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Revista de la Facultad de Medicina

ORIGINAL RESEARCH

Risk factors for ventilator-associated pneumonia in patients with acute respiratory distress syndrome due to COVID-19

Factores de riesgo de neumonía asociada a la ventilación mecánica en pacientes con síndrome de dificultad respiratoria aguda causado por COVID-19

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Open access

Received: 03/07/2023
Accepted: 29/01/2024

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Keywords: COVID-19, SARS-CoV-2, Nosocomial infections, Ventilator-associated pneumonia, Acute Respiratory Distress Syndrome, Critical Care (MeSH).

Palabras clave: COVID-19; SARS-CoV-2; Infecciones nosocomiales; Neumonía asociada a ventilador; Síndrome de dificultad respiratoria aguda; Cuidados críticos (DeCS).

How to cite: Rojas-Martínez R, Espinoza-Almanza JC. Risk factors for ventilator-associated pneumonia in patients with acute respiratory distress syndrome due to COVID-19. Rev. Fac. Med. 2024;72(2):e109746. English. doi: https://doi.org/10.15446/revfacmed.v72n2.109746..

Cómo citar: Rojas-Martínez R, Espinoza-Almanza JC. [Factores de riesgo de neumonía asociada a la ventilación mecánica en pacientes con síndrome de dificultad respiratoria aguda causado por COVID-19]. Rev. Fac. Med. 2024;72(2):e109746. English. doi: https://doi.org/10.15446/revfacmed.v72n2.109746.

Abstract

Introduction: Ventilator-associated pneumonia (VAP) is a common complication in patients on mechanical ventilation that has been associated with a worse prognosis. During the COVID-19 pandemic, the frequency of VAP increased.
Objective: To identify risk factors for VAP in patients with acute respiratory distress syndrome due to COVID-19 (C-ARDS) admitted to an intensive care unit (ICU) in Bogotá, Colombia.
Materials and methods: Nested case-control study. The cohort comprised adult patients with C-ARDS on mechanical ventilation who were admitted to the ICU between May 2020 and June 2021. Patients with VAP were included as cases, and four controls who did not have VAP at the time of the case occurrence were randomly selected from the cohort for each case. Bivariate analyses were performed to evaluate differences between groups, as well as a multivariate analysis (conditional logistic regression model) to determine the association between the variables considered and the development of VAP, calculating odds ratios (OR) (crude and adjusted) and their respective 95% confidence intervals (95%CI).
Results: The cohort comprised 870 patients, of whom 350 were included in the final sample (70 cases and 280 controls). Of these, 68.28% were male, and the mean age was 58 years (±12.5). High blood pressure (40.00%) and diabetes mellitus (20.00%) were the most frequent comorbidities. The following factors were associated with the development of VAP in the multivariate analysis: male sex (aOR: 2.29, 95%CI: 1.2-4.3), days on invasive mechanical ventilation (IMV) (aOR: 1.05, 95%CI: 1.02-1.08), and use of neuromuscular blocking agents (aOR: 3.58, 95%CI: 1.35-9.4).
Conclusion: Male sex, days on IMV, and use of neuromuscular blockers behaved as risk factors for VAP.

Resumen

Introducción. La neumonía asociada a la ventilación mecánica (NAVM) es una complicación frecuente en los pacientes en ventilación mecánica que se asocia con un peor pronóstico y cuya frecuencia aumentó durante la pandemia por COVID-19.
Objetivo. Identificar los factores de riesgo de NAVM en pacientes con síndrome de dificultad respiratoria aguda por COVID-19 (SDRA-C) admitidos a una unidad de cuidados intensivos (UCI) de Bogotá D.C., Colombia.
Materiales y métodos. Estudio de casos y controles anidado. La cohorte estuvo conformada por pacientes adultos con SDRA-C en ventilación mecánica que fueron admitidos a la UCI entre mayo de 2020 y junio de 2021; los pacientes con NAVM fueron incluidos como casos y, por cada caso, se seleccionaron aleatoriamente cuatro controles de la cohorte que al momento de la aparición del caso no tuvieran NAVM. Se realizaron análisis bivariados para evaluar las diferencias entre grupos y un análisis multivariado (modelo de regresión logística condicional) para determinar la asociación entre las variables consideradas y el desarrollo de NAVM mediante el cálculo de *Odds ratios* (OR) (crudos y ajustados) y sus respectivos intervalos de confianza al 95% (IC95%).
Resultados. La cohorte estuvo compuesta por 870 pacientes, de los cuales 350 fueron incluidos en la muestra final (70 casos y 280 controles). De estos, 68.28% eran hombres y la edad promedio fue 58 años (±12.5). La hipertensión arterial (40.00%) y la diabetes mellitus (20.00%) fueron las comorbilidades más frecuentes. En el análisis multivariado los siguientes factores se asociaron con el desarrollo de NAVM: sexo masculino (ORa: 2.29, IC95%: 1.2-4.3), días en ventilación mecánica invasiva (VMI) (ORa: 1.05, IC95%: 1.02-1.08) y uso de bloqueadores neuromusculares (ORa: 3.58, IC95%: 1.35-9.4).
Conclusión. El sexo masculino, los días en VMI y el uso de bloqueadores neuromusculares se comportaron como factores de riesgo de NAVM.

