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Characteristics, risk factors and outcomes of pneumocystis jirovecii pneumonia in HIV infected patients in three hospitals in South Africa

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Characteristics, risk factors and outcomes of pneumocystis jirovecii pneumonia in HIV infected patients in three hospitals in South Africa.

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A research report presented for the degree of MMed in Internal Medicine .

DECLARATION

I, Dr. Justice Gweshe, certify that this thesis is entirely my own. It has not been submitted for any degree or examination at any other institution. All sources used have been properly referenced, and any assistance received during the research and writing process has been acknowledged.

Signature: *Justice Gweshe* 18th of December 2024

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ABSTRACT

Background

Despite advances in chemoprophylaxis and universal coverage of antiretroviral therapy (ART), Pneumocystis Jirovecii Pneumonia (PJP) remains an important opportunistic infection in HIV-infection. We describe clinical characteristics, treatment outcomes of PJP and determinants of mortality among HIV-infected patients in South Africa.

Methods

A retrospective review of demographic and clinical characteristics of adult (≥18 years) patients enrolled in a multicentre surveillance study measuring the burden of physician-diagnosed Community Acquired Pneumonia (CAP) incidence and a prospective cohort study measuring the prospective incidence of Chest X-ray (CXR) confirmed, hospitalized CAP and recurrent CAP from three tertiary hospitals in South Africa. Records of all HIV-infected patients with a diagnosis of PJP between January 2019 and December 2021 were included. Clinical data, admission records (laboratory parameters, radiological assessments, symptoms), and demographic information (age, gender, area of residence) were analysed.

Results

A total of 160 HIV-infected patients were included in the study. The median age of patients was 39 (interquartile range: 32-45) years and 95 (59.4%) were female. A total of 152 (95.0%) were known HIV patients and 64 (40.0%) were on ART. The median log10 viral load (VL) was 5.4 (4.2-5.8) and the median absolute CD4 cell count was 26 (9-76) cells/mm3 at admission. A total of 74(46.3%) patients reported being on cotrimoxazole prophylaxis and 63(39.4%) were not, whereas cotrimoxazole use in the remaining 23(14.4%) was unknown.

Most patients presented with severe symptoms at admission, 75% had hypoxia, 65% had respiratory failure, and 61% had extensive pulmonary involvement on imaging. Lower respiratory tract infections were documented in 66 (41.3%) patients, active pulmonary tuberculosis among 25 (15.6%), SARS-CoV-2 among 14 (8.75%) and pneumonia among 12 (7.5%) patients. Overall, 64 (40.0%) patients died (median time of 23 days (5-100) from admission, while 36 (22.5%) died in the hospital (median of 6 days (4-18). In adjusted analyses, age group ≥50 years, patients newly diagnosed with HIV and having SARS-CoV-2 at admission were significantly associated with higher risk of death in the study.

Conclusion

Regular monitoring of viremia, CD4 count, and adherence to antiretroviral therapy (ART) is imperative in preventing Pneumocystis jirovecii pneumonia (PJP) in individuals infected with HIV, particularly in the context of universal ART coverage. This proactive monitoring approach is essential for optimizing health outcomes in this population. HIV monitoring efforts should target high risk groups such as patients ≥50 years, people with concurrent infections and patients newly diagnosed with HIV.

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LIST OF ABBREVIATIONS

ART	Anti-retroviral therapy
AIDS	Acquired Immune deficiency syndrome
BAL	Bronchoalveolar lavage
BDG	Beta D Glucan
CAP	Community Acquired pneumonia
CD4	Clusters of differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
CMV	Cytomegalovirus
CXR	Chest Xray
HAART	Highly Active Antiretroviral therapy
HIV	Human Immune deficiency Virus
KTHC	Klerksdorp Tshepong Hospital Complex
LDH	Lactate dehydrogenase
NHLS	National Health Laboratory Service
PaO_2	Partial pressure of oxygen
PCP	Pneumocystis carinii pneumonia
PCR	Polymerase chain reaction
PCV13	Pneumococcal conjugate vaccine 13
PJP	Pneumocystis jirovecii pneumonia
PMH	Polokwane/Mankweng Hospital
TB	Tuberculosis
TMP-SMX	Trimethoprim and sulfamethoxazole
TNF-a	Tumour Necrosis Factor alpha

CHAPTER 1 – PROTOCOL WITH EXTENDED LITERATURE REVIEW

CHARACTERISTICS, RISK FACTORS AND OUTCOMES OF PNEUMOCYSTIS JIROVECII PNEUMONIA IN HIV INFECTED PATIENTS FROM THREE HOSPITALS IN SOUTH AFRICA

INTRODUCTION/BACKGROUND

Even with notable advancements in antiretroviral therapy (ART) and the widespread use of preventive measures such as cotrimoxazole prophylaxis, Pneumocystis Jirovecii Pneumonia (PJP) remains a persistent opportunistic infection among HIV-positive populations in sub-Saharan Africa. Although ART has significantly decreased PJP rates, the infection still poses a substantial risk, especially for patients with advanced HIV who face challenges in achieving optimal immune recovery or maintaining consistent treatment adherence.[4, 28].

Historically, before the introduction of ART, the majority of HIV-infected individuals were at risk of developing PJP during the progression of their disease[13]. Although the landscape has changed with improved HIV care, the persistence of PJP highlights ongoing gaps in early diagnosis, consistent ART adherence, and management of co-morbidities [14]. This study aims to address these gaps by analysing the clinical presentation, risk factors, and outcomes of PJP among HIV-positive patients in South African hospitals, providing insights that could enhance both clinical practice and public health strategies.

Epidemiology

PJP remains a common concern for HIV-positive populations across Africa, with prevalence varying significantly between regions. A systematic review has highlighted that approximately 22.4% of hospitalized HIV-infected patients in sub-Saharan Africa are affected by PJP, experiencing a mortality rate of 18.8% [4]. Regional studies report prevalence rates ranging from 1%–4% in some East African countries to as high as 33% in Zimbabwe [6]. Misdiagnosis and underdiagnosis of PJP remain a challenge due to overlapping symptoms with other respiratory infections like tuberculosis (TB), often leading to delayed treatment [6].

In South Africa, PJP is frequently mistaken for TB or bacterial pneumonia, resulting in late detection [6]. Research on post-mortem examinations of miners in South Africa revealed an increasing number of undiagnosed PJP cases from 1996 to 2000, indicating the significant diagnostic challenges faced by clinicians [6].

Pathogenesis and clinical presentation

The fungal pathogen Pneumocystis jirovecii targets the lungs, particularly in individuals with weakened immune systems, resulting in PJP. Since its reclassification as a fungus in 1988, P. jirovecii has posed challenges for standard culture techniques in laboratories [3]. Its infection is often marked by a severe inflammatory response in the lungs, leading to respiratory symptoms such as hypoxia and respiratory distress, particularly when the CD4 count drops below 200 cells/μL [2].

