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Mortality and critical conditions in COVID-19 patients at private hospitals: weekend effect?

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Abstract. – OBJECTIVE: The aim of the study was to find factors associated with the mortality of admission to the intensive care unit (ICU) in patients with COVID-19.

MATERIALS AND METHODS: Retrospective observational study with a database of 1987 patients with COVID-19 who had attended the emergency department of a private hospital network between February 2020 and April 2020 were analyzed. Clinical variables and some laboratory parameters were studied. The Charlson and Elixhauser comorbidity indices were calculated. The dependent variables were mortality and admission to the ICU. A descriptive and correlational analysis was performed. Logistic regression models and Kaplan-Meier survival curves were established.

RESULTS: Positive correlations were observed between age, creatinine, and D-dimer levels, as well as with the scores obtained with the Charlson and Elixhauser indices. Differences in the levels of these parameters were also observed when analyzing variables such as mortality, sex or admission to the ICU. Mortality was associated with high creatinine and D-dimer levels and advanced age. Survival curves indicated longer survival in patients not admitted to the ICU, admitted to the hospital during the week, and in those with lower creatinine and D-dimer levels.

CONCLUSIONS: Mortality in Spanish patients with COVID-19 admitted to private hospitals was associated with high creatinine and D-dimer levels and advanced age. Longer survival was obtained on weekdays. This study provides valuable information on the management and nursing care of these patients in order to optimize resources in pandemic situations.

Key Words:
COVID-19, D-dimer, Comorbilities, Critical care, Intensive care units.

Introduction

Coronavirus disease 2019 (COVID-19) is a new viral infection with highly pathogenic consequences[1]. The causative agent of this coronavirus disease has been identified as SARS-CoV-2[1,2]. Researchers and experts mention that the first case appeared on 8 December 2019. On 31 December 2019, the Wuhan Municipal Health Commission (Hubei, China) reported 27 cases of pneumonia of unknown aetiology with common exposition in a market in Wuhan. The genetic sequence of SARS-CoV-2 was shared on 12 January 2020. On 11 March 2020, the World Health Organization (WHO) declared the world pandemic[2].

Coronaviruses are a group of zoonotic RNA viruses causing a large range of symptoms, from the mild common cold symptoms to extreme respiratory or even neurological, hepatic or enteric symptoms[1]. In the case of people infected with SARS-CoV-2, they could experience mild to moderate respiratory symptoms, recovering without special or intensive treatment. However, there are high-risk cases, such as elderly people and

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people with previous medical conditions, who have a higher probability of developing a serious illness[3]. This multimorbidity is usually defined as the detection of two or more chronic conditions in a single individual[4]. As a consequence of this multimorbidity state, some studies have shown a relationship between in-hospital mortality and comorbidity[5-12].

Background/Justification for Study

This is relevant in countries like Spain, where the present study was carried out. Due to its demographic characteristics, with an ageing population, the increase of comorbidities is significant. This tendency to an increasingly ageing population appears in many regions of the world. The European Union (EU-28) is an example. With an estimated population of 512.4 million on 1 January 2018, people aged 65 or over represent 19.7% of the world's population, with an increase of 2.6% in the last 10 years. Italy shows the highest percentage (22.6%)[13]. In Spain, the situation is similar (19.1%) and shows a relevant increase of octogenarians (6.1%) and centenarians (11 229 registered)[14]. Experts estimate that the percentage of people aged 65 or over in Spain will reach 25.2% by 2033[15]. Attending to the probability of comorbidity in elderly people, those data are relevant in the context of the SARS-CoV-2 pandemic, since they represent a high-risk segment of the population. It is known that the main cause of mortality in elderly people is cardiovascular pathology (29.7%). On the other hand, fragility is closely related to advanced age and a higher risk of adverse health events[16]. In this sense, a recent study in Spain shows a higher prevalence of chronic cardiovascular and non-cardiovascular diseases, wider use of polypharmacy and higher risk of fragility in elderly people[16]. For these reasons, it seems necessary to take of age and comorbidities into account when managing patients in a COVID-19 pandemic context[17]. A recent systematic review[17] showed that comorbidities, such as hypertension, cardiovascular disease, chronic kidney disease, diabetes mellitus or acute cardiac and kidney injury, were related to an increased disease severity and an increased risk of COVID-19-related mortality.