Introduction

According to data from the World Health Organization, as of July 9, 2023, more than 767 million cases of COVID-19, a disease caused by SARS-CoV-2 infection, had been reported.[1] In terms of severity, it has been described that 22.9% of patients with COVID-19 develop severe disease,[2] with hospitalization rates of 0.1% in children under 17 years of age and 17.2% in individuals over 85 years of age.[3,4] It has also been reported that between 9-32% of patients hospitalized with COVID-19 require admission to intensive care units (ICU),[5,6] and that the pooled proportion requiring invasive mechanical ventilation (IMV) in the latter subgroup is 7.1% (95%CI: 4.5-11.0).[2]

On the other hand, it has been described that comorbidities in COVID-19 patients admitted to the ICU are frequent[5,6] and that several of these comorbidities, such as diabetes mellitus and high blood pressure, have been associated with an adverse prognosis in terms of severity and mortality.[7] This situation contributes to prolonged IMV times, which in turn increases the risk of associated complications such as ventilator-associated pneumonia (VAP).[8] In this regard, incidence rates of VAP in COVID-19 patients reported in the literature vary between 48% and 79%.[8]

Concerning the microorganisms associated with VAP in patients on IMV due to COVID-19 acute respiratory distress syndrome (C-ARDS), it has been reported that although they vary between studies, Gram-negative bacteria predominate (>70% in most series), followed by Gram-positive bacteria, mainly *Staphylococcus aureus.* Moreover, since most cases of VAP caused by COVID-19 are diagnosed more than 7 days after initiation of IMV, these patients are at increased risk for multidrug-resistant bacterial strains.[9]

As reported in the literature, the frequency of VAP in patients with C-ARDS varies between 29% and 64%.[10-14] In addition, incidence rates in these patients are generally higher than those reported in non-COVID-19 patients (18-26 episodes of VAP per 1 000 ventilator days [11,12,14] vs. 1-19 episodes of VAP per 1 000 ventilator days[11,15-19]). Finally, the development of this infection in patients with C-ARDS has a serious impact on their prognosis, as it is associated with a longer ICU stay, prolonged IMV, and higher mortality (up to 1.65 times higher at 28 days compared to non-COVID-19 patients [HR: 1.65, 95%CI: 1.11-2.46] and a 90-day mortality rate of 33.33%).[20,21]

Therefore, identifying risk factors for VAP in patients with C-ARDS is essential, as focusing on the early and accurate identification of these factors allows the use of therapies other than IMV to be evaluated and also, if IMV is necessary, to design and implement strategies aimed at preventing the development of this infection in this population. In view of the above, the objective of this study was to identify risk factors for VAP in patients with C-ARDS admitted to an ICU in Bogotá D.C., Colombia.

Materials and methods

Study type and sample

Nested case-control study. The study population consisted of all adult patients (>18 years) admitted between May 2020 and June 2021 to the ICU of the Hospital Universitario Nacional de Colombia (HUN), a quaternary care hospital located in Bogotá D.C., Colombia. Inclusion criteria for enrollment of patients into the cohort were: having a diagnosis of COVID-19 confirmed by polymerase chain reaction (RT-PCR) testing of nasal or pharyngeal swabs or lower respiratory tract aspirates,[22] being on IMV for at least 48 hours, and meeting the Berlin criteria for moderate to severe ARDS.[23] The following patients

were excluded: pregnant or puerperal women, patients who died within 48 hours after admission to the ICU, patients in whom therapeutic effort was limited, and patients who had been diagnosed with VAP in another health care institution.

