Cirugía Cardiovascular xxx (xxxx) xxx-xxx

Original Article

Demographic, clinical, surgical characteristics, and outcomes of postoperative pneumonia in cardiac surgery patients at a Latin American tertiary care center

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ABSTRACT

Background: Cardiac surgeries, which include procedures for congenital heart defects, valve replacements, and coronary artery bypass grafting, are increasingly performed worldwide. Despite extensive data from regions such as the U.S. and Europe, Latin American data remain scarce. Postoperative pneumonia, a significant complication in cardiac surgery, poses serious risks including high mortality and extended critical care resource use.

Methods: This retrospective, cross-sectional study evaluated 485 patients who underwent cardiac surgery with extracorporeal circulation at the National Institute of Cardiology Ignacio Chávez between June 1, 2022, and December 31, 2023. Patients were included based on specific criteria, and those with incomplete records or other infections were excluded. Data collection involved reviewing medical records and imaging studies, with statistical analyses including logistic regression to identify risk factors and outcomes associated with postoperative pneumonia.

Results: Out of 485 patients, 45 developed pneumonia after surgery. Risk factors included age over 60, cerebrovascular disease, combined coronary bypass and aortic valve replacement, and blood transfusions. Pneumonia was associated with severe complications, including higher mortality rates, extended ICU and hospital stays, and increased mechanical ventilation. Chest X-rays were the primary diagnostic tool, and gram-negative bacteria were the most frequently identified pathogens.

Conclusions: Postoperative pneumonia presents a serious challenge in cardiac surgery patients, with substantial impacts on patient outcomes and healthcare resources. Early diagnosis and targeted treatment are crucial, emphasizing the need for improved prevention and management strategies.

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Características demográficas, clínicas y quirúrgicas y resultados de la neumonía postoperatoria en pacientes de cirugía cardíaca en un centro de atención terciaria en América Latina

RESUMEN

Palabras clave: Cirugía cardíaca Neumonía postoperatoria Neumonía nosocomial Antecedentes: Las cirugías cardíacas, que incluyen procedimientos para defectos cardíacos congénitos, reemplazos de válvulas y bypass de arterias coronarias, se realizan cada vez más en todo el mundo. A pesar de la extensa información disponible en regiones como EE. UU. y Europa, los datos en América Latina son escasos. La neumonía postoperatoria, una complicación significativa en la cirugía cardíaca, plantea graves riesgos, incluyendo alta mortalidad y un uso prolongado de recursos críticos.

Métodos: Este estudio retrospectivo y transversal evaluó a 485 pacientes que se sometieron a cirugía cardíaca con circulación extracorpórea en el Instituto Nacional de Cardiología Ignacio Chávez entre el 1 de junio del 2022 y el 31 de diciembre del 2023. Se incluyó a pacientes según criterios específicos, excluyendo a aquellos con registros incompletos o infecciones adicionales. La recolección de datos implicó la revisión de historias clínicas y estudios de imagen, con análisis estadísticos que incluyeron regresión logística para identificar factores de riesgo y resultados asociados con la neumonía postoperatoria.

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; EUROSCORE II, European System for Cardiac Operative Risk Evaluation II; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association; OR, odds ratio; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

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A. Sotelo-Soleno, G.L. Hernández-González, R. Gopar-Nieto et al.

Cirugía Cardiovascular xxx (xxxx) xxx-xxx

Resultados: De los 485 pacientes, 45 desarrollaron neumonía después de la cirugía. Los factores de riesgo incluyeron edad superior a 60 años, enfermedad cerebrovascular, bypass coronario combinado con reemplazo de válvula aórtica y transfusiones de sangre. La neumonía se asoció a complicaciones severas, incluyendo tasas de mortalidad más altas, estancias prolongadas en UCI y hospitalización, y un aumento en la ventilación mecánica. Las radiografías de tórax fueron la herramienta de diagnóstico principal y las bacterias gramnegativas fueron los patógenos más frecuentemente identificados.

Conclusiones: La neumonía postoperatoria representa un desafío serio en pacientes de cirugía cardíaca, con impactos sustanciales en los resultados del paciente y los recursos de salud. El diagnóstico temprano y el tratamiento dirigido son cruciales, lo que enfatiza la necesidad de estrategias mejoradas de prevención y manejo.

