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Associated factors for mortality in a COVID-19 colombian cohort: is the third wave relevant when Mu variant was predominant epidemiologically?

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ABSTRACT

Objectives: To evaluate the association between Colombia's third wave when the Mu variant was predominant epidemiologically (until 75%) in Colombia and COVID-19 all-cause in-hospital mortality.
Methods: In this retrospective cohort, we included hospitalized patients ≥18 years with SARS-CoV-2 infection between March 2020 to September 2021 in ten hospitals from three cities in Colombia. Description analysis, survival, and multivariate Cox regression analyses were performed to evaluate the association between the third epidemic wave and in-hospital mortality.
Results: A total of 25,371 patients were included. The age-stratified time-to-mortality curves showed differences according to epidemic waves in patients ≥75 years (log-rank test p = 0.012). In the multivariate Cox analysis, the third wave was not associated with increased mortality relative to the first wave (aHR 0.95; 95%CI 0.84–1.08),

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but there was an interaction between age ≥75 years and the third wave finding a lower HR for mortality (aHR 0.56, 95%CI 0.36–0.86).
Conclusions: We did not find an increase in in-hospital mortality during the third epidemic wave in which the Mu variant was predominant in Colombia. The reduced hazard in mortality in patients ≥75 years hospitalized in the third wave could be explained by the high coverage of SARS-CoV-2 vaccination in this population and patients with underlying conditions.

1. Introduction

On March 6, 2020, the first positive case of SARS-CoV-2 infection was confirmed in Colombia. Shortly after, the Colombian Ministry of Health declared a sanitary emergency by adopting measures including the provision of supplies, equipment, and human resources, expansion in molecular diagnostic capacity, and increased number of intensive care beds [1].

In collaboration with scientific associations, the Colombian ministry of health led the development of national guidelines for the clinical management of COVID-19, which has been subsequently updated [2]. The document reflects World Health Organization (WHO) recommendations and the severity classification [3]. The Colombian guidelines described the criteria for hospitalization: organ failure, oxygen saturation (SpO2) < 90%, respiratory rate >30 breaths per minute, and the presence of underlying conditions [2,3]. On the other hand, patients with mild pneumonia can be surveilled by telemedicine or at a less complex facility to avoid congestion of the country's hospital services [2].

In 2021, the Colombian National Health Institute (INS, by its Spanish acronym) started a genomic surveillance program to identify predominant SARS-CoV-2 variants over time [4]. In Colombia, until September 2021, there were three identified epidemic waves [5]. The third epidemic wave occurred between March and September 2021, when the B.1.621 (Mu) variant was predominant, accounting for between 52 and 75% of the SARS-CoV-2 cases evaluated for genomic surveillance in a probabilistic sample [4,6]. In this epidemic wave, the greatest number of deaths related to SARS-CoV-2 COVID-19 were reported in Colombia.

The B.1.621 or Mu variant was first described in Colombia in January 2021 and then considered a Variant of interest (VOI) in August 2021; however, it had been isolated from several samples taken since late 2020, which confirms its circulation since the second Colombian epidemic wave and its predominance in the third epidemic wave [4,7]. It was quickly identified in more than 20 countries, mainly in the Americas [8]. This lineage shares several important mutations of the spike protein, such as the insertion 146 N and other amino acid substitutions (Y144T, Y145S, R346K, E484K, N501Y, T95I, D950 N, and P681H). These mutations have been linked to diverse mechanisms that SARS-CoV-2 has developed to elude natural human immunity [9].

The Colombian Ministry of Health has encouraged health institutions to maintain well-organized data recording systems. As part of the WHO COVID-19 Global Clinical Platform initiative, which aims to characterize the phenotype of SARS-CoV-2 and risk factors for severity through anonymized patient-level clinical data collection around the globe [10], the Pan-American Health Organization (PAHO) supported a national registry to obtain data on hospitalized COVID-19 patients. In Colombia, this registry included data from patients hospitalized between March 2020 to September 2021, when the first three epidemic waves of the pandemic occurred. In addition, we aimed to evaluate the association between Colombia's third wave when the Mu variant was predominant epidemiologically (until 75%) and COVID-19 all-cause in-hospital mortality.

2. Methods

2.1. Registry design and study population

The WHO Global Clinical Platform is an open platform where members, countries, and individual facilities are invited to contribute anonymized patient data. Colombia contributed to the platform anonymized individual-level data of patients 18 or older hospitalized with laboratory-confirmed SARS-CoV-2 COVID-19 from March 2020 to September 2021. We included data from ten high-complexity hospitals; seven from Bogota, two from Barranquilla, and one from Cali. Eight hospitals included their entire COVID-19 hospitalization, and two hospitals included a convenience sample of their cohort.

2.2. Variables and definitions

Primary descriptive parameters include demographics, presence of underlying conditions, use of chronic medications, clinical features on admission and during the hospitalization, laboratory findings on admission, clinical interventions on admission and during hospitalization (oxygen use, intensive care unit (ICU) admission, ventilator use, use of therapeutics), length of hospital stay and patient outcomes (death, alive, referral). Case report forms can be found at https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/data-platform.

Cases were defined as severe or critical if they met one or more of the following conditions at hospital admission: room air oxygen saturation (SpO2): <90%, respiratory rate >30 breaths/minute, received extracorporeal membrane oxygenation (ECMO), admitted to an ICU, received an inotrope or vasopressor, or received oxygen therapy, either invasive or non-invasive ventilation. Cases that did not meet the conditions described above were considered mild or moderate Also, tachypnea, tachycardia, and fever were defined by the criteria of systemic inflammatory response syndrome (SIRS) [3].

