

Risk factors associated with the mortality of COVID-19 in patients with type 2 diabetes mellitus

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Abstract. The present study aimed to investigate the risk factors associated with the in-hospital mortality of patients with coronavirus disease 2019 (COVID-19) and type 2 diabetes mellitus (T2DM). Therefore, a cross-sectional study of the medical records of patients hospitalized between April, 2020 and February, 2021 was performed. The demographic, clinical, laboratory and treatment data were compared between COVID-19 survivors and non-survivors. Furthermore, multivariate logistic regression and principal component analyses (PCA) were carried out to identify risk factors associated with mortality in these patients. Among the 287 patients included, 132 (46%) did not survive. The multivariate regression analysis revealed that dyspnea [odds ratio (OR), 7.68; 95% confidence interval (CI), 1.77-40.89; P=0.010], neutrophil count $>6.3 \times 10^9/l$ (OR, 8.17; 95% CI, 3.16-26.62; P<0.001), hemoglobin levels of ≤ 12 g/dl (OR, 3.24; 95% CI, 1.30-8.56; P=0.014) and a partial pressure of oxygen (PaO₂) of <60 mmHg (OR, 7.46; 95% CI, 2.83-21.86; P<0.001) were independent risk factors for in-hospital mortality. By contrast, lung crackles were associated with lower risk of in-hospital mortality (OR, 0.21; 95% CI, 0.08-0.55). In addition, PCA revealed that elevated levels of fraction of inspired oxygen (FiO₂), blood urea nitrogen, serum creatinine and neutrophil count, and a low PaO₂/FiO₂ ratio considerably contributed to the first principal components of the non-survivor group. Overall, the results of the present study demonstrated that patients with COVID-19 and T2DM exhibit a high mortality rate, while several factors in these patients contribute independently to in-hospital mortality.

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to devastating consequences worldwide. Until the end of October, 2023, >771 million individuals were infected and >6 million succumbed to the disease globally (1). The COVID-19 pandemic had an even more detrimental effect in countries with limited resources. Therefore, Peru was one of the countries with the highest COVID-19-related mortality worldwide, with >220,000 related deaths (2).

The most common risk factors associated with COVID-19 severity and mortality include an older age, lower oxygen saturations and the presence of comorbidities, including diabetes. Diabetes is a prevalent comorbidity among patients with COVID-19 and is associated with an increased mortality rate in these patients. More particularly, patients with diabetes mellitus (DM) can have a 2-3-fold higher mortality rate compared with those without the condition (3-5). To date, several factors are known to be associated with worse outcomes in patients with COVID-19 and type 2 DM (T2DM) (6,7), including angiotensin converting enzyme 2 upregulation, poor glycemic control, higher levels of inflammatory markers, as well as several conditions, such as obesity, hypertension, cardiovascular diseases and dyslipidemia (8,9).

Although several studies on the risk factors associated with high mortality rates of patients with COVID-19 and T2DM have been conducted, relevant studies from Latin American countries are lacking. A better understanding of these risk factors in resource-constrained hospitals could be significant for preparedness against global emergencies, such as the recent COVID-19 pandemic. Therefore, in the present study, the data from patients with COVID-19 and T2DM hospitalized in the Hospital Regional de Ica, Ica, Peru were collected to explore the clinical features and the risk factors associated with in-hospital mortality.

Patients and methods

Study design and participants. The present cross-sectional study included the medical records of adult patients (≥ 18 years

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of age) with T2DM and COVID-19 hospitalized at the Hospital Regional de Ica (Ica, Peru) between April, 2020 and February, 2021. All patients were diagnosed with COVID-19 upon hospital admission based on serological or antigenic tests of nasopharyngeal samples, according to the World Health Organization interim guidelines (10). Patients were diagnosed with T2DM based on their medical records (11) or random serum glucose levels of ≥ 200 mg/dl (newly diagnosed with T2DM) (12,13). It was mandatory that the medical records of the included patients included information of the analyzed variables, such as demographic, history, clinical, laboratory and treatment data. Pregnant women, and patients with no information about the outcome variable (deceased or discharged) were excluded from the study.

Data collection and variables. The exposure and outcome data for each patient were extracted from their medical records at the time of admission. The data were reviewed by one physician (LGSH) and one researcher (CBS). Disagreements between the two lead reviewers were resolved by a third researcher (JC). The medical records included the following data: The demographic characteristics of the patients, such as age and sex; their medical history, including smoking status, alcoholism, dyslipidemia, obesity, hypertension, cerebrovascular diseases, cancer, HIV, immunosuppressive disease, chronic kidney disease (CKD), hemodialysis and asthma; their vital signs, such as respiratory rate, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP); signs and symptoms, including fever, cough, sore throat, general malaise, headache, tachypnea, dyspnea, anosmia, dyspnea, dysgeusia, lung crackles, diarrhea, vomiting, asthenia, abdominal pain, weight loss, polyuria, polydipsia, polyphagia and sensory; other laboratory blood findings, such as white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), hemoglobin levels, hematocrit, serum creatinine levels, blood urea nitrogen (BUN) levels, glucose levels, pH, anion Gap, and sodium, potassium, chlorine and calcium levels; and arterial blood gas findings, such as oxygen saturation (SaO_2), fraction of inspired oxygen (FiO_2), $\text{PaO}_2/\text{FiO}_2$ ratio, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide (PCO_2) and bicarbonate (HCO_3). These variables and their categorization were considered according to previous studies (6,7). The outcome variable was in-hospital COVID-19-related mortality, which was assessed by the death certificate included in the medical records.

Ethical aspects. Informed consents from patients were not necessary, since the study solely included retrospective data from their clinical records. The personal information of patients was anonymized prior to storage in the local hospital database. The present study was conducted according to the tenet of the Declaration of Helsinki and was approved by The Research Ethics Committees of the Hospital Regional de Ica (approval no. RD N 561-2021-HRI/DE) and the Universidad Privada San Juan Bautista (approval no. 429-2022-CIEI-UPSJB).

