https://doi.org/10.31925/farmacia.2025.6.17 **ORIGINAL ARTICLE**

THE IMPACT OF INNOVATIVE MONOCLONAL ANTIBODY TREATMENTS ON SARS-COV2 INFECTION

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Abstract

The development of biopharmaceutical products has represented a true turning point in the history of modern medicine. Among them, monoclonal antibodies represent one of the most important therapeutic classes, being used both in diagnosis and research, and especially in the treatment of a wide range of conditions: autoimmune, infectious, oncological, allergic, neurological, degenerative. The COVID-19 pandemic would have had much more serious consequences without the unprecedented mobilisation of all researchers and medical workers around the world. Biological treatments represented by monoclonal antibodies have changed the dire prognosis of this disease, preventing clinical progression, as well as decreasing the number of hospitalizations and mortality rate. We conducted a retrospective study on a group of 197 patients confirmed with SARS-CoV-2 infection, in which we evaluated the impact of administering the combination of monoclonal antibodies Casirivimab - Imdevimab on clinical progression and the need for hospitalisation. The way in which monoclonal antibody treatment has radically altered the course of COVID-19 in patients highlights the essential role of innovative treatment modalities in shaping the trajectory of severe diseases.

Rezumat

Dezvoltarea produselor biofarmaceutice a reprezentat un adevărat punct de cotitură în istoria medicinei moderne. Printre acestea, anticorpii monoclonali reprezintă una dintre cele mai importante clase terapeutice, fiind utilizați atât în diagnostic, cât și în cercetare, și mai ales în tratamentul unei game largi de afecțiuni: autoimune, infecțioase, oncologice, alergice, neurologice, degenerative. Pandemia de COVID-19 ar fi avut consecințe mult mai grave fără mobilizarea fără precedent a tuturor cercetătorilor și personalului medical din întreaga lume. Tratamentele biologice reprezentate de anticorpii monoclonali au schimbat prognosticul sumbru al acestei boli, prevenind progresia clinică, precum și reducând numărul de spitalizări și rata mortalității. Am realizat un studiu retrospectiv pe un grup de 197 de pacienți confirmați cu infecție cu SARS-COV2, în care am evaluat impactul administrării combinației de anticorpi monoclonali Casivirimab - Imdevimab asupra progresiei clinice și a necesității spitalizării. Modul în care tratamentul cu anticorpi monoclonali a schimbat radical cursul bolii la pacienții cu COVID-19 evidențiază rolul esențial al metodelor inovatoare de tratament în schimbarea cursului bolilor severe.

Keywords: biopharmaceutical products, monoclonal antibodies, SARS-COV2 infection

Introduction

The biopharmaceutical industry has met a rapid expansion in recent years, with biological drugs accounting for up to 44% of all medications produced in 2023 [34]. Despite the predominance of chemical drugs, significant investments have been directed towards the development of biological molecules, particularly monoclonal antibodies (mAbs). Since the approval of recombinant insulin in 1982, the range of biopharmaceutical products has expanded to include not only monoclonal antibodies, but also fusion proteins, hormones, enzymes, vaccines, and nucleic acid-based therapies [8].

Monoclonal antibodies are engineered substitutes for natural antibodies that are used in prevention, diagnosis and treatment of cancers, infectious diseases and autoimmune disorders. Initially, they have been developed as murine antibodies and their clinical use was limited by immunogenicity. Later, with the advances in genetic engineering, the development of chimeric (-ximab), humanized (-zumab) and fully human (-umab) antibodies was achieved, thus greatly improving

safety and efficacy [3]. Their major advantages include high specificity and reducing adverse reactions, all while being limited by the high production costs [22].
Statistical data demonstrated that COVID-19 had the most profound impact on people's lives and on the global economy, like no other infectious disease, not even the Spanish flu of the 1900s, has ever had [18]. Up to 40% of symptomatic patients developed acute respiratory distress syndrome (ARDS) during the COVID-19 pandemic, with mortality rates reaching 52.4% in severe cases [15]. Although severe cases were often associated with comorbidities, severe and fatal outcomes also occurred in patients without underlying conditions. Those have been influenced by factors such as age, biomarkers, imaging findings, vaccination status and delayed hospital admission [17].
Early in the pandemic, neutralizing monoclonal antibodies targeting the receptor-binding domain of the SARS-CoV-2 spike protein were developed to block viral entry *via* ACE-2 receptor. These therapies significantly reduced the risk of severe diseases and deaths in unvaccinated people, with worldwide studies confirming that monoclonal antibody treatment decreased severe progression and hospitalization rates, even in high-risk patients.
SARS-COV-2 virus attached to host cells through the spike protein (S), which is composed by the S1 and S2 subunits. The S1 subunit binds to the ACE2 receptor *via* its receptor-binding domain (RBD), while the S2 subunit mediates membrane fusion. Blocking the S1 subunit, especially the RBD, is essential for preventing viral entry. Several antibodies can block the receptor or can induce an unfavourable ACE2 conformation for viral binding or fusion [2]. Although the function of the N-terminal domain (NTD) is not fully understood, antibodies targeting both RBD and NTD show antiviral activity [10].
Most monoclonal antibodies from convalescent COVID-19 patients neutralize the virus by competing with ACE2 for RBD binding. The main ACE2-binding regions on the RBD determine antibody neutralization strength. Antibody cocktails are more effective than single antibodies because they reduce the risk of viral immune escape due to mutations. For an effective cocktail, the antibodies must not compete for the same binding site on the Spike protein [29].
In November 2020, the FDA approved for Emergency Use Authorization a monoclonal antibody cocktail therapy consisting of casirivimab and imdevimab (REGN-COV2) [40].
These antibodies bind to non-overlapping epitopes of the SARS-COV-2 Spike RBD, blocking viral attachment to the ACE2 receptor. The recommended single intravenous dose is 1,200 mg for the treatment of adults and pediatric patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. These therapies significantly reduced the risk of severe diseases and deaths in unvaccinated people. Worldwide studies have confirmed that monoclonal antibody treatment decreased severe progression and hospitalization rates, even in high-risk patients [26].
We aimed to analyse the incidence of comorbidities and risk factors in the group of patients with SARS-COV2 infection who received treatment with the combination of monoclonal antibodies casirivimab-imdevimab, as well as how this treatment influenced the subsequent evolution of the patients.

