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Bacteraemic pneumococcal pneumonia and SARS-CoV-2 pneumonia: differences and similarities

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ABSTRACT

Objective: To analyse differences in clinical presentation and outcome between bacteraemic pneumococcal community-acquired pneumonia (B-PCAP) and sSvere Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pneumonia.
Methods: This observational multi-centre study was conducted on patients hospitalized with B-PCAP between 2000 and 2020 and SARS-CoV-2 pneumonia in 2020. Thirty-day survival, predictors of mortality, and intensive care unit (ICU) admission were compared.
Results: In total, 663 patients with B-PCAP and 1561 patients with SARS-CoV-2 pneumonia were included in this study. Patients with B-PCAP had more severe disease, a higher ICU admission rate and more complications. Patients with SARS-CoV-2 pneumonia had higher in-hospital mortality (10.8% vs 6.8%; P=0.004). Among patients admitted to the ICU, the need for invasive mechanical ventilation (69.7% vs 36.2%; P<0.001) and mortality were higher in patients with SARS-CoV-2 pneumonia. In patients with B-PCAP, the predictive model found associations between mortality and systemic complications (hyponatraemia, septic shock and neurological complications), lower respiratory reserve and tachypnoea; chest pain and purulent sputum were protective factors in these patients. In patients with SARS-CoV-2 pneu-

Abbreviations: AEMPS, Spanish Agency for Medicines and Health Products; B-PCAP, bacteraemic pneumococcal community-acquired pneumonia; CAP, community-acquired pneumonia; CI, confidence interval; COPD, Chronic obstructive pulmonary disease; CURB-65, Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥65 years; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ICU, intensive care unit; IMV, invasive mechanical ventilation; OR, Odds Ratio; PSI, Pneumonia Severity Index; RT-PCR, reverse transcription-polymerase chain reaction; SEPAR, Spanish Society of Pulmonology and Thoracic Surgery.

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monia, mortality was associated with previous liver and cardiac disease, advanced age, altered mental status, tachypnoea, hypoxaemia, bilateral involvement, pleural effusion, septic shock, neutrophilia and high blood urea nitrogen; in contrast, ≥7 days of symptoms was a protective factor in these patients. In-hospital mortality occurred earlier in patients with B-PCAP.

Conclusions: Although B-PCAP was associated with more severe disease and a higher ICU admission rate, the mortality rate was higher for SARS-CoV-2 pneumonia and deaths occurred later. New prognostic scales and more effective treatments are needed for patients with SARS-CoV-2 pneumonia.

Background

Streptococcus pneumoniae remains the most common cause of community-acquired pneumonia (Van der Poll and Opal, 2009; Johansson et al., 2010). Among pneumonia pathogens, it is the leading cause of hospitalization and death in adults (Roson et al., 2001; Shariatzadeh et al., 2005). Approximately 15–25% of cases of pneumococcal pneumonia are bacteraemic (Said et al., 2013), and bacteraemic pneumococcal community-acquired pneumonia (B-PCAP) has traditionally been considered an invasive form of infection related to higher inflammatory status, worse in-hospital course and shorter long-term survival (Capelastegui et al., 2014; Ishiguro et al., 2016; Ruiz et al., 2019).

At the end of 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in China and rapidly developed into a global pandemic (Dhama et al., 2020; (Zhou et al., 2020a).,). SARS-CoV-2 causes coronavirus disease 2019 (COVID-19). The COVID-19 pandemic is a public health emergency, with more than 243 million confirmed cases and more than 4.9 million deaths.

Over recent months, numerous publications have sought to describe the stages of COVID-19; the clinical course, process of care, and predictive factors for poor outcome in SARS-CoV-2 pneumonia. However, few studies have compared the clinical features of SARS-CoV-2 pneumonia with other types of pneumonia (Tian et al., 2020; Zhao et al., 2020;(Zhou et al., 2020b) ; Shi et al., 2021).

The aim of the present study was to analyse the differences and similarities in clinical presentation, host inflammatory response and outcome between B-PCAP (which was previously the most common and invasive pneumonia) and SARS-CoV-2 pneumonia. Factors associated with intensive care unit (ICU) admission and in-hospital mortality were compared, and survival after hospitalization was assessed for both types of pneumonia.

Methods

Study design and population

This observational multi-centre study was based on the analysis of a prospective registry of consecutive immunocompetent adults (aged ≥18 years) hospitalized with B-PCAP between January 2000 and May 2020, and consecutive immunocompetent patients admitted with SARS-CoV-2 pneumonia between March and December 2020 (first and second waves of COVID-19 pandemic) to one of three tertiary medical centres (Cruces University Hospital, La Fe Hospital and Galdakao-Usansolo Hospital) in Spain. This study was approved by the corresponding ethics committee (Code PI2020083), and conducted in accordance with the principles of the Declaration of Helsinki on research in humans.

The bacteriological diagnosis of B-PCAP was based on a positive blood culture for *S. pneumoniae* taken within 24 h of presentation at hospital. Cases of SARS-CoV-2 pneumonia were confirmed by positive reverse transcription polymerase chain reaction (RT-PCR) assay for the virus in nasopharyngeal swabs. Patients were excluded if they were known to be positive for human immunodeficiency virus or chronically immunosuppressed, or had been hospitalized for 14 days preceding the diagnosis of pneumonia.