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Introduction

Background

Cardiac surgery encompasses a broad range of interventions aimed at treating heart conditions, including congenital defect corrections, valve disease repair or replacement, coronary artery bypass grafting, heart failure device implantation, and other complex cardiac disease treatments. The goal is to improve cardiac function, patient quality of life, and overall prognosis. Cardiac surgery has a significant impact on patient outcomes, with a global increase in the number of procedures. For instance, valve surgeries numbered 58,000 in 2017, projected to rise to 850,000 by 2050.¹ Coronary artery bypass surgeries are about 400,000 annually.² While data from the United States, Canada, and Europe indicate coronary revascularization as the most common procedure,³ Latin America lacks sufficient evidence. Studies from Mexico's National Institute of Cardiology suggest valve surgeries are most prevalent.⁴ This period also sees advancements in cardiac surgery, postoperative care, and management of complications, with a growing elderly population undergoing complex cardiovascular procedures. Nosocomial infections, particularly postoperative pneumonia, are a leading cause of non-cardiac mortality and are resource-intensive in critical care settings.⁵

Importance

Postoperative pneumonia, defined by radiographic or tomographic infiltrates and symptoms suggestive of infection,⁶ falls under nosocomial pneumonia, which can overlap with ventilator-associated pneumonia. The incidence of postoperative pneumonia in cardiac surgery patients ranges from 1.2 to 12.4%, with some studies documenting a 20% incidence in coronary revascularization patients linked to increased mortality. Latin American evidence is sparse, though existing data show significant mortality, extended ventilator use, and longer hospital stays associated with postoperative pneumonia.^{7,8} Effective prevention strategies such as chlorhexidine use and intensive pulmonary physiotherapy have been shown to reduce pneumonia incidence and related outcomes.^{9,10} Identifying protective factors and developing predictive models are crucial to managing this complication.^{11–13}

Goals of investigation

This study aims to analyze the demographic, clinical, and surgical differences in patients who developed pneumonia during the postoperative period of cardiac surgery, assess associated risk factors, and their impact on adverse outcomes. It seeks to fill the gap in robust evidence in Latin America regarding how postoperative pneumonia affects cardiac surgery outcomes. Understanding

these factors will aid in developing targeted prevention strategies to improve patient outcomes and guide future research in this area.

Methods

The study was conducted as an observational analytical investigation with a retrospective data collection approach and a cross-sectional design to measure phenomena at a specific point in time. The assessment was carried out with an open blinding method, meaning there was no blinding of the evaluator.

The study focused on patients who were 18 years or older, regardless of gender, and who underwent cardiac surgery with extracorporeal circulation at the National Institute of Cardiology Ignacio Chávez.

A non-probabilistic sampling method was employed, including 485 adult patients who had cardiac surgery at the National Institute of Cardiology Ignacio Chávez between June 1, 2022, and December 31, 2023.

Inclusion criteria for the study were: patients who underwent cardiac surgery with extracorporeal circulation at the National Institute of Cardiology Ignacio Chávez, patients who were 18 years or older, and patients of any gender. Exclusion criteria included: patients who had less than 12 h of stay in the Cardiovascular Intensive Care Unit and patients who died in the operating room during the surgery. Criteria for removal from the study involved: patients with incomplete medical records and patients who developed another type of infectious complication other than pneumonia.

Data were collected through a detailed review of both electronic and physical medical records, as well as electronic imaging studies, to gather demographic, clinical, and surgical information, along with outcomes for the patients included in the study.

For statistical analysis, normality of continuous variables was assessed using the Shapiro–Wilk test. Parametric data were reported as mean \pm standard deviation, while non-parametric data were reported as median with interquartile range (IQR). Comparisons of continuous variables were made using the Mann–Whitney U test. Categorical variables were described using frequencies and percentages, and chi-square and Fisher's exact tests were used for comparisons based on expected values. A logistic regression model, adjusted for age and gender, was created to identify predictors of adverse events. Statistical significance was set at P<0.05 for all analyses, and the analysis was conducted using STATA version 14.

Ethics approval and consent to participate

The local institutional research and ethics committees waived approval for this study. Informed consent was obtained from all individual participants included in the study.

