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ORIGINAL RESEARCH

Analysis of Deaths and Favorable Developments of Patients with SARS-CoV-2 Hospitalized in the Largest Hospital for Infectious Diseases and Pneumo-Phthisiology in the West of the Country

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Purpose: Romania is one of the European countries that has been hit the hardest by the severe acute respiratory syndrome caused by the new coronavirus SARS-CoV-2, with over 1.91 million reported cases and over 59,257 deaths. The aim of this study was to identify the main predictors of death in hospitalized patients.

Patients and Methods: In the period from 1 March 2020 to 30 June 2021, an observational, retrospective, randomized, case-control study was conducted, which included a sample of 139 patients who died in hospital and another sample of 275 patients who had been discharged in an improved or healed condition. Confirmation of COVID-19 cases was performed by RT-PCR from nasopharyngeal and oropharyngeal exudates. Statistical data were analyzed by logistic regression, Cox regression and a comparison of survival curves by the log-rank (Mantel-Cox) test.

Results: The most powerful logistic regression model identified the following independent predictors of death: history of coagulopathy HR = 30.73 [1.94–487.09], p = 0.015; high percentage of neutrophils HR = 1.09 [1.01–1.19], p = 0.027; and decreased blood-oxygenation HR = 53881.97 [1762.24–1647489.44], p < 0.001. Cox regression identified the following factors that influenced the evolution of cases: history of coagulopathy HR = 2.44 [1.38–4.35], p = 0.000; O_2 saturation HR = 0.98 [0.96–0.99], p = 0.043; serum creatinine HR = 1.23 [1.08–1.39], p = 0.001; dyspnea on admission HR = 2.99 [1.42–6.30], p = 0.004; hospitalization directly in the ICU HR = 3.803 [1.97–7.33], p < 0.001; heart damage HR = 16.76 [1.49–188.56], p = 0.022; and decreased blood-oxygenation HR = 35.12 [5.92–208.19], p < 0.001.

Conclusion: Knowledge of the predictors of death in hospitalized patients allows for the future optimization of triage and therapeutic case management for COVID-19.

Keywords: complications, comorbidities, COVID-19, protection factors, risk factors, survival

Introduction

Since the onset of the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, more than 337 million cases and more than 5.5 million deaths have been confirmed worldwide, corresponding to an average fatality of 1.65%.[1]

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In Romania, more than 1.91 million cases have been reported as of 16 January 2022, with 59,257 deaths attributable to coronavirus disease 19 (COVID-19), leading to an average fatality rate of 3.09%, which is higher than the international rate.[2] The first Romanian studies on the risk factors for death with COVID-19 identified endogenous factors, including age, male sex and comorbidities such as cardiovascular, renal, and oncological diseases as well as immunosuppression.[3]

Later, diabetes and obesity were added to the list of risk factors, which is significant for a population in which the prevalence of diabetes is estimated at 11.6%, with 18.4% at the prediabetic stage, and where 31.9% and 34.7% of adults aged 20 to 79 years are obese or, overweight, respectively, according to the National Study on the Prevalence of Diabetes, Prediabetes, Overweight, Obesity, Dyslipidemia, Hyperuricemia and Chronic Kidney Disease (PREDATORR).[4–6] In addition to these factors, there are those who are also undiagnosed, given that one in three diabetic European adults do not know their status.[7] The literature also identifies other comorbidities that have an unfavorable influence on the outcome, such as: dyslipidemia, chronic neurologic diseases (Parkinson's disease), chronic obstructive pulmonary disease (COPD), or pregnancy.[8–11]

In addition, 56.4% of the total Romanian population belongs to the urban environment, with a higher population density that favors the transmission of SARS-COV-2. The proportion of the population over 60 years of age reached 23.5% in 2020, and the number of doctors from 34 to 10,000 inhabitants is lower compared with other European countries, with a systematic migration in the last decades (according to international studies); these factors all contribute to the increase in case fatality rate.[12–15]

Hesitant behavior in the face of vaccination, which places Romania in the penultimate position among European Union countries (38.81% of the population completely vaccinated on 2 December 2021), the relaxation of the population, with non-adherence to preventive behaviors in 2021, and subsequent overcrowding has led the country to the highest COVID-19 mortality rate in the European Union (the second highest as of November 2021 with 586 deaths/day) and one of the highest per capita death rates in the world.[16–19] There are several factors that have contributed to this situation:

- The establishment of severe restrictions, with mandatory hospitalization, even for asymptomatic cases, in the first months of the pandemic, thereby increasing the population's anxiety, resulting in an avoidance of medical services, especially among the population with limited medical knowledge;
- the incomplete application of preventive measures and premature relaxation, without justification in vaccine coverage or pandemic trends;
- only performing a small number of PCR or antigen tests, with a subsequent underdiagnosing and underreporting of the cases;
- the excessive politicization of the COVID-19 pandemic measures, which led to a lack of trust in the established decisions;
- a pro-vaccine campaign not adjusted to the different population categories;
- the spread of false information, the presentation of conspiracy theories, not only in social media networks, but even in traditional media, with encouragement from the anti-vaccine movement;
- the behavior of a segment of healthcare workers refusing the vaccine and being very vocal on social media;
- the ambivalent role of the church.[20–22]

Under these conditions, an efficient management of material and human resources is vital, in a health system with limits accentuated by the pandemic context.

The main objective of the study is to identify predictive factors, both clinical and paraclinical, independent of the in-hospital mortality of COVID-19 patients hospitalized in the largest clinic for communicable diseases in western Romania.

Patients and Methods

Inclusion Criteria

In the period between 1 March 2020 and 30 June 2021, an observational, retrospective, randomized, case-control type 2:1 study was carried out that included 414 patients distributed in 2 samples:

a) EI (N1=139), in which there were included all the patients were included who met the criteria for the definition of a confirmed case of Acute Respiratory Syndrome with the new- coronavirus hospitalized in Clinic II of the Hospital for Infectious Diseases and Pneumophthisiology of Timisoara and who died during hospitalization;

b) EII (N2=275), which included control subjects, admitted to the same clinic for confirmed SARS-CoV-2 infection, with the condition at discharge discharged or improved, appropriate in terms of age and period of hospitalization.

For each deceased case, the first 2 patients from the list of those hospitalized with COVID-19 were included, in the same month as the case, who were included in the same age group (maximum range of 5 years).

Clinical criteria included the presence of at least one of the following signs and symptoms - cough, fever, shortness of breath, sudden onset of anosmia, ageusia or dysgeusia, gastrointestinal manifestations (eg, vomiting, accelerated transit), with radiological/radioimaging evidence of COVID-19 compatible lesions. The epidemiological criteria included at least one of the following: a) direct contact with a confirmed case of COVID-19, within 14 days prior to the date of onset; b) a resident or staff of institutions for the care of vulnerable persons in the period 14 days prior to the date of onset, and the institution was place in which the transmission of SARS-CoV-2 has been confirmed.

Exclusion Criteria

Patients under the age of 18 and those with psychiatric pathology with impaired discernment were excluded, as it was not possible to obtain informed consent.

Data were collected on demographic variables, symptoms, and comorbidities existing at the time of hospitalization, during period of illness and hospitalization, the need for support ventilation, paraclinical parameters at hospitalization, complications, and the main medicinal products administered. The case-fatality rate was calculated as the proportion of patients who died of COVID-19 out of the total number of patients hospitalized with COVID-19 in the monitored ward.