Materials and Methods

Study design and participants
It was conducted a retrospective, observational study on patients with confirmed SARS-CoV-2 infection who were evaluated at the Day Department of the National Institute of Infectious Diseases "Prof. Dr. Matei Balș." The study period was October 15 - December 27, 2021, corresponding to the Delta wave. A total of 197 patients received monoclonal antibody therapy with the casirivimab-imdevimab combination following clinical and imaging evaluation. All patients provided written informed consent prior to participation and treatment.
The study inclusion criteria were represented by the positive RT-PCR test for COVID-19 (nasopharyngeal or oropharyngeal swab) and the indication for treatment with monoclonal antibodies, respectively, the presence of at least one risk factor for the severe form of COVID-19. The exclusion criteria were represented by ages under 12 years and there were excluded patients who did not provide informed consent and patients who came at the hospital more than 7 days after the symptom onset.
The study population was divided into two groups according to hospitalization requirements: Group 1 of the 174 patients treated with monoclonal antibodies in the Day Ward who did not require further hospitalization and Group 2 of the 23 patients admitted for continued specialized treatment and monitoring. For the follow-up, patients in group 1 were contacted by telephone 7 days after discharge.
Ethical considerations
The study was approved by the Ethics Committee of the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" (approval no. C14730/16.12.2021). Data collection was performed in accordance with the Declaration of Helsinki and national regulations. As this was a retrospective study based on anonymized and de-identified data, the requirement for informed consent for study participation was waived. Patient confidentiality was strictly maintained.
Study variables
The analysed demographic and anthropometric factors were: age, sex, weight, height, BMI; comorbidities (cardiovascular, metabolic, respiratory, renal, hepatic,

gastrointestinal, endocrine, autoimmune, oncology); clinical manifestations (fever, chills, sweating, fatigue, anosmia, dysgeusia, headache, myalgia, arthralgia, cough, dyspnoea, chest pain); radiological findings (mild/moderate pneumonia) and laboratory parameters, including: complete blood count, neutrophil-to-lymphocyte ratio, inflammatory markers: C-reactive protein (CRP), fibrinogen, erythrocytes sedimentation rate (ESR) and biochemistry of the blood : albumin, activated partial thromboplastin time (aPTT), creatinine, D-dimers, blood glucose, Interleukin-6 (IL-6), potassium (K), lactate dehydrogenase (LDH), total serum protein, aspartate amino transferase (AST or TGO), glutamyl amino transferase (ALT or TGP), urea.

To estimate the possibility of severe evolution of patients with COVID, we created a risk factor score, which included: high blood pressure (HTA), body mass index (BMI) over 30, blood glucose over 125 mg/dL, fibrinogen over 450 mg/dL, AST>36 U/L, elevated D-dimers (1.5 times normal value), prothrombin concentration (CP) less than 70%. The presence of each parameter was marked with 1, so the maximum score value could be 7.

The cut-off values for blood tests were taken from the reference ranges of the laboratory of our hospital. Glycaemia and BMI follow the WHO reference ranges.

Elevated fibrinogen levels above 450 mg/dl were associated with increased systemic inflammation, supporting its role as reliable inflammatory marker [35].

The impact of monoclonal antibody treatment was assessed using hospitalization rates and mortality as outcome measures.

Statistical analysis

Statistical analysis was performed using MedCalc software (version 23.1.7, MedCalc Software Ltd). Variables with a non-Gaussian distribution were expressed as median and interquartile range (IQR, Q1-Q3). Variables with a Gaussian distribution were expressed as mean ± standard deviation (SD). Distribution normality was tested using the Shapiro-Wilk test for each group and subgroup.

Comparisons were performed as follows: Mann-Whitney U test for non-normally distributed variables, independent samples t-test for normally distributed variables, Chi-square test for categorical variables.

Correlations between binary, ordinal, and continuous variables (with or without normal distribution) were assessed using the Spearman rank correlation test, reported as Spearman's rho with 95% confidence intervals. Simple linear regression was used to evaluate the association between risk score and age. A Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the discriminative power of the severity score. The area under the curve (AUC) and 95% confidence intervals were calculated according to the method of DeLong. Statistical significance was set at $p < 0.05$.

Results and Discussion

Socio-demographic aspects and patients characteristics

We enrolled 197 patients with confirmed SARS-Cov-2 infection in this study. The median age of participants was 52 years (IQR: 42.75 - 69.25). In group 1, the median age was 53 (IQR: 42 - 68), whereas in Group 2, it was 58.65 years (mean: 58.652 ± 18.0696). The male-to-female ratio was 0.858 for the entire cohort. Women accounted for 53.8% of all patients, 54.6% in Group 1, and 47.8% in Group 2. The mean weight of the entire cohort was 82 kg (± 22.5; IQR: 70.25 - 92.75). In Group 1, the mean weight was 82.5 kg (± 22; IQR:71 - 93), and in Group 2, it was 80 kg (IQR: 70 - 86.5) ($p = 0.701$). The mean body mass index (BMI) for the whole group was 30.071 (IQR: 25.53 - 31.244). In Group 1, the mean BMI was 30.057 (IQR: 25.712 - 31.221), while in Group 2 was 29.141 (± 0.2754; median 30.11, IQR: 23.567 - 32.488) ($p = 0.4605$).

Overall, 54% of patients were vaccinated. Vaccination coverage was 55.8% in Group 1 and 40.9% in Group 2 ($p = 0.1214$). The median number of days from symptom onset to admission was 4 (IQR: 3 - 5) for the entire group. This value was the same for non-hospitalized patients (4; IQR 3 - 5) and slightly higher for hospitalized patients (5; IQR: 3 - 6). The median length of hospitalization for Group 2 patients was 8 days (IQR: 5.5 - 10) ($p < 0.000$).

