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Original Research

Severe community-acquired pneumonia at a tertiary academic hospital in Johannesburg, South Africa

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ABSTRACT

Purpose: There is a paucity of data from sub-Saharan Africa describing Severe Community Acquired Pneumonia (SCAP), a condition with significant morbidity and mortality.
Materials and methods: This was a retrospective, single-centre, observational study of consecutive patients with SCAP admitted to the ICU at Charlotte Maxeke Johannesburg Academic Hospital, in South Africa between 1 July 2007 and 31 May 2019. Pneumonia was categorised as community-acquired if there had been no hospitalization in the preceding 2 weeks.
Results: We identified 931 patients, (median age 37 [IQR 30–48] years), with the predominant co-morbidity being HIV co-infection (77.1 %). The median CURB-65 and APACHE II scores were 3 (IQR 2–3) and 18 (IQR 14–23) respectively, and most patients had multilobar consolidation on chest X-ray. *Mycobacterium tuberculosis* was the most common aetiology, followed by *Streptococcus pneumoniae*. The latter, and *Pneumocystis jirovecii* were more common amongst survivors and non-survivors, respectively. ICU mortality was 50.1 % and 85 % of patients required ventilation, mostly invasive mechanical ventilation. Ventilated patients and those requiring inotropic support and/or dialysis were more likely to die.
Conclusion: We have described a cohort of patients with SCAP, with a comprehensive overview of all putative microbiological causes, which to our knowledge, is the largest reported in the literature.

1. Introduction

Community-acquired pneumonia (CAP) is an acute infectious illness causing lung parenchymal inflammation [1]. Its severity may range from a relatively mild disease, which could safely be treated out of hospital, to a life-threatening illness, necessitating hospitalization, and even admission to an intensive care unit (ICU). The overall mortality rate from CAP varies from <1 % to 50 % depending on factors such as severity, age, and presence of immunosuppression or underlying lung disease [2,3]. In fact, CAP remains a major cause of morbidity and mortality worldwide despite significant therapeutic advances. While CAP affects all strata of society and all age groups, it is most common in the very young, the elderly, and in those with comorbidity and/or immunocompromise [4].

The term severe community-acquired pneumonia (SCAP) has been used to describe patients that require admission to an ICU who are increasingly likely to develop complications [1,5]. The mortality of SCAP ranges from 21% to 50 %, being 21 % in those that require ICU admission, and 26 %, and even higher, in those requiring invasive mechanical ventilation [4]. The number of patients requiring ICU care for SCAP has increased worldwide, especially amongst vulnerable populations, with *Streptococcus pneumoniae* (SP) one of the major pathogens [4].

There have been many studies of non-severe CAP, but far fewer of SCAP, and no recent studies from sub-Saharan Africa that describe the clinical features, microbial aetiology, ICU course and outcome. Previous studies, including international studies, and especially those in people living with HIV (PLWH), were either performed prior to the antiretroviral therapy (ART) roll-out, mostly excluded patients with *Mycobacterium tuberculosis* (MTb), and/or opportunistic pathogens, or only evaluated specific pathogens, such as SP, *Pneumocystis jirovecii* (PJP), or other fungal or viral pathogens [6–9].

The aim of the current study was, therefore, to investigate the clinical characteristics, microbial aetiology, ICU course and outcome of all patients with SCAP that were admitted to a tertiary care academic hospital in Johannesburg, South Africa, over a 12-year period, including patients

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with immunocompromise, and encompassing as many microbial pathogens as possible.

2. Materials and Methods

This was a single-centre retrospective review of consecutive patients with CAP admitted to the multidisciplinary ICU at the Charlotte Maxeke, Johannesburg Academic Hospital (CMJAH) between 1 July 2007 and 31 May 2019. The hospital is an accredited, University-affiliated, central hospital, serving patients from across Gauteng and neighbouring provinces, offering a full range of secondary, tertiary, and highly specialized services. Patients were identified from the ICU admission records.

The diagnosis of CAP, was confirmed as previously described [10], and included the presence of a new pulmonary infiltrate on chest radiograph (within 24 h of admission), accompanied by at least one of the following; new or increased cough with/without sputum production, fever (>37.8 °C) or hypothermia (<35.6 °C), leucocytosis, a left shift, or leukopenia, based on local normal values. Patients were considered severe if they required ICU admission.

The data sources were limited to ICU admission records, electronic discharge summaries and/or clinical case notes, and the Picture Archiving and Communication system (PACS; Phillips Intellispace PACS Radiology version 4.4.532.1), a pan-electronic platform at CMJAH to access radiology. Following the identification of patients, the relevant ICU charts were collected, and data manually entered into an Excel spreadsheet in accordance with a defined data dictionary. Data collected included demographic and clinical details, which included symptoms and signs, severity of illness scores, laboratory and microbiological data, clinical management, including initial antimicrobial therapy, ICU course and outcomes. Patients were excluded if they did not fulfil the defined criteria for SCAP, if the patient file could not be found, or if data were insufficient to confirm the diagnosis. Approval for the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Clearance certificate number M2008109) and the Chief Executive Officer of CMJAH.

Severity of illness was assessed using the CURB-65 score (Confusion, Urea >7 mmol/L, Respiratory rate ≥ 30 breaths/minute, Blood pressure <90 mmHg (Systolic) and/or ≤ 60 mmHg (Diastolic), and Age ≥ 65years [11] and the APACHE II score [12,13]. In addition, the ratio of partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PF ratio), one of the minor criteria determining severity of CAP in the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guideline [10], was calculated for each patient.

Routine laboratory testing was performed for all patients on admission, which included full blood count (FBC), biochemistry (renal and liver function studies) and C-reactive protein (CRP). HIV testing was undertaken only with informed consent with the Cobas HIV-1/HIV-2 qualitative assay [Roche], as a screening test, and HIV Ag/Ab combo assay [Abbott], as a confirmatory test, [14], as well as the CD4 cell count (flow cytometry on a Beckman-Coulter MPLFC500 cytometer) and HIV viral load (Roche Cobas® 6800/8800 HIV-1 test).