For a better understanding of the pathology included in the study, we will present the definition of cardiac, hepatic, renal, neurological and pancreatic lesions in COVID-19. Acute cardiac impairment associated with COVID-19 is a decrease in ejection fraction and an increase in troponin I; it is most commonly associated with high blood pressure, coronary heart disease and chronic heart failure.[23–25] Liver damage occurs for a variety of reasons, some may be non-cancerous (benign) and some are cancerous.[26] COVID-19 is often associated with abnormal liver enzymes (with acute liver failure being rare).[27] The kidneys may be affected in COVID-19 and laboratory data will indicate: increased serum creatinine, albuminuria, proteinuria, hematuria and hematoproteinuria; the incidence of acute kidney injury was 5–23% (up to 35%).[28] In patients who have already had acute or chronic kidney damage, the condition may worsen.[29] COVID-19-associated neurological lesions, although often nonspecific, include COVID-19-associated necrotizing leukoencephalopathy, post-hypoxic leukoencephalopathy and clear encephalopathy, and the severity of neurological symptoms ranges from temporary anosmia to dizziness, confusion, convulsions and stroke.[30] Pancreatic lesions caused by COVID-19 include the de novo onset of diabetes mellitus, through direct cell damage to β-pancreatic cells, implicitly numerous ketoacidosis and hyperosmolar coma in critically ill patients and disorders of carbohydrate metabolism.[28]

Molecular Method of Case Certification

The confirmation of acute respiratory syndrome with the new coronavirus was made by detecting SARS-CoV-2 nucleic acid by RT-PCR in the nasopharyngeal and oropharyngeal exudate. In some severe cases, collection was also performed from sputum or tracheobronchial exudate. Confirmation of the COVID-19 case was performed using the CFX-96 Real-Time IVD System (Bio-Rad).

Viral RNA was extracted using the NIMBUS automatic extractor, using the STARMag 96×4 Universal Cartridge Kit (Seegene) extraction kit and amplified with the Allplex 2019-nCoV kit (Seegene, Seoul, South Korea), with amplification of three viral targets and a gene control: a) RdRP gene (Cal Red 610); b) gena N (Quasar 670); c) gene E (FAM); d) internal control (HEX); 45 amplification cycles were used according to World Health Organization (WHO) recommendations. The samples were considered positive when specific SARS-CoV-2 genes were detected.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL). Continuous variables were characterized by median and interval between quartiles (IQR), and category variables were characterized by value and percentage. Data distribution testing was performed with the Kolmogorov–Smirnov test. The numerical variables were compared using the Mann–Whitney *U*-test for independent samples, and the nominal ones were compared using the chi^2 test (Fisher's exact test). In conditions of statistical significance, an OR/RR>1 (95% CI > 1) was considered a risk factor. The variables that met the criteria of statistical significance in the univariate analysis were investigated by logistic regression, with the choice of the model according to the Nagelkerke R^2 coefficient and the test for assessing the deviation from the Hosmer-Lemeshow theoretical model. Predictors of mortality during hospitalization were investigated by Cox proportional hazards regression models. The Kaplan-Meier method with the log-rank (Mantel-Cox) test was used to compare survival. All statistical tests were calculated with 2 extremities and the threshold of statistical significance was considered to be $p \leq 0.05$.

Results

Over a period of one year and three months of pandemic, 139 deaths were recorded on the supervised ward, 84 (60.43%) in 2020 and 55 (39.56%) in the first 6 months of 2021, with a peak frequency in the month of December 2020 (Figure 1). Among the control subjects, 148 (53.82%) patients were discharged as cured and 127 (46.18%) were discharged as improved. The univariate analysis of all the variables studied revealed various variables (Table 1), symptoms (Table 2), comorbidities and complications of the disease (Table 3) and paraclinical investigations and treatment (Table 4).

Logistic regression with all statistically significant variables (excluding those related to treatment) identified three independent risk factors of negative evolution: a) history of coagulopathy HR=30.73 [1.94–487.09], p=0.015; b) high percentage of neutrophils HR=1.09 [1.01–1.19], p=0.027; c) decreased blood-oxygenation HR=53881.97 [1762.24–1,647,489.44], p<0.001 in a model with a Nagelkerke R^2 coefficient of 97.3% and the statistical significance of the test for assessing the deviation from the Hosmer-Lemeshow theoretical model p=0.868.

The logistic regression in which only the variables with the status of risk factors (OR/RR > 1 [CI 95% > 1]), statistically significant, were introduced, led to a model that explains 79.8% of the data variation (Hosmer-Lemeshow test p=0.934), in which the following were noted as independent risk factors for death: a) pulmonary changes identified by CT HR=1.05 [1.02–1.08], p<0.001; b) high percentage of neutrophils HR=1.05 [1.01–1.09], p=0.014; c) serum creatinine HR=2.51 [1.64–3.83], p<0.001; d) IL-6 HR=1.01 [1.00–1.02], p=0.004.

Factors influencing the probability of death during hospitalization, identified by Cox regression, were: a) O_2 saturation - HR=0.98 [0.96–0.99], p=0.043; b) serum creatinine - HR=1.23 [1.08–1.39], p=0.001; c) history of coagulopathy - HR=2.44 [1.38–4.35], p=0.002; d) dyspnea on admission - HR=2.99 [1.42–6.30], p=0.004; e) hospitalization

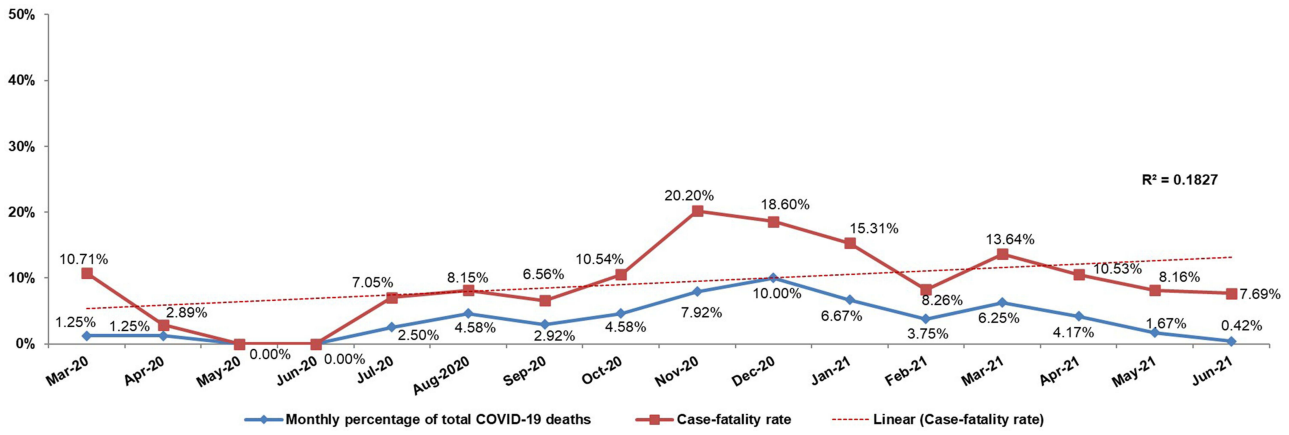

Figure 1 Case-fatality rate and monthly percentage of total COVID-19 deaths between March 2020 and June 2021.