The overall mortality rate was 0.51% whereas in Group 2 it was 4.34%. Only one patient died.

The most common comorbidities were: obesity: 52% overall (51.9% in Group1, 53.8% in Group 2, $p = 0.65$), arterial hypertension: 34.5% overall (34.3% in Group 1, 36.4% in Group 2; $p = 0.8472$). The rate of at least one cardiovascular disease, including arterial hypertension, ischemic heart disease, arrhythmias (sinus tachycardia, atrial fibrillation, atrial and ventricular extrasystoles, cardiac ablation), heart failure, venous thrombosis, left or right bundle branch block (LBBB/RBBB), myocardial infarction, coronary bypass, valvular disease, cardiac defibrillator implantation, and resuscitated cardiorespiratory arrest, was 44.7% in the whole cohort, with not statistically significant difference among groups, 44% in Group 1 and 50% in Group 2 (hospitalized patients).

Other comorbidities were represented by respiratory diseases were present in 11.2% of all patients (12.1% in Group 1 and 0.0% in Group 2; $p = 0.1541$). Reported conditions included atelectasis, pulmonary fibrosis, sinusitis, bronchial asthma, chronic bronchitis, and sleep apnoea syndrome. Gastrointestinal diseases were found in 9.64% of patients (9.7% in Group 1 and 9.1% in Group 2; $p = 0.9258$). These included

gastroesophageal reflux disease, irritable bowel syndrome, oesophageal varices, cholecystectomy, hiatal hernia, intestinal obstruction, gastritis, and gastric ulcer.

Hepatic diseases were diagnosed with 3.05% of patients (2.9% in Group 1 and 4.5% in Group 2; p = 0.6648). Documented conditions included gallstone disease, cholecystectomy, hepatic steatosis, chronic HCV infection, and polycystic liver disease. Renal diseases were present in 5.08% of patients (4.0% in non-hospitalized patients and 13.6% in hospitalized patients; p = 0.0529). These included chronic kidney disease, congenital single kidney, kidney transplant, glomerulonephritis, hydronephrosis, and polycystic kidney disease.

Endocrine diseases, except diabetes discussed separately, were reported in 9.64% of patients (9.1% in Group 1 and 13.6% in Group 2; p = 0.5021). Identified disorders included Graves' disease, hypothyroidism, thyroid nodules, pituitary adenoma, thyroidectomy, prolactinoma, and osteoporosis.

Metabolic diseases, namely dyslipidaemia and gout, were present in 9.14% of patients overall (7.47% in non-hospitalized patients and 21.7% in hospitalized patients; p = 0.1192).

Malignant diseases were diagnosed in 9.14% of patients (8.6% in Group 1 and 13.6% in Group 2; p = 0.4383). Reported cancers included non-Hodgkin lymphoma, multiple myeloma, leukaemia, lung cancer, breast cancer, bladder cancer, cervical cancer, colon cancer, Kaposi's sarcoma, and tongue carcinoma. Neurological and psychiatric diseases were present in 6.09% of patients (4.6% in non-hospitalized patients and 18.2% in hospitalized patients; p = 0.0121). Reported conditions included encephalopathy, ischemic and haemorrhagic stroke, hearing loss, polyneuropathy, sinus thrombosis, cavernoma, and depressive syndrome.

Socio-demographic data, comorbidities, the median number of days from symptoms onset to hospital admission for the studied group, case fatality rate are presented in Table I.

Table I

Socio-demographic characteristics and comorbidities of the patients

Variables		*All patients (n = 197)*	*Group 1 (outpatients = 174)*	*Group 2 (inpatients = 23)*	*p-value (inpatients vs outpatients)*
Sex %	**Female**	53.80%	54.60%	47.80%	0.7046
	Male	46.20%	45.40%	52.20%	
BMI		30.07 (25.530 - 31.244)*	30.057 (25.712 - 31.221)*	29.14 ± 6.06**	0.4605
Weight (Kg)		82.00 (70.25 - 92.75)*	82.50 (71 - 93)*	81.31±17.806**	0.7010
Comorbidities	**Diabetes mellitus**	11.20%	11.70%	7.70%	0.5470
	Hypertension	34.50%	34.30%	36.40%	0.8472
	Obesity	52.00%	51.90%	53.80%	0.6500
	Heart disease	44.70%	44%	50%	0.5946
	Genetic disease	2.54%	2.90%	0%	0.4231
	Chronic gastro-intestinal disorders	9.64%	9.70%	9.10%	0.9258
	Chronic endocrine disease	9.64%	9.10%	13.60%	0.5021
	Chronic haematological disease	2.54%	2.90%	0.00%	0.4231
	Chronic hepatic disease	3.0%	2.90%	4.50%	0.6648
	Chronic malignant disease	9.1%	8.60%	13.60%	0.4383
	Chronic metabolic disease	23.9%	23.4%	27.3%	0.1192
	Chronic neuro-psychiatric disease	6.09%	4.60%	18.20%	0.0121
	Chronic pulmonary disease	11.2%	12.1%	0.00%	0,1541
	Chronic renal disease	5.08%	4.00%	13.60%	0.0529
	Chronic auto-immune disease	5.6%	6.3%	0.00%	0.2274
Vaccination rate		54.00%	55.80%	40.90%	0.1214
Age		52 (42.750 - 69.250)*	52 (42.000 - 68.000)*	58.652 ± 18.0696**	0.2733
Illness day on admission		4 (3 - 5)*	4 (3 - 5)*	5 (3 - 6)*	0.1812

Variables	*All patients (n = 197)*	*Group 1 (outpatients = 174)*	*Group 2 (inpatients = 23)*	*p-value (inpatients vs outpatients)*
Risk score	2 (1 - 3)*	2 (1 - 3)*	3 (2 - 3)*	0.3788
Length of stay (days)	-	-	8 (5.5 - 10)*	< 0.0001
Case fatality rate	0.51%	0.00%	4.34%	

*Data are expressed as median IQR (Q1 - Q3), for variables with non-gaussian distribution, ** Data are expressed as mean ± SD, for variables with gaussian distribution, Chi-square test was used for the binary variables

