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Clinical features, coagulation and inflammatory biomarkers associated with poor in-hospital outcomes in a Honduran population with RT-PCR confirmed COVID-19

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ABSTRACT

Background: SARS-COV-2, in most cases, only generates a mild acute respiratory disease. However, patients with severe disease show an exaggerated response of the immune system, creating a pro-inflammatory state, which could cause abnormalities in the coagulation system that increases mortality. Latin American countries, specially those with limited resources, have few studies about clinical features, coagulation and inflammatory biomarkers that could be useful at admission to assess poor outcomes.

Objective: The objective of this study is to describe the clinical features, coagulation, and inflammatory biomarkers, and identify risk factors at admission that are associated poor outcomes in Honduran population.

Methods: A cohort study was conducted. 210 patients were included, which 105 died during hospitalization due to COVID-19 and 105 were discharged alive, between September 2020 and January 2021. Clinical and laboratory data was retrospectively collected.

Results: 57,6% of the population were male. The median age was 58 years. The median time between symptom onset and hospital admission was 6 days. D-dimer median was higher in the dead group compared with the alive group. Poor prognosis factors in the Cox multivariable model were male gender, age, symptom's duration, obesity and an elevated d dimer at admission.

Conclusion: In low-middle income countries, the assessment of these clinical and laboratory tools, especially in those with risk factors for prothrombotic states, could help clinicians to correctly stratify disease prognosis, establish a baseline to evaluate further evolution, and also predict outcomes, thus improving patient management.

1. Introduction

In early December 2019, a new coronavirus named severe acute respiratory syndrome coronavirus caused a catastrophic international phenomenon of respiratory disease [1]. COVID-19 is caused by the SARS-CoV-2 virus, a member of the Coronaviridae family that includes the SARS-CoV and the MERS-CoV viruses that were responsible for outbreaks of severe respiratory illnesses [2]. In early December 2021, a total of 5,4 million deaths worldwide were reported by World Health Organization (WHO) [3].

Early during the pandemic, it was thought that the clinical characteristics of COVID-19 were fever, cough, and progressive dyspnea caused by respiratory infection [4]. As the pandemic evolved, it was demonstrated that other organs and systems were affected by the virus [5–7]. Emerging evidence suggested that severe COVID-19 may be complicated with coagulopathy, and even severe cases may cause disseminated intravascular coagulation (DIC) [8]. However, the characteristics of COVID-19-associated coagulopathy are distinct from those seen with bacterial sepsis-induced coagulopathy (SIC) and DIC, with COVID-19-associated coagulopathy usually showing increased D-dimer

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but initially minimal abnormalities in prothrombin time and platelet count [9].

This coagulopathy may be explained by a pro-inflammatory state associated with cytokines storm. Severe patients have higher levels of inflammatory biomarkers compared with those in patients with mild or moderate disease, therefore, increasing their mortality [10]. However, in Latin America, especially in low middle income countries, there are few studies regarding coagulation and inflammatory parameters and their use as prognosis tools for mortality in hospitals with limited resources. Thus, the objective of this study is to describe the clinical features, coagulation, and inflammatory biomarkers, and identify risk factors at admission that are associated with elevated mortality risk in low-middle income countries.

2. Methods

An observational, single-center, retrospective, cohort type study was conducted in San Pedro Sula, Honduras, which it is the second most populated city on the country with more than 450,000 inhabitants. A sample of 210 adult patients, with proven COVID-19 diagnosis, hospitalized in the COVID-19 unit, a designated facility prioritized in treating only critically ill patients at the Dr. Mario Catarino Rivas National Hospital, a second level care hospital which contains one of the two COVID-19 units of the city and serves as a major referral center for the entire northwestern area of Honduras. Patients were enrolled from September 2020 to June 2021, creating two groups, according to their main outcome, which was the patient's current condition.