A. Sotelo-Soleno, G.L. Hernández-González, R. Gopar-Nieto et al.

Cirugía Cardiovascular xxx (xxxx) xxx-xxx

Table 1Baseline characteristics.

Variable	Total n = 485	Without POP n = 440	POP n = 45	P value
Momen N(%)	208(42.9)	190(43.2)	18(40)	0.75
Women, N (%)	208(42.9) 277(57.19)	250(56.8)	27(60)	0.75
Men, N (%) Age (years)	57(45-65)	57(45–65)	62(54–70)	< 0.001
Median (IOR)	37(43-63)	37(43-63)	62(34=70)	<0.001
()	C0 F(C0, 70)	C0 F(C0, 70)	C9(C0, 74)	0.70
Height (m)	68.5(60–78)	68.5(60-78)	68(60-74)	0.76
Median (IQR)	1 (2/1 FF 1.7)	1.62(1.55, 1.60)	1 (2/1 57 1 72)	0.72
Weight (kg)	1.62(1.55–1.7)	1.62(1.55–1.69)	1.63(1.57–1.72)	0.73
Median (IQR)	20.11(22.4.20.0)	26 1/22 4 20)	25.0(22.4.20)	0.00
Body mass index (kg/m ²)	26.11(23.4–28.9)	26.1(23.4–29)	25.9(23.4–28)	0.96
Median (IQR)	50(40.5)	50(11.4)	2/1.4	0.00
Hypothyroidism, N (%)	52(10.7)	50(11.4)	2(4.4)	0.20
Myocardial infarction, N (%)	49(10.1)	46(10.4)	3(6.7)	0.60
Heart failure, N (%)	127(26.2)	116(26.4)	11(24.4)	0.78
Atrial fibrillation, N (%)	90(18.6)	81(18.4)	9(20)	0.79
Cerebrovascular disease, N (%)	25(5.1)	22(5)	3(6.7)	0.49
NYHA functional class, N (%)				
I	65(13.4)	60(13.7)	5(11.1)	0.29
II	297(61.4)	268(61)	29(64.4)	
III	109(22.5)	101(23)	8(17.8)	
IV	13(2.7)	10(2.3)	3(6.7)	

NYHA: New York Heart Association; IQR: interquartile range; POP: postoperative pneumonia.

Table 2Surgical characteristics.

Variable	Total n = 485	Without POP $n = 440$	POP <i>n</i> = 45	P value
Aortic valve replacement, N (%)	142(29.3)	132(30)	10(22.2)	0.27
Coronary artery bypass graft, N(%)	75(15.5)	71(16.1)	4(8.9)	0.20
Mitral valve replacement, $N(\%)$	46(9.5)	39(8.9)	7(15.6)	0.14
Mitral valve replacement + tricuspid valve replacement, N (%)	26(5.4)	22(5)	4(8.9)	0.27
Aortic valve replacement + mitral valve replacement, $N(\%)$	31(6.4)	30(6.8)	1(2.2)	0.34
Coronary artery bypass graft + aortic valve replacement, $N(\%)$	22(4.5)	17(3.9)	5(11.1)	0.04
Bentall procedure, N (%)	25(5.1)	22(5)	3(6.7)	0.49
Other surgery, <i>N</i> (%)	121(24.9)	109(24.8)	12(26.7)	0.78
Extracorporeal circulation time (min)	144(112-185)	143(108-183)	159(117-240)	0.02
Median (IQR)				
Aortic clamping (min)	100(76-126)	100(76-124)	101(82-156)	0.12
Median (IQR)				
EuroSCORE 2	1.8(0.9-3.4)	1.7(0.9-3.3)	2.5(1.2-4.9)	0.02
Median (RIC)				

IQR: interquartile range; POP: postoperative pneumonia.

Consent for publication

Written informed consent for patient information and images to be published was provided by the patient or a legally authorized representative.

Results

From June 1, 2022, to December 31, 2023, a total of 485 patients who met the inclusion criteria were recruited from the Cardiovascular Intensive Care Unit. Among these, 440 patients were in the control group without pneumonia, while 45 developed postoperative pneumonia.