Statistical analysis. Categorical and continuous variables are expressed as frequencies with percentages (n, %) and

medians with interquartile range (IQR), respectively. Where appropriate, a Pearson's Chi-squared (χ^2 test), Fisher's exact or Wilcoxon-Mann-Whitney U tests were employed for the bivariate analysis (survivors vs non-survivors). The risk factors associated with in-hospital COVID-19-related mortality were assessed using univariate and multivariate logistic regression models, and the unadjusted and adjusted odds ratios (OR) with their respective 95% confidence intervals (95% CIs) were determined. Self-reported and low-frequency variables and variables without significant differences between groups were excluded from the univariate analysis. To prevent biased estimates caused by overfitting and multicollinearity among predictor variables in the multivariate logistic regression analysis, the variables were selected based on scientific evidence, significance from univariate analysis (Wald test < 0.05), the stepwise modeling method and checking for collinearity. Therefore, correlation analysis was performed for numerical variables and the Spearman's correlation coefficients (Rho) were estimated. Additionally, the generalized variance inflation factor (GVIF) and adjusted generalized standard error inflation factor (aGSIF) values were determined. Principal component analysis (PCA) was carried out to reduce dimensionality and visualize numerical variables (vital signs, laboratory findings and arterial blood gas findings) between the outcome groups. All statistical analyses were performed using R Statistical Software (v4.3.2; R Core Team 2023). The R collection tidyverse v2.0.0 package was used to prepare data (14). Statistical analyses were performed using the gtsurvey package v1.7.2 (15), while the logistic regression models and PCA were evaluated using the performance package v0.10.8 (16) and factoextra package v1.0.7 (17), respectively. A P-value < 0.05 was considered to indicate a statistically significant difference between groups.

Results

Demographic characteristics. In the present study, a total of 287 adult patient with T2DM and COVID-19, who were admitted to the Hospital Regional de Ica, Peru between April, 2020 and February, 2021, were included. Among these patients, 132 (46%) succumbed during hospitalization (Fig. 1). The median age of the patients was 60 years (IQR, 51-68) and 189 (65.9%) were males (Table I).

Comorbidities and symptoms. The most frequent comorbidities identified were hypertension, followed by obesity and CKD. Approximately half of the patients had abnormal respiratory or heart rates, while the majority of them ($> 80\%$) displayed normal blood pressure (Table I). Furthermore, the most common symptoms reported upon admission were dyspnea (84.3%), dry cough (76.0%), general malaise (71.8%) and fever (59.2%). The frequency of the remaining symptoms was $< 50\%$ (Table I).

Blood and biochemical tests. Blood tests revealed leukocytosis in 146 (54.3%) patients, neutrophilia in 196 (68.3%) and lymphopenia in 146 (50.9%) patients. The majority of the patients (92.7%) had a platelet count of $> 125 \times 10^9/l$, while $\sim 80\%$ of them had normal hemoglobin and hematocrit levels (Table II). In addition, the biochemical tests revealed that the

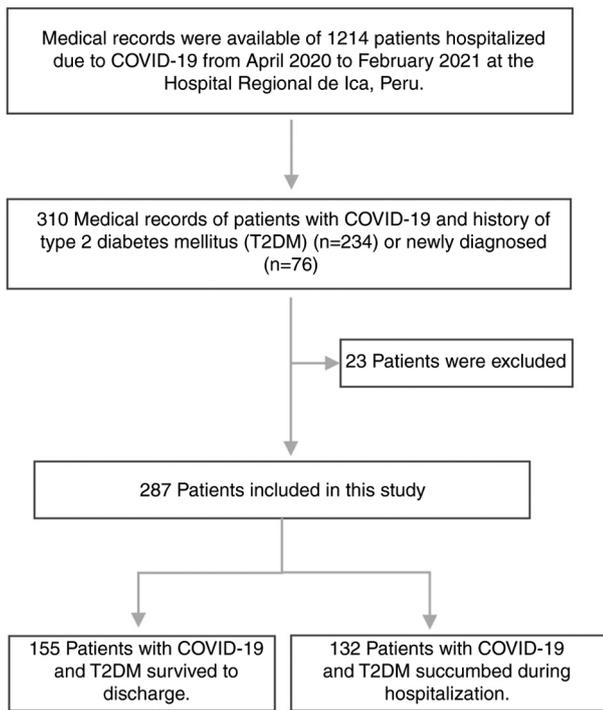


Figure 1. Flow chart of the inclusion process for patients in the present study.

serum creatinine and BUN levels differed significantly between the two groups of patients. Among the 287 patients included, 278 (96.9%) received antibiotics, 232 (80.8%) anticoagulants, 208 (72.5%) corticosteroids, 125 (43.6%) hydroxychloroquine, 115 (44.1%) pronation and 56 (19.5%) ivermectin (Table III). The median time from the onset of illness to either patient discharge or death was 7 days (IQR, 5-10; Table I).

Differences between groups. Data analysis demonstrated that the non-survivors were significantly older than the survivors ($P<0.001$). In addition, hypertension ($P=0.003$), leukocytosis ($P<0.001$), neutrophilia ($P<0.001$) and lymphopenia ($P=0.010$) were significantly more common among the non-survivors compared with the survivors (Table I and II). Furthermore, compared with the survivors, the non-survivors exhibited higher levels of serum creatinine and BUN (both $P<0.001$; Table II). The median FiO_2 value in patients who underwent O_2 therapy was higher in the non-survivors than in the survivors (80 vs. 38%), while the opposite was recorded for the $\text{PaO}_2/\text{FiO}_2$ ratio, PaO_2 and PCO_2 . In terms of therapy, the administration of anticoagulants, corticosteroids and antimalarials were more common among non-survivors (Table III).