Table 1 Univariate Analysis of Study Variable

Items		EI N1=139	EII N2=275	p	OR [95% CI]
Age [median, IQR]		70.00(20)	70.00(18)	0.245	1.01 [0.99–1.02]
No. hospitalization days [median, IQR]		9.00(11)	11.00(6)	0.617	0.99 [0.96–1.02]
No. ICU hospitalization days [median, IQR]		2.00(9)	0.21(0)	<0.001	1.62 [1.40–1.87]
No. previous days of illness [median, IQR]		6.00(22)	7.00(22)	0.423	0.98 [0.93–1.03]
BMI		30.25(7.26)	29.41(7.12)	0.220	1.03 [0.98–1.07]
F [n, %]		65(46.76)	126(45.82)	0.917	1.04 [0.68–1.60]
M [n, %]		74(53.24)	149(54.18)	0.917	1.04 [0.68–1.60]
U environment [n, %]		97(69.78)	184(66.91)	0.579	1.14 [0.72–1.82]
R environment [n, %]		42(30.22)	91(33.09)		
Occupation at risk - Yes [n, %]		5(3.60)	9(3.27)	1.00	1.10 [0.28–3.75]
Smoking status - Yes [n, %]		9(6.47)	23(8.36)	0.563	0.76 [0.32–1.78]
Direct admission to the ICU - Yes [n, %]		17(12.23)	0.00(0.00)	<0.001	40.39 [6.19–1688.70]
From closed communities –Yes [n, %]		7(5.04)	5(1.82)	0.116	2.86 [0.76–11.64]
Transmision	Community [n, %]	6(4.32)	8(2.91)	0.194	/
	Family [n, %]	30(21.58)	78(28.36)		
	Unknown [n, %]	102(73.38)	181(65.82)		
	Nosocomial [n, %]	1(0.72)	8(2.91)		
Clinical form	Medium/severe [n, %]	130(93.52)	185(67.27)	<0.001	7.03 [3.29–15.52]
	Mild [n, %]	9(6.47)	90(32.72)		

Abbreviations: EI, sample I (patients who dies); EII, sample II (patients discharged alive); N1/N2, number of patients from EI/EII; p, p-value; OR [95% CI], odds ratio and 95% confidence interval; No., number; [median IQR], [median, interquartile range]; [n, %], number and percentage of item; BMI, body mass index; F, female; M, male; U/R environment, urban/rural environment; ICU, intensive care unit.

directly in the ICU - HR=3.803 [1.97–7.33], p<0.001; f) heart damage - HR=16.76 [1.49–188.56], p=0.022; g) decreased blood-oxygenation - HR=35.12 [5.92–208.19], p<0.001.

Kaplan-Meier curves show the factors that influence survival in Figure 2.

The quantification of the differences in survival in the case of comorbidities, irrespective of the occurrence of complications during SARS-CoV-2 infection is presented in Table 5.

Discussion

The analysis of the first 15 months of the pandemic shows an upward trend in the case-fatality rate, but the R2 value is low due to the important variation in the monthly values, so the trend line cannot precisely predict the fatality value at a given moment. There was a decrease in the values in the spring and an increase in the autumn/winter months, with a peak reached in November 2020. This pattern of seasonality seemed to be repeated in 2021, when in the same section, in the context of wave 4 of the pandemic, the fatality rate reached 22.75% in September, 39.62% in October and 44.70% in November. The same seasonal pattern of COVID-19 severity in Europe, with the involvement of environmental factors (low temperature and/or solar radiation) in mortality variability has also been identified in other studies, along with

Table 2 Univariate Analysis of Symptoms

Symptoms	EI	EII	p	OR [95% CI]
Fever – Yes [n, %]	79(56.83)	165(60.00)	0.597	0.88 [0.57–1.36]
Chills – Yes [n, %]	34(24.46)	84(30.54)	0.207	0.74 [0.45–1.20]
Fatigue – Yes [n, %]	126(90.65)	247(89.82)	0.863	1.10 [0.53–2.33]
Cough – Yes [n, %]	108(77.70)	206(74.91)	0.546	1.17 [0.70–1.95]
Odynophagy – Yes [n, %]	15(10.79)	28(10.18)	0.865	1.07 [0.52–2.17]
Rhinorhea – Yes [n, %]	8(5.75)	11(4.00)	0.459	1.47 [0.52–4.04]
Dyspnoea – Yes [n, %]	129(92.81)	190(69.09)	<0.001	5.77 [2.78–12.31]
Chest pain – Yes [n, %]	16(11.51)	31(11.27)	1.00	1.02 [0.51–2.03]
Myalgia – Yes [n, %]	39(28.06)	94(34.18)	0.222	0.75 [0.47–1.20]
Arthralgia – Yes [n, %]	21(15.11)	44(16.00)	0.887	0.93 [0.51–1.70]
Headache – Yes [n, %]	36(25.89)	120(43.64)	<0.001	0.45 [0.28–0.72]
Nausea – Yes [n, %]	20(14.39)	45(16.36)	0.669	0.86 [0.47–1.57]
Accelerated intestinal transit – Yes [n, %]	9(6.48)	35(12.73)	0.063	0.47 [0.21–1.07]
Vomiting – Yes [n, %]	11(7.91)	26(9.45)	0.716	0.82 [0.37–1.81]
Conjunctivitis – Yes [n, %]	0.00(0.00)	0.00(0.00)	/	/
Skin manifestations – Yes [n, %]	0.00(0.00)	4(1.45)	0.305	0.00 [0.00–2.99]
Irritability – Yes [n, %]	10(7.19)	14(5.09)	0.382	1.45 [0.58–3.58]
Coma – Yes [n, %]	6(4.32)	0.00(0.00)	0.001	14.42 [1.81–652.08]
Anosmia/ageusia – Yes [n, %]	6(4.32)	27(9.82)	0.051	0.41 [0.14–1.06]
Decreased/loss of appetite – Yes [n, %]	38(27.34)	78(28.36)	0.826	0.95 [0.59–1.54]
Vertigo – Yes [n, %]	4(2.88)	16(5.82)	0.187	0.48 [0.11–1.53]
Sweating – Yes [n, %]	6(4.32)	13(4.73)	0.850	0.91 [0.28–2.63]
% CT changes [median, IQR]	60.00(25)	35.00(20)	<0.001	1.08 [1.06–1.09]
% O2 saturation at admission [median, IQR]	86.00(10)	91.00(7)	<0.001	0.84 [0.81–0.88]
No. O2 days on the mask [median, IQR]	4.00(8)	6.00(10)	0.784	1.00 [0.97–1.04]
No. non-invasive ventilation days [median, IQR]	0.00(0)	0.00(0)	<0.001	4.12 [2.02–8.39]
No. Invasive ventilation days [median, IQR]	1.00(4)	0.00(0)	<0.001	/
No. ECMO days [median, IQR]	0.00(0)	0.00(0)	0.160	/

Abbreviations: %, percentage; CT, computed tomography; ECMO, extracorporeal membrane oxygenation.

immunological, social, behavioral factors (frequency of travel, compliance with preventive and control measures, quarantine, School functionality, etc.).[31–33]

The univariate analysis identified as risk factors for death the following variables: hospitalization directly on the ICU, number of days of hospitalization in the ICU, moderate and severe clinical form, dyspnea/coma at hospitalization, percentage of lung changes on CT, number of days of noninvasive/invasive ventilation, total number of comorbidities, history of cardiovascular/renal pathology, coagulopathy, or the onset of decreased in blood oxygen

