Masters of Medicine

A CLINICAL AUDIT OF SELECTED PREDICTORS OF MORTALITY OF PATIENTS ADMITTED TO CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL INTENSIVE CARE UNIT WITH HUMAN IMMUNODEFICIENCY VIRUS AND TUBERCULOSIS CO-INFECTION

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Masters of Medicine.

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DECLARATION

I, Avani Singh, declare that this research report is my own work.

It is being submitted for the degree of MMed (Internal Medicine) to the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other University.

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Dr Avani Singh

_____day of_____20_____in_____

ETHICAL APPROVAL

Ethical approval had been submitted and approved by the University of Witwatersrand Human Research Ethics Committee. This was further supported by approval by the CEO of Charlotte Maxeke Johannesburg Academic Hospital.

Clearance certificate number: M170372

ABSTRACT

Background: The high level of co-morbid TB/HIV cases with severe organ failure on presentation in South Africa, results in an increased number of ICU admissions often with a poor prognosis at presentation. In this study, the aim was to identify patients admitted with HIV/TB co-infection and calculate the APACHE II scores and SOFA scores for each patient. Predicted percentage mortality was compared with actual mortality. Predictors of mortality were further identified, as well as the benefit of initiating ARV treatment in patients who are ARV naive upon admission to ICU.

Methods: A retrospective audit of consecutive cases over a 24 month period was completed. Patient demographics; CD 4 count; ARV treatment status; ICU and 30 day mortality; the APACHE II Score; SOFA scores and correlating predicted percentage mortality were documented. The survival of patients was assessed using Kaplan Meier survival curves, and a univariate analysis was performed to identify risk factors for mortality. Calculated predicted mortality was compared with actual mortality to validate each scoring system and infer which was the better tool.

Results: Of 75 patients admitted with pulmonary (43 cases) or extra-pulmonary (32 cases) TB, 23 died in the ICU (mortality 30,7%), and a further 10 died in the first 30 days of hospitalisation (30 day mortality 44%). A survival analysis established ARV treatment and CD 4 counts greater than 50 cells/mm^3 were associated with a higher survival rate at any point of the analysis. In the entire study period, only 2 patients were initiated on ARV therapy during their ICU stay, 1 survived to discharge and 1 died in ICU. The APACHE II Predicted Mortality was within the 95% Confidence Intervals for all groups while the SOFA score was outside the upper bound limit of the 95% confidence intervals of actual mortality for those patients taking ARV treatment (52%, 95% CI 43,1% - 59,5% vs actual mortality 30%, 95% CI 17,7% - 46,1%), those with a CD 4 count of more than 50 (53,5% 95% CI 45,4% - 60,6% vs actual mortality 34%, 95% CI 22,1% - 48,4%) and female patients (51,2%, 95% CI 41,6% - 58,1% vs actual mortality 35,1%, 95% CI 21,4% - 50,4%).

Conclusion: The study found that both the APACHE II and SOFA scoring systems were both statistically significant in prognosticating mortality in the study population. The APACHE II scoring system however showed a slightly improved prognostication in specific cohorts who had improved survival. It was also confirmed that patients with a CD 4 count of more than 50 cells/mm^3, and those on ARV therapy had a statistically significant

improved mortality. Further studies reviewing survival benefit of ARV initiation in ICU are warranted.

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LIST OF TABLES **PAGE NUMBER**

LIST OF FIGURES **PAGE NUMBER**

CHAPTER 1

1.1 INTRODUCTION

The burden of Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) in South Africa is one of the highest in the world (1). In spite of a noted decline in the incidence of TB in South Africa, the epidemic is fueled by the huge HIV prevalence in the country (2, 3). The high level of co-morbid TB/HIV cases, results in an increased number of hospital related admissions and in the more severe cases - Intensive Care Unit (ICU) admission may be required (4 - 8).

The Acute Physiology and Chronic Health Evaluation II Score (APACHE II) has been proven in previous studies to predict patient mortality (4, 5, 7, 9). An alternative ICU scoring system, the Sequential (Sepsis Related) Organ Failure Assessment (SOFA) score has been used to define organ dysfunction related to the host response to an infection i.e. sepsis (10 - 12). The primary outcome of this study was to validate these scoring systems and review if actual mortality was reflected by the predicted mortality. In addition a comparison between the APACHE II and the SOFA scores was made as to their prediction of mortality in the study population.

Previous studies have demonstrated that the APACHE II score tends to underestimate the mortality of patients with TB and HIV co-infection (5, 9, 13). While both ICU scoring systems provide an assessment of illness severity and create an estimate of mortality (14, 15), there are currently no major trials in the literature validating the SOFA score in a resource poor setting, especially within the specific population of co-morbid HIV/TB disease in ICU. The underestimation of mortality as defined by the APACHE scoring system is most likely related to the exclusion of the degree of immunosuppression as manifested by the very low CD 4 counts of HIV infected patients (4, 5, 8, 17 - 20).

This study aimed to establish the validity of the scoring systems used and furthermore to identify specific predictors of mortality that may be present in the study population. A recent study notes that patients with co-morbid HIV/TB and very low CD 4 counts, specifically less than 50 cells/mm^3, have an increased mortality if ARVs are not started within two weeks of TB treatment initiation (20). With this in mind, a secondary objective in this study was to identify patients who were not on ARV treatment on admission, who were initiated on therapy during their ICU stay and review whether this had any effect on mortality.

1.2 LITERATURE REVIEW

The high burden of HIV and TB co-infection in South Africa has been well described, with the World Health Organization (WHO) reporting South Africa as having the third highest number of reported cases and the highest population adjusted incidence and prevalence of TB (1). South Africa is also currently documented as having the highest number of HIV related TB cases (1) - and a total mortality of roughly 73 000 TB and HIV related deaths in 2015 (2). A study at the Helen Joseph Hospital in Johannesburg, previously showed that up to 95% of TB inpatients admitted were co-infected with HIV (3).

The high prevalence of HIV/TB co-morbid disease in the South African public health service results in an increased number of ward and ICU admissions due to the severity of illness encountered. A South African based study found that roughly 1.5% of active TB cases admitted to academic hospitals required intensive care and ventilatory support (4, 5). Previous studies have also demonstrated that most patients requiring ICU are in respiratory failure have evidence of ARDS and require ventilatory support (4, 9). Severely ill patients with TB are not limited to those with pulmonary disease, but may also present with extra-pulmonary disease, although studies have demonstrated fewer case numbers (4, 6).

Multiple past studies have also found extremely high mortality rates in patients suffering from active TB who require ICU admission, ranging from 40% to 80% (4 - 8). ICU scoring systems provide an assessment of illness severity and create an estimate of in-hospital mortality (14). Physiology based scoring systems have been preferred to diagnosis based systems due to their universal applicability and ease of use on admission to ICU (14).

The Acute Physiology and Chronic Health Evaluation II Score (APACHE II) is one such scoring tool and has proven to be an effective tool even in resource poor environments if calculated within 24 hours of ICU or hospital admission (5, 7, 8). The scoring system comprises 12 physiological parameters and 2 disease related physiological variables (15). The most deranged physiological parameters from the first 24 hours of admission are used (15). The scoring system then uses these parameters to calculate a total score which can be correlated to a predicted hospital mortality (15). Knaus et al explain that the APACHE II scoring system was designed to allow for more efficient scoring than the older version, the APACHE scoring system - while still maintaining its predictive value in establishing patient mortality by using objective physiological parameters (15). Currently the APACHE II scoring system remains one of the most widely used ICU mortality tools, as it has shown fair estimation of mortality over a vast range of disease processes (14). Newer variants of the APACHE scoring system have been introduced including the APACHE III, IV and V which have greater statistical power than their predecessors, and have been adjusted to account for HIV co-morbidity by means of a more complex weighting system and calculation (14). However, as these newer systems are copyrighted, they are fee based and require a computer based statistical system to complete the assessment - making them less accepted and used internationally (14).

