IL-6 and Other Biomarkers associated with Poor Prognosis in a Cohort of Hospitalized Patients with COVID-19 in Madrid

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ABSTRACT

OBJECTIVES: There are several published works on the prognostic value of biomarkers in relation to the severity or fatal outcome of coronavirus disease 2019 (COVID-19). In Spain, the second European country in incidence of the disease at the time of data collection, there are few studies that include both laboratory parameters and clinical parameters. Our aim is to study the relationship of a wide series of biomarkers with admission to intensive care and death in a hospital in the Autonomous Community of Madrid (Spain), with special attention to IL-6 due to its role in the systemic inflammatory response associated with a worse prognosis of the disease.

METHODS: Data were collected from 546 hospitalized patients with COVID-19. All of them had IL-6 results, in addition to other biochemical and haematological parameters. The difference of the medians for the selected parameters between the groups (ICU vs non-ICU, dead vs survivors) was studied using a Mann-Whitney analysis. The independent variables that predicted death were studied using a Cox proportional hazard regression model.

RESULTS: Higher age and blood concentrations of ALT, creatinine, CK, cTnI, LDH, NT-proBNP, CRP, IL-6, leucocyte count and D-dimer together with lower blood concentrations of albumin and lymphocyte count were associated with mortality in univariate analysis. Age, LDH, IL-6 and lymphocyte count remained associated with death in multivariate analysis.

CONCLUSIONS: Age, LDH, IL-6 and lymphocyte count, as independent predictors of death, could be used to establish more aggressive therapies in COVID-19 patients.

KEYWORDS: Biomarkers, IL-6, COVID-19, prognosis, laboratory medicine, Madrid

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Introduction

At the end of December 2019, the Chinese authorities notified the appearance of a series of cases of atypical pneumonia in the city of Wuhan.[1] Subsequently, it was confirmed that the agent causing this new disease was a virus that belonged to the Coronaviridae family and was named as *SARS-CoV-2*. The new disease caused by it was therefore named as *Coronavirus disease 2019* (COVID-19). The new virus spread rapidly outside of China and on March 11th, 2020, the WHO (World Health Organization) established that the COVID-19 could be categorized as a pandemic.

The incidence and transmission characteristics, the clinical characteristics and the fatality rate of patients, especially severe patients, have been a major concern.[2]

On January 31st, 2020, the first case was recorded in Spain in a patient coming from Germany. Since then, the number of cases increased exponentially, forcing the authorities to take exceptional measures such as the confinement of the population, which occurred on March 14th. During the months of March and April the health emergency situation led to a saturation of the health national system and especially that of the hospitals, due to the higher and higher number of admissions both in medical wards and in intermediate and intensive care units.

The severity of this infection lies in the high contagion capacity of this virus and mainly the morbidity with which the disease manifests itself in some patients, which has led to a high mortality rate. Pandemic management emphasizes on prompt identification and containment, achievable through strict surveillance and early diagnosis.[3,4]

We are still far from knowing most abnormalities found in patients with COVID-19 infection, in spite of the fact that the clinical characteristics have already been extensively defined.[5]

In vitro diagnostic tests as studied in this paper, are valid for assessing disease severity, for defining the prognosis, for following-up patients, for guiding treatment and for their therapeutic monitoring, which provides the laboratory with functions that extend beyond etiological diagnosis and epidemiological follow-up.[6–8]

This study was performed in an inpatient Spanish population sample. In this paper, we aim to determine the evidence-based prognostic value of several biomarkers in hospitalized patients diagnosed with COVID-19. These laboratory parameters profiles at admission and/or through hospital stay will help to predict the evolution of this disease.

If we could find biomarkers that could help differentiate severe from non-severe cases or assess the risk of mortality, it would undoubtedly contribute to a better clinical management of the situation.