Study variables

Patients' clinical and demographic characteristics were recorded, as well as physical examination, laboratory and radiological findings on admission. CURB-65 (confusion, urea nitrogen, respiratory rate, blood pressure, age ≥65 years) (Lim et al., 2003) and Pneumonia Severity Index (PSI) (Fine et al., 1999) scores were used to assess the severity of pneumonia. Measures of in-hospital clinical course and outcome included: development of in-hospital complications; ICU admission; use of invasive mechanical ventilation (IMV); septic shock; in-hospital mortality; and length of hospital stay. Treatment of patients with COVID-19 was based on the recommendations issued by the Spanish Ministry of Health and the Spanish Agency for Medicines and Health Products (AEMPS) at the time of diagnosis (Documento técnico 19 March 2020)(http://www.aeemt.com/web/wpcontent/uploads/2020/03/4_6026300193912129107.pdf, accessed April 2020;(AEMPS1) https://www.aemps.gob.es/laAEMPS/docs/medicamentos-disponibles-SARS-CoV-2-19-3-2020.pdf, accessed May 2020;(AEMPS2) https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%e2%80%9119/tratamientos-disponibles-para-el-manejo-de-la-infeccion-respiratoria-por-sars-cov-2/?lang=en, accessed September 2020;(COVID-19 Treatment Guidelines Panel 2020) https://www.covid19treatmentguidelines.nih.gov/, accessed September 2020). Patients with B-PCAP were treated based on the guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (Menéndez et al., 2010). In-hospital care and medical care following discharge were determined by patients' healthcare providers.

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrates on chest X-ray, together with acute signs and symptoms suggestive of lower respiratory tract infection. The disease was classified as B-PCAP when the blood culture was positive for *S. pneumoniae*, and SARS-CoV-2 pneumonia when RT-PCR was positive for SARS-CoV-2 in nasopharyngeal swabs.

Patients were considered active smokers if they smoked at least 10 cigarettes per day, and heavy alcohol users if they reported a daily alcohol intake of at least 80 g for men or 60 g for women during the previous year (Grau et al., 2014). Septic shock was defined as systolic blood pressure <90 mmHg and the need for vasopressors for ≥4 h after fluid replacement therapy on admission ((Levy et al., 2003).

Statistical analysis

Bivariate tables were constructed for patients with B-PCAP and SARS-CoV-2 pneumonia. Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as means (standard deviations) or medians (interquartile ranges) depending on whether or not data were normally distributed. For continuous variables, comparisons were performed using Student's *t*-test if the data followed a normal distribution, and using the Mann–Whitney *U*-test if the data did not follow a normal distribution. Chi-squared test or Fisher's exact test were used to compare qualitative variables.

Logistic regression models were performed to assess which variables were associated with ICU admission and use of IMV. Cox regression models were built to analyse in-hospital mortality. All variables with $P<0.100$ on bivariate analysis were included in logistic regression models. In the multi-variate logistic regression model, the variables with the highest *P*-values were eliminated one-by-one until all the variables entered were significant ($P<0.05$). The results have been expressed as odd ratios (ORs) with corresponding 95% confidence intervals (CI). In the case of patients with COVID-19, multiple imputations were used to impute any missing respiratory rate values.

Thirty-day survival was analysed using the Kaplan–Meier method. The log-rank test was used to compare survival between groups.

All analyses were performed using R Version 4.0.1.

Results

Six hundred and sixty-three patients hospitalized with B-PCAP and 1561 patients hospitalized with SARS-CoV-2 pneumonia were recruited into this study. Table 1 summarizes the patient baseline characteristics and in-hospital course overall and stratified by pneumonia aetiology. Patients with B-PCAP were older and more likely to have comorbidities. Focusing on clinical presentation, patients with B-PCAP were likely to have more severe disease, but the median duration of symptoms was shorter (3 vs 7 days; $P<0.001$). In addition, patients with B-PCAP had worse laboratory findings, including higher C-reactive protein level and lower lymphocyte count (median 710 vs 990; $P<0.001$), but were less likely to have bilateral lung involvement on chest X-ray (16.9% vs 71.8%; $P<0.001$). Further, patients with B-PCAP were more frequently classified in the higher risk classes according to CURB-65 (2 to 5) and PSI (4 and 5) scores ($P<0.001$). Patients with B-PCAP were more frequently admitted to the ICU (27.9% vs 12.9%; $P<0.001$). In contrast, the IMV rate was similar in the two groups (10.1% vs 9.1%; $P=0.505$). A higher percentage of patients with B-PCAP had complications during hospitalization. In contrast, patients with SARS-CoV-2 pneumonia had a higher in-hospital mortality rate (10.8% vs 6.8%; $P=0.004$) and longer in-hospital stay.

Table 2 shows differences between patients admitted to the ICU with B-PCAP ($n=185$) vs SARS-CoV-2 pneumonia ($n=201$). The clinical presentation showed greater severity in patients with B-PCAP, and these patients were in a higher risk class according to PSI and CURB-65 scores. In contrast, patients with SARS-CoV-2 pneumonia were more likely to have bilateral lung involvement (83.6% vs 34.6%; $P<0.001$) and receive IMV (69.7% vs 36.2%; $P<0.001$). Thromboembolic complications, unlike all other complications, were more common in patients with SARS-CoV-2 pneumonia (12.9% vs 2.2%). Patients with SARS-CoV-2 pneumonia admitted to the ICU, like the overall sample of patients with this type of pneumonia, had a higher in-hospital mortality rate (23.9% vs 13%; $P=0.009$) and longer in-hospital stay.