Table 3 Univariate Analysis of Comorbidities and Complications

Comorbidities – Yes [n, %]	**EI**	**EII**	**p**	**OR [95% CI]**
Pregnancy	0.00(0.00)	1(0.36)	1.00	0.00 [0.00–77.16]
Confined under 6 weeks	0.00(0.00)	1(0.36)	1.00	0.00 [0.00–77.16]
Hypertension	99(71.22)	186(67.64)	0.501	1.18 [0.74–1.90]
Cardiovascular pathology	58(41.73)	73(26.54)	0.002	1.98 [1.26–3.12]
Previous diabetes mellitus	49(35.25)	82(29.82)	0.266	1.28 [0.81–2.02]
Overweight	29(20.86)	85(30.91)	0.036	0.59 [0.35–0.98]
Obesity	77(55.39)	129(46.91)	0.119	1.41 [0.91–2.16]
Chronic liver pathology	13(9.35)	13(4.73)	0.085	2.08 [0.88–4.94]
Neurological pathology	27(19.42)	34(12.36)	0.077	1.71 [0.95–3.08]
Chronic renal pathology	20(14.39)	16(5.82)	0.005	2.72 [1.29–5.74]
Chronic pulmonary pathology	15(19.79)	39(14.18)	0.359	0.73 [0.37–1.44]
Oncological pathology	12(8.63)	22(8.00)	0.851	1.09 [0.49–2.39]
Autoimmune pathology	5(3.60)	22(8.00)	0.095	0.43 [0.12–1.20]
Psychiatric pathology	10(7.19)	16(5.82)	0.669	1.25 [0.51–3.03]
Coagulopathy	15(19.79)	11(4.00)	0.010	2.90 [1.22–7.00]
Ulcerative Pathology	4(2.88)	4(1.45)	0.450	2.01 [0.37–10.93]
No. Comorbidities [median, IQR]	3.00(2)	3.00(1)	0.002	1.29 [1.11–1.51]
Complications - Yes [n, %]				
Decreased blood-oxygenation	137(98.56)	1(0.36)	<0.001	18,769 [1472.91–22,026.47]
Hyperglycemia	110(79.14)	193(70.18)	0.060	1.61 [0.97–2.69]
Pancreatic damage	0.00(0.00)	5(1.82)	0.173	0.00 [0.00–2.15]
Secondary infections	20(14.39)	13(4.73)	0.001	3.39 [1.55–7.49]
Sepsis	79(56.83)	17(6.18)	<0.001	19.98 [10.64–37.95]
Thromboembolism	13(9.35)	10(3.64)	0.022	2.73 [1.09–6.93]
Heart damage	138(99.28)	9(3.27)	<0.001	4078.7 [543.88–22,026.47]
Kidney damage	93(66.91)	50(18.18)	<0.001	9.10 [5.56–14.95]
Liver damage	81(58.27)	126(45.82)	0.022	1.65 [1.07–2.55]
Neurological damage	20(14.39)	7(2.55)	<0.001	6.43 [2.52–18.42]

saturation, secondary infections, sepsis, thromboembolism or cardiac/renal/hepatic/neurological damage. A systematic review and meta-analysis of 42 studies and 423,117 patients showed the association that some chronic comorbidities, including acute kidney injury, COPD, diabetes, hypertension, CVD, cancer, increased D-dimer, complications, demographic variables, male gender, old age, being a current smoker and obesity are clinical risk factors for a fatal outcome associated with coronavirus.[34] Furthermore, a series of paraclinical data associated to the clinical form, met

Table 4 Univariate Analysis of Paraclinical Investigations and Treatment

Paraclinic - [Median, IQR]	**EI**	**EII**	**p**	**OR [95% CI]**
No. leukocytes	9280.00(7040)	7090.00(4400)	<0.001	1.00 [1.00–1.01]
% neutrophils	86.70(10.10)	79.80(18.70)	<0.001	1.07 [1.04–1.09]
% lymphocytes	7.40(7.30)	13.20(13.60)	<0.001	0.92 [0.88–0.95]
C-reactive protein	112.80(123.08)	50.12(90.53)	<0.001	1.01 [1.00–1.01]
Procalcitonin	0.23(0.77)	0.06(0.11)	0.114	1.15 [0.97–1.37]
Fibrinogen	5.47(2.43)	5.19(2.40)	0.041	1.11 [1.00–1.22]
Eritrocyte sedimentation rate	55.00(62.00)	25.00(40.00)	<0.001	1.02 [1.02–1.03]
D-Dimers	0.96(1.73)	0.57(0.45)	<0.001	1.15 [1.05–1.25]
Serum creatinine	1.07(0.89)	0.88(0.34)	<0.001	2.44 [1.69–3.49]
Alanin aminotransferase	32.30(31.90)	30.00(29.50)	0.666	1.00 [0.99–1.01]
Aspartat aminotransferase	43.00(36.30)	31.10(25.80)	<0.001	1.01 [1.01–1.02]
Glycemia	162.00(112)	133.00(69)	<0.001	1.00 [1.00–1.01]
Interleukin 6	30.90(70.01)	7.10(18.22)	<0.001	1.01 [1.01–1.02]
Treatment - Yes [n, %]				
Hydroxychloroquine	0.00(0.00)	0.00(0.00)	/	/
Tocilizumab	19(13.67)	18(6.54)	0.027	2.26 [1.09–4.70]
Corticosteroids	137(98.56)	225(81.82)	<0.001	15.22 [3.87–130.68]
Plasma administration	9(6.47)	2(0.73)	0.001	9.45 [1.91–90.61]
Paracetamol	108(77.70)	222(80.73)	0.518	0.83 [0.49–1.41]
Kineret	53(38.13)	72(26.18)	0.012	1.74 [1.10–2.75]
Clexane	22(15.83)	80(29.09)	0.003	0.46 [0.26–0.80]
Fraxiparine	112(80.57)	172(62.54)	<0.001	2.48 [1.49–4.16]
Without anticoagulant	2(1.44)	18(6.54)	0.022	0.21 [0.02–0.89]
Azithromycin	5(3.60)	31(11.27)	0.014	0.29 [0.09–0.79]
Cefort	95(68.35)	121(44.00)	<0.001	2.75 [1.75–4.32]
Meropenem	24(17.27)	4(1.45)	<0.001	14.14 [4.68–56.95]
Darunavir (Norvir)	47(33.81)	109(39.64)	0.294	0.78 [0.50–1.22]
Favipiravir	23(16.55)	80(29.09)	0.007	0.48 [0.28–0.83]/
Remdesivir	30(21.58)	31(11.27)	0.005	2.17 [1.21–3.89]
Resolsta	14(10.07)	22(8.00)	0.601	1.29 [0.60–2.74]

the statistical criteria of risk factor: increased number of leukocytes at hospitalization, percentage of neutrophils, increased acute phase reactants, D-Dimers, serum creatinine, blood glucose, AST and IL-6. After analyzing 414 articles on COVID-19, 34 studies selected the following biomarkers for severe forms: CRP, amyloid A, IL-6, lactate dehydrogenase, D-dimer, high-sensitivity troponin and renal markers, leukocytosis, lymphopenia and thrombocytopenia.[35]

