European Journal of Respiratory Medicine

2022; 4(3): 344- 351. doi: 10.31488/EJRM.136

Research article

Biomarkers as Prognosis of COVID-19 Disease: Retrospective Cohort Study

Priscila Matovelle-Ochoa[1,2], Barbara Oliván-Blázquez[*3,4,5], Rosa Magallón-Botaya[2,3,4,6], Itziar Lamiquiz-Moneo[7,8], Fátima Méndez-López[3,4], Cruz Bartolomé-Moreno[3,4,6,9]

1. Geriatrics Department, San Juan de Dios Hospital, Zaragoza, Spain

2. Department of Medicine, Psychiatry and Dermatology, Faculty of Medicine, University of Zaragoza, Zaragoza, Spain

3. Group B21-20R, Health Research Institute of Aragon (IISA), Zaragoza, Spain

4. Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS), RD21/0016/0001, Spain

5. Department of Psychology and Sociology, University of Zaragoza, Zaragoza, Spain

6. Aragonese Healthcare Service (SALUD), Zaragoza, Spain

7. Department of Human Anatomy and Histology, School Medicine, University of Zaragoza, Spain

8. Unidad de Lípidos, IIS Aragón, CIBERCV, Miguel Servet Universitary hospital, Zaragoza, Spain

9. Family and Community Care Teaching Department of Zaragoza Sector I, Zaragoza, Spain

[*]**Corresponding author:** Bárbara Oliván-Blázquez. Department of Psychology and Sociology, University of Zaragoza. Pedro Cerbuna, 12, 50009 Zaragoza Spain. Aragonese Research Group in Primary Care (Grupo Aragonés de Investigación en Atención Primaria/GAIAP); Aragón Health Research Institute, San Juan Bosco, 13, 50009 Zaragoza Zaragoza, Spain.

Received: May 16, 2022; Accepted: June 06, 2022; Published: June 09, 2022

Abstract

Background: Coronavirus infection has been the cause of millions of deaths worldwide. Some analytical parameters on admission could help predict prognosis and mortality. This study aims to describe the main Laboratory findings of hospitalized patients with COVID-19 and to identify the relationship between intensive care unit access, length of stay and in-hospital mortality. Methods: A retrospective cohort study was performed. Demographic and analytical variables of all patients diagnosed with COVID-19 hospitalized in Aragon (Spain) between March and June 2020 were analyzed. Results: We describe the characteristics of 2640 patients hospitalized with COVID-19, 85% were significantly older, with a median age of 72.3 ± 16.7 years, predominantly male (52.8%). The in-hospital mortality rate was 30%. Patients admitted to the intensive care unit had significantly higher baseline levels of hematocrit, fibrinogen, lactate dehydrogenase, leukocytes and neutrophils ($p<0.001$ in all). On the other hand, these patients had lower levels of eosinophils, lymphocytes and monocytes ($p<0.001$ in all). Only hemoglobin and D-dimer showed a significant and positive correlation with longer hospital and ICU stays ($r=0.050$ with $p=0.031$; $r=0.203$ with $p=0.008$; $r=0.175$ with $p<0.001$ and $r=0.199$ with $p=0.001$, respectively. Multivariable regression based on death showed that age, higher values of lactate dehydrogenase, neutrophils and lower values of eosinophils and female sex could explain up to 30% of the probability of death. Conclusion: Laboratory parameters can help clinicians predict the severity of COVID-19 and subsequently improve prognosis and decrease mortality rates. However, more studies are needed to better understand these changes and their relationship to prognosis.

Keywords: COVID-19, Laboratory findings, prognosis, in-hospital mortality, intensive care unit

Introduction

At the end of 2019, in Wuhan, China, a disease originated due to coronavirus (COVID-19) [1]. According to the World Health Organization (WHO) (2021), SARS-CoV-2 is a highly transmissible and pathogenic coronavirus that induces severe acute respiratory syndrome; it has caused more than 2 million deaths in the first 12 months since its appearance. It has also generated critical social problems throughout the world. This infection continues to spread, with more than 200 million confirmed cases and 223 countries, areas, or territories [2].

Spain has been one of the European countries most affected by the COVID-19 pandemic as of Mach 17th, with more than 11 000 cases and 491 deaths [3]. Spain had one of the highest

burdens of coronavirus disease worldwide [4]. The first wave period was between March and June 2020 [5].

A total of 611,583 individuals from 5 official national registries (Spain, Italy, China, England, and New York were analyzed in a meta-analysis. The purpose was to study COVID-19 and mortality rates by decades of age. The overall mortality rate was 12.10% and varied widely among countries, with the lowest rate in China (3.1%) and the highest rate in the United Kingdom (20.8%) and New York state (20.99%). Patients younger than 50 years had a mortality rate of less than 1.1%, and mortality increased exponentially after that age in all five national registries [6].

The COVID-19 clinical manifestations can range from asymptomatic, presenting mild respiratory symptoms, to a severe threat of death caused by respiratory and cardiac failure [7,8].