The comorbidities of patients with COVID-19 were registered, together with other data such as vital constants and illness development. The analysis of the comorbidities allows to detect mortality or intensive care risks. Concretely, it offers an opportunity to accurately evaluate the risk factors in patients infected with SARS-CoV-2 having comorbidities and whether these comorbidities are related to patient deterioration[17]. This determination could lead to a better ability to triage or monitor these patients, which could help healthcare providers to optimize resources in the context of limited care supplies[17]. Indeed, this analysis could provide information about the best way of managing patients with SARS-CoV-2 based on their age, comorbidities and another parameter in the future.

Objectives of Study

The aim of the present study was to determine the prognostic factors for mortality and intensive care unit (ICU) admission in patients with COVID-19 admitted in the aforementioned hospitals.

Design and Methods

A retrospective observational study was carried out based on clinical data from a Spanish healthcare entity in the private sphere with implementation throughout the Spanish territory.

Setting, Sample, and Data Collection

The data was transferred after a request and with the corresponding institutional and ethical permissions. This entity represents a group of hospitals, polyclinics and private health centres, which have made their databases related to COVID-19 cases available to the scientific community.

A database that collected clinical information on 1987 patients who had accessed, between 5 February 2020 and 20 April 2020, the emergency services of the aforementioned private hospital network and who were diagnosed with COVID-19 or who were suspicious for COVID-19 and awaiting results were analyzed.

Diagnoses were coded following the International Classification of Diseases, 10th Revision (ICD-10)[18]. Variables such as age, sex, date of hospital admission, date of the emergency room visit that led to admission, admission to ICU, length of stay in ICU, medical discharge, destination of discharged patients and deaths were analyzed. In addition, data related to vital signs (first and last records of temperature, oxygen saturation, heart rate, and blood pressure) were analyzed. Along the same lines, analytical parameters such as blood creatinine, D-dimer, and glucose levels, as well as partial pressure of oxygen (pO_2), were analyzed. Once the data was received by the institution, they were refined.

Tools and Methods

A statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY, USA). In addition, the Charlson and Elixhauser indices were used to predict complications, in-hospital mortality or mortality[19-21]. The Charlson and Elixhauser indices were calculated according to the comorbidities registered using the "comorbidity" package of the free software R (version 3.5.0).

Data Analysis

First, data for each variable was descriptively analyzed in terms of absolute frequencies, percentages, and measures of central tendency. A distribution analysis of the sample data was also carried out using the Kolmogorov-Smirnov test. Given that the distribution of the data did not conform to normality, non-parametric tests were used to perform a correlation analysis through Spearman's test. The Mann-Whitney U test to compare differences between two independent groups and the Kruskal-Wallis test for comparison between two or more groups were also used. Multiple logistic regression analyses were carried out to associate independent variables with mortality and ICU admission, adjusting odds ratios (aORs) and respective 95% confidence intervals (95% CIs). Nagelkerke R^2 was used to explain the amount of variance in each logistic regression model. Due to the wide range of values in some variables, for entry into the regression models, they were transformed into a logarithmic scale. Finally, Kaplan-Meier curves were used to estimate the survival function.

Ethical and Research Approvals

Access to the data was requested and granted in April 2020. The treatment thereof was made taking into account the Declaration of Helsinki, Council of Europe on Human Rights and Biomedicine, UNESCO Universal Declaration on the Human Genome and Human Rights, Oviedo Council on Human Rights and Biomedicine, Organic Law 3/2018 on Protection of Personal Data and Guarantee of Digital Rights and Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and the free circulation of these data. The data was delivered anonymized, so it was not possible to identify the patients.

Results

Data from 1987 (N) patients were analyzed. Of these, 60.3% (n = 1199) were men and 39.7% (n = 788) were women. Of the total number of patients, 54% (n = 1072) were assisted on the weekend (Friday, Saturday or Sunday). Overall, 7.3% of the patients (n = 146) were admitted to the ICU. Considering an administrative loss of 216 records (without data related to death or survival), the percentage of deaths was 15.7% (n = 278); 79.8% (n = 1414) of patients were sent home and 77 patients were transferred to another hospital or social health centre (4.3%).