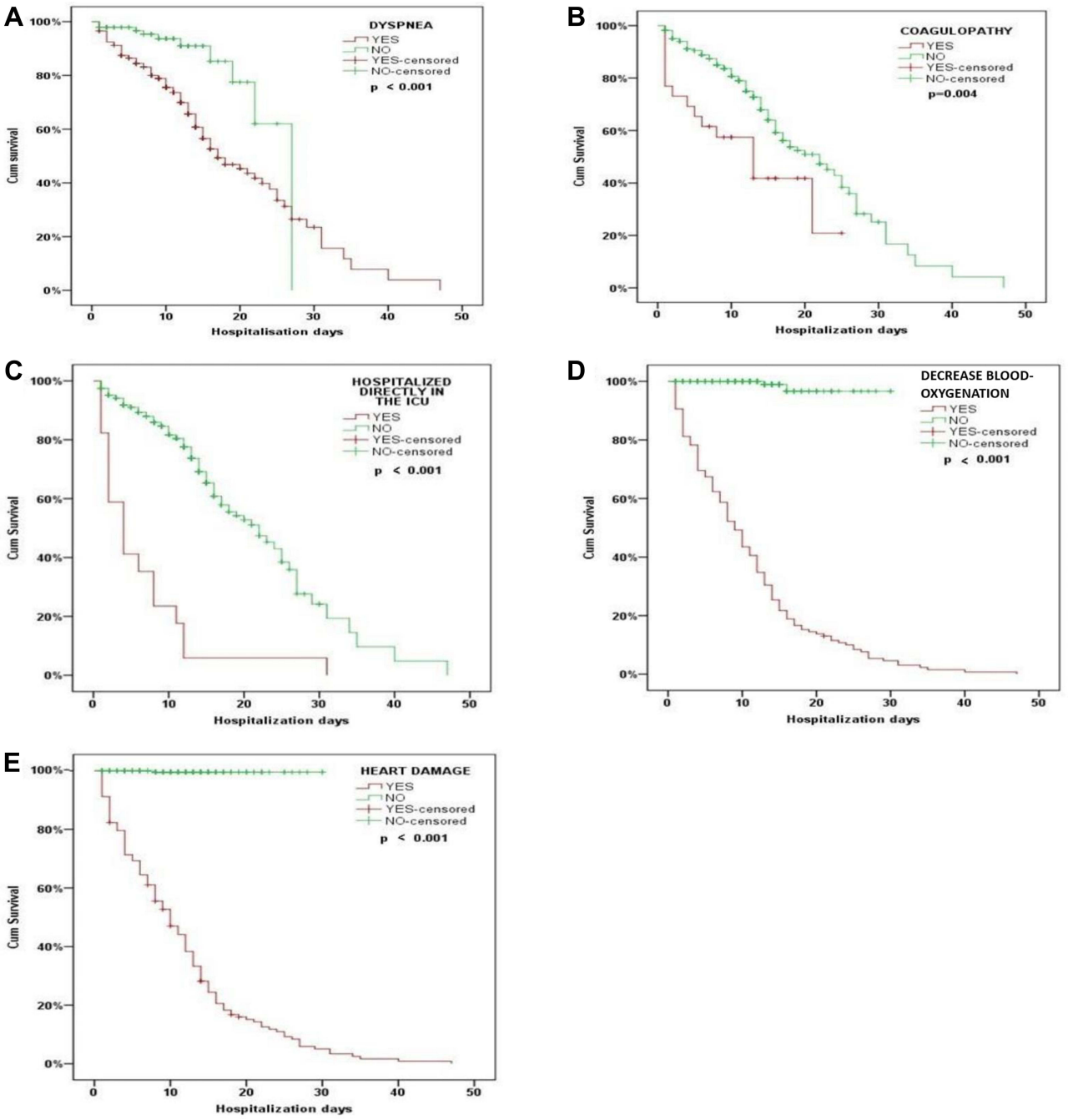

Figure 2 Kaplan Meier curves in the case of the main factors influencing survival. (**A**) Dyspnea on admission. (**B**) Coagulopathy. (**C**) Directly admitted to the ICU. (**D**) Decreased blood-oxygenation. (**E**). Heart damage.

The high saturation of O_2 at hospitalization and the high percentage of lymphocytes, but also the presence of headache at hospitalization and overweight, registered statistical values corresponding to some protection factors for the fatal evolution of the case. A retrospective study of 400 American patients confirmed with COVID-19 (31 patients died in hospital), for which machine learning logarithms were applied to predict hospital mortality using a prediction model based on demographic, clinical and paraclinical predictors, concluded that age > 65 years, SO2 < 88%, neurological/ cardiac comorbidities and diabetes are risk factors for increased in-hospital mortality.[36]

Since the beginning of the pandemic, obesity has emerged as a risk factor for the SARS-CoV-2 infection, for the severe evolution that requires hospitalization, intensive care, mechanical ventilation and increased mortality, due to

Table 5 The Impact of Comorbidities and Complications in Survival

Comorbidities	Log-Rank Mantel-Cox p	Onset of Complications	Log-Rank Mantel-Cox p
Cardiovascular pathology	0.004	Heart damage	<0.001
Previous diabetes mellitus	0.212	Hyperglycemia	0.820
Chronic liver pathology	0.045	Liver damage	0.485
Chronic renal pathology	<0.001	Kidney damage	<0.001
Neurological pathology	0.011	Neurological damage	<0.001
Coagulopathy	0.004	Thromboembolism	0.001
Gastro-duodenal ulcer	0.789	Pancreatic damage	0.224
Overweight	0.192	Secondary infections	0.448
Obesity	0.180	Sepsis	0.001
Hypertension	0.468	Decreased blood-oxygenation	0.001
Oncological pathology	0.782		
Chronic pulmonary pathology	0.150		
Autoimmune pathology	0.235		
Psychiatric pathology	0.285		

impaired lung function but also chronic inflammation with impaired response immune and thrombogenic.[36–38] While most studies have a linear relationship between BMI and the risk of severe COVID-19 development, in 2021 there were also studies showing a nonlinear curve, in which overweight patients (BMI 25–30 kg/ m^2) appear to have the lowest mortality risks.[39] In our study, too, overweight appears to be a protective factor against fatal evolution, although the result may be biased by smoking status, alcohol consumption or possibly other confounding factors.

Headache, one of the most common neurological symptoms of SARS-CoV-2 infection, commonly associated with fever, myalgia and arthralgia, possibly associated with an effective antiviral immune response, occurs according to the Centers for Disease Control and Prevention (CDC) in 14.8% of hospitalized patients.[40,41] In these patients, the presence of headache is an independent predictor of reduced risk of mortality or hospitalization in the ICU.[41–43] The univariate analysis of our study shows the same increased frequency of headache among patients with a favorable outcome.

Following the first logistic regression, three variables were detached as independent factors and predictors of death: history of coagulopathy, high percentage of neutrophils and decreased blood-oxygenation. The SARS-CoV-2 virus increases the risk of venous and arterial thrombosis by inflammation of the vascular endothelium, promoting blood stasis and systemic hypercoagulability. Comorbidities that affect coagulation (for example, atrial fibrillation) and initial coagulation abnormalities that predispose to prothrombotic status are identified as risk factors for adverse evolution of COVID-19 in other studies.[44] The second logistic regression model, with only the analysis of risk factors, indicates four independent factors and predictors of death to be all of the paraclinical variables: pulmonary changes identified by CT; serum creatinine, IL-6 and a high percentage of neutrophils.

The Cox regression revealed the following: a) an increase by 1 unit of oxygen saturation decreased the probability of death by 2%; b) an increase by 1 unit of serum creatinine increased the probability of death by 23%; c) the presence of coagulopathy in the antecedents increased the probability of death by 144%; d) the presence of dyspnea increased the probability of death by 199%; f) direct hospitalization in the ICU increased the probability of death by 280.3%; g) heart damage during COVID-19 infection increased the probability by 16.76 times; h) decreased blood-oxygenation increased the probability by 35.12 times.

In the study conducted by Hosse, who conducted an analysis on the CT results of 265 German patients, chronic and extensive lung disease was shown to be associated with an almost twice as high instantaneous risk of death. The CT imaging characteristics of COVID-19 pneumonia showed 74.3% of patients exhibited peripherally accentuated bilateral consolidations -and this was more extensive in patients intubated or hospitalized at ICUs and opacities in "matte glass" at 89.1%, who rarely showed pleural effusions and lymphadenopathy.[45] The analysis of 23 studies, with a total of 4631 Chinese patients, showed that elevated levels of CK, CK-MB, troponin T/L, LDH and IL-6 and emerging arrhythmia were associated with the development of severe forms of the disease, hospitalization at the ICU or death.[46]

Serum creatinine has been shown to be an independent predictor of death, consistent with the results of other studies. Thus, death rates in patients hospitalized for COVID-19 were significantly higher in those with renal impairment, including those with high serum creatinine/urea levels, with proteinuria, and multivariate analysis revealed that renal impairment from SARS-CoV-2 infection is associated with a statistically significant increased risk of death from changes in serum creatinine greater than 50%.[47,48]

Coagulopathy is an important prognostic factor, being associated in many studies with severe forms and higher mortality in COVID-19 infections.[49–51] Bed rest, hypoxia and sepsis associated with the SARS-COV-2, all increase the risk of thrombogenesis. It should be taken into consideration the fact that prerequisite endogen factors that favor blood hypercoagulation may exist.