The beginning of the pandemic was a real challenge for emergency physicians to identify the prognosis of patients with COVID-19; therefore it was essential that several studies identified the risk factors for an early prediction of the progression of the disease.

Several studies have shown that older age, male sex, and comorbidities such as hypertension, diabetes, and cardiovascular disease have been associated with worse outcomes in COVID-19 patients [8-11].

Laboratory findings were also essential to predict severity, admission to the intensive care unit (ICU) and even death. A multicenter study including 32 hospitals in Spain studied Laboratory data as predictors of in-hospital mortality. They found that C-reactive protein (CRP), troponin levels, creatinine, and platelet count independently associated with an increased risk of in-hospital mortality [11].

This line in a meta-analysis which included 148 studies (12,149 patients), points to hypoalbuminemia, lymphopenia, and also elevated levels of interleukin 6, leucocytes, D-dimer (DD), and lactate dehydrogenase were more commonly seen in patients with severe COVID-19 illness and non-survivors [12].

Another meta-analysis of seven studies with 1905 patients found that severity and the possibility of transferring the patient to the intensive care unit were significantly associated with lymphopenia, increased CRP, and increased LDH [13].

A meta-analysis that included seven studies of diagnosis and prognosis of COVID-19 showed that an elevated count of leukocyte and neutrophils indicate progressive disease. Thrombocyte count is crucial in both diagnosis and prognosis. Additionally, they found that lymphocyte, DD, and CRP levels indicate severity but did not demonstrate diagnostic value of COVID-19 [14].

Another study showed that patients with infection or sepsis admitted to an ICU had higher levels of D-dimer, which were associated with 28-day mortality [15]. Two more studies published that patients with greater severity and mortality had higher levels of DD [16,27].

Also, a systematic review that included 24 studies identified that DD in patients with COVID-19 is associated with greater severity, disease progression, acute respiratory distress syndrome, and death (with low-quality evidence) [18].

As we can see, Laboratory data are essential at the time of diagnosis in patients with COVID-19, and this information may help physicians to predict ICU admission, length of stay and in-hospital mortality, there is not much data in this field. The aim of this study is to describe the main Laboratory findings of hospitalized patients with COVID-19 in Aragon-Spain and to identify the relationship between ICU admission, length of stay and in-hospital mortality.

Materials and Methods

Study design

We conducted a retrospective cohort study and analyzed demographics and analytical variables of all patients diagnosed with COVID-19. They were hospitalized in Aragón (Spain) from the beginning of the current pandemic to 30 June 2020. This information was pseudonymized from the BIGAN platform, where demographics and analytical values were requested from all users with an Aragón health card at the time of their hospital admission and in the Intensive Care Unit (ICU). This information has been obtained pseudonymized from The BIGAN Information Platform, which integrates all the data collected from the Department of Health and the Aragón Health Service. The Clinical Research Ethics Committee of Aragón approved the study protocol (PI20/262).

Participants and sample size

In the present study, all hospitalized adults in Aragón (Spain), older than 18 years, diagnosed with COVID-19 who had a positive result in the polymerase chain reaction (PCR) diagnostic test were included. For each patient included in the study, their age at the time of hospital admission was reported. A total of 6286 adults were diagnosed with COVID-19 in the study period and only 2640 (42%) required hospital admission.

Laboratory measurements

Blood samples were drawn by venipuncture at the time of hospital admission and ICU admission, obtaining two types of tubes for the hemogram with EDTA (ethylenediaminetetraacetic acid) and with citrate in the case of coagulation determinations. All subjects included in the current study had complete blood cell counts and hemostatic parameters, including red cell distribution width (RWD), Basophils, mean corpuscular hemoglobin concentration (MCHC), creatine phosphokinase (CPK), D-dimer concentration, eosinophils, fibrinogen levels, mean cell hemoglobin (MCH), hematocrit, Hemoglobin, lactate dehydrogenase (LDH), leukocytes, lymphocytes, monocytes, neutrophils, platelets, prothrombin time, troponin, medium corpuscular volume (MCV), Mean platelet volume (MPV) and erythrocyte sedimentation rate (ESR).

Hematocrit was calculated as the product of red blood cells times mean corpuscular volume divided by 10. Hemoglobin concentration was calculated from the transmission of light at 535 nm of the lysed solution versus the transmission of light generated by a blank. The MCH is the weight of hemoglobin in the mean erythrocyte, calculated by dividing the hemoglobin and the number of red cells by 10. The MCH is the mean weight of hemoglobin in a measured dilution, calculated as the hemoglobin divided by the hematocrit per 100. The mean corpuscular volume was obtained from the mean volume of the erythrocytes calculated from the histogram of the red blood cells

of each channel. The RDW is the width or width of the size distribution of the erythrocyte population calculated from the red blood cell histogram as the coefficient of variation. Each type of white blood cell was calculated as the number of leukocytes in each series measured directly and multiplied by the calibration factor. The number of platelets was calculated from the platelet histogram multiplied by a calibration factor. At the same time, the VMP represents the mean volume of the platelet population under the fitted platelet curve multiplied by a calibration factor.