Confirmed cases were defined as any patient with a positive result at admission for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) whose sample was obtained by nasopharyngeal swabbing. For medical records screening, all patients over 18 years of age who died due to COVID-19 were included. Clinical records of patients who were discharged or died without an established diagnosis by RT-PCR, patients with only positive rapid tests and/or positive antigen test, patients with a positive RT-PCR test whose discharge/death was not related to COVID-19, patients who died on admission, patients without laboratory tests, and records with 70% of the variables missing were excluded.

A non-probabilistic sample was used, with sampling by availability, enrolling the total number of patients who met the inclusion criteria. A form was made to collect the variables of interest available in the clinical records. The clinical data documented in their records, such as symptoms on admission and comorbidities, were taken into consideration. The sociodemographic variables taken into consideration were the date of onset of symptoms, age (continuous variable) and sex (male or female). Likewise, coagulation parameters (platelets, prothrombin time (PT), partial thromboplastin time (PTT) international normalized ratio (INR) and d-Dimer) and inflammatory biomarkers (C reactive protein, ferritin, and lactate dehydrogenase) were collected. Thrombotic events during hospitalization (categorical variable) and inpatient days (continuous variable). The patient's current condition was taken as the main outcome (dead or discharged alive).

The samples for measuring platelets count, coagulation parameters, and inflammatory biomarkers were collected within 24 h of admission. Venous blood samples were drawn into one Vacuette® (Bad Haller Str. 32 4550 Kremsmünster Austria) sterile 4 ml tube, one Vacuette® sterile 4 ml tube containing sodium citrate (3,2%), and one Vacuette® sterile 6 ml tube containing serum clot activator. The D-dimer level was tested using a Colloidal Immunoassay analyzer and original reagents (Powers, Shenzhen, China).

The data was entered into the STATA 16.0 (StataCorp, College Station, Texas, USA), where the statistical analysis was carried out. Descriptive statistics were used to characterize the sample under study, frequencies and percentages were obtained for categorical variables and compared by Chi-square tests or Fisher's exact test. An analysis for measures of central tendency, dispersion, and summary measures were

performed for continuous variables expressed as median and interquartile ranges, comparing values with Wilcoxon rank sum test as appropriate, after assessing for normal and not normal distributions.

A Cox regression analysis was performed to calculate the unadjusted and adjusted hazard ratio (HR) and its 95% confidence intervals (95% CI) by Breslow tests. Kaplan-Meier curves were used for univariable analysis to assess survival differences among groups of interest as well as variable with known association with survival. The multivariable analysis was performed by using a Cox proportional hazard model. The variables included in the final model were selected based on clinical relevance and significant association.

The project was reviewed and approved by the institutional ethics committee of the Universidad Nacional Autónoma de Honduras. After approval of the study protocol, the patients' medical records were reviewed in the COVID-19 room.

3. Results

A total of 325 clinical records were collected, out of the 303 RT-PCR-confirmed COVID-19 cases, 115 clinical records did not complete baseline information. A sample of 210 patients who were hospitalized due to COVID-19 confirmed by RT-PCR was analyzed, 105 patients who died and 105 patients who were discharged alive were included, creating a 1:1 proportion.

Overall, 57,6% were male. The median age was 58 years [IQR, 47–70.25]. The age group of 71 years accounted for 24.8%. The median time between symptom onset and hospital admission was 6 days [IQR, 2–9.75]. 141 patients (67,2%) had at least one chronic disease. The most frequent comorbidities were HT (48,1%), DM (35,7%) and obesity (16,7%). On admission, 100% of patients were symptomatic. Within the clinical features, the most frequent symptoms among the deceased group were dyspnea (92,4%), fever (82,9%), and cough (82,9%) (See [Table 1](#)).

The coagulation parameters measured at admission were platelets, D-dimer, PT, PTT and, INR. The median platelet count was 270,000 cc/mm³ [IQR, 187,000–351,000] and 254,000 cc/mm³ [IQR, 170,500–325,000] for the alive and dead group, respectively. The alive group manifested thrombocytopenia more frequently than the dead group, 17,1% and 14,3%, respectively.