The results of multi-variate Cox regression of factors potentially associated with in-hospital mortality are listed in Table 3. In the multi-variate Cox regression model, the following factors were independently associated with in-hospital mortality in patients with B-PCAP: chronic obstructive pulmonary disease (COPD) (OR 2.38, 95% CI 1.19–4.78; $P=0.015$); respiratory rate ≥30 breaths/min (OR 2.9, 95% CI 1.43–5.89; $P=0.003$); sodium <130 mmol/L (OR 3.26, 95% CI 1.37–7.81; $P=0.008$); neurological complications (OR 7.25, 95% CI 3.52–14.93; $P<0.001$); and septic shock (OR 2.18, 95% CI 1.06-4.48; $P=0.035$). Purulent sputum production (OR 0.4, 95% CI 0.2–0.79; $P=0.009$) and chest pain (OR 0.41, 95% CI 0.19–0.88; $P=0.022$) were protective factors. In patients with SARS-CoV-2 pneumonia, predictors of in-hospital mortality were: age ≥65 years (OR 4.777, 95% CI 2.814–8.111; $P<0.001$); heart disease (OR 1.587, 95% CI 1.007–2.341; $P=0.02$); liver disease (OR 2.365, 95% CI 1.199–4.662); altered mental status (OR 2.464, 95% CI 1.586–3.827; $P<0.001$); respiratory rate ≥30 breaths/min (OR 2.117, 95% CI 1.362–3.289; $P<0.001$); hypoxaemia (OR 1.599, 95% CI 1.045–2.447; $P=0.03$); blood urea nitrogen ≥30 mg/dL (OR 1.864, 95% CI 1.236–2.81; $P=0.003$); neutrophilia (each 10,000-unit increase in neutrophil count/μL) (OR 1.052, 95% CI 1.018–1.086; $P=0.002$); bilateral lung involvement (OR 1.868, 95% CI 1.142–3.056; $P=0.013$); pleural effusion (OR 2.894, 95% CI 1.282–6.536; $P=0.011$); and septic shock (OR 2.781, 95% CI 1.703–4.542; $P<0.001$). Seven or more days of symptoms on admission was a protective factor against mortality (OR 0.464, 95% CI 0.314–0.685; $P<0.001$). The results of multi-variate logistic regression of factors associated with ICU admission and IMV in patients hospitalized with B-PCAP or SARS-CoV-2 pneumonia are reported in Table 4 and Table S1 (see online supplementary material), respectively.

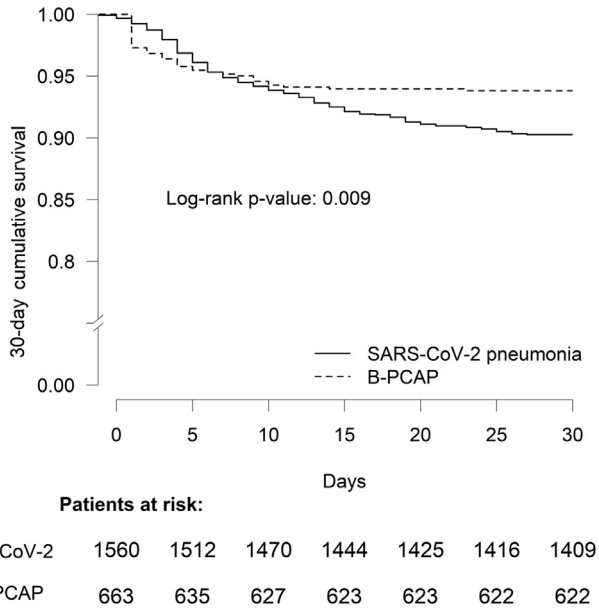

Figure 1. Thirty-day Kaplan–Meier survival curve for patients with bacteraemic pneumococcal community-acquired pneumonia (B-PCAP) and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pneumonia.

Figure 1 compares the 30-day Kaplan–Meier survival curves for patients with B-PCAP and SARS-CoV-2 pneumonia. The 30-day survival rate was significantly lower in patients with SARS-CoV-2 pneumonia (90.2% vs 93.8%; log rank $P\leq0.009$).

Discussion

This study provides a comprehensive evaluation of host-related factors, process of care and outcome in a consecutive series of patients diagnosed with B-PCAP and SARS-CoV-2 pneumonia. The main findings were as follows: (1) patients with SARS-CoV-2 pneu-

Table 1
General characteristics and in-hospital course overall and stratified by pneumonia aetiology.