TABLE 1.1: THE APACHE II SCORE (15)

Physiological Variable	**High Abnormal Range**				**Normal**
	+ 4	**+ 3**	**+ 2**	**+ 1**	**0**
Temperature (°C)	>41	39 - 40.9		38.5 - 38.9	36 - 38.4
Mean Arterial Pressure (mmHg)	>160	130 - 159	110 - 129		70 - 109
Heart Rate	>180	140 - 179	110 - 139		70 - 109
Respiratory Rate	>50	35 - 49		25 - 34	12 - 24
Oxygenation a)Fi)2>0,5 -> A-a $D0_2$ (high normal range) b) FiO2 <0,5 -> PaO_2 (low normal range)	>500	350 - 499	200 - 349		< 200 PO_2 >70
Arterial pH	> 7.7	7.6 - 7.69		7.5 - 7.59	7.33 - 7.49
Serum K (mEq/l)	>7	6 - 6.9		5.5 - 5.9	3.5 - 5.4
Serum Na (mEq/l)	>180	160 - 179	155 - 159	150 - 154	130 - 149
Serum Cr	> 300	171 - 299	132 - 170		53 - 131
Heamatocrit (%)	> 60		50 - 59.9	46 - 49.9	30 - 45.9
WCC (10^3/cc)	> 40		20 - 39.9	15 - 19.9	3 - 14.9
AGE score conversion	<44 = 0	45 - 54 = 2		55 - 64 = 3	
GCS conversion score	15 - GCS value				
Chronic Health Score	Hx of severe organ dysfunction or immunocompromised and for elective surgery - Add 2 points				
	Hx of severe organ dysfunction or immunocompromised and for emergency surgery - Add 5 points				
	Hx of severe organ dysfunction or immunocompromised and not for surgery - Add 5 points				
TOTAL SCORE	**Physiological sum + AGE conversion score + GCS conversion score + Chronic Health Score**				

Physiological Variable	Normal	Low Abnormal Range			
	0	+ 1	+ 2	+ 3	+ 4
Temperature (°C)	36 - 38.4	34 - 35.9	32 - 33.9	30 - 31.9	<29.9
Mean Arterial Pressure (mmHg)	70 - 109		50 - 69		<49
Heart Rate	70 - 109		50 - 69	40 - 59	<39
Respiratory Rate	12 - 24	10 - 11	6 - 9		< 5
Oxygenation **a)Fi)2>0,5 -> A-a $D0_2$ (high normal range)** **b) FiO2 <0,5 -> PaO_2 (low normal range)**	< 200 PO_2 >70	PO_2 61 - 70		PO_2 55 - 60	PO_2 < 55
Arterial pH	7.33 - 7.49		7.25 - 7.32	7.15 - 7.24	<7.15
Serum K (mEq/l)	3.5 - 5.4	3 - 3.4	2.5 - 2.9		< 2.5
Serum Na (mEq/l)	130 - 149		120 - 129	111 - 119	<110
Serum Cr	53 - 131		< 52		
Heamatocrit (%)	30 - 45.9		20 - 29.9		<20
WCC (10^3/cc)	3 - 14.9		1 - 2.9		<1
AGE score conversion	55 - 64 = 3	65 - 74 = 5		> 75 = 6	
GCS conversion score	15 - GCS value				
Chronic Health Score	Hx of severe organ dysfunction or immunocompromised and for elective surgery - Add 2 points				
	Hx of severe organ dysfunction or immunocompromised and for emergency surgery - Add 5 points				
	Hx of severe organ dysfunction or immunocompromised and not for surgery - Add 5 points				
TOTAL SCORE	**Physiological sum + AGE conversion score + GCS conversion score + Chronic Health Score**				

The APACHE II scoring system has been validated multiple times in the past in tertiary institutions and in resource limited settings (4 - 6, 8). Of note has been the underestimation of mortality in HIV/TB co-morbid cases in the ICU setting by this scoring system (5, 9). A study in the Western Cape found that roughly 70% of the HIV and TB co-infected patients admitted to their ICU within the study period, had CD 4 counts < 200 cells/mm^3 (5) - placing these patients in WHO clinical stage 4 or having the Acquired Immune Deficiency Syndrome (AIDS). In this study, a total of 44 patients had HIV/TB co-infection, 18 of whom died. On closer review of this particular sub-population it was noted that 16 of the 18 had CD 4 counts < 200 cells/mm^3 (5). It can thus be hypothesized that the APACHE II scoring system, when assessing patients with HIV/TB co-infections, fails to include the degree of immunosuppression as manifested by the actual CD 4 count and the possibility that the physiologic response may be relatively blunted (17 - 20). Delays in initiation of TB treatment and a miliary pattern on chest radiograph were two other parameters found to be directly related to patient mortality in this study (5).

Surprisingly, outside of the South African setting, where TB prevalence is not as closely related to HIV infection, a few studies have found that HIV infection is not a direct risk factor for mortality (6, 9, 16) in those with HIV/TB co-infection. This is contrary to the many studies which demonstrate the negative effects of HIV infection, specifically in patients with severe immunosuppression requiring ICU admission for sepsis and septic shock (17). In the few South African studies which assessed TB mortality in ICU, HIV with a low CD 4 count, specifically < 200, was identified as a direct risk factor for mortality (4, 5, 8, 18 - 20).

Besides the obvious, i.e.the immunosuppression and healing present in patients with CD 4 counts < 200 cells/mm^3, it has also been noted that the relative paucity of mycobacteria in sputum (due to the lack of cavitation) may delay diagnosis and therefore therapy (19, 21).

It is possible however that this has been ameliorated to some extent by the availability of the GeneXpert MTB/Rif test, a molecular test based on the polymerase chain reaction detecting a region of the TB gene (1, 22, 23). In South Africa, studies document an increase of 300% in the number of new TB cases identified as a result of this testing system as opposed to the previous Acid Fast bacilli smear technique (23).

Studies have also revealed further delays in treatment in this subgroup of severely immunodeficient patients due to the fact that the X-ray findings are frequently atypical (5, 21) with non-cavitatory changes, multiple areas of consolidation, a miliary pattern and diffuse interstitial infiltrates frequent findings(5, 19, 21). As mentioned above, a delay in initiation of TB treatment in patients with active TB has been identified in many studies to be a major contributing factor to the need for ICU admission (4 - 8, 19, 21).

Recent research has also found that patients with co-morbid HIV/TB disease and very low CD 4 counts, specifically < 50 cells/mm^3, have an increased mortality if antiretroviral (ARV) treatment is not started within two weeks of initiation of TB treatment (20). A large multicentre randomized controlled trial by Havlir et al, found that patients with CD 4 counts < 50 cells/mm^3 had a 42% decrease in mortality if ARV treatment was initiated within 2 weeks as opposed to 8 - 12 weeks after initiation of TB therapy (20). This may be due to the coincident effect of ARVs on other AIDS defining illnesses, such as Kaposi Sarcoma, cryptococcal disease and candida oesophagitis however the greatest effect is probably due to enhancement of the immune response to the mycobacteria (20). While previous studies have demonstrated benefit from initiating ARV's early with CD 4 counts < 500 cells/ mm^3 (24), this was not statistically significant in the data presented by Havlir et al, who found that those who had CD 4 counts more than 50 cells/mm^3, did not necessarily benefit from early initiation of ARVs compared to ARV initiation 8 - 12 weeks later (20).

Early ARV initiation, even in ICU, is generally advocated in patients with opportunistic infections (25, 26), where it has been noted that early strengthening of the immune system resulted in a significant decrease in AIDs related morbidity and 6 month mortality (25 - 27). A large multicentre trial by Zolopa et al supported these findings, with only 10% of patients who were started on ARV treatment during their ICU stay developing an immune reconstitution inflammatory syndrome (IRIS) and also a lower mortality rate in this study arm (26). Of note however is that in this study patients with TB were excluded - possibly due to the expected risk of IRIS as well as drug interactions and toxicity (26).

An ICU based study in Brazil performed over a 10 year period, found similar results with regard to 6 month mortality in patients with low CD 4 counts (< 40 cells/mm^3) that had been given ARVs (28). IRIS and specific complications of ARVs, such as drug toxicity were however not included as an endpoint in this study (28). The attributable mortality of IRIS is contentious, with certain studies documenting rates as high as 24% (29) and others recording no related deaths (20, 24, 26). Although all studies concur that the risk of morbidity and mortality related to IRIS associated with early ARV initiation in patients with very low CD 4 counts is higher (20, 24 - 27, 29), appropriate use of steroid therapy and close inpatient monitoring may reduce this effect (20, 24, 26, 27).