Demographic characteristics

The average age of the patients was 57 years, with 42.9% being female. There were no significant differences in weight, height, or body mass index between the groups. Comorbidities were common among the population: 43.4% had hypertension, and 23.1% had type 2 diabetes mellitus. The most frequent cardiac conditions included heart failure at 26.2% and atrial fibrillation at 18.6%. Most patients were classified as NYHA functional class II (61.4%). A significant clinical and statistical difference was observed in age (62 years vs.

57 years) between patients who developed pneumonia and those who did not (Table 1).

Surgical characteristics

The most common surgery was aortic valve replacement, followed by coronary bypass. There were clinically and statistically significant differences in patients who underwent coronary bypass combined with aortic valve replacement (11% vs. 3.9%), as well as in extracorporeal circulation time (159 min vs. 143 min) and EUROSCORE II (1.7% vs. 2.5%) among patients who developed hospital-acquired pneumonia (Table 2).

Hemodynamic characteristics

Significant differences were noted in hemodynamic parameters at 6 h postoperatively. The cardiac index $(2.1 \, L/min/m^2 \, vs. \, 1.9 \, L/min/m^2)$, oxygen delivery $(526 \, mL/min/m^2 \, vs. \, 435 \, mL/min/m^2)$, and oxygen consumption $(130 \, mL/min/m^2 \, vs. \, 124 \, mL/min/m^2)$ were lower in patients who developed pneumonia. Conversely, lactate levels at 6 h $(2.4 \, vs. \, 3.5)$ and capillary refill time at 6 h $(2 \, vs. \, 3)$ were higher in the pneumonia group $(Table \, 3)$.

A. Sotelo-Soleno, G.L. Hernández-González, R. Gopar-Nieto et al.

Cirugía Cardiovascular xxx (xxxx) xxx-xxx

Table 3 Hemodynamic parameters (6 h after surgery).

Variable	Total n = 485	Without POP n = 440	POP n = 45	P value
Cardiac index (L/min/m²)	2.1(1.6-2.6)	2.1(1.6-2.6)	1.9(1.4-2.3)	0.04
Median (IQR)				
Central venous pressure (mmHg)	9(8-11)	9(8-11)	10(8-11)	0.18
Median (IQR)				
Systemic vascular resistance index	2540(1971-3210)	2506(1964-3159)	2884(2120-3505)	0.12
(dynes-sec/cm ⁵ /m ²)				
Median (IQR)				
Global oxygen delivery	510.1(394.3-646.3)	526.3(398.5-652.9)	435.8(330.6-524.2)	< 0.001
(mL/min/m ²)				
Median (IQR)				
Oxygen consumption	128.3(123.5–185.1)	130.5(123.9–189.7)	124.8(115–170)	0.03
$(mL/min/m^2)$				
Median (IQR)				
Lactate	2.5(1.7–4)	2.4(1.7–3.8)	3.5(2.5–6.2)	<0.001
Median (IQR)	0(0.0)	0(0.0)	0(0.0)	
Capillary refill time (seg)	2(2-3)	2(2-3)	3(2-3)	<0.001
Median (IQR)				

IQR: interquartile range; POP: postoperative pneumonia.

Table 4
Outcomes.

Variable	Total <i>n</i> = 485	Without POP $n = 440$	POP n = 45	P value
Mediastinal bleeding, N (%)	56(11.5)	45(10.2)	11(24.4)	<0.001
Low cardiac output syndrome, $N(\%)$	60(12.4)	52(11.8)	8(17.8)	0.24
Vasoplegic syndrome, N (%)	33(6.8)	25(5.7)	8(17.8)	< 0.001
Hipovolemia, N (%)	185(38.3)	167(37.9)	19(42.2)	0.57
Delirium, N(%)	58(12)	33(7.5)	25(55.6)	< 0.001
Cerebrovascular disease, N(%)	18(3.7)	12(2.7)	6(13.3)	< 0.001
Transfusion, N (%)	236(48.8)	197(44.9)	39(86.7)	< 0.001
Acute kidney injury, N (%)	149(30.8)	117(26.6)	32(71.1)	< 0.001
Renal replacement therapy, $N(\%)$	29(6)	17(3.9)	12(26.7)	< 0.001
Liver injury, N (%)	61(12.6)	48(10.9)	13(28.9)	< 0.001
Atrial fibrillation, N (%)	77(15.9)	62(14.1)	15(33.3)	< 0.001
In-hospital mortality, N (%)	29(6)	18(4.1)	11(24.4)	< 0.001
Days in intensive care unit Median (IOR)	3(2-4)	3(2-4)	6(4–13)	<0.001
Days with mechanical ventilation	1(1-1)	1(1-1)	3(1-8)	< 0.001
Median (IQR)				
Days of hospitalization	10(7-17)	9(7-15)	20(14-36)	< 0.001
Median (IQR)				
SOFA at 24 h	5(3-7)	4(3-6)	8(5-10)	< 0.001
Median (IQR)				
SOFA at 72 h	3(2-5)	3(2-5)	7(5-9)	< 0.001
Median (IQR)				