	All patients(n=2224)	B-PCAP (n=663)	SARS-CoV-2 pneumonia (n=1561)	P-value
Demographic characteristics				
Sex (male)	1367 (61.5%)	427 (64.4%)	940 (60.2%)	0.071
Age ≥65 years	1005 (45.1%)	338 (51%)	667 (42.7%)	0.010
Active smoker	293 (13.3%)	220 (33.2%)	73 (4.8%)	<0.001
Alcoholism	218 (11.3%)	115 (17.6%)	103 (8.1%)	<0.001
Nursing home resident	89 (4%)	18 (2.7%)	71 (4.6%)	0.057
Comorbid conditions				
Comorbidities, yes	1332 (59.9%)	394 (59.4%)	938 (60.1%)	0.807
Hypertension	914 (41.2%)	280 (42.5%)	634 (40.6%)	0.440
Diabetes mellitus	400 (18%)	109 (16.4%)	291 (18.6%)	0.240
Dyslipidaemia	694 (31.3%)	156 (23.7%)	538 (34.5%)	<0.001
Heart disease	412 (18.6%)	173 (26.3%)	239 (15.3%)	<0.001
Cerebrovascular disease	92 (4.8%)	42 (6.3%)	50 (3.9%)	0.025
Chronic obstructive pulmonary disease	218 (9.8%)	120 (18.1%)	98 (6.3%)	<0.001
Liver disease	90 (4.1%)	42 (6.3%)	48 (3.1%)	0.001
Chronic severe renal disease	164 (7.3%)	45 (6.8%)	119 (7.6%)	0.548
Neoplastic disease	143 (6.4%)	52 (7.8%)	91 (5.8%)	0.094
Clinical characteristics				
Duration of symptoms (days), median (IQR)	6 (3–8)	3 (2–5)	7 (5–10)	<0.001
Altered mental status	153 (6.9%)	70 (10.6%)	83 (5.3%)	<0.001
Fever	1649 (74.5%)	539 (82.7%)	1110 (71.1%)	<0.001
Cough	1627 (73.6%)	502 (77%)	1125 (72.2%)	0.022
Purulent sputum production	361 (16.3%)	300 (46%)	61 (3.9%)	<0.001
Dyspnoea	1196 (54%)	384 (58.9%)	812 (52%)	0.004
Chest pain	544 (24.6%)	338 (51.8%)	206 (13.2%)	<0.001
Physical examination				
Temperature >39°C	126 (5.7%)	83 (12.5%)	43 (2.8%)	<0.001
Respiratory rate ≥30 breaths/min	299 (15.4%)	172 (26.4%)	127 (9.9%)	<0.001
Heart rate >125 beats/min	161 (7.3%)	115 (17.3%)	46 (3%)	<0.001
Systolic blood pressure <90 mmHg	83 (3.8%)	59 (8.9%)	24 (1.6%)	<0.001
Oxygen saturation <90%	412 (18.6%)	216 (33%)	196 (12.6%)	<0.001
Laboratory and radiological findings				
Glucose, median (IQR), mg/dL	114 (100–142)	129 (107–166)	110 (99–130)	<0.001
Blood urea nitrogen ≥30 mg/dl	492 (22.2%)	303 (45.8%)	189 (12.1%)	<0.001
Sodium <130 mmol/L	83 (3.7%)	63 (9.5%)	20 (1.3%)	<0.001
Haematocrit <30%	52 (2.3%)	19 (2.9%)	33 (2.1%)	0.361
C-reactive protein ≥150 mg/L	449 (22.7%)	171 (40.1%)	279 (17.9%)	<0.001
Platelet count x10^3/µL, median (IQR)	194 (150–246)	197 (159–246)	192 (148–246)	0.193
White blood cell count/µL, median (IQR)	7090 (5115–11408)	14,170 (9600–20,100)	6170 (4730–8070)	<0.001
Neutrophils/µL, median (IQR)	5400 (3590–9514)	12,558 (7900–17,676)	4500 (3250–6240)	<0.001
Lymphocytes/µL, median (IQR)	920 (640–1299)	710 (417–1170)	990 (715–1330)	<0.001
Neutrophil/lymphocyte ratio, median (IQR)	5.94 (3.4–12.1)	15.5 (9.33–26.6)	4.37 (2.93–7.42)	<0.001
Lymphocyte/C-reactive protein ratio, median (IQR)	14.4 (5.82–36.2)	8.05 (2.43–24.6)	15.9 (7.08–42.5)	<0.001
Lung involvement on X-ray				
Single lobe	783 (35.4%)	424 (64.7%)	359 (23.1%)	<0.001
Unilateral multi-lobe	215 (9.7%)	120 (18.3%)	95 (6.1%)	<0.001
Bilateral	1228 (55.5%)	111 (16.9%)	1117 (71.8%)	<0.001
Pleural effusion	154 (6.9%)	119 (17.9%)	35 (2.2%)	<0.001
Severity				
Pneumonia Severity Index IV–V	695 (31.3%)	364 (55.5%)	331 (21.2%)	<0.001
CURB-65 ≥2	774 (35.2%)	409 (64.2%)	365 (23.4%)	<0.001
In-hospital course				
Admission to ICU	386 (17.4%)	185 (27.9%)	201 (12.9%)	<0.001
Length of ICU stay (days), median (IQR)	13 (6–21)	5 (3–11)	14 (7–24)	<0.001
Need for mechanical ventilation	209 (9.4%)	67 (10.1%)	142 (9.1%)	0.505
Length of IMV (days), median (IQR)	14 (8–22)	10 (4–18)	13 (8–21)	0.563
Neurological complications	94 (4.2%)	59 (8.9%)	35 (2.2%)	<0.001
Renal complications	259 (11.7%)	148 (22.4%)	111 (7.1%)	<0.001
Cardiac complications	212 (9.7%)	106 (16.1%)	106 (6.9%)	<0.001
Thromboembolic complications	55 (2.8%)	5 (0.8%)	50 (3.9%)	<0.001
Haematological complications	80 (3.9%)	58 (10.1%)	22 (1.5%)	<0.001
Septic shock	150 (6.8%)	116 (17.7%)	34 (2.1%)	<0.001
Outcomes				
In-hospital mortality	214 (9.6%)	45 (6.8%)	169 (10.8%)	0.004
30-day re-admission	93 (5.3%)	18 (2.7%)	75 (6.9%)	<0.001
Length of hospital stay (days), median (IQR)	8 (5–13)	7 (4–10)	9 (5–14)	<0.001

B-PCAP, bacteraemic pneumococcal community-acquired pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range.