Clinical manifestations

The most common symptoms observed among enrolled patients were: fever in 57.9% of all patients, 56.3% in Group 1, and 69.6% in Group 2 (p<0.00001), dry cough in 54.6% of patients overall, 55.3% in Group 1, and 50% in Group 2 (p = 0.2739) and headache in 45.9% of patients, 47.5% in Group 1, and 34.8% in Group 2 (p = 0.3398). Myalgias was present in 34.4% of patients, with equal distribution between Group1 (34.4%) and Group 2 (34.8%) (p = 0.8389), asthenia was reported by 31.7% of all patients, 29.4% in Group 1 and 47.8% in group 2 (p = 0.0498), dizziness observed in 2.06% of patients, 1.17% in Group 1, and 8.7% in Group 2 (p = 0.014). Dyspnoea was reported by 2.73% of patients, 1.25% in Group 1, and 13% in Group 2 (p = 0.0009), dysphagia was present in 15.3% of patients overall, 16.3% in group 1, and 8.7% in Group 2 (p not significant) and chills were reported in 36.1% of patients, 37.5% in Group1, and 26.1% in Group 2 (p = 0.179). Syncope was observed in 2.19% of patients, 0.0% in Group 1, and 17.4% in Group 2 (p = <0.00001). Analysing the patient profile, we observed that all individuals developed at least one clinical symptom, with fever, cough, and headache being the most frequently reported (Table II).

Table II

Clinical symptoms in Covid-19 patients

Symptom	*All patients (n = 197)*	*Group 1 (outpatients = 174)*	*Group 2 (inpatients = 23)*	*p-value*
Ageusia	3.85%	3.77%	4.35%	0.856
Dizziness	2.06%	1.17%	8.70%	0.014
Anosmia	10.90%	10.60%	13%	0.6652
Asthenia	31.70%	29.40%	47.80%	0.0498
Headache	45.90%	47.50%	34.80%	0.3398
Confusion	0.54%	0.62%	0.00%	< 0.0001
Diarrhoea	7.1%	5.63%	17.40%	0.0315
Dysphagia	15.30%	16.30%	8.70%	0.3897
Dysphonia	2.19%	2.50%	0.00%	0.456
Dysgeusia	0.54%	0.62%	0.00%	0.7116
Dyspnoea	2.73%	1.25%	13.00%	0.0009
Thoracic pain	2.73%	1.88%	8.70%	0.0518
Fever	57.90%	56.30%	69.60%	< 0.0001
Chills	36.10%	37.50%	26.10%	0.179
Nausea	6.56%	5.63%	13%	0.1538
Loss of appetite	3.83%	1.88%	17.40%	0.0002
Syncope	2.19%	0.00%	17.40%	< 0.0001
Myalgia	34.40%	34.40%	34.80%	0.8389
Sweating	5.61%	5.20%	8.70%	0.453
Dry cough	54.60%	55.30%	50.00%	0.2739
Semi productive cough	1.60%	1.20%	4.50%	0.2739
Productive cough	9.30%	8.10%	18.20%	0.2739

Looking at symptoms in our patients we have noticed that in hospitalized group the rate of fever, dizziness, asthenia, confusion, diarrhoea, dyspnoea and syncope were statistically significantly higher compared to out-patient group. This can be explained that some of these symptoms like dyspnoea, syncope, confusion are associated with severe form of COVID 19 and the others were criteria for addition independently from the severe diseases. The variability of symptoms reflects the fact that COVID-19 is a multysistem disease, with a considerable heterogeneity of manifestations [28].

As clinical manifestations, mild pneumonia was diagnosed in 40 % of all patients, 42.4% of patients in the first group and 20% of patients in the second group (p < 0.0001), while moderate pneumonia was present in 17.40% of all the study group, in 12.90% of the patients in the first group and 55% of patients in the second group (p < 0.0001). These statistics data were performed using Chi-square test.

Table III shows the biological parameters evaluated in patients from the two study groups.

Table III

Biological characteristics of patients

Variables	*All patients (n = 197)*	*Group 1 (outpatients = 174)*	*Group 2 (inpatients = 23)*	*p-value (inpatients vs outpatients)*
Albumin (g/dL)	4.50 (4.3 - 4.7) *	4.50 (4.3 - 4.7) *	4.16 ± 0.78 **	0.1221
aPTT (s)	29.45 (25.45 - 32.85) *	29.20 (25.375 - 32.825) *	30.74 ± 4.05 **	0.2610
CP (%)	95.00 (85.8 -104) *	94.80 (85.8 - 104) *	97.48 ± 17.79 **	0.3871
Creatinine (mg/dL)	0.80 (0.7 -1) *	0.80 (0.7 - 1) *	0.9 (0.625 - 1.2) *	0.3829
D-dimer (%)	22.80%	21.80%	30.40% ± 1%	0.2886
Fibrinogen (mg/dL)	365.5 (314 - 426) *	356 (303 - 418) *	432 (368.25 - 527.25) *	0.0003
Glycaemia (mg/dL)	100 (91 - 115) *	100 (91 - 114) *	106 (88.75 -119.25) *	0.4324
Haemoglobin (g/dL)	13.60 (12.4 -14.5) *	13.60 (12.5 -14.5) *	13.10 ± 1.69 **	0.2044
IL6 (pg/mL)	38.60 (16.45- 197) *	37.50 (11.15 - 91.1) *	62.60 (20.2 - 325.15) *	0.6219
LDH (U/L)	225.00 (191 -267.75) *	224.00 (186.75 - 260.5) *	274.31 ± 78.53 **	0.0560
Lymphocyte count (x 10^3/mm^3)	1.00 (0.770 - 1.320) *	1.025 (0.8 - 1.32) *	0.90 (0.608 - 1.2) *	0.2089
Lipase (U/L)	158.667 ± 90.92**	94.00 (61 - 127) *	177.14 ± 94.16 **	0.1880
Neu/Ly ratio	2.79 (1.977 - 5.081) *	2.715 (1.977 - 4.907) *	4.66 (2.762 - 6.212)	0.0703
Neutrophil count (x 10^3/mm^3)	3.21 (2.353 - 4.3126) *	3.125 (2.33 - 4.13) *	4.83 (2.73 - 5.567)	0.1461
White Blood Cell count (x 10^3/mm^3)	4.99 (3.953 - 6.255) *	4.93 (3.925 - 6.145) *	6.37 (4.345- 7.065)	0.4305
CRP (mg/L)	9.39 (4.36 - 27) *	8.58 (3.878 - 20.575) *	44.90 (32.2 - 84.1)	< 0.0001
Total protein (g/dL)	7.50 (7.1 - 7.8) *	7.50 (7.1 - 7.8) *	7.31 ± 0.73 **	0.2159
AST (U/L)	35.50 (28 - 46) *	35.00 (27.25 - 45) *	46.00 (35.25- 53) *	0.0176
ALT (U/L)	27.50 (19.5 - 40) *	27.00 (19.75 - 40) *	32.00 (19.25 - 42.75) *	0.6389
Platelets (x 10^3/mm^3)	189.00 (157.75 - 242.25) *	190.00(158 - 247) *	186.04 ± 55.47 **	0.1050
Urea (mg/dL)	32.00 (25-40.75) *	31.00 (25 - 40) *	35 (27.5 - 44) *	0.5305
ESR (mm/h)	22.00 (13 -33) *	22.00 (12 - 32) *	25.00 (19 - 43) *	0.4673

