ACUTE PANCREATITIS IN A HIGH HIV PREVALENCE ENVIRONMENT: ANALYSIS OF PREVALENCE, DEMOGRAPHICS, PROGNOSTICATORS AND OUTCOMES

BY

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Signature_____Date 15th August 2019 _____

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DECLARATION

I, Mr Frank Anderson, declare as follows:

1. That the work described in this thesis has not been submitted to UKZN or other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party

2. That my contribution to the project was as follows:

    - Recruitment of patients for the project, stipulating the biochemical and imaging investigations for the recruited patients, collating and entering data into a proforma and password protected excel worksheet, basic statistical analysis and drafting of the manuscript, it's figures and tables.

3. Tanya Esterhuizen was involved in the pre-study statistical planning to determine the numbers required for the study and Cathy Connolly was involved in advanced statistical analysis

Signed_____Date 15th August 2019_____

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DEDICATION

My family and Brother Moses

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Cathy Conolly who was concise and accurate in analysing the data. I seldom required additional explanations.

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ACRONYMS

1. ADP: Adenine Dinucleotide Phosphatase
2. AIDS: Acquired Imune Deficiency Syndrome
3. AIS: Abbreviated Injury Scale
4. ALT: Alanine AminoTransferase
5. AST : Aspartate Transaminase
6. APACHE II: Acute Physiology And Chronic Health Evaluation 2nd edition
7. AUC: Area Under the Curve
8. BALI: Blood urea nitrogen, Age, Lactate dehydrogenase and Interleukin 6
9. BISAP: Bedside Index of Severity in Acute Pancreatitis
10. BMI: Body Mass Index
11. CASR: calcium-sensing receptor
12. CBD: Common Bile Duct
13. CCR5: Chemokine Receptor Antagonists
14. CTRC: Chymotrypsinogen C
15. CRP: C - reactive protein
16. CTSI: CT Scan Severity Index
17. CFTR: Cystic fibrosis transmembrane conductance regulator
18. EUS: Endoscopic UltraSound
19. EPIC: Extra-Pancreatic Inflammation on Computed tomography
20. ERCP: Endoscopic Retrograde CholangioPancreatography
21. ESR: Erythrocyte Sedimentation Rate
22. FRAM: Fat Redistribution and Metabolic Change in HIV infection
23. HAART: Highly Active Antiretroviral Therapy
24. HIV: Human Immunodeficiency Virus
25. HIV-ve: HIV seronegative
26. HIV+ve: HIV seropositive
27. IL: Interleukin
28. 3TC: Lamivudine
29. MODS: Multiple Organ Dysfunction Syndrome
30. MRC: Magnetic Resonance Cholangiography
31. NISS: New Injury Severity Scale
32. NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors
33. NPV: Negative Predictive Value
34. NRTIs: Nucleoside Reverse Transcriptase Inhibitors

35. PAF: Platelet Activating Factor
36. PI:Protease Inhibitors
37. PCP: Pneumocystis Carinii Pneumonia
38. PCT: ProCalciTonin
39. PPV: Positive Predictive Value
40. PROPATRIA: Probiotics in Pancreaitis Trial
41. PRSS2: Anionic Trypsinogen
42. PRSS1: Cationic Trypsinogen
43. ROC: Receiver Operating characteristic Curve
44. RRG: Renal Rim Grade
45. SAPS: Simplified Acute Physiology Score
46. SOFA: Sequential Organ Failure Assessment
47. SIRS: Systemic Inflammatory Response Syndrome
48. SPINK1: Serine Protease Inhibitor Kazal 1
49. SOD: Sphincter of Oddi
50. TAP: Trypsinogen Activating Peptide
51. TDF: Tenofovir
52. TNF:Tumour Necrosis Factor
53. VARD: Video Assisted Retroperitoneal Debridement

Abstract

Background

It is unclear what is the true prevalence of HIV related acute pancreatitis and whether diagnostic and prognostic markers used in patients without HIV infection are as effective in HIV related pancreatitis and if morbidity is worse in HIV infected patients.