Routine microbiological testing was mostly in accordance with the recommendations of the South African community-acquired pneumonia guideline [1], which included testing of respiratory samples obtained spontaneously or induced (and evaluated according to the Bartlett score [15]), and/or bronchoalveolar lavage (BAL). All available samples were submitted for microscopy, culture and sensitivity testing (MC + S), acid-fast staining (Ziehl-Nielsen, Auramine stains), GeneXpert MTB/RIF (Xpert) (Cepheid, Sunnyvale, Ca, USA) from 2012 [16], immunofluorescent staining (IFA) (pre-2018) or polymerase chain reaction (PCR) (post-2018) for PJP, as well as polymerase chain reaction (PCR) screening for viruses, *Legionella pneumophila* (LP), *Chlamydia pneumoniae* (CP) and *Mycoplasma pneumoniae* (MP), if indicated. Blood cultures were routinely collected on all patients using the BactT/Alert automated blood culture system (BioMerieux, Marcy l'Etoile, France).

Additional microbiological tests performed at the discretion of the attending physician, included serum [1,3]-β-D-glucan (BDG) test (Fungitell®) (for PJP), serology (for LP, MP, cytomegalovirus [CMV] and measles), and EDTA-blood CMV PCR. Where appropriate, investigation of pleural fluid, urine antigen tests (pneumococcal and legionella), blood antigen tests (*Cryptococcus neoformans* [CN] and CMV), cerebrospinal fluid (CSF) investigation, lymph node aspiration, bone marrow aspiration and/or culture and post-mortem lung biopsies (using Grocott's methenamine silver stain, modified Papanicolaou stain for PJP) were performed. The diagnosis of pneumonia due to Candida and CMV was made only where the pathogen was identified on post-mortem lung specimens, and other fungi (CN and *Aspergillus fumigatus* [AF]) were diagnosed by bronchoalveolar lavage (BAL).

The data analysis was performed using GraphPad Prism (v9) and Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA version 21.0. Data were captured and tabulated in a Microsoft Excel spreadsheet. The continuous variables were presented as means and standard deviations or medians and interquartile ranges, as appropriate, and for comparison, unpaired t-tests or Mann-Whitney U tests were used. The categorical variables were presented as percentages, and association in the categorical variables was assessed using the Chi-squared or Fisher's exact tests. The Baptista Pike method was used to determine exact two-sided confidence limits for the odds ratio in the 2X2 tables. All tests were 2-tailed. Multivariable analysis (MVA) was performed to identify which parameters, that were significant for mortality on univariate analysis, were independent risk factors for mortality (Supplementary data and Supplementary Tables 1–3). Three different models were used including different combinations of parameters, to control for co-linearity between variables and odds ratios were reported. In MVA1, APACHE II and CURB-65 were not included in the analysis, in MVA2, APACHE II and CURB-65 were included in the analysis, but comorbid HIV infection and cardiovascular disease were not included in the analysis, in MVA3 all these parameters were included in the model. A P value of <0.05 was taken as statistically significant.

3. Results

Following exclusion of cases for various reasons, 931 patient records were included in the final analysis (Fig. 1). The median age of the patients was 37 years (IQR 30–48 years), and there were 448 (48.1 %) males and 483 (51.9 %) females. Overall, 391 (42 %) patients had a comorbid illness other than HIV co-infection. The most common comorbidity was cardiovascular disease (CVD), followed by chronic respiratory disease and diabetes mellitus (Fig. 2). Although a comprehensive evaluation of cardiovascular comorbidities was not undertaken, diagnoses noted in the case reports included cardiomyopathy (peripartum, hypertensive, idiopathic), viral myocarditis, ischaemic heart disease, cor pulmonale, and peripheral vascular disease.

The clinical and laboratory data and radiological findings are shown in Table 1. The median CURB-65 score was 3 (IQR 2–3), median APACHE II 18 (IQR 14–23) and the median PF ratio 144 (IQR 97–229). Renal function was deranged, and the median CRP level was 202 (IQR 118–288) mg/L and median BDG 103 (IQR 31–501) pg/mL. Overall, 248 (26.6 %) patients had bacteraemia.

Microbial organisms considered to be aetiological pathogens were detected in 519 patients (55.7 %) from 706 specimens, while no microorganisms were detected in 412 (44.3 %) (Table 2). A comparison of baseline demographic and comorbid conditions of patients with, and without, isolated microorganisms indicated that the former patients were younger and had fewer cardiovascular conditions, but there were no other significant differences (Supplementary Table 4). Most isolates (317 [45.4 %]) were from respiratory samples (sputum, tracheal aspirates or BAL). The remaining sites from which microorganisms were isolated are depicted in Supplementary Fig. 1. Overall, 421 (44.7 %) infections were monomicrobial and 98 (13 %) polymicrobial, with some isolates cultured from multiple specimens (Table 2). MTb was the most common cause of infection (33.7 % of patients) while SP was the second

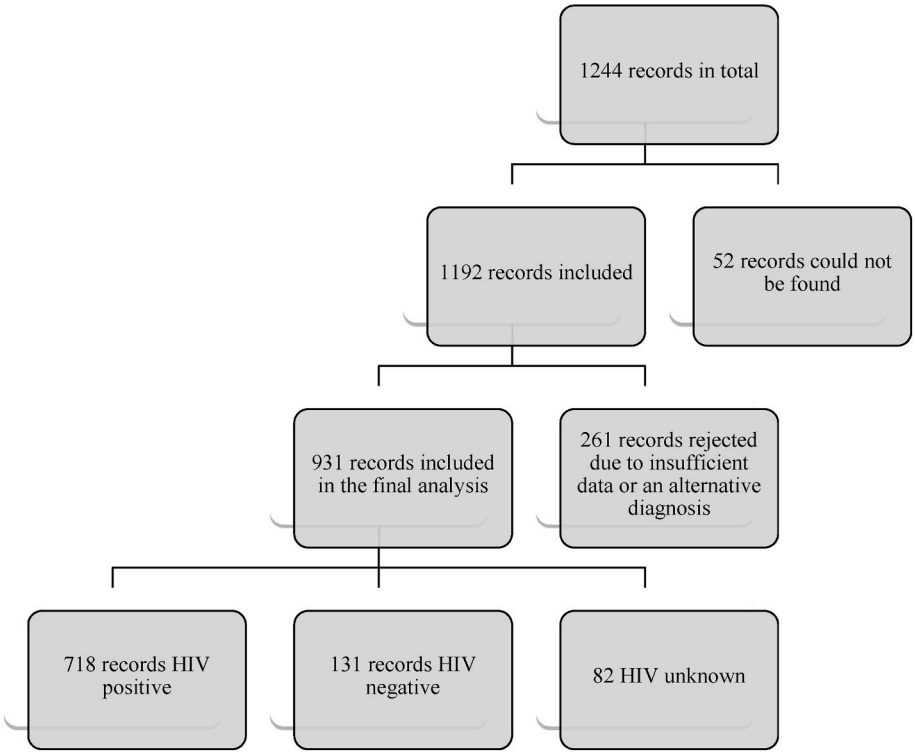

Fig. 1. Method of data acquisition for the study cohort.