Table 2
Differences between patients admitted to the intensive care unit with bacteraemic pneumococcal community-acquired pneumonia (B-PCAP) vs Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pneumonia.

	All patients(n=386)	B-PCAP (n=185)	SARS-CoV-2 pneumonia (n=201)	P-value
Demographic characteristics				
Sex (male)	272 (72.5%)	131 (70.8%)	141 (70.1%)	0.976
Age ≥65 years	124 (32.1%)	68 (36.8%)	56 (27.9%)	0.854
Active smoker	95 (24.8%)	87 (47%)	8 (4%)	<0.001
Alcoholism	69 (20.1%)	51 (27.9%)	18 (11.2%)	<0.001
Nursing home resident	6 (1.5%)	4 (2.2%)	2 (1%)	0.432
Comorbid conditions				
Comorbidities, yes	243 (63%)	101 (54.6%)	142 (70.6%)	0.002
Hypertension	159 (41.3%)	64 (34.8%)	95 (47.3%)	0.017
Diabetes mellitus	70 (18.1%)	22 (11.9%)	48 (23.9%)	0.003
Dyslipidaemia	115 (29.9%)	42 (22.8%)	73 (36.3%)	0.005
Heart disease	54 (14%)	27 (14.7%)	27 (13.4%)	0.839
Cerebrovascular disease	10 (2.9%)	7 (3.8%)	3 (1.9%)	0350
Chronic obstructive pulmonary disease	54 (14%)	39 (21.1%)	15 (7.5%)	<0.001
Liver disease	24 (6.2%)	20 (10.8%)	4(2%)	0.001
Chronic severe renal disease	21 (5.4%)	9 (4.9%)	12 (5.9%)	0.800
Neoplastic disease	21 (5.4%)	10 (5.4%)	11 (5.5%)	1
Clinical characteristics				
Duration of symptoms (days), median (IQR)	5 (3–7)	3 (2–5)	7 (5–9)	<0.001
Altered mental status	38 (9.8%)	25 (13.5%)	13 (6.5%)	0.032
Fever	292 (76.2%)	143 (78.6%)	149 (74.1%)	0.368
Cough	293 (76.5%)	139 (76.4%)	154 (76.6%)	1
Purulent sputum production	88 (23%)	82 (45.1%)	6 (3%)	<0.001
Dyspnoea	255 (66.6%)	124 (68.1%)	131 (65.2%)	0.614
Chest pain	109 (28.5%)	92 (50.5%)	17 (8.5%)	<0.001
Physical examination				
Temperature >39°C	34 (9.04%)	24 (13%)	10 (5.2%)	0.015
Respiratory rate ≥30 breaths/min	143 (40.6%)	87 (47.8%)	56 (32.9%)	0.006
Heart rate >125 beats/min	63 (16.3%)	53 (28.6%)	10 (5%)	<0.001
Systolic blood pressure <90 mmHg	47 (12.1%)	44 (23.8%)	3 (1.4%)	<0.001
Oxygen saturation <90%	155 (40.2%)	93 (50.8%)	62 (30.8%)	0.180
Laboratory and radiological findings				
Glucose (mg/dL), median (IQR)	120 (102–150)	120 (99–153)	121 (106–147)	0.363
Blood urea nitrogen ≥30 mg/dL	139 (36%)	119 (64.3%)	20 (9.9%)	<0.001
Sodium <130 mmol/L	34 (8.8%)	28 (15.1%)	6 (2.9%)	0.001
Haematocrit <30%	11 (2.8%)	5 (2.7%)	6 (2.9%)	0.544
C-reactive protein ≥150 mg/L	108 (33.5%)	54 (44.3%)	54 (27%)	0.002
Platelet count x10^3/µL, median (IQR)	187 (143–236)	182 (141–227)	191 (143–239)	0.405
White blood cell count/µL, median (IQR)	7750 (5200–12100)	11300 (6230–16300)	6595 (5032–8418)	<0.001
Neutrophils/µL, median (IQR)	6420 (3892–10902)	10081 (5100–14626)	5105 (3678–7192)	<0.001
Lymphocytes/µL, median (IQR)	735 (430–1082)	564 (300–1064)	805 (598–1090)	<0.001
Neutrophil/lymphocyte ratio, median (IQR)	9.83 (5.33–18.6)	15.5 (7.89–26.9)	6.85 (4.27–10.5)	<0.001
Lymphocyte/C-reactive protein ratio, median (IQR)	7.5 (2.9–17.4)	4.59 (1.62–15.7)	9.4 (4.36–17.6)	<0.001
Lung involvement on X-ray				
Single lobe				
Unilateral multi-lobe	91 (23.8%)	63 (34.6%)	28 (13.9%)	<0.001
Bilateral	63 (16.4%)	56 (30.8%)	7 (3.5%)	<0.001
	231 (60.3%)	63 (34.6%)	168 (83.6%)	<0.001
Pleural effusion	41 (10.6%)	38 (20.5%)	3 (1.5%)	<0.001
Severity				
Pneumonia Severity Index IV–V	186 (48.3%)	128 (69.6%)	58 (28.9%)	<0.001
CURB-65 ≥2	197 (53.8%)	137 (75.7%)	60 (29.9%)	<0.001
In-hospital course				
Need for mechanical ventilation	207 (53.6%)	67 (36.2%)	140 (69.7%)	<0.001
Length of IMV (days), median (IQR)	13 (7.25–21)	10 (4–18)	13 (8–21)	0.563
Complications				
Neurological complications	48 (12.5%)	29 (15.8%)	19 (9.6%)	0.093
Stroke	1 (0.3%)	0	1 (0.7%)	0.445
Renal complications	128 (33.4%)	89 (48.4%)	39 (19.6%)	<0.001
Cardiac complications	90 (23.8%)	51 (27.9%)	39 (20%)	0.094
Thromboembolic complications	26 (7.3%)	4 (2.2%)	22 (12.9%)	<0.001
Haematological complications	52 (14.6%)	46 (27.9%)	6 (3.1%)	<0.001
Septic shock	130 (33.9%)	107 (57.8%)	23 (11.6%)	<0.001
Outcomes				
In-hospital mortality	72 (18.7%)	24 (13%)	48 (23.9%)	0.009
30-day re-admission	11 (3.79%)	5 (2.7%)	6 (5.7%)	0.218
Length of hospital stay, median (IQR)	18 (10–33)	12 (7–20)	25 (16–41)	<0.001