Besides the risks related to IRIS, there are multiple other considerations when initiating ARV's in an ICU setting. The process is not always easy as intravenous ARV formulations are not available and patients commonly have dysfunctional gastrointestinal tracts with poor absorption as well as altered pharmacokinetics (17, 25, 27). Drug reactions in the face of new ARV treatment are common, ranging from benign hypersensitivity to toxic epidermal necrolysis; hepatotoxicity; nephrotoxicity; pancreatitis and myopathy (25, 27). It

TABLE 1.2: THE SOFA SCORE (12)

Physiological Markers	**Variable Points**				
	0	**1**	**2**	**3**	**4**
Neurological Score - Glasgow Coma Scale	15	13 - 14	10 - 12	6 - 9	< 6
Respiratory Score - PaO_2 / FiO_2	> 400	400 - 300	300 - 200	200 - 100 (with respiratory support)	< 100 (with respiratory support)
Cardiovascular Score - Mean Arterial Pressure (mmHg)	No hypotension	Mean Arterial Pressure (mmHg) < 70 not requiring inotropes	Mean Arterial Pressure (mmHg) < 70 requiring Dopamine or Dobutamine < 5	Mean Arterial Pressure (mmHg) < 70 requiring Dopamine or Dobutamine 5 - 15 or Adrenaline < 0.1 or Noradrenaline < 0.1	Mean Arterial Pressure (mmHg) < 70 requiring Dopamine > 15 or Adrenaline > 0.1 or Noradrenaline > 0.1
Renal Score - Serum Cr (umol/ L)	< 110	110 - 170	171 - 299	300 - 440	> 440
Coagulation Score - Serum platelets (10^3/uL)	> 150	150 - 100	100 - 50	50 - 20	< 20
Liver Score - Serum Bilirubin (umol/L)	< 20	20 - 32	33 - 101	102 - 204	> 204

is also often difficult to differentiate these and similar inflammatory drug reactions from the systemic inflammatory response syndrome secondary to sepsis with or without multiple organ dysfunction and the requirement for organ support (17, 25). Another concern is the potential for acquisition of resistance to ARVs that might develop in patients related to reduced gastrointestinal absorption and decreased therapeutic levels due to possible drug interactions (17).

Most of this information is garnered from observational data as there are no large prospective studies which investigate the administration of ARV therapy in an ICU setting (17, 25, 27). It is important to note however that the benefits of prior initiation of ARV therapy in HIV positive patients admitted to ICU are well documented (17, 25, 27, 28, 30).

Unfortunately due to the paucity of data related to initiation of ARVs in ICU, specifically with regard to patients with TB/HIV comorbidity, the decision as to the timing of initiation of therapy remains individualised and subjective (17, 27, 30).

Unlike the APACHE II Score, the Sequential (Sepsis Related) Organ Failure Assessment (SOFA) score has not previously been validated as a mortality prediction tool in the setting of HIV/TB co-morbid infection in many South African studies. However - as per the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) - sepsis, is currently defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” (10). Therefore, patients admitted to ICU with active TB infection and evidence of organ dysfunction, are considered to have sepsis. Organ dysfunction is described as an increase in the SOFA score of ≥ 2 (10). This mortality prediction score is based on the presence of dysfunction of 6 organ systems; cardiovascular, renal, respiratory, nervous system, coagulation and liver (14). Each system dysfunction is graded out of 4 - to create a maximum score of 24 (14).

The SOFA score was created as a tool to quantify organ failure over a series of time - and thus establish the initial severity of organ dysfunction as well as the patient’s response to treatment while in ICU (11). When initially developed the SOFA score was introduced as a as a tool that could follow the extent of organ dysfunction in the septic ICU patient, and not necessarily as a predictive tool (11). However as the seminal study by Vincent et al explained, mortality is expected to be directly related to worsening organ failure and so a linear relationship between increasing SOFA scores for each organ system and predicted mortality could be hypothesized (11). Vincent et al also highlighted a review of a previous study which described the relationship of higher admission SOFA scores to increasing

mortality (11). Using this information, the SOFA score on admission to ICU was then retrospectively related to observed mortality in large multicentre trials (12, 31 - 33), and found to correlate well (12; 31). It was however, the increase in SOFA score from the initial admission score, which demonstrated the most statistically significant correlation with mortality (12, 31 - 33). Ferriera et al found that the admission SOFA score was closely linked to vital status, and derived a predicted percentage mortality based on the admission SOFA score (12). Through their statistical analysis, they derived an admission SOFA score of less than 9 predicted a mortality of < 33% and a score of > 11 predicted a mortality of > 95% (12). Although the admission score showed a strong correlation with mortality, univariate analysis demonstrated that the mean SOFA score correlated best with ultimate mortality and that an increase in score over the first 48 hours post admission predicted a mortality of at least 50% (12).

A few small studies have looked at the admission SOFA and compared it to the APACHE II score in its ability to predict mortality post admission. Only two studies were found which looked at TB mortality in ICU specifically with reference to ICU scoring systems. The first study by Lee et al was a prospective study in South Korea looking at the SOFA and APACHE II on admission to ICU in patients with miliary TB and found that the SOFA score did correlate well with mortality, although little mention was made of the APACHE II score in this regard (13). This was probably because on review of the results, it is evident that the p value assessing the difference in APACHE II in survivors and non-survivors was not statistically significant and therefore the authors chose not to comment further (13). The second study was a small prospective review of 35 included cases, and found both the APACHE II and SOFA scores to be statistically significant in their prognostic ability (34). Of interest, this study highlighted an increased prevalence of multidrug resistant TB, with almost a third of cases reflecting resistance to at least one of the key drug therapies used

in TB treatment (34). Both studies demonstrated a low proportion of HIV/TB co-morbidity - only 1 included case was found in each study (13, 34).

Other studies which compared SOFA and APACHE II scoring tools in the ICU setting have had mixed results. An Egyptian trial which reviewed 110 cases of ARDS, found that the APACHE III was the most accurate with regard to prediction of mortality (35), followed by the APACHE II, in contrast the SAPS II and SOFA scores did not achieve a significant correlation (35). Another study in Romania, found insignificant correlates with both the APACHE II and SOFA scores whereas the SAPS II correlates were significant (36). This study focused on patients admitted with septic shock and no mention was made of other organ dysfunction or co-morbidities (36). A larger retrospective study reviewed the records of roughly 700 trauma patients and found that both the APACHE II and SOFA scores were fairly similar with regard to prognostication, but found the SOFA scoring system to be preferable because of its ease of use (37).

These mixed results with regard to the ability of ICU scoring tools to predicting mortality is hoped to be addressed in this study, with particular reference to HIV and TB co-infection. The assumption is that variables such as CD 4 count and ARV use will have a significant influence on mortality. It is hoped that this study will further validate the use of the APACHE II score in HIV/TB co-infected patients admitted to ICU, similarly to previous South African studies (4, 5, 7, 8). This score will also be compared to the SOFA score to establish which is more appropriate in a high HIV/TB burdened country (1, 2). Furthermore new information will also be reviewed, specific to HIV/TB infection and ARV treatment in ICU and its effect on patient mortality.

CHAPTER 2

2.1 METHOD

2.1.1 Study Population

A retrospective, descriptive study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Intensive Care Unit (ICU) assessing cases during the time period January 2014 to December 2015. The study was approved by both the University of the Witwatersrand Human Research Ethics Committee and the CEO of Charlotte Maxeke Johannesburg Academic Hospital (Clearance certificate number: M170372) to allow for patient data retrieval.

All patients included in the study were admitted to the CMJAH ICU during this time period, with a diagnosis of HIV and TB infection. The diagnoses of both the HIV and TB were made prior to admission to ICU or while in ICU. Patients with confirmed extra-pulmonary and pulmonary TB or both were included in this study population, as well as those with probable TB that had been initiated on empiric TB treatment. Patients with confirmed TB were defined as having a positive TB culture or positive acid fast bacilli or GeneXpert on sputum, lymph node or other sterile site. Patients with probable TB were defined as per the WHO Global TB program (38) where it is described as the empiric use of TB treatment in patients with serious illness and high clinical and/ or radiological suspicion of TB infection and/ or perceived high risk of TB without bacterial confirmation (38).

2.1.2 Data Collection

Patients for inclusion, with HIV and pulmonary or extra pulmonary tuberculosis admitted to the CMJAH ICU from January 2014 - December 2015, were identified from ICU admission and computer records in the ward and computer files. Patient files were then located and an audit of the required information was done. This included:

- Basic demographic profile of patients
- Duration of ICU stay
- CD 4 count
- ARV treatment status
- Patient outcome - Patient outcome was noted as specifically whether the patient died in ICU, whether the patient was discharged to the ward and died there or whether the patient was discharged from the hospital and had not died 30 days post initial admission according to hospital records
- APACHE II Score for each patient was calculated and documented
- SOFA score for each patient was calculated and documented.

Data was obtained from the discharge summary computer files, patient hospital notes and further hospital records to ensure that all calculated scores and patient details were correct.

2.1.3 Data Analysis

The data obtained for each patient, as described above, was used to calculate the patients' APACHE II and SOFA scores and for this the predicted mortality. This was compared to the actual mortality (discharged / death in ICU / death within 30 days of admission). It was documented as to whether patients were on ARV treatment at admission, whether ARVs were initiated in ICU and an assessment was made as to whether this affected mortality.