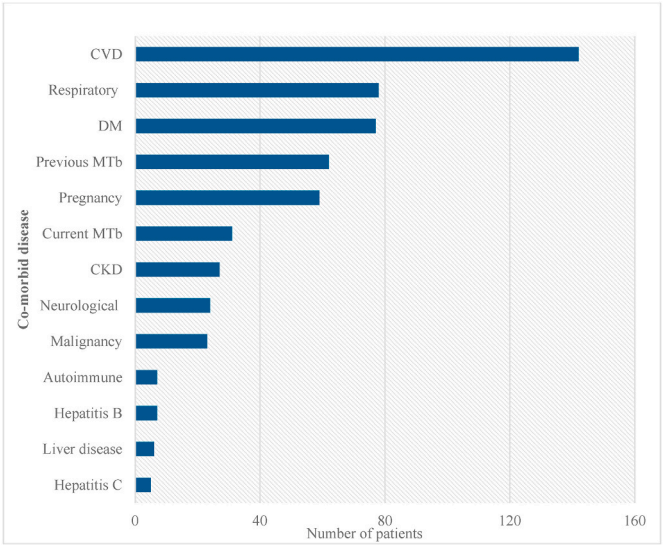

Fig. 2. Distribution of co-morbid diseases other than HIV within the entire cohort

Abbreviations: CKD: chronic kidney disease; CVD: cardiovascular disease; DM: Diabetes mellitus; MTb: *Mycobacterium tuberculosis*.

most common pathogen, identified in 24.1 % of patients. Varicella zoster virus (VZV), diagnosed on clinical grounds, was the predominant viral infection, and PJP the most common fungal pathogen. The median CRP level varied according to microbial aetiology. It was highest with SP (292 [IQR 239–350] mg/l), and lowest with PJP (139 [IQR 64–198] mg/l). Significant differences in CRP levels were noted between patients with SP, MTb, and PJP infections.

Most of the MTb infections were identified from respiratory samples (136 isolates [65.1 %]) and a further 47 (22.8 %) from blood using the BACTEC™ blood culture system. Other specimens from which MTb was isolated included bone marrow aspirate and trephine biopsy (BMAT) (5.7 %), pleural fluid (2.9 %), and lymph node biopsy (1.5 %). Two (1 %) patients had concurrent MTb meningitis. Most SP infections were diagnosed from blood culture (102 isolates, 76.7 %), with 15 % from sputum, 2.3 % from pleural fluid and 0.8 % using the urinary pneumococcal antigen test. Seven (5.3 %) patients had concurrent pneumococcal meningitis.

Drug-resistant pathogens were identified in 30 patients, the majority of which were extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* (KP) isolates (40 %) followed by drug-resistant MTb (26.7 %). Two isolates of SP were identified with intermediate resistance, and there were five methicillin-resistant *Staphylococcus aureus* (MRSA) isolates.

Chest radiograph (CXR) findings were available for 803 patients (86.3 %) (Table 1). The predominant finding was multilobar consolidation, followed by bilateral ground glass opacities (GGO). Lobar consolidation was most common with SP (60 %). Multilobar consolidation was most common with SP (46.5 %) and MTb (41 %). GGO were most common with MTb (39 %) and PJP (33 %). Nodules were only present in MTb (59 %) and viral infections (41 %), and pleural effusions with MTb (66.7 %) and SP (33.3 %).

In the ICU, all patients fulfilled commonly used criteria for defining the systemic inflammatory response syndrome (SIRS), as well as sepsis, while 200/788 (25.4 %) of cases, in whom data were available, fulfilled septic shock criteria; similarly, 190/766 (24.8 %) met the criteria for acute respiratory distress syndrome (ARDS). The latter was mild in 4 % of cases, moderate in 10.4 % and severe in 10.3 %. Overall, 85.8 % of patients were ventilated, by invasive mechanical ventilation (IMV) in 83.8 % and non-invasive ventilation (NIV) in 2 %. Furthermore, 49.8 % of patients needed inotropic support, 22.4 % received dialysis and most received corticosteroids (76.3 %). Initial antibiotic use in ICU is documented in Supplementary Table 5, although reasons for these choices could not be ascertained. Nevertheless, those whose treatment included amoxicillin-clavulanic acid, or a macrolide, had a significantly lower

Table 1
Clinical presentation, laboratory data, and chest radiographs of 931 patients admitted to ICU for severe CAP.