The differences between the survival curves were extremely statistically significant in the case of history of chronic renal pathology, but also cardiac comorbidity (excluding hypertension), chronic liver disease, neurological pathology and coagulopathy generated significant differences. In terms of complications, cardiac, renal, neurological damage, sepsis and thromboembolism have statistically significantly reduced survival. The results are in line with general scientific knowledge; - thus, according to the European Center for Disease Prevention and Control (ECDC), the risk factors for in-hospital mortality of COVID-19 patients, identified by age and sex-adjusted analysis, were renal pathology, diabetes mellitus, neurological pathology (dementia), heart ischemia/stroke, obesity and oncological pathology.[52]

In a 12-month longitudinal observational study, which included 244 Italian patients, analysis of the prevalence of comorbidities between survivors and the deceased showed that chronic kidney disease, coronary heart disease and heart failure, dementia and cerebrovascular disease were more common in the deceased patients.[53] Additionally, a French cohort study showed that chronic liver diseases increase the risk of death of hospitalized patients for SARS-CoV-2 infection by 80%, while thromboembolic events, occur at a frequency of 20–30% of cases. According to other sources, this number has been shown to be 40–70%, and the risk of mortality was shown to increase by 74% (OR, 1.74; 95% CI, 1.01–2.98; $p = 0.04$) in a meta-analysis performed on 42 studies with 8271 patients.[52,54]

COVID-19 infection itself is a viral sepsis because it affects not only the lungs, but also causes cardiovascular, renal, hepatic or CNS dysfunction, because in many cases, the death is due to multiple organ failure, according to autopsies and the presence of RNA. The viral response has been identified in all organs, and the immune response is no different from that of sepsis from other causes. In addition, the need for hospitalization in the ICU of severe cases, namely the risk of mechanical ventilation and consequent bacterial pneumonia, the use of corticosteroids and sometimes antibiotics, generates additional risks of secondary bacterial or fungal infections, with the possibility of generalization. In fact, the prevalence of sepsis among COVID-19 cases was estimated at 39.9% (95% CI, 35.9–44.1) in a first meta-analysis published in December 2020.[55]

In the published studies, the high values of the evaluation indices of sepsis, septic shock, multiple organ failure, sequential organ failure assessment (SOFA), quick SOFA, acute physiology, chronic health evaluation II and systemic inflammatory response syndrome scores were associated with an increased risk of death from COVID-19, along with lymphocyte counts, PaO2/FiO2, IL-6 and CRP.[56,57] In this study, the highest statistical values as a predictor of in-hospital death were obtained for decreased blood-oxygenation. This progression from viral pneumonia to ARDS has been associated with fatal cases, with a significantly higher risk when associated with acute renal failure or septic shock, and in other studies, in which the crude 30-day mortality rate reached 41% (95% CI 38–45%).[58,59] In contrast, in our study, neither obesity nor diabetes were found to be risk factors, not even in the bivariate analysis.

The treatment of the viral infection is complex and according to the guidelines includes: antiviral drugs (remdesivir, chloroquine or hydroxychloroquine and/or azithromycin, lopinavir/ritonavir or other HIV protease inhibitors and, nitazoxaxides), anti-SARS-CoV-2 monoclonal antibodies, plasma convalescent, SARS-CoV-2-specific and nonspecific immunoglobulin, immunomodulators (colchicine, corticosteroids, fluvoxamine, cell therapy, granulocyte-macrophage colony growth factor inhibitors, Alpha and Beta interferon and Il-1 inhibitors) 6-tocilizumab or sarilumab and kinase inhibitors), antibiotics, anticoagulants, anti-inflammatory drugs (and other symptomatic drugs), vitamin C, D and zinc supplements, as well as support for vital functions.[60]

The design of the study did not focus on establishing the effectiveness of the therapeutic preparations used. Regarding the therapeutic variables, the statistically significant differences are explained by the differences in the therapeutic protocol applied according to the clinical form of the disease, with the administration of Tocilizumab (humanized monoclonal antibody Ig G1 human antireceptor of Il-6, obtained by the recombinant DNA technology in ovarian cells of Chinese hamsters), plasma, corticosteroids, Remdesivir (when pneumonia requiring oxygen therapy has been combined), Kineret (Anakinra - r-metHULL-Ira, antagonist of human Il-1 receptors, produced in Escherichia cells sheets by recombinant DNA technology), Fraxiparine and antibiotics such as Cefort and Meropenem, significantly more common in more severe forms. At the same time, the administration of Azithromycin (especially at the beginning of the pandemic) and Favipiravir are characteristic of mild or moderate forms, and the lack of anticoagulants means a mild clinical form, which explains their preponderance among surviving patients.

In our study, Enoxaparin showed values of protective factors in bivariate analysis, in line with the results of recent research, while in others unfractionated heparin appeared to be more effective in.[61,62] Some researchers claim that heparin, compared to other anticoagulants, improves the survival of the host in COVID-19 and through its direct anti-inflammatory and antiviral effects by controlling the cytokine storm and delaying the progression of the disease. A meta-analysis of 4421 potentially relevant studies (of which only 2107 were identified as relevant) including 11 studies on the impact of anticoagulant treatment on COVID-19 mortality and bleeding events, indicates a reduction in the risk of mortality through anticoagulant therapy, even in critically ill patients admitted to intensive care.[63] The results of another prospective cohort study conducted on 6195 patients in 14 hospitals and 60 clinics in the United States show that SARS-CoV-2 is associated with a state of hypercoagulability and that the presence of cardiovascular, immunological and coagulatory comorbidities has been associated with a higher risk of death, especially for inpatients, ICUs and mechanically ventilated and non-ventilated patients.[64–66]

The Limitations of the Study

The extrapolation power of the results in this study has been reduced due to its unicentric nature. The design did not focus on determining the efficacy of therapeutic preparations, which is why these variables were not included in the multivariate logistic regression or Cox regression. The impact of outpatient therapy was not estimated before hospitalization - in most cases, the symptomatic preparations were similar (antipyretic, antitussive, vitamin C, D and Zn) and the differences (prescription of Azithromycin in the first half of 2020 and oral anticoagulant, sometimes replaced in mild forms with antiplatelet agent) were due to the updating of the therapeutic protocol, which was adopted at the national level. The samples did not include patients with severe immunosuppression (eg, HIV/AIDS infection, organ transplantation) and racial differences could not be investigated because all patients were Caucasian. The vaccine status of the patients in 2021 was not investigated because the percentage of the population vaccinated during that period was very small (23.45% on 30.06.2021) and most of the hospitalized patients were unvaccinated.[18]

Conclusion

The study identified several main factors influencing the evolution of the cases: history of coagulopathy, oxygen saturation, high percentage of neutrophils at hospital admission, serum creatinine and IL-6 and the increase of the lung injury with decreasing oxygen saturation during hospitalization. Survival was significantly reduced in patients with a history of cardiovascular, renal, liver and neurological diseases, coagulopathies. The outcome was unfavorable in patients who developed thromboembolic events, sepsis, neurologic damage, cardiac or renal failure. A future study investigating the impact of the anti-SARS-COV-2 vaccine on outcomes in COVID-19 patients regarding the vaccine type

that is used and the infectious viral strain is needed. Knowledge of these predictors allows for the optimization of triage and therapeutic case management, especially in medical systems with limited material resources.

Abbreviations

AIDS, acquired immunodeficiency syndrome; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; DNA, deoxyribonucleic acid; EI, sample I; EII, sample II; ECDC, European Center for Disease Prevention and Control; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; HR, hazard ratio; ICU, intensive care unit; Ig G1, immunoglobulin G1; IL-1/-6, interleukin-1/-6; LDH, lactate dehydrogenase; N1/N2, number of participants from EI/EII; OR/RR [95% CI], odds ratios/relative risk and 95% confidence interval; p, statistical significance; PaO2/FiO_2, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; RNA, ribonucleic acid; RT-PCR, real time polymerase chain reaction.

Data Sharing Statement

The datasets generated/analyzed during the current study are available. The datasets generated/analyzed during the current study are available in the corresponding author repository.

Ethics Statements

The data collection was carried out in compliance with the provisions of European Union Regulation No. 679 on the protection of individuals with regard to the processing of personal data. Study approval was provided by the Ethics Commission of the Hospital for Infectious Diseases and Pneumophtisiology "Doctor Victor Babes" of Timisoara with no. 11822/26.11.2021.