Data was analysed using STATA 12.0. Continuous variables were expressed as averages with 95% confidence levels and were compared using the unpaired t-test. Categorical variables were expressed as a proportion and were compared using the Chi-square test. The survival of patients was assessed using Kaplan Meier survival curves, and a univariate analysis was performed to identify risk factors for mortality. A comparison was made between the calculated APACHE II predicted mortality with true patient outcomes and similarly with the calculated SOFA score predicted mortality to infer which was the better tool in this specific patient cohort. A two-sided p value < 0.05 was considered statistically significant for all analysis. An independent statistician was employed to calculate the necessary statistical evaluation.

CHAPTER 3

3.1 RESULTS

3.1.1 Patient characteristics

During the time period of January 2014 to December 2015, a total of 75 patients were admitted to the CMJAH ICU with HIV and TB co-infection. This represents 2.43% of the total of 3081 patients admitted to ICU over this time. In this specific cohort of patients, most required immediate or urgent organ support (ventilatory, inotropic or both) while 16 were admitted post operatively for observation or to wean off ventilation, as an elective admission.

Of the 75 patients admitted with TB, 42% (32 cases) had extrapulmonary disease - which included 7 cases of TB Meningitis (diagnosed on lumbar puncture and radiological evidence); 8 cases of disseminated TB confirmed on abdominal fluid or histology; 4 cases of empiric TB treatment with radiological evidence of TB abdomen (ultrasound evidence of enlarged abdominal lymph nodes and splenic microabscesses were described); 4 with TB positive pleural effusions; 2 cases given empiric TB treatment for non-resolving empyemas; 3 cases of disseminated TB based on lymph node histology; 3 cases of TB Spine based on histology and lastly 1 case of miliary TB based on a positive blood culture and radiological findings. A total of 43 patients had pulmonary TB, 20 of whom were started on empiric TB therapy based on radiological and clinical evidence while 22 were based on sputum GeneXpert (1 patient was noted to be Sputum positive for acid fast bacilli as a Gene Xpert study was not possible as he had haemoptysis.

Thirty seven (49,3 %) of the patients were females and the average age was 37 years (range 23 to 59 years). The included patients stayed an average of 7.5 days (range 1 to

		Frequency	Percentage (%)
Gender	Female	37	49,3%
	Male	38	50,7%
ARV therapy	No	35	46,7%
	Yes	40	53,3%
Outcome in ICU	Discharged	52	69,3%
	Death (in ICU)	23	30,7%
Reason of ICU admission	Post operative	16	21,3%
	Urgent admission	59	78,7%
Type of TB	Pulmonary	43	57,3%
	Extrapulmonary	32	42,7%

Table 3.1: Clinical Characteristics of HIV/TB Co-infected Patients

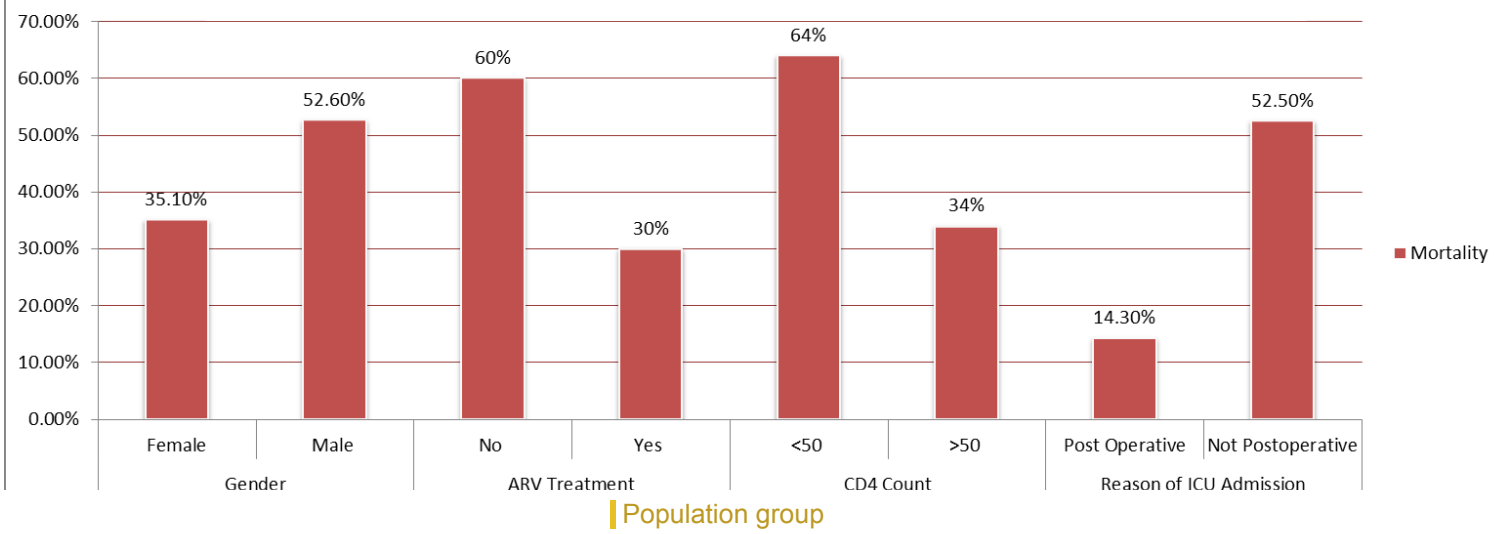
51 days) while in ICU.

3.1.2 Patient Mortality

Post admission to the ICU, more than two thirds (69,3% or 52 patients) were discharged to the ward while 23 (30.7%) died during their ICU stay. Post discharge to the ward, a further 10 patients died in the 30 days subsequent to admission to the ward such that the 30 day mortality was 44%. Furthermore it was established that all of the deaths were related to TB related deaths whether during the ICU stay or post discharge to the ward. Septic shock related deaths accounted for 52% of ICU deaths and 42% of total 30 day mortality and respiratory failure 30% of ICU deaths and 42% of 30 day mortality).

A higher mortality rate was noted amongst males as opposed to females however this could also be attributed to more female patients being on ARV therapy at the time of

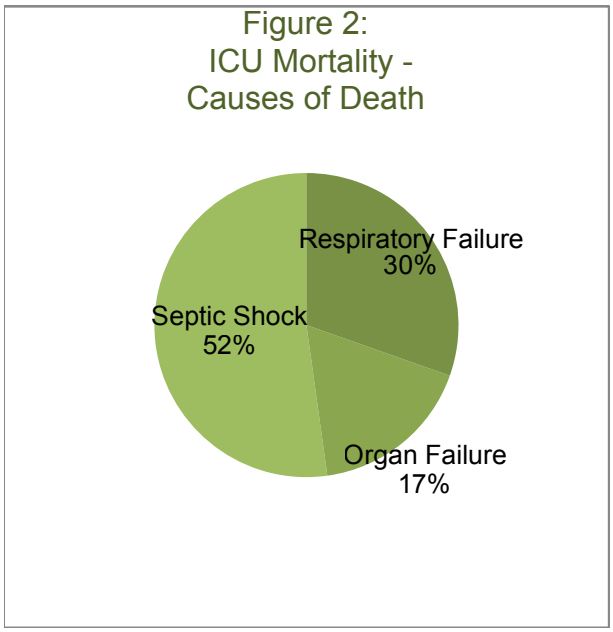
Figure 1: Mortality rates amongst different population groups

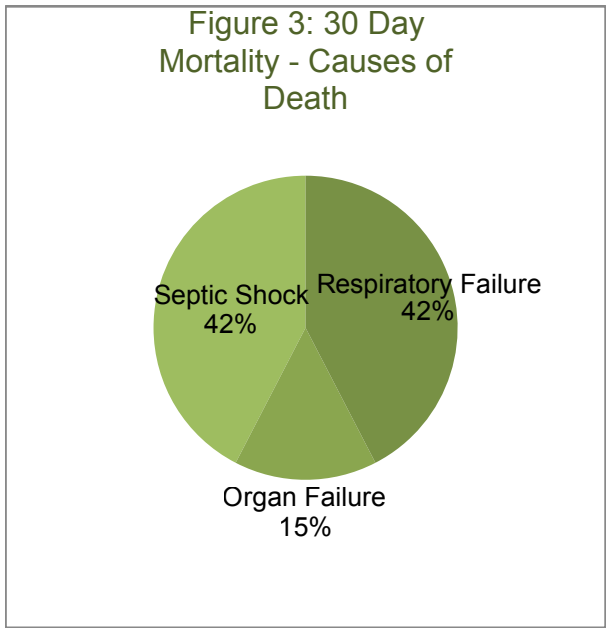


		Frequency	Percentage
ICU Outcome	Discharged	52	69.3
	Death(Mortality)	23	30.7
30 Day Mortality	Discharged	42	56.0
	Death(Mortality)	33	44.0
CAUSE OF DEATH (Death in ICU)	Organ Failure	4	17.4
	Respiratory Failure	7	30.4
	Septic Shock	12	52.2
CAUSE OF DEATH (30 Day Mortality)	Respiratory Failure	14	42.4
	Septic Shock	14	42.4
	Organ Failure	5	15.2

Table 3.2: Mortality characteristics of HIV/TB Co-infected Patients admitted to ICU

admission (only 14 females were not on ARVs compared to 21 males). As would be expected, patients who were electively admitted post operatively had a better outcome then those requiring urgent ICU admission for organ support.