Logistic regression analysis. The univariate logistic regression analysis (unadjusted) revealed that the odds of in-hospital mortality were higher in patients aged >60 years and in those with hypertension, obesity, tachypnea, dyspnea, lung crackles, an increased heart rate, increased SBP, leukocytosis, neutrophilia, anemia and increased serum creatinine, and BUN levels. The decreased levels of gas parameters ($\text{SaO}_2<94\%$, $\text{PaO}_2<60$, $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 and $\text{HCO}_3^- < 21$) and the administration of corticosteroids were also associated with increased mortality. In the adjusted multivariate regression

analysis, a total of 217 patients were included, and in particular, 114 in the survivor group and 103 in the non-survivor group. For this analysis, we excluded highly correlated variables ($\text{Rho} > 0.6$) were excluded (Fig. S1). Thus, WBC, diastolic blood pressure, MCV, hematocrit, PaO_2 , FiO_2 and serum creatinine were excluded from the analysis. The analysis revealed that the presence of dyspnea (OR, 7.68; 95% CI, 1.77-40.89; $P=0.010$), neutrophilia (OR, 8.17; 95% CI, 3.16-23.62; $P<0.001$), anemia (OR, 3.24; 95% CI, 1.30-8.56; $P<0.014$) and $\text{PaO}_2 < 60$ mmHg (OR, 7.46; 95% CI, 2.83-21.86; $P<0.001$) were associated with increased odds of mortality. By contrast, lung crackles were associated with reduced mortality rates (OR, 0.21; 95% CI, 0.08-0.55; $P<0.002$; Table IV). The aGSIF value of the adjusted model was <1.4 , thus indicating that the control for highly associated variables that provided the same information was effective in avoiding collinearity.

PCA. The biplots of PCA revealed that the $\text{PaO}_2/\text{FiO}_2$ ratio, BUN levels, hematocrit, hemoglobin, serum creatinine, FiO_2 , potassium, SaO_2 , neutrophils and PaO_2 were the variables with the highest representation and contribution in PC1 and PC2. In addition, chlorine, calcium, sodium, age, HCO_3^- , WBC, PCO_2 and neutrophils were the variables with the highest representation and contribution in PC3 and PC4. PC1 and PC2 contributed to 23.3% of total variance, while PC3 and PC4 to 17.8%. For these principal components, no clear separation between the survivors and non-survivors was observed (Fig. 2). However, based on the results of the bivariate analysis and PCA, in the non-survivor group, the high values of FiO_2 , BUN, serum creatinine, neutrophils and $\text{PaO}_2/\text{FiO}_2$ ratio considerably contributed to PC1 and PC2 (Fig. 2A), while WBC, neutrophils, age and PCO_2 to PC3 and PC4 (Fig. 2B).

Discussion

Once diagnosed with COVID-19, patients with diabetes are more likely to develop severe illness and can be at higher risk of mortality (18). The results of the present study reported a mortality rate of 46%, which was higher compared with that reported in other regions. Additionally, dyspnea, the absence of lung crackles, neutrophilia, anemia and PaO_2 of <60 mmHg were identified as significant risk factors for COVID-19-related mortality in patients diagnosed with T2DM. Although the PCA results revealed a substantial contribution of multiple numerical variables, neutrophilia remained constant in non-survivors.

The mortality rate in the present study (46%) was among the highest reported in Peruvian populations, which ranged between 33-50% (19-21). A previous meta-analysis, including 42 studies from several regions worldwide, revealed that the prevalence of COVID-19-related mortality ranged from 3.14 (95% CI, 2.34-4.14%) to 61.51% (95% CI, 55.02-67.71%) (18). The mortality rate was higher in Latin American countries. In fact, regionally, Andean Latin America had the highest mortality rate compared with other regions worldwide (22).

Herein, the univariate analysis revealed that an advanced age, hypertension, and obesity were associated with an increased risk of COVID-19-related mortality in patients with T2DM. Consistently, the aforementioned factors have been extensively reported by previous studies as risk factors for

Table I. Demographics, clinical findings, and sign and symptoms of patients with COVID-19 and T2DM.

Characteristic	All patients (n=287) ^a	Mortality		P-value ^b
		Non-survivors (n=132)	Survivors (n=155)	
Demographics and history				
Age (years)	60.0 (51.0-68.0)	64.5 (57.8-73.0)	56.0 (47.0-64.5)	<0.001
<61	149 (51.9%)	47 (35.6%)	102 (65.8%)	<0.001
≥61	138 (48.1%)	85 (64.4%)	53 (34.2%)	
Sex				0.46
Female	98 (34.1%)	48 (36.4%)	50 (32.3%)	
Male	189 (65.9%)	84 (63.6%)	105 (67.7%)	
Smoking	2 (0.7%)	1 (0.8%)	1 (0.6%)	>0.99
Alcoholism	2 (0.7%)	1 (0.8%)	1 (0.6%)	>0.99
Dyslipidemia	4 (1.4%)	1 (0.8%)	3 (1.9%)	0.63
Obesity	44 (15.3%)	15 (11.4%)	29 (18.7%)	0.085
Hypertension	102 (35.5%)	59 (44.7%)	43 (27.7%)	0.003
Cerebrovascular disease	4 (1.4%)	4 (3.0%)	0 (0.0%)	0.044
Cancer	1 (0.3%)	1 (0.8%)	0 (0.0%)	0.46
HIV	1 (0.3%)	1 (0.8%)	0 (0.0%)	0.46
Immunosuppressive disease	3 (1.0%)	2 (1.5%)	1 (0.6%)	0.60
CKD	10 (3.5%)	5 (3.8%)	5 (3.2%)	>0.99
Hemodialysis	5 (1.9%)	4 (3.0%)	1 (0.8%)	0.37
Asthma	6 (2.1%)	2 (1.5%)	4 (2.6%)	0.69
Time from illness onset to death or discharge (days)	7.0 (5.0, 10.0)	7.0 (5.0, 10.0)	7.0 (5.0, 10.0)	0.23
Signs and symptoms				
Fever	170 (59.2%)	88 (66.7%)	82 (52.9%)	0.018
Dry cough	218 (76.0%)	105 (79.5%)	113 (72.9%)	0.19
Sore throat	92 (32.1%)	33 (25.0%)	59 (38.1%)	0.018
General malaise	206 (71.8%)	91 (68.9%)	115 (74.2%)	0.32
Headache	62 (21.6%)	13 (9.8%)	49 (31.6%)	<0.001
Tachypnea	99 (34.5%)	34 (25.8%)	65 (41.9%)	0.004
Dyspnea	242 (84.3%)	122 (92.4%)	120 (77.4%)	<0.001
Anosmia	16 (5.6%)	5 (3.8%)	11 (7.1%)	0.22
Dysgeusia	13 (4.5%)	5 (3.8%)	8 (5.2%)	0.58
Lung crackles	141 (49.1%)	50 (37.9%)	91 (58.7%)	<0.001
Diarrhea	18 (6.3%)	10 (7.6%)	8 (5.2%)	0.40
Vomiting	17 (5.9%)	11 (8.3%)	6 (3.9%)	0.11
Asthenia	48 (16.7%)	14 (10.6%)	34 (21.9%)	0.010
Abdominal pain	12 (4.2%)	4 (3.0%)	8 (5.2%)	0.37
Weight loss	3 (1.0%)	0 (0.0%)	3 (1.9%)	0.25
Polyuria	12 (4.2%)	3 (2.3%)	9 (5.8%)	0.14
Polydipsia	10 (3.5%)	2 (1.5%)	8 (5.2%)	0.11
Polyphagia	5 (1.7%)	1 (0.8%)	4 (2.6%)	0.38
Sensory state				<0.001
Awake	250 (91.2%)	99 (83.2%)	151 (97.4%)	
Sleepy	17 (6.2%)	14 (11.8%)	3 (1.9%)	
Drowsy	7 (2.6%)	6 (5.0%)	1 (0.6%)	
Vital signs				
Respiratory rate (bpm)	26.0 (23.0-30.0)	28.0 (24.0-32.0)	26.0 (22.3-28.0)	<0.001
24-30	138 (51.7%)	62 (51.2%)	76 (52.1%)	0.006
<24	70 (26.2%)	23 (19.0%)	47 (32.2%)	
>30	59 (22.1%)	36 (29.8%)	23 (15.8%)	