D-dimer median was higher in the dead group (709 ng/ml [IQR 400–1712]) compared with the alive group (539,23 [IQR, 191.75–1167.25]). More than half of the dead group (65,7%), manifested elevated d-dimer (>500 ng/ml) compared with the alive group (33,4%).

A 17,1% of the sample had d-dimer levels in between 1000–1999 ng/ml and 21,9% had values above 2000 ng/ml. PT, PTT, and INR had no observable alterations. The median TP was 12,0 s in both groups (See [Table 2](#)).

The C reactive protein median at admission was 96 mg/L [IQR, 47,6–192]. There was no significant difference between both groups (p = 0,67). The ferritin levels were higher in the dead group with a median of 985,5 ng/mL [IQR, 653,7–1500]. No significant difference between both groups. The measured lactate dehydrogenase was higher in the dead group with a median of 566,5 U/L [IQR, 357,5–759,5] (See [Table 2](#)).

The median in-hospital length of stay was 6 days [IQR, 3–11]. The dead group had a prolonged length of stay compared with the alive group (See [Table 1](#)). Within the dead group, sixteen patients presented at least one thrombotic event, comprising 15,2% of the studied sample. The most frequent were cerebral ischemic attack (5,7%), myocardial infarction (3,8%), and pulmonary embolism (2,9%). Among these patients, the median hospital length of stay was 3 days [IQR, 2–13,7].

3.1. Risk of mortality

A Cox regression analysis was performed to calculate the unadjusted hazard ratios and a multivariable model was used to calculate adjusted

Table 1
Sociodemographic and clinical characteristics at admission of 105 patients with COVID-19.

Variable	Total (n = 210)	Dead (n = 105)	Alive (n = 105)	P value ^a
Age, years [IQR]	58 [47–70.25]	65,0 [56.5–72]	51 [39–62]	<0.001
18–30	11 (5.2%)	1 (1.0%)	10 (9.5%)	<0.001
31–40	22 (10.5%)	5 (4.8%)	17 (16.2%)	
41–50	33 (15.7%)	11 (10.5%)	22 (21.0%)	
51–60	49 (23.3%)	23 (21.9%)	26 (24.8%)	
61–70	43 (20.5%)	32 (30.5%)	11 (10.5%)	
>71	52 (24.8%)	33 (31.4%)	19 (18.1%)	
Gender				
Male	121 (57.6%)	72 (68.6%)	49 (46.7%)	0.001
Female	89 (42.4%)	33 (31.4%)	56 (53.3%)	
Comorbidities presence				
None	63 (30.0%)	17 (16.2%)	46 (43.8%)	<0.001
1 comorbidity	57 (27.1%)	27 (25.7%)	30 (28.6%)	
2 comorbidities	54 (25.7%)	39 (37.1%)	15 (14.3%)	
≥ 3 comorbidities	36 (17.2%)	22 (20.9%)	14 (13.4%)	
Comorbidities ^b				
Hypertension	101 (48.1%)	66 (62.9%)	35 (33.3%)	<0.001
Diabetes mellitus	75 (35.7%)	44 (41.9%)	31 (29.5%)	0.06
Obesity	35 (16.7%)	23 (21.9%)	12 (11.4%)	0.04
Chronic kidney disease	21 (10.0%)	13 (12.4%)	8 (7.6%)	0.25
Chronic heart disease	13 (6.2%)	7 (6.7%)	6 (5.7%)	0.77
COPD	13 (6.2%)	7 (6.7%)	6 (5.7%)	0.77
Acute kidney disease	5 (2.4%)	4 (3.8%)	1 (1.0%)	0.67
Chronic liver disease	4 (1.9%)	3 (2.9%)	1 (1.0%)	0.31
Symptom duration in days, [IQR]	6 [2–9.75]	8 [6–8]	2 [1–5.75]	<0.001
Symptoms				
Dyspnea	146 (69.5%)	97 (92.4%)	49 (46.7%)	<0.001
Fever	139 (66.2%)	87 (82.9%)	52 (49.5%)	<0.001
Cough	151 (71.9%)	87 (82.9%)	64 (61.0%)	<0.001
Headache	109 (51.9%)	64 (61.0%)	45 (42.9%)	0.009
Fatigue	61 (29%)	46 (43.8%)	15 (14.3%)	<0.001
Myalgia	72 (34.3%)	40 (38.1%)	32 (30.5%)	0.25
Costal retraction	41 (19.5%)	29 (27.6%)	12 (11.4%)	0.003
Odynophagia	41 (19.5%)	27 (25.7%)	14 (13.3%)	0.02
Cyanosis	27 (12.9%)	22 (21.0%)	5 (4.8%)	<0.001
Diarrhea	24 (11.4%)	18 (17.1%)	6 (5.7%)	0.009
Vomiting	24 (11.4%)	17 (16.2%)	7 (6.7%)	0.03
Rhinorrhea	22 (10.5%)	17 (16.2%)	5 (4.8%)	0.02
General malaise	47 (22.4%)	16 (15.2%)	31 (29.5%)	0.01
Length of stay, days	6 [IQR, 3–11]	7 [IQR, 3–13]	5 [IQR, 3–9]	0.23