3.1.3 Effect of Antiretroviral use and CD 4 count

More than half the included patients (40 out of 75) were on ARV therapy on admission to ICU (53,3%), and as expected, in general had higher CD 4 counts with a mean of 257,35

	Patients on ARVs	Patients Not on ARVs	p - Value
Age (mean)	37	37,7	0,738
CD 4 Count (mean)	257,4	84,9	0,000
APACHE II Score (mean)	22	27	0,011
SOFA Score (mean)	8	10,6	0,013

Table 3.3: T-test analysis of patient characteristics based on ARV treatment

cells/mm^3

(95% CI 159 cells/mm^3 - 345 cells/mm^3) compared to those not on ARV therapy, who had a CD 4 count of 84,88 cells/mm^3 (95% CI 41 cells/mm^3 - 129 cells/mm^3). Only 2 patients were started on ARV therapy during their ICU stay, both of whom were not on ARVs on admission. Of statistical significance was that patients on ARV therapy had lower SOFA scores, with a mean of 8 (95% CI 4,2 - 12,3) vs. 10,6 (95% CI 9,2 - 13) in those not on ARV therapy. Similarly the APACHE II scores in patients on ARV therapy were lower than those off ARV therapy, with a mean of 22 (95% CI 14,8 - 29,4) vs. a mean of 27 (95% CI 21 - 31,2). Of the 75 patients included, 18 had been on TB treatment > one month at the time of their admission to ICU and of these, only 3 were not on ARV therapy. One of the

Figure 4: Kaplan-Meier survival estimates

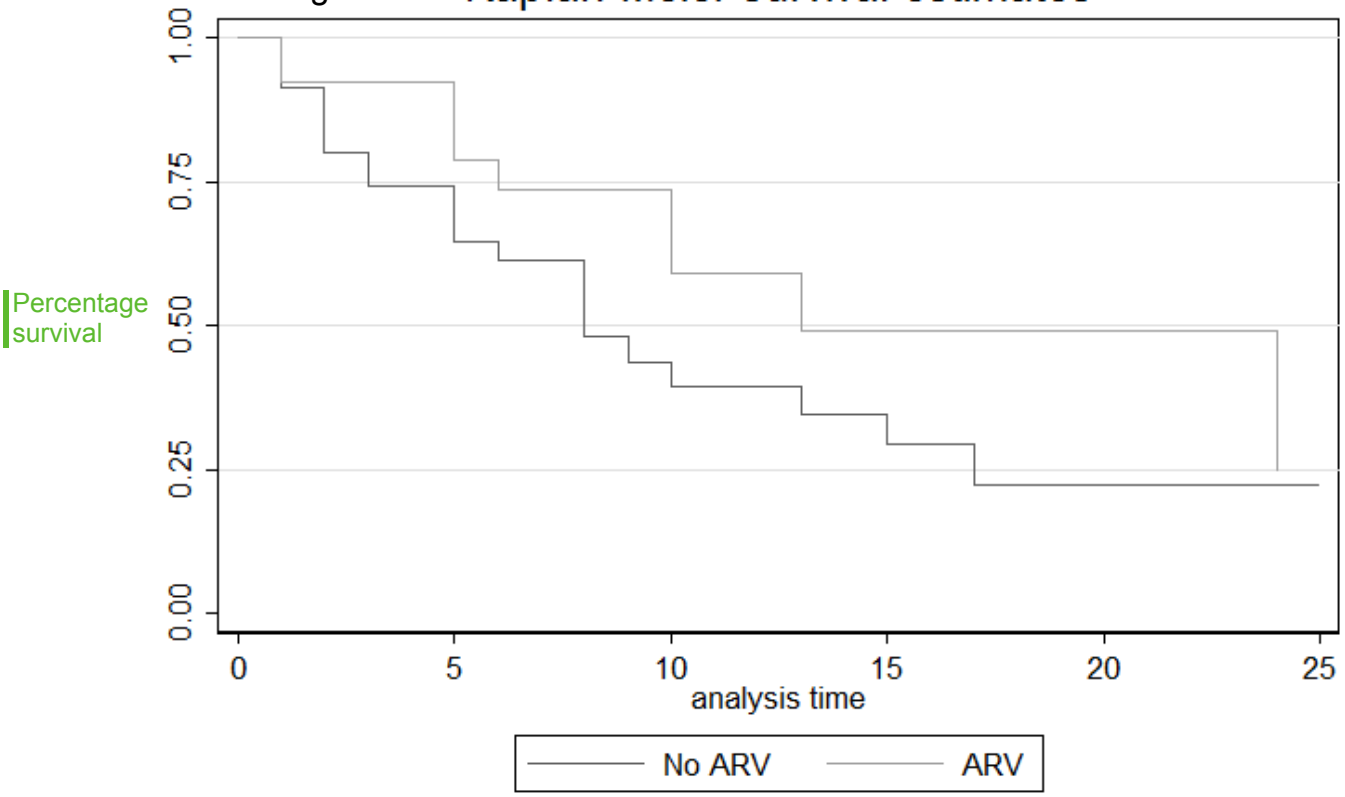
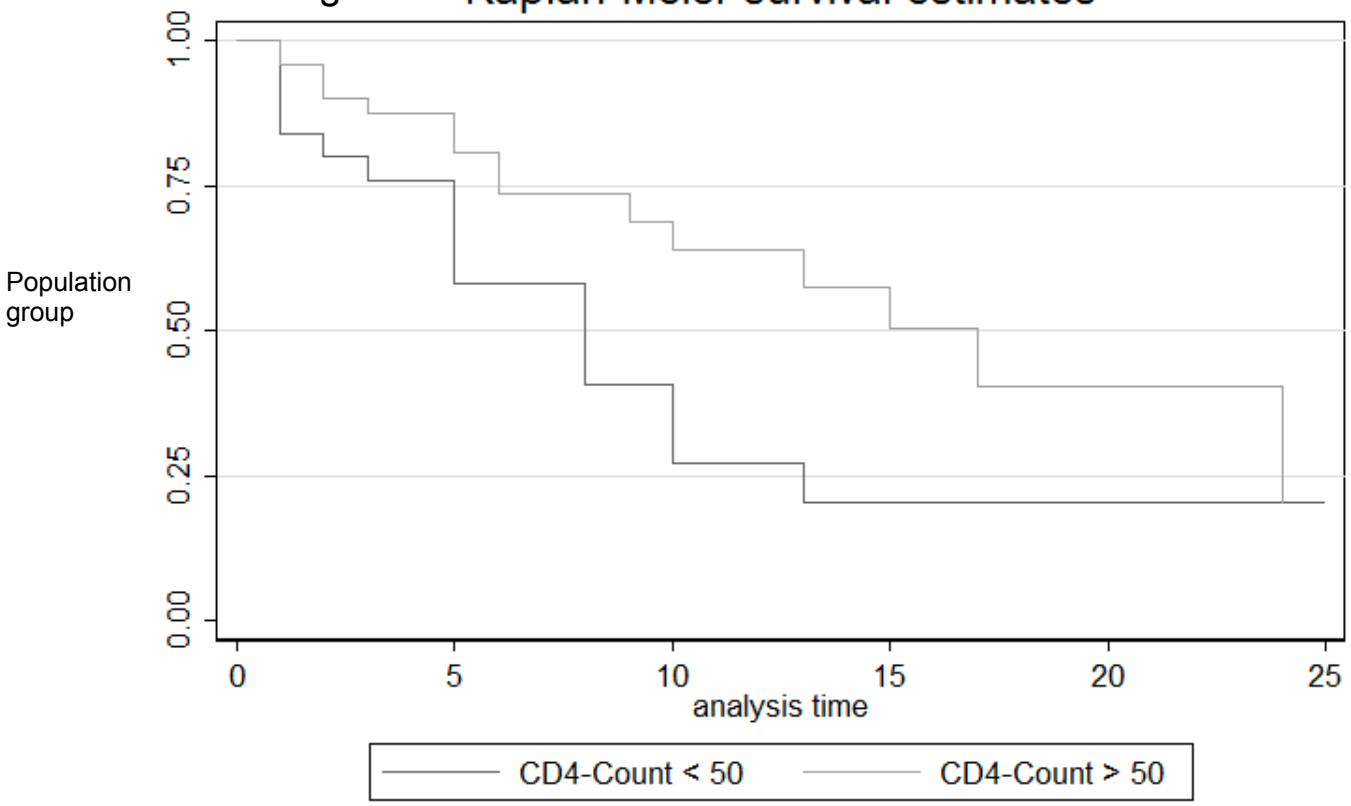