Table I. Continued.

Characteristic	All patients (n=287) ^a	Mortality		P-value ^b
		Non-survivors (n=132)	Survivors (n=155)	
Heart rate (bpm)	100.0 (85.8, 113.0)	105.5 (92.0, 115.8)	98.0 (82.3, 107.8)	<0.001
<100	133 (46.3%)	47 (35.6%)	86 (55.5%)	<0.001
≥100	154 (53.7%)	85 (64.4%)	69 (44.5%)	
SBP (mmHg)	115.0 (100.0-130.0)	120.0 (100.0-130.0)	110.0 (100.0-120.0)	0.25
<140	246 (85.7%)	104 (78.8%)	142 (91.6%)	0.002
≥140	41 (14.3%)	28 (21.2%)	13 (8.4%)	
DBP (mmHg)	70.0 (60.0-80.0)	70.0 (60.0-80.0)	70.0 (60.0-80.0)	0.13
<90	258 (89.9%)	112 (84.8%)	146 (94.2%)	0.009
≥90	29 (10.1%)	20 (15.2%)	9 (5.8%)	

Data are presented as the median (IQR) or n (%). ^aSome variables may not sum to the total number of patients due to missing data. ^bP-values were calculated using the Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. Values in bold font indicate statistically significant differences (P<0.05). COVID-19, coronavirus disease 2019; T2DM, type 2 diabetes mellitus; HIV, human immunodeficiency virus; CKD, chronic kidney disease; bpm, beats per minute or breaths per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure.

COVID-19-related mortality (7,18,23). In hospitals in Peru, an older age, low oxygen saturation and different drugs, such as ivermectin, hydroxychloroquine and corticosteroids, were all associated with COVID-19-related mortality. However, the comorbidities were not significant (19,21,24). Another study including patients from three hospitals of Peru, demonstrated that patients aged ≥60 years, those with low oxygen saturation and with two or more comorbidities were at an increased risk of COVID-19-related mortality (25). Similar findings were reported in other populations, including patients with COVID-19, T1DM and T2DM (26). In the present study, an age >60 years, hypertension, and obesity did not reach significance in the multivariate analysis. This finding may be due to the fact that the patients included in the present study were already older when they were diagnosed with T2DM or other diseases. Although herein, hepatic damage was not assessed, previous studies have demonstrated that chronic liver disease and hepatic fibrosis are associated with an increased risk of in-hospital COVID-19-related mortality (27,28).

Dyspnea was the most prevalent symptom in the present study, and it was associated with COVID-19-related mortality in the multivariate regression analysis. Fever, dry cough, fatigue and dyspnea are the most common symptoms of COVID-19 (7,29), with dyspnea being present in most severe cases (29). Furthermore, a previous systematic review and meta-analysis revealed that dyspnea, fatigue, myalgia and a low respiratory rate were the optimal predictors of mortality (7). Other studies have also reported that dyspnea is an independent risk factor associated with COVID-19-associated mortality (30-32). In addition, in patients with diabetes, dyspnea upon admission was associated with a reduced risk of hospital discharge and an increased mortality at day 28 (6). Aksel *et al* (33) demonstrated that dyspnea was an early predictor of mortality in patients with moderate or severe SARS-CoV-2 infection (hazard ratio, 4.26; 95% CI, 1.19-15.28). Lung damage caused by inflammatory responses that compromise gas exchange could explain dyspnea as an

early predictor of mortality. The early recognition of this symptom could help to recognize patients who are at high risk.

The utility of vital signs as predictors of COVID-19-related mortality is inconclusive. In the present study, an elevated heart rate (≥100) upon admission was identified as a risk factor associated with an increased mortality. In several studies, an increased heart rate was found to be significantly more common among non-survivors of COVID-19 (34,35). In previous a study including 8,770 patients with COVID-19 from 53 health centers in New York City found that a higher heart rate was associated with an increased risk of mortality (OR, 1.00; 95% CI, 1.00-1.01), thus suggesting that the higher heart rate and other clinical risk factors could serve as effective predictors of COVID-19-related mortality, regardless of the patient's level of consciousness (34). Notably, a higher heart rate variability could predict improved survival in elderly patients with COVID-19 (35).

Furthermore, the results of the present study revealed that neutrophilia and anemia were also independent predictors of COVID-19-related mortality in patients with diabetes. An increased neutrophil count (≥8.0x10⁹/l), hemoglobin levels of <12.5 g/dl, creatinine levels of ≥1.36 mg/dl, an age ≥65 years and CKD have been shown to be associated with the need for intensive care unit (ICU) admission, invasive mechanical ventilation and in-hospital mortality (36). Additionally, three previous meta-analyses of early studies revealed that an increased neutrophil count, and decreased lymphocyte and platelet counts could increase the risk of progression and mortality in patients with COVID-19; however, there was high heterogeneity and publication bias (7,37,38). During SARS-CoV-2 infection, neutrophils release a web-like structures to kill viruses. However, neutrophil overactivation and the subsequent enhanced formation of neutrophil extracellular traps can also lead to lung injury and thrombosis (39). Emerging evidence has also indicated that the neutrophil to lymphocyte ratio (NLR), a known indicator of systemic inflammation, is a valuable prognostic marker in patients with

Table II. Laboratory findings of the patients with COVID-19 and T2DM.