Clinical features	n (%) or median (IQR), n
Body temperature °C	36.8 (36–37.5), 909
MAP mmHg	80 (66–92), 883
Confusion	500 (54.4 %), 918
Severity of Illness scores (SOI)	**n (%) or median (IQR), n**
CURB-65	3 (2–3), 895
APACHE II	18 (14–23), 868
APACHE II ≥ 25	169 (19.5 %), 868
PF ratio	144 (97–229), 878
PF ratio ≤250	698 (79.3 %), 878
Laboratory data	**median (IQR), n**
Hb g/dL	10.6 (8.6–12.2), 921
Hct%	0.3 (0.3–0.3), 921
White cell count x10^9/L	9.9 (5.8–15.0), 920
Platelet count x10^9/L	206 (125–304), 915
Sodium mmol/L	136 (131–141), 921
Potassium, mmol/L	4.4 (3.9–5.1), 921
Urea mmol/L	12 (6.4–23.6), 921
Creatinine μmol/L	126 (73–304), 920
CRP mg/L	202 (118–288), 878
Total protein g/L	63 (53–74), 883
Albumin g/L	26 (21–30), 884
Total bilirubin μmol/L	11 (6–23), 887
AST U/L	82 (44–181), 888
ALT U/L	45 (24–94), 886
ALP U/L	97 (70–145), 886
GGT U/L	57 (28–109), 887
BDG pg./mL	103 (31–501), 491
Bacteraemia	248 (26.6 %)
Chest radiograph	
Multilobar consolidation	333 (41.5 %)
Bilateral GGO	243 (30.3 %)
Lobar consolidation	155 (19.3 %)
Nodules	49 (6.1 %)
Pleural effusion	22 (2.7 %)

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate transaminase; BDG: (1,3)-β-D glucan; CAP: community-acquired pneumonia: C: Celsius; CRP: C-reactive protein; GGO: ground glass opacities; GGT: gamma-glutamyl transferase; Hb: haemoglobin; Hct: haematocrit; IQR: interquartile range; MAP: mean arterial pressure; n: number; PF: partial pressure of oxygen/fraction of inspired oxygen; %: percentage.

mortality (P = 0.03 and P = 0.002, respectively). However, there was no apparent impact of combination beta-lactam (amoxicillin-clavulanic acid or cephalosporin) plus macrolide therapy on outcome (Supplementary Table 5).

The median length of ICU stay was 4 days (IQR 2–8 days) and was longer in those on IMV (5 [IQR 2–8] days vs 2.5 [IQR 2–4.8] days; P < 0.001), and in those requiring dialysis (5 [IQR 3–8] days vs 4 [IQR 2–8] days; P = 0.08); but it was shorter in those who died compared with those that lived (4 [IQR 2–8] days versus 5 [IQR 3–8] days; P = 0.025). Corticosteroid use had no impact on ICU length of stay.

Overall, 465 patients (49.9 %) survived, and 466 (50.1 %) died. However, fewer survived to hospital discharge (433 [46.5 %] survived and 498 [53.5 %] died). There were no differences in age, sex or cigarette smoking between the patients who lived and those who died. The risk of dying was lower in those with underlying chronic CVD compared with those without (OR, 0.62; 95 % CI 0.44–0.90; P = 0.01) (Table 3).

Table 4 compares the clinical, laboratory, and radiological findings in cases that lived versus those that died. Among the latter, median body temperature and MAP were lower, and more were confused. Both the CURB-65 and APACHE II scores were higher in those that died and more patients with an APACHE II score ≥ 25 died than lived (P = 0.001). The median PF ratio was significantly lower in those that died and more patients who died had a PF ratio ≤250.

Among the laboratory findings, BDG levels were significantly higher in those that died compared to those that lived; however, CRP levels were lower. Radiologically, a significantly higher proportion of patients

Table 2
Microbiological findings among 931 patients with severe CAP.

Microbial aetiology	MM, n (%)	PM, n (%)	Total, n (%)
***Mycobacterium* spp.**	131 (31.1 %)	47 (48 %)	178 (34.3 %)
MTb	130 (30.9 %)	45 (46 %)	175 (33.7 %)
MAC	1 (0.2 %)	2 (2 %)	3 (0.6 %)
Gram-positive pathogens	135 (32 %)	54 (55.1 %)	189 (36.4 %)
Streptococcus pneumoniae	103 (24 %)	22 (22.4 %)	125 (24.1 %)
Staphylococcus aureus	28 (6.7 %)	22 (22.4 %)	50 (9.6 %)
Streptococcus milleri	0	1 (1 %)	1 (0.2 %)
Streptococcus pyogenes	3 (0.7 %)	0	3 (0.6 %)
Streptococcus viridans	0	4 (4 %)	4 (0.8 %)
Enterococcus spp.	1 (0.2 %)	5 (5 %)	6 (1.2 %)
Gram-negative pathogens	82 (19.5 %)	65 (66.3 %)	147 (28.3 %)
Haemophilus influenzae	2 (0.5 %)	5 (5.1 %)	7 (1.3 %)
Enterobacterales			
Klebsiella pneumoniae	29 (6.9 %)	21 (21.4 %)	50 (9.6 %)
Escherichia coli	12 (2.9 %)	3 (3.1 %)	15 (2.9 %)
Enterobacter spp.	8 (1.9 %)	1(1 %)	9 (1.7 %)
Salmonella spp.	2 (0.5 %)	5 (5.1 %)	7 (1.3 %)
Citrobacter freundii	1 (0.2 %)	0	1 (0.2 %)
Proteus mirabilis	0	2 (2 %)	2 (0.4 %)
Providencia	0	1 (1 %)	1 (0.2 %)
Serratia marcescens	0	3 (3.1 %)	3 (0.6 %)
Other Gram-negative pathogens			
Pseudomonas aeruginosa	18 (4.3 %)	13 (13.3 %)	31 (6.0 %)
Acinetobacter spp.	8 (1.9 %)	4 (4.1 %)	12 (2.3 %)
Burkholderia cepacia	1 (0.2 %)	1 (1 %)	2 (0.4 %)
Stenotrophomonas maltophilia	1 (0.2 %)	3 (3.1 %)	4 (0.8 %)
Chryseobacterium indulgenes	0	1 (1 %)	1 (0.2 %)
Sphingobacterium multivorum	0	1 (1 %)	1 (0.2 %)
Ochrobactrum anthropic	0	1 (1 %)	1 (0.2 %)
So-called "atypical" pathogens	1 (0.2 %)	1 (1 %)	2 (0.4 %)
Chlamydophila pneumoniae	1 (0.2 %)	1 (1 %)	2 (0.4 %)
Viruses	32 (7.6 %)	23 (23.5 %)	55 (10.6 %)
VZV	15 (3.6 %)	9 (9.2 %)	24 (4.6 %)
CMV	1 (0.2 %)	3 (3.1 %)	4 (1 %)
Measles	4 (1 %)	2 (2.0 %)	6 (1.2 %)
Respiratory viruses			
Influenza virus (A, H1N1, B)	12 (2.9 %)	7 (7.1 %)	19 (3.7 %)
Adenovirus	0	2 (2 %)	2 (0.4 %)
Fungi	40 (9.5 %)	17 (17.3 %)	57 (11 %)
PJP	35 (8.3 %)	14 (14.3 %)	49 (9.4 %)
Candida spp.	2 (0.5 %)	0	2 (0.4 %)
Other fungi			
Cryptococcus neoformans	1 (0.2 %)	0	1 (0.2 %)
Aspergillus fumigatus	0	3 (3.1 %)	3 (0.6 %)
Saccharomyces cerevisiae	1 (0.2 %)	0	1 (0.2 %)
Stephanoascus ciferrii	1 (0.2 %)	0	1 (0.2 %)