IMV, invasive mechanical ventilation; IQR, interquartile range.

Table 3
Multi-variate Cox regression of factors associated with in-hospital mortality in patients hospitalized with bacteraemic pneumococcal community-acquired pneumonia (B-PCAP) and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pneumonia.

B-PCAP			SARS-CoV-2 pneumonia		
	OR (95% CI)	*P*-value		OR (95% CI)	*P*-value
Chronic obstructive pulmonary disease	2.38 (1.19–4.78)	0.015	Age ≥65 years	4.777 (2.814–8.111)	<0.001
Purulent sputum production	0.4 (0.2–0.79)	0.009	Heart disease	1.587 (1.077–2.341)	0.02
Chest pain	0.41 (0.19–0.88)	0.022	Liver disease	2.365 (1.199–4.662)	0.013
Respiratory rate ≥30 breaths/min	2.9 (1.43–5.89)	0.003	Altered mental status	2.464 (1.586–3.827)	<0.001
Sodium <130 mmol/L	3.26 (1.37–7.81)	0.008	≥7 days of symptoms	0.464 (0.314–0.685)	<0.001
Neurological complications[a]	7.25 (3.52–14.93)	<0.001	Respiratory rate ≥30 breaths/min	2.117 (1.362–3.289)	<0.001
Septic shock	2.18 (1.06–4.48)	0.035	Oxygen saturation <90%	1.599 (1.045–2.477)	0.03
			Blood urea nitrogen ≥30 mg/dL	1.864 (1.236–2.81)	0.003
			Neutrophil count/μL/10,000[b]	1.052 (1.018–1.086)	0.002
			Bilateral lung involvement	1.868 (1.142–3.056)	0.013
			Pleural effusion	2.894 (1.282–6.536)	0.011
			Septic shock	2.781 (1.703–4.542)	<0.001

OR, odds ratio; CI, confidence interval.
[a] Neurological complications: stroke, delirium and/or seizure.
[b] Neutrophil count is presented for each 10,000-unit increase.

Table 4
Multi-variate logistic regression of factors associated with intensive care unit (ICU) admission in patients hospitalized with bacteraemic pneumococcal community-acquired pneumonia (B-PCAP) and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pneumonia.

B-PCAP			SARS-CoV-2 pneumonia		
	OR (95% CI)	*P*-value		OR (95% CI)	*P*-value
Age ≥65 years[a]	0.28 (0.17–0.47)	<0.001	Nursing home resident	0.132 (0.002–0.486)	0.009
Active smoker	2.09 (1.29–3.4)	0.003	Age ≥65 years[a]	0.563 (0.375–0.833)	0.005
Respiratory rate ≥30 breaths/min	3.39 (2.11–5.46)	<0.001	Respiratory rate ≥30 breaths/min	3.09 (1.891–5)	<0.001
Systolic blood pressure <90 mmHg	12.53 (6.09–27.2)	<0.001	Oxygen saturation <90%	4.483(2.812–7.125)	<0.001
Oxygen saturation <90%	2.39 (1.46–3.92)	<0.001	Lymphocytes/μL/1000[c]	0.364 (0.231–0.557)	<0.001
Blood urea nitrogen ≥30 mg/dL	3.45 (2.15–5.63)	<0.001			
White blood cell count/μL/1000[b]	0.95 (0.92–0.98)	<0.001			
Bilateral lung involvement	3.17 (1.84–5.48)	<0.001			

OR, odds ratio; CI, confidence interval.
[a] Indicates the negative influence of advanced age on eligibility for ICU admission.
[b] White blood cell count is presented for each 1000-unit increase.
[c] Lymphocytes are presented for each 1000-unit increase.

monia had higher in-hospital mortality, although patients with B-PCAP had more comorbidities, more severe clinical presentation and laboratory findings, higher ICU admission rates and in-hospital complications; (2) in comparison with patients with B-PCAP, patients with SARS-CoV-2 pneumonia requiring ICU admission were more likely to receive IMV and had poorer outcomes with a higher mortality rate; (3) factors and clinical scales (PSI and CURB-65) classically associated with severity and mortality on admission in patients with B-PCAP demonstrated lack of predictive value in patients with SARS-CoV-2 pneumonia; and (4) B-PCAP was characterized by early in-hospital mortality, whereas in-hospital mortality occurred later in patients with SARS-CoV-2 pneumonia.