Epidemic waves were selected according to the Colombian daily COVID-19 incident report [5] and defined as the period where there was an increase in the number of incidents of COVID-19 cases, with a steadily increasing achieving a peak and then a rapidly decreasing number of cases [11]. Cases were assigned to the first, second, and third epidemic waves if they were admitted on the following dates: March 6, 2020, to September 30, 2020; October 1, 2020, to February 28, 2021; and March 1, 2021, to September 30, 2021.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All the methods in this study were conducted following national (Resolution 8430 of 1993, stated by The Colombian Health Ministry) and international (The declaration of Helsinki) standards. Informed consent was not required since there were no interventions performed.

2.3. Statistical analysis

Extreme values, missing data, and possible data entry errors were verified and corrected, when needed, by the site coordinator. After that process, we obtained less than 20% of missing data on clinical variables and 52–66% of missing laboratory data.

There were two phases in the analysis, and the first one included all data retained for the general cohort set (Fig. 1) for descriptive and clinical characterization of all patients using descriptive statistics

according to the type of variables. Records with missing values were excluded, and the denominator represents the available data. The second phase of the analysis included only data from those facilities that collected patients throughout the three epidemic waves and excluded patients with home hospitalization (Fig. 1). For this phase, multiple imputations were performed, considering data were missing at random (MAR). Laboratory data was not used in the second phase of the analysis.

To evaluate the association of all-cause in-hospital mortality across the epidemic waves, at first Kaplan Meier (KM) curves were drawn with administrative censorship at 30 days of hospital admission. Log-rank tests were performed to compare KM curves. Cox proportional hazards models were fitted to estimate the hazard risk during epidemic waves second and third relative to first epidemic wave. Age and sex were included in the models a priori, while other variables were selected based on clinical relevance, p-value <0·1 on bivariate analyses, and not highly correlated with other variables were included in the model. The final model contained covariates with statistical significance at 0.05. Models were compared using the likelihood ratio test. We tested for interaction between predictors when appropriate. Finally, we assessed the proportional hazard assumption when comparing subgroups of interest, using visual inspection of a smoothed hazard ratio (smoothed scaled Schoenfeld residual plots) and a plot of the log cumulative hazard vs. the log time plot, as well as the Schoenfeld test for non-proportional hazards. In the construction of the model, age did not fulfill the proportionality assumption, thus making it necessary to perform a stratified model by age. Patients discharged before day 30 of follow-up had their survival checked 30 days from the admission using data from the Colombian Ministry of Health.

All analyses were conducted in R software version 4.1 (R Project for Statistical Computing, Vienna, Austria). We used the*survival, survminer, ggplot,* and *mice* package [12,13].

3. Results

3.1. General cohort dataset: descriptive phase

A total of 25,371 hospitalized patients with laboratory-confirmed SARS-CoV-2 infection were included in this study. The study sample was 53·9% male, and the overall median age was 52·7 years (IQR 36·4–67·2), with 38.1% in <45 years age group, 35.1% in the 45–65 years age group, and 26.8% in >65 years age group. At admission 47·7% (n: 12,109) had tachypnea, 23·2% (n:5892) had tachycardia, and 2·8% (n: 708) had hypotension. Additionally, as oxygen saturation of less than 90% and 94% were observed in 25·6% (n: 6485) and 59·9% (n: 15,195) of the patients, respectively and the Glasgow coma scale was inferior to 15 in 10·9% of the patients (n: 2756).

The main symptoms reported at admission were cough (15,504, 61·1%), fever (14,370, 56·6%), and shortness of breath/tachypnea (13,158, 52%). The most frequent underlying conditions were malnutrition (n: 5189, 27·8%) and arterial hypertension (n: 3725, 17·8%). Besides, 30·3% (n: 7695) of the patients presented at least one underlying condition, from which 66·6% (n: 5122), 21·9% (n: 1685), 11·5% (n: 888) presented 1, 2 or more than 2 underlying conditions, respectively. Table 1.

In the patients with laboratory data, 31·0% (3341/10,781) had a C reactive protein (CRP) greater than 100 mg/dl, 18·9% (1667/8499) had a serum creatinine greater than 1·2 mg/dl, and 39·8% (3508/8816) had an LDH over 350 U/L. (Table 1).

Regarding treatment during hospitalization, a total of 65·9% (n:16,708) were treated with steroids, 1·3% (n:342) were treated with