Abbreviations: CMV: Cytomegalovirus; MAC: *Mycobacterium avium intracellulare*; MM: monomicrobial; MTb: *Mycobacterial tuberculosis*; n: number; PJP: *Pneumocystis jirovecii*; PM: polymicrobial; spp.: species; VZV: Varicella zoster virus; %: percentage.

who died had GGO on chest radiograph, whereas more patients who lived had lobar consolidation (P = 0.002) (Table 4).

Whether or not a microbial aetiology was identified had no impact on survival (Odds Ratio [OR]; 0.84; 95 % CI 0.80–1.34; P = 0.84) nor did the presence of polymicrobial versus monomicrobial infections (OR 0.73; 95 % CI 0.47–1.12; p = 0.28). However, when considering monomicrobial infections, PJP was a predictor for higher mortality (OR, 4.03; 95 % CI, 1.80–8.61; P = 0.003) and SP a predictor for lower mortality (OR, 0.49; 95 % CI 0.31–0.77; P = 0.002) (Table 5). Among those with drug-resistant pathogens, a similar proportion lived 16 [53.3 %] versus died (OR, 1.15; 95 % CI, 0.57–2.42; P = 0.85). Further analysis was not performed, because of small numbers of isolates. However, all five cases with MRSA and the only patient with XDR-MTb died.

Patients that required any form of ventilation had a higher risk of dying (OR, 10.98; 95 % CI, 6.27–19.78; P < 0.001). However, risk for mortality was lower for NIV (OR, 0.35; 95 % CI, 0.13–0.86; P = 0.034) relative to IMV. Furthermore, patients who received inotropic support and those who were dialysed were also more likely to die (OR, 3.38; 95

Table 3
Co-morbid diseases and their association with mortality (n = 931).

Co-morbid disease, n	Lived, 465 (%)	Died, 466 (%)	OR	95 % CI	P value
PLWH, 718	354 (49.3 %)	364 (50.7 %)	1.61	1.10-2.34	**0.01**
Chronic CVD, 142	85 (59.9 %)	57 (40.1 %)	0.62	0.44-0.90	**0.01**
Chronic respiratory disease, 78	43 (55.1 %)	35 (44.9 %)	0.80	0.50-1.26	0.35
COPD, 44	26 (59.1 %)	18 (40.9 %)	0.68	0.38-1.27	0.22
Diabetes mellitus, 77	39 (50.6 %)	38 (49.4 %)	0.97	0.61-1.53	0.91
Previous MTb, 62	32 (51.6 %)	30 (48.4 %)	0.93	0.57-1.58	0.79
Pregnancy, 59	28 (47.5 %)	31 (52.5 %)	1.00	0.58-1.76	>0.99
Current MTb, 31	13 (41.9 %)	18 (58.1 %)	1.44	0.66-2.84	0.47
Chronic kidney disease, 27	18 (66.7 %)	9 (33.3 %)	0.49	0.21-1.08	0.08
Chronic neurological disease, 24	14 (58.3 %)	10 (41.7 %)	0.71	0.32-1.54	0.42
Malignancy, 23	12 (52.2 %)	11 (47.8 %)	0.91	0.41-2.12	0.84

P values were assessed using the Fisher's Exact two tail test.
Odds ratios assessed by the Baptista Pike method.
Abbreviations: % = percent; CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; CVD: cardiovascular disease; HIV: Human Immunodeficiency Virus; MTb: *Mycobacterium tuberculosis*; n: number; OR: odds ratio; PLWH: People Living with HIV; 95 % CI: 95 % confidence intervals; Bold numbers represent significant P values.

% CI, 2.58–4.42; P < 0.001; and OR, 1,54; 95 % CI, 1.13–2.10; P = 0.008, respectively). Use or not of corticosteroids had no impact on mortality.

In the MVA, model MVA1 found that increased MAP, PaO_2, and FiO_2 were associated with a decreased mortality, whereas need for IMV or NIV was associated with a higher mortality. In MVA2, APACHE II score and PJP infection were each associated with a higher risk of dying, as was the use of IMV and inotropes. However, patients who underwent renal dialysis were at a lower risk of dying and similar to MVA1, mortality decreased with increasing CD_4 cell count and CRP, and also with lobar consolidation on chest radiograph. In MVA3, APACHE II and PJP infection were each associated with a higher risk of dying, as was the use of IMV and inotropes. Conversely, risk for mortality was lower amongst patients who were dialysed, had lobar consolidation, and decreased as the CD_4 cell count and CRP increased. (Supplementary Tables 1–3).

4. Discussion

This large retrospective study describes a cohort of 931 patients with SCAP admitted to an ICU at a tertiary referral hospital in Johannesburg, South Africa. The main findings were that the patients were relatively young (median age of 37 [IQR 30–48] years), and although the predominant co-morbidity was HIV co-infection (77.1 %), 42 % had other comorbidities. The median CURB-65 score was 3 (IQR 2–3), the median APACHE II score was 18 (IQR 14–23), and most patients had multilobar consolidation on chest radiograph. Overall, MTb was the most common aetiological pathogen identified, followed by SP and KP. The ICU mortality and overall hospital mortality were both very high (466 [50.1 %] and 498 [53.5 %], respectively) and a number of factors were significantly associated with mortality on univariate analysis, including the presence of confusion on admission, higher severity of illness score, higher BDG levels, and the presence of bilateral GGO on chest radiograph, while higher MAP, higher PF ratio, and the presence of lobar consolidation, were associated with lower mortality. Several of these parameters remained as independent risk factors for ICU mortality on the MVA. Infection with SP was associated with a significantly lower mortality, while PJP infection was significantly more common in those that died.