Methods

Using a prospective, descriptive design, HIV prevalence was compared in trauma and acute pancreatitis patients. Serum amylase was used to diagnose acute pancreatitis. Prognostication was by CRP, BISAP, Glasgow and APACHE II scores at 24 hours. Sensitivity, specificity and AUC were compared in predicting a severe outcome in acute pancreatitis. Complications and mortality were compared in 238 HIV+ve and HIV-ve patients admitted to 2 regional hospitals in Durban between August 2013 and October 2015. One hundred and eighty one patients were admitted with trauma.

Results

Between August 2013 and October 2015, 238 patients were admitted with acute pancreatitis and 181 with trauma. HIV infection was higher in patients with acute pancreatitis (38% vs 16%) (p=0.001) and they were also older (40 vs 33 years) (p=0.001). Fifty three percent of HIV +ve patients were female and 65% of the HIV-ve patients were male in the pancreatitis cohort and 59% of the trauma and pancreatitis patients were on Highly Active Antiretroviral Therapy. The prevalence of gallstone (27% vs 30%), alcohol (41% vs 52%), dyslipidaemia (0% vs 3%) and idiopathic (6% vs 14%) aetiologies were similar in HIV+ve and HIV-ve patients and a drug related aetiology (24% vs 0%) ($p<0.001$) was more prevalent in HIV related acute pancreatitis.

CRP was more effective in predicting severe disease in HIV-ve patients (AUC= 0.75) and patients with CD4 counts of ≥ 200 cells/mm^3 (AUC=0.73) and not HIV+ve patients (AUC= 0.59) or patients with counts below 200 cells/mm^3 (AUC= 0.46). The BISAP system had similar efficacy with AUC of 0,71 and 0.74 in HIV-ve and HIV+ve patients respectively, was poor in CD4 count < 200 cells/mm^3 (AUC=0.68) and good in CD4 count> 200 cells/mm^3 (AUC=0.9). The Glasgow score was of similar efficacy in HIV-ve (AUC = 0.72) and HIV+ve patients (AUC=0.78) and better in patients with CD4 count < 200 cells/mm^3 (AUC=0.83) and CD4 count $\geq$ 200 cells/mm^3 (AUC=0.81). The

APACHE II had uniform efficacy in both HIV-ve and HIV+ve patients (AUC >0.8) and both CD4 count ranges (AUC > 0.80).

Septic complications occurred in 10(8%) of HIV-ve patients and 4(4%) HIV+ve patients. There was no difference in morbidity (25% vs 33%) and mortality (6% vs 6%).

Conclusions

HIV infections is more prevalent in acute pancreatitis than in a hospital trauma cohort which represented the general population. The APACHE II system was the most accurate in predicting morbidity and CRP least accurate. The outcomes were similar in HIV+ve and HIV-ve patients but the statistical assumptions in calculating the sample size, given the low frequency of morbidity and mortality observed in this study may have resulted in an alpha error.

CHAPTER 1: INTRODUCTION

1.1 Context

Individuals afflicted with acute pancreatitis present with features of an acute abdomen. The diagnosis is established by differentiating the condition from other causes of the acute abdomen based on a combination of typical clinical symptoms (epigastric pain, nausea and vomiting) and pancreatic enzyme elevation 3 times or more than the upper limit of normal. The disease runs a variable clinical course from a mild self-limiting disease in most instances to a severe disease with organ failure and mortality**.** Predicting severe disease with organ failure aids in determining the need for intensive care support. It also facilitates comparison of outcomes between different centres and patient selection to compare established or novel therapies or interventions. Predicting a severe outcome is preferably done at presentation to enable closer monitoring for the development of organ failiure. The disease has a number of aetiological associations that are detailed in **Table 1**. The majority are associated with alcohol and gallstones but there is wide geographical variation in the frequency of these aetiologies that is summarised in **Table 2** (2-19) that have implications for therapy. Reports that acute pancreatitis is associated with Human Immunodeficiency Virus (HIV) infection initially emanated from countries that had an HIV infection prevalence of under 1%. (1) The relationship between HIV and acute pancreatitis has not been fully elucidated but there are a number of factors to be considered.