IQR: interquartile range; POP: postoperative pneumonia.

Outcomes

There were significant clinical and statistical differences in outcomes among patients who developed postoperative pneumonia. These included a higher incidence of vasoplegic syndrome (17.8% vs. 11.8%), delirium (55.6% vs. 7.5%), cerebrovascular disease (13.3% vs. 2.7%), blood transfusion needs (86.7% vs. 44.9%), acute kidney injury (71.1% vs. 26.6%), need for renal replacement therapy (26.7% vs. 3.9%), liver damage (28.9% vs. 10.9%), postoperative atrial fibrillation (33.3% vs. 14.1%), and in-hospital mortality (24.4% vs. 4.1%). Additionally, patients with postoperative pneumonia had longer ICU stays (6 days vs. 3 days), more days on mechanical ventilation (3 days vs. 1 day), longer total hospitalizations (20 days vs. 9 days), and higher SOFA scores at 24 h (8 points vs. 4 points) and 72 h (7 points vs. 3 points) compared to the control group (Table 4).

The logistic regression model identified several perioperative variables (preoperative, intraoperative, and immediate postoperative) that predict the development of postoperative pneumonia. These variables included blood transfusion (OR 7.98; 95% CI 3.31–19.24), cerebrovascular disease (OR 5.46; 95% CI 1.94–15.34),

vasoplegic syndrome (OR 3.58; 95% CI 1.51–8.51), mediastinal hemorrhage (OR 2.83; 95% CI 1.34–5.99), coronary bypass combined with aortic valve replacement (OR 3.11; 95% CI 1.09–8.87), and age over 60 years (OR 2.24; 95% CI 1.19–4.22) Additionally, patients who developed pneumonia had increased risks of delirium (OR 15.4; 95% CI 7.7–30.56), renal replacement therapy (OR 9.02; 95% CI 3.97–20.48), acute kidney injury (OR 6.77; 95% CI 3.43–13.35), liver damage (OR 3.30; 95% CI 1.62–6.73), postoperative atrial fibrillation (OR 3.04; 95% CI 1.54–5.97), and higher in-hospital mortality (OR 7.56; 95% CI 3.30–17.31) (Table 5).

Clinical, imaging, microbiological and therapeutic characteristics of pneumonia episodes

Clinical and imaging characteristics

Among the patients who developed pneumonia, 66% had a preoperative hospital stay, with a median duration of 5 days. Clinical diagnosis was the most common method, being positive in 69% of the cases. For imaging diagnosis, the distribution was as follows: 64.3% were diagnosed via chest X-ray, 28.6% through CT scans,

A. Sotelo-Soleno, G.L. Hernández-González, R. Gopar-Nieto et al.

Cirugía Cardiovascular xxx (xxxx) xxx-xxx

Table 5Logistic regression model.

Variable	OR	95% CI	P
Perioperative variables that predict the development of POP			
Age >60 years	2.24	1.19-4.22	0.012
Coronary artery bypass graft + aortic valve replacement	3.11	1.09-8.87	0.03
Mediastinal bleeding	2.83	1.34-5.99	0.006
Vasoplegic syndrome, N (%)	3.58	1.51-8.51	0.004
Cerebrovascular disease	5.46	1.94-15.34	< 0.001
Transfusion	7.98	3.31–19.24	<0.001
Outcomes associated with POP			
Delirium	15.4	7.7–30.56	< 0.001
Renal replacement therapy	9.02	3.97-20.48	< 0.001
Acute kidney injury	6.77	3.43-13.35	< 0.001
Liver injury	3.30	1.62-6.73	0.001
Atrial fibrillation	3.04	1.54-5.97	0.001
In-hospital mortality	7.56	3.30–17.31	<0.001

OR: odds ratio; CI: confidence interval.