Table 4
Comparison of the clinical features, laboratory results and chest radiographs amongst survivors and non-survivors of severe CAP (n = 931).

Parameter	Lived	Died	P value
Clinical features	median (IQR), n or n (%)	median (IQR), n or n (%)	
Body temperature °C	36.9 (36.2–37.6), 452	36.8 (36.0–37.5), 456	**0.04**
MAP mmHg	82 (69–95), 448	77 (64–88), 435	**<0.001**
Confusion	222 (48.7 %)	278 (60 %)	**0.001**
SOI scores	**median (IQR), n or n (%)**	**median (IQR), n or n, (%)**	
CURB-65	2 (2–3), 449	3 (2–3), 446	**<0.001**
APACHE II	17 (13–21), 440	20 (15–24), 428	**<0.001**
APACHE II ≥ 25	66 (15 %)	103 (22.1 %)	**0.001**
PF ratio	170 (117–245), 440	121 (83–200), 438	**<0.001**
PF ≤ 250	334 (71.8 %)	364 (78.1 %)	**0.01**
Hb g/dL	10.6 (4.5–10.6), 462	10.5 (8.5–12.2), 459	0.61
Hct %	0.3 (0.1–0.4), 462	0.3 (0.3–0.4), 459	0.96
White cell count $x10^9$/L	9.2 (6.1–15.1), 462	10.4 (5.6–14.8), 458	0.67
Platelets $x10^9$/L	206 (136–298), 460	207 (108–310), 455	0.32
Sodium mmol/L	136 (131–141), 462	136 (132–141), 459	0.80
Potassium, mmol/L	4.3 (3.7–4.9), 462	4.5 (4–5.1), 459	**0.002**
Urea mmol/L	12 (6.5–22), 462	12.2 (6.4–25.5), 459	0.54
Creatinine μmol/L	121.5 (74–286.5), 462	135.5 (73–316), 458	0.45
CRP mg/L	216.5 (121.8–301.5), 442	193 (115–273), 435	**0.01**
Total protein g/L	64 (55–75), 443	61 (51.3–72.8), 440	**0.001**
Albumin g/L	27 (22–31), 443	25 (20–29), 441	**0.001**
Total bilirubin μmol/L	11 (6–22), 444	11 (6–25), 443	0.88
AST U/L	76 (41–167), 445	87 (49–213), 443	**0.02**
ALT U/L	43 (23–92), 442	47 (26–94), 443	0.40
ALP U/l	95 (65–144), 443	99 (73–148), 443	0.20
GGT U/L	57.5 (28–112), 444	56 (29–106), 443	0.91
CD_4 count cells/mm^3	53.5 (19–138.3), 314	27.5 (10–81), 260	**<0.001**
BDG pg/mL	61 (31–227), 234	270 (49–501), 257	**<0.001**
Bacteraemia	113 (24.3 %)	100 (21.5 %)	0.49
Chest radiograph, n (%)	**n (%)**	**n (%)**	
Multilobar consolidation	178 (42.9 %)	155 (40 %)	0.43
Bilateral GGO	94 (22.7 %)	149 (38.5 %)	**<0.001**
Lobar consolidation	101 (24.3 %)	54 (13.9 %)	**0.002**
Nodules	29 (7.0 %)	20 (5.2 %)	0.31
Pleural effusion	13 (3.1 %)	9 (2.3 %)	0.40

P values analysed using Fisher's exact two-tail test.
CD_4 cell counts only measured in HIV-positive population.
Abbreviations: %: percent; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BDG: (1–3) β-D-Glucan; C: Celsius; CAP: community-acquired pneumonia; CD_4: cluster of differentiation 4; CRP: C-reactive protein; GGO: ground glass opacities; GGT: gamma glutamyl transferase; Hb: haemoglobin; Hct: haematocrit; IQR: interquartile range; MAP: mean arterial pressure; n: number; PF: partial pressure of oxygen/fraction of inspired oxygen; SOI: severity of illness; temp: temperature; Bold numbers indicate significant P values.

The younger age of this cohort is similar to that of previous studies of SCAP from South Africa [6,17–19], but differs from international data with older cohorts [20–24]. However, as in studies by Quah et al. [21], and Erdem et al. [24], the current study found no differences in age between those who lived and those who died, which is also in contrast to other international SCAP studies in which age was an independent predictor of mortality [20,22,23,25,26].

Males and females were equally distributed in this study and sex was not associated with a mortality difference, which also differs from

Table 5
Monomicrobial CAP and mortality in patients with SCAP (n = 421).

Microbial aetiology, n	Lived, n (%)	Died, n (%)	OR	95 % CI	P value
***Mycobacterium* spp.**					
MTb, 130	67 (51.1 %)	63 (48.5 %)	1.01	0.68-1.55	>0.99
MAC, 1	1 (100 %)	0			
Gram-positive pathogens					
Streptococcus pneumoniae, 99	67 (67.7 %)	36 (36.4 %)	0.49	0.31-0.77	**0.002**
Staphylococcus aureus, 28	16 (57.1 %)	12 (42.9 %)	0.79	0.37-1.73	0.70
Streptococcus pyogenes, 3	1 (33.3 %)	2 (66.7 %)			
Enterococcus faecalis, 1	1 (100 %)	0 (0.00 %)			
Gram-negative pathogens					
Haemophilus influenzae, 2	1 (50 %)	1 (50 %)			
Enterobacterales					
Klebsiella pneumoniae, 29	16 (55.2 %)	13 (44.8 %)	0.86	0.42-1.84	0.85
Escherichia coli, 12	6 (50 %)	6 (50 %)			
Enterobacter spp., 8	3 (37.5 %)	5 (62.5 %)			
Salmonella spp., 2	0 (0.0 %)	2 (100 %)			
Citrobacter freundii, 1	0 (0.0 %)	1 (100 %)			
Pseudomonas aeruginosa, 18	8 (44.4 %)	10 (55.6 %)			
Acinetobacter spp., 8	1 (12.5 %)	7 (87.5 %)			
Other Gram-negative pathogens					
*Burkholderia cepacia,*1	1 (100 %)	0 (0.0 %)			
Stenotrophomonas maltophilia, 1	1 (100 %)	0 (0.0 %)			
So called "Atypical" pathogens					
Chlamydophila pneumoniae, 1	0 (0.0 %)	1 (100 %)			
Viruses	18 (56.3 %)	14 (43.8 %)	0.82	0.39-1.66	0.71
VZV, 15	11 (73.3 %)	4 (26.7 %)			
CMV,1	0	1 (100 %)			
Measles, 4	1 (25 %)	3 (75 %)			
Respiratory viruses, 12	6 (50 %)	6 (50 %)			
Fungi					
PJP, 34	8 (23.5 %)	27 (79.4 %)	4.03	1.80-8.61	**0.003**
Candida albicans, 2	0 (0 %)	2 (100 %)			
Cryptococcus neoformans, 1	1 (100 %)	0			
Saccharomyces cerevisiae, 1	0	1 (100 %)			
Stephanoascus ciferri, 1	1 (100 %)	0			