The disease is characterized by non-productive cough, fever, and difficulty breathing, making clinical differentiation from other respiratory conditions challenging [3]. It has a strong affinity for the lungs and typically does not spread to other organs, though the immune response it triggers can cause significant damage, leading to compromised gas exchange and severe hypoxia [13].

Risk Factors

Individuals with advanced HIV and severely depleted CD4 counts, especially those not on ART or struggling with adherence, are most at risk for PJP [2]. The vulnerability to PJP becomes particularly pronounced when CD4 counts dip below 200 cells/μL Besides HIV, other at-risk groups include patients with haematological cancers, organ transplant recipients, and those on long-term immunosuppressive therapies such as corticosteroids [8].

Additional risk factors include older age, severe anaemia, and co-infections like CMV, which can further exacerbate PJP symptoms and lead to poorer outcomes [8]. These factors often interact to heighten the severity of the disease, emphasizing the need for targeted interventions in high-risk populations.

Diagnosis

The diagnosis of PJP is often complicated by its non-specific clinical manifestations and concurrent opportunistic infections. A definitive diagnosis typically involves microscopic analysis of bronchoalveolar lavage (BAL) fluid, as the organism cannot be cultured using conventional methods [3]. PCR tests and Beta-D-Glucan (BDG) assays have also become valuable tools for supporting diagnosis, though PCR may detect colonization rather than active infection [27].

The gold standard for diagnosis remains the detection of P. jirovecii through microscopy using samples obtained via BAL or immunohistochemical staining, especially in patients with a clinical presentation that does not respond to conventional treatments [11]. High clinical suspicion remains crucial in recognizing PJP in settings where advanced diagnostic resources are not available.

Treatment

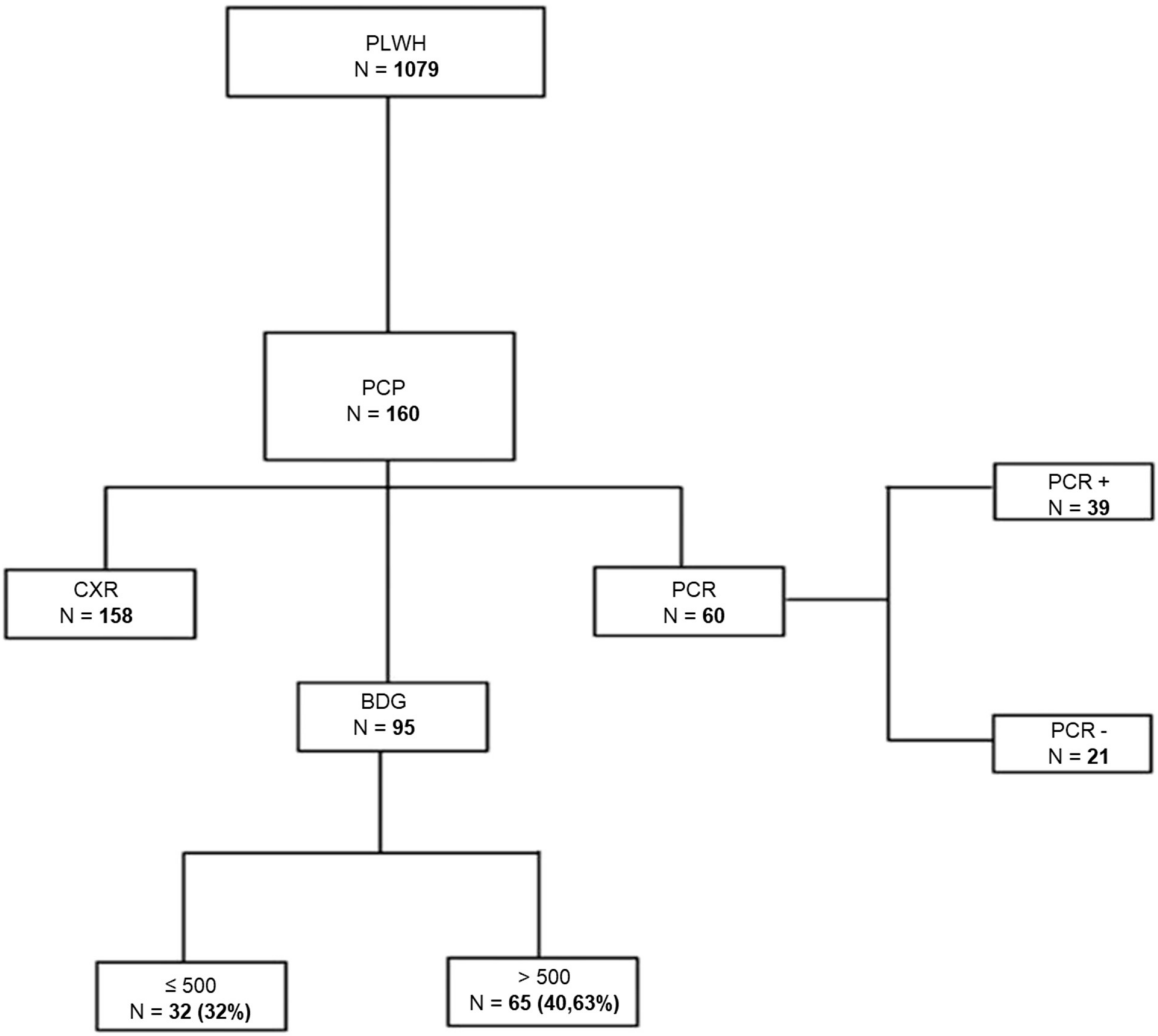
The standard treatment for PJP involves Trimethoprim-Sulfamethoxazole (TMP-SMX), with corticosteroids advised for cases of severe hypoxia, defined by PaO2 levels below 70 mmHg[32]. In cases where diagnostic tools are limited, empirical treatment based on clinical suspicion may be necessary, with patient response guiding further management decisions[11].

Despite the availability of these treatments, managing PJP in resource-limited settings can be difficult due to delays in diagnosis and limited access to diagnostic tests. This study seeks to expand understanding of PJP's clinical characteristics, mortality risk factors, and treatment outcomes among HIV-positive patients in South Africa, with the goal of informing better clinical practice.

STUDY OBJECTIVES

1. To describe the clinical characteristics of HIV-positive patients with Pneumocystis jirovecii pneumonia.
2. To describe the key prognostic factors for mortality in these patients.
3. To describe the treatment outcomes for PJP in the context of HIV care.

METHODS



Study design

This research is a retrospective descriptive analysis, focusing on the records of HIV-positive patients diagnosed with PJP across three South African public hospitals. Data for this study was drawn from a larger multicentre epidemiological project titled "The Potentially Preventable Burden of Community-Acquired Pneumonia in South African Adults," conducted between January 2019 and December 2021[4].

Sample size

The study included all available records of HIV-positive adults diagnosed with PJP within the database, providing a comprehensive review of patient characteristics, treatment responses, and outcomes.

Setting

The analysis was conducted using data from three high-volume tertiary care hospitals: Chris Hani Baragwanath Academic Hospital (CHBAH) in Gauteng, Klerksdorp Tshepong Hospital Complex (KTHC) in the Northwest Province, and Polokwane/Mankweng Hospital (PMH) in Limpopo. These hospitals serve as key referral centres in their respective regions, offering insight into PJP management in South Africa's public health sector [14].

Inclusion criteria:

Inclusion criteria were HIV-positive adults aged 18 years or older with a diagnosis of PJP. A probable PJP diagnosis was defined by clinical features in combination with laboratory evidence such as positive BDG or PCR results, while a definitive diagnosis required direct microscopic identification of P. jirovecii in BAL or sputum samples [3].

Exclusion criteria

Exclusions were applied to patients who tested negative for HIV and those under the age of 18, ensuring a focused study on adult HIV-positive cases [6].

Data collection

A data collection sheet will be used. See appendix 1

DATA ANALYSIS

Descriptive statistics will be used to characterize the study population, with means and medians summarizing continuous variables, while categorical variables will be compared using Pearson's Chi-square tests. Continuous variables with non-normal distributions were analysed using the Wilcoxon Mann-Whitney test. A multivariate Cox proportional hazards model will be employed to assess factors influencing mortality. Analysis will be conducted using STATA version 17 (StataCorp, TX).

ETHICS

Ethical approval was secured from the University of Witwatersrand Health Research Ethics Committee (certificate number M221197). Permissions obtained from hospital CEOs and Departments of Health. Due to the retrospective nature of this research, a waiver of individual informed consent was granted. Data was anonymized to protect patient privacy, and a data transfer agreement was established with Wits Health Consortium (Pty) Ltd for access to the study database.

STUDY STRENGTHS

1. This study addresses a critical gap in the understanding of PJP epidemiology in sub-Saharan Africa, providing locally relevant data for clinical and policy use.
2. It draws on data from a multicentre study that spans several seasons and regions, enhancing its representativeness of HIV-associated respiratory conditions in South Africa.
3. The use of a large dataset from major referral hospitals contributes to a detailed characterization of PJP among HIV-infected patients in the country.

LIMITATIONS

1. Due to the retrospective nature of this study, establishing direct causal relationships between observed factors and outcomes is challenging.
2. Furthermore, differences in diagnostic methods across various study locations could have affected the consistency in identifying PJP cases.
3. The study focuses on patients treated at tertiary centres, which may introduce a selection bias towards those with more severe disease.
4. Missing data and unrecorded variables, such as ART adherence, may impact the depth of analysis and interpretation [4].

TIMELINE

Phase	Year	Months	Details
Protocol Submission	2022	October	Submission of study protocol
Protocol Approval	2022-2023	November (22) - January (23)	Awaiting protocol approval
Ethics Approval	2023	January - February	Ethics board review
Data Collection	2023	March - May	Gathering study data
Data Analysis	2023-2024	February - April (23)	April (24)
Analysing collected data			
Thesis Write-Up	2024	February - May	Writing the thesis
Thesis Submission	2024	June	Submission of final thesis

FUNDING

No funding will be required as this is a secondary data analysis from an existing database.

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CHAPTER 2 – SUBMISSIBLE ARTICLE

Characteristics, Risk factors, Outcomes of Pneumocystis Jirovecii Pneumonia in HIV-infected Patients in Three Hospitals in South Africa.

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ABSTRACT

Background

Despite advances in chemoprophylaxis and universal coverage of antiretroviral therapy (ART), Pneumocystis Jirovecii Pneumonia (PJP) remains a significant opportunistic infection in HIV-positive individuals. We describe the clinical characteristics, treatment outcomes, and determinants of mortality among HIV-infected patients with PJP in South Africa.

Methods

A retrospective review was conducted, examining demographic and clinical data of adult (≥18 years) patients enrolled in a multicenter study measuring the burden of physician-diagnosed community-acquired pneumonia (CAP) and a prospective cohort study measuring the incidence of chest X-ray (CXR)-confirmed, hospitalized CAP from three tertiary hospitals in South Africa between January 2019 and December 2021. We included records of HIV-infected patients diagnosed with PJP, analyzing clinical data, laboratory parameters, and demographic information.

Results

The study included 160 HIV-infected patients, with a median age of 39 years (interquartile range: 32–45) and 95 (59.4%) female. Most patients (95.0%, n=152) had a known HIV diagnosis, with only 40.0% (n=64) on ART. The median log10 viral load (VL) was 5.4 (IQR: 4.2–5.8), and the median CD4 cell count was 26 cells/mm^3 (IQR: 9–76). Cotrimoxazole prophylaxis was reported in 46.3% (n=74), with 39.4% (n=63) not using it. Severe symptoms were prevalent at admission, with 75% having hypoxia, 65% respiratory failure, and 56% pulmonary involvement on imaging. Sputum PCR results were positive in 65.0% of survivors and 61.9% of deceased patients. Co-infections included lower respiratory tract infections (41.3%), tuberculosis (15.6% active TB, 11.9% previous TB), SARS-CoV-2 (8.8%), and other forms of pneumonia (7.5%). A total of 64 (40.0%) patients died, with an in-hospital mortality rate of 22.5% and a late mortality rate of 17.5%. Key risk factors for mortality included age ≥50 years, newly diagnosed HIV, and SARS-CoV-2 at admission.

Conclusion

Monitoring of viral load, CD4 counts, and ART adherence is essential for preventing PJP among HIV-infected individuals. Targeted HIV monitoring efforts are needed for high-risk groups, including patients aged 50 years and older, those with concurrent infections, and newly diagnosed patients.

Key words

Pneumocystis pneumonia, Pneumocystis jirovecii, HIV-infected, SARS-CoV-2, antiretroviral therapy

BACKGROUND

Pneumocystis Jirovecii Pneumonia (PJP) is a fungal opportunistic infection caused by Pneumocystis jirovecii, primarily affecting immunocompromised individuals such as those with advanced HIV/AIDS characterized by CD4 cell counts below 200 cells/mm³ and high viral loads[1-5]. In non-HIV settings, high-risk groups include those with haematological malignancies, elderly populations, and individuals on long-term immunosuppressive therapy[1-5].

PJP presents with symptoms such as non-productive cough, fever, dyspnoea, and hypoxia[2-5]. Radiographic findings often show diffuse, bilateral, or interstitial infiltrates[2]. Due to the non-specificity of these symptoms, clinical differentiation between PJP and other pulmonary conditions is challenging, often leading to misdiagnosis or under-diagnosis[4]. This is further complicated in immunocompromised patients with overlapping infections. For instance, a South African study of autopsies among miners revealed frequent misdiagnosis of PJP as tuberculosis (TB) or bacterial pneumonia[6]. As a result, the disease can progress rapidly without timely intervention, leading to high mortality.

Globally, an estimated 500,000 cases of PJP are reported annually, with a fatality rate between 10% and 30% [1]. During the peak of the HIV pandemic in the 1990s, nearly two-thirds of HIV-infected individuals were expected to develop PJP [7]. The widespread rollout of ART has since led to a significant decline in PJP incidence[4-8]. In sub-Saharan Africa, expanded ART programs over the last two decades have been instrumental in reducing PJP morbidity and mortality. Cotrimoxazole prophylaxis, when administered alongside ART, has further reduced the burden of PJP in high-HIV-burden regions[1-8]. Other factors contributing to lower PJP rates include baseline immunity from early-life exposure to Pneumocystis jirovecii and immunomodulation from other prevalent opportunistic infections [4].

Despite these advances, PJP remains a public health challenge. In the United States, it continues to be a leading AIDS-defining infection[9-10]. In Africa, PJP accounts for 20% to 30% of community-acquired pneumonia cases among inpatients [4-10]. In South Africa, where PJP prevalence among HIV-infected individuals is approximately one in five [11], the infection remains a significant concern, particularly in the context of delayed HIV diagnosis, ART interruptions, and non-adherence [2]. Recent European data suggest shifting epidemiological

patterns, with increased PJP incidence and mortality among non-HIV risk groups, such as patients with solid organ malignancies and autoimmune conditions [1, 12].

While PJP's epidemiology and clinical presentation have been well-documented in high-income countries, there is a gap in knowledge in developing countries, partly due to challenges in diagnosis [6, 13, 14]. This study aims to fill this gap by describing the clinical characteristics and treatment outcomes of PJP and identifying the determinants of mortality among HIV-infected patients receiving care in South African public hospitals. These findings could inform clinical strategies and public health interventions in South Africa and similar settings.

METHODS

Study design and setting

This retrospective descriptive study analysed records of HIV-infected patients with PJP who sought care in South Africa's public health sector. Data were sourced from patients enrolled in a multicentre epidemiological surveillance study measuring community-acquired pneumonia (CAP) incidence and a cohort study assessing the prospective incidence of CXR-confirmed, hospitalized CAP among adults [15]. The study was titled "The Potentially Preventable Burden of Community-Acquired Pneumonia in South African Adults" and was conducted at three high-volume tertiary hospitals: Chris Hani Baragwanath Academic Hospital (CHBAH), Klerksdorp Tshepong Hospital Complex (KTHC), and Polokwane/Mankweng Hospital (PMH), located in Gauteng, Northwest, and Limpopo provinces, respectively.

Recruitment into the primary study

Patients aged 18 years and older were enrolled between January 2019 and December 2021. Sub-study 1 focused on patients with physician-diagnosed CAP, and sub-study 2 followed a cohort of patients with CXR-confirmed, hospitalized CAP. Recruitment involved daily reviews of emergency room logs, ward registers, x-ray reports, and intensive care unit records. Clinical and demographic data were abstracted into anonymized electronic case report forms (eCRFs).

Sampling for this study

All records of HIV-infected adults with a diagnosis of Pneumocystis jirovecii pneumonia from the primary study database were included in this analysis.

Study procedures

PJP cases were defined according to the following criteria:

1. Probable PJP: Symptoms consistent with World Health Organization (WHO) guidelines, along with mycological evidence such as positive Beta-D-Glucan levels (>80 pg/mL) or PCR detection [33].
2. Definite PJP: Symptoms consistent with PJP, radiological findings, and identification of the organism through microscopy in tissue, bronchoalveolar lavage (BAL), or sputum[5].

Data on demographic information, clinical characteristics, treatment outcomes, and prognostic factors for mortality were extracted for analysis.

Data analysis

Descriptive statistics characterized the study population, while Pearson's Chi-square tests and binomial regression models were employed for categorical variable comparisons. Continuous variables were summarized using means (SD) or medians (IQR), with non-normally distributed data analysed using the Wilcoxon Mann-Whitney test. A multivariate Cox proportional hazards model assessed mortality risk factors, with variables included based on clinical significance. Statistical analyses were conducted using STATA version 17 (StataCorp, TX).

Ethics

Ethics approval was obtained from the Health Research Ethics Committee (HREC) of the University of the Witwatersrand (certificate number M221197). A waiver of individual informed consent was granted due to the retrospective nature of the study.

RESULTS

Characteristics of study participants

A total of 160 HIV-infected patients meeting the diagnostic criteria for Pneumocystis jirovecii pneumonia (PJP) were identified from the primary study database. The median age was 39 years, with an interquartile range (IQR) of 32 to 45 years, and 95 patients (59.4%) were female. Among the cohort, 8 patients (5.0%) were newly diagnosed with HIV, while 152 (95.0%) had a known HIV diagnosis.

Antiretroviral therapy (ART) use was reported in 64 patients (40.0%). The median log10 viral load (VL) at admission was 5.7 (IQR: 5.4-6.1) for newly diagnosed patients (n=7) and 5.3 (IQR: 3.9-5.8) for those with a known HIV status (n=152), with no significant difference between these groups (p=0.093). CD4 lymphopenia was prevalent, with a median absolute CD4 count of 26 cells/mm^3 (IQR: 9-76) documented in 155 patients (96.9%). Cotrimoxazole prophylaxis was reported in 74 patients (46.3%), while 63 (39.4%) were not on prophylaxis, and the status of 23 patients (14.4%) was unknown.

Comorbid conditions are detailed in Table 1. Tuberculosis (TB) was divided into "Active TB" (15.6%) and "Previous TB" (11.9%) for clarity. Lower respiratory tract infections were the most prevalent, affecting 66 patients (41.3%). Abnormal radiological findings were noted in 150 patients (93.8%), with pulmonary infiltrates being the most common finding. The proportion of abnormal chest X-rays was similar among patients who died (60/64, 93.8%) and those who survived (90/96, 93.8%), with no significant differences in the distribution of radiological findings between the two groups.

Clinical and Laboratory Parameters

Table 2 presents the laboratory parameters at admission. Hypoxia, defined as oxygen saturation <90% under room air, was observed in 120 patients (75.0%). Of these, mild hypoxia (86–90%) was noted in 48 patients (30%), moderate hypoxia (75–85%) in 50 patients (31.3%), and severe hypoxia (<75%) in 22 patients (13.8%). No significant differences were found in median oxygen saturation levels between patients with SARS-CoV-2 (80%, IQR: 69-86) and those without (84%, IQR: 73-90; p=0.319). Similar findings were noted for glycaemia, with median random blood glucose values of 6.3 mmol/L (IQR: 5.3-8.3) in SARS-CoV-2-positive patients and 6.8 mmol/L (IQR: 5.3-8.1) in SARS-CoV-2-negative patients (p=0.844).

Beta-D-glucan (BDG) levels were measured in 95 patients (59.38%), 65 (40.63%) with values >500 pg/ml at admission. A negative correlation between BDG values and CD4 cell count was observed (Pearson correlation coefficient = -0.28, p=0.007, n=93). However, no significant difference in median BDG values was observed between newly diagnosed and known HIV patients (p=0.147), nor between those with and without SARS-CoV-2 (p=0.372). Similarly, no associations were identified between positive PJP sputum test results and HIV status (p=0.449) or SARS-CoV-2 status (p=0.750).

Among the 90 patients (56.3%) who had bacterial cultures processed within 48 hours of admission, 8 patients (5.6%) tested positive for GeneXpert, with 4 (50.0%) showing RIF sensitivity and 4 (50.0%) showing indeterminate results. Positive PJP sputum results were associated with higher median BDG values compared to negative results (p=0.019), while the association between CD4 count and sputum positivity approached significance (p=0.051).

Treatment Modalities and Outcomes

Supplemental oxygen therapy was provided to 129 patients (80.6%) at admission. Of the 25 patients (15.6%) co-infected with tuberculosis (TB), 11 (44.0%) were initiated on TB treatment. Overall, 96 patients (60.0%) recovered and were discharged, while 64 patients (40.0%) died. Among the deceased, 36 patients (56.3%) died during hospitalization (within 30 days of admission), resulting in an in-hospital early mortality rate of 22.5%. The remaining 28 patients (43.8%) died after discharge, representing a late mortality rate of 17.5%. The causes of mortality are illustrated in Figure 1.

Prognostic Factors for Mortality

The median time to death was 23 days (IQR: 5-100) overall, with a median of 6 days (IQR: 4-18) for in-hospital deaths. Although not statistically significant, patients with SARS-CoV-2 at admission had a 1.5 times higher likelihood of early death compared to those without the virus (risk ratio = 1.5, 95% CI: 0.96-2.38). Patients with positive PJP sputum results were 2.5 times more likely to experience early mortality compared to those with negative results (risk ratio = 2.46, 95% CI: 0.67-8.80). Additionally, patients with both BDG values ≥500 pg/ml and positive PJP sputum results had a slightly increased risk of early death (risk ratio = 1.08, 95% CI: 0.54-2.15). Among the 4 newly diagnosed HIV patients who died, all deaths occurred early.

Survival rates are detailed in Figure 2. Survival outcomes did not significantly differ between patients with BDG values ≥500 pg/ml and those with lower values (log-rank test p=0.863), nor between patients with positive and negative sputum PCR results (log-rank test p=0.995). Similarly, no significant differences in survival were observed between patients with high BDG and positive sputum PCR results versus those with low BDG and negative results (p=0.325). Multivariate Cox proportional hazards modelling revealed that older age (≥50 years), SARS-CoV-2 co-infection, and newly diagnosed HIV status were significantly associated with an increased risk of death (Table 3).

DISCUSSION

This study provides insights into the clinical characteristics, treatment outcomes, and factors influencing mortality among HIV-infected patients with Pneumocystis jirovecii pneumonia (PJP) in the public healthcare setting. A key observation was the high prevalence of severe immunosuppression, characterized by significant CD4 lymphopenia and elevated viral loads, even with widespread access to antiretroviral therapy (ART) in South Africa. Notably, only 5% of the sample were newly diagnosed with HIV. Additionally, 40% of patients presented with lower respiratory tract infections, and roughly one-third had either a history of active tuberculosis (15.6%) or previous TB (11.9%), clearly distinguishing these two categories for accuracy.

Our findings align with prior research highlighting the vulnerability of individuals with low CD4 counts, particularly below 200 cells/mm^3, and elevated Beta-D-Glucan (BDG) levels (≥500 pg/ml), which are strong indicators of PJP risk [17-19]. Approximately 40% of participants had BDG levels above this threshold, consistent with studies focusing on HIV-related Pneumocystis jirovecii [20]. The median CD4 count for the cohort was below 50 cells/mm^3, indicating that our study primarily involved severely ill patients with advanced HIV disease [4]. Although the majority of patients were known to be HIV-positive and thus likely to have been on ART, the persistently low CD4 counts, and high viral loads suggest issues with ART adherence and the lack of PJP prophylaxis as key contributing factors. These issues are well-documented in the literature, with ART non-adherence linked to increased disease severity and poor outcomes [21-24].

A significant portion of the study population presented with severe symptoms upon admission. Specifically, hypoxia affected 75% of patients, while respiratory failure and widespread pulmonary involvement were observed in 66% and 62% of cases, respectively. This highlights the severity of PJP among the participants at the time of hospitalization. The need for supplemental oxygen in 80% of cases underscores the extent of respiratory compromise. Diagnosing PJP is often challenging, particularly in the presence of other infections, which can obscure the clinical picture and complicate management [4-6]. In our study, 40% of patients had concurrent lower respiratory tract infections, a third had TB, and under 10% had other forms of pneumonia, either viral or bacterial. These co-infections may have worsened the clinical course of PJP, a trend observed in other studies [6, 19, 25].

The survival analysis revealed a significantly increased mortality risk in older patients (≥50 years), those newly diagnosed with HIV, and patients with SARS-CoV-2 infection at admission. The results were clarified to ensure statistical comparisons were robust and appropriately framed for the older age group. While the analysis showed trends associating SARS-CoV-2 infection and BDG values ≥500 pg/ml with mortality, these did not reach statistical significance, likely due to the small sample size.

The overall mortality rate in our study was high, reaching 40%. While the era of ART has generally been associated with reduced PJP incidence and mortality [28-29], the COVID-19 pandemic has been associated with a resurgence of severe cases [28]. ART is known to enhance immune function, thereby decreasing the risk of opportunistic infections like PJP. However, the high mortality observed in our study is likely reflective of a sample biased toward patients with advanced disease, both in terms of HIV progression and severe PJP. Multivariate analysis confirmed that patients with SARS-CoV-2, those newly diagnosed with HIV, and those aged 50 and above had a significantly higher risk of death compared to SARS-CoV-2 negative patients, those with a known HIV diagnosis, and younger patients. Similar observations have been reported in other studies [19, 30, 31]. It is critical for clinical services to focus on these high-risk groups to improve patient outcomes.

Several limitations should be considered when interpreting our findings. As a retrospective study, standardized treatment protocols and follow-up procedures were not in place. Additionally, the dataset lacked information on some clinical variables, such as detailed treatment regimens. This restricted our ability to evaluate the impact of specific therapeutic interventions on outcomes. For instance, while corticosteroids have been shown to benefit patients with moderate to severe PJP [17, 32], we were unable to determine their use or effects in this cohort. Furthermore, missing data in key variables may have limited the study's power to detect significant associations. Given the multisite nature of the study, variability in diagnostic practices, such as the non-use of bronchoalveolar lavage, could introduce heterogeneity. Moreover, the study sample was skewed towards patients with advanced HIV, potentially limiting the generalizability of the findings to broader HIV populations with better viral control. The absence of a control group also restricts the ability to draw comparisons with non-PJP patients.

In conclusion, optimal management of PJP in HIV-infected individuals necessitates early detection and timely intervention. Consistent monitoring of CD4 counts and viral loads in patients on ART is vital to ensuring adherence and identifying potential drug resistance. Maintaining viral suppression can prevent opportunistic infections like PJP and reduce mortality among those living with HIV. Enhanced monitoring should focus on vulnerable groups, including those aged 50 years and above, individuals with concurrent infections, and newly diagnosed patients. Addressing these areas is essential for improving survival outcomes in this population.

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CHAPTER 3: APPENDICES

ANNEXURE A

DATA COLLECTION SHEET

ANNEXURE B

ETHICS CLEARANCE

ANNEXURE C

RESULTS

Table 1

Demographic and clinical characteristics of HIV-positive patients hospitalized for PJP in three teaching hospitals in SA, 2019-2021.

Table 2

Clinical parameters at admission among HIV-positive patients hospitalized for PJP in three teaching hospitals in SA, 2019-2021.

Table 3

A Cox proportional hazards model demonstrating factors associated with mortality in the study population.

Figure 1

Primary causes of death among study participants

Figure 2

Kaplan Meier curves showing survival rates (A. Overall, B. stratified by BDG values, C. stratified by sputum PCR result) during follow up among HIV infected patients hospitalized for PJP in three teaching hospitals in SA, 2019-2024

ANNEXURE A: Data collection sheet

CHARACTERISTICS AND TREATENT OUTCOMES OF PJP IN HIV INFECTED PATIENTS IN THREE TEEACHING HOSPITALS IN SA

Instruction: Tick the relevant box (√) where applicable

1.1	Sex	Male			1	
		Female			2	
1.2	Age				Years	
1.4	**PJP**					
	Method of diagnosis					
	BDG value	Actual	>500	<500		
	Sputum PCP PCR	positive	Yes 1	No 0		
	Radiological: Chest Xray					
	Clinical signs & symptoms					
2	**Comorbid conditions**					
2.1	Active Tuberculosis	no			0	
		yes			1	
2.2	Previous Tuberculosis	no			0	
		yes			1	Completed treatment
2.3	Chronic Lung Disease	no			0	
		yes			1	Previous TB
						COPD
						Mining history
2.4	Smoking History	no			0	
		yes			1	
2.5	HIV					
2.5.1	Newly diagnosed	no			0	
		yes			1	CD4
						Viral load
						ART regimen
2.5.2	Known/ pre-existing HIV positive	no			0	
		yes			1	CD4
						Viral load
						ART regimen

	Duration on ART	>6 months	<6 months		
	History of previous treatment default	yes	1	no	0
2.6	COVID 19				
		no	0		
		yes	1		
2.7	**Other co infections other than TB**				
	Bacterial pneumonia				
	Viral pneumonia				
3.	**Clinical parameters**				
3.1	Oxygen saturation (pulse oximetry) < 94% on room air	no	0		
		yes	1		
3.2	Respiratory rate > 20 breaths/min	no	0		
		yes	1		
3.3	PaO2/FiO2 <300	no	0		
		yes	1		
3.4	Blood pressure SBP<90	no	0		
		yes	1		
3.5	Temperature >37.5 deg Celsius	no	0	yes	1
	fever	no	1	yes	1
	Cough	no	o	yes	1
	dyspnea	no	0	yes	1
4	**Laboratory values**				
4.1.1	White cell count				
4.1.2	Hemoglobin				
4.1.3	Platelets				
4.2	C reactive protein (CRP)				
4.3	Creatinine				
4.5	Urea				
4.6	B D Glucan				
4.7	LDH				
4.8	Serum Albumin				

4.9	Sputum PCP PCR								
4.9.1	Sputum GXP	Positive	1	Rif sensitive	yes	1	negative	0	
					no	0			
5	**Treatment**								
5.1	corticosteroids	no	0						
		yes	1						
5.2	antibiotics	no	0						
		yes	1						
5.3	Oxygen therapy	no	0						
		yes	1						
5.4	Mechanical Ventilation	no	0						
		yes	1						
6	**Outcome**								
6.1	In hospital Mortality								
6.2	Discharged								
6.3	Mechanical ventilation								

ANNEXURE B

ETHICS CLEARANCE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr J Gweshe

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M221197

NAME: (Principal Investigator)	Dr J Gweshe
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	*Characteristics, risk factors and outcomes of pneumocystis jirovecii pneumonia in HIV infected patients in three hospitals in South Africa*
DATE CONSIDERED:	2022/11/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professors E Variava and N Martinson
APPROVED BY:	Dr N Naran, CC-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/01/03

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

ANNEXURE C

RESULTS

Table 1: Demographic and clinical characteristics of HIV-positive patients hospitalized for PJP in three teaching hospitals in SA, 2019-2021.

Characteristic	Total N=160	Survived n=96	Died n=64	P value
Demographics				
Age (Years)				0.252
<30	22 (13.8%)	11 (11.5%)	11 (17.2%)	
30-39	61 (38.1%)	40 (41.7%)	21 (32.8%)	
40-49	53 (33.1%)	34 (35.4%)	19 (29.7%)	
50 +	24 (15.0%)	11 (11.5%)	13 (20.3%)	
Median age (IQR)	39 (32-45)	39 (32-45)	40 (32-46)	
Female sex	95 (59.4%)	55 (57.3%)	40 (62.5%)	0.432
Year of admission				0.544
2019	23 (14.4%)	15 (15.6%)	8 (12.5%)	
2020	80 (50.0%)	50 (52.1%)	30 (46.9%)	
2021	57 (35.6%)	31 (32.3%)	26 (40.6%)	
Clinical characteristics				
BDG values pg/ml	95	52	43	0.598
>80	93 (97.9%)	51 (98.1%)	42 (97.7%)	
≤80	2 (2.1%)	1 (1.9%)	1 (2.3%)	
Sputum PCP PCR	61	40	21	0.057
Negative	22 (36.1%)	14 (35.0%)	8 (38.1%)	
Positive	39 (63.9%)	26 (65.0%)	13 (61.9%)	
Radiological (chest Xray)				
Pulmonary infiltrates	99 (61.9%)	57 (59.4%)	42 (65.6%)	0.425
Consolidation	17 (10.6%)	12 (12.5%)	5 (7.8%)	0.346
Pulmonary opacities/infiltrates	16 (10.0%)	11 (11.5%)	5 (7.8%)	0.451
Opacities	13 (8.1%)	6 (6.3%)	7 (10.9%)	0.288
Cavities	8 (5.0%)	4 (4.2%)	4 (6.3%)	0.554
Suggestive of pneumonia	6 (3.8%)	1 (1.0%)	5 (7.8%)	0.027
Pleural effusion	5 (3.1%)	4 (4.2%)	1 (1.6%)	0.649
Suggestive of pulmonary TB	5 (3.1%)	3 (3.1%)	2 (3.1%)	1.000
Fibrosis	4 (2.5%)	3 (3.1%)	1 (1.6%)	0.650

Lobar consolidation	4 (2.5%)	3 (3.1%)	1 (1.6%)	0.650
Multilobar consolidation	4 (2.5%)	1 (1.0%)	3 (4.7%)	0.303
Air bronchograms	3 (1.9%)	0 (0.0%)	3 (4.7%)	0.062
Hyperinflated	3 (1.9%)	2 (2.1%)	1 (1.6%)	1.000
Collapsed lung/atelectasis	1 (0.6%)	1 (1.0%)	0 (0.0%)	1.000
Pneumothorax	1 (0.6%)	1 (1.0%)	0 (0.0%)	1.000
Comorbid conditions				
TB status				0.657
Active TB	25 (15.6%)	16 (16.7%)	9 (14.1%)	
Previous TB	19 (11.9%)	7 (7.3%)	12 (18.8%)	
Lower respiratory tract infection				0.896
Yes	66 (41.3%)	40 (41.7%)	26 (40.6%)	
Sputum PCR positive				0.328
Yes	39 (24.4%)	26 (27.1%)	13 (20.3%)	
SARS CoV2				0.819
Positive	14 (8.8%)	8 (8.3%)	6 (9.4%)	
Co-infections other than TB				
Bacterial pneumonia	6 (3.8%)	3 (3.1%)	3 (4.7%)	0.684
Viral pneumonia	6 (3.8%)	3 (3.1%)	3 (4.7%)	0.684
Patient on Bactrim Cotrimoxazole Prophylaxis				
Unknown	23 (14.4%)	10 (10.4%)	13 (20.3%)	0.0486
Yes	74 (46.3%)	48 (50.0%)	26 (40.6%)	0.1875
No	63 (39.4%)	30 (31.3%)	25 (39.1%)	0.5834

Abbreviations: PJP Pneumocystis jirovecii pneumonia, PCR polymerase chain reaction, BDG Beta-D-glucan, TB tuberculosis, IQR interquartile range

Table 2. Clinical parameters at admission among HIV-positive patients hospitalized for PJP in three teaching hospitals in SA, 2019-2021.

	Median (IQR)		
	Overall	**Survived**	**Died**
Median Respiratory rate (breaths/min), n=160	20 (18-24)	20 (18-24)	20 (18-24)
Oxygen saturation (room air), (n=160)	84.5 (73.0-89.5)	86 (76.5-90)	80.5 (69.5-88.0)
Oxygen saturation (on oxygen), (n=129)	97.0 (94.0-99.0)	97.0 (94.0-99.0)	97.0 (94.0-99.0)

White Cell Count, (n=157)	7.8 (5.8-10.5)	7.5 (5.7-10.0)	8.4 (6.2-11.0)
C-reactive protein, (n=153)	108 (58-184)	108 (50-188)	110 (59-170)
Creatinine, (n=158)	72 (59-91)	72 (59-86)	72 (55-97)
Beta-D-Glucan, (n=95)	500 (437-500)	500 (429-500)	500 (437-500)
Haemoglobin, (n=157)	11.4 (10.0-12.9)	11.6 (10.2-12.9)	11.1 (9.7-12.9)
Platelets, (n=157)	322 (234-412)	350 (247-434)	282 (226-359)
Urea, (n=158)	4.7 (3.7-6.8)	4.5 (3.7-6.0)	4.9 (3.7-8.0)
Random Glucose mmol/L, (n=139)	6.5 (5.3-8.1)	6.4 (5.5-8.1)	7.0 (5.3-8.2)

Table 3. A Cox proportional hazards model demonstrating factors associated with mortality in the study population.

Variable	N (%)	Unadjusted HR 95% CI	P value	Adjusted HR 95% CI	P value
Age/Years					
<50	51 (37.5%)	1.0		1.0	
≥50	13 (54.2%)	1.67 [0.91-3.07]	0.101	0.02 [0.00-0.64]	0.027
Sex					
Female	40 (42.1%)	1.0		1.0	
Male	24 (36.9%)	0.92 [0.56-1.53]	0.751	1.13 [0.09-14.62]	0.927
TB status					
Previous TB	12 (63.2%)	1.0		1.0	
Active TB	9 (36.0%)	0.50 [0.21-1.18]	0.113	0.17 [0.01-2.39]	0.191
SARS-CoV-2					
Negative	36 (38.3%)	1.0		1.0	
Positive	6 (42.9%)	1.21 [0.51-2.87]	0.668	17.9 [5.34-60.22]	0.004
HIV status					
Known positive	60 (39.5%)	1.0		1.0	
Newly diagnosed	4 (50.0%)	1.62 [0.58-4.41]	0.362	11.2 [3.16-39.97]	0.010

LRTI					
No	38 (40.4%)	1.0		1.0	
Yes	26 (39.4%)	1.06 [0.64-1.75]	0.815	1.57 [0.17-14.48]	0.690
WCC	64 (40.0%)	1.05 [1.00-1.10]	0.072	1.08 [0.94-1.25]	0.265
Oxygen saturation (room air) %	64 (40.0%)	0.99 [0.98-1.01]	0.111	1.02 [0.93-1.11]	0.725
Platelet count	64 (40.0%)	1.00 [0.99-1.01]	0.280	1.00 [0.99-1.02]	0.599
Creatinine	64 (40.0%)	1.00 [0.99-1.00]	0.023	1.01 [0.97-1.05]	0.689
Urea	64 (40.0%)	1.05 [1.01-1.08]	0.013	1.41 [0.78-2.58]	0.250
Random blood glucose	57 (35.6%)	1.02 [0.91-1.15]	0.721	1.25 [0.71-2.21]	0.441

Abbreviations: N number with outcome, HR hazard ratio TB tuberculosis, WCC white blood cell count, CI confidence interval

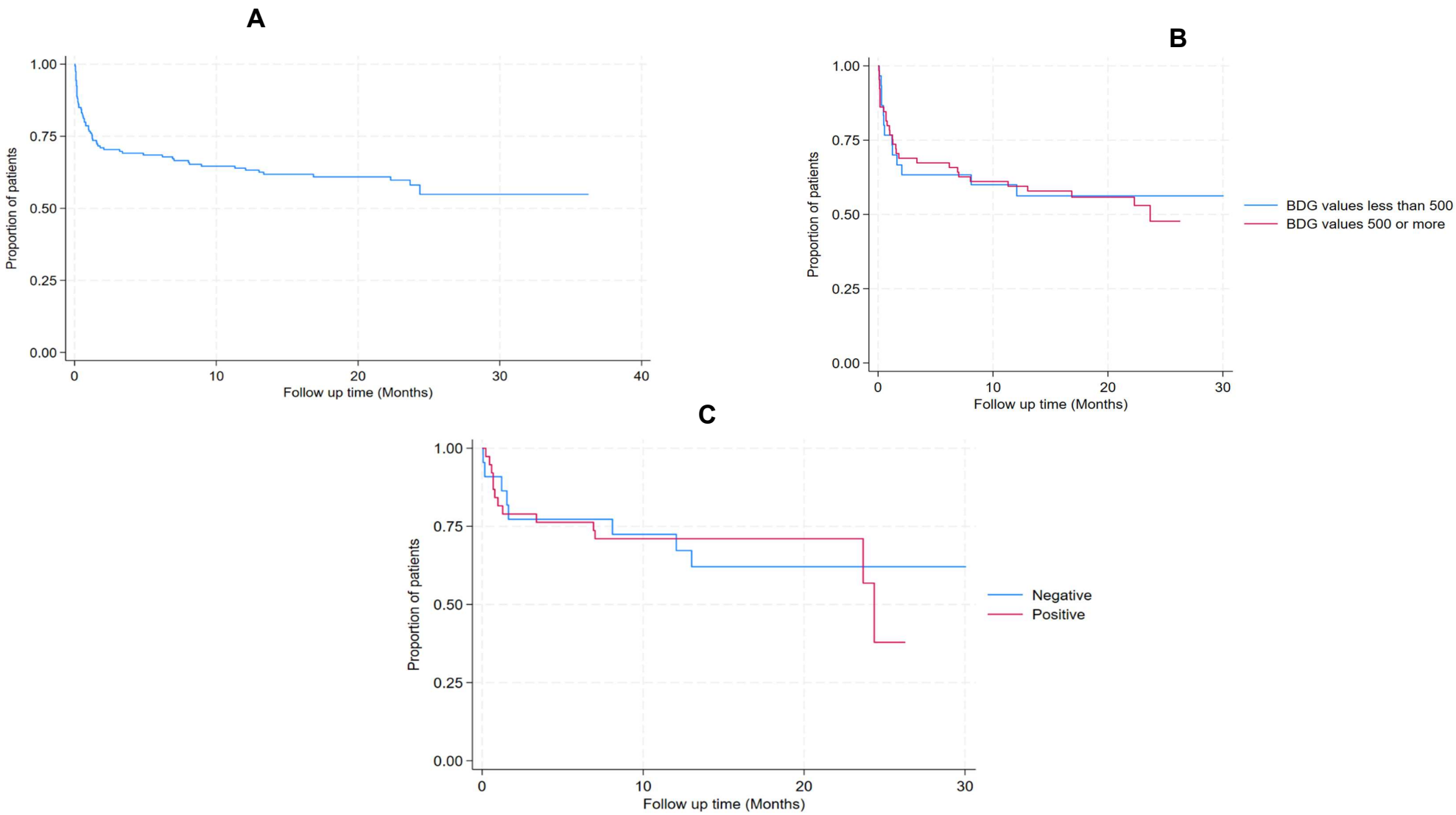


Figure 2 Kaplan Meier curves showing survival rates (A. Overall, B. stratified by BDG values, C. stratified by sputum PCR result) during follow up among HIV infected patients hospitalized for PJP in three teaching hospitals in SA, 2019-2021

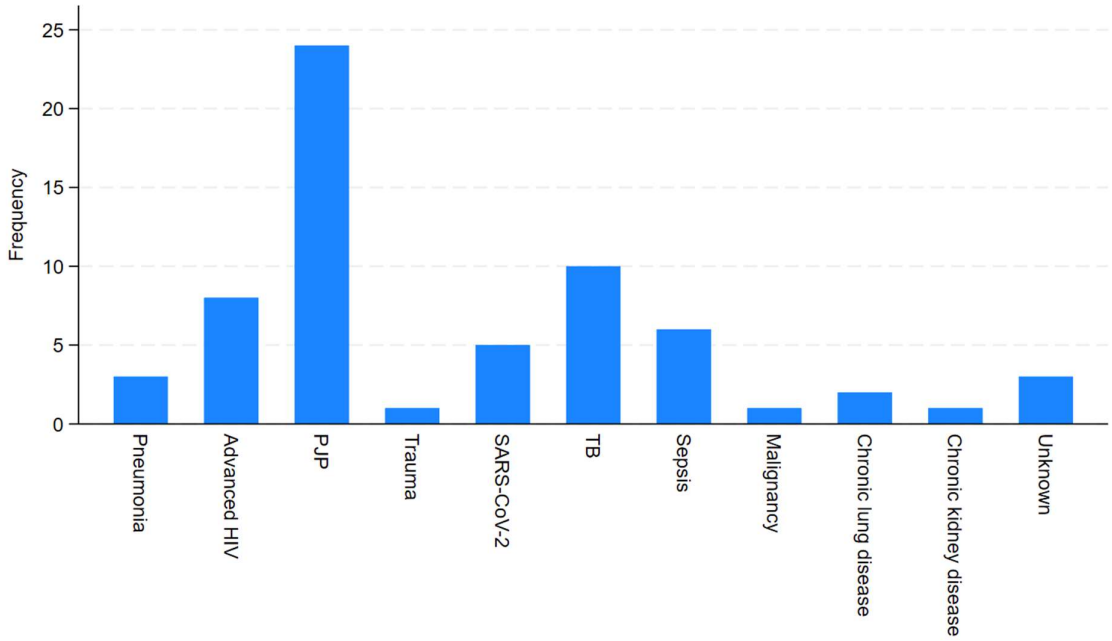


Figure 1. Primary causes of death among study participants