The study sample is particularly interesting for several reasons: the types of pneumonia studied, the type of population studied, the size of the sample, and the multi-centre design of the study. The types of pneumonia that were compared were the pneumonia that has previously been the most common, invasive and virulent pneumonia, able to produce documented inflammatory status and systemic complications (B-PCAP, all cases diagnosed by positive blood culture), and the pneumonia caused by the current pandemic (SARS-CoV-2 pneumonia, all cases diagnosed by positive RT-PCR), which has also been related to exaggerated systemic inflammation. In terms of the type of population studied, only immunocompetent patients were included for both types of pneumonia. This enabled the authors to avoid the confounding effect of immunosuppression. Regarding the size of the sample and the multi-centre design of the study, to the authors' knowledge, this is among the largest series published on this topic including data for both types of pneumonia collected prospectively.

The results of this study illustrate that there are clear differences between the clinical presentation of B-PCAP and SARS-CoV-2 pneumonia. B-PCAP can be considered a clear example of classic pneumonia, in which patients present with a history of a few days of typical symptoms, showing high severity on physical examination and laboratory parameters, and unilobar involvement on X-ray. In contrast, SARS-CoV-2 pneumonia was observed to have a more dormant clinical course, bilateral lung involvement and higher in-hospital mortality. Few studies have compared COVID-19 with other types of pneumonia, and all previous series have compared SARS-CoV-2-positive pneumonia with SARS-CoV-2-negative pneumonia, without specifying the aetiology in the latter case (Tian et al., 2020; Zhao et al., 2020; (Zhou et al., 2020b)). Furthermore, previous studies included few cases, and just compared the groups in terms of general characteristics and in-hospital course. No previous studies performed and compared multi-variate analysis of severity or survival curves.

The present study confirmed the underestimation of the risk of death from viral pneumonia obtained with CURB-65 and PSI scores reported by previous studies (Guo et al., 2019; Nguyen et al., 2020). In the present series, these severity scales were not useful for identifying patients with severe SARS-CoV-2 pneumonia, as among patients with this type of pneumonia, just 28.9% of those admitted to the ICU had high-risk PSI scores and 29.9% had high-risk CURB-65 scores, but 23.9% died during hospital admission. Moreover, in the entire sample of patients with SARS-CoV-2 pneumonia, only 21.2% and 23.4% were identified as high risk by the PSI score and the CURB-65 score, respectively, and the in-hospital mortality rate was 10.8%. Wynants et al. (2020) published a systematic review of pre-

diction models for COVID-19, and concluded that they were unable to recommend any of them for use in clinical practice.

The present study found that patients with B-PCAP had worse clinical presentation and laboratory findings, but in-hospital mortality was much higher in patients with SARS-CoV-2 pneumonia. The prognosis of B-PCAP has improved in recent years due to new vaccines (Whitney et al., 2003), early diagnosis and improvements in treatment (Gattarello et al., 2014). In contrast, SARS-CoV-2 pneumonia is a new illness and there is currently no specific antiviral treatment. Furthermore, although vaccines against COVID-19 are being administered in most countries, herd immunity has not yet been achieved. Moreover, the effectiveness of the vaccines is not the same in all patients, and the duration of immunity is not well known (Altawalah, 2021). The inflammatory response also plays an important role in COVID-19-related mortality. Previous research has suggested that excessive immune response triggers pathogenesis in other severe viral types of pneumonia, such as influenza and SARS (Van den Brand et al., 2014). It has also been documented that SARS-CoV-2 pneumonia triggers a strong innate inflammatory immune response which leads to a cytokine storm that causes acute respiratory distress syndrome (Xu et al., 2020; Ye et al., 2020).The present study did not find an association between in-hospital mortality in patients with COVID-19 and lymphopenia, whereas Zheng et al. (2020) did find an association in a meta-analysis analysing risk factors of critical cases of COVID-19. This is despite the fact that the lymphocyte count on admission in the patients with SARS-CoV-2 pneumonia in the present study was low and similar to that documented by previous studies (Richardson et al., 2020), although curiously, the median lymphocyte count was lower among patients with B-PCAP than among patients with SARS-CoV-2 pneumonia in the present study. These results indicate that lymphopenia is associated with severity in any type of pneumonia, and is not specific for SARS-CoV-2 as has been reported previously (Méndez et al., 2019).

The present study found two distinct mortality mechanisms in the two types of pneumonia. In B-PCAP, the predictive model related mortality to systemic complications (hyponatraemia, septic shock and neurological complications), lower respiratory reserve (COPD) and high respiratory rate; these risk factors have been associated with mortality previously (Naucler et al., 2013) or are currently included in pneumonia severity scores (Fine et al., 1999; Lim et al., 2003). Chest pain and purulent sputum production were found to be protective factors against mortality in patients with B-PCAP, probably because they were alarm symptoms that prompted the patient to seek medical attention and start treatment earlier (Fine et al., 1996). In contrast, in patients with SARS-CoV-2 pneumonia, mortality was more closely related to an exaggerated inflammatory response (blood urea nitrogen $\geq$30 mg/dL and neutrophilia) or respiratory failure (respiratory rate $\geq$30 breaths/min, oxygen saturation $<$90% and bilateral lung involvement). As in previous studies (Berenguer et al., 2020; Gallo et al., 2021), advanced age, altered mental status, and heart and liver diseases were associated with in-hospital mortality, and indicated worse baseline status. Further, septic shock was predictive of mortality, likely because it was related to bacterial superinfection, although microbiological aetiology data were not available. Pleural effusion was also related to in-hospital mortality, as this indicates severe inflammation and could be associated with viral pleuritis, bacterial superinfection or congestive heart failure (Zhan et al., 2021). Seven or more days of symptoms at hospital admission was found to be a protective factor against mortality for patients with SARS-CoV-2 pneumonia, as has been reported previously (Ciceri et al., 2020), probably because the patient is admitted at a later stage of the disease in which the risk of worsening is lower, or because the disease is milder and it takes longer to show severe symptoms.