The methodology for the coagulometry tests was spectrophotometry, based on the change in scattered light associated with fibrin clot formation, analyzing two wavelengths of 671 nm and 405 nm, using the ACL TOP 550 CTS and ACL TOP 750 CTS auto analyzers available in the clinical Laboratories of the Aragon's Health Service.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (25th percentile - 75th percentile) as applicable, and categorical (nominal) variables are reported as percentages of the total sample. Differences between independent variables were calculated by T-Student or U Mann Whitney test, as appropriate, while categorical variables were compared using the chi-squared test. The lineal regression model adjusted the differences between independent variables by sex and age. Multivariable regression based on UCI admission or death was analyzed by binary logistic regression. All statistical analyses were performed with R version 3.5.0, and significance was set at $p < 0.05$.

Results

There were 6286 adults diagnosed with COVID-19 from March through June 30, 2020 in Aragon (Spain), 2640 (42%) required hospital admission, and of these, 268 (10% of total hospital admissions) were admitted to the ICU. The 2268 hospitalized subjects were significantly older, with 72.3 ± 16.7 years old, and predominantly male with 1393 subjects (52.8%) versus 3646 positive Covid-19 non-hospitalized adults, who had a mean age of 54,9 ± 21.5 years old and were primarily female (63.2%) ($p<0.001$ and $p<0.001$, respectively). Of the total of 2268 hospitalized subjects, 779 died (29.5%), compared to 100 subjects (37.3%) who died among those admitted to the ICU, indicating that the percentage of death was significantly higher for ICU admission patients ($p<0.001$). The hospitalized subjects who died were especially older, with a mean age of 83.1 ± 10.3 years old, versus the rest of those who did not die, who had a mean age of 67.5 ± 16.7 ($p<0.001$, Figure 1).

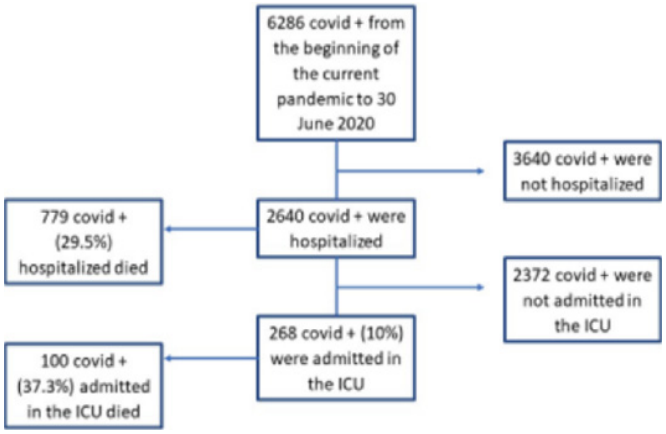

Figure 1. Flow chart
ICU: Intensive care unit

Table 1 shows the comparison of baseline analytical values as a function of the need for ICU admission, indicating that subjects admitted to the ICU have significantly higher baseline levels of MCHC, hematocrit, fibrinogen, LDH, leukocytes,

Table 1. Comparison of analytical reference values according to their need for ICU admission.

	Subjects not admitted to the ICU (N=2372)	Subjects admitted to the ICU (N=268)	*p*
Hematocrit, %	41.1 (37.3 – 44.4)	42.1 (38.1 – 46.0)	<0.001
Haemoglobin, g/dL	13.6 (12.3 – 14.7)	13.8 (12.7 – 15.2)	0.138
MCH, pg	30.3 (28.9 – 31.5)	30.2 (29.0 – 31.4)	0.781
MCHC, g/dL	33.4 (32.8 – 34.1)	33.6 (33.03- 34.2)	0.027
RDW, %	14.0 (13.3- 15.1)	13.8 (13.1- 14.5)	0.018
MCV, fL	90.3 (86.6 – 93.8)	89.9 (86.9 – 93.1)	0.544
ESR, mm/h	50.0 (20.0 – 86.0)	49.0 (19.0 – 83.0)	0.618
Platelets, $U10^3/\mu L$	188 (145 – 245)	191 (143- 249)	0.767
VPM, fL	9.30 (8.60 – 10.1)	9.30 (8.50 – 10.1)	0.995
Leukocytes, $U10^3/\mu L$	6.47 (4.67 – 8.60)	7.65 (5.17 – 10.0)	<0.001
Lymphocytes, $U10^3/\mu L$	1.02 (0.700 – 1.49)	0.803 (0.595 – 1.100)	<0.001
Monocytes, $U10^3/\mu L$	0.532 (0.378 – 0.717)	0.414 (0.292 – 0.587)	<0.001
Eosinophils, $U10^3/\mu L$	0.010 (0.000- 0.050)	0.000 (0.000 – 0.008)	<0.001
Basophils, $U10^3/\mu L$	0.020 (0.010- 0.036)	0.017 (0.009- 0.031)	0.027
Neutrophils, $U10^3/\mu L$	4.73 (3.30 – 6.90)	6.23 (4.13- 8.88)	<0.001
CPK, U/L	72.5 (43.0 – 148)	107 (54.0 – 215)	0.847
D-dimer, ng/mL	840 (482 – 1680)	1023 (563 – 1736)	0.130
Fibrinogen, mg/dL	669 (513 – 794)	798 (661 – 947)	<0.001
LDH, U/L	290 (224- 383)	453 (307 – 630)	<0.001
Prothrombin time, s	13.5 (12.4– 14.9)	13.9 (12.8 – 15.2)	0.254
Troponin, ng/L	13.0 (7.10– 31.67)	14.5 (11.8- 29.6)	0.191