Consent for Publication

Written informed consent from the patients was requested, and in hospitalized patients for whom the state of consciousness was altered, this consent was obtained from the relatives.

Author Contributions

Significant contribution to the work was provided by all authors in with respect to the conception, study design, execution, acquisition of data, analysis and interpretation. All authors took part in drafting, revising, or critically reviewing the article and gave their final approval of the version submitted for publication. All authors have agreed on the journal for submission and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Coronavirus disease (COVID-19) pandemic [homepage on the internet]. Geneva: World Health Organization; 2022. Available from: https://www.who.int/. Accesed January 21, 2021.
2. Bucharest: National Institute of Public Health Romania. Covid 19 weekly surveillance report [homepage on the internet]; 2022. Available from: https://www.cnscbt.ro/index.php/analiza-cazuri-confirmate-covid19/2955-raport-saptamanal-episaptamana02-2022/file. Accesed January 21, 2022.
3. Bucharest: National Institute of Public Health Romania. Risk factors for death in cases confirmed with COVID-10 [homepage on the internet]; 2020. Available from: https://www.cnscbt.ro/index.php/analiza-cazuri-confirmate-covid19/2064-analiza-epidemiologica-2-factori-de-risc-pentru-deces-cu-covid-19/file. Accesed November 30, 2021.
4. Pantea Stoian A, Pricop-Jeckstadt M, Pana A, et al. Death by SARS-CoV 2: a Romanian COVID-19 multi-centre comorbidity study. *Sci Rep*. 2020;10(1):21613. doi:10.1038/s41598-020-78575-w
5. Mota M, Popa SG, Mota E, et al. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. *J Diabetes*. 2016;8(3):336–344. doi:10.1111/1753-0407.12297
6. Popa S, Moţa M, Popa A, et al. Prevalence of overweight/obesity, abdominal obesity and metabolic syndrome and atypical cardiometabolic phenotypes in the adult Romanian population: PREDATORR study. *J Endocrinol Invest*. 2016;39(9):1045–1053. doi:10.1007/s40618-016-0470-4

7. Brussels: International Diabet Federation. Europe: diabetes report 2000–2045 [homepage on the internet]; 2021. Available from: https://diabetesatlas.org/data/en/region/3/eur.html. Accesed November 30, 2021.
8. Hariyanto TI, Kurniawan A Dyslipidemia is associated with severe coronavirus disease. Clin Res Rev. 2020;14(5):1463–1465.
9. Putri C, Hariyanto TI, Hananto JE, Christian K, Situmeang RF, Kurniawan A. Parkinson's disease may worsen outcomes from coronavirus disease 2019 (COVID-19) pneumonia in hospitalized patients: a systematic review, meta-analysis, and meta-regression. *Parkinsonism Relat Disord*. 2021;87:155–161. doi:10.1016/j.parkreldis.2021.04.019
10. La Verde M, Riemma G, Torella M, et al. Maternal death related to COVID-19: a systematic review and meta-analysis focused on maternal co-morbidities and clinical characteristics. *Int J Gynaecol Obstet*. 2021;154(2):212–219. doi:10.1002/ijgo.13726
11. Dessie Z, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis*. 2021;21(1):855. doi:10.1186/s12879-021-06536-3
12. Bucharest: National Institute of Statistics. Romania in figures [homepage on the internet]; 2021. Available from: https://insse.ro/cms/sites/default/files/field/publicatii/romania_in_figures_2021_0.pdf. Accesed November 30, 2021.
13. Bucharest: Statista. Number of medical staff in Romania per 10,000 inhabitants 2020 [homepage on the internet]; 2021. Available from: https://www.statista.com/statistics/1139432/romania-medical-staff-per-10-000-inhabitants/. Accesed November 30, 2021.
14. Kim J, Hong K, Yum S, et al. Factors associated with the difference between the incidence and case-fatality ratio of coronavirus disease 2019 by country. *Sci Rep*. 2021;11(1):18938. doi:10.1038/s41598-021-98378-x
15. Tchicaya A, Lorentz N, Leduc K, de Lanchy G. COVID-19 mortality with regard to healthcare services availability, health risks, and socio-spatial factors at department level in France: a spatial cross-sectional analysis. *PLoS One*. 2021;16(9):e0256857. doi:10.1371/journal.pone.0256857
16. Bucharest: Graphs.ro. Evolution of COVID-19 Romania (1 p.m.) [homepage on the internet]; 2022. Available from: www.graphs.ro. Accesed January 21, 2022.
17. Stockholm: European Centre for for Disease Prevention and Control. COVID-19 vaccine tracker [homepage on the internet]; 2022. Available from: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab. Accesed January 21, 2022.
18. Bucharest: Graphs.ro. Vaccination - Percentage of people vaccinated vs. national incidence [homepage on the internet]; 2022. Available from: https://www.graphs.ro/vaccinare_daily_percentage.php. Accesed January 21, 2022.
19. Bucharest: Euobserver. Romania reaches historic high in Covid deaths [homepage on the internet]; 2021. Availeble from: https://euobserver.com/coronavirus/153428. Accesed November 30, 2021.
20. Dascalu S, Geambasu O, Raiu CV, Azoicai D, Popovici ED, Apetrei C. COVID-19 in Romania: what went wrong? *Front Public Health*. 2021;9:813941. doi:10.3389/fpubh.2021.813941
21. Dascalu S, Geambasu O, Covaciu O, et al. Prospects of COVID-19 vaccination in Romania: challenges and potential solutions. *Front Public Health*. 2021;9:644538. doi:10.3389/fpubh.2021.644538
22. Marcau FC, Purec S, Niculescu G. Study on the refusal of vaccination against COVID- 19 in Romania. *Vaccines*. 2022;10(2):261. doi:10.3390/vaccines10020261
23. Washington: American College of Cardiology. ACC clinical bulletin focuses on cardiac implications of coronavirus (COVID-19) [homepage on the internet]; 2020. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/02/13/12/42/acc-clinical-bulletin-focuses-on-cardiac-implications-of-coronavirus-2019-ncov. Accesed January 21, 2021.
24. Bucharest: raportuldegarda.ro. Cardiac injury, a common complication of COVID-19 infection, is associated with increased mortality. Patients with comorbidities have an increased risk of severe development [homepage on the internet]; 2020. Available from: https://raportuldegarda.ro/boli-cardiovasculare-diabet-evolutie-severa-covid-19/. Accesed February 26, 2022.
25. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5
26. Cleveland: 100 Years of Cleveland Clinic. Liver lesions [homepage on the internet]; 2022. Available from: https://my.clevelandclinic.org/health/diseases/14628-liver-lesions. Accesed February 28, 2022.
27. Ghoda A, Ghoda M. Liver injury in COVID-19 infection: a systematic review. *Cureus*. 2020;12(7):e9487. doi:10.7759/cureus.9487
28. Bucharest: Romanian Society of Anaesthesia and Intensive Care. SRATI guide [homepage on the internet]; 2020. Available from: https://www.srati.ro/public/data_files/content-static/ghid-covid-19-editia-2.pdf. Accesed February 26, 2022.
29. Pittsburgh: Inside life changing medicine. COVID-19 may worsen America's kidney disease crisis: more severe acute kidney injury and extremely high mortality [homepage on the internet]; 2020. Available from: https://inside.upmc.com/covid-19-may-worsen-americas-kidney-disease-crisis/. Accesed March 7, 2022.
30. Manchester: Support the Guardian. Covid can shrink brain and damage its tissue, finds research [homepage on the internet]; 2022. Available from: https://www.theguardian.com/world/2022/mar/07/covid-can-shrink-brain-and-damage-its-tissue-finds-research. Accesed March 7, 2022.
31. Kifer D, Bugada D, Villar-Garcia J, et al. Effects of environmental factors on severity and mortality of COVID-19. *Front Med*. 2020;7:607786. doi:10.3389/fmed.2020.607786
32. Nichols GL, Gillingham EL, Macintyre HL, et al. Coronavirus seasonality, respiratory infections and weather. *BMC Infect Dis*. 2021;21(1):1101. doi:10.1186/s12879-021-06785-2
33. Sagripanti JL. Seasonal Effect of sunlight on COVID-19 among Countries with and without Lock-Downs. *Open J Epi*. 2021;11(3):303–325. doi:10.4236/ojepi.2021.113027
34. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis*. 2021;21(1):855. doi:10.1186/s12879-021-06536-3
35. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life Sci*. 2020;254:117788. doi:10.1016/j.lfs.2020.117788
36. Banoei MM, Dinparastisaleh R, Zadeh AV, Mirsaeidi M. Machine-learning-based COVID- 19 mortality prediction model and identification of patients at low and high risk of dying. *Crit Care*. 2021;25(1):328. doi:10.1186/s13054-021-03749-5
37. Elmore R, Schmidt L, Lam J, et al. Risk and protective factors in the COVID-19 pandemic: a rapid evidence map. *Front Public Health*. 2020;8:582205. doi:10.3389/fpubh.2020.582205
38. Cai Z, Yang Y, Zhang J. Obesity is associated with severe disease and mortality in patients with coronavirus disease 2019 (COVID-19): a meta-analysis. *BMC Public Health*. 2021;21(1):1505. doi:10.1186/s12889-021-11546-6