Table 6Clinical and radiological characteristics of patients with pneumonia.

Hospitalization prior surgery	Variable	N (%)
Median (IQR) Radiography 27(64.3) Tomography 12(28.6) Ultrasound 7(16.7) Consolidation 25(59.5) Ground-glass opacification 25(59.5) Infiltrate 12(28.6) Clinical diagnosis 29(69) Microbiological diagnosis 28(66.7) Systemic inflammatory response syndrome 35(83.3) Leucocytes (×10°/L) 48(10.9–18.6) Median (IQR) 86(81–90) Median (IQR) 157(96–200) Median (IQR) 157(96–200) Median (IQR) 8(5–11) Median (IQR) 212(160–268) Median (IQR) 212(160–268) Median (IQR) 27(64.3) Widdian (IQR) 27(64.3) Without mechanical ventilation at diagnosis 25(61) With mechanical ventilation at diagnosis 16(38.1) Need of reintubation 7(16.7) Acute respiratory distress syndrome 15(35.7) Pleural effusion 15(35.7) Sepsis 29(69) Septic shock<	Hospitalization prior surgery	28(66.7)
Radiography 27(64.3) Tomography 12(28.6) Ultrasound 7(16.7) Consolidation 25(59.5) Ground-glass opacification 25(59.5) Infiltrate 12(28.6) Clinical diagnosis 29(69) Microbiological diagnosis 28(66.7) Systemic inflammatory response syndrome 35(83.3) Leucocytes (×10.9/L) 14.8(10.9-18.6) Median (IQR) 86(81-90) Median (IQR) 157(96-200) Median (IQR) 8(5-11) Median (IQR) 8(5-11) Median (IQR) 212(160-268) Median (IQR) 13(30.9) Diagnosis at hospitalization floor 13(30.9) Diagnosis at ICU 27(64.3) Without mechanical ventilation at diagnosis 25(61) With mechanical ventilation at diagnosis 16(38.1) Need of reintubation 7(16.7) Acute respiratory distress syndrome 15(35.7) Pleural effusion 15(35.7) Sepsis 29(69) Septic shock 18(42.9)	Days to diagnosis	5(3-7)
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Sepsis 29(69) Septic shock 18(42.9)	Acute respiratory distress syndrome	15(35.7)
Septic shock 18(42.9)	Pleural effusion	15(35.7)
1	Sepsis	29(69)
Need of tracheostomy 2(4.8)	Septic shock	18(42.9)
	Need of tracheostomy	2(4.8)

IQR: interquartile range.

and 16.7% with ultrasound. The most frequent imaging patterns were consolidation and ground-glass opacities (59.5%), followed by infiltrates (28.6%). Microbiological diagnosis was achieved in only 66.7% of the cases. Biochemical and clinical characteristics of patients with pneumonia included a median white blood cell count of $14.8 \times 10^3 / \mu l$ (with 86% neutrophils) and a median C-reactive protein (CRP) level of 157 mg/dl. The median PaO₂/FiO₂ ratio was 212 mmHg. The most common setting for pneumonia diagnosis was the Cardiovascular Critical Care Unit (64.3%), followed by general hospitalization floor (30.9%). At the time of diagnosis, 61% of patients were extubated, and reintubation was necessary in 16.7% of the cases. Patients who developed pneumonia experienced the following complications, listed in descending order: sepsis, septic shock, acute respiratory distress syndrome (ARDS), pleural effusion, and the need for tracheostomy (Table 6).

Table 7Description of the antimicrobial therapy.

Variable	N (%)
Ceftriaxone	15(35.7)
Days of ceftriaxone treatment	6(3-8)
Median (IQR)	
Cefepime	11(26.2)
Days of cefepime treatment	7(4-9)
Median (IQR)	
Levofloxacin	10(23.8)
Days of levofloxacin treatment	10(7–13)
Median (IQR)	
Moxifloxacin	2(4.8)
Days of moxifloxacin treatment	4.5(1-8)
Median (IQR)	
Meropenem	7(16.7)
Days of meropenem treatment	12(8-14)
Median (IQR)	
Ertapenem	7(16.7)
Days of ertapenem treatment	7(3–13)
Median (IQR)	
Vancomycin	13(30.9)
Days of vancomycin treatment	6(4-10)
Median (IQR)	

IQR: interquartile range.