Quantitative variables following not normal distribution were expressed as median (percentile 25th- percentile 75th). The p-value was adjusted by sex and age. MCH: mean cell hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RWD denotes red cell distribution width; MCV: medium corpuscular volume; ESR: erythrocyte sedimentation rate; VPM: Mean platelet volume; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; s: seconds. ICU: intensive care unit.

and neutrophils (p=0.027, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001, respectively). On the other hand, these patients had significantly lower baseline levels of basophils, eosinophils, lymphocytes, and monocytes (p=0.027, p<0.001, p<0.001, and p<0.001, respectively, Table 1).

Interestingly, the multivariable regression model shows that higher concentrations of fibrinogen and leucocyte; and lower concentrations of monocytes, as well as older age and being male, are risk factors for ending up in the ICU. They showed that combining these five factors could explain 10% of the probability of requiring admission to the ICU (Table 2).

Table 2. Multivariable regression based on ICU admission

	OR	95% CI	P	R^2 Nagelkerke
Fibrinogen, mg/dL	0.0013	0.000480 to 0.00218	0.003	0.10289
Leukocytes, $U10^3/\mu L$	0.1435	0.08196 to 0.2080	<0.001	
Monocytes, $U10^3/\mu L$	-2.2083	-3.38536 to -1.1500	<0.001	
Age, years	-0.030	-0.0458 to -0.0148	<0.001	
Sex, Women	-0.682	-1.248 to -0.1477	<0.001	

Multivariable binary logistic regression with the ICU admission as the dependent variable. OR: Odd Ratio; CI: Confidence Interval. ICU: intensive care unit.

The mean hospitalization time was 17.01 ± 23.2 days, with a maximum of 222 days, compared to the mean length of stay in the ICU, which was 19.0 days ±18.6 with a maximum of 157 days (Table 3), showing a correlation between baseline Laboratory parameters and hospitalization and ICU hospitalization time. Higher values of Hemoglobin, MCH, MCHC, RDW, ESR, Platelets, VPM, D-dimer, fibrinogen, and prothrombin time correlated significantly and positively with longer hospital stay time. In contrast, hematocrit, leukocytes, and lymphocytes' values correlated significantly and negatively with hospital stay time. Regarding ICU hospitalization time, higher values of hemoglobin and D-dimer correlated significantly and positively with longer ICU stay time. In comparison, lower values of RDW, MCV, ESR, VPM, and basophils correlated significantly and inversely with ICU stay time. Interestingly, only hemoglobin and D-dimer showed significant and positive correlation with both longer hospital stays and ICU stays (r=0.050 with p=0.031; r=0.203 with p=0.008; r=0.175 with p<0.001 and r=0.199 with p=0.001, respectively, Table 3).

Among the 2,268 hospitalized patients during the first wave of COVID-19 in Aragón, 779 adults who died had significantly higher values of RDW, MCV, ESR, VPM, leukocytes, neutrophils, CPK, D-dimer, LDH, prothrombin time and troponin. (p<0.001, p=0.014, p<0.001, p=0.005, p<0.001, p<0.001, p=0.007, p=0.004, p<0.001, p<0.001 and p=0.023, respectively). On the other hand, those patients had significantly lower values of hematocrit, Hemoglobin, MCHC, lymphocytes, and eosinophils (p=0.036, p<0.001, p<0.001, p=0.00,1, and p<0.001, respectively, Table 4).