39. Huang HK, Bukhari K, Peng CC, et al. The J-shaped relationship between body mass index and mortality in patients with COVID-19: a dose-response meta-analysis. *Diabetes Obes Metab*. 2021;23(7):1701–1709. doi:10.1111/dom.14382
40. García-Azorín D, Sierra Á, Trigo J, et al. Frequency and phenotype of headache in covid- 19: a study of 2194 patients. *Sci Rep*. 2021;11(1):14674. doi:10.1038/s41598-021-94220-6
41. Trigo J, Garcia-Azorin D, Planchuelo-Gomez A, et al. Factors associated with the presence of headache in hospitalized COVID-19 patients and impact on prognosis: a retrospective cohort study. *J Headache Pain*. 2020;21(1):94. doi:10.1186/s10194-020-01165-8
42. Membrilla JA, de Lorenzo Í, Sastre M, Díaz de Terán J. Headache as a cardinal symptom of coronavirus disease 2019: a cross-sectional study. *Headache*. 2020;60(10):2176–2191. doi:10.1111/head.13967
43. Gonzalez-Martinez A, Fanjul V, Ramos C, et al. Headache during SARS-CoV-2 infection as an early symptom associated with a more benign course of disease: a case-control study. *Eur J Neurol*. 2021;28(10):3426–3436. doi:10.1111/ene.14718
44. Frydman GH, Boyer EW, Nazarian RM, Van Cott EM, Piazza G. Coagulation status and venous Thromboembolism risk in African Americans: a potential risk factor in COVID-19. *Clin Appl Thromb Hemost*. 2020;26:1076029620943671. doi:10.1177/1076029620943671
45. Hosse C, Büttner L, Fleckenstein FN, et al. CT-based risk stratification for intensive care need and survival in COVID-19 patients-a simple solution. *Diagnostics*. 2021;11(9):1616. doi:10.3390/diagnostics11091616
46. Li X, Pan X, Li Y, et al. Cardiac injury associated with severe disease or ICU admission and death in hospitalized patients with COVID-19: a meta-analysis and systematic review. *Crit Care*. 2020;24(1):468. doi:10.1186/s13054-020-03183-z
47. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97(5):829–838. doi:10.1016/j.kint.2020.03.005
48. Xu H, Garcia-Ptacek S, Annetorp M, et al. Acute kidney injury and mortality risk in older adults with COVID-19. *J Nephrol*. 2021;34(2):295–304. doi:10.1007/s40620-021-01022-0
49. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844–847. doi:10.1111/jth.14768
50. Winata S, Kurniawan A. Coagulopathy in COVID-19: a Systematic Review. *Medicinus Jurnal Kedokteran*. 2020;8(2):72–80. doi:10.19166/med.v8i2.3444
51. Sarkar M, Madabhavi I, Quy PM, Govindagoudar M. COVID-19 and coagulopathy. *Clin Respir J*. 2021;15(12):1259–1274. doi:10.1111/crj.13438
52. Stockholm: European Centre for Disease Prevention and Control. Risk factors and risk groups [homepage on the internet]; 2021. Available from: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups. Accesed November 30, 2021.
53. Bagnato G, La Rosa D, Ioppolo C, et al. The COVID-19 Assessment for Survival at Admission (CASA) Index: a 12 Months Observational Study. *Front Med*. 2021;8:719976. doi:10.3389/fmed.2021.719976
54. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *E Clin Med*. 2020;29:100639. doi:10.1016/j.eclinm.2020.100639
55. Karakike E, Giamarellos-Bourboulis EJ, Kyprianou M, et al. Coronavirus disease 2019 as cause of viral sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2021;49(12):2042–2057. doi:10.1097/CCM.0000000000005195
56. Jin M, Lu Z, Zhang X, et al. Clinical characteristics and risk factors of fatal patients with COVID-19: a retrospective cohort study in Wuhan, China. *BMC Infect Dis*. 2021;21(1):951. doi:10.1186/s12879-021-06585-8
57. Gao J, Zhong L, Wu M, et al. Risk factors for mortality in critically ill patients with COVID-19: a multicenter retrospective case-control study. *BMC Infect Dis*. 2021;21(1):602. doi:10.1186/s12879-021-06300-7
58. El-Solh AA, Meduri UG, Lawson Y, Carter M, Mergenhagen KA. Clinical course and outcome of COVID-19 acute respiratory distress syndrome: data from a national repository. *J Intensive Care Med*. 2021;36(6):664–672. doi:10.1177/0885066621994476
59. Hsu CY, Lai CC, Yeh YP, Chang-Chuan C, Chen HH. Progression from Pneumonia to ARDS as a predictor for fatal COVID-19. *J Infect Public Health*. 2021;14(4):504–507. doi:10.1016/j.jiph.2020.12.026
60. Bethesda: National Institutes of Health from USA. COVID-19 treatment guidelines [homepage on the internet]; 2021. Available from: https://www.covid19treatmentguidelines.nih.gov/. Accessed November 16, 2021.
61. Pawlowski C, Venkatakrishnan AJ, Kirkup C, et al. Enoxaparin is associated with lower rates of mortality than unfractionated Heparin in hospitalized COVID-19 patients. *E Clin Med*. 2021;33:100774. doi:10.1016/j.eclinm.2021.100774
62. Oliynyk O, Barg W, Slifirczyk A, et al. Comparison of the effect of unfractionated heparin and enoxaparin sodium at different doses on the course of COVID-19-associated coagulopathy. *Life*. 2021;11(10). doi:10.3390/life11101032
63. Jiang L, Li Y, Du H, Qin Z, Su B. Effect of anticoagulant administration on the mortality of hospitalized patients with COVID-19: an updated systematic review and meta-analysis. *Front Med*. 2021;8:698935. doi:10.3389/fmed.2021.698935
64. Hozayen SM, Zychowski D, Benson S, et al. Outpatient and inpatient anticoagulation therapy and the risk for hospital admission and death among COVID-19 patients. *E Clin Med*. 2021;41:101139. doi:10.1016/j.eclinm.2021.101139
65. Laza R, Musta VF, Nicolescu ND, et al. Cutaneous manifestations in SARS-CoV-2 infection-a series of cases from the largest infectious diseases hospital in Western Romania. *Healthcare*. 2021;9(7):800. doi:10.3390/healthcare9070800
66. Dehelean L, Papava I, Musat MI, et al. Coping strategies and stress related disorders in patients with COVID-19. *Brain Sci*. 2021;11(10):1287. doi:10.3390/brainsci11101287