* Data are expressed as median IQR (Q1-Q3), for variables with non-gaussian distribution, ** Data are expressed as mean ± SD, for variables with gaussian distribution

It was analysed the distribution of abnormal biological tests, presented in Table III including levels of: albumin and seric protein, hepatic enzymes (alanine-aminotransferase), tissue injury (aspartate aminotransferase, lactate dehydrogenase), renal markers (urea, creatinine), inflammation markers (fibrinogen, erythrocytes sedimentation rate, C reactive protein), blood cells number (leucocytes, neutrophils, lymphocytes, platelets), haemoglobin, coagulation markers (D Dimers, aPTT). We observed that only some inflammation makers, namely CRP and fibrinogen as well as AST were statistically significantly higher among hospitalized patients. As shown in table III, CRP levels were markedly elevated in hospitalized patients with more severe clinical presentations, indicating that the rise in CRP is significant both clinically and statistically.

The distribution was assessed, for each lot and sublot separately, using Shapiro Wilk test, P value was assessed using Mann-Whitney test for non-normally distributed variables and independent sample t-test for normally distributed variables.

Risk Factor Score Development

At least one comorbidity was present in the patients enrolled in the study. To better assess the risk of adverse outcomes in individuals with SARS-CoV-2 infection, we developed a composite risk score. This score consisted of seven parameters assessed at first presentation: high arterial hypertension (arterial pressure over 140/90 mmHg), BMI over 30, blood glucose over 125 mg/dL, fibrinogen over 450 mg/dL, TGO over 36 U/L, elevated D-dimer (1.5 times normal levels), and prothrombin concentration (CP) less than 70%.

These parameters were selected based on their association with unfavourable outcomes in our cohort. Hypertension and obesity were chosen because the most severe forms of disease were observed in patients with these conditions. Blood glucose higher than 125 mg/dL was included to account for patients with previously well-controlled diabetes or undiagnosed diabetes, many of whom developed glycemic disturbances during COVID-19 infection. Fibrinogen was selected as the most relevant inflammatory marker in our study. TGO (AST) was included as a marker of cellular injury, frequently correlated with poor outcomes in COVID-19. D-dimers level and prothrombin concentration were incorporated as indicators of coagulation dysfunction, both of which have been linked to severe disease progression.

Each patient included in the study had at least one risk factor for which they could have been hospitalized. The median risk score for the entire

cohort was 2 (IQR: 1-3). In Group 1 (non-hospitalized patients), the median score was 2 (IQR: 1-3), while in Group 2 (hospitalized patients) it was 3 (IQR: 2-3). The highest recorded score was 6, observed in a non-hospitalized patient from Group 1 who subsequently experienced a favorable evolution after receiving monoclonal antibody therapy with casirivimab-imdevimab. Although the presence of risk factors would have recommended hospitalization of all our studied patients, only 23 patients (group 2) remained hospitalized following administration of monoclonal antibody therapy.

The diagnostic performance of the risk score was evaluated using ROC curve analysis, yielding an AUC of 0.662 (SE = 0.0380; 95% CI: 0.590-0.729; z = 4.265; p < 0.0001). The optimal cut-off value, determined by the Youden index (J = 0.2457), was > 2, corresponding to a sensitivity of 46.79% and a specificity of 77.78 (Figure 1)

Correlation of the Risk Score with Clinical and Biological Parameters

Our risk score demonstrated moderate discriminatory power (AUC = 0.662), with a specificity of 77.78%, making it useful for excluding non-severe cases. Although sensitivity was lower (46.79%), the score retained statistical significance. (Figure 1).

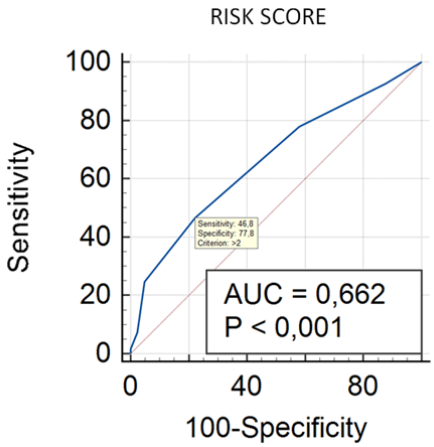

Figure 1.
Specificity and sensitivity of calculated Risk Score in our study

We further explored correlations between the risk score and a set of biological parameters, EKG findings, clinical symptoms, comorbidities, and pneumonia characteristics.