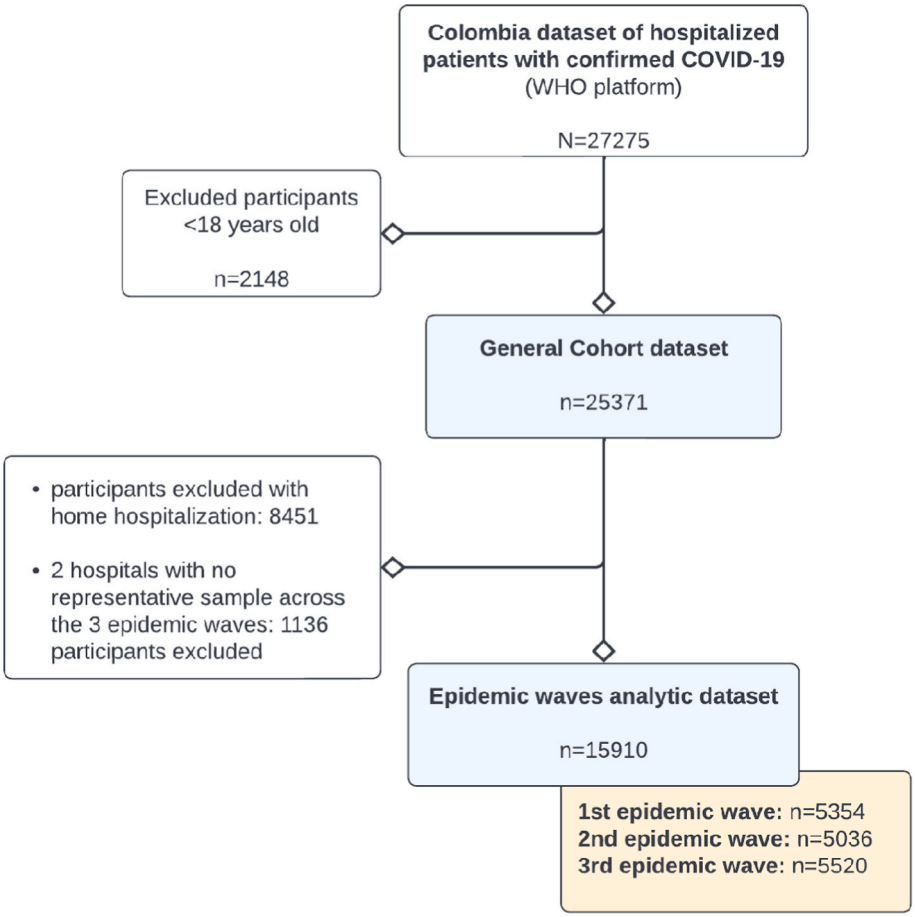

Fig. 1. Flow diagram for participant selection.

Table 1
Patient characteristics, laboratory values, clinical treatment, complications, and outcomes of study population. Colombian COVID Cohort - WHO World Platform. March 2020 to September 2021.

Characteristics[a]	Total (N = 25,371)[b]
Age (years)	
< 45	9667 (38.1%)
45 to 65	8899 (35.1%)
66 to 75	3446 (13.6%)
> 75	3359 (13.2%)
Sex	
Male	13,680 (53.9%)
Female	11,691 (46.1%)
Symptom onset in days	4 (2–7)
Signs and symptoms on admission	
History of fever (>38 °C)	14,370 (56.6%)
Cough	15,504 (61.1%)
Shortness of breath/Tachypnea	13,158 (52.0%)
Sore throat	4036 (15.9%)
Runny nose	1803 (7.1%)
Chest pain	406 (1.6%)
Loss of taste	1519 (6.0%)
Loss of smell	1688 (6.7%)
Headache	4529 (18.7%)
Vomiting/Nausea	839 (3.3%)
Muscle aches	2522 (9.9%)
Joint pain (arthralgia)	1655 (7.1%)
Fatigue/malaise	3242 (12.8%)
Altered consciousness/confusion	2756 (10.9%)
Diarrhea	4760 (18.8%)
Admission vital signs and Anthropometrics	
Temperature[c] (n: 23,600)	36.5 (36.1–37.0)
Heart rate[d] (n: 22,966)	86 (76–98)
Respiratory rate[e] (n: 24,292)	19 (18–21)
Systolic blood pressure[f] (n: 24,217)	122 (110–133)
Diastolic blood pressure[f] (n: 23,897)	75 (68–84)
Oxygen saturation	92 (89–95)
Glasgow Coma Scale (GCS)	15 (15–15)
Height (cm) (n: 6294)	165 (159–170)
Weight (Kg) (n: 7526)	73 (65–84)
BMI[g] (Kg/m^2) (n: 6231)	
Low weight (<18.5)	90 (1.4%)
Normal weigth (18.5 - <25)	2006 (32.2%)
Overweigth (25 - <30)	2403 (38.6%)
Obesity (≥30)	1734 (27.8%)
Severity classification (n: 24,683)	
Severe or critical	20,779 (84.2%)
Mild or moderate	3904 (15.8%)
Chronic Conditions	
None	14,977 (59.0%)
Chronic cardiac disease (n: 20,860)	716 (3.4%)
Hypertension (n: 20,983)	3725 (17.8%)
Chronic Pulmonary Disease (n: 21,107)	766 (3.6%)
Asthma (n: 20,997)	272 (1.3%)
Diabetes (n: 21,132)	1695 (8.0%)
Malnutrition (n: 18,694)	5189 (27.8%)
Malignant neoplasm (n: 21,107)	746 (3.5%)
Chronic Liver Disease (n: 20,995)	233 (1.1%)
Chronic Kidney Disease (n: 21,021)	1255 (6.0%)
Chronic Neurological Disease (n: 25,212)	318 (1.3%)
HIV[h]	298 (1.2%)
Tuberculosis (active and previous) (n: 20,982)	15 (0.1%)
Current Smoking (n: 18,914)	472 (2.5%)
Pre-admission or Chronic Medications (in previous 14 days)	
ACE inhibitors[i] (n: 23,662)	1219 (5.2%)
ARBs[j] (n: 22,636)	2153 (9.5%)
NSAIDs[k] (n: 18,698)	406 (2.2%)
Hydroxychloroquine (n: 23,502)	37 (0.2%)
Azithromycin (n: 24,171)	5351 (21.1%)
Laboratory test on admission	
Haemoglobin (g/dl) (n: 8504)	14.2 (12.8–15.6)
WBC count[l] (× 10^3 cells per μL) (n: 8504)	7.8 (5.9–10.5)
Haematocrit (%) (n: 8504)	40.9 (36.6–45.0)
Platelets (cells per μL) (n: 8504)	236,000 (178,000–308,400)
Sodium mEq/L (n: 6673)	138 (135–140)
Potassium mEq/L (n: 6982)	4.3 (4.0–4.7))
Creatinine (mg/dL) (n: 8499)	0.9 (0.8–1.1)
LDH[m] (U/L) (n: 8816)	311 (231–428)
ALT/SGPT[n] (U/L) (n: 676)	46 (28.8–75.1)
AST/SGOT[o] (U/L) (n: 676)	46 (32.0–72.0)
CRP[p] (mg/L) (n: 10,781)	31.4 (7.5–103)
Troponin (ng/ml) (n: 462)	0.3 (0.1–3.2)
Lactate (mmol/L) (n: 6500)	1.9 (1.3–88.8)
Ferritin (ng/mL) (n: 6255)	772.2 (343.4–1486.5)
Diagnostic Testing	
Infiltrate in Chest x-ray or CT[q] (n: 25,344)	17,275 (68.1%)
Influenza virus at admission	230 (0.9%)
Treatment during hospitalization	
IV fluids	24,659 (97.2%)
Antiviral	342 (1.3%)
Lopinavir/ritonavir	254 (1%)
Oseltamivir	54 (0.2%)
Acyclovir	26 (0.1%)
Other	8 (0.04%)
Corticosteroid	16,708 (65.9%)
Dexamethasone	15,921 (62.8%)
Methylprednisolone	154 (0.6%)
Other	633 (2.5%)
Antibiotics in the first 24 h	8447 (33.3%)
Antibiotic during hospitalization	9403 (37.1%)
Ampicillin/sulbactam	4171 (16.4%)
Vancomycin	682 (2.7%)
Piperacillin/tazobactam	1998 (7.9%)
Meropenem	1171 (4.6%)
Other	3230 (12.7%)
Hydroxychloroquine	148 (0.6%)
Antifungal	782 (3.1%)
Fluconazole	191 (0.8%)
Caspofungin	331 (1.3%)
Unknown	321 (1.0%)
Systemic anticoagulation (n: 19,216)	12,677 (66.0%)
ACE inhibitors[i] (n: 16,613)	8758 (52.7%)
NSAID[k] (n: 16,613)	4316 (26.0%)
Respiratory	
Oxygen therapy	21,008 (82.8%)
Non-invasive ventilation: BiPAP[r] or CPAP[s]	142 (0.6%)
Invasive ventilation in the first 24 h	1138 (4.5%)
Invasive ventilation during hospitalization	2479 (9.8%)
Critical care interventions and complications	
ICU[t] admission in first 24 h	1141 (4.5%)
ICU[t] admission during hospitalization	2616 (10.3%)
Shock	1286 (5.1%)
Inotropes/Vasopressors	999 (3.9%)
Renal replacement therapy/hemodialysis	173 (0.7%)
Acute Respiratory Distress Syndrome (ARDS)	1534 (6.0%)
Bacteremia (n: 23,515)	1856 (7.9%)
Cardiac arrhythmia	195 (0.8%)
Cardiac arrest	207 (0.8%)
Cardiomyopathy	84 (0.3%)
Endocarditis	3 (0.01%)
Myocarditis/pericarditis	176 (0.7%)
Stroke (ischemic stroke or intracerebral haemorrhage)	52 (0.2%)
Meningitis/encephalitis	3 (0.01%)
Liver dysfunction	538 (2.1%)
Hospital Outcomes	
Length of hospital stay	3.7 (0.6–9.2)
Length of ICU[t] stay	9 (4.0–15.0)
Length of Invasive Ventilation	12.5 (10.0–17.0)
Outcome	
Alive	21,605 (85.2)
Referral	1239 (4,9)
Death	2434 (9,6)