Significant differences in the timing of in-hospital death were found between the groups. In patients with B-PCAP, in-hospital death occurred in the first few days after admission. As has been observed previously, pneumococcal mortality tends to be observed early, as prompt adequate targeted treatment improves outcomes in these patients (Garnacho-Montero et al., 2010). In contrast, in patients with SARS-CoV-2 pneumonia, survival started to decrease from day 4–5 of admission, this corresponding to day 10–12 after symptom onset, when the exaggerated inflammatory phase started (Siddiqi and Mehra, 2020).

Finally, regarding patients admitted to the ICU, the admission rate was lower in patients with SARS-CoV-2 pneumonia, but they had a longer ICU stay and greater need for IMV. These data reinforce the association of COVID-19 severity with respiratory failure, while the severity of B-PCAP was also associated with septic shock or other complications. All complications were observed more frequently in patients with B-PCAP, except for thromboembolic complications, which were more common in patients with SARS-CoV-2 pneumonia. Coagulopathy has been documented previously in patients with severe COVID-19, and this could lead to thromboembolic complications (Levi et al., 2020). Predictive factors associated with ICU admission in patients with B-PCAP were factors previously associated with severity (smoking, tachypnoea, hypotension, high blood urea nitrogen levels, respiratory failure or bilateral lung involvement). Older age had a negative association with ICU admission: as previous studies have documented, this indicates the negative influence of advanced age on eligibility for ICU admission (Boumendil et al., 2012; Ruiz et al., 2017). Leucocytosis was identified as protective against ICU admission, whereas leukopenia indicates abnormalities in the host's inflammatory response associated with increased susceptibility to severe disease and mortality (Hanada et al., 2016). Once again, in patients with SARS-CoV-2 pneumonia, respiratory failure (tachypnoea and oxygen saturation $<$90%) and cytokine storm (lymphopenia) were related to severity and ICU admission. Old age and nursing home residence were negatively associated with ICU admission; as in patients with B-PCAP, such patients were likely not eligible for ICU admission because of their poor baseline status.

This study has some limitations. It was an observational study and data on the two types of pneumonia were collected prospectively in different time periods. B-PCAP cases registered over 20 years were compared with SARS-CoV-2 cases registered over 10 months (March–December 2020), and this could introduce differences related to external uncontrollable factors. On the other hand, only patients from the first and second waves of the COVID-19 pandemic were included. This may be a limitation but also a strength, because it enabled the authors to eliminate the bias of the pandemic effect that would have had to analyse the first-wave patients alone, and avoided the effect of vaccination on subsequent waves (in Spain, vaccination started in January 2021). Further, in patients with B-PCAP, data were not gathered on factors that seem to be commonly altered in SARS-CoV-2 pneumonia (i.e. D-dimer, lactate dehydrogenase or ferritin), so it was not possible to compare these laboratory data. Furthermore, some therapies such as high-flow oxygen therapy and extracorporeal membrane oxygenation have started to be used in recent years, and it was not possible to compare their effect in the two groups. On the other hand, as there have been millions of cases of SARS-CoV-2 pneumonia in a short time, the authors consider that the approach followed is the only way to compare patients with this type of pneumonia with a similarly sized sample of patients with B-PCAP.

Conclusions

This study examined differences between general characteristics, clinical presentation and in-hospital course of patients with B-

PCAP and SARS-CoV-2 pneumonia, and analysed factors associated with in-hospital mortality and ICU admission in both groups. This study demonstrated differences in the behaviour of the two entities, which may facilitate differential diagnosis and enable the provision of differentiated treatment. Although patients with B-PCAP have more severe disease on admission and a higher ICU admission rate, in-hospital mortality associated with SARS-CoV-2 pneumonia is higher and occurs later during hospital admission. These results reinforce the need for new prognostic scales and effective treatment for patients with SARS-CoV-2 pneumonia.

Declaration of Competing Interest

None declared.

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Ethical approval

This study was approved by the corresponding the ethics committee is COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS DE EUSKADI (CEIm-E) (Code PI2020083) and conducted in accordance with the principles of the Declaration of Helsinki on research in humans.

Author contributions

LSF and LAR take responsibility for the manuscript as a whole. LSF, LAR, RZJ, RMV, RMO and PPE conceived and designed the study. AUE, PGH, PGJ, ETH, RMO and LAR enrolled patients, and collected and compiled data. SPF performed the statistical analysis. LSF, RZJ, LAR, RMO, ATM, PPE and RMV analysed and interpreted the data. LSF, RZJ and LAR wrote the manuscript. RMV, RMO, ATM, AUE and PPE commented on and revised the report. All authors read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.11.023.

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