We identified correlations of the severity score using p value statistically significant <0.05 for the following biological parameters: TGP (ALT): Spearman's rho = 0.246, 95% CI 0.106-0.376, p = 0.0007, n = 188; LDH: Spearman's rho = 0.311, 95% CI 0.175-0.435, p < 0.0001, n = 187; ESR: Spearman's rho = 0.369, 95% CI 0.218-0.502, p < 0.0001, n = 144; CRP: Spearman's rho = 0.338, 95% CI 0.190-0.471, p < 0.0001, n = 154 and Urea: Spearman's rho = 0.343, 95% CI 0.209-0.463, p < 0.0001, n = 187. The severity score also correlates with the presence of ECG abnormalities (any type): Spearman's rho = 0.178, 95% CI 0.023-0.324, p = 0.0244, n = 160 and with QTc interval changes: Spearman's rho = 0.333, 95% CI 0.187-0.464, p < 0.0001, n = 160.

Analysing clinical symptoms, the severity score correlates with ageusia (p value <0.05): Spearman's rho = 0.170, 95% CI 0.025-0.308, p = 0.0216, n = 183; anosmia: Spearman's rho = 0.200, 95% CI 0.057-0.335, p = 0.0066, n = 183 and headache: Spearman's rho = -0.166, 95% CI -0.304 to -0.0215, p = 0.0247, n = 183.

Comorbidities that correlate with severity score (p value <0.05) are: metabolic diseases: Spearman's rho = 0.203, 95% CI 0.065-0.333, p = 0.0042, n = 197; diabetes mellitus: Spearman's rho = 0.222, 95% CI 0.085-0.351, p = 0.0017, n = 197; hepatic disease: Spearman's rho = 0.151, 95% CI 0.012-0.285, p = 0.0340, n = 197 and cardiac disease: Spearman's rho = 0.512, 95% CI 0.401-0.608, p < 0.0001, n = 197.

The severity score has a significant correlation with the presence of pneumonia (of any kind): Spearman's rho = 0.286, 95% CI 0.149-0.411, p < 0.0001, n = 190 and also with the type of pneumonia (mild or moderate): Spearman's rho = 0.332, 95% CI 0.199-0.453, p < 0.0001, n = 190 (Figure 2).

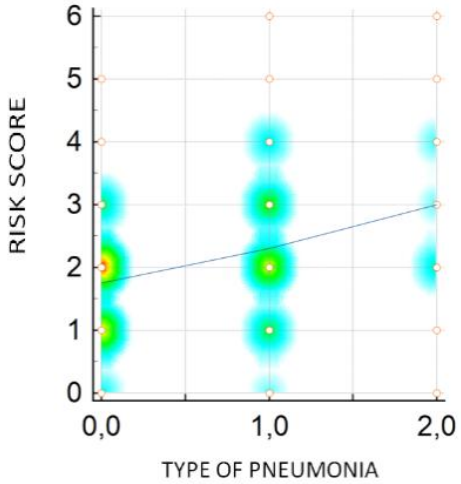

Figure 2.
Risk Score distribution by type of pneumonia

A simple linear regression was performed to evaluate the relationship between the risk score and patient age. The model was statistically significant (F (1,195) = 41.264, p < 0.0001), with an R^2 = 0.1747, indicating that approximately 17.47% of the variance in the risk score was explained by age. The regression equation was: Risk score (y) = 0.4603 +

0.03184 × Age. Colour intensity corresponds to the number of cases - the transition from cool to warm colours represents the variation from fewer to more cases (red-yellow-green-blue), warmer colours is for higher values, while cooler is for lower values. The analysis of variance indicates that the regression model explains part of the variability in the risk score, with a regression sum of squares of 58.4508 (DF = 1, mean square = 58.4508), compared to a residual sum of squares of 276.2193 (DF = 195, mean square = 1.4165).

The slope was statistically significant (β = 0.03184, 95% CI 0.02206-0.04161, p < 0.0001), whereas the intercept was not (β = 0.4603, 95% CI -0.09727-1.0179, p = 0.1051) supporting the fact that there is no significant bias in our Risk Score. Residuals were normally distributed, as confirmed by the Shapiro-Wilk test (W = 0.9862, p = 0.0514).

The analysis of the correlation between the risk score and the age is significant: Spearman's rho = 0.432, 95% CI 0.311 to 0.539, *P*<0,0001, *n* = 197, (Figure 3).

Severity scores have also been developed in other countries and have been described in numerous articles. In the USA, a short-term mortality prediction score called VACO was developed [16].

Among individuals who test positive for COVID-19, the VACO Index provides an accurate estimate of short-term mortality risk across diverse patient groups. Although is slightly overestimates risk in more recent periods, it consistently identifies those at highest relative risk. The VACO Index may help determine which individuals should maintain social distancing, guide prioritization for vaccination, and, in outpatients with SARS-CoV-2 infection, highlight those who require closer clinic monitoring or mono-clonal antibody therapy.

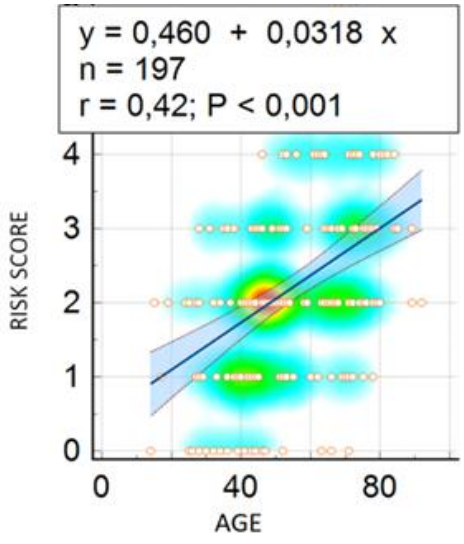

Figure 3.
Age *vs*. Risk score: Regression and Density Visualization

Another kind of score, used as a triage tool, based only on clinical assessment, for the prediction of adverse outcome in acutely ill adults suspected for COVID-19 infection, was described in an article published in 2021[13]. This score can be used to support decision-making in emergency care.