[a] n if fewer patients were assessed relative to the total number of patients in the study.
[b] n (%) for categorical; median (IQR) for continuous; percentage by row.
[c] Temperature in degrees centigrade.
[d] Heart rate in pulsation/minute (p/min).
[e] Respiratory rate in breath/minute (b/min).
[f] Blood pressure in millimeters of mercury (mmHg).
[g] BMI: body mass index.

[h] HIV: human immunodeficiency virus.
[i] ACE: Angiotensin-converting enzyme inhibitors.
[j] ARBs: Angiotensin II Receptor Blockers.
[k] NSAIDs: non-steroidal anti-inflammatory drugs.
[l] WBC: White blood cells.
[m] LDH: Lactate dehydrogenase.
[n] ALT: Alanine Transaminase.
[o] AST: Aspartate transaminase.
[p] CRP: *C*-reactive protein.
[q] CT: computed tomography.
[r] BiPAP: bilevel positive airway pressure.
[s] CPAP: continuous positive airway pressure.
[t] ICU: Intensive care unit.

antivirals, and 0·6% (n:148) received hydroxychloroquine. Moreover, 37·1% (n:9403) were on antibiotic therapy, mainly ampicillin/sulbactam, and 3·1% (n:782) received antifungals. 21,008 (82·2%) patients required oxygen therapy. (Table 1).

A total of 10·3% (n:2616) patients were admitted to the ICU. The most common complication was the development of bacteriemia (7·9%), followed by shock (5·1%). The median hospital stay was 3·7 days and 9 days for general hospitalization and ICU, respectively, and 9·6% (n:2434) patients died during follow-up.

3.2. Variants (three epidemic waves) analytic dataset: modeling phase

For the second phase of the analysis, 15,910 hospitalized patients were included, from which 5,354, 5,036, and 5520 accounted for the first, second, and third waves, respectively (see Fig. 1). Age distribution in the third wave skewed with greater frequency of younger people (28·9%) being hospitalized compared to those in the first wave (22·6%) and the second wave (17·9%) (See Table 2).