P values were assessed using the Fisher's Exact two tail test.
Odds ratios assessed by the Baptista Pike method.
Abbreviations: CMV: Cytomegalovirus; MTb: *Mycobacterium tuberculosis*; MAC: *Mycobacterium avium intracellulare*; n: number; OR: odds ratio; PJP: *Pneumocystis jirovecii*; Respiratory viruses: Influenza virus (A, H1N1, B, respiratory virus screen); spp.: species; VZV: Varicella zoster virus; %: percentage; 95 % CI: 95 % confidence intervals; Bold numbers indicate significant P values.

international SCAP studies that noted a higher proportion of male patients [8,20,21,23–25,27,28] and in at least one study of pneumococcal CAP, male sex was independently associated with mortality (OR 2.83 [95 % CI 1.16–6.91]; P = 0.01) [9]. The majority (95.6 %) of patients in the current study did not smoke, which also differs from international SCAP data [9,24,25], but is similar to data from Turkey [24], and smoking did not contribute to mortality [24].

Comorbid conditions were common in the current study and in the 42 % of cases with comorbidity other than HIV, CVD was the most common. The frequency of comorbidities varies between different SCAP studies, reflecting local disease patterns, the average age of the population and their habits [20,21,23,25].

The CURB-65 score was higher in non-survivors (P < 0.001) and the median APACHE II score was 18 (IQR 14–23), with a lower predicted mortality of 24 % (15%–40 %) than the actual mortality at 50 %. This is not surprising as previous studies have shown that the APACHE II can underestimate mortality, particularly in patients on IMV [29]. The APACHE II score was, however, higher in non-survivors and was an independent predictor of mortality on MVA, as in other studies of SCAP [21,29].The majority (79.3 %) of the patients in the current study had a mean PF ratio ≤250, which was also more common in non-survivors (P = 0.01). In contrast to a validation study of the individual criteria for SCAP which demonstrated that a PF ratio <250 was independently associated only with need for ICU admission [30], the PF ratio in the current cohort was shown to be an independent predictor of mortality on MVA.

Although in previous studies uraemia has been shown to predict mortality [31], in this study a urea ≥7 mmol/L alone did not; however, as the median urea level was elevated overall (12 [IQR 6.4–23.6] mmol/L), it may have been too high both in survivors and non-survivors to detect a difference. Overall, 22.4 % of patients required dialysis and although this predicted mortality on univariate analysis, on MVA, patients on dialysis were more likely to survive. This may possibly be due to control of confounding variables, or the fact that sicker patients on inotropes or IMV, may not have been dialysed, being deemed too unstable or hypotensive to tolerate it. In contrast, another study showed that 17.2 % of patients required renal replacement therapy (RRT) in the first ICU week, and this was associated with an increased 28-day and 6-month mortality [32].

The median CRP for the entire cohort was 202 (IQR 118–288) mg/L but lower values were associated with increased mortality on MVA. In contrast, other studies [21,29] have not found a relationship between CRP and survival. CRP levels differed according to the culprit pathogens, it was highest with SP, and thereafter MTb, and PJP infection, and was still lower with viral infections, similar to data elsewhere [21]. These data are similar to previous CAP studies from South Africa [33,34] and other international studies [35]. The lower CRP in non-survivors could be explained by the higher mortality with MTb and PJP, both of which had lower CRP levels, and the association of survival in those with higher CRP due to the lower mortality from *S. pneumoniae* infections.

The BDG test [36] has been used as part of the diagnostic strategy for PJP at CMJAH since 2009. A recent meta-analysis demonstrated that high levels of BDG had a reasonable sensitivity and specificity for PJP infection [37–39] and in the current study levels were elevated (≥80 pg/ml) in the entire cohort. Interestingly, a prospective study of critically ill ICU patients demonstrated that BDG was increased in ICU patients with confirmed infections compared to those without [40]. In the current study, not all patients with elevated BDG had an identifiable microbial cause, and as such it may act as a marker of more severe inflammation [41].

In the current study GGO was an independent risk factor for mortality and lobar consolidation an independent risk factor for survival, similar to data from Pune [8]. This corresponds with the fact that GGO were present in most patients with PJP, which had a high mortality, whereas SP with lobar involvement was associated with significantly lower mortality.

For a large period of this study, microbiological diagnosis relied heavily on blood culture, sputum smear and culture and histopathology, as extended PCR panels including GeneXpert™ and urinalysis were not available. Even when more advanced microbiological techniques were introduced later in the study, they were used sparingly because of resource constraints. Despite this, a putative pathogen was documented in 519 (55.7 %) of cases, including monomicrobial and polymicrobial

infections, although identification of an organism was not associated with increased mortality. This is similar to some studies in SCAP [27], but does differ from those that had access to more comprehensive diagnostic techniques [8,21]. There were few differences in the baseline characteristics or comorbidities in those in whom microbial pathogens were, or were not, isolated (Supplementary Table 4).