Table 3. Correlation between baseline analytical parameters and hospitalization - ICU hospitalization time

	Correlation with hospitalization time	p	Correlation with ICU stay	p
Hematocrit, %	-0.101	<0.001	0.085	0.171
Haemoglobin, g/dL	0.050	0.031	0.203	0.008
MCH, pg	0.055	0.006	0.104	0.092
MCHC, g/dL	0.049	0.015	0.110	0.075
RDW, %	0.053	0.012	-0.127	0.046
MCV, fL	-0.008	0.693	-0.127	0.046
ESR, mm/h				
Platelets, $U10^3/\mu L$	0.053	0.012	-0.051	0.429
VPM, fL	0.175	<0.001	-0.156	0.015
Leukocytes, $U10^3/\mu L$	-0.077	<0.001	-0.099	0.124
Lymphocytes, $U10^3/\mu L$	-0.055	0.027	-0.087	0.281
Monocytes, $U10^3/\mu L$	0.025	0.245	0.030	0.647
Eosinophils, $U10^3/\mu L$	-0.036	0.092	-0.079	0.216
Basophils, $U10^3/\mu L$	-0.029	0.170	-0.156	0.015
Neutrophils, $U10^3/\mu L$	-0.024	0.266	-0.026	0.703
CPK, U/L	-0.045	0.121	0.003	0.968
D-dimer, ng/mL	0.175	<0.001	0.199	0.001
Fibrinogen, mg/dL	0.088	0.002	0.109	0.161
LDH, U/L	-0.039	0.118	0.004	0.964
Prothrombin time, s	0.172	<0.001	0.055	0.455
Troponin, ng/L	0.038	0.064	0.072	0.243

The p value calculated by Spearman correlation. MCH: mean cell hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RWD denotes red cell distribution width; MCV: medium corpuscular volume; ESR: erythrocyte sedimentation rate; VPM: Mean platelet volume; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; s: seconds. ICU: intensive care unit.

In the same line, multivariable regression based on death showed r values of RDW, LDH, neutrophils, MCV, and age, and lower values of MCHC, eosinophils, and female sex could explain up to 30% of the probability of death (Table 5).

Discussion

In this study, we describe the characteristics of 2640 hospitalized patients with COVID-19 infection admitted in the hospitals of Aragón-Zaragoza, focusing on the alterations in Laboratory tests.

Our study found an in-hospital mortality rate of 29%, like a multicenter study performed in Spain. In contrast, the reported mortality rate in other the dies in Spain has ranged from 11-24% [19-21].

The mortality rate of hospitalized patients diagnosed with COVID-19 worldwide varies from 1.4% in a case series in China to 16% in Ireland and the United States [22,23].

Mortality differences have been attributed to the different diagnostic techniques for COVID-19, demographic characteristics, and prevalence of comorbidities, which also may influence the inclusion criteria in the studies [24].

Regarding demographics, the median age in our cohort was 72

Table 4. Comparison between analytical reference values and whether the patient is dead or not.

	Deceased patients (N=779)	Non-deceased patients (N=1861)	p
Hematocrit, %	39.8 (36.0 – 43.7)	41.72 (38.3 – 44.73)	0.036
Haemoglobin, g/dL	12.9 (11.7- 14.3)	13.8 (12.7- 14.9)	<0.001
MCH, pg	30.4 (28.8 – 31.8)	30.2 (29.0 – 31.4)	0.878
MCHC, g/dL	33.2 (32.5 – 33.8)	33.6 (32.9 – 34.2)	<0.001
RDW, %	14.6 (13.9 – 15.9)	13.8 (13.2 – 14.7)	<0.001
MCV, fL	91.7 (87.0 – 95.6)	89.9 (86.5 – 93.0)	0.014
ESR, mm/h	73.0 (39.3 – 108)	42.0 (16.0- 79.0)	<0.001
Platelets, $U10^3/\mu L$	181 (138- 234)	191 (149 – 251)	0.154
VPM, fL	9.50 (8.70 – 10.4)	9.20 (8.50 – 10.0)	0.005
Leukocytes, $U10^3/\mu L$	7.80 (5.40 – 10.7)	6.29 (4.60 – 8.20)	<0.001
Lymphocytes, $U10^3/\mu L$	0.822 (0.531 – 1.27)	1.04 (0.745 – 1.50)	0.001
Monocytes, $U10^3/\mu L$	0.497 (0.321 – 0.745)	0.528 (0.387 – 0.700)	0.732
Eosinophils, $U10^3/\mu L$	0.002 (0.000 – 0.021)	0.010 (0.000 – 0.052)	<0.001
Basophils, $U10^3/\mu L$	0.018 (0.010 – 0.036)	0.020 (0.010 – 0.036)	0.654
Neutrophils, $U10^3/\mu L$	6.29 (4.17 – 9.10)	4.48 (3.22 – 6.50)	<0.001
CPK, U/L	93.0 (45.0 – 189)	74.0 (44.0 – 143)	0.007
D-dimer, ng/mL	1388 (773 – 3011)	721 (452 – 1337)	0.004
Fibrinogen, mg/dL	677 (542 – 824)	686 (525 – 822)	0.091
LDH, U/L	337 (244 – 474)	289 (223 – 379)	<0.001
Prothrombin time, s	14.1 (12.8 – 16.33)	13.4 (12.4 – 14.5)	<0.001
Troponin, ng/L	38.8 (21.8 – 78.9)	13.0 (6.09 – 18.65)	0.023

Quantitative variables following not normal distribution were expressed as median (percentile 25th- percentile 75th). The p-value was adjusted by sex and age. MCH: mean cell haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RWD denotes red cell distribution width; MCV: medium corpuscular volume; ESR: erythrocyte sedimentation rate; VPM: Mean platelet volume; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; s: seconds. ICU: intensive care unit.

