektivne i tropske bolesti UKCS u periodu od 1. marta 2020. do 1. decembra 2021. godine koji su lečeni zbog *SARS-CoV-2* infekcije. Statističkim analizama su poređene socioepidemiološke, kliničke, radiografske i laboratorijske karakteristike pacijenata kroz različite talase pandemije kovida 19.

Rezultati: U studiju su uključena 523 pacijenta. Povišena telesna temperatura je bila prvi i najčešći simptom *SARS-CoV-2* infekcije tokom sva četiri talasa pandemije, dok su kašalj i malaksalost bili najzastupljeniji simptomi u četvrtom talasu. Drugi najčešći simptom posle povišene telesne temperature u trećem talasu bio je kašalj ($p<0,05$), a malaksalost u drugom talasu. Dijareja i mučnina su bili statistički značajno češći u četvrtom talasu u poređenju sa prethodnim talasima ($p=0,04$ i $p=0,02$).

Zaključak: U drugom i četvrtom talasu su primećene najviše vrednosti biomarkera zapaljenja. U četvrtom talasu je zabeležen najveći broj hospitalizovanih pacijenata. Izbor terapije se menjao tokom talasa, te je u četvrtom talasu primećeno značajno češće korišćenje kortikosteroida u bolničkim uslovima.

Ključne reči: kovid 19, pandemija, *SARS-CoV-2*, klinička slika

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