Methods

Study subjects

We conducted a retrospective observational study in *Hospital Universitario Puerta de Hierro Majadahonda* (HUPHM), Madrid. A total number of 1579 patients with laboratory-confirmed positive PCR for SARS-CoV-2 infection[9] attended to the Emergency room and consequently were admitted to this hospital, between March 27th and April 30th, 2020. Out of all these inpatients, those who had IL-6 results (n = 546) were finally enrolled. The study was approved by the local ethics committee. Informed consent was waived due to the nature of the retrospective study.

Data were extracted from the clinical electronic record, including sex, age and the laboratory findings.

Patients who died, those who were discharged, or those who required intensive care supports were also recorded and the length of their stay was also determined. ICU wards also include those from Post-Surgical Recovery Units that had to be set up at the critical moment of the pandemic as wards for the care of critical patients.

Samples and clinical laboratory data

Whole blood tests (leucocyte, lymphocyte and platelet counts) were measured using a Sysmex NX10 (Sysmex Corporation, Kobe, Japan).

Serum biochemistry parameters (albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, creatinine, creatine kinase [CK], lactic dehydrogenase [LDH], C-reactive protein [CRP] and ferritin) were measured using an Advia XPT automated biochemistry analyser. Interleukin-6 [IL-6] was measured using an Advia Centaur XPT Immunoassay System. Troponin I [cTnI] and N-terminal pro-brain natriuretic peptide [NT-proBNP] were measured using a VISTA 500 analyser.

ADVIA XPT, Advia Centaur XPT and Vista 500 analysers and their respective reagents were supplied by Siemens Healthineers (Erlangen, Germany).

Coagulation analysis (D-dimer and fibrinogen) were determined using a Sta R Max analyser (Diagnostica Stago, Asnières, sur-Seine, France).

For each patient, the values of the different parameters at admission and at the point where they reached their maximum (or minimum, ie, albumin, lymphocyte and platelet counts) value were selected for the study.

Statistical analysis

No statistical sample size calculation was performed a priori, and sample size was equal to the number of patients admitted to hospital during the study period. Continuous variables are presented as median and interquartile range (IQR). Categorical variables are expressed as absolute frequencies as well as percentages. Mann-Whitney Rank sum test was used to compare nonparametric continuous variables between groups. Chi Square or Fisher exact test was used for categorical variables as appropriate.

The primary outcome was death and the secondary outcome was admission to the ICU. The time to event started the day of admission to hospital. The primary analysis was conducted with the Cox proportional hazards regression model, after ruling out collinearity among the studied variables. The associations between the different variables and death was evaluated through a univariate Cox proportional hazard regression model. Variables with a P value $\leqslant .1$ were selected to build a multivariate Cox proportional regression model trying to identify the variables independently associated with the outcome. Adjusted hazard ratio was calculated with 95% confidence intervals (CI). The proportionality of the hazards was evaluated with the goodness of fit test, both checking the significance level or 'P value' and the graphic of each variable on the final model versus time.

All statistical tests were 2-tailed, and statistical significance was defined as $P < .05$. Analysis were performed using R and R commander.[10,11]

Results

A total of 546 hospitalized patients diagnosed with COVID-19 were included in this study and 57 out of them (10.4%) were at the ICU. The mean age was 66 (±15) years and 357 (65%) were male. A total of 79 (14.5%) patients died during hospital stay, and 14% out of them were at the ICU (8 of 57). Mortality rate was higher in women (32/189, 17%) than in men (47/357, 13%).

The complete descriptive laboratory data of the population under study are shown in Table 1.

ICU vs non-ICU patients

When comparing the median values at admission time on ICU versus non-ICU patients, statistically significant differences were obtained for albumin, ALT, AST, bilirubin, creatinine, CK, LDH, ferritin, leucocyte and platelet counts and D-dimer. However, statistically significant differences were not obtained for cTnI, NT-proBNP, CRP, IL-6, lymphocyte count and fibrinogen.

Table 1. Characteristics of studied population.