Table 5. Multivariable regression based on death

	OR	95% CI	p	R^2 Nagelkerke
RDW, %	0.2653	0.181 to 0.353	<0.001	0.3017
MCHC, g/dL	-0.1489	-0.288 to -0.0192	0.031	
Eosinophils, $U10^3/\mu L$	-2.546	-4.617 to -0.655	0.012	
LDH, U/L	0.002219	0.001 to 0.003	<0.001	
Neutrophils, $U10^3/\mu L$	0.08678	0.051 to 0.124	<0.001	
MCV, fL	0.04043e	0.0174 to 0.064	<0.001	
Age, years	0.07655	0.064 to 0.090	<0.001	
Sex, women	-0.3947	-0.678 to -0.114	0.006	

Multivariable binary logistic regression with death as the dependent variable. OR: Odd Ratio; CI: Confidence Interval. RWD denotes red cell distribution width; MCHC: mean corpuscular hemoglobin concentration; LDH: lactate dehydrogenase; MCV: medium corpuscular volume.

years old, like the results found in a multicenter study conducted in the United Kingdom (UK) [25]. Lower ages were reported in Spanish reports [19,20,26]. One Chinese study described a median age of less than 50 [27].

It is also important to mention that several studies found the highest mortality rate among older patients, as described in this study [20,26,28,29].

In relation to gender, multiple studies found that male sex is another risk factor for severity, admission to ICU, and mortality of COVID-19 [12,30,31]. As described by Klein and Flanangan, this difference would be associated with sex differences in the immune response that may impact the susceptibility to infectious diseases, inflammatory response, and consequences of COVID-19 [32].

Regarding Laboratory tests in this study, we described that patients with higher levels of fibrinogen, LDH, leukocytes, and lymphopenia at admission were associated with a higher probability of being admitted to the ICU. Similar results were found in a systematic review and meta-analysis written by Zhang et al. [13], in which patients with elevated LDH, CRP, and lymphopenia require appropriate management and, if necessary, admission to the ICU.

In this line, we found that a combination of 5 variables (older age, male, elevated fibrinogen and leukocyte counts, and lower

concentration of monocytes) can explain 10% of the probability of requiring admission to the ICU. Studies conducted in USA and Europe also have similar findings (older age, male, elevated counts of fibrinogen and leucocytes) [23,33].

A report found differences in Leucocytes between severe and non-severe COVID-19 patients [34]. Patients in both groups increased their leukocyte count due to activation of the immune system to fight a viral infection. However, the severe group had a significantly higher leukocyte count [34,35]. Also, it is essential to remember that leukocytes alone may be influenced by many factors such as inflammatory response and glucocorticoid treatment, which increases it. In this line, a Chinese report describes that also mononuclear cells (monocytes and lymphocytes) play an essential role in immune response and pathogen elimination. The immune defense activates monocytes and natural killer cells, so they found an increased number of monocytes in patients with COVID-19 infection, in contrast to our study [36,37]. Contrastingly, lower levels of lymphocyte counts were related to severe COVID-19 infection and higher mortality [13,14,38]. These Laboratory findings may help physicians to know the prognosis and whether or not the patient will need to be admitted to the ICU.

It should also be noted that the analytical parameters may be related to the length of stay. Our study found that hemoglobin and D-dimer showed a significant and positive correlation with more extended hospital stays and ICU stays. One study written by Pillai et al. found that an NLR >18 and high levels of procalcitonin, sodium, and potassium were associated with a hospital stay of >14 days [39]. There are few studies on this subject. It would be of interest to study it as prognostic predictor.

Also, some Laboratory parameters are related to in-hospital mortality, as it has been shown in many studies that D-dimer is higher in survivors than in non-survivors [18,40,41]. This Laboratory parameter originates from fibrin lysis, with higher levels denoting activation of coagulation and fibrinolysis, with COVID-19 being associated with hemostatic abnormalities [42]. Zhan et al. found that higher levels (cutoff point >2.0 μg/mL) of D-dimer at admission can help predict in-hospital mortality [43] and could play a role as a triage marker for intensive care patients [28], which could help clinicians tailor treatment and prognosis.

As mentioned above, a higher number of leukocytes and neutrophils were associated with severe COVID-19 and were also found in several studies to be associated with mortality.

Another parameter found to be higher in patients who died was LDH. Increased lactate dehydrogenase denotes tissue/cell destruction and is a sign suggesting viral infection or lung damage, such as SARS-CoV-2 induced pneumonia [44]. Yan et al. developed a mortality prediction model using machine learning tools. They included 485 patients diagnosed with COVID-19 in Wuhan and analyzed 75 clinical features, including the concentrations of blood markers.

They found that three blood markers (LDH, lymphocytes, and high-sensitivity-CRP) could predict patient mortality 10 days in advance with an accuracy of more than 90%. Particularly just one elevated biomarker (LDH) in blood, it was highly indicative of COVID-19 mortality [45].