1.1.1 Incidence of acute pancreatitis in HIV infection

The aetiologies include those specifically related to HIV infection such as drug therapy, opportunistic infections and malignancies as well as the known causes of acute pancreatitis. Prior to the introduction of Highly Active Antiretroviral Therapy (HAART), clinical pancreatitis was demonstrated in 12(23.5%) of 51 patients but asymptomatic elevations of amylase and lipase were identified in 10 additional patients.(20) In the same era 14(32%) of 44 patients had raised amylase levels but only 7(16%) had acute pancreatitis. (21) These levels are higher than the 0.004.- 0.045 percent of the general population who develop acute pancreatitis every year. (22)

In data from the period prior to 1996, 22% of patients with AIDS developed pancreatitis whilst in the next decade which corresponds to the introduction of HAART, a reduced incidence of 14% has been reported.(23) In 2008 when HAART was well established across the globe an assessment of an Italian cohort of 1081 HIV-infected patients revealed prolonged laboratory enzyme abnormalities with signs of organ involvement in 15% of patients. (24) These three reports suggest a temporal fall in the prevalence in HIV infection related acute pancreatitis that has now stabilised. This aetiological

association between HIV infection and acute pancreatitis is highly pertinent to South African clinical practice with its 19.2% prevalence of HIV in the 15-49 year old population group. (25)

In the setting of HIV infection the diagnosis of acute pancreatitis is complicated by several factors. Asymptomatic elevation of amylase and lipase in this population is common. (26, 27) This may be due to parotid disease, macroamylasemia or pancreatic disease. (27) There was no difference between patients with hyperamylasaemia and normoamylasaemia in terms of age, CD4 counts or medications. (27) Others have found hyperamylasemia more frequently in those with concomitant chronic hepatitis B or C infection, previous intravenous cotrimoxazole use, stage 2 HIV disease and intravenous drug use. (28) In a study of 1081 HIV infected individuals at least one episode of abnormal amylase levels was observed in 435(40.2%) individuals over a minimum follow-up of 12 months. (24) These patients had a longer duration of seropositivity, exposure to protease inhibitors, more frequently had Acquired Imune Deficiency Syndrome (AIDS), chronic liver or biliary disease and hypertriglyceridaemia. There was no relation between antiretroviral administration and the duration or type of nucleoside analogues, when compared with those with and without amylase elevations. In the same study prolonged amylase abnormalities developed in 166 (38.2%) patients and were related to the administration of antiretroviral medications, cotrimoxazole or antitubercular/antimycobacterial therapy, cytotoxic chemotherapy, illicit substance or alcohol abuse, opportunistic infections, chronic liver or biliary disease, a protease inhibitor-based HAART regimen and hypertriglyceridaemia. In 46 patients there were clinical signs or imaging evidence of pancreatitis and 120 were asymptomatic. (24)

In a HIV study by Murthy, prior to the HAART era, 21 of 39 patients with AIDS had hyperamylasemia (2/3 pancreatic amylase, 1/3 salivary amylase) but only 6 patients had pancreatitis. (27) Biliary tract disease, alcohol intake and opportunistic infections were similar in those with normal and elevated amylase. Non-Caucasian race, pentamidine use and infection with mycobacterium avium-intracellulare were shown to be significant independent predictors of hyperamylasemia.(27) Fatal outcomes were also similar in those with and without hyperamylasemia. The origin of hyperamylasaemia in this setting was not clarified. These abnormalities were not confined to serum amylase as Argiris found asymptomatic elevations of amylase and lipase in 52 of 86 HIV infected patients.(23) However, a minority 14% had elevations of greater than 2-fold the upper limit of normal. None of these patients had macroamylasemia and the majority were pancreatic in origin on isoenzyme testing. In this series elevated amylase and lipase were associated with symptomatic HIV infection, chronic hepatitis B or C infection, treatment with Pentamidine or intravenous Cotrimoxazole, Pneumocystis Carinii Pneumonia (PCP) infection and treatment with Zidovudine.

Dutta found that in a total of 321 patients with HIV disease, 45(14%) patients developed at least one episode of acute pancreatitis as defined by clinical and laboratory criteria during a period of one year.

They demonstrated a significant correlation between CD4 counts and serum amylase levels, and asymptomatic elevation of amylase levels were reported in symptomatic HIV and AIDS patients but not in asymptomatic HIV infection.(28) The origin of hyperamylasaemia in this setting was also not clarified.