Concerning the symptoms of patients, breathlessness appeared more frequently (54.2%, n = 1076), followed by fever (12.9%; n = 256), cold symptoms (11.3%; n = 225), cough (6.8%; n = 136), and malaise or general malaise (5.9%; n = 118). Other clinical symptoms, such as diarrhea, syncope, and abdominal or chest pain, made up no more than 1% of the total. In the data managed, no information was obtained on cases of anosmia or ageusia. Regarding the measures of central tendency, the mean age was 67.95 years (SD = ± 16.28). The length of hospital stay was recorded for 1810 patients, and the average length of hospital stay was 7.87 days (SD = ± 5.44). The data on days in the ICU were recorded for 132 patients of the total of 146 patients that were hospitalized in the ICU. The average time of admission to the ICU was 5.79 days (SD = 7.18).

The mean blood creatinine level was 1.03 mg/dl (SD = 0.66) (n = 1638), with a maximum of 15.06 mg/dl. The average D-dimer level was 2392.02 ng/ml (SD = 7379.88) (n = 1363), with a maximum of 102.622 ng/ml. Regarding the p02 in the blood, the mean was 61.56 mmHg (SD = 26.51) (n = 665).

Regarding the Charlson index, congestive heart failure (n = 17; 0.9%) was the most frequent comorbidity, followed by chronic lung disease (n = 10; 0.5%), diabetes and cancer (n = 6; 0.3% in each case). Twelve of the 17 possible comorbidities, according to this index, were observed. On the other hand, considering the Elixhauser index, congestive heart failure and chronic lung disease were also the most frequent (0.9% and 0.5%, respectively). In this case, 20 of the 31 possible comorbidities were observed. The mean scores obtained were 0.04 (SD = 0.28) for the Charlson index and 0.05 (SD = 0.22) for the Elixhauser index.

Except for age and time of admission ($p = 0.99$ and $p = 0.48$, respectively), the other variables were not normally distributed ($p < 0.05$), so the use of non-parametric tests was chosen.

The correlational analysis is showed in Table I, observing correlations between age, creatinine levels, D-dimer levels and the Elixhauser and Charlson indices. The time of admission was correlated with the number of days admitted to the ICU. In turn, a negative correlation, albeit weak, was found between days of hospital admission and pO_2. A more moderate negative correlation was also observed between days of admission to the ICU and pO_2. Creatinine levels were positively correlated with D-dimer levels and negatively with pO_2. D-dimer levels also showed a negative correlation with pO2 and a positive correlation with the Elixhauser index. A strong correlation was observed between the Elixhauser and Charlson indices.

Significant differences were found for age (Z = -17.06; $p < 0.01$), time of admission (Z = -3.43; p < 0.01), creatinine levels (Z = -9.88; $p < 0.01$), D-dimer levels (Z = -10.50; $p < 0.01$) and the scores for the Elixhauser (Z = -3.06) and Charlson (Z = -2.63; $p < 0.01$) indices in relation to mortality. Regarding gender, there were also significant differences in age (Z = -6.51; $p < 0.01$), time of admission (Z = -3.85; $p < 0.01$), creatinine levels (Z = -16.68; $p < 0.01$) and D-dimer levels (Z = -2.16; $p < 0.01$). No significant differences were observed for the Elixhauser and Charlson indices and for the length of stay in the ICU according to gender ($p > 0.05$).

In relation to ICU admissions, no significant differences were observed relative to age (Z = -1.86; $p = 0.06$). Differences were observed for the total time of admission (Z = -7.93; $p = 0.00$) and creatinine levels (Z = -2.31; $p = 0.02$). Regarding hospital admissions on the weekend, no statistically significant differences were observed with the rest of the variables analyzed. The comparison of medians (M) and interquartile ranges (IR), considering the significant variables, is showed in Table II.

The logistic regression analysis for the death outcome (Table III), which was carried out with 1215 cases, showed an association with creatinine (OR = 36.07; $p < 0.01$), D-dimer (OR = 2.77; $p < 0.01$) and age (OR = 1.09; $p < 0.01$). On the other hand, the model considering ICU admission as a dependent variable did not show statistically significant results for age and creatinine and D-dimer levels.

In relation to the Kaplan-Meier survival curves (Figure 1), there was a statistically significant higher survival rate among patients who were not admitted to the ICU, although, as the length of hospital stay increased, the accumulated survival was equal or even slightly higher among patients admitted to the ICU.

Statistically significant differences also appeared with respect to survival according to the day of admission, being lower in those who were admitted on the weekend (Friday, Saturday, and Sunday).

Creatinine and D-dimer levels (high and low concentrations) were dichotomized according to the median. After this dichotomization, curves showed longer survival for people with lower creatinine and D-dimer levels.

Discussion

The findings obtained in the present work correspond to the analysis of the data offered by a private hospital consortium. The main findings were that mortality was associated with older age and higher levels of creatinine and D-dimer.

Table I. Correlation coefficients (Spearman's Rho) between the variables, age, length of hospital stay, levels of creatinine and D-dimer, pO_2, days in ICU and the scores for the Elixhauser and Charlson indices.

	1	2	3	4	5	6	7
1 Age							
2 Length of hospital stay	0.04						
3 Creatinine	0.26**	0.05					
4 D-dimer	0.31**	0.04	0.11**				
5 pO_2†	-0.05	-0.12**	-0.17**	-0.16**			
6 Lenght of stay in ICU‡	-0.06	0.50**	0.02	0.10	-0.32**		
7 Elixhauser index	0.11**	0.01	0.03	0.07**	0.03	-0.03	
8 Charlson index	0.11**	-0.02	0.04	0.04	0.06	-0.05	0.65**

***p*-value is < 0.01; †Oxigen Pressure; ‡Intensive Care Unit.

Table II. Medians and interquartile ranges for age, length of hospital stay, length of stay in ICU, creatinine and D-dimer levels; according to gender, having or not having been admitted to the ICU and death or not.

		Age (years)	Length of hospital stay	Length of stay in ICU†	Creatinine (mg/dL)	D-dimer (ng/ml)
Gender	Female	72.50 [60, 84]	6 [4, 9]	1 [0, 5]	0.73 [0.62, 0.92]	814 [491, 1630]
	Male	67.00 [56, 78]	7 [5, 11]	4 [1, 10]	0.98 [0.86, 1.17]	719 [450, 1345]
ICU†	No	69.00 [57, 81]	7 [4, 10]		0.91 [0.73, 1.1]	737 [459, 1415]
	Yes	66.50 [60, 74]	11 [7, 19]	3 [1, 9]	0.98 [0.79, 1.21]	902.50 [532, 1730]
Death	No	65.00 [54, 76]	7 [5, 10]	1 [0, 5]	0.88 [0.71, 1.05]	661.50 [428, 1186]
	Yes	83.00 [76, 89]	6 [3, 10]	2 [0, 7]	1.14 [0.89, 1.68]	1498 [897, 3826]

†Intensive Care Unit.

Survival curves showed greater survival among patients who were not admitted to the ICU and those who were not admitted on weekends. Also, patients with lower levels of creatinine and D-dimer had greater survival.

Data related to vital signs and parameters (such as levels of blood glucose, D-dimer, creatinine, and pO_2) or comorbidities suffered by the patients were provided. Even though a very small number of patients presented with comorbidities, we must take the results related to the Charlson and Elixhauser indices in the present work with caution.

Although the reason for the scarcity of comorbidities among the individuals in the sample cannot be determined, we do not have an objective answer to this situation. It should also be taken into account that, in many cases, the data recorded for some variables was not complete, so our analyses were carried out considering this fact. Mention should also be made that, during the pandemic situation, due to the saturation of public hospitals, many patients were referred to private hospitals, a fact that hindered the continuity of care and record.

Regarding the frequency of the symptoms presented, our results differ from those offered by other authors in a recent meta-analysis of 43 studies (N = 3600)[22]. In our case, respiratory distress was the most frequent symptom, followed by fever, while in the aforementioned meta-analysis, fever represented the most frequent sign (83.3%), followed by cough (60.3%) and fatigue (38.0%)[22].

With regard to the correlational analysis, it is observed that the higher age is, the higher the levels of creatinine and D-dimer are. The Elixhauser and Charlson indices followed this same line, which would be consistent with the national trend that shows an ageing of the population together with an increase in comorbidities[15,16]. However, it should be noted that the number of comorbidities belonging to these indices and that appear in the analyzed sample is low; therefore, we cannot generalize this trend to the results obtained. In this sense, a recent systematic review[23] has detected several studies with models for predicting risk or prognosis in which an important role of these variables is also observed during the disease process. Thus, some authors point to age and the Charlson index as predictors in their final model, along with other undisclosed variables related to medical history and social determinants of health. These characteristics seem to form a predictive model of risk of complications from COVID-19 in the general US population, with a

Table III. Variables independently associated with mortality in COVID-19 patients.