Microbiological characteristics

The most frequently identified microbiological agents were: *Klebsiella* spp. (38.1%), *Pseudomonas* spp. (19%), *Enterobacter* spp. (19%), *Escherichia coli* (14.3%), *Acinetobacter* spp. (7.1%), *Haemophilus* spp. (4.9%), *Stenotrophomonas* spp. (4.8%), with *Staphylococcus aureus* and *Candida* spp. both at 2.4%. The incidence of multidrug resistance was 33.3%. The most commonly used antibiotics, in descending order, were: ceftriaxone, cefepime, levofloxacin, moxifloxacin, meropenem, ertapenem, vancomycin, and inhaled amikacin (Table 7).

Discussion

In this retrospective observational study, several significant risk factors for developing pneumonia in postoperative patients in the intensive care unit (ICU) were identified. These factors include being over 60 years old, a history of cerebrovascular disease, undergoing coronary bypass surgery with aortic valve replacement, perioperative complications such as mediastinal hemorrhage or vasoplegic syndrome, and the use of blood transfusions. However, many demographic variables and cardiovascular histories did not show a statistically significant association with the risk of postoperative pneumonia, such as heart failure or previous myocardial infarction, as well as functional class.

A. Sotelo-Soleno, G.L. Hernández-González, R. Gopar-Nieto et al.

Cirugía Cardiovascular xxx (xxxx) xxx-xxx

Regarding clinical diagnosis, chest X-rays remained the preferred method due to their accessibility and cost compared to other imaging studies like CT scans or ultrasounds. The most common radiographic patterns found were ground-glass opacities and consolidation, which are typical in patients with ICU stays.

It is noteworthy that only 35% of pneumonia cases presented with systemic inflammatory response syndrome (SIRS). In contrast, the median SOFA score was 8 points, with significant elevations in leukocytes and C-reactive protein (CRP) at the time of diagnosis, as well as a markedly reduced median PaO₂/FiO₂ ratio of 212 mmHg. These findings suggest that combining the SOFA score with elevated acute-phase reactants and respiratory distress, indicated by the marked reduction in the PaO₂/FiO₂ ratio, might have higher sensitivity than SIRS for diagnosing postoperative pneumonia. However, comparisons with control groups are needed to confirm this increased sensitivity, and it can be assumed that this combination may have lower specificity than SIRS due to the acute pro-inflammatory state common in postoperative patients, especially those with aortic clamping.

Microbiological diagnosis was not achieved in 33.3% of cases, leading to empirical antibiotic treatment without certainty of the causative microorganism, similar to previous studies of hospital-acquired pneumonia. In contrast to other studies where gram-positive bacteria were common, our study found these to be virtually absent. Gram-negative bacteria predominated in 97% of isolated cases, and a high prevalence (33.3%) of multidrug resistance was identified, similar to previous studies. This underscores the importance of considering specific antimicrobial regimens targeted at gram-negative organisms, even empirically, and evaluating the need for escalation to carbapenems early.

Most studied variables showed significant associations with complications in the context of postoperative pneumonia, reflecting worsened prognosis and a considerable increase in in-hospital morbidity and mortality. Specifically, blood transfusion emerged as the most significant risk factor, increasing the risk nearly 8-fold compared to other centers where the risk increase was lower.

Study limitations

This study was conducted at a single medical center and should be replicated at other centers to assess the protocol's reproducibility. In addition, study outcomes should be interpreted with caution due to the small sample size and because it was performed in a specific subpopulation (postoperative cardiac surgery patients). Thus, the findings may not generalize to all critical care patients.

Conclusions

Diagnosing pneumonia in postoperative cardiac surgery patients presents a complex challenge due to the diversity of factors involved. It is crucial to employ multiple diagnostic methods simultaneously for patients with risk factors, initiate early and empirical antibiotic treatment, and actively search for the causative agent. The risks associated with not acting precisely and promptly outweigh the costs involved.

CRediT authorship contribution statement

ASS: data collection, writing the original draft; GLHG: data collection; RGN: methodology, analysis; GRV: review; DMS: original idea, methodology, analysis and writing the original draft, review and editing.