Moreover, comparing symptoms at admission, it was more common to have altered mental status (21·2%) and fever (58·5%) in the third epidemic wave than in the second and first epidemic waves ($p < 0·01$), Regarding individual underlying conditions during the third wave, chronic cardiac disease, chronic pulmonary disease, arterial hypertension, diabetes mellitus, and cancer were less common than in the other waves. However, chronic kidney and neurologic diseases were predominant in the third wave (18·2% and 2·0%) (See Table 2). Additionally, antibiotic use was reduced from 63.5% in the first epidemic wave to 38.4% in the third wave. More severe cases were detected in the second wave (n:4941; 98·1%), but more patients were admitted to the ICU (16.5%) and required mechanical ventilation (15.6%) or had ARDS (16.8%) in the first wave. The mortality for each wave was 11·5%, 12·0%, and 9·3%, respectively.

3.3. Survival analysis and associated factors with mortality

Overall, 30 days in-hospital mortality was 10.1% (n:1613), 10·3% (551/5354) in the first, 11·4% (223/5036) in the second, and 8·8% (206/5520) in the third epidemic wave. For seven days in-hospitalization instead, overall, 3·8% (n:622) of hospitalized patients died, of which 3·6% (193/5354) where in the first wave, 4·4% (223/5036) in the second wave, and 3·7% (206/5520) in the third wave. KM curves for 30 days of in-hospital mortality showed significant differences among the three epidemic waves (log-rank test $p < 0·001$) (Fig. 2A). Furthermore, when stratified by age group, we found significant differences in survival across three epidemic curves for hospitalized patients older than 75 years (log-rank test $p = 0·012$) (Fig. 2B.4).

In the multivariate Cox model (model 1, Table 3), there were no significant independent association between the second (HR 1·03, 95% CI 0·93-1·16) or third (HR 0·95, 95% CI 0·84-1·08) epidemic waves and mortality compared to the first wave. However, increased risk for mortality was observed in older hospitalized patients compared to younger patients, for age groups 45–65 years (HR 1·53, 95% CI 1·28-

Table 2
Description of the Clinical Characteristics, Clinical Management, and Outcomes of the Colombian cohort by an epidemic wave from March 2020 to September 2021. WHO World Platform.

Clinical Characteristics, Clinical Treatment, and Outcomes	First (N = 5354)[a]	Second (N = 5036)[a]	Third (N = 5520)[a]	P value
Age (years)				<0.01
< 45	1208 (22.6%)	903 (17.9%)	1597 (28.9%)	
45 to 65	2251 (42.0%)	1952 (38.8%)	2274 (41.2%)	
66 to 75	932 (17.4%)	1081 (21.5%)	875 (15.9%)	
> 75	963 (18.0%)	1100 (21.8%)	774 (14.0%)	
Sex				0.03
Male	3057 (57.1%)	2959 (58.8%)	3104 (56.2%)	
Female	2297 (42.9%)	2077 (41.2%)	2416 (43.8%)	
Signs and symptoms on admission				
Altered consciousness/ confusion	663 (12.4%)	589 (11.7%)	1173 (21.2%)	<0.01
Fever	2644 (49.4%)	2164 (43.0%)	3229 (58.5%)	<0.01
Cough	2880 (53.8%)	2089 (41.5%)	2933 (53.1%)	<0.01
Shortness of breath	2767 (51.7%)	2865 (56.9%)	3118 (56.5%)	<0.01
Headache	510 (9.5%)	347 (6.9%)	1089 (19.7%)	<0.01
Nausea or vomiting	232 (4.3%)	108 (2.1%)	120 (2.2%)	<0.01
Loss of taste	186 (3.5%)	153 (3.0%)	156 (2.8%)	0.14
Loss of smell	161 (3.0%)	145 (2.9%)	162 (2.9%)	0.93
Chest pain	81 (1.5%)	33 (0.7%)	157 (2.8%)	<0.01
Myalgia or Arthralgia	615 (11.5%)	183 (3.6%)	235 (4.3%)	<0.01
Abdominal pain	249 (4.7%)	163 (3.2%)	180 (3.3%)	<0.01
Diarrhea	687 (12.8%)	720 (14.3%)	1013 (18.4%)	<0.01
Admission vital signs				
Heart rate >100 p/min	1117 (20.9%)	1436 (28.5%)	1492 (27.0%)	<0.01
Respiratory rate >20 b/ min	2753 (51.4%)	2792 (55.4%)	2987 (54.1%)	<0.01
Systolic blood pressure <90 mmHg	173 (3.2%)	164 (3.3%)	202 (3.7%)	0.39
Oxygen saturation <90%	1572 (29.4%)	1595 (31.7%)	1981 (35.9%)	<0.01
Glasgow score <15	663 (12.4%)	589 (11.7%)	1173 (21.2%)	<0.01
Severity classification at admission				<0.01
Severe or critical	4972 (92.9%)	4941 (98.1%)	5045 (91.4%)	
Mild or moderate	382 (7.1%)	95 (1.9%)	475 (8.6%)	
Underlying conditions				
Chronic cardiac disease	271 (5.1%)	134 (2.7%)	120 (2.2%)	<0.01
Hypertension	1494 (27.9%)	1366 (27.1%)	942 (17.1%)	<0.01
Chronic Pulmonary Disease	471 (8.8%)	500 (9.9%)	353 (6.4%)	<0.01
Asthma	70 (1.3%)	56 (1.1%)	63 (1.1%)	0.61
Diabetes	770 (14.4%)	739 (14.7%)	525 (9.5%)	<0.01
Malignant neoplasm	485 (9.1%)	513 (10.2%)	372 (6.7%)	<0.01
Chronic Liver Disease	190 (3.5%)	97 (1.9%)	88 (1.6%)	<0.01
Chronic Kidney Disease	507 (9.5%)	428 (8.5%)	1007 (18.2%)	<0.01
Chronic Neurological Disease	66 (1.2%)	69 (1.4%)	112 (2.0%)	<0.01
HIV[b]	81 (1.5%)	107 (2.1%)	68 (1.2%)	<0.01
Any underlying condition	2879 (53.8%)	2273 (45.1%)	2543 (46.1%)	<0.01