Characteristic	All patients (n=287) ^a	Non-survivors (n=132)	Survivors (n=155)	P-value ^b
Laboratory findings				
WBC (x10 ⁹ /l)	10.6 (7.8-16.6)	14.5 (10.0-19.2)	9.0 (6.5-13.1)	<0.001
4-10	104 (38.7%)	29 (24.2%)	75 (50.3%)	<0.001
<4	19 (7.1%)	4 (3.3%)	15 (10.1%)	
>10	146 (54.3%)	87 (72.5%)	59 (39.6%)	
Neutrophils (x10 ⁹ /l)	9.0 (6.0-14.8)	13.0 (8.8-17.9)	7.2 (4.5-11.7)	<0.001
≤6.3	91 (31.7%)	24 (18.2%)	67 (43.2%)	<0.001
>6.3	196 (68.3%)	108 (81.8%)	88 (56.8%)	
Lymphocytes (x10 ⁹ /l)	0.9 (0.6-1.3)	0.7 (0.4-1.2)	1.0 (0.7-1.5)	<0.001
≥1	141 (49.1%)	54 (40.9%)	87 (56.1%)	0.010
<1	146 (50.9%)	78 (59.1%)	68 (43.9%)	
Platelets (x10 ⁹ /l)	254.5 (193.5-342.0)	251.0 (200.0-331.0)	255.0 (190.0-344.0)	0.93
≥125	266 (92.7%)	122 (92.4%)	144 (92.9%)	0.88
<125	21 (7.3%)	10 (7.6%)	11 (7.1%)	
MCV (mm ³)	90.9 (87.7-93.6)	91.3 (88.2-94.4)	90.2 (87.2-92.8)	0.048
MCH (pg)	29.3 (28.1-30.3)	29.4 (28.4-30.6)	29.2 (27.9-30.1)	0.045
Hemoglobin (g/dl)	13.7 (12.0-14.9)	13.7 (11.4-14.9)	13.7 (12.6-15.0)	0.42
>12	216 (75.3%)	91 (68.9%)	125 (80.6%)	0.022
≤12	71 (24.7%)	41 (31.1%)	30 (19.4%)	
Hematocrit (%)	42.0 (37.5-46.0)	41.7 (35.3-46.0)	42.7 (38.5-46.0)	0.23
≥36	229 (79.8%)	98 (74.2%)	131 (84.5%)	0.031
<36	58 (20.2%)	34 (25.8%)	24 (15.5%)	
Serum creatinine (mg/dl)	0.8 (0.6-1.2)	1.0 (0.7-1.5)	0.7 (0.6-1.0)	<0.001
<1.3	213 (74.2%)	86 (65.2%)	127 (81.9%)	<0.001
≥1.3	74 (25.8%)	46 (34.8%)	28 (18.1%)	
BUN (mg/dl)	36.1 (26.8-52.0)	42.5 (30.0-56.5)	32.0 (24.0-44.0)	<0.001
<20	30 (10.5%)	8 (6.1%)	22 (14.2%)	0.025
≥20	257 (89.5%)	124 (93.9%)	133 (85.8%)	
Blood glucose (mmol/l)	13.26 (9.49-17.15)	13.82 (10.84-17.65)	12.65 (8.71-16.46)	0.18
pH	7.4 (7.4-7.5)	7.4 (7.4-7.5)	7.4 (7.4-7.5)	0.28
7.35-7.45	173 (62.0%)	81 (63.3%)	92 (60.9%)	0.37
<7.35	42 (15.1%)	22 (17.2%)	20 (13.2%)	
>7.45	64 (22.9%)	25 (19.5%)	39 (25.8%)	
Anion gap (mEq/l)	10.5 (7.1-14.0)	11.4 (7.8-14.4)	10.0 (6.4-13.4)	0.057
7-13	128 (46.5%)	60 (48.0%)	68 (45.3%)	0.16
<7	67 (24.4%)	24 (19.2%)	43 (28.7%)	
>13	80 (29.1%)	41 (32.8%)	39 (26.0%)	
Sodium (mmol/l)	137.0 (133.0-142.0)	137.0 (133.0-142.0)	137.0 (133.5-142.0)	0.65
Potassium (mEq/l)	3.8 (3.5-4.2)	4.0 (3.5-4.4)	3.8 (3.6-4.1)	0.057
Chlorine (mmol/l)	1.2 (1.1-1.2)	1.2 (1.1-1.2)	1.2 (1.1-1.2)	0.34
Calcium (mmol/l)	1.2 (1.1-1.2)	1.2 (1.1-1.2)	1.2 (1.1-1.2)	0.34

Data are presented as the median (IQR) or n (%). ^aSome variables may not sum to the total number of patients due to missing data. ^bP-values were calculated using the Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. Values in bold font indicate statistically significant differences (P<0.05). COVID-19, coronavirus disease 2019; T2DM, type 2 diabetes mellitus; WBC, white blood cells; MCV, median corpuscular volume; MCH, median corpuscular hemoglobin; BUN, blood urea nitrogen.

COVID-19 with or without diabetes (40,41). Therefore, a study including 201 patients with COVID-19 and T2DM demonstrated that a NLR of ≥ 7.36 was an independent predictor of

disease severity (42). Although a previous study indicated that renal impairment and respiratory frequency were associated with higher COVID-19-related mortality (43), the results of the

Table III. Arterial blood gas findings and treatment of the patients with COVID-19 and T2DM.