Ethical approval

The local institutional research and ethics committees (Instituto Nacional de Cardiología Ignacio Chávez) waived approval for this study.

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Conflict of interest

The authors declare that there are no conflicts of interest to disclose.

Data availability

To all the staff of the Cardiovascular Critical Care Unit of the Instituto Nacional de Cardiología Ignacio Chávez.

The data that support the findings of this study are available on request from the corresponding author [DMS].

References

- Lancellotti P, Galderisi M, Donal E, Edvardsen T, Delgado V, Dulgheru R, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17:589–90, http://dx.doi.org/10.1093/ehjci/jew007.
- Alexander JH, Smith PK. Coronary-artery bypass grafting. N Engl J Med. 2016;374:1954–64, http://dx.doi.org/10.1056/NEJMra1406945.
 D'Agostino RS, Jacobs JP, Badhwar V, Fernández FG, Paone G, Wormuth DW,
- 3. D'Agostino RS, Jacobs JP, Badhwar V, Fernández FG, Paone G, Wormuth DW, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2018 update on outcomes and quality. Ann Thorac Surg. 2018;105:15–23, http://dx.doi.org/10.1016/j.athoracsur.2017.08.034.
- 4. Rodríguez A, García M, Bucio E, Baranda F. Análisis de mortalidad y estancia hospitalaria en cirugía cardiaca en México 2015: datos del Instituto Nacional de Cardiología. Arch Cardiol Mex. 2018;88:397–402, http://dx.doi.org/10.1016/j.acmx.2018.02.003.
- Costa MAC, Botta VC, Schafranski MD, Reis ESS, Kuchler S, Souza ACMF. Influence of preoperative serum albumin levels on postoperative complications in cardiac surgery. Res Soc Dev. 2022;11, http://dx.doi.org/10.33448/rsd-v11i10.33185, e534111033185.
- Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint task-force on perioperative outcome measures. Eur J Anaesthesiol. 2015;32:88–105, http://dx.doi.org/10.1097/EJA.000000000000234.
- Ibañez J, Riera M, Amezaga R, Herrero J, Colomar A, Campillo-Artero C, et al. Long-term mortality after pneumonia in cardiac surgery patients: a propensity-matched analysis. J Intensive Care Med. 2016;31:34–40, http://dx.doi.org/10.1177/0885066614558271.
- Sanagou M, Leder K, Cheng AC, Pilcher D, Reid CM, Wolfe R. Associations of hospital characteristics with nosocomial pneumonia after cardiac surgery can impact on standardized infection rates. Epidemiol Infect. 2016;144:1065–74, http://dx.doi.org/10.1017/S0950268815002307.
- 9. Bardia A, Blitz D, Dai F, Hersey D, Jinadasa S, Tickoo M, et al. Preoperative chlorhexidine mouthwash to reduce pneumonia after cardiac surgery: a systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2019;158:1094–100, http://dx.doi.org/10.1016/j.jtcvs.2019.01.014.
- Cheng W, Chen J, Sun J, Zhang J, Li D, Wang H, et al. Role of intensified lung physiotherapy bundle on the occurrence of pneumonia after cardiac surgery. Front Med. 2022;9:844094, http://dx.doi.org/10.3389/fmed.2022.844094.
- 11. Strobel RJ, Liang Q, Zhang M, Wu X, Rogers MA, Theurer PF, et al. A preoperative risk model for postoperative pneumonia after coronary artery bypass grafting. Ann Thorac Surg. 2016;102:1213–9, http://dx.doi.org/10.1016/j.athoracsur.2016.03.074.
- Kilic A, Ohkuma R, Grimm JC, Magruder JT, Sussman M, Schneider EB, et al. A novel score to estimate the risk of pneumonia after cardiac surgery. J Thorac Cardiovasc Surg. 2016;151:1415–20, http://dx.doi.org/10.1016/j.jtcvs.2015.12.049.
- 13. Wang D, Huang X, Wang H, Le S, Yang H, Wang F, et al. Risk factors for post-operative pneumonia after cardiac surgery: a prediction model. J Thorac Dis. 2021;13:2351–62, http://dx.doi.org/10.21037/jtd-20-3586.