Number of cases	546		
Males (%)	357 (65)		
Deceased (%)	79 (14.4)		
Admitted to ICU (%)	57 (10.4)		
Age, median (range)	67 y (15-99)		
LABORATORY DATA	REFERENCE LIMITS	OUT OF REFERENCE LIMITS AT ADMISSION (%)	OUT OF REFERENCE LIMITS DURING STAY (%)
Albumin (g/dL)	<3.5	162/518 (31)	281/528 (53)
ALT (U/L)	>40	173/546 (32)	395/546 (72)
AST (U/L)	>40	242/546 (44)	399/546 (73)
Bilirubin (mg/dL)	>1.1	48/541 (9)	142/542 (26)
Creatinine (mg/dL)	F(>0.9)-M(>1.2)	134/546 (25)	182/546 (33)
CK (U/L)	F(>170)-M(>195)	105/512 (21)	153/513 (29)
cTnI (µg/L)	>0.06	85/285 (30)	132/524 (25)
LDH (U/L)	>246	410/545 (75)	493/545 (91)
NT-proBNP (pg/mL)	⩽75 y (>125)->75 y (>450)	191/347 (55)	273/352 (77)
CRP (mg/L)	>10.0	502/546 (92)	531/546 (97)
Ferritin (ng/mL)	F(>180)-M(>300)	435/528 (82)	465/528 (88)
IL-6 (pg/mL)	>4.4	401/438 (92)	406/546 (74)
Leucocyte count ($\times 10^3$/µL)	>11.5	102/546 (19)	295/546 (54)
Lymphocyte count ($\times 10^3$/µL)	<1.2	398/546 (73)	482/546 (88)
Platelet count ($\times 10^3$/µL)	<150	101/546 (19)	215/546 (39)
D-dimer (µg/mL)	>0.5	452/545 (83)	508/545 (93)
Fibrinogen (mg/dL)	>450	434/532 (82)	479/533 (89)

Abbreviations: F, female; M, male.

When comparing the worst value (maximum or minimum value, as stated in methods) obtained during hospital stay in ICU versus non ICU patients, statistically significant differences were obtained for cTnI, IL-6 and lymphocyte count, in addition to the parameters above mentioned. Only NT-proBNP, CRP and fibrinogen did not show significant differences between ICU versus non-ICU patients (Table 2).

Dead vs survivors

When comparing median values at admission time on patients who died versus patients who survived, statistically significant differences were obtained for albumin, ALT, creatinine, CK, cTnI, LDH, NT-proBNP, IL-6, leucocyte and lymphocyte counts and D-dimer. However, statistically significant differences were not obtained for AST, bilirubin, CRP, ferritin, and fibrinogen.

When comparing only the worst value obtained during hospital stay in patients who died versus patients who survived, statistically significant differences were obtained for all parameters, except for ferritin and fibrinogen (Table 3).

Higher age and blood concentrations of ALT, creatinine, CK, cTnI, LDH, NT-proBNP, CRP, IL-6, leucocyte count and D-dimer and lower blood concentrations of albumin and lymphocyte count were associated with mortality in univariate analysis. Age, LDH, IL-6 and lymphocyte count remained

Table 2. Comparison of laboratory parameters between ICU and non ICU patients at admission (A) and the worst value during the stay (B).