MTb was the predominant pathogen identified in both mono- and polymicrobial infections. This contrasts with a study from Singapore (an area with endemic TB), where MTb was documented in only 2.6 % of cases [21]. However, in a previous study from South Africa, there was a 1.5 % incidence of respiratory failure amongst patients admitted to hospital with MTb, a 33 % mortality following ICU admission, and a 3-month mortality of 47 % [42].

SP was the second most common pathogen isolated, and although this differs from other data [43], most other SCAP studies excluded MTb from their analysis [6,8,20,23,24,27]. The incidence of SA in the current cohort at 3 % was higher than in data from Spain, but lower than that of other studies [8,20]. SA infection is well described following or during viral infections, especially with influenza virus [44], but in the current study SP appeared to be more common in those in whom data on viral infections was available. Gram-negative bacteria were identified in 82 (19.5 %) of monomicrobial infections, with KP and *Pseudomonas aeruginosa* (PA) the most common (6.9 % and 4.3 %, respectively). This compares with 4.3 % and 22 % for the former and 3.4 %, 1.8 % and 5.5 % for the latter pathogen in other studies [8,21]. There was no increased risk of mortality amongst patients with Gram-negative infections, which is in contrast to other studies in which the mortality was high overall (67 %) and 33 % for PA [17,45].

Overall, 10.5 % of patients had polymicrobial infections, which was the third most common cause of SCAP after MTb and SP, similar to other studies [35]. MTb was identified in 46 % of the polymicrobial infections, possibly due to mycobacterial suppression of monocyte function [46]; and SP was a common co-pathogen, which has also been described [25], Finally, although mortality was not increased with polymicrobial infections, in other studies there was more frequent need for IMV in such infections [25,29].

Bacteraemia occurred in 22.7 %, and although this was not associated with increased mortality it has previously been shown to be independently associated with mortality [23]. In other studies of SCAP, bacteraemia was reported in 18 % of cases [25], and Ferrer et al., found no difference in the need for IMV [29].

According to commonly used definitions [47,48] all patients met the criteria for SIRS and sepsis, while 25.4 % had septic shock and 24.8 % had ARDS of varying degrees, the latter being similar to the prevalence reported in ICU previously among ventilated patients [48]. Initial antibiotic use in ICU is documented in Supplementary Table 5, although reasons for these choices could not be ascertained. Nevertheless, those whose treatment included amoxicillin-clavulanic acid, or a macrolide, had a significantly lower mortality ($P = 0.03$ and $P = 0.002$, respectively). However, there was no apparent impact of combination beta-lactam (amoxicillin-clavulanic acid or cephalosporin) plus macrolide therapy on outcome (Supplementary Table 5). The higher mortality in those who were on co-trimoxazole, most likely represented cases with PJP infections, who were documented in the study to have a high mortality, and the lower mortality in those with acyclovir use may represent cases treated for VZV pneumonia, most of whom survived.

Requirement for IMV is one of the major criteria of severity in the ATS/IDSA guideline [10]. Within the existing cohort, 800 patients (85 %) were ventilated, the predominant mode being IMV. This, as in other studies, was associated with an increased mortality [29,30,32,49]. Despite considerable variation in the use of IMV in other CAP studies (13%–67.2 %) the frequency of ventilation (both IMV and NIV) in the current study is very high [20,25,29,50].

CS were used in most patients (711 [76.3 %]), but use was not associated with any mortality difference. This is in contrast to other studies that have shown some benefit in patients with severe CAP [51, 52] including a lower 28 day mortality in at least one investigation [53]. The difference may be due to the fact that in the current study there were a significant number of patients with viral (7.6 %) including influenza, and PJP infections (8.3 %), and some studies have suggested a higher mortality with CS in severe influenza pneumonia [54], while the overall mortality of PJP was high. Fifty percent of all patients required inotropic support, which was associated with a higher mortality. As inotrope use reflects severity of illness and possibly septic shock [10] their use is unsurprisingly associated with increased mortality [23,24,55–57].

The overall ICU LOS was increased in those that were ventilated, and/or required renal dialysis, but was shorter amongst patients who died. Other studies have also reported longer LOS amongst SCAP patients on IMV [29,35].

The strength of this study is that it investigated a very large cohort of patients with SCAP, including immunocompromised individuals, and reviewed a comprehensive spectrum of putative pathogens. However, the study does have some potential limitations. First, this was a single-centre study, and so the findings may not be generalizable to other ICUs, to other regions of South Africa or the rest of the world. Second, it included only cases with SCAP who were admitted to an ICU, and so the findings are only pertinent to patients with CAP in this setting. Third, the study was a record review and since there was limited access to electronic medical records, much of the data had to be retrieved from stored files, some of which were incomplete, and others damaged. Thus, in a significant proportion (21 %) there were insufficient data to confirm the diagnosis of SCAP, so these cases were excluded, which may have significantly underestimated the prevalence of SCAP in the ICU. Fourth, the chest radiographic findings were largely based on the physician reporting in the case notes. However, the director of the ICU during this period was a senior pulmonology consultant, and all pneumonia admissions were seen by the pulmonology team. The accuracy of reporting was verified in the latter part of the study, when an electronic radiology reporting system was introduced (2016). Finally, access to advanced microbiological testing was not yet available for causative pathogens in the earlier years of this study, and only used sparingly once they became available because of resource constraints. It is, therefore, highly likely that a significant proportion of the microorganisms, particularly viral pathogens, such as influenza, and the so-called “atypical pathogens” were undiagnosed.

5. Conclusions

This was a large study of patients with SCAP admitted to ICU at a tertiary referral hospital in Johannesburg, South Africa. The patients were young, and the predominant co-morbidity was HIV co-infection (77.1 %). MTb was the most common aetiology identified and SP was the next most common pathogen identified. Overall mortality was high and need for ventilation, inotropes and dialysis were associated with an increased risk of death. This appears to be the largest ICU cohort of patients with SCAP reported in the literature.

CRediT authorship contribution statement

Jacqueline P. Venturas: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Guy A. Richards:** Writing – review & editing, Visualization, Supervision, Data curation. **Charles Feldman:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

CF acts on the Speaker’s bureau of Sandoz and Aurogen. All the other authors declare that they have no conflict of interests in relation to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107823.

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