Another elevated parameter that denotes worse prognosis and increased mortality is troponins. Several studies have found the same results as ours [19,28,46,47].

Conclusions

Coronavirus infection has been a challenge for the health system worldwide and knowing the analytical parameters at the time of admission could help to understand the prognosis and severity of the disease. It will be essential to see this parameter.

Our study concludes that five factors (being old, male, higher concentrations of fibrinogen, leucocyte, and lower levels of monocytes) may explain 10% of the probability of requiring admission to the ICU. Biomarkers such as Hemoglobin and D-dimer showed a significant and positive correlation with the index hospital stay, and ICU stays, so up to 30% of the probability of death could be explained if you are old and have higher values of LDH, neutrophils, and lower values of eosinophils. Laboratory findings may help physicians to predict the severity of COVID-19 and subsequently improve prognosis and decrease mortality rates. Nonetheless, further studies are needed to understand better these changes and their relation to prognosis [11,19].

Acknowledgments

We wish to thank the Network for Research on Chronicity, Primary Care, and Health Promotion (RD21/0016/0001) (RICAPPS-Health Institute Carlos III, Spain); Research Group B21_20R of the Department of Research, Innovation and University of the Government of Aragon (Spain); Feder Funds "A way to make Europe", for their support in the development of the study.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Dhakal BP, Sweitzer NK, Indik JH, et al. SARS-CoV-2 Infection and Cardiovascular Disease: COVID-19 Heart [Internet]. Vol. 29, Heart Lung and Circulation. 2020. p. 973–87. Available from: https://doi.org/10.1016/j.hlc.2020.05.101
2. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 2021. Available at: https://covid19.who.int/ (Accessed: Septiembre 2021).
3. Cardinal-Fernández P, Cuesta EG, Barberán J, et al. Clinical characteristics and outcomes of 1,331 patients with covid-19: Hm spanish cohort. Rev Esp Quimioter. 2021;34(4):342–52.
4. Akaninyene Otu, Egbe Osifo-Dawodu PA, Emmanuel Agogo BE. Since January 2020, EElsevierr has c,reatElsevierVID-19 resource center with free information in English and Mandarin on the novel coronavirus COVID- research available on the COVID-19 resource center centering this Comment Beyond vaccine hesitancy : Lancet. 2021;2(January):2020–2.
5. Iftimie S, Lopez-Azcona AF, Vallverdu I, et al. First and second waves of coronavirus disease-19: A comparative study in hospitalized patients in Reus, Spain. PLoS One. 2021;16(3 March 2021):1–13.
6. Bonanad C, García-Blas S, Tarazona-Santabalbina F, et al. The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects. J Am Med Dir Assoc [Inter-

net]. 2020;21(7):915–8. Available from: https://doi.org/10.1016/j.jamda.2020.05.045

7. Wu Z, Jennifer M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Vol. 323, Jama. 2021. p. 2019–22.

8. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China Supplemental content. JAMA Intern Med [Internet]. 2020;180(7):934–43. Available from: https://jamanetwork.com/

9. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5.

10. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular, metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531–8.

11. García de Guadiana-Romualdo L, Morell-García D, Morales-Indiano C, et al. Characteristics and laboratory findings on admission to the emergency department among 2873 hospitalized patients with COVID-19: the impact of adjusted laboratory tests in multicenter studies. A multicenter study in Spain (BIOCOVID-Spain study). Scand J Clin Lab Invest [Internet]. 2021;81(3):187–93. Available from: https://doi.org/10.1080/00365513.2021.1881997

12. Jutzeler CR, Bourguignon L, Weis C V, et al. Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis [Internet]. 2020;37:101825. Available from: https://doi.org/10.1016/j.tmaid.2020.101825

13. Zhang ZL, Hou YL, Li DT, et al. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scand J Clin Lab Invest [Internet]. 2020;80(6):441–7. Available from: https://doi.org/10.1080/00365513.2020.1768587

14. Vita G, Syambani Z. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An. Med Clin Barcelona. 2020;155(4):143–51.

15. Rodelo JR, De La Rosa G, Valencia ML, et al. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. Am J Emerg Med [Internet]. 2012;30(9):1991–9. Available from: http://dx.doi.org/10.1016/j.ajem.2012.04.033

16. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

17. Tang H, Gao J, Guo Z, et al. Analysis of clinical characteristics and laboratory findings of 131 cases of neurosyphilis. Chinese J Dermatol. 2020;53(10):774–80.

18. Moreno G, Carbonell R, Bodí M, et al. Systematic review of the prognostic utility of D-dimer, disseminated intravascular coagulation, and anticoagulant therapy in COVID-19 critically ill patients. Med Intensiva. 2021;45(1):42–55.

19. Moreno-Torres V, de la Fuente S, Mills P, et al. Major determinants of death in patients hospitalized with COVID-19 during the first epidemic wave in Madrid, Spain. Medicine (Baltimore). 2021;100(16):e25634.