"COVID-19 Severity Index" is a score developed as another triage tool, based on the NEWS-2 score, that was demonstrated that it can rapidly and reliably be used by healthcare personnel to identify high risk patients. The authors of the article made a comparison between COVID-19 Severity Index, NEWS score adapted by Liao *et al*.5 and NEWS-2 score was made. All three EWS were measured on the first, second and third day after hospital admission [14].

The COVID-19 pandemic constituted an unprecedented challenge for the whole world, demanding pressing prevention and treatment research.

The World Health Organization (WHO) estimated 14.83 million excess deaths globally, which represents 2.74 times more deaths than the 5.42 million cases reported due to COVID-19 for 2020 and 2021. There are wide variations in the excess death estimates across the six World Health Organization regions.

These include both direct COVID-19 deaths but also deaths due to the broader impact of the pandemic [25].

The estimate for the number of deaths between January 1,202, up to February 11, 2024, in 234 countries and territories is 7.031 million cases, and the number of infections was 774631 million cases [7].

During a critical period, when the wave of infections seemed unstoppable, the introduction of monoclonal antibody treatment has brought a new hope, as numerous studies conducted in different countries around the world have confirmed a decrease in disease progression and a reduction in the need of hospitalization of patients with SARS-COV-2 infection, despite the presence of comorbidities or risk factors.

Several monoclonal antibodies (mAbs) direct against the Receptor binding domain of the S protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) received an Emergency Use Authorization for outpatient management of mild to moderate manifestation from COVID-19. The FDA, in United States, and the EMA, in European countries have given advice for the use of two combinations of monoclonal antibodies, casirivimab and imdevimab (REGN-COV2) and bamlanivimab and etesevimab in outpatients who are not needing supplemental oxygen and who are at high risk of progressing severe disease. Casirivimab (REGN10933) and imdevimab (REGN1098) are two noncompeting, neutralizing human IgG1 antibodies that target the receptor-binding domain of the SARS-CoV-2 spike protein, thus blocking the attachment and entry of

SARS-CoV-2 into human cells. *A single intravenous dose of* the "cocktail" of casirivimab 1200 mg and imdevimab 1200 mg (REGN-COV2) reduced SARS-CoV-2 viral load (VL), COVID-19 hospitalization days or medical visits when administered within seven days from the onset of symptoms compared to placebo [24].

The authorisation was based on the results of a study from 799 non-hospitalised patients (so-called "outpatients") in a randomised, double-blind, controlled trial with a placebo. Significant reductions were observed in the level of the viral load, with fewer medical visits within 28 days of receiving the cocktail of mAb [9].

The efficacy of the combination of monoclonal antibodies casirivimab and imdevimab was demonstrated in a trial that showed a significant reduction in viral load and faster recovery rates in the group that received treatment with monoclonal antibodies than those in the control group. In the sub-analysis of the same study, the combination of antibodies was administered preventively in children between 12 and 17 years of age, showing that none of the infected patients developed symptoms related to the infection and only 2% of participants under 50 years of age showed symptomatic disease [12].

The course of SARS-CoV-2 infection has proven unpredictable, often marked by the development of severe, life-threatening complications or death even in otherwise healthy persons, more so in older patients, with comorbidities and particular

Pre-existing cardiovascular diseases significantly increases the risk of severe COVID-19, which negatively impact on survival. A study published in 2022 reported that the risk of death among patients with heart disease was more than 3,5 times higher than in patients without a prior history of cardiovascular disease [5].

In some patients the outcome was unfavourable, leading to septic shock, acute kidney injury, rhabdomyolysis, and disseminated intravascular coagulation. Moreover, multiple organ dysfunctions-including cardiac, renal, hepatic, and neurological damage-was also observed [31].

The most common complications of COVID-19 reported from the beginning of the pandemic were: acute respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, disseminated intravascular coagulation, renal or hepatic dysfunction, and pulmonary thromboembolism. According to the CDC, among all underlying medical conditions associated with a higher risk of severe COVID-19, age remains the most important factor, as the risk of adverse outcomes increases significantly with advancing age [6]. A Chinese meta-analysis reported higher rates of cardiometabolic diseases in patients admitted to the ICU (Intensive Care Units) compared with non-hospitalised patients. Arterial hypertension and diabetes were twice as frequent, and cardio-cerebrovascular diseases were three times more frequent in the group of patients hospitalised in the ICU, than the group of non-ICU patients [5]. In addition to cardiovascular disease, diabetes and age, obesity represent as well one of the most important risk factors for severe progression of SARS-COV2 infection [5].

We aimed to analyse the incidence of comorbidities and risk factors in the group of patients with SARS-COV2 infection who received treatment with the combination of monoclonal antibodies casirivimab-imdevimaB, as well as how this treatment influenced the subsequent evolution of the patients.

In our study, the mean age of patients was similar between analyzed groups 53 and 58.65 years respectively, with interquartile range overlapping, findings consistent with previously published data. Stratan and colleagues published a study from our hospital, finding a similar mean age for 330 in-patients with SARS CoV 2 infection, 58.2 ± 14.8 years [38]. Patients with one or more comorbidities were at increased risk of poor outcome, as many studies showed [41]. Among the numerous comorbidities that influence the course of SARS-CoV-2 infection, hypertension, obesity, and diabetes mellitus were identified as having the greatest impact. In a study of 5,700 patients with COVID-19 in New York City, hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) were the most frequently reported comorbidities [44,39].