Data are of RT-PCR-confirmed COVID-19 cases. Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; RT-PCR, reverse transcriptase polymerase chain reaction; COPD, chronic obstructive pulmonary disease.

^a P values were calculated by Mann-Whitney *U* test, χ^2 test, or Fisher's exact test, as appropriate. χ^2 test comparing all subcategories.

^b Defined as a preexisting medical condition at baseline.

hazard ratios using the Breslow method (See Table 3). In the unadjusted model, the male gender (HR 1.92 (CI 95%, 1.27–2.92); $p = 0.002$), age (HR 1.03 (CI 95%, 1.01–1.04) $p < 0.001$), symptomatic days (HR 1.07 (CI 95%, 1.04–1.11); $p = 0.001$), and HT (HR 1.79 (CI 95%, 1.20–1.67) $p = 0.004$) had an elevated risk of mortality in-hospital stay (See Fig. 1). Also, an elevated d-dimer and lactate dehydrogenase at admission was associated with poor prognosis (See Fig. 2). DM and obesity were not associated with mortality in the univariable analysis (Supplementary 1).

In the multivariate model was performed taking into consideration all significant factors in the univariate analysis. Male gender continued to be a risk factor for mortality (HR 2.21 (CI 95%, 1.02–3.98), $p = 0.04$) once adjusted for all significant factors. After adjustment, age (HR 1.12 (CI 95%, 1.01–1.05) $p = 0.007$) is a risk factor for in-hospital mortality. Obesity (HR 2.75 (CI 95%, 1.27–5.91) $p = 0.01$) was associated with poor prognosis. Regarding the d-dimer, it remains as a poor prognosis tool when elevated levels (>500 ng/ml) are manifested at admission. Other multivariate models were assessed (Supplementary 2).

Table 2
Coagulation and inflammatory markers parameters at admission in 105 patients who died of COVID-19.

Variables	Dead (n = 105)	Alive (n = 105)	P value ^a
Platelet count (cc/mm ³), median	254,000 [IQR, <50,000–170,500]	270,000 [IQR, 187,000–351,000]	0.31
<50,000	2 (1.9%)	4 (3.8%)	0.73
50,001–150,000	13 (12.4%)	14 (13.3%)	
150,001–300,000	54 (51.4%)	45 (42.9%)	
300,001–450,000	28 (26.7%)	33 (31.4%)	
>450,001	8 (7.6%)	9 (8.6%)	
D-dimer (ng/ml), median	709 [IQR 400–1712]	539,23 [IQR, 191.75–1167.25]	0.009
<499	36 (34.3%)	70 (66.7%)	<0.001
500–999	28 (26.7%)	15 (14.3%)	
1000–1999	18 (17.1%)	11 (10.5%)	
>2000	23 (21.9%)	9 (8.6%)	
PT (s)	12,0 [IQR, 11–13,7]	12,0 [IQR, 11–14]	0.48
PTT (s)	29,6 [IQR, 25–34,9]	27 [IQR, 24–33]	0.03
INR	0,99 [IQR, 0,92–1,10]	1,03 [IQR, 0,92–1,14]	0.15
C-reactive protein (mg/L)	96 [IQR, 47,6–192]	96 [IQR, 47–192]	0.67
Ferritin (ng/ml)	985,5 [IQR, 653,7–1500]	852 [IQR, 396.25–1582]	0.70
Lactate dehydrogenase (U/L)	566,5 [IQR, 357,5–759,5]	412 [IQR, 265.5–556.7]	<0.001