Once the cohort was formed, all patients with a diagnosis of VAP were included as cases. In this regard, it should be noted that the HUN epidemiological committee evaluates all probable VAP cases on a monthly basis and applies internationally approved criteria to make the diagnosis, as follows: body temperature >38.5°C or <36.5°C, leukocyte count >12 000 cells/µL or <4 000 cells/µL, evidence of progressive bilateral pulmonary infiltrates on radiological examination (chest X-ray or chest CT scan), and microbiological confirmation of nosocomial pneumonia in tracheal secretion or bronchoalveolar lavage specimen (isolation of at least 105 colony forming units [CFU] of a pathogenic germ).[24,25]

On the other hand, controls were randomly included taking into account the timing of occurrence of each case (1:4 ratio), in other words, once the case was identified, a list of patients in the cohort without VAP who were admitted to the ICU at the time of occurrence of the case was generated to select the 4 controls using the random feature of Microsoft Excel (version 2019).

Procedures and variables

The following data were collected for each patient based on the review of the case and control medical records: sociodemographic variables (sex and age), clinical variables (comorbidities such as high blood pressure, diabetes mellitus, advanced chronic kidney disease [stage 5], chronic obstructive pulmonary disease [COPD], obesity, and cancer; Charlson comorbidity index score; SOFA [Sequential Organ Failure Assessment] score; 24-hour fluid balance; antibiotic use on admission to the ICU, length of ICU stay, occurrence of sepsis [sepsis-3], and 30-day mortality); anthropometric variables (weight, body mass index); laboratory test results on admission (blood count, blood creatinine test, D-dimer test, ratio of partial pressure of arterial oxygen [PaO_2] to fraction of inspired oxygen [FiO_2] [PaO_2/FiO_2 ratio], and arterial blood gases); characteristics of interventions performed during ICU stay (use of pronation therapy, duration of pronation therapy, duration of IMV, sedation time, duration of opioid analgesia, use of neuromuscular blockers, and duration of use of neuromuscular blockers); and characteristics on the occurrence of VAP (isolated germs and antimicrobial resistance patterns).

Statistical analysis

The sample size was calculated using Kelsey's formula[26] with an alpha of 0.05, a beta of 0.2, an expected frequency of the exposure factors to be studied between 20 and 30%, and a target odds ratio (OR) of 2.5 (taking 4 controls for each case), thus obtaining a minimum sample of 270 patients. The data collected were entered into a database created in Microsoft Excel (version 2019) and subsequently analyzed using the statistical software STATA (version 15.0).

Qualitative variables are described using absolute frequencies and percentages, and quantitative variables are described using means and standard deviations (SD).[27] Regarding inferential analysis, bivariate analyses were performed to establish differences between groups: for quantitative variables, Student's t-tests or Wilcoxon rank sum tests were used, depending on the normality of the data, and for qualitative variables, chi-square or Fisher's exact tests were used, depending on the expected values in each case. A significance level of $p<0.05$ (two-tailed test) was considered.[27,28]

Finally, a multivariate analysis, in which a conditional logistic regression model was constructed, was performed. The variables were selected using purposive sampling as described by Hosmer & Lesmeshow.[29] The initial model included all the variables of interest and the set of multiplicative interactions. The final or main effects model was obtained by stepwise regression (backward elimination), for which the usefulness of the multiplicative interactions was first tested by means of a LrTest (likelihood ratio test), and then the remaining model was evaluated for each variable by means of a Wald test, excluding those variables with a p-value >0.20 (14). Finally, confounding was tested with the remaining variables through the modifications of the adjusted OR value (aOR) made when the variables were removed; the variables with modifications >20% of the OR value were considered positive.[27,30] A statistical significance level of $p<0.05$ (two-tailed test) was also considered in this case.[27,28]

Ethical considerations

The study was approved by the Ethics and Research Committee of the HUN in accordance with minutes CEI-HUN-ACTA-2021-05. Likewise, the research followed the ethical principles of biomedical research involving human subjects established in the Declaration of Helsinki[31] and the scientific, technical and administrative standards for health research of Resolution 08430 of 1993 issued by the Colombian Ministry of Health.[32]

Results

During the study period, 3 056 patients were admitted to the ICU and COVID-19 diagnosis was confirmed by PCR-RT test in 1 370 (44.83%) of them. Of these 1 370 patients, 870 (63.50%) required IMV and met the Berlin criteria for the diagnosis of moderate to severe ARDS, so the cohort comprised these 870 patients. A total of 112 probable cases of VAP were identified in the cohort, but 42 were removed after implementing strict diagnostic and exclusion criteria; on the other hand, 280 controls were randomly selected from the remaining individuals in the cohort who did not have this outcome (Figure 1). Thus, the final sample consisted of 350 patients: 68.28% (n=239) were male, the mean age was 58 years (±12.5), the mean body weight was 78.4 kg (± 17), and the body mass index was 26.5 (± 5.22).