Several studies worldwide have further demonstrated that COVID-19 patients with hypertension had a higher risk of mortality compared to those without hypertension. In our study, 34.5% of patients had high blood pressure [44,43]. SARS-CoV-2 infection also revealed unexpected cardio-vascular vulnerabilities at all stages of disease (pre-infection, acute, and chronic phases). In our cohort, 44.7% of patients had at least one cardiovascular disease with similar distribution among groups (44% versus 50%), suggesting that in our studied cases, cardiovascular diseases, including arterial hyper-tension was not associated with higher risk of hospitalization. Our results are consisting with results from another study carried on in our hospital in the same period [32]. On the other hand, the results of another study identified higher percentages of hospitalized patients who had hypertension (51.4%), which was the most common associated condition. [1];

Obesity significantly impacts the severity of COVID-19, as is already well known. Although adipose tissue was once considered an inert energy store, it is now recognized as an active endocrine organ, secreting adipokines, chemokines, and cytokines that profoundly affect metabolism and immune function. Normal adipose tissue maintains a

delicate balance between pro-inflammatory and anti-inflammatory states, mediated by T helper cells (Th2), M2 macrophages, and regulatory T cells (Treg). Obesity disrupts this balance, with reduced Th2, Treg, and M2 macrophages, and increased pro-inflammatory CD8+ T cells and M1 macrophages. This shift promotes systemic inflammation, which may be further amplified by the acute inflammatory response to COVID-19, ultimately resulting in more severe disease and poorer prognosis [23]. This is the main rationale for using cytokine blockers in severe forms of hospitalized COVID 19 cases [38].

Studying the body weight in our patients, we found a mean of 82 kg (±22.5; 70.25-92.75) and mean BMI of 30.07 (25.53 - 31.24) for the entire cohort, with similar distribution among groups, as it was presented in Table I, showing a high rate of obesity (52%) in studied cases. Our results are similar with those from published data by many researchers all over the world, including our country [19, 27].

In addition to hypertension and obesity, diabetes mellitus is strongly associated with the severity and prognosis of COVID-19 [4, 36].

Large-scale studies have shown that individuals with type 2 diabetes have an increased risk of death compared to non-diabetics, while those with type 1 diabetes are at even higher risk [4, 21, 30, 37]. Fatal or critical cases of COVID-19 among diabetic patients were often associated with poor glycaemic control, more comorbidities, diabetes-related complications (*e.g.*, retinopathy), and prior hospitalizations for events such as ketoacidosis or hypoglycaemia [20, 39]. In our study, diabetes mellitus was present in 11.2% of patients (11.7% in group 1 and 7.7% in group 2, $p = 0.547$). Thus, diabetes was not a common condition in our cohort, though these patients require particular attention.

Clinical manifestation analysis showed that in our studied patients, taste or smell impairment was not associated with a higher rate of hospitalisation, while dizziness, confusion, diarrhoea, dyspnoea and dyspnoea were statistically significantly less frequent among outpatients. Our results are similar with conclusion of other studies from Romania, showing that asthenia, dizziness, confusion and dyspnoea are frequent symptoms at admission in hospital [11].

Notably, 49 - 75% of patients with COVID-19 world-wide had no comorbidities yet could still develop severe disease or even die, pointing out to implication of the immune response to the SARS CoV 2 infection in poor outcome. A study published in early 2022 analysed the risk factors associated with disease progression in patients without preexisting comorbidities [17]. The overall severity rate was 34.29%, with a mortality rate of 2.1%. Indicators associated with progression from mild to severe disease included older age, impaired respiratory function ($SpO_2 < 95\%$, dyspnoea), coagulation disorders (prolonged APTT, elevated D-dimer), and markers of tissue injury (elevated AST and LDH). In our patients only tissue injury markers AST and LDH were statistically significant more frequently in hospitalized patients, but the other above mentioned biologic markers, suggesting that in our study we included higher number of mild cases, due to criteria of inclusion in our study and natural history of SARS CoV 2 infection. There were included in this study patients in just few days after symptoms onset, while severe manifestations are usually present in the second week of the disease.

Severe bacterial infections, as reflected by inflammatory markers, also significantly increased the risk of severe COVID-19 in otherwise healthy individuals. Laboratory changes indicating multi-organ involvement were strongly correlated with mortality in these patients [17]. Our studied groups had similar distribution of the markers multisystemic impairment, mainly due to inclusion criteria, mentioned above. We found high levels of inflammation markers more often in hospitalized studied patients, which can be explained by the characteristics of the disease, namely inflammatory response is the main mechanism of complication in COVID 19.

Coagulation markers, particularly D-dimers and fibrin degradation products, are essential in assessing the prothrombotic state. Patients who died had significantly higher levels of D-dimers, fibrin degradation products, prothrombin time, and activated partial thromboplastin time compared to survivors, situation noted by the researchers from the beginning of the pandemic, as a Velavan and Meyer highlighted in an article published in International Journal of Infectious Diseases in April 2020. In our study, hospitalized patients had similar levels of coagulation markers as outpatients, due to early diagnosis of SARS Cov2 infection in our study [42]. Coagulopathy and disseminated intravascular coagulation were both associated with high mortality rates, with D-dimers > 1µg/L being the strongest independent predictor of death [41]. Common biochemical abnormalities in COVID-19 include elevated LDH, ALT, AST, and total bilirubin, along with decreased albumin [33]. Patients with severe disease are more frequently developed liver dysfunction compared to those with milder disease.

Based on these observations, we developed a severity score incorporating seven relevant variables: presence of hypertension, blood glucose > 125 mg/dl (indicating poor glycaemic control), BMI >30, fibrinogen > 450 mg/dl, AST > 36 U/L, elevated D-dimers, and CP < 70%.

Each patient was evaluated according to this scoring system, and the results were compared between the two study groups. Patients in group 1 had scores ranging from 1 to 3, with a mean of 2. Patients in

group 2 had scores ranging from 2 upward. The risk scores correlated significantly with ALT, LDH, urea, ESR, as well as with age, cardiovascular disease, and pneumonia.

The study had limitations due to retrospective observational design, selection bias induced by the fact that the patients were not randomized and they were addressed to one hospital, mainly according to the catch-up area, the small number of included in the group of hospitalized patients and lack of a control group not treated with mAb.

Conclusions

The severity score proved to be a useful tool for evaluating and managing patients, as it facilitated rapid prognosis estimation and treatment planning. Despite the presence of significant risk factors, the administration of monoclonal antibodies was followed by a marked reduction in hospitalizations (174 patients included in group 1) and a very low mortality rate, with only one death among hospitalized patients.

The way in which monoclonal antibody treatment has radically changed the course of the disease in patients with COVID-19 highlights the essential role of innovative treatment methods in changing the course of severe diseases.

Conflict of interest

The authors declare no conflict of interest.

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