(*continued on next page*)

Table 2 (*continued*)

Clinical Characteristics, Clinical Treatment, and Outcomes	First (N = 5354)[a]	Second (N = 5036)[a]	Third (N = 5520)[a]	P value
Underlying conditions number				<0.01
No-underlying conditions	2475 (46.2%)	2763 (54.9%)	2977 (53.9%)	
One-underlying condition	1784 (33.3%)	1531 (30.4%)	1807 (32.7%)	
Two-underlying conditions	687 (12.8%)	505 (10.0%)	493 (8.9%)	
More than two underlying conditions	408 (7.6%)	237 (4.7%)	243 (4.4%)	
Pre-admission or Chronic Medications (in previous 14 days)				
Use of ACE[c] inhibitors pre-admission	441 (8.2%)	395 (7.8%)	205 (3.7%)	<0.01
Treatment during hospitalization				
Antiviral during hospitalization	127 (2.4%)	71 (1.4%)	66 (1.2%)	<0.01
Corticosteroid during hospitalization	4395 (82.1%)	4550 (90.3%)	4744 (85.9%)	<0.01
Antibiotic during hospitalization	3401 (63.5%)	2402 (47.7%)	2122 (38.4%)	<0.01
Complication during hospitalization				
ICU[d] admission during hospitalization	884 (16.5%)	587 (11.7%)	625 (11.3%)	<0.01
Invasive Ventilation	836 (15.6%)	575 (11.4%)	575 (10.4%)	<0.01
Inotropes/Vasopressors	652 (12.2%)	483 (9.6%)	436 (7.9%)	<0.01
Pneumonia	4855 (90.7%)	4652 (92.4%)	4296 (77.8%)	<0.01
Acute Respiratory Distress Syndrome	898 (16.8%)	674 (13.4%)	616 (11.2%)	<0.01
Length of hospital stay	6.9 (3.4–13.2)	5.9 (3.1–11.2)	6.2 (3.1–12.0)	<0.01
Mortality	617 (11.5%)	603 (12.0%)	511 (9.3%)	<0.01

[a] n (%) for categorical; median (IQR) for continuous; percentage by column.
[b] HIV: human immunodeficiency virus.
[c] ACE: Angiotensin-converting enzyme inhibitors.
[d] ICU: Intensive care unit.

1·82), 66–75 years (HR 2·67 95% CI 2·22-3·20), and older than 75 years (HR 3·74, 95% CI 3·13- 4·46) relative to patients younger than 45 years. We also found an increased risk for in-hospital mortality in patients with hypertension (HR 1·19, 95% CI 1·06-1·34), malignant neoplasm (HR 1·59, 95% CI 1·37-1·85), chronic heart disease (HR 1·38, 95% CI 1·12-1·70), and chronic neurologic disease (HR 2·07, 95% CI 1·62-2·65), on the other hand, there was a decreased risk for mortality in women (HR 0·81, 95% CI 0·74-0·90) when compared to men.

These findings were similar to model 2, adjusting for the number of underlying conditions rather than individual conditions (See supplementary material table 1). However, in model 2, when assessing the interaction between age and epidemic wave, having 75 years or more and being hospitalized in the third epidemic wave was associated with a lower hazard for mortality (HR 0·63.95% CI 0·41-0·97) (See supplementary material Table 3). This finding is consistent with the Cox model stratified by age, where patients 75 years or older in the third wave had a lower hazard for mortality, although not statistically significant. (HR 0.80 95%CI 0.63–1.00) (See supplementary material Table 7).

4. Discussion

Our study, a retrospective multicenter cohort from hospitalized patients with COVID-19 in Colombia showed that patients hospitalized during the third wave, consisting mainly of cases of the Mu variant, did not have a higher hazard for mortality after adjusting for age and several underlying conditions. Taken together, our adjusted models are highly consistent with what has been seen worldwide in patients requiring hospitalization [14].

In our study, the COVID-19 in-hospital mortality was 10·1%, which is within the range of what has been described previously in other reports fluctuating from 10·8–39% [15–17]. The mortality per each epidemic wave was 10·3%, 11·4%, and 8·8% ($p < 0.001$), respectively. Our results could relate to the findings by Xia et al. where the in-hospital mortality was reduced from the first to the third epidemic wave, probably linked to a better understanding of the disease and compliance with evidence-based guidelines worldwide [18], such as vaccination.

Despite the small but significant differences in mortality among the three epidemic waves, when we carried out the multivariate Cox model and adjusted by variables that are known for being risk factors for mortality, such as age, sex, or underlying conditions, we did not find that hospitalized patients in the third epidemic wave would have a lower hazard for mortality. However, we found that people older than 75 in the third epidemic wave had a lower hazard for mortality than hospitalized patients in the same age group during the first wave. We believe these findings could be related to the Colombian National COVID-19 vaccination plan, which started by the end of February 2021, prioritizing older adults and people with underlying conditions predominantly with inactivated vaccines [19]. By the end of the third epidemic wave in September 2021, over a quarter of the population was fully vaccinated, and up to 80% were 60 years or older [19].

Moreover, despite previous evidence suggesting an increased risk of hospitalization and mortality in patients with the Mu variant [7], we did not find an increased hazard in in-hospital mortality during the third epidemic wave in which the Mu variant was predominant in Colombia, probably explained by the protective effect of vaccination surpassing the potential effect of immune evasion of the Mu variant.

Many risk factors for unfavorable outcomes in COVID-19 patients have been described. For instance, older ages have been consistently associated with higher COVID-19 mortality, similar to our findings [20,21]. Moreover, we found that females had a lower hazard for in-hospital mortality, which has been widely reported among different cohorts [15,22]. Also, we observed an association between having at least one underlying condition and a greater mortality hazard following a gradient, where the greater the number of underlying conditions, the higher the mortality hazard. This relates to what has been previously reported on this topic in which underlying conditions and their number increase the risk for critical outcomes such as ICU admission or COVID-19 mortality [23,24]. The strongest association regarding underlying conditions found for in-hospital mortality was malignant neoplasms and chronic neurologic disease, which has also been described before [25].

With regards to antimicrobial treatment in the cohort at the time of admission, a considerable number of patients were taking either azithromycin (21·1%) or lopinavir/ritonavir (8·7%) which relates to the previous description in Latin America, reflecting the difficulties generated by antimicrobial sale without prescription due to the lack of compliance of the established regulations [26]. Additionally, in our cohort, overall antibiotic prescription during hospitalization was 49·8%, decreasing by each epidemic wave being 38·4% for the third one contrasting with data from other countries in which antibiotic use ranged from 68·3%–80% [27]. This probably reflects the uncertainty regarding care strategies at the beginning of the pandemic and later on, a better understanding derived from data reported in the different cohorts in which the rate of bacterial coinfection was only between 3·5 and 8% [28,29], as opposed to the previous AH1N1 influenza pandemic where coinfections exceeded 50% [30]. Also, the adequate response of hospital antimicrobial stewardship programs in our population favored this decrease [26].

Our study has several limitations. First, we do not have genomic characterization in our patient samples to confirm that SARS-CoV-2 infections during the third epidemic wave were caused by the Mu

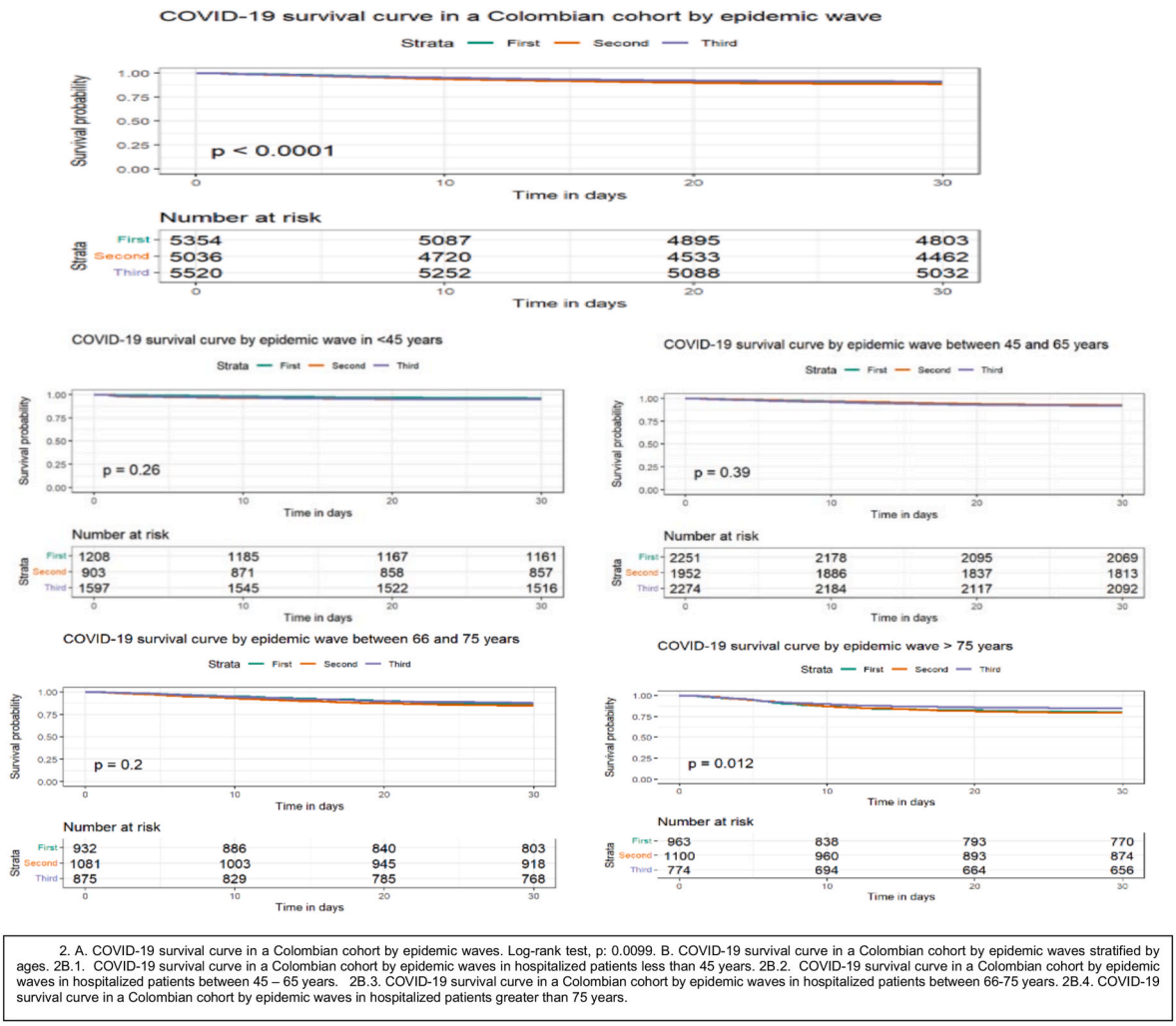

Fig. 2. A.COVID-19 survival curve in a colombian cohort by epidemic waves.Log-rank test,p:0.0099. B. COVID-19 survival curve in a Colambian cohort by epidemic waves stratified by ages. 2B.1. COVID-19 survival curve in a Colombian cohort by epidemic waves in hospitalized patients less than 45 years. 2B.2. COVID-19 survival curve in a colombian cohort by epidemic waves in hospitalized patients between 45 and 65 years. 2B.3. COVID-19 survival curve in a colombian cohort by epidemic waves in hospitalized patients between 66 and 75 years. 2B.4. COVID-19 survival curve in a colombian cohort by epidemic waves in hospitalized patients between 75 years.

variant. Nevertheless, national data supports that this variant was predominant in Colombia's third epidemic wave of COVID-19. Second, for some key variables which had a significant amount of missing data, imputation was not possible, for instance, body mass index or obesity, despite the higher number of individuals in Colombia at risk [19]; thus, raising awareness to improve data management systems throughout the country leading to better data quality for further research. Also, we do not have data on vaccination in our cohort, which has modified the risk of hospitalization and death [19]. Therefore, this variable could not adjust the regression models, and our hypothesis regarding vaccination's protective effect in the third wave cannot be confirmed. Nonetheless, we do not believe this would change our study's conclusions. Third, we did not have the scope to evaluate the clinical outcomes throughout the whole country since only three cities and only high-complexity health institutions are included; our results probably reflect the situation of hospitals with similar complexity levels.

In this Colombian cohort of COVID-19, we did not find an increase in in-hospital mortality during the third epidemic wave when the Mu variant was predominant in Colombia. We believe the main reason is that by the end of the third epidemic wave, a considerable number of people were vaccinated in the country, prioritizing high-risk populations such as older adults and people with underlying conditions.

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Ethical approval statement

The study was approved by each IRB or Ethics Committee of the participant institutions.

CRediT authorship contribution statement

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Table 3
Description of the general population by in-hospital mortality and Cox mixed effects model by in-hospital mortality in a Colombian cohort from March 2020 to September 2021. WHO World Platform.

Clinical and Epidemiological Characteristics	Total (N = 15,910)[a]	Non-survivors (N = 1731)[a]	Survivors (N = 14,179)[a]	HR crude (95%CI)[b]	Model aHR (95%CI)[b]
Age (years)					
< 45	3708 (23.3%)	182 (10.5%)	3526 (24.9%)	ref	ref
45 to 65	6477 (40.7%)	554 (32.0%)	5923 (41.8%)	1.27 (1.07–1.51)	1.53 (1.28–1.82)
66 to 75	2888 (18.2%)	429 (24.8%)	2459 (17.3%)	1.94 (1.62–2.31)	2.67 (2.22–3.20)
> 75	2837 (17.8%)	566 (32.7%)	2271 (16.0%)	3.18 (2.69–3.77)	3.74 (3.13–4.46)
Sex					
Male	9120 (57.3%)	1047 (60.5%)	8073 (56.9%)	ref	ref
Female	6790 (42.7%)	684 (39.5%)	6106 (43.1%)	1.03 (0.93–1.14)	0.81 (0.74–0.90)
Any underlying condition	7695 (48.4%)	1046 (60.4%)	6649 (46.9%)		
Underlying conditions number					
No-underlying conditions	8215 (51.6%)	685 (39.6%)	7530 (53.1%)	ref	
One-underlying condition	5122 (32.2%)	537 (31.0%)	4585 (32.3%)	1.24 (1.10–1.39)	
Two-underlying conditions	1685 (10.6%)	273 (15.8%)	1412 (10.0%)	2.00 (1.73–2.31)	
More than two underlying conditions	888 (5.6%)	236 (13.6%)	652 (4.6%)	3.43 (2.94–4.00)	
Underlying conditions					
Chronic cardiac disease	525 (3.3%)	111 (6.4%)	414 (2.9%)	2.08 (1.70–2.53)	1.38 (1.12–1.70)
Hypertension	3802 (23.9%)	631 (36.5%)	3171 (22.4%)	1.89 (1.71–2.10)	1.19 (1.06–1.34)
Chronic Pulmonary Disease	1324 (8.3%)	248 (14.3%)	1076 (7.6%)	1.91 (1.66–2.20)	
Asthma	189 (1.2%)	22 (1.3%)	167 (1.2%)	1.03 (0.66–1.60)	
Diabetes	2035 (12.8%)	327 (18.9%)	1708 (12.0%)	1.61 (1.42–1.83)	
Malignant neoplasm	1370 (8.6%)	276 (15.9%)	1094 (7.7%)	2.10 (1.83–2.39)	1.59 (1.37–1.85)
Chronic Kidney Disease	1942 (12.2%)	314 (18.1%)	1628 (11.5%)	1.68 (1.49–1.91)	
Chronic Neurological Disease	247 (1.6%)	75 (4.3%)	172 (1.2%)	3.22 (2.53–4.10)	2.07 (1.62–2.65)
Epidemic wave					
First	5354 (33.7%)	617 (35.6%)	4737 (33.4%)	ref	ref
Second	5036 (31.7%)	603 (34.8%)	4433 (31.3%)	1.36 (1.21–1.53)	1.03 (0.92–1.16)
Third	5520 (34.7%)	511 (29.5%)	5009 (35.3%)	1.01 (0.89–1.14)	0.95 (0.84–1.08)

[a] n (%) for categorical; median (IQR) for continuous; percentage by column.
[b] HR = Hazard Ratio, CI = Confidence Interval.

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2023.102579.

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