Figure 5: Kaplan-Meier survival estimates



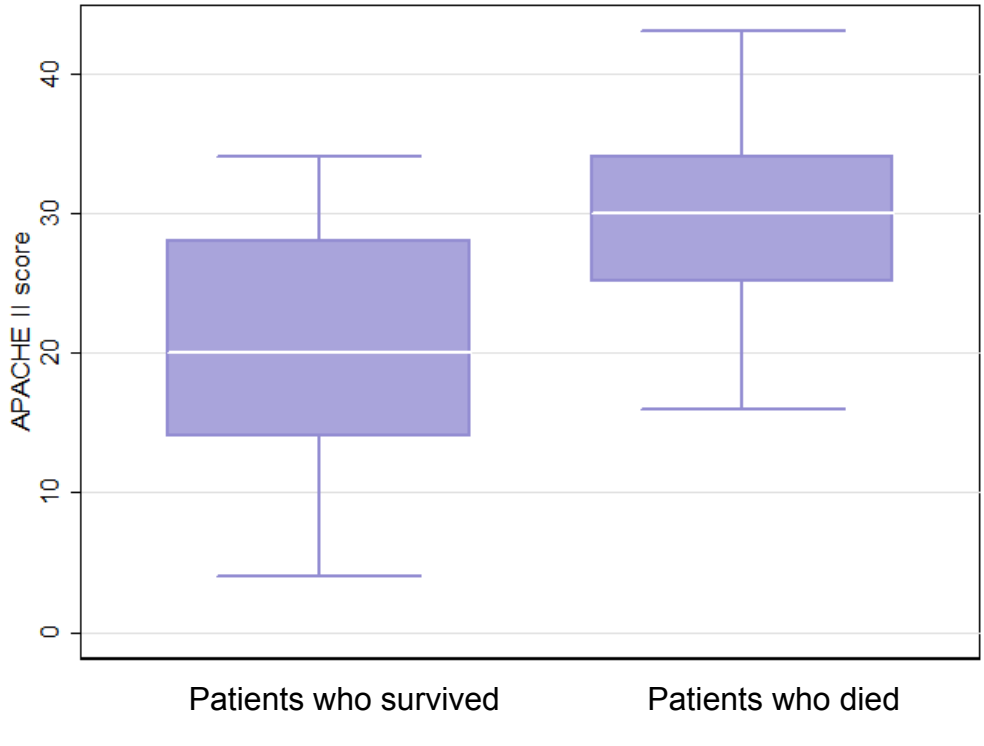
three patients had had treatment stopped previously due to the development of a drug induced liver injury.

It was further established that patients on ARV therapy, as well as those with a CD 4 count of more than 50 were significantly more likely to survive then their counterparts. A survival analysis using Kaplan Meier survival estimates established that at any point, ARV treatment was associated with higher survival. Similarly survival analysis showed that patients with CD 4 counts greater than 50 cells/mm^3 were also associated with a higher survival rate at any point of the analysis.

As mentioned previously, of the 35 patients included who were not on ARV therapy on admission to ICU, only 2 were initiated on ARV therapy during their ICU stay. The first was in ICU for 9 days, and had disseminated TB diagnosed on pleural fluid. The patient had a CD 4 count of 10 and had previously been on ARV therapy, but defaulted prior to her

admission. She was initiated on a “renal friendly” ARV regimen as she was found to have multi-organ failure on admission (requiring dialysis, ventilation and inotropes). The patient improved on treatment, was discharged to the ward and was noted to have survived further. The second patient however, was a 51 year old female, with a CD 4 count of 32 who had a prolonged ICU stay of 26 days due to post-operative complications. She had required a bowel resection secondary to small bowel ischaemia and also required ventilatory and inotropic support through her stay. The patient had been started on TB treatment empirically as she had features of TB on Chest Xray as well as evidence of TB abdomen intra-operatively. This patient had been initiated on first line ARV therapy as she had no evidence of liver or renal dysfunction initially, however near the end of her stay she complicated further, developed liver failure, and demised.

Figure 7: Box and whisker chart showing



3.1.4 APACHE II Score Assessment

The APACHE II Predicted Mortality was within the 95% Confidence Intervals for all groups. There was however a significant underestimation of percentage predicted mortality in patients who were not taking ARV treatment (52,5%, 95% CI 45% - 59,8% vs actual mortality 60%, 95% CI 42.9%- 75%); those with a CD 4 count < 50 (51%, 95% CI 44,5% - 57,4% vs actual mortality 64%, 95% CI 43.5% - 80.4%) and to a lesser extent in male patients (49,9%, 95% CI 41,6% - 58,1% vs actual mortality 52.6%, 95% CI 36.7% - 68.1%). It is important to note that in all these cohorts of patients there was a worse survival rate. This underestimate of percentage prediction occurred despite a significantly higher predicted mortality when compared to patients with a CD 4 count of more than 50 (42,2%, 95% CI 34% - 50,4% vs actual mortality 34%, 95% CI 22.06% - 48.39%) or those on ARV treatment (38,7%, 95% CI 30,1% - 47,3% vs actual mortality 30%, 95% CI 17.7% - 46.1%).

The highest APACHE II Score achieved in the patient population was 43, which correlated with an 85% mortality risk. A total of 36 patients had a > 50% predicted mortality (calculated using the APACHE II Score, co-morbidities and need for emergency surgery), from which 24 (67%) patients died when reviewing their 30 day mortality.

Figure 6: Mean Apache II Score predicted percentage mortality vs actual mortality