20. Gil-Rodrigo A, Miró Ò, Piñera P, et al. Evaluación de las características clínicas y evolución de pacientes con COVID-19 a partir de una serie de 1000 pacientes atendidos en servicios de urgencias españoles. Emergencias. 2020;32(4):233–41.

21. Gutiérrez-Abejón E, Tamayo E, Martín-García D, et al. Clinical profile, treatment and predictors during the first covid-19 wave: A population-based registry analysis from castile and leon hospitals. Int J Environ Res Public Health. 2020;17(24):1–15.

22. Beatty K, Kavanagh PM. A retrospective cohort study of outcomes in hospitalised COVID-19 patients during the first pandemic wave in Ireland. Ir J Med Sci [Internet]. 2021;(0123456789). Available from: https://doi.org/10.1007/s11845-021-02753-6

23. Kim L, Garg S, Halloran AO, et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis [Internet]. 2021;4(72):206–14. Available from: https://pubmed.ncbi.nlm.nih.gov/32674114/

24. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA - J Am Med Assoc. 2020;323(18):1775–6.

25. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. BMJ. 2020;369(April):1–14.

26. Berenguer J, Ryan P, Rodríguez-Baño J, et al. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. 2020;26(11):1525-1536. doi:10.1016/j.cmi.2020.07.024. Clin Microbiol Infect. 2020;26(11)(November):1525–36.

27. 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.

28. Pandita A, Gillani FS, Shi Y, et al. Predictors of severity and mortality among patients hospitalized with COVID-19 in Rhode Island. PLoS One [Internet]. 2021;16(6 June):1–15. Available from: http://dx.doi.org/10.1371/journal.pone.0252411

29. Lithander FE, Neumann S, Tenison E, et al. COVID-19 in older people: A rapid clinical review. Age Ageing. 2020;49(4):501–15.

30. Jin JM, Bai P, He W, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Heal. 2020;8(April):1–6.

31. Minnai F, De Bellis G, Dragani TA, et al. COVID-19 mortality in Italy varies by patient age, sex and pandemic wave. Sci Rep [Internet]. 2022;12(1):1–9. Available from: https://doi.org/10.1038/s41598-022-08573-7

32. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16(10):626–38.

33. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related Severe

Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. 2020;998–1000.

34. Qin C, Zhou L, Hu Z, et al. Dysregulation of Immune Response in Patients with COVID-19 in Wuhan, China. SSRN Electron J. 2020;

35. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9.

36. Zeng X, Xing H, Wei Y, et al. Monocyte volumetric parameters and lymph index are increased in SARS-CoV-2 infection. Int J Lab Hematol. 2020;42(6):e266–9.

37. Colak A, Oncel D, Turken M, et al. Usefulness of laboratory parameters and chest CT in the early diagnosis of COVID-19 Ayfer. Rev Inst Med Trop Sao Paulo. 2022;64:e28(February):1–10.

38. Ghahramani S, Tabrizi R, Lankarani KB, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: A systematic review and meta-analysis. Eur J Med Res [Internet]. 2020;25(1):1–10. Available from: https://doi.org/10.1186/s40001-020-00432-3

39. Pillai J, Mistry PPK, Le Roux DA, et al. Laboratory parameters associated with prolonged hospital length of stay in COVID-19 patients in Johannesburg, South Africa. South African Med J. 2022;112(3):201–8.

40. Kermali M, Khalsa RK, Pillai K, et al. The role of biomarkers in diagnosis of COVID-19 – A systematic review. Life Sci. 2020;254(January):117788.

41. Paul Weiss, DRM. Clinical course and mortality risk of severe COVID-19. Lancet [Internet]. 2020;395(March):1014–5. Available from: https://doi.org/10.1016/%0AS0140-6736(20)30633-4

42. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7.

43. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324–9.

44. Konstantinos Bartziokas KK. Lactate dehydrogenase, COVID-19 and mortality. Med Clin (Barc) [Internet]. 2021;156(1):37–43. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7518167/pdf/main.pdf

45. Yan L, Zhang H-T, Goncalves J, et al. An interpretable mortality prediction model for COVID-19 patients. Nat Mach Intell [Internet]. 2020;2(5):283–8. Available from: http://dx.doi.org/10.1038/s42256-020-0180-7

46. Salvatici M, Barbieri B, Cioffi SMG, et al. Association between cardiac troponin I and mortality in patients with COVID-19. Biomarkers [Internet]. 2020;25(8):634–40. Available from: https://doi.org/10.1080/1354750X.2020.1831609

47. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811–8.

To cite this article: Matovelle-Ochoa P, Oliván-Blázquez B, Magallón-Botaya R, et al. Biomarkers as Prognosis of COVID-19 Disease: Retrospective Cohort Study. European Journal of Respiratory Medicine. 2022; 4(2): 344 - 341. doi: 10.31488/EJRM.136.