Characteristic	All patients (n=287)	Non-survivors (n=132)	Survivors (n=155)	P-value ^a
Arterial blood gas findings				
SaO ₂ (%)	90.0 (83.0-94.0)	85.0 (78.0-91.3)	92.0 (88.0-95.0)	<0.001
≥94	80 (27.9%)	28 (21.2%)	52 (33.5%)	0.020
<94	207 (72.1%)	104 (78.8%)	103 (66.5%)	
FiO ₂ (%)	40.0 (21.0-80.0)	80.0 (32.0-80.0)	38.0 (21.0-40.0)	<0.001
>21 (O ₂ therapy)	203 (70.7%)	98 (74.2%)	105 (67.7%)	0.23
21	84 (29.3%)	34 (25.8%)	50 (32.3%)	
PaO ₂ :FiO ₂ ratio	191.0 (95.1-298.0)	123.0 (77.6-249.5)	238.5 (145.0-325.3)	<0.001
>200	135 (47.0%)	47 (35.6%)	88 (56.8%)	<0.001
≤200	152 (53.0%)	85 (64.4%)	67 (43.2%)	
PaO ₂ (mmHg)	73.1 (61.0-91.0)	64.9 (52.2-80.5)	78.0 (68.0-93.9)	<0.001
≥60	223 (77.7%)	82 (62.1%)	141 (91.0%)	<0.001
<60	64 (22.3%)	50 (37.9%)	14 (9.0%)	
PCO ₂ (mmHg)	31.4 (27.9-35.0)	30.2 (26.4-35.0)	32.2 (28.9-35.0)	0.021
<36	222 (77.4%)	100 (75.8%)	122 (78.7%)	0.55
≥36	65 (22.6%)	32 (24.2%)	33 (21.3%)	
HCO ₃ (mmol/l)	20.7 (17.9-23.0)	19.9 (16.0-22.5)	21.1 (19.7-23.1)	0.003
21-28	119 (42.8%)	44 (34.4%)	75 (50.0%)	0.032
<21	148 (53.2%)	78 (60.9%)	70 (46.7%)	
>28	11 (4.0%)	6 (4.7%)	5 (3.3%)	
Type of treatment				
Antibiotics	278 (96.9%)	132 (100.0%)	146 (94.2%)	0.004
Corticosteroids	208 (72.5%)	111 (84.1%)	97 (62.6%)	<0.001
Anticoagulants				<0.001
No	55 (19.2%)	14 (10.6%)	41 (26.5%)	
Enoxaparin	232 (80.8%)	118 (89.4%)	114 (73.5%)	
Antiparasitic				0.085
No	231 (80.5%)	112 (84.8%)	119 (76.8%)	
Ivermectin	56 (19.5%)	20 (15.2%)	36 (23.2%)	
Antimalarials				0.003
No	162 (56.4%)	62 (47.0%)	100 (64.5%)	
Hydroxychloroquine	125 (43.6%)	70 (53.0%)	55 (35.5%)	
Pronation	115 (44.1%)	54 (40.9%)	61 (47.3%)	0.30

Data are presented as the median (IQR) or n (%). ^aP-values were calculated using the Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. Values in bold font indicate statistically significant differences (P<0.05). COVID-19, coronavirus disease 2019; T2DM, type 2 diabetes mellitus; SaO₂, oxygen saturation; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of oxygen; PCO₂, partial pressure of carbon dioxide; HCO₃, bicarbonate.

present study demonstrated that low CDK frequencies (n=10 patients) and respiratory frequency were significant predictors in the descriptive analysis and PCA, but not in the univariate logistic regression analysis.

Herein, in terms of arterial blood gas parameters, an increased FiO₂, and a decreased PaO₂ and PaO₂/FiO₂ ratio were associated with COVID-19-related mortality. However, only PaO₂ remained significant in the multivariate analysis. The PaO₂/FiO₂ ratio reflects the level of respiratory failure and it is an oxygenation index commonly used in the management of respiratory distress syndrome (44). Therefore, it is considered as a significant predictor of COVID-19 outcomes (45-47).

Previously, two different studies demonstrated that the decreased PaO₂/FiO₂ ratio was an independent risk factor associated with mortality in patients with COVID-19 in the ICU (45,46). One of these studies further suggested that a 10% increase in FiO₂ at admission was also associated with mortality in patients admitted to the ICU (45). In the present study, the high prevalence (53%) of patients with moderate-to-severe respiratory failure (PaO₂/FiO₂ ratio of ≤200) could explain why statistically significance (of PaO₂/FiO₂ ratio) was not reached at the multivariate analysis. On the other hand, it has been argued that hypoxemia (SaO₂ <90%) is a less useful predictor for mortality in patients with

Table IV. Mortality risk factors in patients with COVID-19 and T2DM.

Characteristic	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age (years)				
≤60	-		-	
>60	2.80 (1.63 to 4.90)	<0.001	1.71 (0.77 to 3.83)	0.188
Sex				
Female	-		-	
Male	0.79 (0.45 to 1.37)	0.394		
Obesity				
No	-		-	
Yes	0.40 (0.17 to 0.89)	0.030	0.38 (0.11 to 1.23)	0.114
Hypertension				
No	-		-	
Yes	1.83 (1.05 to 3.21)	0.035	1.37 (0.59 to 3.21)	0.471
Fever				
No	-		-	
Yes	1.63 (0.94 to 2.84)	0.082		
Dry cough				
No	-		-	
Yes	1.39 (0.74 to 2.66)	0.305		
Tachypnea				
No	-		-	
Yes	0.49 (0.27 to 0.86)	0.015	1.11 (0.45 to 2.81)	0.816
Dyspnea				
No	-		-	
Yes	5.59 (2.04 to 19.70)	<0.002	7.68 (1.77 to 40.89)	0.010
Lung crackles				
No	-		-	
Yes	0.38 (0.22 to 0.66)	<0.001	0.21 (0.08 to 0.55)	<0.002
Respiratory rate (bpm)				
24-30	-		-	
<24	0.61 (0.31 to 1.19)	0.154		
>30	1.85 (0.94 to 3.69)	0.077		
Heart rate (bpm)				
<100	-		-	
≥100	2.51 (1.45 to 4.39)	<0.001	2.23 (1.00 to 5.11)	0.053
SBP (mmHg)				
<140	-		-	
≥140	2.69 (1.26 to 6.05)	0.012	1.68 (0.57 to 5.24)	0.355
DBP (mmHg)				
<90	-		-	
≥90	2.44 (1.02 to 6.26)	0.051		
WBC (x10 ⁹ /l)				
4-10	-		-	
<4	0.50 (0.11 to 1.69)	0.304		
>10	4.14 (2.29 to 7.66)	<0.001		
Neutrophils (x10 ⁹ /l)				
≤6.3	-		-	
>6.3	7.01 (3.43 to 15.60)	<0.001	8.17 (3.16 to 26.62)	<0.001
Lymphocytes (x10 ⁹ /l)				
≥1	-		-	
<1	1.71 (1.00 to 2.96)	0.053	1.87 (0.82 to 4.41)	0.143

Table IV. Continued.

Characteristic	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Platelets (x10 ⁹ /l)				
≥125	-			
<125	0.85 (0.29 to 2.37)	0.757		
MCV (mm ³)	1.04 (0.99 to 1.10)	0.143		
MCH (pg)	1.17 (1.02 to 1.34)	0.026	1.14 (0.94 to 1.39)	0.180
Hemoglobin (g/dl)				
>12	-		-	
≤12	2.18 (1.17 to 4.83)	0.015	3.24 (1.30 to 8.56)	0.014
Hematocrit (%)				
≥36	-			
<36	2.40 (1.23 to 4.83)	0.012		
Serum creatinine (mg/dl)				
<1.3	-			
≥1.3	2.28 (1.23 to 4.31)	0.010		
BUN (mg/dl)				
<20	-		-	
≥20	3.44 (1.30 to 10.78)	0.020	0.90 (0.19 to 4.55)	0.894
SaO ₂ (%)				
≥94	-		-	
<94	1.95 (1.06 to 3.67)	0.034	0.80 (0.30 to 2.12)	0.661
FiO ₂ (%)	1.02 (1.01 to 1.04)	<0.001		
PaO ₂ :FiO ₂ ratio				
>200	-		-	
≤200	2.14 (1.24 to 3.73)	0.006	1.34 (0.60 to 3.05)	0.474
PaO ₂ (mmHg)				
≥60	-		-	
<60	7.45 (3.62 to 16.70)	<0.001	7.46 (2.83 to 21.86)	<0.001
PaCO ₂ (mmHg)	0.97 (0.93 to 1.01)	0.115		
HCO ₃ (mmol/l)				
21-28	-		-	
<21	2.10 (1.20 to 3.72)	0.010	1.49 (0.65 to 3.41)	0.346
>28	1.72 (0.45 to 6.62)	0.419	2.25 (0.35 to 13.87)	0.376
Corticosteroids				
No	-		-	
Yes	2.00 (1.02 to 4.08)	0.049	1.65 (0.61 to 4.57)	0.326
Anticoagulants				
No	-			
Enoxaparin	1.30 (0.56 to 3.16)	0.547		
Antiparasitics				
No	-			
Ivermectin	0.55 (0.28 to 1.07)	0.082		
Antimalarials				
No	-			
Hydroxychloroquine	1.51 (0.88 to 2.59)	0.132		
Pronation				
Yes	-			
No	1.35 (0.79 to 2.31)	0.277		

Values in bold font indicate statistically significant differences (P<0.05). COVID-19, coronavirus disease 2019; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval; bpm, beats per minute or breaths per minute; WBC, white blood cells, SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; SaO₂, oxygen saturation; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of oxygen; PCO₂, partial pressure of carbon dioxide; HCO₃, bicarbonate.

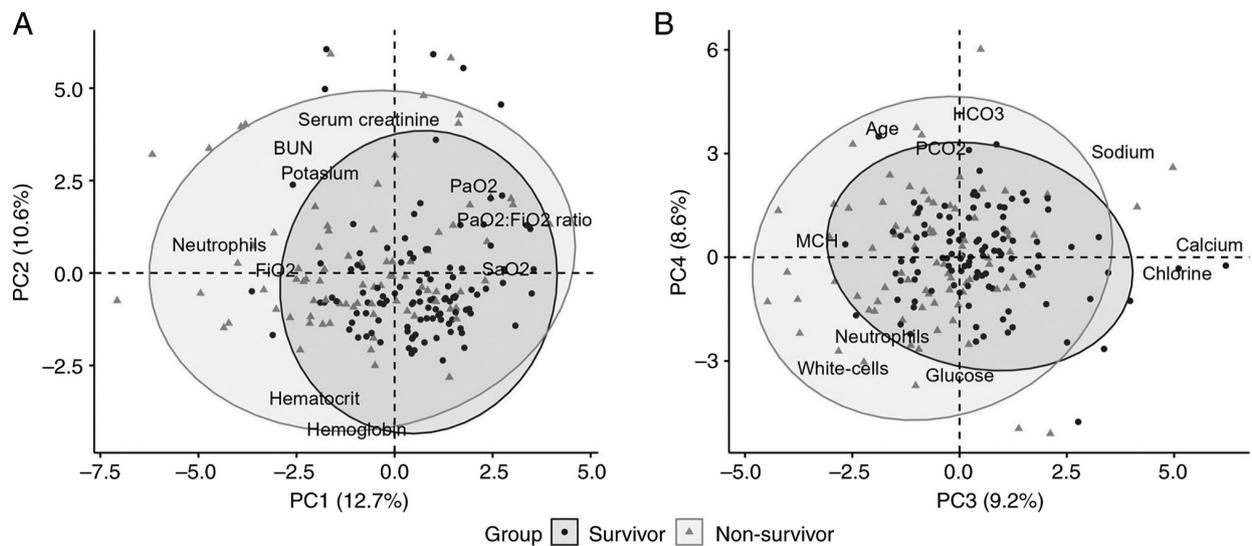


Figure 2. Results of principal component analysis. Principal component analysis was employed to reduce the dimensionality of the multivariate data, facilitating the visualization of patients and the numerical variables. The results are presented in a biplot for each of the two principal components, with each point representing a single patient separated by outcome groups. (A) For PC1 and PC2, there was no discernible separation between the survivors and non-survivors. However, among the non-survivors, the values of FiO_2 , BUN, serum creatinine, neutrophils, and $\text{PaO}_2:\text{FiO}_2$ ratio demonstrated a significant contribution. (B) For PC3 and PC4, there was no discernible separation between the groups. High values of white cells, neutrophils, age, and low values of PCO_2 were found to be notable contributors to the group of non-survivors. BUN, blood urea nitrogen; SaO_2 , arterial oxygen saturation; FiO_2 , fraction of inspired oxygen; PaO_2 , partial pressure of oxygen; PCO_2 , partial pressure of carbon dioxide; HCO_3 , bicarbonate.

COVID-19, since it could hide hypoxia (48,49). It has been reported that the $\text{PaO}_2/\text{FiO}_2$ ratio and SaO_2 are good predictors of COVID-19-related mortality. When combined with the 12-field lung ultrasound score, they could be even more useful in predicting mortality and clinical progression of patients with COVID-19 (50).

The use of drugs against COVID-19 without sufficient evidence was promoted as a national policy during the so called ‘first wave’ of the COVID-19 pandemic in Peru. Subsequent studies revealed the detrimental effects of this policy. A previous study conducted in hospitals of the Seguro Social de Salud del Perú (EsSalud) revealed no benefits of hydroxychloroquine, ivermectin or azithromycin administration in preventing all-cause mortality in hospitalized patients with COVID-19. In fact, treatment with hydroxychloroquine in combination with azithromycin showed an increased risk of all-cause death (51). In a previous phase III clinical trial among Peruvian health-care workers, hydroxychloroquine was tested as preventive drug against SARS-CoV-2 infection. However, no differences in the incidence of SARS-CoV-2 infection were recorded (52). Furthermore, another study conducted in a Peruvian hospital found that ivermectin and azithromycin were associated with a higher risk of COVID-19-related mortality (19). Herein, the analysis revealed that the drugs administered were not associated with an increased mortality. In the univariate analysis, only corticosteroids were identified as significant predictors. A study demonstrated that low doses of corticosteroids could be beneficial in patients who were subjected to respiratory support (53). In addition, two observational studies conducted in Perú found that low or low-to-moderate doses of corticosteroids were associated with reduced mortality (19). In patients with or without diabetes, corticosteroids could further lead to severe hyperglycemia, and life-threatening ketoacidosis and hyperglycemic hyperosmolar state (54).

The present study has a cross-sectional design; therefore, it could not examine a cause-effect association between the factors assessed and in-hospital mortality. Additionally, the present study has other limitations. According to the American Diabetes Association, diabetes can be diagnosed based on the random glucose levels in combination with the presence of classic hyperglycemic symptoms/crises. For this subset of patients, herein, the data on hyperglycemic symptoms were lacking. However, it has been suggested that random plasma glucose levels can exhibit a good diagnostic value in predicting diabetes, even when glucose levels are well below the conventional ‘diagnostic’ range (12). Furthermore, the plasma glucose levels were measured upon admission. Therefore, corticosteroids, if administered, could not have any effect on glucose levels. Secondly, working conditions in a pandemic context led to resource constraints and therefore the levels of hemoglobin A1c (HbA1c) were not measured. The lack of measurements of glycemic control could constrain the findings of the present study, as elevated HbA1c could be associated with worse outcomes and poor immunological response to COVID-19 vaccines (55). Thirdly, the majority of patients included in the present study were diagnosed with COVID-19 based on serological tests. Fourth, a control group, namely patients without T2DM, was lacking in the present study. Finally, the sample size was not sufficient to draw firm conclusions. Despite these limitations, the present study provided notable findings, while performing mixed statistical analyses (logistic regression and PCA) on patients with T2DM and COVID-19 from Peru. These issues had been poorly reported in Peru.

In conclusion, the present study reported that the risk of mortality was increased in patients hospitalized with COVID-19 and T2DM at the Hospital Regional de Ica. Several factors, including dyspnea, neutrophilia, anemia and low PaO_2 levels could be independently associated with an increased

risk of in-hospital mortality in patients with COVID-19 and T2DM. Overall, the results of the present study provided data on risk factors associated with COVID-19-related mortality, thus assisting the development of novel treatment strategies for patients with COVID-19 in Peru.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JC was involved in the conceptualization of the study, in the study methodology, validation, investigation and data curation, as well as in the writing of the original draft, and in the writing, reviewing and editing of the manuscript. CBS was involved in the conceptualization of the study, in the study methodology, data validation, formal analysis, investigation, provision of resources, data curation, as well as in the writing of the original draft, and in the writing, reviewing and editing of the manuscript. LJUC was involved in the study methodology, data validation, formal analysis, investigation, provision of resources, data curation, and in the writing of the original draft of the manuscript. GGS was involved in the study methodology, data validation, investigation, provision of resources, data curation, and in the writing of the original draft of the manuscript. SSCA was involved in the study methodology, data validation, investigation, provision of resources, data curation, and in the writing of the original draft of the manuscript. MJL was involved in the study methodology, data validation, investigation, provision of resources, data curation, and in the writing of the original draft of the manuscript. AR was involved in the study methodology, data validation, investigation, data curation, and in the writing of the original draft of the manuscript. JA was involved in the conceptualization of the study, in the study methodology, data validation, investigation, provision of resources, data curation, and in the writing of the original draft of the manuscript. JAP was involved in the conceptualization of the study, in the study methodology, validation, formal analysis, investigation, in the writing, reviewing and editing of the manuscript, in study supervision and in project administration. KJP was involved in the conceptualization of the study, in the study methodology, validation, formal analysis, investigation, data curation, in the writing of the original draft of the manuscript, in the writing, reviewing and editing of the manuscript, in the preparation of the figures, and in project administration. LGSH was involved in the conceptualization of the study, in the study methodology, data validation, formal analysis, investigation,

resources, data curation, in the writing of the original draft of the manuscript, reviewing and editing of the manuscript, in study supervision and in project administration. All authors have read and approved the final manuscript. JC and LGSH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Informed consents from patients were not necessary, since the study solely included retrospective data from their clinical records. The personal information of patients was anonymized prior to storage in the local hospital database. The present study was conducted according to the tenet of the Declaration of Helsinki and was approved by The Research Ethics Committees of the Hospital Regional de Ica (approval no. RD N 561-2021-HRI/DE) and the Universidad Privada San Juan Bautista (approval no. 429-2022-CIEI-UPSJB).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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