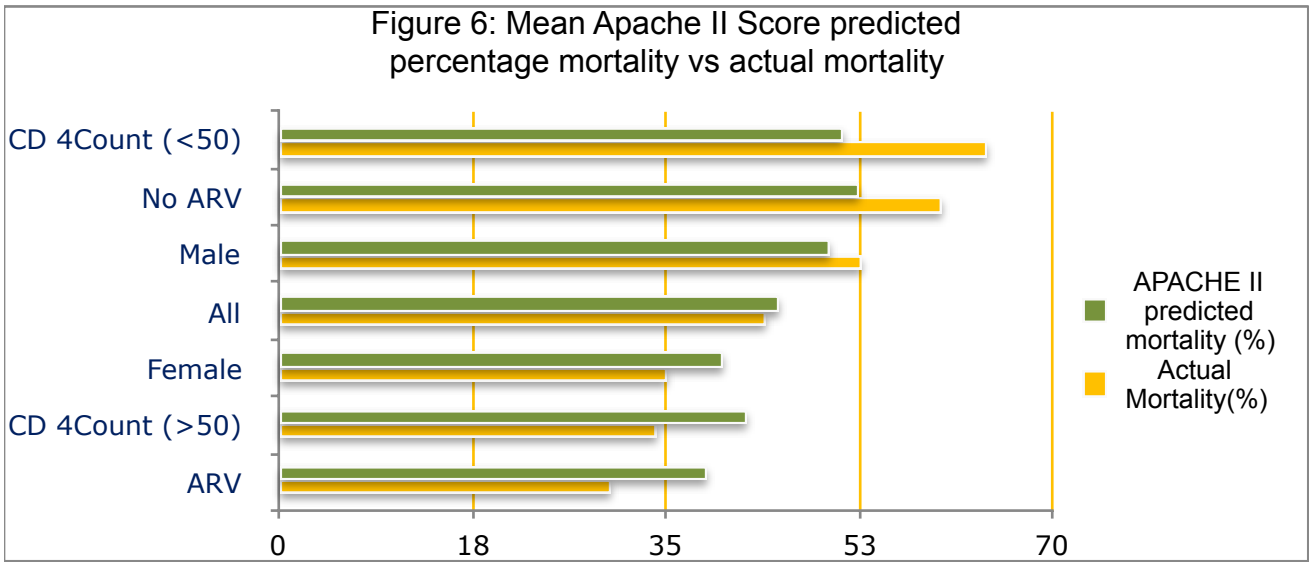
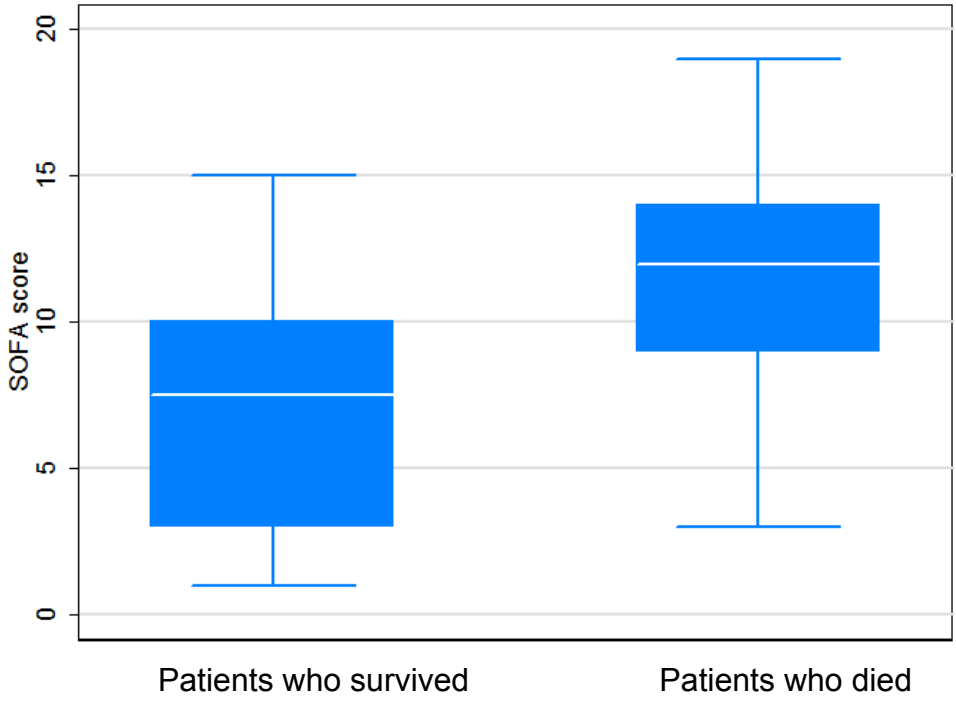
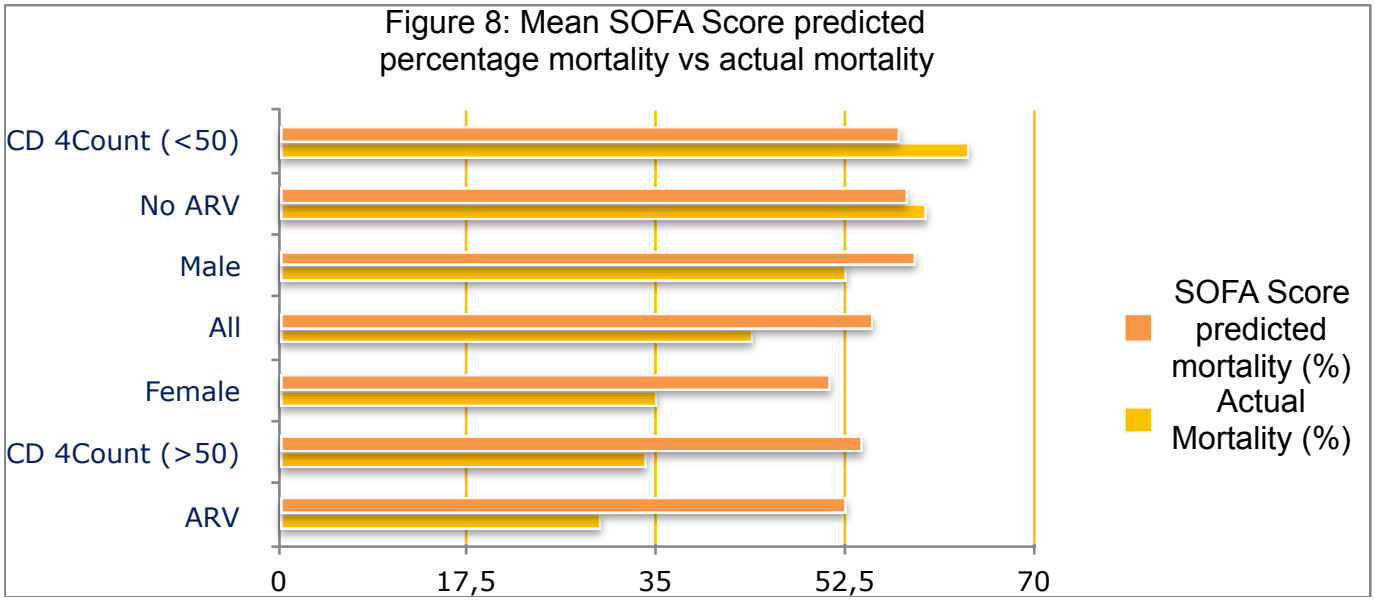


Figure 9: Box and whisker chart showing



Furthermore, 39 patients had a predicted mortality < 50% whereas 31(79%) survived beyond 30 days post initial admission. The sensitivity of the score for prediction of mortality in this setting was 75% (95% CI 56% - 88%)e whereas the specificity 76,5% (95% CI 62.51% to 87.21%). The negative predictive value (NPV) was 83% (95% CI 72.4% to 90.1%) and the positive predictive value (PPV) 66% (95% CI 53.98% to 77.33%). A wider distribution of data was noted in the subgroup of patients who survived however

Figure 8: Mean SOFA Score predicted percentage mortality vs actual mortality



then in those who ultimately died.

3.1.5 SOFA Score Assessment

When doing the mortality analysis it was found that the predicted mortality of the SOFA Score was outside the upper level of the 95% confidence interval for those patients taking ARV treatment (52%, 95% CI 43,1% - 59,5% vs actual mortality 30%, 95% CI 17,7% - 46,1%); those with a CD 4 count of more than 50 (53,5% 95% CI 45,4% - 60,6% vs actual mortality 34%, 95% CI 22,1% - 48,4%) and female patients (51,2%, 95% CI 41,6% - 58,1% vs actual mortality 35,1%, 95% CI 21,4% - 50,4%). These were all groups of patients with a generally higher survival rate. In these cases, the mortality predictions achieved by the calculated SOFA scores were greater than the actual mean percentage mortality.

The highest SOFA Score achieved in the patient population was 19, which correlated with a 95% mortality risk. The highest possible SOFA score is 24 however in general scores > 12 correlate with a 95% mortality risk (12). A total of 24 patients had a 95% predicted mortality, with a 30 day mortality of 75% (18 patients).

	APACHE II Score	SOFA Score
Sensitivity	75% (95% CI 56% - 88%)	75% (95% CI 56.6% to 88.5%)
Specificity	76,5% (95% CI 62.51% to 87.21%)	76,2% (95% CI 60.6% to 88%)
Positive Predictive Value	66% (95% CI 53.98% to 77.33%)	70, 6% (95% CI 57.4% to 81%)
Negative Predictive Value	83% (95% CI 72.4% to 90.1%)	80% (95% CI 68.2% to 88.2%)

Table 3.4: APACHE II and SOFA scores statistical parameters

Thirty-four patients had a 50% or more predicted mortality of whom 24 (70%) died. Using

this as a parameter of comparison, sensitivity was calculated at 75% (95% CI 56.6% to 88.5%) with a specificity of 76,2% (95% CI 60.6% to 88%). As with the APACHE II the NPV at 80% (95% CI 68.2% to 88.2%) was greater than the PPV, 70, 6% (95% CI 57.4% to 81%). If patients with a 95% predicted mortality were assessed separately, the PPV was 75% (95% CI 57.3% to 87%) and the specificity 85,7% (71.46% to 94.57%). Interestingly there was a wider distribution of data noted in those that died than those that survived.

3.1.6 Comparison of SOFA and APACHE scores

Both the APACHE II and SOFA scores showed statistically significant differences between survivors and non-survivors at 30 days; (APACHE II Score: 20.43 vs 29.48 p-value = 0,0000 and the SOFA Score: 7.12 vs 11.87 p-value = 0,0000).

While both scores had a statistically significant prediction of patient survival, there was a marked over-estimation of mortality using the SOFA score in patients taking ARV treatment, those with CD 4 counts > 50 cells/mm^3 and female patients. In these three specific cohorts, an improved survival was noted which was not adequately assessed by the corresponding SOFA scores. Although the APACHE II Score showed a similar over-estimation, its prediction remained within the 95% confidence intervals of actual mortality, making it more accurate in its prediction of mortality for these specific cohorts.

Comparing the statistical variants of both the APACHE II and SOFA scores in their prediction of mortality - both scoring systems had almost the same sensitivity and specificity. While the SOFA score had a slightly elevated PPV, the APACHE II Score had a better NPV.