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

^a P values were calculated by Mann-Whitney *U* test, χ^2 test, or Fisher's exact test, as appropriate. χ^2 test comparing all subcategories.

Table 3
Risk factors in fatal outcome using an unadjusted analysis and an adjusted Cox regression model (95% CI).

Variables	Unadjusted HR (CI 95%)	P value	Adjusted HR ^a (CI 95%)	P value
Male sex	1.92 (1.27–2.92)	0.002	2.01 (1.02–3.98)	0.04
Age, years*	1.03 (1.01–1.04)	<0.001	1.12 (1.01–1.05)	0.007
Symptomatic days*	1.07 (1.04–1.11)	0.001	1.12 (1.07–1.18)	<0.001
Comorbidities				
Hypertension	1.79 (1.20–2.67)	0.004	1.71 (0.86–3.36)	0.11
Diabetes mellitus	1.22 (0.82–1.81)	0.31	0.95 (0.51–1.77)	0.88
Obesity	1.44 (0.90–2.32)	0.12	2.75 (1.27–5.91)	0.01
D-dimer (ng/ml)				
<500	Reference	–	Reference	–
>500	1.93 (1.29–2.88)	0.001	2.67 (1.47–4.86)	0.001
Ferritin >300 U/L	1.71 (0.68–4.27)	0.25	–	–
Lactate dehydrogenase >200 U/L	1.92 (1.14–3.23)	0.01	1.19 (0.61–2.35)	0.61
PTT	1.03 (0.99–1.06)	0.04	1.03 (0.98–1.08)	0.21

Abbreviations: CI; confidence interval, HR; hazard ratio, PTT, partial thromboplastin time. * Per 1 unit increase.

P values are from Cox proportional hazards regression model.

^b Defined as a preexisting medical condition at baseline.

^a The final model was adjusted for sex and age.

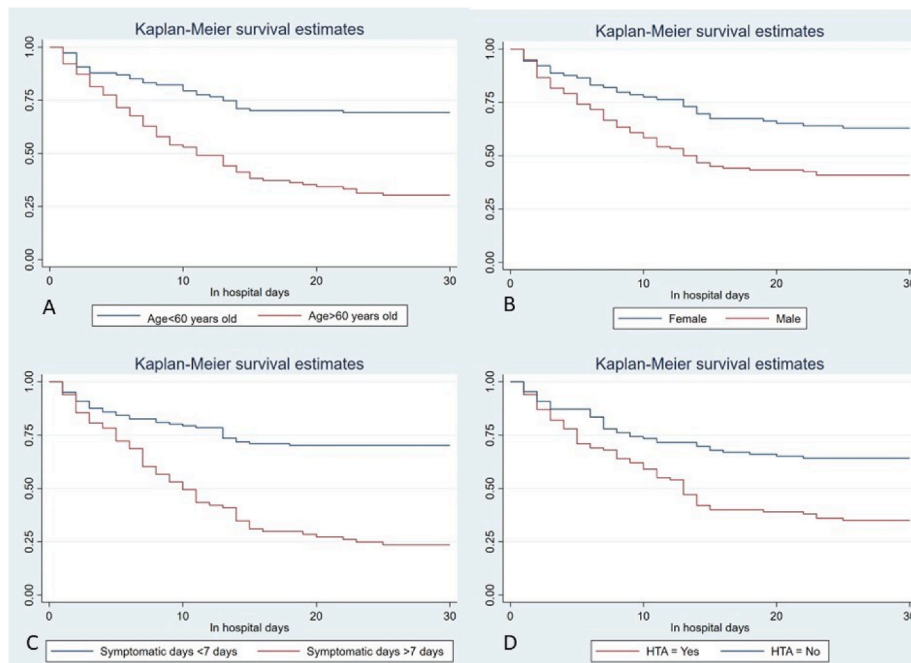


Fig. 1. Kaplan Meier curves for sociodemographic and clinical characteristics at admission in the univariable analysis.

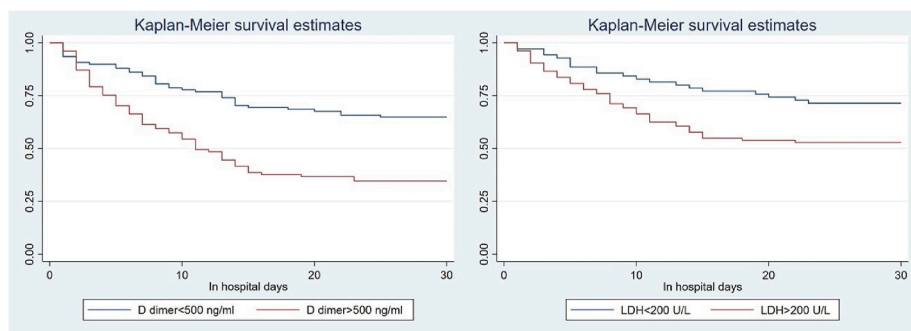


Fig. 2. Kaplan-Meier survival curves for D-dimer and lactate dehydrogenase levels at admission. Abbreviations: LDH; lactate dehydrogenase.

4. Discussion

The main findings of this study were to describe clinical and laboratory characteristics at admission associated with poor outcomes in a low-middle-income country. Clinical features such as age, male sex, prolonged evolution, and obesity were associated with mortality. Also, patients with elevated d dimer, PTT and inflammatory biomarkers such as lactate dehydrogenase at admission had a poor prognosis in the univariate analysis. Elevated d dimer persisted as a poor prognosis coagulation marker in the multivariate model.

The clinical and sociodemographic characteristics of our study are similar to other studies published in the area, where it was observed male sex had predominance among the cases. Also, the most frequent clinical presentation at admission was fever, cough, and dyspnea, similar to our findings [11].

In our study, an advanced age increases risk for mortality which is consistent with previous studies [12–14]. Also, in early pandemic studies, it was stated that COVID-19 is more likely to affect older men with comorbidities [15]. Our population has a very high prevalence of comorbidities, even in young age groups [11] and it is known that the presence of chronic diseases increases the risk for mortality with a high prevalence in fatal cases [16,17]. In our study, at least one chronic disease was observed in 27,1% of the total sample.

It has been established that several chronic conditions in a patient, such as obesity [18] and DM [19], increases chronic inflammation by different mechanisms; dysregulating the immune response against viruses, such as COVID-19, making more likely a cytokine storm, that can cause endothelial damage. Interestingly, in our study, obesity was associated with a worse outcome in the multivariable model.

A significant finding of our study was associating a prolonged symptomatic evolution with mortality. After approximately 7–10 days of symptoms, a subgroup of patients progresses to severe disease and are more likely to decrease due to hypoxemia, potentially evolving towards ARDS [20]. Patients with a prolonged symptom evolution develop a stage which is characterized by high levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1 β , IL-18, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [20]. Similar to our findings which describe a median symptom onset time of 8 days in patients who died, compared with the median symptom onset time of 2 days in patients who were discharged alive.

Moreover, SARS-CoV-2 affects other systems, aside pulmonary system. It infects the host using the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in several organs. Also, ACE2 receptors are expressed by endothelial cells [21,22]. SARS-CoV-2 directly infects vascular endothelial cells and leads to cellular damage and apoptosis, thus decreasing the antithrombotic activity of the normal

endothelium [23,24].

The patients that died due to thrombotic events in our study, might be consequence of the propensity of SARS-CoV-2 to cause microvascular, venous, and arterial thrombosis, and thereby exacerbating organ injury [25]. The occurrence of a COVID-19-specific coagulopathy is suggested by elevated levels of fibrinogen, von Willebrand factor (VWF), and the fibrin degradation product D-dimer in the blood, although patients generally show minor or no changes in prothrombin time, activated partial thromboplastin time, antithrombin levels, activated protein C levels, and platelet count [20].

As described in previous studies, elevated d-dimer levels are associated with both increased disease severity and in-hospital mortality [26,27]. Accordingly, our observation was that the dead group had a higher median d-dimer level, compared with the alive group. Other authors have described that d-dimer levels above 2001 ng/ml during hospital stay are a predictor of mortality in COVID-19 patients. (HR, 3.165 (CI 95%, 2.013–4.977), $p < 0.0001$) [28]. Interestingly, in our study, an elevated d dimer level at admission with lower cutoff level (>500 ng/ml) was associated with 2.6-fold increase in risk for in hospital mortality.

Our results found that lactate dehydrogenase was the only inflammatory biomarker that was independently associated with poor prognosis, as described in other studies [29], but was not a risk factor for mortality in the adjusted Cox analysis. Other inflammatory biomarkers were not significantly associated with mortality. Despite the known utility of inflammatory biomarkers such as C reactive protein, as a great prognosis tool and thrombotic event predictor [30], our study states that it had no association with mortality. However, our population has a high prevalence of metabolic diseases, which are known to cause an increase in the inflammatory baseline and response [31] which could have affected the survivor group. Also in our study, inflammatory biomarkers were only assessed at admission and it is necessary to assess their further evolution and progression during hospitalization to establish their prognosis utility.

Finally, SARS-COV-2 indirectly causes endothelial damage by inducing a pro-inflammatory state due to the high levels of circulation cytokines, which sometimes could progress to a cytokine storm. Also, the virus directly infects endothelial cells altering their anticoagulant function. Both, direct and indirect effect of the virus over the coagulation system, most likely in patients with a high prevalence of comorbidities, predisposing to a prothrombotic state. This might be the reason for the laboratory characteristic of COVID-19 patients, which manifest high levels of d-dimer.

This study has limitations, as a relatively small, single-center study, the mortality and characteristics of enrolled patients may not be representative. Its retrospective design limits the variable collection which was only available in paper medical records. Also, the reported laboratory parameters were measured only at admission. ICU requirement and mechanical ventilation use was not assessed in this study due to limited resources and wide ICU gap. Disease's severity could not be considered due to the lack of arterial blood gases and other laboratory variables that were not available in all patients and this could cause a bias at severity stratification. Applied therapies were not assessed due to that this study was performed in a low-income public institution, which several medications lacked during pandemic, and therapies were not the same to all patients.

Nevertheless, this is the first study describing clinical and laboratory characteristics, such as inflammatory and coagulation parameters, of COVID-19 in our population. In addition, it provides data among our population which is associated with poor outcomes. Also, it provides a real overview of the disease behavior population previous to the vaccination era.

5. Conclusion

Many risk factors should be taken into consideration at admission

that could help clinicians to assess prognosis and poor outcomes in a low middle income country. Our results contribute to previous evidence, in which, an advanced age, male gender, obesity and a prolonged symptom duration previous hospitalization are clinical risk factors for mortality.

Also, d-dimer level assessment at the admission of every patient, especially those with risk factors for prothrombotic states, could help clinicians to correctly stratify disease prognosis, establish a baseline to evaluate further evolution, and also predict outcomes, thus improving patient management.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tru.2022.100124>.

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