		95% Confidence Interval for OR		
	OR	Inferior	Superior	Sig.
Age	1.09	1.07	1.19	< 0.01
Creatinine	36.07	13.05	99.71	< 0.01
D-dimer	2.77	1.92	3.94	< 0.01
Constant	0.00			< 0.01

Variables specified in step 1: age, Creatinine, D-dimer. Creatinine and D-dimer were previously transformed into a logarithmic scale. Nagelkerke R^2 value = 0.41.

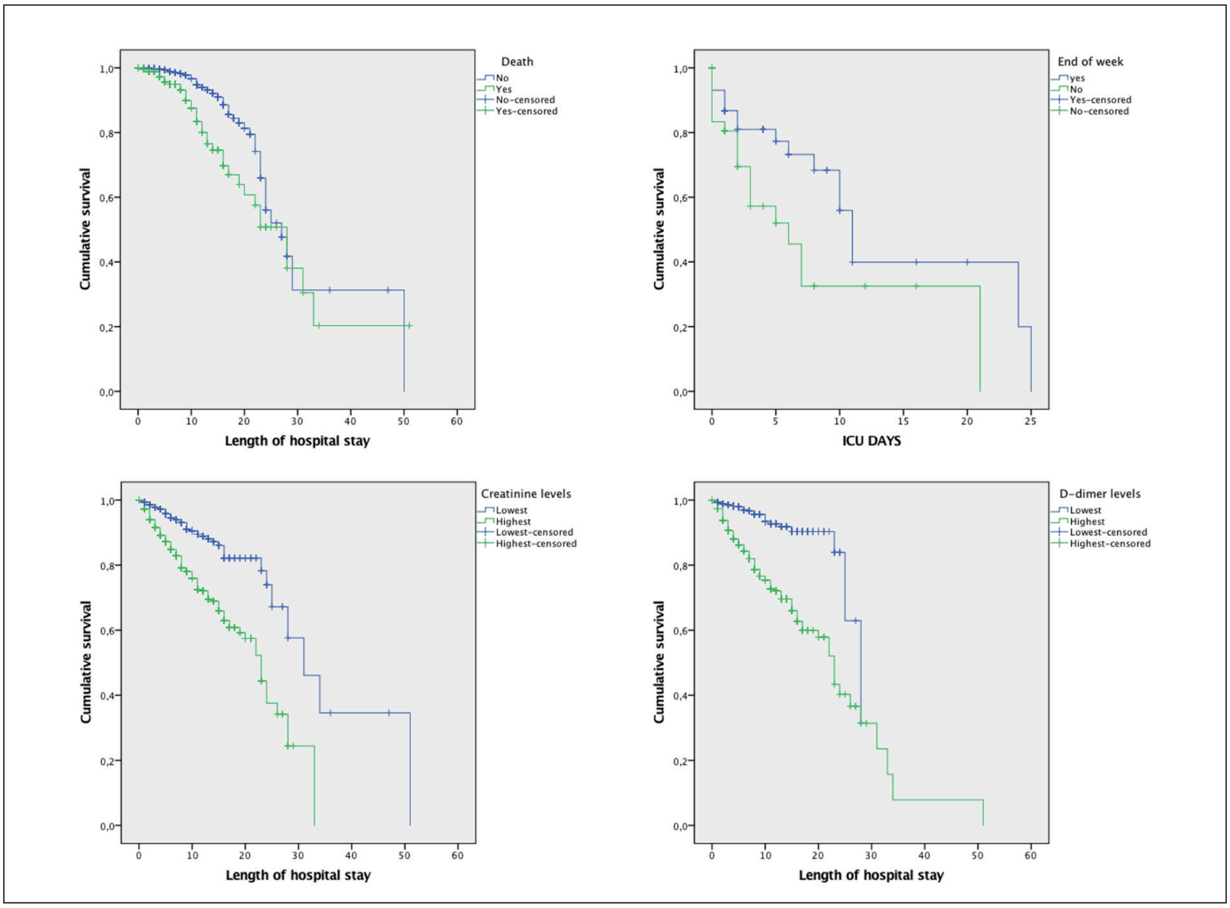

Figure 1. Kaplan Meier survival curves.

C index of 0.81[23,24]. Other COVID-19 diagnosis prediction models also include age and creatinine levels[23,25,26]. In the case of Wu et al[27], as well as those offered by other researchers, the classification of patients based on severity also included D-dimer levels[27]. Another analysis based on the study of 53 patients using artificial intelligence tools, which sought to offer predictions about patients at risk of developing more severe alterations, showed a model within which creatinine levels were also found[28]. However, it should be noted that, according to the authors of the previous review, the selected articles are at risk of bias, after a critical analysis through PROBAST (Prediction model Risk of Bias Assessment Tool)[23].

Another systematic review[29] focused on the prognostic utility of D-dimer levels[29] pointed out such levels are associated with greater severity, disease progression, acute respiratory distress syndrome (ARDS) and death, although with a low quality of evidence. In this sense, although, in our logistic regression models, no significant differences appeared when assessing creatinine and D-dimer levels in patients with greater severity (ICU), a significant influence of these parameters was observed together with age on mortality. We also observed through the survival curves that higher levels of creatinine and D-dimer mean higher mortality throughout the length of hospital stay. Other authors have also pointed out an increase in D-dimer and creatinine levels in patients with COVID-19, differentiating between critical and non-critical patients[22]. According to Flu et al[22], in critical cases, higher levels of both D-dimer and creatinine were observed, with a prevalence of 59.6% and of 6.4%, respectively. Non-critical cases presented a lower prevalence[22].

On the other hand, statistically significant differences were observed in the survival of patients with COVID-19 who were admitted to the ICU, depending on whether admission occurred on the weekend (Friday, Saturday, and Sunday), with greater survival in those patients who were admitted between Monday and Thursday. Some authors call this effect the “weekend effect”, explaining that, on average, patients admitted on the weekend obtain worse results than those admitted during the rest of the week. In summary, the weekend effect is defined as “the difference in results experienced by patients depending on whether they are admitted or treated on the weekend or during the week”[30]. However, there is controversy around this concept, since multiple variables must be taken into account[31]. Also, in the case of our study, we cannot assess this concept given the absence of information on data management. Therefore, it would be necessary to delve deeper into this question to determine the causes, which determine this increase in mortality on weekends. Although to our knowledge, there are no studies that deeply analyze this issue in patients with COVID-19, some authors consider the weekend (Saturday and Sunday) as a factor associated with the increase in the probability of death in patients with COVID-19 in France. Such mortality increases among patients discharged from the ICU on the weekend, with an adjusted relative risk of 1.54, compared to patients who are discharged from the ICU during the week[32]. However, other authors, after a spectral analysis of the daily evolution of deaths due to COVID-19 in France and throughout the world, indicated a weekly pattern in daily deaths. This pattern shows a decrease on Friday and Saturday, in other areas of the world and only on Sundays in France[33]. However, authors hypothesize that such a pattern may be determined by the death counting system, as well as by sociodemographic factors or biomedical effects related to the hospital organisation[33].

With regard to nursing personnel, this study provides interesting findings that may be useful when managing patients with COVID-19, since they offer data that would allow anticipating possible complications in these patients. This would allow optimizing the use of resources in the current pandemic situation.

Limitations

There are a number of limitations that need to be noted. First, the data obtained only refer to patients treated in private hospitals, so it is necessary to treat the results with caution if these results are to be generalized to other contexts. Second, aspects such as comorbidities cannot be compared with patients from other institutions because the number of comorbidities is low in this sample. Third, among the variables included in the database, some of them have important missing data, so the present manuscript has been limited to analyzing those variables with a more complete registry. And ultimately, the retrospective design can introduce selection bias and/or misclassification.

Conclusions

Positive correlations between age, creatinine levels, and D-dimer levels, as well as scores on the Charlson and Elixhauser indices, were found. In relation to pO_2, a negative correlation was observed with respect to ICU admission time and length of stay, creatinine levels, and D-dimer levels. In turn, age, length of hospital stay, blood creatinine, and D-dimer concentrations showed statistically significant differences in relation to gender. Differences were also seen in creatinine concentrations, depending on whether the patients had been admitted to the ICU or not.

Age, creatinine levels, and D-dimer levels were statistically associated with mortality. Greater survival was observed for patients not admitted to the ICU and who were not admitted on the weekend, as well as those with lower creatinine and D-dimer levels.

Our findings can help health professionals when managing patients suffering from COVID-19, especially in those most critical cases, helping to optimize resources in a pandemic.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Statement

This review was undertaken according to the ethical principles used by PRISMA. An ethical approval was given for HM hospitals (Care Provider Company).

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