CHAPTER 4

4. DISCUSSION

4.1.1 Patient mortality

TB and HIV co-infection although very prevalent in the South African Health system (1), remains a small percentage of total ICU admissions. A prevalence of 2.43% of TB and HIV co-infected patients is documented in CMJAH ICU in the two years studied. While the total number of HIV/TB co-infected cases admitted to CMJAH during the period of 2014 and 2015 was not documented in this study, previous studies have documented that roughly 1.5% of active TB cases admitted to academic hospitals require intensive care and ventilatory support (4, 5). The small percentage of patients admitted to ICU may be attributed to the scarcity of ICU beds and the perception that such patients, particularly those in poor physical condition have an extremely high mortality rate, however, this was not assessed in this study. Similar results have been seen in previous studies, where a high mortality rate is documented ranging from 40 - 80% (4 - 8). This study documented an overall 30 day mortality of 44%, which is similar to many other current South African based studies reviewed in the literature (4, 5). The lower ICU mortality of 30.7% in our study is possibly related to early discharge of patients where treatment is considered to be futile but who warrant further palliation as well as those that sufficiently recovered to be discharged but who complicated in the ward thereafter.

Importantly in this study, all mortality was related to TB, specifically septic shock (52% of ICU deaths and 42% of 30 day mortality) or respiratory failure (30% of ICU deaths and 42% of 30 day mortality). The strongest correlates with mortality were not being on ARV therapy, a CD 4 count < 50 and male sex. More female patients were on ARV therapy at the time of admission as opposed to males, which is a possible explanation for the effect

of gender on outcome. Similarly, patients who were admitted electively for post-operative care fared better than those requiring urgent ICU admission for organ support secondary to TB infection. As with previous South African studies mortality was associated with poor immune status (4, 5, 8, 18 - 20) in ARV naïve patients. The improved mortality in patients that were admitted on ARV therapy is also similar to numerous other studies in the literature which demonstrate the benefits of prior initiation of therapy in HIV positive patients admitted to ICU (17, 25, 27, 28, 30).

In most other studies that were reviewed, a CD 4 count of < 200 was identified as a risk factor for patient mortality (4, 5, 8, 18 - 20). In this study, a CD 4 count of < 50 was highlighted specifically as research has shown co-morbid HIV/TB patients with very low CD 4 counts, have an increased mortality if antiretroviral treatment is not started within two weeks of TB treatment initiation (20). Congruent with this, the study survival analysis demonstrated that patients on ARV therapy and similarly those with a CD 4 count of > 50 were more likely to survive.

These results while similar to most centres with a high TB/HIV prevalence - are quite different from literature describing the situation outside of South Africa, where a few studies found that HIV infection was not a direct risk factor for mortality (6, 9, 16). This is contrary to the many studies in South Africa which have demonstrated the negative effects of HIV infection, specifically in those with severe immunosuppression requiring ICU admission for sepsis and septic shock (4, 5, 8, 17 - 20), the major cause of death in this study.

4.1.2 ARV therapy initiation

An important aim of the study was to review those cases in which ARV therapy was initiated in ICU. This however only occurred in 2 of the 35 patients who were not on ARVs at the time of admission. Both of these patients had a CD 4 count < 50 and while one improved and survived post discharge on 'renal friendly' ARV therapy, it is important to note that this patient had very recently defaulted therapy and had been in ICU for roughly a week prior to re-initiation. The second case had a prolonged ICU stay and developed multiple post-operative complications as well as requiring TB therapy based on an empirical diagnosis. Her demise was reported to be related to liver failure and most likely a drug induced liver injury. The infrequent initiation of ARV therapy in this cohort makes comment on its benefit or otherwise in this study difficult. Although the literature seems to agree that early ARV initiation is beneficial in reducing mortality (25 - 27), there is minimal data with regard to HIV and TB co-infection as the risks of drug interactions and toxicity are high in this cohort (26). Other difficulties highlighted in the literature with regard to ARV initiation include the unavailability of intravenous ARV formulations, decreased drug availability secondary to poor absorption as well as altered pharmacokinetics (17, 25, 27).

These difficulties, as well as the risk of a possible immune reconstitution syndrome are all possible reasons why ARV therapy was not initiated in the other 33 ARV naive patients. However future prospective studies are necessary to assess if the benefits accrued from early initiation of ARV therapy with other opportunistic infections in the ICU setting (25 - 27) also apply to TB. This is particularly so as whether or not ARV therapy is initiated remains individualised and subjective (17, 27, 30).

4.1.3 SOFA and APACHE II scores

This study demonstrated that both the SOFA and APACHE II scores showed statistically significant differences between survivors and non-survivors with regard to 30 day mortality (APACHE II Score: 20.43 vs 29.48 p-value = 0,0000; SOFA Score: 7.12 vs 11.87 p-value = 0,0000), validating the use of both scoring systems. This is congruent with many studies which have previously validated the APACHE II scoring system in similar settings (4 - 6, 8). Unlike the APACHE II Score, the SOFA score has not previously been validated in many South African trials, especially in the specific population of ICU patients with HIV/TB co-infection. In the few international trials where TB mortality was assessed with regard to the APACHE II and SOFA scores, both scores were statistically significant in one (34) and only the SOFA score was significant in the other (13). These were however small trials with few cases of HIV co-infection.

Similarly to other studies mentioned previously (4 - 6, 8), this study also demonstrated that the APACHE II and the SOFA scores underestimated the mortality in those that were not taking ARV therapy, those with CD 4 counts < 50 cells/mm^3 and in males patients identified as having a much lower chance of survivals. This is probably because the SOFA, like the APACHE II (4 - 6, 8), fails to account for the degree of immunosuppression and the blunted physiological responses as manifest in patients with very low CD 4 counts. In spite of this, the prediction of mortality with both scores remained within the 95% confidence intervals.

Interestingly both the scoring systems were also found to have overestimated the mortality of patients taking ARV treatment, those with CD 4 counts > 50 cells/mm^3 and in females. The overestimate with the SOFA was greater than the upper limit of the 95% confidence

interval whereas that of the APACHE II remained within the 95% confidence intervals of the actual mortality, making it the more accurate score in these specific cohorts.

These results differ from other studies in the literature where the APACHE II and SOFA were poor predictors of mortality in patients with septic shock and ARDS not necessarily due to TB (35,36). In this study, looking specifically at HIV/TB comorbidity, while both underestimate mortality in those with the worst survival and overestimate mortality in those with better outcome, the comparisons between survivors and non-survivors were still statistically significant. Similar to a large multicentre retrospective study reviewing trauma cases (37), this study noted that both the APACHE II and SOFA were similar in their prediction of mortality in that both had almost the same sensitivity and specificity.

4.1.4 Study Limitations

There are many limitations to this study. The first, relates to a profound selection bias as a single site was used during a set time period with no randomisation as all patients with the inclusion criteria were all included. This selection bias was further exacerbated by the resource-poor setting where typically patients with better predicted survival are given preference with regard to access to ICU beds.

A further limitation was the difficulty in assessing the potential benefits of ARV initiation in the ICU setting as only 2 cases were encountered during the study period. Furthermore, as a retrospective study, the calculated APACHE II and SOFA scores were based on documented readings from records which relies on previous record keeping as opposed to the greater reliability of real time data collection.

4.2. Conclusion

In conclusion, this study found that patients with HIV and pulmonary or extra pulmonary TB co-infection admitted to the CMJAH ICU during the study period had a high mortality. The APACHE II and SOFA scoring systems were both statistically significant in the prediction of mortality in the study population. Unlike the APACHE II, the SOFA score has not previously been validated in this specific population especially within a South African setting where both diseases are so frequent. Both scores overestimated mortality in subgroups with improved survival although the APACHE II prediction remained within the 95% confidence intervals of actual mortality, while the prediction by SOFA exceeded the upper limit. In other words, in the specific cohorts on ARV therapy, with CD 4 counts > 50 cells/mm^3 and in females, the APACHE II was more accurate. It also confirmed that this same cohort had a statistically significant improved mortality compared to those with CD 4 counts < 50 cells/mm^3 or not on ARV therapy. No conclusion can be made as to whether ARV therapy initiated during ICU stay is of benefit and further studies are warranted.

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APPENDIX 1:

R14/49 Dr Avani Singh

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170372

NAME: (Principal Investigator)	Dr Avani Singh
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Clinical Audit of Selected Predictors of Mortality of Patients Admitted to Charlotte Maxeke Johannesburg Academic Hospital Human Immunodeficiency Virus and Tuberculosis co-infection
DATE CONSIDERED:	31/03/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof GA Richards
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/04/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised 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 resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES