EVALUATION OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, 2007-2019

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DECLARATION:

I, Jacqueline Penelope Venturas declare that this research report is my own work. It is being submitted in partial fulfilment for the degree of the Master of Medicine in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

20 June 2023

Jacqueline Penelope Venturas

Date

This work is dedicated to my parents, Dawn and Byron Venturas who taught me to aim for the stars.

ABSTRACT

Severe Community Acquired Pneumonia (SCAP) is associated with significant morbidity and mortality worldwide, and there are a paucity of data relating to infections in South Africa, a country with a high prevalence of HIV co-infection. The aim of this study was to investigate a cohort of HIV-positive and HIV-negative patients with SCAP, who were admitted to ICU at a tertiary hospital in Johannesburg, South Africa.

This was a retrospective single-centre observational study. Consecutive patients admitted to the Medical ICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 July 2007 and 31 May 2019 with a diagnosis of community-acquired pneumonia were included in the study. Patients were identified by using the ICU admission books, electronic discharge summaries and/or clinical case notes. Pneumonia was considered to be community-acquired if there was no hospitalization in the 2 weeks prior to the current admission.

After excluding 313 records, the cohort consisted of 931 patients with SCAP. The patients were young (median age 37 [IQR 30-48] years), and the predominant co-morbidity was HIV co-infection (77.1%). 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 X-ray. Overall *Mycobacterium tuberculosis* was the most common microbial aetiology identified amongst both HIV-positive and HIV-negative patients. *Streptococcus pneumoniae* was more common amongst the patients who lived, whereas infection with *Pneumocystis jirovecii* was more common amongst patients who died. Overall mortality was high (50.1%), and PLWH had a higher risk of mortality than their HIV-negative counterparts on univariable analysis (OR, 1.61; 95% CI 1.07-2.34; P=0.01).

In conclusion, we describe a cohort of patients with SCAP in Johannesburg, an area with high HIV prevalence. To our knowledge, this is the largest ICU cohort of patients with SCAP reported in the literature.

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NOMENCLATURE AND ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
aHR	adjusted Hazard ratio
AIDS	Acquired Immune Deficiency Syndrome
APACHE	Acute Physiology and Chronic Health Evaluation
ARB	Angiotensin II receptor blocker
ART	Antiretroviral therapy
AST	Aspartate transaminase
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ATS	American Thoracic Society
ASDR	Age standardized death rates
AUROC	Area under the receiver operator curve
BAL	Bronchoalveolar lavage
BDG	(1-3)-□-D- Glucan
CAP	Community-Acquired Pneumonia
CDC	Centres for Disease Control and Prevention
CD_4	Cluster of differentiation 4
CEO	Chief Executive Officer
CHBH	Chris Hani Baragwanath Hospital
CI	Confidence Interval
CKD	Chronic kidney disease
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CN	*Cryptococcus neoformans*
CP	*Chlamydophila pneumoniae*
CRB-65	Confusion, Respiratory rate, Blood pressure –Age $\geq$ 65years
CRP	C-reactive protein
CS	corticosteroid
CURB-65	Confusion, Urea, Respiratory rate, Blood pressure –Age $\geq$ 65years
CVA	Cerebrovascular accident
DALYS	Disability-Adjusted Life Years
DKA	Diabetic ketoacidosis

DLCO	Diffusion capacity for carbon monoxide
EDTA	Ethylenediaminetetraacetic acid
FEV_1	Forced Expiratory Volume in one second
$Fi0_2$	Fraction of inspired oxygen
FVC	Forced Vital Capacity
GBD	Global Burden of Disease Study
GenOSept	Genetics of Sepsis in Europe
GIT	Gastrointestinal tract
GGO	Ground glass opacities
GGT	Gamma-glutamyl transferase
GNEB	Gram-negative Enterobacterales
HI	*Haemophilus influenzae*
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSV	Herpes simplex Virus
ICU	Intensive Care Unit
IDU	Intravenous drug use
IDSA	Infectious Diseases Society of America
IMV	Invasive Mechanical Ventilation
IL-6	Interleukin-6
IPD	Invasive Pneumococcal Disease
KP	*Klebsiella pneumoniae*
KZN	KwaZulu Natal
LP	*Legionella pneumophila*
LRTI	Lower Respiratory Tract Infections
LOS	Length of stay
MAC	*Mycobacterium avium-intracellulare*
MM	monomicrobial
MP	*Mycoplasma pneumoniae*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MTB	*Mycobacterium tuberculosis*
MV	Mechanical ventilation
MVA	Multivariable analysis
NIV	Non-invasive ventilation

NFκB	Nuclear factor kappa B
NHLS	National Health Laboratory Services
OR	Odds ratio
$Pa0_2$	Partial pressure of oxygen
PACS	Picture Archiving and Communication System
PAMPS	Pathogen-Associated Molecular Patterns
PF	$Pa0_2/Fi0_2$
PA	*Pseudomonas aeruginosa*
PCR	Polymerase Chain Reaction
pH	potential Hydrogen
PJP	*Pneumocystis jirovecii*
PM	polymicrobial
PPV	Positive pressure ventilation
PSI	Pneumonia Severity Index
PVL	Panton Valentine Leucocidin (PVL) toxin
RIFLE	Risk, Injury, Failure, Loss, End-Stage Kidney
RR	Relative risk
RRT	Renal replacement therapy
RSV	*Respiratory syncytial virus*
SA	*Staphylococcus aureus*
SADHS	South African Demographic and Health Survey
SAfr	South Africa
SCAP	Severe Community-Acquired Pneumonia
SD	Standard deviation
SOI	Severity of illness
SP	*Streptococcus pneumoniae*
spp	Species
TNFα	Tumour necrosis factor α
USA	United States of America
Vs	versus
VZV	Varicella zoster virus
WHO	World Health Organisation

CHAPTER ONE-INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Community-acquired pneumonia (CAP) is an acute illness resulting from infection of the lungs with subsequent parenchymal lung inflammation (1). The spectrum of infection ranges from a relatively mild infection that may safely be treated as an outpatient, to a life-threatening illness, necessitating hospitalization, and even intensive care unit (ICU) admission. Severe community-acquired pneumonia (SCAP) is a term that has been used to describe patients who require admission to an Intensive Care Unit (ICU) and who are likely to develop complications (1, 2). The mortality of SCAP ranges from 25%-50%. The number of patients requiring ICU care for SCAP has increased worldwide, especially amongst vulnerable population groups such as the elderly, patients with co-morbid disease and patients who are immunocompromised, with *Streptococcus pneumoniae* (pneumococcus) being the main pathogen (3).

Despite all the advances in medicine, CAP remains a major cause of increased morbidity and mortality worldwide. In the United States of America (USA) in 2006, CAP was second only to childbirth as the most common reason for hospital admission (4). CAP affects all age groups, but especially the young and the elderly, as well as all strata of society.

There have been a myriad of studies of non-severe CAP, but there have been much fewer studies of SCAP. In addition, in several CAP studies, immunocompromised patients, such as those with human immunodeficiency virus (HIV) infection, who are infected with a broader spectrum of pathogens including *Mycobacterium tuberculosis* (MTB) and *Pneumocystis jirovecii* (PJP), have been excluded. Furthermore, there are relatively few recent studies on SCAP in sub-Saharan Africa. This research report addresses the issue of SCAP in a predominately HIV-positive population in South Africa, including the entire spectrum of microorganisms.

1.2 Literature Review

1.2.1 Incidence

The Global Burden of Diseases, Injuries and Risk Factors (GBD) Study approximated that in 2016, lower respiratory tract infections (LRTIs), including pneumonia as a prominent cause, were the sixth leading cause of death overall and the leading infectious disease cause of death worldwide, accounting for 2,377 697 million deaths and 9,184 4600 disability-adjusted life years (DALYS) (5). A recent study from the United States (US) estimated that the annual number of in-hospital all-cause deaths in patients hospitalized with CAP was 102,821, while the 30-day mortality was 205,642 (6). The GBD study estimated that there were 650,639 lower respiratory tract infection (LRTI) deaths in sub-Saharan Africa alone in 2016 (5).

1.2.2 Aetiology

The reported aetiology of CAP varies in different geographical areas. Part of the reason for these differences is that many studies reporting aetiology exclude immunocompromised patients, including those with HIV, as well as certain pathogens, particularly MTB (7). In up to 50% of cases of CAP the aetiology is unknown; however, this figure is lower in ICU settings (47%) with the utility of broader diagnostic techniques (8).

The GBD study reported that *Streptococcus pneumoniae* (SP) was the most common aetiology of LRTIs worldwide, accounting for 1,189 937 deaths (5). Other organisms causing LRTIs include *Haemophilus influenzae* (HI), atypical organisms such as *Mycoplasma pneumoniae* (MP), *Chlamydophila pneumoniae* (CP) and *Legionella pneumophila* (LP), *Staphylococcus aureus* (SA), Gram-negative pathogens including *Klebsiella pneumoniae* (KP), *Pseudomonas aeruginosa* (PA) and enteric organisms, and respiratory viruses such as Influenza virus, Respiratory syncytial virus (RSV), Adenovirus and SARS-CoV-2 (1, 7, 9). MTB is a common cause of CAP in TB endemic areas (7, 10, 11). Gram-negative *Enterobacterales* (GNEB), SA and polymicrobial (PM) infections have been frequently identified in patients with higher Confusion, Urea >7mmol/, Respiratory rate ≥30 breaths/minute, Blood pressure <90mmHg (Systolic) and/or <60mmHg (Diastolic), Age ≥ 65years (CURB-65) scores (8) (12). PJP, Cytomegalovirus (CMV), Herpes simplex virus (HSV), *Mycobacterium avium-intracellulare* (MAC), *Cryptococcus neoformans* (CN) and *Aspergillus species* (spp.) are also causes of CAP in areas of high HIV prevalence (13).

Feldman *et al*., performed a retrospective study of SCAP in a South African ICU between January 1982 and December 1992, which excluded patients with MTB infection. SP infection was identified in 51.3% of isolates, and KP in 31.9% of isolates. KP infection carried a higher mortality than SP (68.4% vs 33.9%) (14).

A 15-year retrospective Spanish study of SCAP between 1999 and 2013, identified SP as the predominant pathogen. LP was the second most common pathogen detected, but this incidence decreased over the time period. However, of note, was an increase in viral pneumonia between 2009 and 2013 of which 64% of cases were due to influenza infection (15).

In a prospective North American study, Park *et al*., recruited patients with CAP between 1 June 1994 and 30 May 1996. They found that the pathogens most commonly involved in cases of SCAP were SP, CP, LP and HI in the HIV-negative group. However, the common pathogens in patients who were co-infected with HIV were PJP, PA, CMV and MAC. Overall, MTB was found in four cases, three in HIV-negative patients (16).

A prospective study of SCAP in Pune, India, between January 2012 and 2014 enrolled 111 HIV-positive patients. Overall, 79.3% of infections were monomicrobial (MM) aetiologies, with MTB accounting for 23.3% of infections and SP being the cause of 17.8% infections. Of the 20.7% of infections, which were PM, 63% had MTB as a co-pathogen. Patients with mycobacterial, fungal and viral aetiologies were excluded from further analysis (17).

Studies from sub-Saharan Africa on patients fitting the description of CAP have shown that MTB infection is a leading cause of CAP. In a prospective CAP study in KwaZulu Natal between June 2000 and July 2001, Kennedy *et al*., identified MTB as the most common pathogen (39.6%) regardless of HIV status, followed by SP (34.5%) and MP (17%). Overall, 81.4% of patients tested were HIV-positive (10). Co-infections occurred in 16% of patients, most commonly MTB and SP infections. Another study from Malawi identified MTB as the predominant pathogen amongst hospitalized CAP patients with HIV infection and this was associated with a higher mortality (11).

PJP is a cause of severe pneumonia in HIV-infected individuals, as well as in patients on immunosuppressive therapy (18). A meta-analysis reported a 22% prevalence of PJP amongst in-patients in sub-Saharan Africa with a calculated case fatality rate of 18.8%, higher than that

for most other respiratory infections. Overall, 29.3% of patients had additional pulmonary pathology and 14.8% of patients had co-infection with MTB, 8.7% with bacterial pneumonia and 4.1% also had Kaposi's sarcoma. This study included patients aged ≥13 years from any clinical setting, and the diagnosis of PJP was made using WHO-based clinical criteria or laboratory data (19).

1.2.3 Risk Factors

The risk factors for developing CAP are numerous and include age, cigarette smoking, comorbid diseases and immunocompromise, in particular HIV infection (6, 20). Furthermore, host genetics and pathogen-specific virulence factors have been implicated in the progression to SCAP (21, 22).

The Centres for Disease Control and Prevention (CDC) includes recurrent bacterial pneumonia as an AIDS-defining condition (23). Among HIV-infected patients, and before the use of anti-retroviral therapy (ART), rates of bacterial pneumonia occurred up to 25 times more often than among HIV-uninfected individuals (24, 25). Moreover, rates of pneumococcal bacteraemia and the frequency of invasive pneumococcal disease (IPD) are significantly higher amongst patients with HIV co-infection and have remained unchanged, despite a stable HIV prevalence and a comprehensive roll-out of ART (25). In 2021 there were 7,500,000 people in South Africa living with HIV and only 74% were accessing ART (26). Thus, HIV infection is a major driving force for the development of CAP, particularly in sub-Saharan Africa, where HIV infection is so common (25).

1.2.4 Severity of Illness Scoring Systems

Many different severity of illness (SOI) scoring systems have been developed to aid in the identification of patients with severe CAP. The CURB-65 (27) and Pneumonia Severity Index (PSI) (28) are the most commonly used scoring systems. They both predict 30-day mortality, but neither are useful in ICU triage decisions. The IDSA/ATS guideline (29) which has more specific features for severe pneumonia, performs better in the identification of SCAP (2). These scoring systems have not been extensively validated in the HIV-positive population nor in patients from low-income settings.

Kabundji and colleagues, assessed a cohort of 152 patients with CAP from a Johannesburg Hospital emergency department, describing the potential utility of the CRB-65 (CURB-65 without the urea value) as a SOI score. The score accurately identified which hospitalized patients had a higher risk of mortality, as well as those who could be safely managed as out-patients (30). In another study, Almeida *et al*., recruited 396 patients with CAP of which 49 were HIV-positive, and 347 HIV-negative. The mean CURB-65 score was lower in the HIV-positive patients, furthermore the in-hospital mortality was 4.1% in HIV-positive patients and 12.1% in HIV-negative patients (31). Both studies excluded patients with MTB, PJP and fungal pneumonia. In contrast, data from two studies in Malawi have shown a poor correlation between mortality risk, the CURB-65 score (7) and the CRB-65 score (32).

1.2.5 Mortality

Despite antimicrobial therapy, there appears to have been an increase in hospital admissions and mortality from CAP over the last few years, especially amongst the elderly and those with co-morbid disease (4). Some studies have suggested that the mortality of severe pneumonia is similar in HIV-positive and HIV-negative patients (33); however, other studies have contradicted this. Feldman *et al.*, in a prospective study comparing mortality in HIV-positive and HIV-negative patients with bacteraemic pneumococcal pneumonia, determined that the 14-day mortality was significantly higher in the HIV-positive patients when age and SOI were adjusted for. In addition, the median CD_4 count was significantly lower in the HIV-positive patients who died compared with those who lived (14, 34).

The mortality rate from CAP varies between <1% to 50% depending on the severity of pneumonia (35, 36), being 21% in patients with CAP who are admitted to hospital requiring ICU admission, and 26% in those patients requiring mechanical ventilation (3). Furthermore, a 2010 study showed that there was a significant decrease in long-term survival for up to 7.5 years of follow-up amongst patients who were discharged from hospital with CAP (37).

1.2.6 Conclusion

There are limited data from sub-Saharan Africa on the aetiology, ICU course and outcome of SCAP, especially in the setting of HIV infection and in the era of the ART roll-out. Studies that have been done were either performed prior to the ART roll-out, have excluded patients with tuberculosis, or have only included cases with a specific pathogen, such as the

pneumococcus or suspected PJP (14, 38). International studies of SCAP have also only studied certain specified pathogens and often excluded MTB, PJP, and fungal and viral infections from the analysis (17, 39).

1.3 Aim and Objectives

1.3.1 Aims of the Study

The aims of the study were, therefore, to investigate the aetiology, clinical characteristics and outcomes of patients with SCAP, admitted to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) multidisciplinary Intensive Care Unit (ICU) in Johannesburg over a 12-year period.

1.3.2 Study Objectives

1) To describe the demographics of the patients admitted with severe CAP.
2) To evaluate the microbiological aetiology of SCAP.
3) To report the clinical features with regard to SOI scoring systems.
4) To describe the treatment, clinical course, complications and outcome in the ICU setting.
5) To compare all the characteristics described above in HIV-infected and HIV-uninfected patients.

CHAPTER TWO – MATERIALS AND METHODS

2.1 Study Design

This study was a single-centre retrospective observational study. Consecutive patients admitted to the General ICU (area 576) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 July 2007 and 31 May 2019 with a diagnosis of CAP were included in the study. The hospital is an accredited central hospital, serving patients from across the Gauteng province and neighbouring provinces, and offers a full range of secondary, tertiary, and highly specialized services. Patients were identified by using the admission books in Ward 576 (Intensive Care Unit).

2.2 Criteria for Inclusion

The criteria that were used to confirm the diagnosis of CAP, were the same as those as described before (29). These included a new pulmonary infiltrate (within 24 h of admission) associated with at least one of the following:

A 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.

Pneumonia was considered to be community-acquired if there was no hospitalization in the two weeks prior to the current admission, and severe if the patient required ICU admission.

2.3 Sources of Data

Sources of data were limited to:

Admission medical records from the medical ICU (Ward 576)

Electronic discharge summaries and/or clinical case notes.

Picture Archiving and Communication system (PACS; Phillips Intellispace PACS Radiology version 4.4.532.1), an electronic platform at CMJAH to access radiology.

Admission records from the medical ICU (Ward 576) were accessed manually, and details of all patients who were admitted between 1 July 2007 and 31 May 2019, with a diagnosis of "community-acquired pneumonia", were collected. Following the identification of patients, the relevant ICU charts were collected, and data were manually entered into an Excel

spreadsheet in accordance with the data dictionary shown in Appendix A. Patient files were excluded from the data collection if they did not fulfil the defined diagnostic criteria for SCAP, if the file could not be found, or if data were insufficient to confirm the diagnosis of SCAP. The data extraction was undertaken once approval has been obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) and the Chief Executive Officers (CEOs) of CMJAH (Clearance certificate number M2008109 appendix B and appendix C respectively).

The SOI was assessed using the CURB-65 score (Confusion, Urea >7 mmol/L, Respiratory rate ≥30 breaths/minute, Blood pressure <90mmHg (Systolic) and/or <60mmHg (Diastolic), Age ≥ 65years (27) and APACHE II score (a 12 point scoring system to predict ICU mortality (40, 41)). In addition, the $Pa0_2/Fi0_2$ ratio, one of the minor criteria from the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines (29), was calculated for each patient.

As was practice in the medical ICU, routine laboratory results were collected for all patients on admission. These tests included full blood count (FBC), biochemistry (renal function and liver function) and C-reactive protein (CRP). HIV results (Cobas HIV-1/HIV-2 qualitative assay [Roche], as a screening test and HIV Ag/Ab combo assay [Abbott] as confirmatory test) were collected only from patients in whom informed consent was obtained (in accordance with South African HIV testing policy (42)), with corresponding CD_4 cell counts (flow cytometry on a Beckman-Coulter MPLFC500 cytometer) and HIV viral loads (Roche cobas® 6800/8800 HIV-1 test).

Routine microbiological testing in the patients was usually done in accordance with the South African CAP guideline (1). Results of the microbiological testing was collected, where available, including testing of respiratory samples obtained either spontaneously or via induced sputum (considered adequate according to the percentage of neutrophils and absence of epithelial cells in the specimens (43)), and/or bronchoalveolar lavage (BAL). The samples were variously submitted for microscopy, culture and susceptibility testing (MC+S); acid fast staining (Ziehl-Neelsen, Auramine stains), with the addition of GeneXpert MTB/RIF® (Xpert) (Cepheid, Sunnyvale, Ca, USA) from 2012 (44), immunofluorescent staining (IFA) (pre 2018) or polymerase chain reaction (PCR) (after 2018) for PJP, as well as PCR for viruses, LP and MP. All results were collected when available. Blood cultures were also routinely collected on all patients using the BactT/Alert automated blood culture system

(BioMerieux, Marcy l'Etoile, France). Additional microbiological tests, which were collected at the discretion of the attending physician may have included serum [1,3]- β-D-glucan test, Fungitell ® (for PJP), serological tests (for LP, MP, CMV and measles), and EDTA-blood PCR (for CMV). Additional testing, based on the findings in individual patients, may have included investigation of pleural fluid, urine antigen tests (pneumococcal and legionella), blood antigen tests (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). VZV infection was a clinical diagnosis. The diagnosis of pneumonia due to Candida and CMV was made only in cases where the pathogen was identified on post-mortem lung specimens, and for other fungi (CN and *Aspergillus fumigatus* (AF)) cases were based on positive BAL.

2.4 Statistical Analysis

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 are 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 are presented as percentages, and association in the categorical variables is assessed using the Chi-squared or Fisher's exact tests. All tests were 2-tailed. Variables that were considered significant for mortality on univariable analysis were included in three different multivariable logistic regression models to control for collinearity, and odds ratios are reported. A P value of <0.05 was taken as statistically significant.

2.5 Ethical Considerations

The protocol for the study was approved by the Graduate Studies Committee of the School of Clinical Medicine, University of the Witwatersrand. Written approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand prior to the initiation of any data collection (Date 14/06/2019; Protocol number M190586) (Appendix B), and permission to access patient records was obtained from the Head of the ICU at CMJAH as well as the Clinical Director and CEO of the institution (Appendix C). Strict measures were taken to ensure patient confidentiality was maintained at all times. In order to achieve this, each patient record was consecutively allocated a study number. A list correlating the study number with the respective patient was then isolated from

the rest of the collected data and only the principal investigator had access to this information, which was kept securely stored.

CHAPTER THREE-RESULTS

ENTIRE COHORT

3.1 Patient Selection

There were 1,244 ICU admissions identified between 1 July 2007 and 31 May 2019 with a diagnosis of "community-acquired pneumonia". Of these, 52 were immediately excluded, as the files could not be found. Of the remaining 1192, another 261 were further excluded as the diagnosis of SCAP was incorrect, the patients were younger than 18 years old, or there were insufficient data. Therefore, 931 patient records were included in the final analysis. Of these 718 patients were HIV-positive and 131 were HIV-negative. In addition, 82 patients had an unknown HIV status (Figure 3.1).

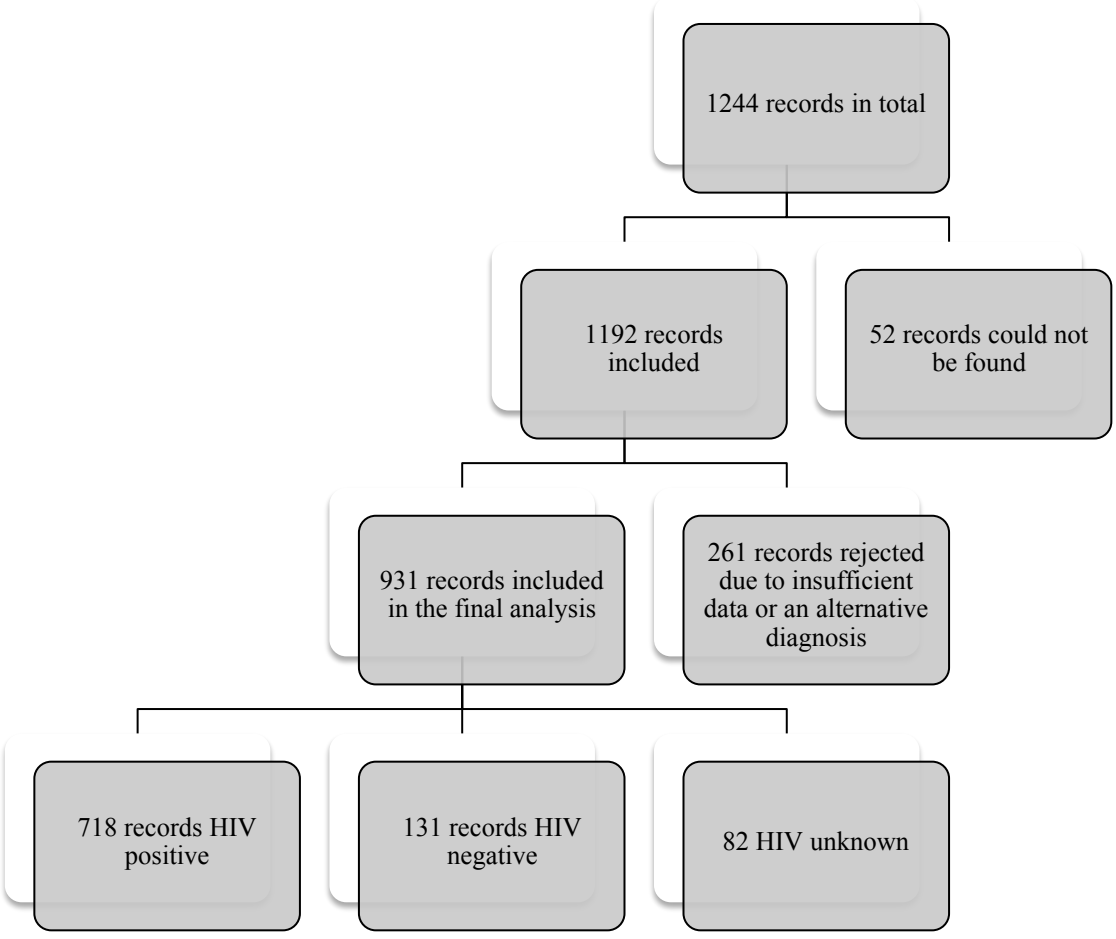

Figure 3.1: Method of data acquisition for the cohort

3.2 Demographics of the Entire Cohort

There were 931 patients included in the final analysis. The median age was 37 years (IQR 30-48 years), and 76 patients (8.2%) were 65 years of age or older. There were 448 (48.1%) male patients and 483 (51.9%) female patients. Overall, 41 (4.4%) patients were current smokers (Table 3.1).

Table 3.1 Demographics of the entire cohort (n=931)

Demographics	median (IQR) or n (%)
Age, years	37 (30-48)
Age ≥65 years	76 (8.2%)
Sex (male)	448 (48.1%)
Sex (female)	483 (51.9%)
Smoker	41 (4.4%)

Abbreviations: IQR: interquartile range; n: number; %: percentage; ≥: greater than or equal to.

3.3 Co-morbid Disease

Within the entire cohort, 718 patients (77.1%) were HIV-positive and 131 (14.1%) were HIV-negative. The HIV status was unknown for 82 patients (8.8%). Overall, 391 patients (42%) had a co-morbid disease other than HIV co-infection, and of these, the most common comorbidity was cardiovascular disease (CVD) (n=142, 15.3%), followed by chronic respiratory disease (n=78, 8.4%). In addition, 93 patients (10%) had a history of current or previous MTB infection. Figure 3.2 depicts all the co-morbidity within the cohort, excluding HIV coinfection.

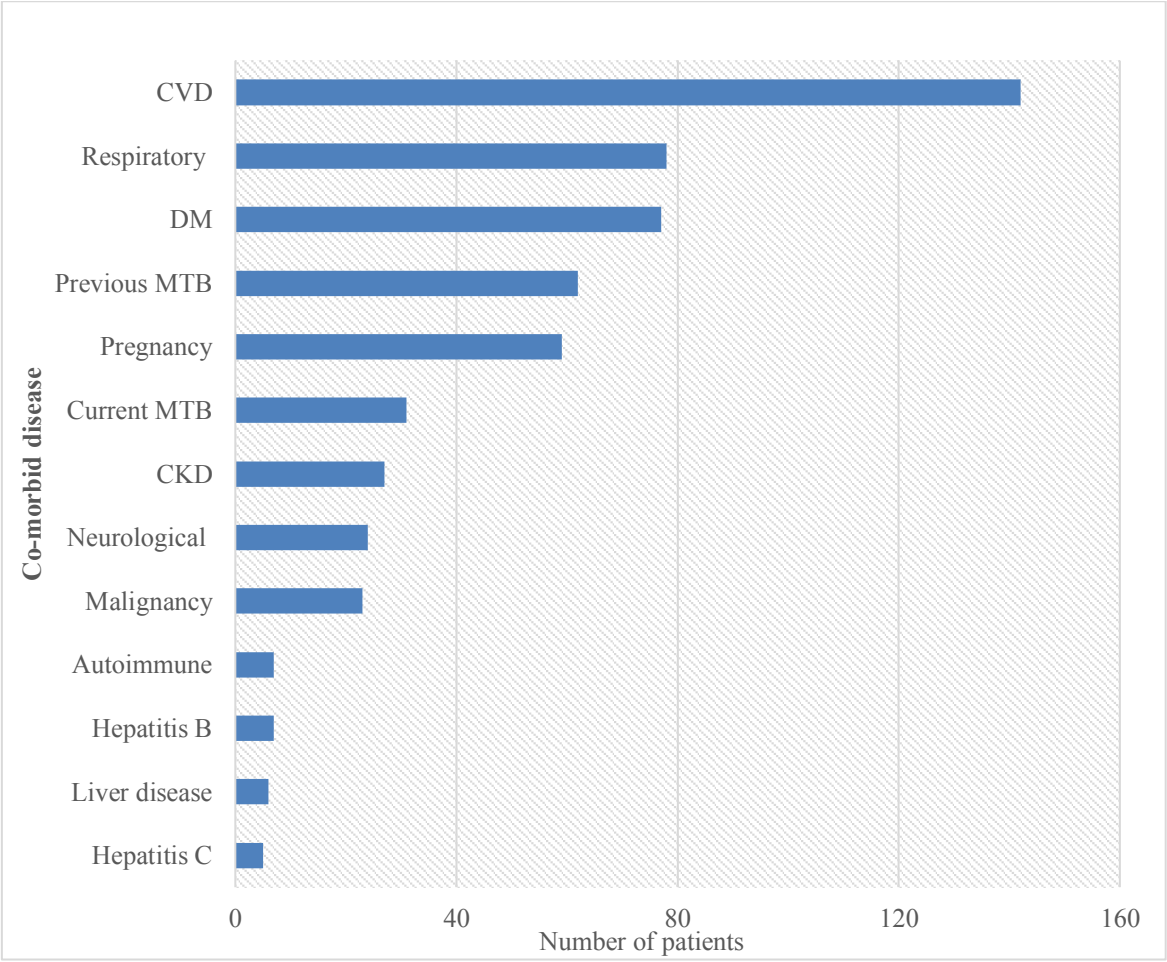

Figure 3.2 Distribution of co-morbid disease other than HIV within the entire cohort

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

3.4 Clinical Presentation, Laboratory Data and Chest Radiographs

The median body temperature on admission was 36.8°C (IQR 36-37.5)°C. Overall, 500 patients (54.4%) were confused, and the median MAP (mean arterial blood pressure) was 80mmHg (IQR 66-92) mmHg. The median CURB-65 score was 3 (IQR 2-3), median Apache II score was 18 (IQR 14-23) and the median $Pa0_2/Fi0_2$ ratio was 144 (IQR 97-229). Altogether 169 patients (19.5%) had an APACHE II score ≥25, and 698 patients (79.3%) had a PaO_2/FiO_2 ratio ≤ 250 (Table 3.2).

In terms of laboratory findings, the median haemoglobin level was 10.6g/dL (IQR 8.6-12.2) g/dL, median white cell count 9.9 x 10^9/L(IQR 5.8-15.0) x 10^9/L and median platelet count 206 x 10^9/L (IQR 125-304) x10^9/L. Renal function for the entire cohort was deranged, with a

median urea of 12mmol/L (IQR 6.4-23.6) mmol/L, and median creatinine level of 126μmol/L (IQR 73-304) μmol/L. The median C-reactive protein (CRP) level was 202mg/L (IQR 118-288) mg/L. Other laboratory abnormalities included elevated aspartate aminotransferase (AST 82U/L [IQR 44-181] U/L), elevated alkaline phosphatase (ALP 97 U/L [IQR 70-145] U/L) and elevated (1,3)-β-D-glucan (BDG) (103pg/mL [IQR 31-501] pg./mL). 248 (26.6%). Amongst the HIV-positive patients, the median CD_4 count was 44 cells/mm^3 (IQR 14-112) cells/mm^3 (Table 3.2).

Chest radiograph (CXR) findings were available for 803 patients (86.3%). The predominant radiological finding was multilobar consolidation in 333 patients (41.5%), followed by bilateral ground glass opacities (GGO) in 243 patients (30.3%) (Table 3.2).

3.5 Microbiology

3.5.1 Microbial Pathogens

Microbial organisms considered likely to be responsible for the SCAP were detected in 519 patients (55.7%), and these organisms were isolated on 706 specimens. No microorganisms were detected in 412 cases (44.3%). In some patients, the same organism was isolated from different sites. Most isolates (317 [45.4%]) were from respiratory samples (sputum, tracheal aspirates or bronchoalveolar lavage [BAL]), identified using microscopy, culture, immunofluorescence and PCR techniques. Blood samples (blood cultures and viral polymerase chain reaction [PCR]) made up 274 (39.3%) of the isolates. The remaining sites from which microorganisms were isolated are depicted in Figure 3.3.

Table 3.2 Clinical presentation, laboratory data and chest radiographs of the entire cohort

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
$Pa0_2$/ $Fi0_2$ ratio	144 (97-229), 878
$Pa0_2$/ $Fi0_2$ ratio ≤250	698 (79.3%), 878
Laboratory	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
CD_4 cell count (HIV positive), cells/mm^3	44 (14-112), 591
BDG pg./mL	103 (31-501), 491
Bacteraemia	248 (26.6%)

Chest radiograph	n (%), 803 (86.3%)
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; C: Celsius; 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; $Pa0_2/Fi0_2$: partial pressure of oxygen/fraction of inspired oxygen; %: percentage

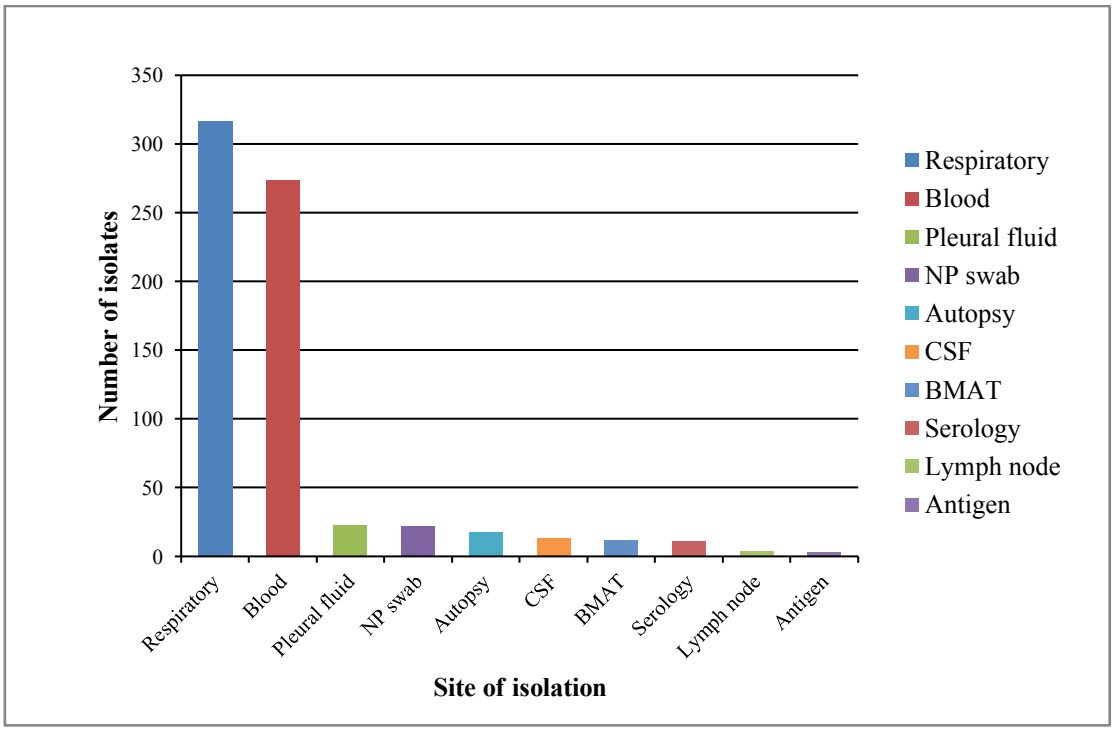

Figure 3.3 Sites of isolation of microbial pathogens

Abbreviations: BMAT: Bone marrow aspirate and trephine; CSF: Cerebrospinal fluid; NP: nasopharyngeal

Overall, 421 (44.7%) infections were MM and 98 (13%) were PM, which corresponded to 499 (70.7%) isolates for the MM infections and 207 (29.3%) for the PM infections. MTB, the most common bacterial cause of infection, was identified in 175 patients (33.7%), of which 130 infections were MM and 45 were PM. SP, identified in 125 patients (24.1%), 103 MM

and 22 PM, was the second most common microbial pathogen, and KP, identified in 50 patients (9.6%), 29 MM and 21 PM, was the third most common. Varicella zoster virus (VZV), diagnosed on clinical grounds, was the predominant viral infection documented in 24 (4.6%) cases, 15 MM and 9 PM, and PJP, associated with 49 cases (9.4%) of SCAP, 35 MM and 14 PM, was the most common fungal pathogen identified. The only "atypical organism" that was recorded was CP and this was responsible for two infections. Table 3.3 demonstrates the distribution of MM and PM isolates. The PM isolates, of which there were 207 in number, reflect the individual pathogens identified in 103 cases of SCAP. In these patients, two pathogens were identified in 76 cases, and three in nine cases.

The diagnosis of MTB infection relied solely on culture techniques initially, with the addition of GeneXpert after 2012. The majority of these 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 in which MTB were isolated included 12 (5.7%) from bone marrow aspirate and trephine (BMAT); six (2.9%) from pleural fluid and three (1.5%) from lymph node biopsy. Two (1%) patients had concurrent TB meningitis with identification of MTB on cerebrospinal fluid samples (CSF). In contrast, most SP infections (102 isolates, 76.7%) were diagnosed on blood cultures; 20 (15%) on sputum; three (2.3%) on pleural fluid and only one (0.8%) using the urinary pneumococcal antigen test. Seven (5.3%) patients had concurrent pneumococcal meningitis. The methods and sites used to determine microbial aetiology of SCAP are further depicted in Table 3.4

Table 3.3 Microbial aetiology of SCAP infections (n=519; column %)

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%)
Pseudomonas aeruginosa	18 (4.3%)	13 (13.3%)	31 (6.0%)
Acinetobacter spp.	8 (1.9%)	4 (4.1%)	12 (2.3%)
Other Gram-negative			
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 anthropi	0	1 (1%)	1 (0.2%)

Microbial aetiology	MM, n (%)	PM, n (%)	Total, n (%)
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

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Table 3.4 Isolation sites of the microorganisms and the number of microbiological isolates (n=706, row %)

Microbial aetiology, n (%)	Resp	Blood	Serology	Antigen	Pl fluid	BM	CSF	LN	NP	Autopsy
All microbial pathogens, 706	320 (45.3%)	280 (39.7%)	11 (1.6%)	3 (0.4%)	23 (3.3%)	12 (1.7%)	13 (1.8%)	4 (0.6%)	22 (3.1%)	18 (2.6%)
Mycobacterium spp, 209	136 (65.1%)	50 (23.9%)			6 (2.9%)	12 (5.7%)	2 (1%)	3 (1.4%)		
MTB, 206	136 (66.1%)	47 (22.8%)			6 (2.9%)	12 (5.8%)	2 (1%)	3 (1.5%)		
MAC, 3		3 (100%)								
Gram-positive bacteria, 199	48 (15%)	129 (46%)		1 (0.3%)	12 (6%)		8 (4%)	1 (0.5%)		
Streptococcus pneumoniae, 133	20 (15%)	102 (76.7%)		1 (0.8%)	3 (2.3%)		7 (5.3%)			
Staphylococcus aureus, 52	26 (50%)	18 (34.6%)			6 (11.5%)		1 (1.9%)	1 (1.9%)		
Streptococcus milleri, 1	0				1 (100%)					
Streptococcus pyogenes, 3	1 (33.3%)	1 (33.3%)			1 (33.3%)					
Streptococcus viridans, 4	0	3 (75%)			1 (25%)					
Enterococcus spp., 6	1 (16.7%)	5 (83.3%)								
Gram-negative bacteria, 158	94 (59.5%)	59 (37.3%)			5 (3.2%)					
Haemophilus influenzae, 6	4 (66.7%)	2 (33.3%)								
Enterobacterales										
Klebsiella pneumoniae, 55	31 (56.4%)	22 (40%)			2 (3.6%)					
Escherichia coli, 17	7 (41.2%)	10 (58.8) %								
Enterobacter cloacae, 10	7 (70%)	2 (20%)			1 (10%)					
Salmonella spp., 7		7 (100%)								
Citrobacter freundii, 1	1 (100%)									

Microbial aetiology, n (%)	Resp	Blood	Serology	Antigen	Pl fluid	BM	CSF	LN	NP	Autopsy
Proteus mirabilis, 2	2 (100%)									
Providencia, 1	1 (100%)									
Serratia spp., 5	3 (60%)	1 (20)%			1 (20%)					
Pseudomonas aeruginosa, 32	26 (81.3%)	6 (19.7%)								
Acinetobacter spp., 13	10 (76.9%)	3 (23%)								
Other gram-negatives, 9	2 (22.2%)	6 (66.7%)			1 (11.1%)					
Burkholderia cepacia, 2	1 (50%)	1 (50%)								
Stenotrophomonas maltophilia, 4	1 (25%)	2 (50%)			1 (25%)					
Chryseobactrum indulgenes, 1		1 (100%)								
Sphingobactrum spp., 1		1 (100%)								
Ochrobactrum anthropic, 1		1 (100%)								
So called "atypical" pathogens, 2			1 (50%)						1 (50%)	
Chlamydophila pneumoniae, 2			1 (50%)						1 (50%)	
Viruses, 52		16 (30.8%)	10 (19.2%)	1 (1.9%)					21 (40.4%)	4 (7.7%)
CMV, 25		16 (64%)	4 (16%)	1 (4%)						4 (16%)
Measles, 6			6 (100%)							
Respiratory viruses, 19									19 (100%)	
Adenovirus, 2									2 (100%)	
Fungi, 86	42 (48.8%)	26 (30.2%)		1 (1.1%)			3 (3.5%)			14 (16.3%)
PJP, 49	37 (75.5%)									12 (24.5%)
Candida spp., 19		17 (89.4%)								2 (10.5%)

Microbial aetiology, n (%)	Resp	Blood	Serology	Antigen	Pl fluid	BM	CSF	LN	NP	Autopsy
Other fungi										
Cryptococcus neoformans, 12	1 (8.3%)	7 (58.3%))		1 (5%)			3 (15%)			
Aspergillus fumigatus. 3	3 (100%)									
Saccharomyces cerevisiae, 1		1 (100%))								
Stephanoascus ciferri, 2	1 (50%)	1 (50%)								

Note: Includes all organisms isolated- monomicrobial and polymicrobial.
Some organisms were isolated from different sites in the same patient.
Respiratory viruses: Influenza A, H1N1, Influenza B.
VZV infections were based on clinical examination.
CMV pneumonia was proven in 4 autopsy specimens
Candida pneumonia was proven on biopsy in 2 cases.

Annotations: BM: Bone marrow; CSF: cerebrospinal fluid; CMV: Cytomegalovirus: number; LN: lymph node; n: number; MTB: *Mycobacterium. Tuberculosis*; MAC: *Mycobacterium avium intracellulare*; NP: Nasopharyngeal; PJP: *Pneumocystis jirovecii*; Pl: Pleural; Resp: Respiratory; spp.: species; %: percentage

3.5.2 Drug-Resistant Pathogens

Drug-resistant pathogens were identified in 30 patients, and the majority of these were extended-spectrum β-lactamase (ESBL)-producing KP isolates (40%) followed by eight cases of drug-resistant MTB (26.7%). Only two cases (6.7%) of penicillin-resistant SP were identified, both with intermediate resistance to penicillin, and there were five cases (16.7%) of methicillin-resistant *Staphylococcus aureus* (MRSA) (Table 3.5).

3.5.3 Microbiology and Radiological Findings

There were no significant differences in any radiographic pattern amongst patients with MM and PM infections. However, lobar consolidation was more common with SP (60 %) and PTB (40%), and of the patients with multilobar consolidation, 46.5% had SP, 41% had PTB, 6% had PJP and 7% were viral infections. GGO were described in 39% MTB infections, 33% PJP infections, 19% viral infections and 8% SP infections. Nodules were only described in PTB (59%) and viral infections (41%), and pleural effusions with PTB (66.7%) and SP (33.3%).

3.5.4 Microbiology and CRP

The median CRP varied according to the microbial aetiology. It was highest amongst patients with SP infection (292 [IQR 239-350] mg/l), and lowest amongst patients with PJP infection (139 [IQR 64-198] mg/l). In addition, significant differences in CRP were noted amongst patients with SP, MTB, and PJP infections and between patients with viral and non-viral infections. There were no differences in CRP amongst patients with PM versus MM infections (Table 3.6).

Table 3.5 Distribution of drug-resistant pathogens (n=30)

Pathogen	n (%)	Resistance pattern
Mycobacterium spp.		
MTB	8 (26.7%)	2 INH-resistant
		2 Rifampicin-resistant
		3 MDR-TB
		1 XDR-TB
Gram-positive pathogens		
Streptococcus pneumoniae	2 (6.7%)	Intermediate-resistant
Staphylococcus aureus	5 (16.7%)	MRSA
Enterobacterales*		
Klebsiella pneumoniae	12 (40%)	ESBL-producing
Enterobacter cloacae	1 (3.3%)	ESBL-producing
Salmonella spp.	1 (3.3%)	ESBL-producing
Serratia liquefans	1 (3.3%)	ESBL-producing

Abbreviations: ESBL: extended spectrum β-lactamase producing; INH: Isoniazid; MDR: multidrug resistant (resistant to rifampicin and isoniazid); MRSA: methicillin resistant *Staphylococcus aureus*; MTB: *Mycobacterium tuberculosis*; n: number; spp: species; TB: tuberculosis; XDR: Extensively drug-resistant tuberculosis (resistant to rifampicin, isoniazid, fluoroquinolones, aminoglycosides, ethambutol, ethionamide and pyrazinamide); %: percentage

Note: *Breakdown of the ESBL-producing Enterobacterales, (n=15):

1. HIV-unknown (n=2).
    a. Both *Klebsiella pneumoniae*.
        i. One patient had measles (aged 29 year).
        ii. One patient had Type 1 Diabetes mellitus (aged 65 years).
2. HIV-negative (n=2).
    a. Both *Klebsiella pneumoniae.*
        i. One patient had poorly controlled Type 1 diabetes (aged 21 years).
        ii. One patient had cardiovascular disease and chronic lung disease (aged 70 years).
3. HIV-positive (n=11).
    a. 8 *Klebsiella pneumoniae; 1 Enterobacter cloacae; 1 Salmonella* spp; 1 *Serratia liquefans.*
        i. Three patients had co-morbidities (1 CVD; 1 previous TB; 1 current TB).
        ii. One patient had newly diagnosed TB (polymicrobial infections).
        iii. One patient had VZV infection.
        iv. One patient was a current smoker.
        v. One patient was on ARV therapy (CD_4=68cells/mm^3.
        vi. Ten patients were not on ARV therapy.

Table 3.6 Comparison of CRP in different microbial infections (n=519)

Microbial aetiology	CRP mg/l, median (IQR), n	P value[+]
MTB	158 (104-249), 118	MTB vs PJP: 0.07 **MTB vs SP: <0.001** **PJP vs SP: <0.001**
PJP	139 (64-198), 33	
SP	292 (239-350), 100	
Viruses	167 (51-234), 28	**0.001**
Non-viruses	229 (134-306), 328	
Monomicrobial	215 (122-298), 394	0.29
Polymicrobial	186 (132-279), 95	

[+]Fisher's exact

Abbreviations: CRP: C- reactive protein; IQR: interquartile range; MTB: *Mycobacterium tuberculosis*; n: number; PJP: *Pneumocystis jirovecii*; SP: *Streptococcus pneumoniae*; vs: versus; Bold numbers indicate significant P values.

3.6 Complications

The majority of patients (692, 74.3%) developed no complication during the course of their ICU admission; however, in total 250 complications were reported; 230 (24.7%) patients experienced one complication and nine (1%) patients experienced two or more. The predominant complications were pulmonary, occurring in 78 (8.4%) cases, followed by tachyarrhythmia (60, 6.4%). Other complications are recorded in Table 3.7.

3.7 Management

Overall, 799 (85.8%) patients were ventilated, and the predominant mode was invasive mechanical ventilation (IMV) which was used in 780 [83.8%] patients, with non-invasive ventilation (NIV) utilised in 19 [2%] patients. Furthermore, 209 (22.4%) patients received dialysis and 464 (49.8%) inotropic support. Corticosteroids were used in the majority of patients (710, 76.3%) (Table 3.8).

Table 3.7 ICU complications for the entire cohort (n=931)

Complications	n (%)
Nil	692 (74.3%)
1 complication	230 (24.7%)
≥ 2 complications	9 (1%)
Pulmonary	78 (8.4%)
Pneumothorax	47 (5.1%)
Lung necrosis/empyema	25 (2.7%)
Haemoptysis	5 (0.5%)
ARDS	1 (0.1%)
Tachyarrhythmia	60 (6.4%)
Neurological	41 (4.4%)
Thromboembolism	21 (2.3%)
Metabolic	13(1.4%)
CD infection	11(1.2%)
GIT	7 (0.8%)
Haematological	7 (0.8%)
Cardiac arrest	6 (0.6%)
Skin/ soft tissue	6 (0.6%)

Abbreviations: ARDS: acute respiratory distress syndrome; CD: Clostridiodes difficile infection; GIT: gastrointestinal tract; n: number; SVT: supraventricular tachycardia, % percentage

Table 3.8 Overall ICU management (n=931)

Management	n (%)
Ventilation – total	799 (85.8%)
Ventilation-invasive	780 (83.8%)
Ventilation–non-invasive	19 (2.04%)
Corticosteroid use	710 (76.3%)
Dialysis	209 (22.4%)
Inotropes	464 (49.8%)

Abbreviations: n: number; %: percent

3.8 Length of Stay

The median length of ICU stay was 4 days (IQR 2-8 days). LOS was increased amongst the patients who were ventilated (5 [IQR 2-8] days vs 2.5 [IQR 2-4.8] days; P<0.001) and those who required dialysis (5 [IQR 3-8] days vs 4 [IQR 2-8] days; P=0.08) (Table 3.9).

Table 3.9 Effect of ICU intervention on length of stay (n=931)

ICU intervention	LOS days median (IQR), n	P value[+]
Ventilated	5 (2-8), 799	**<0.001**
Not ventilated	2.5 (2-4.8), 132	
Inotropes	4 (2-8), 464	0.08
No inotropes	5 (2-8), 467	
Corticosteroids	5 (2-8), 710	0.45
No corticosteroids	4 (2-9), 208	
Dialysis	5 (3-8), 209	**0.01**
No dialysis	4 (2-8), 722	

[+]Fisher's exact

Abbreviations: ICU: Intensive Care Unit; IQR: Interquartile range; LOS: length of stay; Bold numbers indicate significant P values

3.9 **ICU Outcomes**

In total, 465 patients (49.9%) survived ICU, compared to 466 (50.1%) patients who died. However, fewer patients survived to hospital discharge (433 [46.5%]) survived compared to 498 [53.5%)] who died) (Table 3.10).

Table 3.10 Overall ICU outcomes (n=931)

Outcome	n (%)
LOS, days (IQR)	4 (2-8)
ICU survival	465 (49.9%)
ICU death	466 (50.1%)
Survival to discharge	433 (46.5%)
In-hospital death	498 (53.5%)

Abbreviations: ICU: Intensive Care Unit; IQR: interquartile range; LOS: Length of stay; n: number; %: percentage

3.10 **ICU Mortality**

3.10.1 Demographics

There were no differences in age, sex nor cigarette smoking between the patients who lived and those who died. Moreover, in the group of patients aged 65 and older, a similar proportion lived, compared to those who did not survive to ICU discharge.

3.10.2 Co-morbid Disease

The risk of dying was higher amongst patients who were HIV-positive compared to their HIV-negative counterparts (OR, 1.61; 95% CI, 1.10-2.34; P=0.01); but was lower amongst patients with underlying chronic CVD compared to those without CVD as a co-morbidity (OR, 0.62; 95% CI 0.44-0.90; P=0.01). There were no differences in mortality amongst patients with other co-morbidities, such as lung disease, COPD, kidney disease, liver disease, neurological disease, malignancy, pregnancy and current or previous MTB infection (Table

3.11). Patients with other co-morbidities were not analysed further, as the numbers were too small to determine statistical significance.

Table 3.11 Co-morbid disease and mortality (n=931, row %)

Co-morbid disease, n	Lived, 465 (%)	Died, 466 (%)	OR*	95% CI	P value+
HIV-positive, 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

+ Fisher's Exact; * Baptista Pike

Abbreviations: CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; CVD: cardiovascular disease; HIV: Human Immunodeficiency Virus; MTB: *Mycobacterium tuberculosis*; n: number; OR: odds ratio; 95% CI: 95% confidence intervals; Bold numbers represent significant P value

3.10.3 Clinical Presentation, Laboratory Results and Chest Radiographs

Amongst the patients who died body temperature and MAP were lower, and more patients were confused (Table 3.12). Both the CURB-65 and Apache II scores were higher amongst non-survivors; specifically, the median CURB-65 score was 3 (IQR 2-3) in patients who died, compared to 2 (IQR 2-3) in those who lived ($P < 0.001$), and the median Apache II score was 20 (IQR 15-24) in patients who died and 17 (IQR 13-21) in those who lived ($P <0.001$). Similarly, the median $Pa0_2/Fi0_2$ ratio was significantly higher amongst survivors (170 [IQR 117-245] versus 121 [IQR 83-200], $P<0.001$). In addition, more patients with an APACHE II score ≥25 died than lived (103 [61%] died vs 66 [39%] lived; P=0.001), whereas more patients who died had a $Pa0_2/Fi0_2$ ratio ≤250 compared to those who lived (364 (52.1%) died vs 334 (47.9%) lived; $P<0.001$) (Table 3.12).

Serum potassium, aspartate transaminase (AST), and BDG levels were higher in the patients who died compared to those who lived; however, CRP, total protein, and serum albumin levels were lower. Radiologically, a higher proportion of patients who died had GGO on chest radiograph (149 [38.5%] versus 94 [22.7%] in those that lived; P=<0.001), whereas more patients who lived had lobar consolidation (101 [24.3%] versus 54 [13.9%] in those that died; P=0.002). The proportion of patients with findings of multilobar consolidation, pulmonary nodules and pleural effusions on chest radiographs were similar between the two groups (Table 3.12).

3.10.4 Microbiology

3.10.4.1 Microbial pathogens and mortality

The inability to determine microbial aetiology of infection was not associated with increased mortality, and neither were there any differences in survival noted amongst patients with PM infections compared with MM infections (Table 3.13). Nonetheless, when considering only patients with a defined microbial aetiology for SCAP, PJP was a predictor of higher mortality (OR, 4.03; 95% CI, 1.80-8.61; P=0.003) and SP a predictor of lower mortality (OR, 0.49; 95% CI 0.31-0.77; P=0.002) (Table 3.14).

3.10.4.2 Drug-resistant pathogens and mortality

Within the entire cohort there were 30 cases of SCAP involving drug-resistant pathogens, and of these, a similar proportion of patients lived and died (14 [46.7%] lived versus 16 [53.3%] died; OR, 1.15; 95% CI, 0.57-2.42; P=0.85). Further statistical analysis was not performed, as numbers within each sub-group were small, however all five patients with MRSA and the only patient with XDR-MTB died, whereas both (two) patients with SP intermediate resistance lived. As mentioned before, it is possible that cases of resistant MTB have been underestimated.

Table 3.12 Comparison of clinical features, laboratory results and chest radiographs amongst patients who lived and those who died (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**
$Pa0_2$/ $Fi0_2$ ratio	170 (117-245), 440	121 (83-200), 438	**<0.001**
PaO_2/ FiO_2 ≤250	334 (71.8%)	364 (78.1%)	**0.01**
Laboratory	median (IQR), n	median (IQR), n	
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**

Laboratory	Lived, median (IQR), n	Died, median (IQR), n	P value
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

[+] Fisher's exact
[#] CD_4 count only measured in HIV-positive population

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BDG: (1-3)-□-D- Glucan; C: Celsius; 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; $Pa0_2/Fi0_2$: partial pressure of oxygen/ fraction of inspired oxygen; SOI: severity of illness; temp: temperature; Bold numbers indicate significant P values.

Table 3.13 Microbial aetiology and mortality (n=931, row %)

Microbial aetiology, n	Lived, n (%)	Died, n (%)	OR[*]	95% CI	P value[+]
No microorganism, 412	204 (49.5%)	208 (50.5%)	0.84	0.80-1.34	0.84
Polymicrobial, 96	43 (44.8%)	55 (56.1%)	0.73	0.47 -1.12	0.18
Monomicrobial, 421	218 (51.8%)	203 (48.2%)			

[+] Fisher's Exact; [*] Baptista Pike

Abbreviations: n: number; OR: odds ratio; 95% CI: 95% confidence intervals; % Percentage

Table 3.14 Monomicrobial CAP and mortality (n=421, row %)

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-negatives					
*Burkholderia cepacia,*1	1 (100%)	0 (0.0%)			
Stenotrophomonas maltophilia, 1	1 (100%)	0 (0.0%)			
So called "atypical" pathogens					
Chlamydia pneumoniae, 1	0 (0.0%)	1 (100%)			
Viruses	Lived, n(%)	Died, n (%)	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	Lived, n (%)	Died, n (%)	OR*	95% CI	P value++
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			

+ Fisher's Exact; *Baptista Pike

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.

3.10.5 Effect of Complications on Overall Mortality

Overall, the number of ICU complications experienced was similar amongst patients who lived and died, and did not increase the risk of dying, even amongst patients who experienced more than one complication. However, all patients who experienced a gastrointestinal tract (GIT) complication died (seven [100%] died versus zero [0%] who lived), and these complications included GIT ulceration, oesophagitis and one patient with acalculous cholecystitis (Table 3.15).

Table 3.15 Complications and mortality (n=931, row %)

Complications, n	Lived, n (%)	Died, n (%)	OR*	95% CI	P value+
Overall, 239	119 (49.8%)	120 (50.2%)	1.01	0.75-1.35	>0.99
1 complication, 230	115 (50%)	115 (50%)	0.80	0.24 -2.75	>0.99
≥ 2 complications, 9	4 (44.4%)	5 (55.6%)			
Pulmonary, 76	38 (50%)	38 (50%)	0.99	0.57-1.70	>0.99
Pneumothorax, 45	21 (46.7%)	24 (53.3%)	1.17	0.60- 2.18	0.52
Lung necrosis/empyema, 25	16 (64%)	9 (36%)	0.52	0.21-1.19	0.14
Tachyarrhythmia, 60	26 (43.3%)	34 (56.7%)	1.41	0.79-2.60	0.30

+ Fisher's Exact; * Baptista Pike

Abbreviations: n : number; OR: odds ratio; 95% CI: 95% confidence intervals.

3.10.6 ICU Management and Mortality

Overall, patients who required any form of mechanical ventilation had a higher risk of dying compared to those who were not ventilated (OR, 10.98; 95% CI, 6.27-19.78; P<0.001), and this was observed amongst patients who required IMV (OR, 8.75; 95% CI, 5.37-14.14; P<0.001); and non-invasive ventilation (NIV) (OR, 3.89; 95% CI, 1.21-11.28; P=0.022). However, compared to the use of IMV, patients who used NIV had a lower risk of mortality (OR, 0.35; 95% CI, 0.13-0.86; P=0.034). Furthermore, patients who received inotropic support and those who were dialysed were also more likely to die (OR, 3.38; 95% CI, 2.58 - 4.42; P<0.001; and OR, 1,54; 95% CI, 1.13-2.10; P=0.008, respectively). Figure 3.4 depicts the proportion of patients who lived and died requiring a specific ICU intervention.

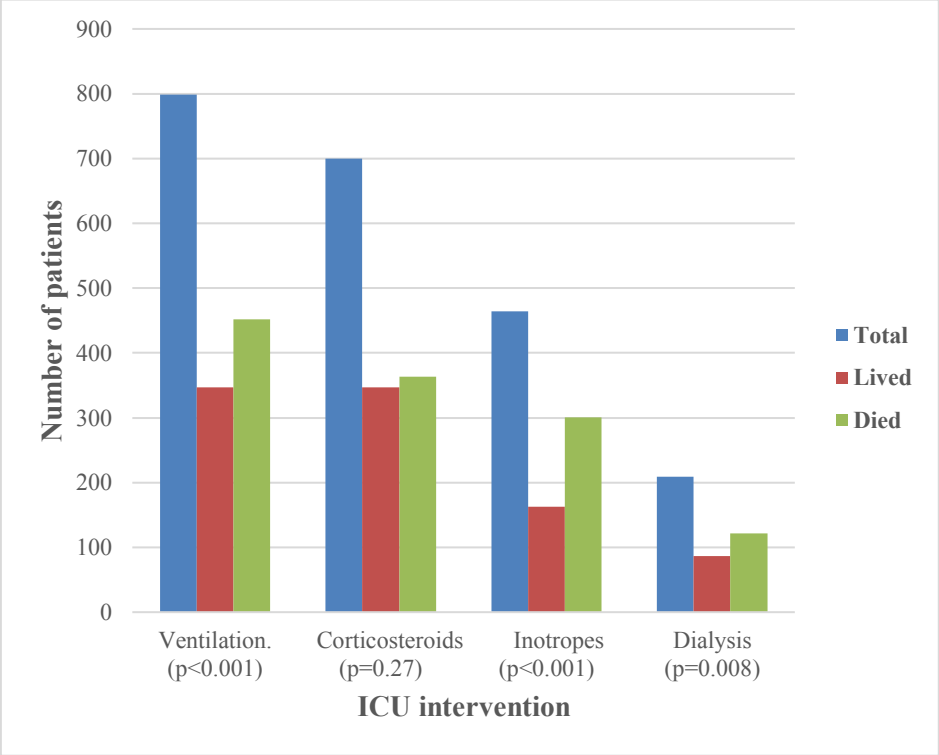

Figure 3.4 ICU management of SCAP and effect on mortality.

3.10.7 Length of Stay

The ICU length of stay was shorter amongst those who died compared with those that lived (4 [IQR 2-8] days versus 5 [IQR 3-8] days; P=0.025). Altogether 465 patients (49.9%) survived

ICU compared with 467 (50.1%) who died; however fewer patients survived to hospital discharge 433 (46.5%) vs 498 (53.5%); P<0.001.

3.10.8 Independent Predictors of Mortality

Multivariable analysis (MVA) was performed to identify which parameters were independent risk factors for mortality. Three different models were used with various combinations, in order to attempt to control for co-linearity between variables (Appendix D).

When APACHE II and CURB-65 scores were not included in the analysis (MVA 1, Table 3.16, Appendix D), MAP, PaO_2:$Fi0_2$ ratio, CD_4 count, the use of mechanical ventilation and inotropic support were each associated with mortality. With the increase in MAP, PaO_2:$Fi0_2$ ratio and CD_4 count mortality decreased, respectively (aOR, 0.99; 95% CI, 0.98-0.99; P=0.03; aOR, 0.99; 95% CI, 0.99-0.99; P=0.001; aOR, 0.99; 95% CI, 0.99-0.99; P=0.006); whereas patients who utilised IMV (aOR, 5.68; 95% CI, 2.25-14.37; P=0.001) or NIV (aOR, 9.55; 95% CI, 1.95-46.63; P=0.005) had a significantly higher risk of dying respectively, than patients who did not utilise mechanical ventilation. Moreover, in this model, although patients who were HIV-positive or had an unknown HIV status, had an increased risk of dying compared to patients who were HIV-negative, these findings were not statistically significant (HIV-positive; aOR, 1.67; 95% CI 0.35-7.93; P=0.61 and HIV-unknown; aOR, 6.42; 95% CI, 0.13-330.72); P=0.31).

MVA 2 (Table 3.17, Appendix D), included APACHE II and CURB-65 scores, but excluded co-morbid HIV infection and CVD. In this model, APACHE II score and PJP infection were each associated with a higher risk of dying (aOR, 1,06; 95% CI, 1.02-1.10; P=0.005; and aOR, 2.85; 95% CI,1.04-7.84; P=0.04; respectively), as were the use of mechanical ventilation and inotropes (IMV; aOR, 6.59; 95% CI, 2.61-16.68; P<0.001; NIV; aOR, 8.12; 95% CI, 1.75-36.63; P=0.007; aOR, 3.31 95%CI, 2.09-5.22; P<0.001). However, patients who underwent renal dialysis were at a lower risk of dying (aOR, 0.55; 95% CI, 0.32-0.93; P=0.03) and similar to multivariable analysis 1, mortality decreased with increasing CD_4 cell count and CRP (aOR; 0.99; 95% CI 0.99-0.99; P=0.001; aOR 0.99; 95% CI 0.99-0.99; P=0.01; respectively). Furthermore patients with lobar consolidation on chest radiograph (aOR, 0.53; 95% CI, 0.28-0.98; P=0.04) had a lower risk of dying.

MVA 3 (Table 3.18, Appendix D), included APACHE II and CURB-65 scores, as well as co-morbid HIV and CVD. Similar to multivariable 2, APACHE II and PJP infection were each associated with a higher risk of dying (aOR, 1.06; 95% CI 1.02-1.10; P=0.007; aOR, 2.71; 95% CI, 0.99-7.42; P=0.053; respectively), as well as the use of mechanical ventilation and inotropes (IMV; aOR, 6.81; 95% CI, 2.66-16.69; P<0.001; NIV; aOR, 9.50; 95% CI, 1.74-38.01; P=0.008; inotropes; aOR, 3.19; 95% CI, 1.86-4.53; P<0.001). However, risk of mortality was lower amongst patients who were dialysed (aOR; 0.59; 95% CI, 0.34-0.99; P=0.045), had lobar consolidation on chest radiograph (aOR, 0.54; 95% CI, 0.92-2.35; P=0.045), and risk of mortality decreased as the CD_4 cell count and CRP increased (aOR, 0.99; 95% CI, 0.99-0.99; P=0.002; aOR, 0.99; 95% CI, 0.99-0.99; P=0.01, respectively). Moreover, in this model, HIV status was not significantly associated with a higher risk of mortality (HIV- negative; aOR, 1.000; HIV-positive; aOR, 0.947; 95% CI 0.239-3.817; P=0.95; HIV unknown; aOR, 4.31; 95% CI, 0.089-209.43; P=0.46).

CHAPTER FOUR – RESULTS

COMPARISON BETWEEN HIV-POSITIVE AND HIV-NEGATIVE PATIENTS

4.1 Demographics

HIV-positive patients were younger than their HIV-negative counterparts (36 years [IQR 29-44] years versus 52 years [IQR 34-65] years; P< 0.001), and a smaller proportion were aged 65 years and older (17 [2.4%] in PLWH versus 33 [25.2%] in those without HIV; P<0.001). More of the PLWH were female (387 [53.9%] female versus 331 [46.1%] male; P=0.046); however, there were fewer HIV-positive smokers (19 [2.6%] vs 14 [10.7 %]; P<0.001) (Table 4.1).

Table 4.1 Comparison of demographics between HIV-positive and HIV-negative patients (n=849)

Demographics	HIV+ve, median (IQR), n or n (%)	HIV-ve, median (IQR), n or n (%)	P value[+]
Age, years	36 (29-44),718	52 (34-65),131	**<0.001**
Age ≥65, years	17 (2.4%)	33 (25.2%)	**<0.001**
Sex (male)	331 (46.1%)	73 (55.7%)	**0.046**
Sex (female)	387 (53.9%)	58 (44.3%)	
Smoker	19 (2.6%)	14 (10.7%)	**<0.001**

[+] Fisher's Exact

Annotations: HIV: Human Immunodeficiency Virus; IQR: interquartile range; n: number; +ve: positive; -ve: negative; %: percentage; Bold numbers indicate significant P values.

4.2 Co-morbid Disease

Overall, 87 (66.4%) HIV-negative patients had at least one comorbidity, compared with 255 (35.6%) PLWH who had other comorbid diseases in addition to HIV (P<0.001). More HIV-positive patients had a history of previous MTB infection (58 [8.1%] versus two [1.5%] in HIV-negative patients; P=0.005). However, a higher proportion of HIV-negative patients compared with HIV-positive patients had diabetes mellitus (DM) (24 [18.3%)] versus 27 [3.8%]; P<0.001), chronic CVD (38 [29%] versus 77 [10.7%]; P<0.001), chronic respiratory disease (29 [22.1%] versus 35 [4.9%]; P<0.001), chronic kidney disease (CKD)(12 [9.2%]

versus 12 [1.7%]; P<0.001). In addition, amongst those patients with chronic respiratory disease, a higher proportion of HIV-negative compared with HIV-positive patients had chronic obstructive pulmonary disease (COPD) (20 [15.3%] versus 14 [2.0%]); P<0.001) (Table 4.2). Chronic neurological disease (11 [8.4%] versus 7 [1%]) and hypothyroidism (7 [5.3%] versus 1 [0.1%]) were also more common amongst the HIV-negative cohort, but the numbers were too small to perform further statistical analysis.

Table 4.2 Co-morbid disease in HIV-positive and HIV-negative patients (n=849, column %)

Co-morbid disease, n	HIV +ve, 718	HIV-ve, 131	P value[+]
Total, 342	255 (35.6%)	87 (66.4%)	**<0.001**
Chronic CVD, 115	77 (10.7%)	38 (29%)	**<0.001**
Chronic Respiratory disease, 64	35 (4.9%)	29 (22.1%)	**<0.001**
COPD, 34	14 (2.0%)	20 (15.3%)	**<0.001**
Diabetes mellitus, 51	27 (3.8%)	24 (18.3%)	**<0.001**
Previous MTB, 60	58 (8.1%)	2 (1.5%)	**0.005**
Pregnancy, 59	54 (7.5%)	5 (3.8%)	0.14
Current MTB, 31	29 (4.03%)	2 (1.53%)	0.21
Chronic kidney disease, 24	12 (1.7%)	12 (9.2%)	**<0.001**
Malignancy, 20	15 (2.1%)	5 (3.8%)	0.22

[+] Fisher's Exact

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; CVD: cardiovascular disease; HIV: Human Immunodeficiency Virus; MTB: *Mycobacterium tuberculosis;* n: number; +ve: positive; -ve: negative; %: percentage; Bold numbers indicate significant P values.

4.3 Clinical Presentation, Laboratory Results and Chest Radiographs

The median body temperature was significantly higher in PLWH (36.9°C [IQR 36.2-37.7]°C versus 36.5°C [IQR 35.9 -37]°C in those without HIV; P< 0.001). In addition, the median APACHE II score was higher in PLWH (18 [IQR 14-23] versus 17 [IQR 12-21] in HIV-negative cases; P=0.02), but there were no significant differences in the CURB-65 score nor $PaO_2/Fi0_2$ ratio, nor the proportion of patients with APACHE II>25 and $Pa0_2/ Fi0_2 \leq 250$ when comparing HIV-positive and HIV-negative cases (Table 4.3).

Significant differences in the laboratory findings were that the haemoglobin level, white cell count, platelet count, sodium, potassium and albumin, were lower in PLWH, whereas total protein, AST and gamma-glutamyl transferase (GGT) were higher compared to the HIV-negative group. Furthermore, a higher proportion of PLWH developed bacteraemia (182 [25.4%] versus 15 [11.5%] in those without HIV; P=0.003). In both the HIV-positive and HIV-negative groups, the predominant radiological finding was multilobar consolidation (not significantly different). However, a higher proportion of PLWH had bilateral GGO (217 [35.1%] compared with 16 [14.0%] in the HIV-negative group; P<0.001)), whereas more HIV-negative patients presented with lobar consolidation (41 [36%] versus 99 [16%] in the HIV-positive group; P<0.001) (Table 4.3).

4.4 Microbiology

4.4.1 Monomicrobial Infections

Amongst the patients in whom none or one microbial pathogen could be identified, more were HIV-negative (Table 4.4). Of these, SA infections (8 [13.8%] versus 16 [4.9%]; P=0.02), were greater in the HIV-negative cohort, although among PLWH, there were more PJP infections (35 [4.7%] versus [0%]; P=0.005). The proportion of MTB infections (105 [31.9%] in HIV-positive patients versus 15 [25.9%] in HIV-negative patients; P=0.54) and SP infections (84 [25.5%] versus 13 [22.4%]; P=0.74) were similar between both groups (Table 4.5). More respiratory viruses were detected in HIV-uninfected patients; however further statistical analysis was not performed as these numbers were small.

4.4.2 Polymicrobial Infections

More PM infections occurred amongst PLWH (86 [12%] versus five [3.8%] in the HIV-negative group; P=0.02), (Table 4.4). In addition, amongst the PLWH there were more infections with mycobacteria, viruses and PJP, but fewer infections with gram-positive and gram-negative pathogens, compared to the HIV-negative patients (not significantly different).

Table 4.3 Comparison of clinical presentation, laboratory results and chest radiographs in HIV-positive and HIV-negative patients

Parameter	HIV+ve	HIV-ve	P value[+]
Clinical features	median (IQR), n or n (%)	median (IQR), n or n (%)	
Body temperature °C	36. 9 (36.2-37.7), 699	36.5 (35.9-37), 128	**<0.001**
MAP mmHg	79 (66-92), 683	80 (68-94), 125	0.72
Confusion	372 (52.5%)	71 (55.5%)	0.56
SOI scores	median (IQR), n or n (%)	median (IQR), n or n (%)	
CURB-65 score	2 (2-3), 693	3 (2-3), 126	0.06
Apache II score	18 (14-23), 671	17 (12-21), 124	0.02
Apache II score>25	133 (19.9%)	21 (16.8%)	0.54
$Pa0_2$/ $Fi0_2$ ratio	149 (96-230), 678	134 (104-208),126	0.29
$Pa0_2$/ $Fi0_2$ ratio≤250	533 (79%)	106 (84%)	0.24
Laboratory	median (IQR)	median (IQR)	
Hb g/dL	10.2 (8.3-11.8), 713	11.7 (9.5-13.7), 130	<0.001
Hct %	0.3 (0.3-0.4), 713	0.4 (0.3-0.4), 130	<0.001
White cell count $x10^9$/L	9.1 (5.1-14.1), 713	13.3 (8.7-19.2), 129	<0.001
Platelet counts $x10^9$/L	206 (118-303), 711	220 (163-320),127	0.02
Sodium mmol/dL	135 (131-140), 714	138 (134-142),130	<0.001
Potassium mmol/dL	4.3 (3.8-5), 714	4.6 (3.9-5.1), 130	0.04
Urea mmol/L	12 (6.1-23.5), 714	11.4 (6.62-21.75), 130	0.99
Creatinine µmol/L	124 (71-297), 713	128 (75-288),130	0.87
CRP mg/L	196 (116-283), 676	209 (114-300), 121	0.50
Total protein g/L	64 (54-76), 687	59 (53-67),123	**0.001**
Albumin g/L	25 (21-29), 686	28 (25-34), 124	**<0.001**
Total bilirubin µmol/L	11 (6-23), 690	10 (6-18), 124	0.60
AST U/L	91(59-203), 691	58 (33-122), 124	**<0.001**
ALT U/L	48 (25-95),688	40 (22-88),124	0.18
ALP U/L	99 (70-152),688	103 (73-134),124	0.67
GGT U/L	59 (29-113),690	48 (25-95), 124	**0.054**
BDG pg./mL	114 (31-501). 437	78 (38-178), 39	0.29

Parameter	HIV+ve	HIV-ve	P value[+]
Bacteraemia	182 (25.4%)	15 (11.5%)	**0.003**
CXR	n (%)	n (%)	
Multilobar consolidation	244 (39.4%)	50 (43.9%)	0.41
Bilateral GGO	217 (35.1%)	16 (14.0%)	**<0.001**
Lobar consolidation	99 (16%)	41 (36%)	**<0.001**
Nodules	42 (5.8%)	5 (3.8%)	0.29
Pleural effusion	16 (2.6%)	2 (1.8%)	>0.99

[+] Fisher's Exact

Abbreviations: ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; BDG: (1-3)-β-D- glucan; CRP: C-reactive protein; CXR: chest radiograph; GGO: ground glass opacities GGT: gamma-glutamyl transferase; Hb: haemoglobin; Hct: haematocrit; IQR: interquartile range; MAP: mean arterial pressure; n: number; SOI: severity of illness; %: percentage; Bold number indicate significant P values.

Table 4.4 Distribution of monomicrobial and polymicrobial infections amongst HIV-positive and HIV-negative patients (n=849, column %)

Microbial aetiology	HIV +ve, n (%)	HIV-ve, n (%)	P value[+]
No microorganism	303 (42.2%)	68 (51.9%)	**0.04**
Monomicrobial infection	329 (79.3%)	58 (92.1%)	**0.02**
Polymicrobial infections	86 (12.0%)	5 (3.8%)	

[+] Fisher's Exact

Abbreviations: HIV: Human Immunodeficiency Virus positive; n: number; +ve: positive; -ve: negative; %: percentage; Bold number indicate significant P values

Table 4.5 Aetiology of monomicrobial infections amongst HIV-positive and HIV-negative patients (n=42l, column %)

Microbial aetiology	HIV+ve, n (%)	HIV-ve, n (%)	P value+
Mycobacterium spp.			
MTB,120	105 (31.9%)	15 (25.9%)	0.54
MAC, 1	1 (0.3%)	0 (0.0%)	
Gram +ve pathogens			
Streptococcus pneumoniae, 97	84 (25.5%)	13 (22.4%)	0.74
Staphylococcus aureus, 24	16 (4.9%)	8 (13.8%)	**0.02**
*Streptococcus pyogenes,*2	1 (0.3%)	1(1.7%)	
Enterococcus faecalis,1	1 (0.3%)	0 (0.0%)	
Gram-ve pathogens			
Haemophilus influenzae, 2	2 (0.6%)	0 (0.0%)	
Enterobacterales			
Klebsiella pneumoniae, 24	18 (5.5%)	6 (10.3%)	0.22
Escherichia coli, 9	8 (2.4%)	1 (1.7%)	
Enterobacter spp, 6	5 (1.5%)	1 (1.7%)	
Salmonella spp, 2	2 (0.6%)	0 (0.0%)	
Citrobacter freundii, 1	1 (0.3%)	0 (0.0%)	
Pseudomonas aeruginosa, 15	12 (3.7%)	3 (5.2%)	
Acinetobacter spp, 7	6 (1.8%)	1 (1.7%)	
Other Gram-ve			
Burkholderia cepacian, 1	1 (0.3%)	0 (0.0%)	
Stenotrophomonas maltophilia, 1	1 (0.3%)	0 (0.0%)	
So called “atypical” pathogens			
Chlamydia pneumoniae,1	0 (0.0%)	1 (0.7%)	
Viruses, 31	24 (7.3%)	7 (12.1%)	0.29
VZV, 15	14 (4.3%)	1 (0.7%)	
CMV, 1	1 (0.3%)	0 (0.0%)	
Measles, 4	4 (1.2%)	0 (0.0%)	
Respiratory viruses, 11	5 (1.5%)	6 (10.3%)	

Fungi			
PJP, 35	35 (10.6%)	(0.0%)	**0.005**
Candida albicans, 2	2 (0.6%)	0 (0.0%)	
Cryptococcus neoformans, 1	1 (0.3%)	0	
Saccharomyces cerevisiae, 1	1 (0.3%)	0	
Stephanoascus ciferii, 1	1 (0.3%)	0	

[+] Fisher's Exact

Abbreviations: CMV: Cytomegalovirus; HIV: Human Immunodeficiency Virus; KP: *Klebsiella pneumoniae*; MAC: *Mycobacterium avium intracellulare;* MTB: *Mycobacterium tuberculosis*; PJP: *Pneumocystis jirovecii*; n: number; Respiratory viruses: Influenza virus (A, H1N1, B, respiratory virus screen); spp.: species; VZV: Varicella zoster virus; +ve: positive; -ve: negative; %: percent; Bold numbers indicate significant p values

4.4.3 Drug-Resistant Pathogens

There were similar proportions of drug-resistant pathogens distributed amongst the HIV-positive and HIV-negative patients, being 22 (3.1%) amongst PLWH and 4 (3.1%) amongst patients who were HIV-negative; P>0.99. However, all the drug-resistant MTB infections were amongst PLWH (7 (1%) vs 0 (0%)); but these numbers were too small to obtain statistical meaning, and therefore were not analysed further (Table 4.6).

Table 4.6 Drug-resistant pathogens in HIV-positive and HIV-negative patients (n=26)

MDR	HIV-positive, n (%)	HIV-negative, n (%)	P value[+]
Total	22 (3.1%)	4 (3.1%)	>0.99
ESBL-producing	11 (1.5%)	2 (1.5%)	
MRSA	3 (0.4%)	1 (0.8%)	
SP	1 (0.1%)	1 (0.8%)	
MTB	7 (1.0%)	0 (0.0%)	
INH	1 (0.1%)	0	
Rif	2 (0.3%)	0	
MDR	3 (0.4%)	0	
XDR	1 (0.1%)	0	

[+] Fisher's Exact

Abbreviations: ESBL: extended spectrum β-lactamase ; INH: Isoniazid; MDR: multidrug-resistant (resistant to rifampicin and isoniazid); MRSA: methicillin-resistant *Staphylococcus aureus*; MTB: *Mycobacterium tuberculosis* n: number; Rif: Rifampicin; SP: *Streptococcus pneumoniae*; XDR: Extensively drug-resistant tuberculosis (resistant to rifampicin, isoniazid, fluoroquinolones, aminoglycosides, ethambutol, ethionamide and pyrazinamide); % percentage

4.5 Complications

The proportion of patients within each group who developed complications was similar (175 [24.3%] HIV-positive patients, versus 41 [31.3%] HIV-negative patients; P=0.10). However, when analysing patients with only one complication, a greater proportion of HIV-negative patients developed lung necrosis or an empyema (9 [6.9%] versus 14 [1.9%]; P=0.045) (Table 4.7).

Table 4.7 Complications amongst HIV-positive and HIV-negative patients (n=849)

Complication	HIV +ve, (n.%)	HIV-ve, (n,%)	P value[+]
Total, 216	175 (24.3%)	41 (31.3%)	0.10
1 complication, 207	170 (23.7%)	37 (28.2%)	0.07
≥ 2 complications, 9	5 (0.7%)	4 (3.1%)	
Pulmonary,74	57 (7.9%)	17 (13.0%)	0.07
Pneumothorax,47	39 (5.4%)	8 (6.1%)	0.68
Lung necrosis/empyema, 23	14 (1.9%)	9 (6.9%)	**0.045**
Tachyarrhythmia, 53	43 (6.0%)	10 (7.6%)	0.44
Neurological, 37	33 (4.6%)	4 (3.1%)	0.64
Thromboembolism, 20	14 (1.9%)	6 (4.6%)	0.11

[+] Fisher's Exact

Abbreviations: CD infection: *Clostridioides difficile* infection; HIV: Human Immunodeficiency Virus; n: number; +ve: positive; -ve: negative; %: percentage; Bold numbers indicate significant P values.

4.6 Management

There were no differences in the use of mechanical ventilation (invasive or non-invasive), dialysis or inotropic support between the HIV-positive group and the HIV-negative group. In addition, corticosteroid (CS) use was similar.

4.7 Outcomes

Overall, the risk of dying was higher amongst PLWH compared with HIV-negative patients (OR, 1.61; 95% CI,1.10-2.34; P=0.014) and 354 (49.3%) PLWH survived ICU compared with 80 (61.1%) HIV-negative patients. A similar, but non-significant trend was seen when survival to hospital discharge was analysed (331 [46.0%] PLWH versus 72 [55.0%] HIV-negative; P=0.071; OR 1.43; 95% CI, 0.98-2.07; P=0.07).

4.8 HIV-unknown Patients

Within the cohort, there were a total of 82 patients of unknown HIV status. The median age of these patients was 36 [IQR 20-57] years and 31.7% were ≥ 65 years old. The majority were male (53.7%), and 9.8% were smokers. Overall, 59.8% had co-morbid disease, most commonly CVD (32.9%) and DM (31.7%). A high proportion were confused (71.3%). The median CURB-65 score was 3 (IQR 2-4), median APACHE II score was 19 (IQR 14-24) and 93.8% patients had an APACHE II score >25. In terms of blood results, median urea was (17 [IQR 9.3-27] mmol/L), median creatinine was (170 [IQR 91-363] μmol/L) and median CRP was (246 [IQR 154-343] mg/L). In addition, most patients had multilobar consolidation on CXR (55.7%).

More HIV-unknown patients were infected with Gram-negative pathogens than the HIV-positive and HIV-negative groups (KP infection [14.7%], *E. coli* [8.8%], *Enterobacter* spp. [5.9%], and *Acinetobacter* spp. [2.9%]). Seven (8.5%) patients had PM infections, in 41 (50%) patients no microbial pathogen was detected, and four (4.87%) patients were infected with MDR pathogens. Complications occurred in 23 (28%) of patients, the majority of which were tachyarrhythmias (seven (30.4%) followed by metabolic complications (five [21.7%]). In total, 73 patients (89%) were ventilated, and 43 patients (52.4%) required inotropic support. The overall length of ICU stay was 3 (IQR 2-5) days, and 31 (37.8%) patients survived ICU.

CHAPTER FIVE-DISCUSSION

This retrospective study describes a large cohort of 931 patients with Severe Community Acquired Pneumonia (SCAP), who were admitted to ICU at a tertiary hospital in a region with a high burden of HIV infection. These data describe the demographics, co-morbidities, clinical features, clinical management, complications and outcomes of these patients. In addition, all these characteristics are compared between HIV-infected and HIV-uninfected patients.

5.1 Demographics

5.1.1 Age

The median age of this cohort was 37 years (IQR 30-48) years. This is similar to that of other studies of SCAP from South Africa; for example from Johannesburg (mean 43.6 years [range 14-74] years) (14, 45), Cape Town (mean 44.7 [SD±16.88] years) (46), and KwaZulu Natal (KZN) (where only 2% of all patients with SCAP were older than 60 years of age) (47). However, this is different to international SCAP data; for example from Spain (mean age 61.3 [SD±16] years) (15), Singapore (mean age 62.5 [SD±16.1] years) (48), Thailand (mean age 70.9 [±14.8] years) (49), Reunion (mean age 54.7 [SD±15.1] years) (50) and Turkey (median age 63.8 [range 23-80] years) (51). Within this cohort, only 76 (8.2%) patients were aged ≥65 years.

Age is an important parameter in the CURB-65 (26) and PSI (28) SOI scores, but not in the markers of severe illness described in the IDSA/ATS CAP guideline (29). Like Quah *et al.* (48), and Erdem *et al.* (51), the current study found no differences in age between those who lived and those who died. Neither was age an independent predictor of mortality, which also differs from other international SCAP studies (12, 15, 16, 49, 52).

Nonetheless, Park *et al.* (16), also described a younger CAP population in Seattle, particularly amongst the HIV-positive compared with HIV-negative patients (median 38 years (range 24-68 years) vs 47 years (range 18-100 years); P<0.001), respectively, although of the 18% who were classified as SCAP, more were aged ≥65 years than < 65 years (80% vs 65%, P=0.01). In their study there was a high incidence of homelessness, cigarette smoking, intravenous

drug use and alcoholism. Moreover, within another CAP cohort of HIV-positive patients from Barcelona, the median age was 42.1 (SD ±9.5) years (18), and other studies have also noted a younger age amongst bacteraemic SP patients who are HIV-positive compared to their HIV-negative counterparts (34, 53).

The younger age of this cohort is representative of the South African population, which has a median age of 27.6 years, 62.2% of whom are between 15-60 years (54). In addition, 18.7% of the population aged between 15-49 years are HIV-positive (54). Thus, although these data differ from other international SCAP data, it is congruent with HIV-positive CAP cohorts, both internationally and locally, and represents the known risk of CAP amongst HIV-infected individuals (55). Furthermore, "accelerated aging" of at least 4.9 years, associated with an increased mortality rate of almost 20%, is well described amongst PLWH despite the use of ART (56). These factors may explain the lack of an observed association between age and mortality.

5.1.2 Sex

Despite an equal distribution of male and female patients within the entire cohort, more HIV-positive patients with SCAP were female. This differs from other international SCAP studies, which have a higher proportion of male patients (12, 15, 17, 48, 50, 51, 57, 58). Furthermore, in the current cohort overall, and within the HIV-positive subgroup, sex made no difference to mortality; however, in a multicentre study of severe pneumococcal CAP, male sex was independently associated with mortality (OR 2.83 [95% CI 1.16-6.91]; P=0.01) (39).

Our finding is partially explained by the higher incidence of HIV infection amongst women in South Africa, (24% [95% CI 22%-26%] female compared with 16.6% [15%-18.4%] male patients; P<0.001) (54). This is especially noted in the 15-24 year old age group, with women in their early 20's having a four times higher incidence of HIV than males of the same age (59). Data from critically ill ICU patients, have also demonstrated that oestradiol levels are an independent predictor of death, regardless of sex, age or body-mass index (60). These authors suggested that this effect could be explained by the pro-inflammatory effects of oestradiol, its ability to activate nitric oxide synthase and induce insulin resistance (60). Going forward, this is an important area of further research.

5.1.3 Cigarette Smoking

The majority (95.6%) of patients in the current study did not smoke cigarettes, and this differs from other international SCAP data. For example, in one study from Barcelona, 31% of patients studied with severe SCAP were smokers (12), in another study from France this was 40% (39), whereas in Turkey, more than 60% of the patients studied smoked cigarettes (51). Other data show a higher incidence of cigarette smoking amongst patients aged less than 65 years compared to patients aged 65 years and older (70.5% vs 40% respectively; $P<0.05$) (61). All these differences likely represent the influence of cultural and socioeconomic factors, resulting in different smoking rates in different countries throughout the world (62).

Similar to data from Turkey (51), in this cohort, there was no difference in the proportion of patients who were cigarette smokers who lived, compared to those who died. However, other SCAP data has determined that patients who were current cigarette smokers had a lower risk of 30-day mortality on univariable analysis (OR, 0.48; 95% CI, 0.28-0.81; P=0.006) (63); whereas another CAP study ascertained that amongst CAP patients with pneumococcal pneumonia, current cigarette smoking was an independent risk factor for septic shock (OR, 2.11; 95% CI, 1.02 - 4.34; P=0.044) (64). Cigarette smoking is a recognised risk factor for CAP (65), and has associated immunomodulatory effects that are well-described (66-68). Further investigation of the effects of current, passive and previous cigarette smoking and outcomes amongst patients with SCAP are warranted.

5.2 Co-morbid Disease

Overall, HIV was the most common co-morbidity amongst patients in this cohort; however, 42% of all patients had co-morbid diseases other than HIV, and amongst these patients CVD was the most prevalent and was associated with a lower mortality. In addition, more HIV-negative patients had co-morbid disease such as DM, chronic CVD, chronic respiratory disease (including COPD), chronic neurological, CKD and hypothyroidism, whereas more HIV-positive patients had a history of previous MTB infection, though this was not associated with a higher mortality.

The frequency of comorbidities varies between different SCAP studies, and most likely

reflects local disease patterns, the average age of the population and their habits. COPD and chronic respiratory disease were predominant amongst SCAP cohorts in Spain (12, 15), COPD was most common in Reunion (50), whereas hypertension was the most common in a SCAP study from Singapore (48). On review of HIV CAP data, Hepatitis C virus (HCV), chronic liver disease and chronic respiratory disease were predominant in Spain (18); previous pneumonia and COPD in Seattle (16), and previous pneumonia (23%) and previous MTB (18%) in Malawi (11), but neither made any difference to mortality. In addition, a review of the CAPO database determined that COPD, CVD, CVA, renal disease, cancer and diabetes were higher amongst HIV-negative patients with CAP, whereas liver disease and alcohol/drug use were higher in the HIV-positive cohort (69).

5.2.1 HIV Co-infection

The majority of patients within this cohort were HIV-positive (77.1%). Other SCAP data from Spain (15), report a much lower incidence of HIV, and some studies have excluded HIV-positive patients (8, 12, 49). The overall risk of mortality was increased in the current study in the HIV-positive population on univariable analysis, but not MVA, In another CAP study, Feldman *et al* (34), showed that although on univariable analysis, HIV-infected patients appeared to have less severe disease than their HIV-negative counterparts, after adjusting for age and severity of illness, critically ill patients with bacteraemic pneumococcal pneumonia had a higher risk of death if they were HIV-positive compared to being HIV-negative (OR, 4.56; 95% CI, 2.1-9.7; P<0.001).

South Africa has the largest HIV population in the world, with 13.7% of the general population infected, and up to 20% in those aged between 15 and 49 years old (59). As such, South Africa has the largest ART roll-out programme in the world, and 62% PLWH are on treatment, of whom 52% are virally suppressed (5, 59). Despite this, only 16.6% of the HIV-positive patients in this study were using ART. Globally, retention in ARV programmes is imperfect (70-72), and factors associated with this are male sex, higher CD_4 cell count, a shorter duration on ART (6 months), socio-economic factors, cultural factors as well as side effects of therapy (72, 73).

In the current study, lower CD_4 cell counts were reported amongst the HIV-positive patients who died, regardless of whether they were using ART or not; furthermore, within each multivariable model, CD_4 cell count was an independent predictor of mortality (albeit small), with higher mortality as CD_4 cell count dropped. Feldman *et al.,* also demonstrated that amongst HIV-infected patients with bacteraemic pneumococcal pneumonia (CAP), there was an increased mortality amongst patients with lower CD_4 cell counts ($P < 0.05$), and the median CD_4 count was 111 cells/mm^3 in non-survivors compared to 179 cells/mm^3 in survivors (P=0.05) (34), whereas in Ugandan CAP data, CD_4 cell counts <50 cells/mm^3 were associated with an increased mortality (74). However, a review of HIV-positive patients in the CAPO database (CAP) showed no impact of differing CD_4 cell counts on the risk of mortality at 28 days (75), and similar data from Pune (SCAP) showed no difference in mortality amongst patients with CD4 counts greater or less than 100 cells/mm^3 (17).

Lymphopenia is well-described with sepsis, and represents apoptosis induced T cell loss and possibly the redistribution of lymphocytes into tissues during infection (76-78). However, it was not possible in the current study to determine whether the lower CD_4 cell count noted amongst the HIV-positive patients was a marker of SOI or the degree of underlying immunosuppression from HIV co-infection.

5.2.2 Cardiovascular Disease

CVD was the second most common co-morbidity noted, both in PLWH and HIV-negative patients. However, in the current study, patients with cardiovascular comorbidity, had a higher chance of survival on univariable analysis, with a similar, though non-significant, trend on MVA, which is difficult to fully understand. Nonetheless, amongst a cohort of patients with SCAP in Turkey, patients with comorbid hypertension had a lower risk of ICU mortality (OR; 0.297, 95% CI 0.094-0.943; P=0.039) (51).

There are data to suggest that aspirin (79), statins (80) and antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBS) are protective in patients with pneumonia (81, 82). Although the “healthy user hypothesis” has been used to explain these findings, patients with CAP who were using statin therapy (including those with higher PSI scores), have been shown in other studies to have lower CRP levels, lower risk of empyema and parapneumonic effusions, as well as a lower 30-day mortality (80). This suggests that the benefits from statin use are related to their anti-inflammatory effects. In addition, ACE inhibitors have been shown to increase substance P,

which increases the cough reflex (82), and has immunomodulatory effects on cytokines (83). However, the current cohort differs from these studies in that the study population was younger and predominately HIV co-infected. In addition, it relied on self-reporting to obtain a history of co-morbid disease, and there was no way to check compliance with therapy. Nevertheless, this study demonstrated that underlying CVD was associated with lower mortality and this needs further evaluation.

5.3 Clinical Presentation, Laboratory Data and Radiology

5.3.1 Body Temperature

In the IDSA/ATS guideline for CAP (29), body temperature >37.8° C and <35.6° C are used as minor criteria for severity in patients with CAP. Although the median body temperature recorded in the current study was 36.8 (IQR 36-37.5) °C, 54% of patients had admission temperatures <35.6 °C and/or >37.8 °C. Furthermore, significant differences were noted in the current study between survivors and non-survivors, with lower body temperatures recorded amongst patients who died; however, given the differences in these measurements was small, they are unlikely to be clinically relevant.

The lower body temperature noted amongst survivors is concordant with other international data. Amongst patients with SCAP in Singapore, 60.7% had fever (48), and although more survivors had a temperature >38°C compared with non-survivors (survivors [62.4%] vs non-survivors [50%]), this difference was not significant, (P=0.35). In Barcelona, 78% of patients admitted to ICU with pneumonia had fever, which was more likely to be associated with MM than PM infections (84% vs 69%; P=0.034), and these patients had a lower chance of dying (OR, 0.43; 95% CI; 0.19-0.95; P=0.037) (12). Furthermore, amongst patients admitted to hospital with bacterial sepsis, of which the most common cause was pneumonia, those with a lower body temperature (<36°C) also had a lower chance of survival (84). These findings could be a explained by studies which have shown that the protective mechanisms of fever work by enhancing host immune cell function (neutrophil activity, phagocytosis, antibody

production and natural killer cell function) as well as increasing environmental stress to enhance pathogen destruction (85). Therefore a lower body temperature may imply an inadequate immune response to pneumonia and therefore a worse prognosis.

5.3.2 Confusion

Just over half (54%) of the patients in this cohort were reported to be confused, and this was more common amongst those who died overall. Of all the IDSA minor criteria for CAP, confusion is the strongest predictor of mortality (OR, 5; 95% CI, 2,3-11; P<0.01) (86). Encephalopathy is a well-recognised sign of sepsis and clinically varies from mild confusion to comatose states, with short- and long-term consequences (87). Confusion is a subjective clinical sign, which can be easily misinterpreted by a physician in a busy admission ward and is dependent on medication, and language barriers. Nevertheless, the current study found a significant proportion of patients labelled “confused”, and this was associated with death.

5.3.3 Blood Pressure

Blood pressure is a component of most SOI scoring systems (29). In this cohort, although most of the current patients were normotensive on admission, MAP was lower amongst patients who died, regardless of their HIV status, but this was still ≥ 65mmHg. However, MAP was an independent risk factor for mortality (i.e. for every 1mmHg decrease in MAP there was a 1% increase in mortality). Ferrer *et al*., demonstrated that patients with SCAP who required IMV were younger and had a higher admission diastolic blood pressure than those who did not require mechanical ventilation (MV) (73±19 vs 68 ±16; P=0.006) (63). In another prospective CAP study, blood pressure was shown to be an independent predictor of 30-day mortality and the requirement for mechanical ventilation (88), and in another CAP cohort, which included HIV-positive patients, MAP <65 mmHg was a predictor of 30-day mortality (12.4% vs 23.8%; OR, 2.21; 95% CI 1.14-4.26; P=0.02) (11). Despite this, other SCAP studies have determined that by itself, hypotension is not associated with mortality (89).

5.3.4 Severity of Illness Scoring (SOI)

Three severity of index scoring systems were used in the current study to identify which patients were at highest risk of poor outcome. These were CURB-65, Apache II score and $PaO_2/Fi0_2$ ratio.

5.3.4.1 CURB-65 score

In accordance with the South African pneumonia guideline (1), the CURB-65 score is used in South African healthcare facilities as a tool to assist in determining severity of illness, and, therefore, where a patient with CAP would most appropriately be managed. Patients with CURB 0-1 are deemed at low risk of death and may be considered for home treatment, whereas those with a score of ≥3 have a higher risk of death and should be managed in hospital, with referral to ICU as necessary. Initial validation of the CURB-65 score (27) excluded patients who were HIV-positive and those with suspected PTB, and studied a population which was older than the current cohort (median age 69 [IQR 17-100] years) compared to 37 [IQR 30-48] years), respectively. The median CURB-65 score for the current cohort was 3 (IQR 2-3) and was higher amongst patients who died compared to those who survived (3 [IQR 2-3] died vs 2 [IQR 2-3] lived; P< 0.001).

A meta-analysis of studies evaluating Pneumonia Severity Index scores from low- and-middle income countries (LMIC) in Africa and South Asia, some of which excluded patients with HIV, determined that “high risk” patients (i.e. those with CURB-65 and CRB-65 scores ≥3) had an increased risk of dying (pooled RR, 9.16%; 95% CI, 3.61%-23.25 and 6.67%; 95% CI; 3.19%-13.95%, respectively) (90). However, in other SCAP data from Spain, although fewer ICU patients with CURB-65 scores of 3-5 were mechanically ventilated ([49% ventilated vs 63% not ventilated], P=0.002), this higher score was accounted for by an older population with more underlying renal disease. Furthermore, in the latter study, CURB-65 was not associated with an increased 30-day mortality on MVA, but the use of IMV was (63).

Within the present study PLWH had lower CURB-65 scores compared to those without HIV, although they were all admitted to ICU. This trend is consistent with other CAP data, in which more hospitalised HIV-positive patients with CAP had lower CRB-65 scores (0-2) and PSI scores compared to their HIV-negative counterparts (69), which could be explained by the perception that PLWH were at a higher risk from CAP and thus warranted hospital admissions at lower SOI scores. It is difficult to accept whether the same argument holds true within this current data set, as it is unlikely that in a resource-limited setting a patient would be taken to ICU simply because their HIV status made them more "high risk". Furthermore, the younger age of this population and lack of association of age with mortality may make the CURB-65 score an imprecise tool for assessing disease severity. Going forward validation and the development of more appropriate SOI scores remains an important area of further research.

5.3.4.2 APACHE II score

The APACHE II score is determined using 12 physiological variables (41). Patients with a score ≥25 calculated within the first 24 hours of ICU admission, have a 50% mortality (91). The median APACHE II score within the current cohort was 18 (IQR 14-23), giving a predicted mortality of 24% (15%-40%), which is lower than the mortality in this study (50%). Ferrer *et al.* (63), also showed that APACHE II score underestimated mortality in SCAP patients who required IMV (26% predicted to die vs 33% who actually died). Similarly, another small retrospective study (92), of HIV-positive patients admitted to an ICU, documented that APACHE II score underestimated the mortality amongst HIV-positive patients with a total lymphocyte count ≤200 cells/mm^3, especially those who had pneumonia or sepsis (50.5% expected vs 85.7% observed, n=14; p<0.01). Unfortunately, there were no data on lymphocyte counts for the current cohort.

However, within the existing cohort, the APACHE II score was higher amongst patients who died and was shown to be an independent predictive of mortality on MVA. Other SCAP studies have also shown APACHE II to be an independent predictor of mortality (48, 63), and although mean scores vary between studies (48, 63) a higher score is consistent with worse outcomes. This was also shown to be true amongst the HIV-positive group in the current study.

5.3.4.3 $Pa0_2$/ $Fi0_2$ ratio (PF ratio)

A $Pa0_2$/ $Fi0_2$ ratio ≤250 is part of the minor severity criteria for patients with SCAP (29) and is a useful determinant of the degree of physiological shunt fraction and hypoxemia present (93). In keeping with what is expected from an ICU cohort, the majority (79.3%) of the current patients had a mean PF ratio ≤250, with a median PF ratio of 144 [IQR 97-229], and this was significantly lower amongst patients who died. In comparison, the mean PF ratio amongst patients with SCAP in Barcelona, of whom 20% were mechanically ventilated, was higher (247.6, SD±99.5) (12), whereas 85.6% of the current cohort required mechanical ventilation.

While more patients with PF ratios ≤250 died, the difference in numbers were smaller than expected, (334 [71.8%] lived vs 364 [78.1%] died, P=0.001), and this is similar to data from Turkey (93 [75%] lived vs 222 [75%] died; P=0.33) (51). A validation study of the individual criteria for severe pneumonia, demonstrated that PF ratio <250 had a low sensitivity (64%), specificity (65%), low PPV (28%) and NPV (89%) in determining the need for ICU admission, and was not associated with death (94). However, on MVA, PF ratio <250 was independently associated with ICU admission (RR 2.7; 95% CI, 1.4- 5.2), but not mortality (94). Furthermore, Li *et al.,* demonstrated that PF ratio ≤250mmHg was independently associated with mortality (OR 9.808; 95% CI, 5.571-17.266; P<0.001), as well as the need for ICU admission in a group of patients with SCAP (89), and that the combination of PF ratio ≤250, confusion and uraemia carried a higher mortality than other combinations of minor criteria. In another study, no difference in PF values was noted amongst patients with severe pneumonia who had PM versus MM infections (12), despite a higher requirement for mechanical ventilation and higher mortality within the PM group. All three aforementioned studies included patients with SCAP and excluded patients with HIV co-infection. Nonetheless there are other data supporting the validity of ATS severity criteria amongst a cohort of HIV-positive patients with bacterial CAP (95).

In the current cohort, PF ratio was shown to be an independent, yet small predictor of mortality on MVA. Its use may be as an adjunct in guiding ICU admission, in order to identify patients who would benefit from increased care. Further study in a population not requiring ICU admission may be beneficial.

5.3.5 Laboratory Parameters

5.3.5.1 Urea, creatinine, white cell count and platelets

Urea is a component of the CURB-65 score (27), and the minor IDSA/ATS criteria (29). It has also been shown in other studies to be a predictor of hospital mortality in patients with severe CAP (OR 13.4; 95% CI, 7.334-24.485; P<0.001) (89). Within the current cohort, uraemia (urea ≥7 mmol/L), was not associated with mortality; however, as the median level was elevated overall (12 [IQR 6.4-23.6] mmol/L), it may be too high to detect a difference. Another SCAP study, found no differences in creatinine, white cell count, platelet count or CRP between patients who required ventilation and those who did not; although, raised serum creatinine (OR 1.22; 95% CI, 1.03-1.43; P=0.023), platelet count (OR 1.22; 95% CI, 1.03-1.47; P=0.034) and serum sodium (OR 1.03; 95%CI, 1-1.06; P=0.044) were associated with 30-day mortality (63).

The lower white cell count amongst the current HIV-positive patients may be related to the high number (83.4%) of these patients not being on ART prior to admission. In other SCAP data, white cell count was lower amongst patients with PM infections than MM infections (OR 0.61; 95% CI 0.38-0.98; P=0.041); however, this was not shown to be an independent predictor of in-hospital mortality (12). The association of lymphopenia and sepsis has been discussed previously.

5.3.5.2 Serum potassium

Other SCAP data have shown potassium levels to be associated with increased mortality (OR 2.54; 95%CI, 1.32-4.90; P=0.005) (63). In the current study serum potassium was elevated in all patients who died, although the differences were small and levels were still within normal limits; therefore, this may not be clinically significant. Although there were no data on lactate levels nor pH, the group who died had lower MAP and higher inotrope use; therefore, they

were more likely to have an increased lactic acidosis and hyperkalaemia. In addition, the background renal impairment observed likely contributed to decreased potassium clearance.

5.3.5.3 Liver enzymes

Overall, in the current study, median levels of AST (82 [IQR; 44-181] IU/L) were higher than alanine transaminase (ALT) (median 45 [IQR; 24-93] IU/L), and higher overall amongst patients who died. As AST is an enzyme not specific to the liver and is found in the heart, skeletal muscle, kidneys, lungs, red blood cells and white cells, which raises the possibility that the elevation observed may be related to multi-organ involvement from sepsis. Liver function abnormalities from pneumonia are thought to arise from the hepatotoxic effect of pathogens, hepatic ischaemia, right ventricular failure or haemolysis. In addition, atypical pathogens (especially with *Mycoplasma pneumoniae* and *Legionella pneumophila* infections) are commonly associated with hepatocellular dysfunction (96).

The median albumin level was 26 (IQR 21-30) g/l, and this was lower amongst patients who died, regardless of their HIV status. There are data showing that lower albumin levels portend a higher mortality risk in patients with CAP (97, 98). In addition, using different serum albumin levels (<30g/l (97) and <33g/l (98), respectively), as an additional factor in the CURB-65 and PSI scores, increases the accuracy of their mortality predictions, and specifically with PSI more accurately predicts the need for ICU admission, inotropes and mechanical ventilation (98). In sepsis, lower albumin levels are multifactorial, resulting from increased breakdown and capillary leak with extravasation of albumin into the interstitium (99). Furthermore, animal studies have demonstrated that the administration of albumin in rats with endotoxin-induced septic shock improves endothelial dysfunction, reduces oxidative stress and reduces the activation of (NF-κB), thus attenuating the inflammatory response (100). Albumin levels in HIV-positive patients have also been documented to be lower pre-ART and correspond to weight and CD_4 cell count (101). The overall lower albumin levels within the current cohort most likely reflects the severity of pneumonia (median CURB-65=3 and APACHE II =18), as well as the large proportion of HIV-positive patients (77.1%), the majority of whom (62%) were not on anti-retroviral therapy.

5.3.5.4 C-reactive protein (CRP)

The median CRP for the entire cohort was 202 (IQR 118-288) mg/L, with no differences when comparing HIV-positive and HIV-negative patients, although the CRP was lower amongst all patients who died. In addition, lower CRP was associated with increased mortality on MVA. Other SCAP studies (48, 63) have reported no relationship between CRP and survival, similar CRP levels in patients who required ventilation and who did not (63) and no differences in CRP amongst patients with MM and PM infections (12). In the current study, there were no differences in CRP levels amongst patients with MM and PM infections.

Within the current cohort, CRP levels differed with the pathogens observed. Highest levels were noted amongst patients with SP, then MTB and then PJP infection. These data are similar to other HIV CAP data from South Africa; in one study a CRP ≥246mg/L and PCT >3ng/l were highly predictive of SP infection, compared with MTB (102). In another study, amongst patients who met WHO criteria for severe illness, Mendelson *et al*. demonstrated that the median CRP levels for SP, MTB and PJP infection were 193 (95% CI;108-264) mg/l, 141 (95% CI; 97-203) mg/l and 106.5 (95% CI; 79.5-131.5) mg/l, respectively, and a CRP level >147mg/dl had high specificity for differentiating PJP from bacterial CAP, and a high sensitivity for differentiating PJP from MTB (103). Furthermore, other international CAP data from Barcelona, amongst an HIV-positive CAP cohort, CRP levels ≥220mg/l were predictive of a bacterial aetiology (MVA; OR, 4.3; 95% CI, 2.3-8.2; P<0.0001), whereas a CRP level <120mg/l was more likely to be a consequence of PJP infection (univariable analysis OR, 3.2; 95% CI, 1.5-6.9; P=0.002) (18). However, it is worth noting that the median CRP level (139 mg/L; IQR, 64mg/L-198mg/L) within the existing cohort is higher than in the aforementioned studies, and this is difficult to explain fully. It may represent more severe illness, as in one study, only 8 (19.5%) of patients with PJP infection received mechanical ventilation, and 6 patients (14.2%) died (18), compared with 33 patients (94.3%) who received mechanical ventilation and 27 (79.5%) deaths within this cohort. Furthermore, the more elevated CRP could represent an additional undiagnosed polymicrobial infection. Whatever the reason, the elevated CRP seems to be an indicator of more severe illness amongst patients with PJP infection, and this should be investigated going forward.

Finally, in the current study lower CRP levels were also documented amongst patients with viral infections compared to those without. This is similar to SCAP data from Singapore (mean; 127.8 [SD±105] mg/L in cases in which viruses were detected vs mean; 178.1 [SD±117.6] mg/L in cases in which no viruses were detected; P=0.021) (48).

The lower CRP amongst patients who died in the current study could be explained by the fact that the mortality was higher amongst patients with MTB and PJP and these infections had lower CRP levels, while SP infection had a higher CRP and lower mortality. Furthermore, given the observation, from the current study and other international data, that CRP is higher amongst patients with SP infection, compared with MTB, PJP and viral infections, it is possible that the large proportion of patients with no microbial aetiology detected had undiagnosed PTB, PJP or viral infections.

5.3.5.5 (1-3)-B-d-glucan (BDG)

(1-3)-B-d-glucan (BDG) has been used as part of the diagnostic strategy at CMJAH since 2009 to assist in the diagnosis of PJP and other invasive fungal infections as it is a constituent of the cystic wall of PJP and cell wall of other fungi (with lower levels in *Cryptococcus* spp.) (102). A recent meta-analysis demonstrated that a positive BDG test had a pooled sensitivity of 91 % (95% CI; 87%-94%) and specificity of 79% (95% CI; 72%-84%) for detecting PJP infection, and the tests performed better in HIV-positive compared with HIV-negative patients (104). This is higher than the sensitivity and specificity for invasive fungal infections in another meta-analysis (76.8% vs 85.3%) (105).

In the current study, in accordance with the manufacturer's instruction, a BDG level ≥80pg/ml was considered positive (106), and therefore, overall, BDG levels were elevated in the entire cohort and higher amongst the PLWH compared to their HIV- negative counterparts. This latter finding is not surprising as a significant proportion of the HIV-positive patients were likely to have fungal infections such as PJP and/or oral candidiasis. Very high BDG levels (mean 1299; SD ± 1151 pg/ml) have been described with PJP infection, and these are much higher than levels recorded in invasive fungal infections (107).

Interestingly, a prospective study of critically ill ICU patients demonstrated that BDG was elevated (20pg/ml) amongst patients with mycotic infections, Gram-negative and Gram-positive bacterial infections, and there was no significant difference in BDG levels between patients with fungal infections or bacterial infections. The authors postulated that this might indicate the presence of glucan, glucan-like products, or other undefined microbial components, which cross-react with the BDG assay (108). Moreover, there are data which demonstrate that high levels of BDG are associated with a hyperinflammatory phenotype in critically ill patients, and are predictive of a poor outcome (109) These high levels of BDG are postulated to represent translocating fungal Pathogen Associated Molecular Patterns (PAMPS) (109), and this raises an interesting point. In this cohort not all patients with raised BDG had an identifiable microbial cause, and although it is possible that certain microbial pathogens were undiagnosed, it is also intriguing that the elevated BDG could be a marker of severe inflammation for the points mentioned above, and would therefore be an interesting area for ongoing research.

5.3.6 Radiology

Similar to other SCAP studies in both HIV-negative and HIV-positive patients (12, 18, 48, 63, 89, 94), multilobar consolidation was the predominant radiological finding overall (41.6%). Multilobar infiltrates are one of the minor criteria in the ATS/IDSA guidelines (29); however, Quah *et al.* reported no differences in the proportion of patients with SCAP who lived and died with multilobar consolidation on chest radiography, and further determined that multilobar consolidation was not an independent predictor of hospital mortality (48). Moreover, multilobar pneumonia has also been reported to occur more commonly amongst SCAP patients with PM infections than MM infections (69% vs 47%; P=0.003) (12); however, in the existing cohort, this was not the case.

In the current study, on MVA, more patients with ground-glass opacities had a higher risk of dying. However, patients with lobar consolidation were more likely to live, regardless of HIV status, and this is similar to data from Pune (aOR, 0.12; 95% CI 0.02-0.95; P=0.044) (17). HIV-positive immunocompromised patients, have considerable overlap in radiographic presentations with SP, PJP and PTB infections (110, 111). In the current study, ground glass infiltrates were found in most patients with PJP and viral infection, while lobar and multilobar

involvement occurred more commonly in SP and PTB. In another study of HIV-positive patients with CAP, multilobar infiltrates were independent predictors of PJP infection (OR 5.8; 95% CI 1.9-19.5; P=0.002) (18),

Pleural effusions were an uncommon finding in this study (2.7%), which is similar to other HIV/SCAP data from Pune in which only four patients (3.6%) presented with pleural effusions (17). Risk factors for the development of parapneumonic effusions and empyema include alcohol and drug use, as well as albumin levels <30g/L, CRP level >100mg/L, platelet counts >400x10^9/l, serum sodium levels <130mmol/l and smoking (112, 113). Whereas, prior use of inhaled steroids (amongst patients with chronic lung disease) is protective, probably by attenuating the inflammatory response in the lungs (112, 114). Furthermore, another in-patient study of bacterial CAP in HIV-positive patients (which excluded patients with PTB), determined that the presence of a pleural effusion, multilobar infiltrates and cavities were associated with radiological progression of disease, and these patients were predominately male, with a high incidence of IDU, smoking and alcohol abuse (95). A combination of the aforementioned risk factors may explain the lower numbers of cases of pleural disease noted radiographically in the current study. Finally, despite the predominance of MTB infection in the current study and the common occurrence of pleural effusions with MTB (115), the current data suggests a lower SOI amongst patients with MTB with this as a predominant radiological feature, as only eight patients with MTB had CXR changes of a pleural effusion.

5.4 Microbiology

5.4.1 Pathogen Identification

Accurate identification of microbial pathogens relies on timely specimen collection (prior to antibiotic administration), the ability to collect appropriate specimens in critically ill patients and availability of appropriate diagnostic tools. At CMJAH, within the time period of this study (2007-2019), there was limited access to urinary pneumococcal antigen testing, serology and extended PCR panels for bacteria and virus identification. In addition, the

GeneXpert System (Cepheid, Sunnyvale, CA), with improved diagnostic capabilities for rifampicin-resistant TB, was rolled out in South Africa only in 2012 (43). Thus, for a large period in this study, diagnostics relied heavily on blood cultures, sputum smear and cultures and histopathological samples, where available. Viral detection by nasopharyngeal swabs was low, but this reflects more the fact that although the use of swabs was introduced at CMJAH in 2009 with the H1N1 epidemic, their use has continued only sporadically thereafter, due to financial constraints and laboratory availability. Viruses are well described causes of severe CAP, causing MM and PM infections, and it is thus concerning that a significant number of these pathogens were not detected (14, 47).

Interestingly, despite this, an identifiable microbial cause was found in more than 50% of cases in the current cohort, more commonly amongst the HIV-negative patients, and this was not associated with an increased mortality. Overall, 519 (55.7%) cases had an identifiable microbial aetiology in the current study, and this is similar to other SCAP data (53%) (52). However, other SCAP data from Pune (82.9%) (16) and Singapore (71.9%) (48), had better yields, probably related to more use of comprehensive diagnostic techniques.

Of all the 706 isolates identified, 317 (45.4%) were from sputum and 274 (39.3%) from blood. Only 22 nasopharyngeal swabs in the cohort yielded results, one being CP and the rest were respiratory viruses. This is in contrast with other SCAP data, in which 48.7% pathogens were detected using PCR techniques on nasopharyngeal swabs (48). In addition, within this cohort the diagnostic yield from pleural effusion aspiration was 86%, and this is higher than has been reported elsewhere, albeit in non-CAP studies (116, 117),

5.4.2 *Mycobacterium tuberculosis* (MTB)

MTB was the predominant organism identified overall in both MM and PM infections. In other SCAP data from Singapore (an area with endemic TB), MTB was documented in only 2.6% of cases (48); however amongst an HIV-positive SCAP cohort from Pune, although MTB was the most common pathogen, these patients were excluded from the final analysis (17).

The current study found that MTB was the most common organism causing SCAP, regardless of HIV status. However, although Park *et al.,* demonstrated more MTB infections amongst the PLWH in their entire CAP cohort (12% HIV positive vs 5% HIV negative; P=0.03), there were similar numbers within the SCAP subgroup (5% HIV-positive vs 4% HIV-negative, P=1.0) (16). The current data reflects the high burden of TB in the community and is further supported by the strong relationship between TB and HIV (11, 20). The occurrence of MTB had no impact on mortality, even in the HIV-positive group.

MTB is a well-documented cause of SCAP and carries a high mortality amongst patients admitted to ICU. In other ICU data from South Africa, there was a 1.5% incidence of respiratory failure amongst patients admitted to hospital with pulmonary TB, and of those who were admitted to ICU, 33% did not survive the ICU admission. In this study, 3-month mortality after ICU admission was 47% (118). Another systematic review, which included 35 studies of patients with MTB who were admitted to ICU, demonstrated that the pooled incidence of ICU admission amongst hospitalized patients with MTB was 3.4% (95% CI; 1.6-5.7%), and of these patients, acute respiratory failure (mean 64.1% [95% CI; 53.5%-74.7%]), predominately because of pneumonia and ARDS, were the most common reasons for ICU admission (119). ARDS from MTB is a pro-inflammatory response within the lung to mycobacterial antigens (120) and carries a high mortality (OR, 57%; 95% CI,51-53%; P=0.004), compared to cases without ARDS (119, 120).

As in other SCAP studies (17, 48), MTB was also identified in PM infections (46%). In an

HIV negative CAP cohort from Manila, 28.5% of patients with PTB had bacterial co-infections, and 2-week mortality was increased in these patients (OR, 1.67; 95% CI, 1.03-2.72]). Moreover, TB bacillary load was not associated with an increased risk of bacterial co-infection (121). It is thought that TB suppresses monocyte functioning and therefore increases the hosts' predisposition to other infections (119).

In the current cohort, Gram-negative infections were the most common co-pathogens with MTB, and KP was the highest in number, followed by SP and PJP. SP was the most common co-pathogen in the KZN CAP cohort (10); however 3% of bacterial/mycobacterial, 6% of viral/mycobacterial and 2% of bacterial/mycobacterial/viral co-infections were described in CAP in Malawi (11); and 21.2% HI and 7.9% SP in Manila (121). There are a paucity of data describing KP and MTB co-infection; however, KP has been more commonly associated with underlying cardiorespiratory disease, alcoholism and diabetes, and carries a high mortality.

Eight patients with TB drug resistance were noted in the entire cohort, and the majority were in PLWH. There were no differences in mortality noted between those with and those without drug-resistant pathogens, but the numbers were small and therefore the analysis is unlikely to yield any significance. The only patient with XDR TB died. As mentioned previously, it is worth noting that for the first 5 years at least of this study, GeneXpert was unavailable and diagnosis was reliant on sputum smear and culture.

5.4.3 Gram-positive Pathogens

5.4.3.1 Streptococcus pneumoniae (SP)

Amongst the current cohort, SP was the second most common bacterium isolated. This differs from GBD data (5) and other pneumonia studies, which have identified SP as the predominant pathogen. However, most SCAP studies have excluded patients with TB and/or HIV (14, 15, 17, 50, 51, 57). In one SCAP cohort, the authors included immunocompromised patients, and after excluding all patients with MTB infection, SP was the predominant bacterial aetiology (16). In the current study there were a similar number of SP infections when comparing PLWH and the HIV-negative group, which differs from other CAP data in which there were more SP infections amongst the HIV-negative patients (11, 16). The current study also found that SP was a common co-pathogen in PM infections (10.2%), similar to what has been described in SCAP cohorts elsewhere (12).

Interestingly, on univariable analysis, patients with SP had a lower risk of mortality than those with other defined infections, and this finding was consistent amongst PLWH. Ferrer *et al.*, noted a similar number of SP infections amongst patients who required IMV and those who did not (63), although another CAP study demonstrated that the distribution of patients presenting with SP fitted evenly into all SOI groups (determined by CURB-65 and PSI), but at the higher levels of SOI scores, SP was responsible for the most deaths (8). The lower mortality observed in the current study in SP-infected patients may reflect the low level of high level antimicrobial resistance to SP in South Africa. There were only two isolates with intermediate resistance to penicillin. The local South African CAP guideline recommends appropriate beta-lactam antimicrobials effective against SP as first line therapy for all cases, and in adequate doses, which is likely to cover for most pneumococci other than the most highly resistant ones, which are uncommon (1).

5.4.3.2 Staphylococcus aureus (SA)

Although SA is a common cause of CAP amongst HIV-positive patients (9% cases) (122, 123), SA infections were more common in the HIV-negative group in the current study. The overall numbers of SA within the current cohort (3%) were higher than SCAP data from Spain (15), but lower than SCAP data from Pune (17). Valles and colleagues (15), also reported no significant changes in the numbers of SA in patients with SCAP over a 15-year period (1.1-3.2%).

In the current study there was no increased risk of mortality with SA infections. Ferrer *et al.,* reported similar numbers of SA infections amongst patients who required mechanical ventilation and those who did not (63). Moreover, SCAP data from the GenOSept cohort, showed that SA infection was associated with increased mortality at 28 days and 6 months (124). Other SCAP studies have also reported more MSSA PM infections than MM infections (12), but this was not noted within the current cohort. In addition, although SA infection is well described in conjunction with viral infections, especially influenza virus (125), in the current study more co-infections were noted with SP. However as mentioned before it is possible that the influence of viral infections have been underestimated.

Finally, all five cases of MRSA in the current study died. This is not a surprising finding, as the empiric antibiotics for CAP do not cover MRSA, and MRSA is associated clearly with severe pneumonia (126).

5.4.4 Gram-negative Pathogens

In the current study, Gram-negative bacteria were identified in 82 (19.5%) MM infections, and PA and KP were the most common (4.3% vs 6.9% respectively). This compares to 3.4% PA, 4.3% KP (48); 1.8% PA, 22.4% KP (50), and 5.5% PA in other SCAP data (17).

In the current study, there was no increased risk of mortality amongst patients with Gram-negative infections. Nevertheless, other studies which included ICU patients with SCAP, demonstrated a high mortality rate (67%) with Gram-negative bacteria, and for PA this was 33% (8). In addition, even at lower SOI scores (e.g. PSI1) the mortality from GNEB was 14% compared to 1% SP (8). Furthermore, a high mortality was also observed in a comparison of bacteraemic patients with SCAP from South Africa (mortality 80% KP vs 67% SP) (45) and in another SCAP study, KP infection was shown to be an independent risk factor for mortality (RR,18; 95% CI, 25-149; P=0.001) (50).

The current study also noted a similar number of Gram-negative infections amongst PLWH compared with the HIV-negative group. However, in other SCAP studies, a higher incidence of GNEB occurred in the HIV-positive group compared with the HIV-negative group (20% vs 0%; P<0.001) (16), and in another study, a high incidence of PA was noted amongst HIV-positive patients with SCAP (17.9%), which was associated with a mortality of 20.6% (95).

Gram-negative infections, including PA, have also been reported to have a higher incidence in PM SCAP infections (12), and the authors have postulated that the presence of more structural lung disease within this group likely contributed to this finding. Moreover, within the SCAP cohort from Reunion, there was a higher incidence of alcohol abuse amongst patients with KP infection than amongst patients with other type of SCAP (50). Other risk factors for GNEB infections are known to include structural lung disease, severe pneumonia, use of CS and prior antibiotic administration (127). Within the current cohort, there were only seven patients with chronic lung disease who had PM infections, and only three were caused by gram-negative infections (KP, *Acinetobacter* spp., HI).

Finally, there were no differences in survival amongst patients infected with ESBL-producing bacteria compared with those who did not have these infections. In a large study, which excluded patients with HIV and MTB, CAP caused by PES pathogens (PA, Enterobacteriaceae ESBL-producing bacteria and MRSA) occurred in 6% of cases, and risk factors included older age, having received previous antimicrobials and acute kidney injury (128). Furthermore, patients in whom PES pathogens were identified had an increased 30-day mortality (OR 2.51; 95% CI, 1.2-5.25; P=0.015) (128). Additionally, amongst a cohort of HIV-positive patients with SCAP in Pune, Mane et al., report an incidence of 23.6% MDR isolates and in this study, infection with an MDR pathogen was independently associated with mortality (adjusted odds ratio [AOR]=0.07, 95% CI,0.01-0.55; P=0.012) (16).

5.4.5 Viral Pathogens

In the current cohort, VZV infections were the most common viral infection, and this was a clinical diagnosis. Most infections were amongst HIV-positive patients and most of the patients with VZV survived (11 [73.3%] VZV infected lived vs 4 [6.7%] VZV infected died). VZV is an uncommon cause of pneumonia and carries a high mortality, especially amongst immunocompromised patients. Over time, these mortality rates have improved considerably (19%-6%) with the use of acyclovir and in some studies, corticosteroids (129, 130).

In the current study, other respiratory viruses were more common amongst HIV-negative patients; however, there were no differences in mortality overall and within each HIV subgroup. Data shows that viral causes of CAP are spread across the range of SOI scores and carry a lower mortality rate than bacterial causes of CAP, which is further highlighted by the higher proportion of patients with viral pneumonia who were treated in a ward rather than ICU (12% ward vs 4% ICU, P<0.001) in one study (8). The significance of respiratory viruses in PLWH is unclear; however, patients who are not well-controlled on ART are likely to have a worse prognosis than those well-controlled on ART (131). A recent prospective CAP study from Kenya, which included 77 patients (of which 13% were HIV-positive), identified a virus in 48% cases and Influenza A was the predominant pathogen. Patients with influenza were more likely to be diabetic and require critical care (132).

Similarly, CMV infection as a causal pathogen in CAP is unclear and difficult to establish (133). Acknowledging this, the four cases, which were included in the current cohort, all had

HIV and there was cytopathic evidence of CMV infection on post-mortem lung specimens. In other CAP data (Seattle, 1994-1996), there were more CMV infections within the HIV-positive group, and this correlated with the SOI (16).

The six cases of measles noted in the current study, corresponded to the measles outbreak in South Africa that occurred between 2009 and 2010 (134). Within the current cohort, a non-significantly greater number of measles cases, and subsequent deaths, occurred in the HIV-positive group. Another study which included all admitted measles cases at CMJAH, both in ICU and the medical ward, also reported non-significantly more deaths amongst the HIV-positive patients compared with the HIV-negative cases (OR 2.9; 95% CI, 0.13-65.3; P=0.55) (134).

Over a 15-year period up to 2013, there has been an increase in viral causes of SCAP, which also coincided with the H1N1 epidemic, and is likely due to increased and improved diagnostics (15). However, earlier CAP data (1994–1996), reported a lower incidence of viral infections, as diagnostics in this period relied heavily upon cultures and serology (16). For reasons stated earlier, the results in our study are likely to be an underestimate of the viral pathogens present in the cohort. It is also possible that the higher numbers of respiratory viruses documented in the HIV-negative patients is a result of more testing and bias, as clinicians were more likely to test these patients with features of an atypical pneumonia and a low pre-test probability of PJP infection.

5.4.6 Fungal Pathogens

In the current cohort, all PJP infections occurred in HIV-positive patients, and were responsible for 10.6% of all MM infections. In other international data, Park *et al.,* demonstrated that PJP was the most common cause of infection amongst HIV-positive patients with SCAP (16). In another CAP study from Barcelona, PJP occurred in 13% of patients with HIV (18); PJP infection was more common amongst patients in whom HIV was diagnosed in-hospital and had a CD_4 cell count <200 cells/mm^3; and it carried a higher 30-day mortality than SP infection (14% patients with PJP died compared to 4% in those with SP infection) (18).

Within the existing cohort, mortality from MM and PM PJP infections were 77.1% and 79% respectively, and on MVA, PJP infection was an independent predictor of mortality. In other PJP/ICU data, such as from Thailand, mortality was 63.6% overall, with CMV co-infection being an independent predictor of mortality (0% lived vs 100% died, P=0.004) (135). Data from Cape Town, showed that amongst 124 patients admitted to hospital with PJP infection (68 cases laboratory confirmed and 56 "probable cases"), although 90-day mortality was higher amongst patients admitted to ICU compared to patients admitted to the ward (61.9% vs 25.9% respectively), ICU admission was not an independent risk factor for in-patient nor 90 day mortality on multivariate analysis (38). In addition, in the latter study, there was a trend to higher 30-day and 90-day mortality amongst patients using concurrent TB therapy (38). Data from London showed an overall PJP mortality of 51% from 1990-2005, which decreased from 71% in 1996 to 34% thereafter, and was independent of ART, and most likely a result of improved ICU management overall (136). Lastly, data from the USA (1986-2005; i.e. from pre-chemoprophylaxis to ARV era), documented that ventilator deaths from PJP decreased from 79% to 31%, despite an increase in the use of mechanical ventilation amongst patients with PJP (5%-11%) (137).

Overall then the mortality from PJP within the current cohort is high and the reasons for this are not immediately clear. Whilst this observation could be a consequence of the lack of ART use apparent in this cohort, it is unlikely to be related to a delay in initiating PJP-specific anti-microbial therapy, as all patients with suspected PJP infection were started empirically on

treatment. Furthermore, lung protection ventilation strategies are routinely practised in the ICU, and thus ventilation is unlikely to be a more significant contributor to mortality when compared to the studies above. The higher mortality rate than reported elsewhere may represent undiagnosed co-infections, such as with MTB (as noted in other studies (38)), differences in patient demographics (male predominance in the London cohort (136)) or the occurrence of dihydropteroate synthase mutations (DHPS), which in one study (which analysed respiratory specimens from clinics and hospitals) was noted to occur in 56% PJP isolates (138).

The two cases of candida pneumonia in the current study were diagnosed on post-mortem lung biopsies. Candida pneumonia is a rare and often fatal cause of pneumonia in immunocompromised patients and radiological and histopathological presentation can resemble MTB infection (139).

5.4.7 Polymicrobial Infections

Overall, 10.5% of patients in the current cohort had PM infections and these occurred more commonly amongst HIV-infected patients. The study documented that PM infections were the third most common after MTB and SP infections, and this is similar to another HIV-positive CAP cohort (18), in which 11.5% of infections were PM (after SP and PJP infections). In addition, although Park *et al.,* demonstrated that the proportion of PM infections was higher amongst PLWH with SCAP, this was not significantly different to their HIV-negative counterparts (11% HIV negative vs 30% HIV-positive; p=0.1) (16).

In the current study, there was no increased mortality amongst patients with PM infections. Amongst patients with SCAP, Ferrer *et al.* (63), and Cilloniz *et al.* (12), demonstrated that PM aetiology was associated with a greater need for IMV. The latter study also determined that patients with ARDS and chronic respiratory disease were more likely to have PM infections, but there were no differences in septic shock, length of stay or hospital mortality compared to patients with MM infections. Furthermore, there were more respiratory viruses in the PM than in the MM group (39% vs 10%; P<0.001) and of these, Influenza A was the predominant (12).

5.4.8 Bacteraemia

Although 22.7% of the current study infections were bacteraemic, and this was more common amongst PLWH, bacteraemia was not more common in patients who died compared to those who lived. Park *et al.*, report a trend towards more bacteraemia amongst patients with SCAP compared to those without (14% vs 8%; P=0.07) (16); however the percentages were lower than in the current study. In other SCAP studies, bacteraemia was reported in 18% of cases (12), with no differences amongst patients with MM/PM CAP; Ferrer *et al.* (63), found no difference in the need for mechanical ventilation in patients with bacteraemia, although more bacteraemic patients were admitted to ICU; a similar proportion of patients with bacteraemia had ARDS, compared to patients without ARDS (57); and positive blood culture were independently associated with mortality (50).

5.5 Complications

Overall, 5.8% of patients with SCAP in this analysis developed cardiac arrhythmias during their ICU admission. In one study, critically ill patients with new-onset AF were older, had more co-morbid disease, higher APACHE IV scores and more organ dysfunction on admission (renal failure, cardiac failure, respiratory failure) than patients without AF. Furthermore, patients with new onset atrial fibrillation had an increased chance of dying (140). Infection, either directly (via bacterial infiltration of the myocardium) or indirectly (via inflammatory mediators) can cause myocardial fibrosis and remodelling, despite appropriate anti-microbial therapy (141-143). This area of the myocardium serves as a focus from which arrythmias may originate under the influence of catecholamines, inotropes and electrolyte abnormalities which are common in critically ill patients (140).

Other data have also shown that arrhythmias occur commonly in association with CAP (144), and were the primary cardiac event in 10.8% of inpatients with pneumonia and 1% of outpatients. Factors that were associated with cardiac complications included age (mean, 73 years; SD±14 years vs mean, 53 years; SD±21 years; P<0.01), hypertension, cardiac failure,

nursing home resident, pH<7.35, Hct <30% and being an inpatient (144). In the current study, the proportion of patients with cardiac arrhythmias were similar in patients who survived and those who died. The lower incidence of cardiac arrhythmias noted is likely due to the younger age of the study group and lower incidence of co-morbid hypertension and cardiac disease.

All six (0.6%) patients who developed GIT complications died. A multicentre ICU study, which included 1034 critically ill patients, reported clinically severe GIT bleeding in 2.6% patients (95% CI, 1.6%-3.6%), and the risk factors included the presence of three or more co-existing diseases, including liver disease, renal replacement therapy, pre-existing or acute coagulopathy, higher organ failure score, and the use of acid suppressant therapy. The aOR (adjusted odds ratio) for mortality was 1.7; 95% CI, 0.7-4.3), and the authors postulated that mortality was more likely to be a consequence of their underlying illness rather than GIT bleeding itself (145).

In the current cohort, lung necrosis was more common amongst the HIV-negative patients than HIV-positive patients but had no impact on survival. Bacterial pathogens which are most commonly associated with lung necrosis include SP, SA (especially MRSA Panton-Valentine leucocidin [PVL]), KP, HI and PA (146). Furthermore, the long term follow up of patients with CAP/ HIV has shown persistent abnormalities in gas transfer (diffusing capacity for carbon monoxide [DLCO]), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC (147). There are no long-term data available for this cohort, but going forward this would be an important area for future research.

There were more metabolic complications (hyperglycaemia, DKA) amongst the HIV-negative patients in the current cohort than among the HIV-positive patients, and this was not associated with any difference in mortality. Given that there were more diabetics amongst the HIV-negative cohort and that hyperglycaemia is a complication of severe illness and CS use (76% of the entire cohort), this is not surprising.

5.6 ICU Management

5.6.1 Mechanical Ventilation

The requirement for mechanical ventilation (MV) is one of the major criteria in the ATS/IDSA guidelines (29). Within the existing cohort, 800 patients (85%) were ventilated, the predominant mode was IMV, and a similar proportion of HIV-positive and HIV-negative patients were ventilated. Despite considerable variation in the use of MV in other CAP studies (13%-67.2%) the frequency of ventilation in the current study is very high (6, 12, 15, 50, 63). In other SCAP data (15), there has been shown to be a progressive increase in the use of mechanical ventilation (56.9%, 63%, 72%; P=0.02) over a 15 year period (1999-2013), with an improvement in overall mortality (37.9%, 20.9%, 19.9%; P=0.001), and this has also been associated with less bacteraemia and septic shock. Overall in that study, 8.1% of the patients were HIV positive and 9.6% were immunocompromised (primary immunodeficiency or immunodeficiency secondary to radiation treatment, use of cytotoxic drugs or corticosteroids or AIDS) (15).

Within the current cohort, an increased risk of dying was noted amongst patients with SCAP in whom IMV was used, compared to those who received no ventilatory support. Mechanical ventilation amongst ICU patients is associated with an increased risk of death in all patients (148), and amongst patients with pneumonia (63, 94, 124, 149). Furthermore, in one study, the combination of IMV, septic shock, hyperkalaemia and hypoxaemia led to a higher 30-day mortality (AUROC 0.78; 95% CI, 0.7-0.86) (63). In addition, amongst another HIV-positive CAP cohort, 15.4% of all patients required mechanical ventilation and this was associated with an increased 30-day mortality (18).

In the current study, only nineteen patients utilised NIV and these patients had a higher risk of death compared to those who were not ventilated, and on MVA this risk was even higher than those who received IMV. In some studies, the use of NIV amongst patients with CAP, including those with COPD, is associated with a high chance of failure (150-152). Whereas in other studies, with more carefully selected patients, NIV was associated with less risk of endotracheal intubation, ICU stay (153), and lower mortality than IMV (OR, 0.192; 95% CI, 0.079-0.466; P=0.001) (51). Furthermore, the use of NIV amongst HIV-infected patients with

PJP has been studied successfully, as a tool to improve oxygenation (136, 154), avoid IMV and improve survival (155). It is possible that the increased risk of death associated with NIV, which is noted within the existing cohort, could be related to a less aggressive intubation policy amongst patients who were considered unlikely to survive further escalation of care.

The current study describes a cohort of predominately HIV-positive patients in a resource limited setting. As such, a large proportion of patients with CAP/SCAP are managed in the medical wards until MV is deemed necessary and an ICU bed becomes available, thus explaining the large number of ventilated patients within this cohort. In addition, the high mortality, overall, could also be explained by the inclusion of patients with MTB and PJP, as although in some cohorts ICU mortality has improved in association those pathogens (134, 135), in other cohorts mortality remains high (38, 119, 135).

5.6.2 Corticosteroids (CS)

Corticosteroids were used in most patients in the current study (711 (76.3%)), and there were no differences in mortality noted overall, in those that did or did not get corticosteroids. The significantly higher number of HIV-positive patients treated with corticosteroids was probably as an adjunct in suspected PJP. One meta-analysis showed, that the use of corticosteroids was associated with lower mortality and a reduction in the need for mechanical ventilation, amongst patients with SCAP (156). Also, in this analysis, although there was no increased risk of GIT bleeding; more patients were at an increased risk of developing hyperglycaemia (156). In another SCAP study (130), the use of methyl prednisone 0.5mg/kg twice daily amongst patients with a CRP ≥150mg/dl, was associated with less treatment failure (OR 0.34; 95% CI, 0.14-0.87; P=0.02), but no improvement in mortality (157). Finally, in another more recent study, 200 mg of intravenous hydrocortisone administered in divided doses daily amongst a cohort of patients with SCAP was associated with a lower 28 day mortality in the treatment group (6.2%.; 95% CI 3.9%-8.6%) compared with the placebo group (11.9%; 95% CI 8.7%-15.1%); P=0.006) (158). CS therapy has also been shown to have a mortality benefit amongst patients with SCAP from SARS-CoV-2 infection (159), and in some studies of patients with SCAP and VZV infection (130, 160, 161), but not all (162).

The lack of apparent benefit from CS use in the current cohort, could possibly be explained by the underrepresentation of viruses, especially Influenza virus, within this cohort, for reasons discussed elsewhere. Furthermore, distinguishing clinically between viral pneumonia and PJP is difficult, and patients with influenza pneumonia are thought to have a higher mortality when CS are administered during the course of their infection (163). This is in contrast with the treatment of hypoxemic PJP pneumonia, in which the recommendations are the adjunctive use of CS (at an initial dose equivalent to prednisone 40mg orally twice a day) which is said to be associated with an improved patient outcome (1). Additionally in the current study, choice and dosing of corticosteroids varied significantly between the patients, based on the clinicians' choice as well as being influenced by the clinical presentation of the patient (e.g. underlying COPD, or asthma) and drug availability. There were not enough data to analyse this further.

5.6.3 Inotropic Support

Within the current cohort, 50% of all patients required inotropic support, and this was associated with a higher chance of dying. Inotrope use reflects SOI and is the second major criterion within the IDSA/ATS guidelines (29). Despite some studies reporting low inotrope requirements amongst patients with CAP (6), this need is much higher in SCAP ICU cohorts (23%) (164); moreover if septic shock is used as a proxy (165), 20%-47.2% of patients in SCAP cohorts (12, 15, 50) require inotropic support, especially amongst patients who additionally require IMV (63). In addition, a higher in-patient mortality (50, 51, 61) and 30-day mortality has been noted amongst both HIV-positive patients (95) and HIV-negative patients with SCAP who required inotropes (90).

5.6.4 Dialysis

Overall, 22.4% of patients received dialysis in the existing cohort, and although on univariable analysis dialysis was a predictor of mortality, on MVA, patients who were dialysed were more likely to survive. Although confusing, this observation could be explained by Simpson's paradox, a statistical occurrence in which a trend reverses when confounding

variables are controlled for (166-168). Other SCAP data demonstrate that 17.2% of patients required renal replacement therapy within the first week in ICU, and the need for RRT was associated with an increased 28-day and 6-month mortality (124). The 22.4% requirement for dialysis within this current cohort is high; however, only ICU patients were included in the study, almost all of whom also required MV and inotropes.

Despite rigid chronic dialysis criteria at CMJAH, patients with acute kidney injury are supported with dialysis, and amongst patients with sepsis this is only performed within an ICU setting, especially if inotropes are required (and if the patient is mechanically ventilated). The only caveat to this is that patients, who require high levels of inotropes to maintain hemodynamic stability, may be excluded from dialysis as they are too unstable. This may explain our observation that patients who were dialysed had a lower risk of mortality, as sicker patients may have been excluded from dialysis. In this study patients who required dialysis were not matched by age, APACHE II scores, inotropes or use of mechanical ventilation. Furthermore, although the median urea and median creatinine were elevated overall, there were insufficient data to determine which patients had AKI with subsequent recovery of renal function. Therefore, going forward, these are important areas of further research.

5.7 Length of Stay

The overall ICU length of stay in this study was increased amongst patients who were ventilated, and who required renal dialysis, but was shorter amongst patients who died. Furthermore, LOS was similar between PLWH and HIV-negative patients. Other studies have reported longer LOS amongst SCAP patients on IMV (median 10 [SD $\pm$ 5-19] days) (63) compared to our data (median 5 [95% CI 2-8] days), $P<0.001$); amongst HIV-infected CAP patients (10 days with PJP infection versus 7 days with bacterial CAP, $P=0.03$) (18) and amongst ICU patients with PM compared with MM CAP (15 versus 12 days, $P=0.082$) (12). Overall, and in each sub-group, the LOS within our cohort was shorter than these data, but we did not analyse this further with respect to microbial pathogens. The shorter length of stay we noted may represent the need to discharge “stable” patients from ICU as soon as interventions such as IMV and inotropic support are stopped, in order to make space for other critically ill

patients. The observation that additional deaths occurred after ICU discharge and before home discharge, further supports this hypothesis.

5.8 Mortality

In the current study, ICU mortality was 50.1% which is similar to that in another SCAP study from Johannesburg, South Africa (47.4%) (14), but higher than other SCAP data (15, 17, 49-51). Amongst the GenOSept cohort, which excluded immunocompromised patients, a 19% mortality was noted amongst patients with a median APACHE II of 20 (IQR, 15-28), of whom 17.2% required renal replacement therapy, 85% mechanical ventilation and 49.4% developed septic shock (124). Another study, which included immunocompromised patients, reported a mortality of 27.9% amongst patients with a mean APACHE II score of 18.9 (SD± 7.4), and this figure decreased to 25% when immunocompromised patients were excluded (169). Finally, Cilloniz *et al.,* demonstrated that 30-day mortality increased accordingly if patients had mild, moderate or severe ARDS (32%, 33%, 60%), although on univariable and MVA, ARDS was not associated with increased mortality (57).

Within the current cohort, HIV-positive patients had a higher risk of mortality than their HIV-negative counterparts, (although this trend was similar but non-significant on MVA). In another HIV-positive CAP cohort, 30-day mortality was 6.6%, and this was lower among patients with a bacterial aetiology compared to PJP infection (5.5% vs 14.3%, P=0.033) (18). Cordero *et al.,* also report an attributable mortality of 13.1% for HIV-positive patients with SCAP, compared to 3.5% for HIV positive patients with CAP (P=0.02), and radiological progression, septic shock and CD_4 count <100 cells/mm^3 were associated with increased mortality (95). Within our cohort, the median CD_4 count was 42 (95% CI, 14-108.3) cells/mm^3. Thus, the higher mortality we noted may reflect the larger proportion of patients with HIV co-infection, MTB, PJP and other opportunistic infections.

Although a similar number of HIV-positive and HIV-negative patients survived ICU, fewer HIV-positive patients survived until hospital discharge, and follow-up data beyond this period were not included in the analysis. Of the patients who survived ICU, some were discharged to the medical wards as further ICU care was deemed futile (due to intracerebral events or failure to wean from ventilation). In total then, a further 32 patients died in hospital before

discharge home,

5.9 HIV-unknown Patients

Within the current cohort, patients with an unknown HIV status were more likely to die than HIV-positive and HIV-negative patients, respectively. These patients had higher SOI scores, and the majority required mechanical ventilation. Furthermore, 53.7% of this group were male and although the median age was 36 (IQR, 20-57) years, a significant proportion (31.7% of cases) were aged 65 years and older. Also, almost 50% of patients had an undefined microbial aetiology. A similar trend was noted amongst a cohort of patients from Cape Town who were admitted to hospital with PJP infection, in whom patients with unknown HIV status had increased 90 day mortality (OR 1.9; 95% CI, 0.9-4.1;P=0.082) on univariable analysis. (38)

A study in a New York Emergency Department (2006-2011) showed that patients in lower (<18 years) and higher (≥45 years) age categories were less likely to know their HIV status than those in middle age categories, and women with a prior pregnancy had the lowest rate of unknown HIV status across all age groups (OR, 0.17; 95% CI, 0.16-0.19) (170). Late or delayed diagnosis of HIV infection ($CD_4 \leq 350$ cells/mm^3 or with an AIDS-defining illness) portends an increased risk of death in the year following diagnosis (171).

It is likely that a significant proportion of the HIV-unknown cohort represents a group of undiagnosed and therefore untreated HIV-positive patients who would benefit from targeted therapy for SCAP. For example, a significant proportion had no defined microbial aetiology for SCAP, and as discussed before this could have represented MTB or PJP infections. Given the SOI scores in this group, many of these patients are unable to give informed consent for HIV testing which is a legal requirement in South Africa. Therefore, a case can be made that routine HIV testing of all patients with SCAP is essential to provide targeted anti-microbial therapy.

Finally, it is interesting to note that the majority of patients of unknown HIV status were male, and it is tempting to suggest that this is due to the fact that SA females are more likely to seek healthcare and know their HIV status for other reasons such as pregnancy and child-care related problems.

5.10 Potential Limitations

This was a single-centre study, and so the findings may not be generalizable to other ICUs, or other regions of South Africa, or to other parts of the world. In addition, it only included cases with severe CAP who were admitted to an ICU, and so the findings are really only pertinent to patients with CAP in this setting. The study was essentially 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. Overall, 4.2% of records could not be found at all, and in a significant proportion (21%) there were insufficient data to confirm the diagnosis of CAP and so these cases were excluded, but may have had CAP. The chest radiographic findings were largely based on the physician reporting in the case notes. However, as the medical ICU during this period was directed by a senior Pulmonology consultant, and all pneumonia admissions were seen by the Pulmonology team the reporting of the chest radiograph is likely to be relatively accurate, a point that was verified in the latter part of this study, when the electronic radiology PACS system was introduced (2016). Due to resource constraints, the patients often had limited testing for causative microbial pathogens, especially viruses and atypical bacterial infections, and it is likely that a significant proportion of the former microorganisms were undiagnosed.

5.11 Conclusions

This was a study of 931 patients with SCAP admitted to ICU at a tertiary referral hospital in Johannesburg, South Africa. The patients were young, with a median age of 37 (IQR 30-48) years, and the predominant co-morbidity was HIV co-infection (77.1%). 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 X-ray. Overall, MTB was the most common aetiology identified amongst both HIV-positive and HIV-negative patients, and SP was the next most common pathogen identified. SP infection was more common amongst the patients

who lived, whereas PJP infection was more common amongst patients who died. Overall mortality was high (50.1%) and PLWH had a higher risk of mortality than their HIV-negative counterparts (OR,1.61; 95% CI 1.07-2.34; P=0.01). This appears to be the largest ICU cohort of patients with SCAP reported in the literature.

5.12 Future Research

The current study identifies a number of areas to which further research should be directed.

This study should be repeated prospectively, so that all the information which the investigators wish to collect can be collected prospectively and thereafter securely stored.

The newer techniques that are available for making a microbiological diagnosis should be used in all consecutive patients, in order to obtain a more comprehensive evaluation of the role of the various respiratory pathogens, particularly viruses and atypical bacteria, in SCAP in a South African ICU setting, and determine their significance in a largely HIV-positive population.

Further evaluation of the occurrence (or not) of cardiovascular events as a complication of SCAP in largely HIV-positive South African patients is needed, with the determination of their impact on short-term and long-term outcomes.

Documentation prospectively of the impact of underlying co-morbidities on the outcome of SCAP in a South African population is needed, as well as confirmation as to whether the current finding of a lower mortality risk in patients with CVD persists, and likely causes for this.

There needs to be prospective evaluation of various SOI scores and prognostic indicators, to determine which of these scoring systems work best in a largely HIV-positive South African population with severe CAP.

Further investigation of the relationship between BDG and mortality of patients with severe CAP is required, to evaluate whether the elevated BDG level noted is a result of undiagnosed fungal infections/ PJP or represents translocation of fungal PAMPS.

Investigation of the value of CS use on outcome in SCAP, in a largely HIV-positive South African population, is needed, with evaluation of the optimal CS preparation and its dosing recommendations.

There needs to be an evaluation of the incidence and outcome of acute kidney injury in a predominantly HIV-positive cohort of patients with SCAP, with documentation of the reasons for lack of dialysis in some patients, as well as the impact of renal dialysis on outcome of SCAP.

Further analysis is needed of patients with an unknown HIV status to determine if, and why, the mortality is higher in this group, and what interventions could be put in place to mitigate this, based on the findings in the current study.

Lastly, there is a need to investigate medium- and long-term outcomes of patients with SCAP in a largely HIV-positive South African population, especially regarding ongoing cardiac events, impact on lung function testing, and the potentially beneficial impact of ART.

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pneumonia

7.0 APPENDICES

APPENDIX A-DATA DICTIONARY

Parameter	Description	Code
Number	Hospital admission number	
Admission date		
Discharge date		
Discharge status	Discharged ICU alive	1
	Discharged home alive	1
Age	Age of patient at admission	
Sex	Female	1
	Male	2
x-ray	Bilateral GGO	1
	Multilobar	2
	Lobar	3
	bilateral GGO	4
	effusion	5
HIV status	unknown	0
	positive	1
	negative	2
ARVS	Patient on Antiretrovirals at admission	
Smoker	Patient is a smoker	
Comorbid_DISEASE	chronic_respiratory_disease	1
	chronic_cardiovascular_disease	2
	neurological_disease	3
	chronic_kidney_disease	4
	chronic_liver_disease	5
	Diabetes_mellitus	6
	hypothyroid	7
	chronic_rheumatological_conditions	8
	pregnant	9
	malignancy	10
	Hepatitis B	11
	Hepatitis_ C	12
	Previous tb	13
	current_tb	14
	Other	15
temp	first temperature recorded	
Fi02	fraction of inspired O2	
ph	first blood gas recorded	
Pa02	first blood gas recorded	
PCO2	first blood gas recorded	
Oxygen saturation		
heart rate		
respiratory rate		
GCS	level of confusion	
systolic BP		
diastolic BP		
CURB-65		
Apache_II		
ICU Course	Use of Invasive mechanical ventilation	
	Use of non-invasive mechanical ventilation	
	Use of dialysis	

Parameter	Description	Code
	Use of inotropes	
Med complications	Respiratory	1
	Cardiovascular	2
	Neurological	3
	Thrombotic	4
	C diff	5
	Metabolic	6
	Haem	7
	GIT	8
	Skin	9
	Cardiac arrest	10
	Other	11
Meds	steroids	1
	ART	2
survived ICU		
survived home		
Laboratory parameters	Haemoglobin (Hb) g/dL	
	Haematocrit (Hct) %	
	White cell count (WCC)x10^9/l	
	Platelet count (Plt)x10^9/L	
	Sodium (Na)mmol/L	
	Potassium (K) mmol/L	
	Chloride (Cl) mmol/L	
	Bicarbonate (HCO3) mmol/L	
	Urea mmol/L	
	Creatinine mmol/L	
	T_protein g/L	
	albumin g/L	
	T_bili umol/L	
	D_bili umol/L	
	Alkaline phosphatase (ALP) U/L	
	Gamma GT (GGT) U/L	
	Alanine transaminase (ALT)	
	Aspartate transaminase (AST)	
	C reactive protein (CRP)mg/L	
	HIV	
	CD4 count cells/mm^3	
	HIV Viral load	
	1.3 Beta_D_Glucan (BDG) pg/ml	
	Hepatitis B	
	Hepatitis C	
Microbiology	No organism identified	
	MTB	
	Streptococcus pneumonia	
	Klebsiella Pneumonia	
	Haemophilus Influenza	
	Staphylococcus Aureus	
	Pseudomonas Aeruginosa	
	Escherichiae Coli (E coli)	
	Enterobacter spp	
	Salmonella spp	
	Acinetobacter spp	
	Streptococcus species	
	Cytomegalovirus	
	Influenza virus	

Parameter	Description	Code
	Measles	
	VZV	
	Other Viruses	
	Pneumocystis Jirovecii	
	Candida spp	
	Aspergillus	
	polymicrobial infections	
	other	
Site of isolation	blood cultures	
	sputum mc+s	
	bal	
	Lymph_node	
	pleural_fluid	
	CSF	
	Bone marrow aspirate and trephine	
	Viral nasopharyngeal swab	
	Viral PCR (blood)	
	Serology	
	Autopsy/post mortem biopsy	

APPENDIX B- ETHICS CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr JP Venturas
School of Clinical Medicine
Department of Medicine
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CC: Supervisor: Professor C Feldman <Charles.Feldman@wits.ac.za>
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DATE: 2019/06/14

REF: *R14/49*

PROTOCOL NO: **M190586** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Retrospective review of patients severe pneumonia admitted to an ICU*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

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APPENDIX C-PERMISSION FROM THE CHIEF EXECUTIVE OFFICER

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011): 488-4812
Email: Nolwazi.Mzila@gauteng.gov.za
26th June 2019

GP_201906_029

Dear Dr. J. Venturas

STUDY TITLE: Retrospective review of patients severe pneumonia admitted to an ICU

Permission is granted for you to conduct the above mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~not supported~~

Dr. M.I. Mpfokeng
Clinical Director
DATE: 28/06/2019

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer
Date: 28/06/2019

APPENDIX D- MULTIVARIABLE ANALYSIS

Table 3.16: Multivariable analysis 1 (excluding CURB-65 score and APACHE II score)

Variables	OR	95% CI	P Value
MAP	0.99	0.98-0.99	**0.03**
$Pa0_2/Fi0_2$	0.99	0.99-0.99	**0.001**
Potassium	1.09	0.88-1.35	0.45
T protein	0.99	0.98-1.01	0.71
Alb	0.99	0.96-1.02	0.45
AST	1.00	0.99-1.00	0.57
CD_4	0.99	0.99-0.99	**0.006**
CRP	0.99	0.99-1.00	0.07
Streptococcus pneumoniae	0.84	0.39-1.77	0.64
PJP	2.43	0.88-6.71	0.10
CXR			
GGO	1.35	0.84-2.19	0.22
Lobar	0.59	0.31-1.18	0.14
HIV			
Negative	1.00		
Positive	1.67	0.35-7.93	0.61
Unknown	6.42	0.13-330.72	0.31
Chronic CVD	0.61	0.31-1.18	0.14
Ventilation			
No	1.00		
IMV	5.68	2.25-14.37	**0.001**
NIV	9.55	1.95-46.63	**0.005**
Dialysis	0.95	0.57-1.91	0.85
Inotropes	3.64	2.29-5.79	**<0.001**

Annotations: Alb: albumin; AST: aspartate transaminase; CD_4 : cluster of differentiation 4; CI: Confidence Intervals CRP: C-reactive protein, CXR: Chest X-Ray; CVD: cardiovascular disease; GGO: ground glass opacities; HIV: Human Immunodeficiency Virus; IMV: invasive mechanical ventilation; MAP: mean arterial pressure; NIV: non-invasive mechanical ventilation; OR: odds ratio; $Pa0_2/Fi0_2$: Ratio of partial pressure of oxygen to the fraction of inspired oxygen; PJP: *Pneumocystis jirovecii* ; STD: standard; T; total; Bold numbers indicate significate P values

Table 3.17: Multivariable analysis 2 (including CURB-65 score and APACHE II score; excluding HIV co-infection and chronic cardiovascular disease)

Variables	OR	95% CI	P value
CURB-65 score	1.09	0.88-1.36	0.43
APACHE 11 score	1.06	1.02-1.10	**0.005**
CD_4	0.99	0.99-0.99	**0.001**
CRP	0.99	0.99-0.99	**0.01**
Streptococcus pneumoniae	0.79	0.41-1.54	0.49
PJP	2.85	1.04-7.84	**0.04**
CXR			
GGO	1.47	0.92-2.34	0.10
Lobar	0.53	0.28-0.98	**0.04**
Ventilation			
No	1.000		
IMV	6.59	2.61-16.68	**<0.001**
NIV	8.12	1.75-36.63	**0.007**
Dialysis	0.55	0.32-0.93	**0.03**
Inotropes	3.31	2.09-5.22	**<0.001**

Annotations:CD_4 : cluster of differentiation 4; CI: Confidence Intervals CRP: C-reactive protein, CXR: Chest X-Ray; CURB-65 (Confusion, Urea>7mmol/L, Respiratory rate ≥30 breaths/ min, Systolic blood pressure<90mmHg and /or diastolic blood pressure ≤60mmHg; and age≥65 years);GGO: ground glass opacities; IMV: invasive mechanical ventilation; NIV: non-invasive mechanical ventilation; OR: odds ratio; PJP: *Pneumocystis jirovecii ;*STD: standard; Bold numbers indicates significant P values

Table 3.18: Multivariable analysis 3 (including CURB-65 score, APACHE II score, HIV co-infection and chronic cardiovascular disease)

Variables	OR	95% CI	P value
CURB-65 score	1.09	0.87-1.35	0.45
APACHE 11 score	1.06	1.02-1.10	**0.007**
CD_4	0.99	0.99-0.99	**0.002**
CRP	0.99	0.99-0.99	**0.01**
Streptococcus pneumoniae	0.75	0.38-1.46	0.39
PJP	2.71	0.99-7.42	**0.053**
CXR			
GGO	1.59	0.92-2.34	0.10
Lobar	0.54	0.29-1.00	0.05
HIV			
Negative	1.00		
Positive	0.85	0.24-3.82	0.95
Unknown	4.65	0.08-209.43	0.46
Chronic CVD	0.54	0.28-1.02	0.06
Ventilation			
No	1.00		
IMV	6.81	2.66-16-69	**<0.001**
NIV	9.50	1.74-38.01	**0.008**
Dialysis	0.59	0.34-0.99	**0.045**
Inotropes	3.19	1.86-4.53	**<0.001**

Annotations: CD_4 : cluster of differentiation 4; CI: Confidence Intervals CRP: C-reactive protein, CXR: Chest X-Ray; CURB-65 (Confusion, Urea>7mmol/L, Respiratory rate ≥30 breaths/ min, Systolic blood pressure<90mmHg and /or diastolic blood pressure ≤60mmHg; and age≥65 years);CVD: cardiovascular disease; GGO: ground glass opacities; HIV: Human Immunodeficiency Virus; IMV: invasive mechanical ventilation; MAP: mean arterial pressure; NIV: non-invasive mechanical ventilation; OR: odds ratio; $Pa0_2/Fi0_2$: Ratio of partial pressure of oxygen to the fraction of inspired oxygen; PJP: *Pneumocystis jirovecii*; STD: standard; Bold numbers indicates significant P values

APPENDIX E- PLAGARISM REPORT

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