	A					B				
	NON ICU PATIENTS		ICU PATIENTS		*P*	MAXIMUM/MINIMUM NON ICU PATIENTS		MAXIMUM/MINIMUM ICU PATIENTS		*P*
	MEDIAN	IQR	MEDIAN	IQR		MEDIAN	IQR	MEDIAN	IQR	
Age	67	56-79	64	58-70	.0400	–	–	–	–	
Albumin (g/dL)	3.7	3.4-3.9	3.5	3.2-3.8	.0145	3.5	3.1-3.7	3	2.6-3.3	<.0001
ALT (U/L)	27	18-46	47	31-72	<.0001	62	36-108	135	59-212	<.0001
AST (U/L)	37	27-54	46	31-79	.0096	53	39-79	89	59-139	<.0001
Bilirubin (mg/dL)	0.5	0.4-0.8	0.6	0.5-0.85	.0306	0.8	0.6-1.1	1.15	0.9-1.9	<.0001
Creatinine (mg/dL)	0.82	0.66-1.07	0.98	0.69-1.5	.0229	0.94	0.75-1.26	1.1	0.86-1.96	.0039
CK (U/L)	75	47-147	86	37-276	.0296	90	54-192	296	118-645	<.0001
cTnI (µg/L)	0.03	0.02-0.09	0.03	0.02-0.05	.1832	0.02	0.02-0.06	0.06	0.03-0.25	<.0001
LDH (U/L)	315	242-396	388	311-455	.0002	388	294-509	556	465-794	<.0001
NT-proBNP (pg/mL)	536	160-2243	646	162-1880	.8086	871	190-3382	910	222-3403	.7797
CRP (mg/L)	93	46-151	76	29-150	.6392	134	67-204	155	80-246	.1138
Ferritin (ng/mL)	643	386-1184	964	607-1756	.0008	806	439-1470	1416	817-2200	<.0001
IL-6 (pg/mL)	24.6	8.7-73	31.2	10.75-90	.2432	16	3.6-74	59.3	8-275	.0009
Leucocyte count ($\times 10^3$/µL)	7.14	5.21-9.75	10.63	7.33-14.28	<.0001	11.6	8.1-15.6	22.5	16-27.1	<.0001
Lymphocyte count ($\times 10^3$/µL)	0.89	0.64-1.26	0.8	0.5-1.33	.1424	0.65	0.42-0.91	0.44	0.24-0.68	<.0001
Platelet count ($\times 10^3$/µL)	218	159-286	252	185-324	.0232	172	131-225	128	80-177	<.0001
D-dimer (µg/mL)	1.03	0.59-2.05	2.19	0.73-4.29	.0001	1.62	0.81-3.8	8.63	3.74-13.97	<.0001
Fibrinogen (mg/dL)	609	494-704	581	401-753	.2706	673	548-766	700	526-785	.4733

IQR, interquartile range.

associated with death in multivariate analysis. Bilirubin also remained associated with death in multivariate analysis, but it was excluded due to the fact that it did not follow the hazard proportionality assumption. The results of Cox proportional hazard models are shown in Table 4.

Discussion

The main interest of this work has been the identification of laboratory markers which may help to select those COVID-19 patients with increased risk of developing severe forms of the disease needing admission to ICU or even which may lead them to death.

Our ICU admission rate (10.4%) is similar to those published by others[12,13] (11.3%) and lower than some others studies carried out in Spain[14] and in New York.[15] This variety of results, ranging from 9% in Italy[16] to 32% in China,[17] may respond to differences among patients, as well as the care received in each country and hospital.

Our low global mortality figures (14.5%) compares with other studies[12,14,15,18] do not seem to be explained by demographic characteristics (similar median age, male/female ratio to other studies) and may have to be found in the presence of comorbidities, necessity of assisted ventilation, differences in pharmacological treatments, etc.

The mortality of our ICU patients is lower (14%) than those figures previously published.[12–14,16] On the other hand, our mortality data hardly differ between ICU patients and those not admitted at ICU, which indicates that admission to the ICU in our hospital does not imply a greater probability of death, as occurs in the other studies cited.

This study shows several biomarkers that point to significant abnormalities (both at admission and during hospital stay) in patients who need ICU admission compared to those who don't need it, as well as patients who died compared to those who survived.

Table 3. Comparison of laboratory parameters between survivors and non survivors at admission (A) and the worst value during the stay (B).

	A					B				
	SURVIVORS ADMISSION VALUE		DECEASED ADMISSION VALUE		*P*	SURVIVORS MAXIMUM/MINIMUM		DECEASED MAXIMUM/ MINIMUM VALUE		*P*
	MEDIAN	IQR	MEDIAN	IQR		MEDIAN	IQR	MEDIAN	IQR	
Age	64	55-74	82	75-87	<.0001	–	–	–	–	
Albumin (g/dL)	3.7	3.4-3.9	3.4	3.2-3.7	<.0001	3.5	3.1-3.8	3.1	2.8-3.4	<.0001
ALT (U/L)	31	20-53	21	15-33	<.0001	69	40-125	48	27-78	.0003
AST (U/L)	37	27-56	40	28-53	.6159	53	39-83	64	46-98	.0123
Bilirubin (mg/dL)	0.5	0.4-0.8	0.7	0.4-0.9	.0636	0.8	0.61-1.1	1	0.7-1.4	.0030
Creatinine (mg/dL)	0.81	0.65-1.05	1.09	0.75-1.83	.0001	0.91	0.74-1.17	1.39	1.04-2.6	<.0001
CK (U/L)	74	45-140	129	54-274	.0053	88	54-192	228	109-561	<.0001
cTnI (µg/L)	0.03	0.02-0.07	0.04	0.02-0.15	.0456	0.02	0.02-0.04	0.07	0.03-0.29	<.0001
LDH (U/L)	386	121-1550	1935	721-5537	<.0001	471	155-1955	2867	1159-10131	<.0001
NT-proBNP (pg/mL)	314	243-395	378	305-463	.0001	382	292-493	595	446-793	<.0001
CRP (mg/L)	89.1	43.8-150.2	106.1	89-150	.1752	130.5	63.7-200.3	195.8	125.1-250	<.0001
Ferritin (ng/mL)	677	393-1305	692	418-1119	.8346	827	449-1549	959	472-1847	.1306
IL-6 (pg/mL)	24.55	8.4-61.4	44.05	24.85-61.25	.0031	14.8	3.3-60.1	109	18.6-489.4	<.0001
Leucocyte count ($\times 10^3$/µL)	7.22	5.31-9.85	9.06	7.25-9.69	.0293	11.5	8.1-15.7	16.2	12.2-21.7	<.0001
Lymphocyte count ($\times 10^3$/µL)	0.92	0.66-1.31	0.67	0.4-1.95	<.0001	0.67	0.46-0.93	0.36	0.22-0.54	<.0001
Platelet count ($\times 10^3$/µL)	223	161-303	196	150-268	.0648	172	130-226	143	108-203	.0017
D-dimer (µg/mL)	0.99	0.59-2.02	2.11	0.13-2.5	<.0001	1.6	0.81-3.87	4.63	2.54-11.46	<.0001
Fibrinogen (mg/dL)	600	492-710	609	478-705	.9179	673	546-767	694	563-785	.4585

Result are shown as median and interquartile range.

ICU vs non-ICU patients

Eleven laboratory parameters (albumin, ALT, AST, bilirubin, creatinine, CK, LDH, ferritin, leukocyte and platelet counts and D-Dimer) – out of 17 studied – proved relevant differences between ICU patients in comparison to those who did not require this admission.

It is striking that we found no differences for cTnI or NT-proBNP at admission, while Henry et al[17] did. However, the maximum cTnI value during stay was higher in patients who were admitted to the ICU compared to those who were not. This could be related to the occurrence of acute coronary events.

Unlike other authors,[6,12,19] we found no significant differences for CRP, lymphocyte count and IL-6. The maximum IL-6 and minimum lymphocyte count values reached by ICU patients were significantly different from the values of non-ICU patients, possibly indicating a worsening in the inflammatory status of those patients during ICU stay.

Dead vs survivors

Likewise, our data reflect significant differences between patients who died and survivors for the following parameters: albumin, ALT, creatinine, CK, cTnI, NT-proBNP, LDH, IL-6, leucocyte and lymphocyte counts, and D-dimer, results similar to those presented in the 2 main studies carried out in our country[12,14] and quite consistent with those of other authors.[6,19,20] Major differences with other studies[14,19,20] are to be found in the lack of statistically significant association of AST and bilirubin with mortality in our population. However, unlike our results, most studies find significant differences for

Table 4. Univariate and multivariate analysis of age, sex and laboratory parameters associated to mortality.

	UNIVARIATE					MULTIVARIATE				
	COEF	HR	LOWER 95% CI	UPPER 95% CI	*P*	COEF	ADJUSTED HR	LOWER 95% CI	UPP 95%	*P*
Age	0.087	1.091	1.071	1.114	<.0001	0.09	1.100	1.079	1.126	<.0001
Albumin (g/dL)	−1.012	0.36	0.24	0.54	<.0001					
ALT (U/L)	−0.02	0.976	0.963	0.988	.0002					
AST (U/L)	−0.0009	0.999	0.993	1.004	.7					
Bilirubin (mg/dL)	0.14	1.150	0.97	1.360	.09					
Creatinine (mg/dL)	0.11	1.110	1.003	1.243	.04					
CK (U/L)	0.0005	1.00058	1.00011	1.001	.01					
cTnI (µg/L)	0.12	1.130	1.066	1.210	<.0001					
LDH (U/L)	0.0016	1.0016	1.001	1.003	.0004	0.002	1.002	1.001	1.0036	.0001
NT-ProBNP (pg/mL)	0.0002	1.00002	1.00001	1.00003	.003					
CRP (mg/L)	0.0025	1.0025	1.000	1.005	.05					
Ferritin (ng/mL)	0.00007	1.00007	0.9999	1.00029	.4					
IL-6 (pg/mL)	0.0009	1.00094	1.00054	1.0013	<.0001	0.001	1.0011	1.001	1.0016	<.0001
Leukocyte count (x10^3/µL)	0.04	1.0400	1.001	1.083	.04					
Lymphocytes count (x10^3/µL)	−1.25	0.286	0.158	0.516	<.0001	−0.66	0.514	0.301	0.878	.001
Platelet count (x10^3/µL)	−0.0018	0.998	0.995	1.000	.100					
D-dimer (µg/mL)	0.016	1.016	1.003	1.031	.01					
Fibrinogen (mg/dL)	0.00008	1.00008	0.998	1.001	.898					
Sex	−0.31	0.726	0.46	1.141	.16					

CRP and ferritin. We did not find either any differences for platelet count, agreeing with the result of Bonetti et al.[20] Among the inflammation parameters, the only one that is different between dead patients and survivors is IL-6, which would demonstrate that the increase of this cytokine would play a role in relation to a possible fatal outcome. Fibrinogen is a parameter that does not appear to be related to severity or mortality. In most studies reviewed, as well as in ours, the parameters that always seem to be related to mortality are albumin, creatinine, CK, cTnI, LDH, leucocyte and lymphocyte counts and D-dimer. In addition to the state of systemic inflammation, this association could be explained because of the serious and fatal forms of the disease with multiorgan involvement that can include liver, lung, kidney and/or cardiac failure, as well as significant alterations of the coagulation system.

When comparing maximum or minimum value during hospital stay, almost all the laboratory markers showed significant differences between patients treated in ICU versus those not treated in ICU, and also between patients that survived versus those who died, except LDH, ferritin and fibrinogen in the first case and only ferritin and fibrinogen in the second case. Both markers act as acute phase reactants and, therefore, they appeared at high rates practically since the beginning of the disease, independently of the severity of the process that could lead to admission in the ICU or to a fatal outcome.

Added to the increase in age, it is observed that LDH, IL-6 and the decrease in lymphocyte count appear as independent predictors of death. LDH is cited in the works of Bonetti et al[20] and Liang et al.[21] In the latter, LDH is included in the Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients. Bonetti et al[20] also includes lymphocyte

count as an independent predictor of death. IL-6 does not appear as an independent variable among the studies consulted, although as mentioned, in some studies[22] significant differences are found between dead and survivors[23] or in severe cases for this parameter.

Advanced age has been associated to higher risk of in-hospital death,[18,24] and it had been previously reported as an independent predictor of mortality in SARS and MERS.[25,26] It is remarkable that any of these inpatients have a risk of death which is 8.9% higher than those 1 year younger (ie, the risk of dead of a 71-year-old inpatient is 8.9% higher than that of a 70-year-old inpatient).

Our study shows lymphocyte count as a strong independent risk factor of poor prognosis.

Age-dependent defects in T-cell and B-cell function and the excess production of type 2 cytokines could lead to a deficiency in control of viral replication and more prolonged inflammatory responses.[27] In particular, this study shows lymphocyte count as a strong independent risk factor of poor prognosis. Both in the SARS and in COVID-19, virally infected cells seem to be specifically eliminated by lymphocytes.[28,29] Taking this into account, lymphocyte count may be used as a clinical predictor of severity and prognosis.

Several studies show that Angiotensin Converting Enzyme 2 (ACE2), leading SARS-CoV-2 receptor at cell surface,[30] is expressed by lymphocytes. It is therefore possible that the virus would damage these cells, and that their decrease into the circulation may be related with lymphocytic dysfunction and immunosuppression, eventually playing its part to expose patients to a higher risk of co-infections and worse prognosis, as previously reported patients to both a higher risk of co-infections and worse prognosis, as previously reported.[31]

Serum markers such as IL-6 were markedly increased in non-survivors as compared with survivors, and this parameter showed independent prediction of mortality among the study patients. This biomarker elevation could correlate with the development of a systemic inflammatory response syndrome (SIRS) or, even multiorgan failure[32,33] could be correlated with this biomarker escalation. As a result, prognosis in COVID-19 patients over the course of hospitalization could be monitored using IL-6 parameter.

There is some evidence that has proved that increased LDH values reflect the extent of lung injury in patients with ARDS, including those with the previous coronavirus disease SARS.[20,21,34] Our results are in agreement with Liang et al,[21] as the increase of this enzyme has proved to be as an independent predictor of mortality.

Sex has not shown a significant association with mortality in the univariate or multivariate analysis. In our series, there are more men who required hospitalization, but mortality is proportionally higher in women, although these differences do not reach statistical significance. Although there are some articles which have found higher mortality, in men,[14,35] or the clinical course was more severe[13] also in men, perhaps in our series women had a higher degree of comorbidities. In any case, these data have not been collected as object of our study.

There is no significant difference in CRP upon admission because possibly all the patients had a high degree of inflammation. Nevertheless, at the maximum value, the difference becomes significant between survivors and dead. For this one reason, in our study, CRP is not a marker of prognosis at admission, but its increase during the stay could be a marker of severity.

Our study has some limitations. There is a possible bias in having only collected patients who had IL-6 determinations, however we considered that fact an essential parameter within the objective of our study. It is also noticeable that there were no statistically significant differences between COVID-19 patients admitted to the hospital (n = 1306, 12.5% death) and IL-6 requested patients enrolled in the study (n = 546, 14.5% death).

IL-6 and ferritin are not routinely measured at the emergency setting, and, in consequence, their role could be underestimated in predicting in-hospital death. However, it can be stated that more than 94% of patients had results of all studied parameters. Variability of administered therapy as high-dose corticosteroid use might have also contributed to a poor clinical outcome.[18] Concerning the validity of the multivariate models performed in this study, it can be confirmed that the final Cox proportional hazard model as well as the individual hazards showed an adequate proportionality.

In summary, we consider remarkable that advanced age and some laboratory parameters have relevant prognosis value in COVID-19 hospitalized patients. Specifically, elevated values in both IL-6 and LDH as well as decreased lymphocyte count showed as independent predictors of mortality.

Author Contributions

All authors have equally contributed to data collection, data analysis, article writing and discussion.

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