High blood pressure (40.00%; n=140), diabetes mellitus (20.00%; n=70), and COPD (10.00%; n=35) were the most common comorbidities. Regarding the severity of the participants' clinical condition, the following was found: the mean SOFA score on admission to the ICU was 7.2 (SD= 2.62), the mean time on IMV was 16.2 days (SD= 10. 1), the average time under sedation (benzodiazepines and/or propofol) was 13.45 days (SD= 8.87), the average duration of analgesia with opioids was 13.60 days (SD= 8.04), and the average time using neuromuscular blockers was 2.66 days (SD ± 2.70). Moreover, pronation therapy was used in 80.57% of patients (mean duration 4 days [SD= 3.52], mean PaO_2/FiO_2 ratio on admission was 164 (SD= 47.9), and 30-day mortality rate was 53.43% (n=187) (Table 1). Finally, the overall incidence rate of VAP was 8.2 episodes per 1 000 ventilator days.

With respect to the comparison between cases and controls, the following was observed: mean age was 59 years in cases (SD= 12.8) and 58 years in controls (SD= 12.4); the mean BMI was 26.9 (SD= 5.22) in cases and 26.4 (SD= 5.69) in controls; and the mean Charlson comorbidity index score was 2.38 (SD= 2.31) in cases and 1.94 (SD ±1.52) in controls, without these differences being statistically significant ($p>0.05$). There were also no significant differences between groups in the frequency of comorbidities such as high blood pressure, COPD, diabetes mellitus, or advanced chronic kidney disease (Table 1).

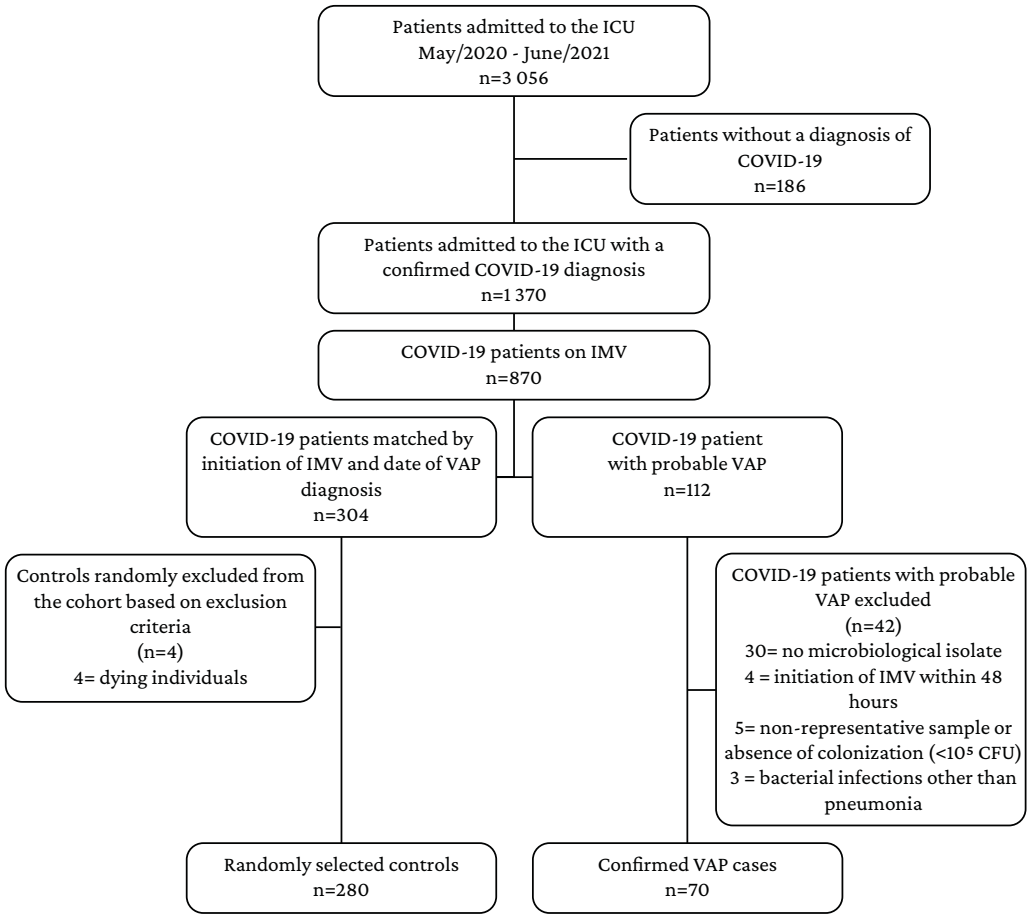

Figure 1. Flowchart of the study participant selection process.

However, significant differences were observed in the proportion of men (81.43% in cases vs. 65.00% in controls; p=0.008), proportion of patients requiring pronation therapy (67.14% vs. 83.93%; p=0.004), proportion of participants in whom neuromuscular blockers were used (91.43% vs. 76.43%; p=0.005), duration of pronation therapy (5.14 days vs. 3.75 days; p=0.003), duration of IMV (20.47 days vs. 15.33 days; p=0.000), length of ICU stay (22.6 days vs. 16.6 days; p=0.000), time of analgesia with opioids (18.14 days vs. 12.47 days; p=0.000), time under sedation (17.65 vs. 12-4; p=0.000), time of neuromuscular blockers use (4.84 vs. 3.36; p=0.000), proportion of patients in whom antibiotic use was reported on admission (54.28% vs. 36.75%; p=0.007), and frequency of sepsis (62.86% vs. 46.07%; p=0.012) (Table 1).

No significant differences were observed in 30-day mortality, nor in the results of laboratory tests, except for hemoglobin level (g/L) on admission (15.2 vs. 14.3; p=0.000) (Table 1).

As for multivariate analysis (conditional logistic regression model), male sex, time (days) on IMV, use of neuromuscular blockers, Charlson comorbidity index score, and SOFA score were significantly associated with the development of VAP in the crude model (Table 2). However, after adjusting the model for possible confounders, only the following variables showed statistically significant measures of association: male sex (aOR: 2.29, 95%CI: 1.2-4.3), days on IMV (aOR: 1.05, 95%CI: 1.02-1.08), and use of neuromuscular blockers (aOR: 3.58, 95%CI: 1.35-9.4) (Table 3).

Table 1. Characteristics of participants (cases vs. controls)

Variable	Cases (n= 70) n (%)	Controls (n=280) n (%)	Total (n=350) n (%)	*p*-value
Male	57 (81.43)	182 (65.00%)	239 (68.28)	**0.008**
Age (years) Mean (SD)	59 (12.8)	58 (12.4)	58 (12.5)	0.77
High blood pressure	31 (44.28)	109 (38.93)	140 (40.00)	0.445
Diabetes mellitus	17 (24.28)	53 (18.93)	70 (20.00)	0.263
COPD	5 (7.14)	30 (10.71)	35 (10.00)	0.333
Stage 5 CKD (dialysis)	2 (2.86)	10 (3.57)	12 (3.43)	0.878
Cancer	3 (4.29)	12 (4.28)	15 (4.28)	1.0
Charlson Comorbidity Index Mean (SD)	2.38 (2.31)	1.94 (1.52)	2.03 (1.71)	0.053
Weight Mean (SD)	80.7 (17.9)	77.8 (16.7)	78.4 (17)	0.209
BMI Mean (SD)	26.9 (5.22)	26.4 (5.69)	26.5 (5.22)	0.486
Class 1 obesity (BMI ≥30)	22 (31.43)	87 (31.07)	109 (31.14)	0.954
Pronation therapy	47 (67.14)	235 (83.93)	282 (80.57)	**0.004**
Use of neuromuscular blockers	64 (91.43)	214(76.43)	278 (79.43)	**0.005**
Hemoglobin level on admission Mean (SD)	15.2 (1.72)	14.3 (2.19)	14.4 (2.14)	**0.000**
Platelet count x10³ on admission Mean (SD)	259 (97 445)	280 (209 110)	276 (192 108)	0.411
Blood creatinine level on admission Mean (SD)	0.97 (0.31)	1.23 (1.5)	1.18 (1.39)	0.159
D-dimer on admission Mean (SD)	1 832 (3001)	2 414 (2554)	2 298 (3454)	0.208
PaO_2/FiO_2 on admission Mean (SD)	156 (46.7)	166 (48.1)	164 (47.9)	0.117
Duration of pronation therapy (days) Mean (SD)	5.14 (3.72)	3.75 (3.42)	4 (3.52)	**0.003**
SOFA Score Mean (SD)	7.8 (2.57)	7.15 (2.63)	7.2 (2.62)	0.065
Time on IMV (days) Mean (SD)	20.47 (9.92)	15.33 (9.92)	16.2 (10.1)	**0.000**
Length of ICU stay (days) Mean (SD)	22.6 (10.70)	16.6 (9.90)	17.8 (10.3)	**0.000**
Duration of analgesia with opioids (days) Mean (SD)	18.14 (7.81)	12.47 (7.71)	13.60 (8.04)	**0.000**
Time under sedation (days) Mean (SD)	17.65 (8.89)	12.4 (8.57)	13.45 (8.87)	**0.000**
Time of neuromuscular blocker use (days) Mean (SD)	4.84 (2.72)	3.36 (2.61)	2.66 (2.70)	0.000
24-hour fluid balance (mL)	522 (689)	664 (867)	636 (635)	0.206
Lactate level on admission Mean (SD)	1.67 (0.64)	1.55 (0.63)	1.57 (0.82)	0.298
Antibiotic use on admission	38 (54.28)	103 (36.78)	141 (40.28)	**0.007**
Sepsis 3	44 (62.86)	129 (46.07%)	173 (49.43)	**0.012**
30-day mortality	37 (52.86)	150 (53.57)	187 (53.43)	0.91

SD: standard deviation; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; BMI: body mass index; PaO_2/FiO_2: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit; IMV: invasive mechanical ventilation.

Table 2. Multivariate analysis (crude conditional logistic regression model).

VAP cases	Crude OR	Standard error	*Z*-value	*p*-value	95%CI
Male sex	2.29	0.75	2.53	0.01	1.2-4.3
Days on IMV	1.04	0.13	3.73	0.00	1.02-1.07
CCI score	1.16	0.89	1.96	0.04	1.0-1.35
SOFA score	1.11	0.62	1.98	0.04	1.0-1.24
Use of neuromuscular blockers	3.50	1.61	2.73	0.00	1.42-8.63

CI95%: 95% confidence interval; CCI: Charlson comorbidity index; VAP: ventilator-associated pneumonia; OR: odds ratio; SOFA: Sequential Organ Failure Assessment; IMV: Invasive mechanical ventilation.

Table 3. Multivariate analysis (adjusted logistic regression model).

VAP cases	aOR	Standard error	*Z*-value	*p*-value	95%CI
Male sex	2.8	0.99	2.92	0.003	1.4-5.6
Days on IMV	1.05	0.01	3.57	0.000	1.02-1.08
CCI score	1.16	0.10	1.76	0.079	0.98-1.38
SOFA score	1.10	0.06	1.71	0.087	0.98-1.24
Use of neuromuscular blockers	3.58	1.77	2.58	0.01	1.35-9.4

CI95%: 95% confidence interval; CCI: Charlson comorbidity index; VAP: ventilator-associated pneumonia; aOR: adjusted odds ratio; SOFA: Sequential Organ Failure Assessment; IMV: Invasive mechanical ventilation.

Lastly, 77 isolates were reported in patients with VAP, of which 81.82% were Gram-negative and 18.18% were Gram-positive. In the case of Gram-negatives, the most frequently isolated germs were *K. pneumoniae* (38.96%), *P. aeruginosa* (9.09%), *K. oxytoca* (6.49%), and *E. cloacae* (6.49%). In the case of Gram-positive cocci, *S. aureus* was the most frequent (92.86%). Furthermore, in 40.23% of the isolates, a degree of bacterial resistance different from the natural antibiotic susceptibility pattern of the germ (Wild Type) was reported. Also, the most frequent phenotypic resistance profiles were AmpC (22.20 %), KPCs (9.50 %), and ESBLs (4.70 %) in Gram-negative and MRSA (28.50 %) in Gram-positive (Figure 2).

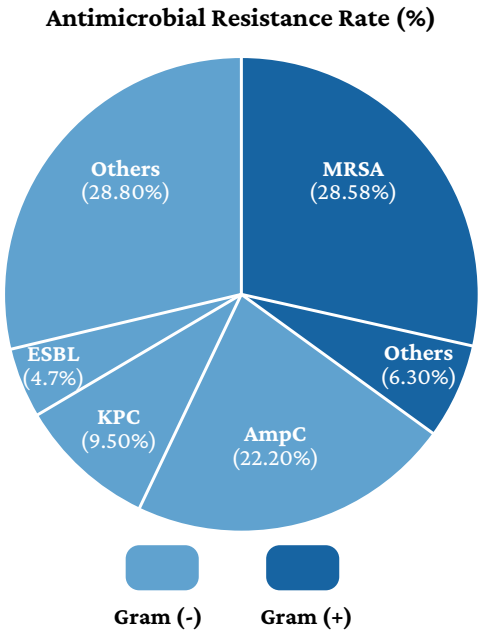

Figure 2. Distribution of antimicrobial resistance patterns in the isolates identified.

Discussion

In the present study, being male (aOR: 2.29, 95%CI: 1.2-4.3; *p*=0.003), time (days) on IMV (aOR: 1.05, 95%CI: 1.02-1.08; *p*=0.000), and the use of neuromuscular blockers (aOR: 3.58, 95%CI: 1.35-9.4; *p*=0.01) were risk factors for VAP.

These factors were initially described as risk factors for VAP in small cohorts of patients with C-ARDS, such as the study by Razazi *et al.*,[10] conducted in France in 172 patients on IMV (90 with C-ARDS and 82 with non-COVID-19 ARDS), in which male sex was associated with the development of VAP [OR: 2.2, 95%CI:1.04-4.5; *p*=0.04). Subsequently, other studies with larger and more representative samples demonstrated the same results, such as the multicenter study conducted by Garnier *et al.*[33] in 3 388 critically ill COVID-19 patients admitted to 149 ICUs in Europe, in which male sex (HR: 1.26, 95%CI: 1.09-1.46; *p*=0.002), use of neuromuscular blockers (HR: 0.89, 95%CI: 0.76-0.998, *p*=0. 046), and severity of respiratory failure at the time of IMV initiation (HR: 0.99, 95%CI: 0.98-0.99 per 10 mmHg increase in PaO_2/FiO_2 ratio; *p*=0.001) —which is directly related to IMV duration—, were risk factors for VAP.

In critically ill patients on IMV, the development of nosocomial pneumonia is favored by the excessive inflammatory response of the host. In COVID-19 patients, this response contributes to a greater susceptibility to bacterial superinfection and the interaction of multiple factors that generate an imbalance in the host-virus relationship, such as bacterial colonization of the endotracheal or orotracheal tube, alteration of the defense mechanisms of the respiratory system, the positive pressure exerted by IMV (which, in turn, reduces cilia movements of the respiratory mucosa), and the loss of airway reflex mechanisms such as coughing and expectoration.[34,35]

In this regard, in the present study, time (in days) on IMV and the use of neuromuscular blockers, factors that promote the development of abnormalities in the reflex mechanisms of the airway, were significantly associated with an increased risk of VAP.

In the case of time on IMV, it is known that patients with C-ARDS require more days of IMV than those with non-COVID-19 ARDS. For example, according to the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE), conducted on 3 022 ARDS patients admitted during the winter of 2014 to 459 ICUs from 50 countries in 5 continents, the median duration of IMV was 8 days (IQR: 4-16 days).[36] Also, according to the systematic review by Fumagali *et al.*[9] (16 studies; 6 484 patients), the median duration of IMV in patients with C-ARDS is 10 days (IQR: 6-17 days), and, on a par with our findings, Fumagali *et al.*[9] report that the duration of IMV is an independent risk factor for VAP in patients with C-ARDS. Furthermore, studies such as the one performed by Maes *et al.*[37] in England in 225 patients on IMV (81 COVID-19 patients and 144 non-COVID-19 patients) point out that these patients have a significantly higher risk of developing VAP than those without this infection (Cox proportional hazards rate: 2.01, 95%CI: 1.14-3.54; *p*=0.0015), with an incidence density of 28/1 000 days on IMV versus 13/1 000 for patients without COVID-19 (*p*=0.009).

Another matter to consider regarding the association between the duration of IMV and the risk of VAP found in our study is that the risk increased by 5% for each day on IMV (aOR: 1.05, 95%CI: 1.02-1.08). This finding is consistent with other studies such as the one conducted in Turkey by Ekiz *et al.*[38] in 471 patients with COVID-19 admitted to the ICU, in which the duration of IMV was associated with the development of VAP (OR: 1.199, 95%CI: 1.088-1.322; *p*<0.001). Accordingly, it has been described that the early requirement of IMV in patients with C-ARDS is evidence of a greater severity of pulmonary disease and, consequently, a longer exposure time of the airways to biotrauma, which may lead to a higher risk of bacterial superinfection and, therefore, VAP.[39]

In view of the foregoing, similar to non-COVID-19 ARDS, it is essential to prevent the need for IMV in patients with C-ARDS and, if IMV is necessary, to try to reduce the duration of IMV as much as possible. Moreover, measures such as reducing the intensity of sedation and early use of assisted and spontaneous ventilatory modes are also helpful in shortening the duration of IMV.[40]

Concerning the association between the use of neuromuscular blockers and an increased risk of VAP, our findings are in line with those reported by Wu *et al.*[41] in a study conducted with data from the 1 000 patients with ARDS registered in the Early versus Delayed Enteral Nutrition randomized controlled trial, in which the use of these drugs behaved as an independent risk factor for the development of VAP (OR: 2.570, 95%CI: 1.355-4.7171; p=0.003). However, our findings differ from what was reported by Garnier *et al.*[33] in a study conducted on data from 3 888 COVID-19 patients on IMV with at least 48 hours of admission to 148 ICUs in France, Switzerland and Belgium, in which, in fact, the use of neuromuscular blockers was associated with a lower incidence of VAP due to COVID-19 (HR: 0.89 [0.76-0.998]). Hence, further studies are needed to determine whether the administration of neuromuscular blockers could be a risk factor for the development of VAP in COVID-19 patients on IMV.

Also in the present study, biological sex was the only patient-related factor that showed a significant association with the risk of VAP, as male sex was independently associated with the development of VAP. This association of male sex as a risk factor for VAP in COVID-19 patients on IMV has been reported in several studies such as that of Garnier *et al.*[33] (HR: 1.26, 95%CI: 1.09-1.46). Furthermore, according to the study by Solis *et al.*,[42] conducted in Mexico in 1 540 patients with severe COVID-19, male sex was independently associated with the development of hospital-acquired infections (HAI) (HR: 1.52, 95%CI: 1.03-2.24), with HAP (hospital-acquired pneumonia)/VAP being the most common HAI.

Additionally, as evidenced above, this finding has not only been reported in critically ill COVID-19 patients,[10, 33, 42] but also in pre-pandemic times. For example, Forel *et al.*,[43] in a multicenter study performed in 339 patients with ARDS and requiring IMV admitted to 20 ICUs in France, and Bornstain *et al.*,[44] in a study also conducted in France in 747 critically ill patients requiring mechanical ventilation, found that being male was independently associated with the development of VAP (HR: 2.39, 95%CI: 1.39-4.14, p=0.002 and OR: 2.06, 95%CI: 1.18-3.63; p=0.003). In turn, Tejerina *et al.*,[45] in a multicenter study conducted in 2 897 adults admitted to 361 ICUs in 20 countries who were on mechanical ventilation for more than 12 hours, reported that men had a 30% higher probability of VAP compared to women (OR: 1.3, 95%CI: 1.0-1.16; p<001). Likewise, similar findings have been reported in specific clinical scenarios; for instance, Sharpe *et al.*[46] report that in their cohort of 854 trauma patients who presented with VAP, 79% were males. These findings show a general trend of susceptibility to the occurrence of VAP in men.

In this regard, although the mechanisms involved are not clear, it has been proposed that differences in the risk of VAP between men and women may be related to differences in sex hormones, to sex-related polymorphisms affecting immune responses to bacterial agents, differences in the distribution of infectious pathogens between men and women, and differences in the presence of chronic comorbidities.[43]

Our research has several strengths, namely: i) its nested design ensures that the included cases and controls come from a representative cohort; ii) the selection of controls, based on the timing of case occurrence, allows controlling time-related confounding factors related to patient management (supplies, treatments, protocols available at the time of case occurrence, among others); and iii) the consecutive selection of cases from the HUN hospital infection committee reports ensures independent selection.

On the contrary, its retrospective design is its main limitation, given that such a study design often induces measurement biases in the data reported in the medical records, does not allow ensuring that all patients were studied and treated with the same effort, and does not allow assessing key confounding factors such as those related to the implementation of VAP prevention protocols (e.g., use of mouth rinses, compliance with head-of-bed elevation, accurate timing of respiratory therapies, etc.)[47,48] Notwithstanding the above, we believe that this research provides important data on this phenomenon in Latin America, a region where there is not much information on this subject.

Conclusion

In the present study, male sex, duration (days) of IMV, and the use of neuromuscular blockers behaved as risk factors for VAP in patients with C-ARDS.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgments

The authors would like to thank the Hospital Universitario Nacional de Colombia and its research committee for the epidemiological advice provided during the research process.

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