Prior to HAART, histological assessment of the pancreas in post-mortem studies revealed that 10% of patients had significant pancreatic lesions caused by infection or tumours. (29) In a series of asymptomatic individuals the pancreas was infected by mycobacteriosis (22%), toxoplasmosis (13%), cytomegalovirus (9%) and pneumocystis carinii (9%) at post-mortem assessment. (30) Ultrasound and CT scan evaluation of the pancreas in HIV infected individuals also showed abnormalities in the pancreas which included local or diffuse enlargement, a dilated pancreatic duct, pseudocysts and abscesses. (31)

The advent of HAART in 1996 resulted in prolonged HIV-1 viral remission with a decline in HIV virus-related complications and death. The management of HIV infection is focused on the suppression of the viral load and prevention of opportunistic infections.

1.1.2 Prevalence of HIV infection in Acute Pancreatitis in South Africa

In South Africa we have observed an increase in the prevalence of HIV infection in patients presenting with acute pancreatitis from 5% in 2008 to 17% in 2017. (17, 19)

1.1.3 Aetiology of acute pancreatitis in HIV Infection

There have been attempts to set the causation criteria for drugs and infection in patients with pancreatitis but proving that HAART or other drugs for opportunistic infection prophylaxis are the cause of the pancreatitis remains difficult. This is pertinent since the rate of pancreatitis in HIV+ve patients was higher prior to the advent of HAART. Six classes of antiretroviral agents currently exist. The Nucleoside Reverse Transcriptase Inhibitors (NRTIs) were the first agents available for the treatment of HIV Infection and Emtricitabine, Lamivudine(3TC) and Tenofovir (TDF) are used in treatment regimens in South Africa. They were associated with pancreatitis as a result of impaired cellular respiration and tissue damage. The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) commonly utilized in South Africa are Efavirenz and Nevirapine. Neurological symptoms, rash and hepatotoxicity are the main side effects in this group. The Protease Inhibitors (PI), Integrase Inhibitors, Fusion inhibitors and Chemokine Receptor Antagonists (CCR5) groups are not commonly utilised in the public hospitals in the Durban region.

The criteria used to determine whether a drug is a likely cause of acute pancreatitis were described by Mallory and Kerr (32) and modified by Badalov.(33)(**Annexure Table 1**) When these criteria are

applied to medications commonly used in the treatment of HIV, the medications, and their assigned likelihood associated with acute pancreatitis are, in decreasing likelihood, Pentamidine(Ia), Didanosine(Ib), Lamivudine(Ib), Nelfinavir(Ib) and Ritonovir(IV). Similarly among the antimicrobials commonly used in patients with HIV infection, Sulfamethoxazole(Ia), Isoniazid(Ia), Trimethoprim-Sulfamethoxazole(Ib) and Rifampicin(IV) have been linked to acute pancreatitis. (33) These drugs are central to the management of these patients and there are no guidelines for altering drug regimens following an episode of acute pancreatitis where an alternate aetiology has been excluded. The management is individualized and takes into account the temporal relations between drug therapy and episodes of acute pancreatitis. Altering drug regimens may also compromise the primary goal of viral suppression. Opportunistic infections of the pancreas are common in post-mortem studies of these patients. A post-mortem pancreatic study in AIDS with normal antemortem ultrasound of the pancreas and normal serum amylase revealed mycobacteriosis (22%) and toxoplasmosis (13%) infection of the pancreas. There was no information on the diagnostic modalities appropriate for detecting these infections antemortem and therefore establishing them as a cause of acute pancreatitis is nigh impossible.(34,35) The evaluation of pancreatic infections is complicated by the relative inaccessibility of the pancreas and the risk of needling the pancreas that precludes routine sampling and culture. The criteria for ascribing a pathogen as a cause of acute pancreatitis is difficult to fulfil. Mild attacks with rapid resolution are unlikely to be investigated as additional therapy may be questioned. In addition, before an infective agent is assigned as the cause of acute pancreatitis other known aetiological associations must be excluded. In a symptomatic and biochemically diagnosed acute pancreatitis, the demonstration of the pathogen in pancreatic juice or blood, may make it permissible to attribute the cause to the microbe. (36)

1.1.4 Severity grading in HIV related pancreatitis

There is a paucity of information on whether the prognostic systems currently in use in grading acute pancreatitis are appropriate and effective in HIV associated pancreatitis. Dutta, in a retrospective review, using Ranson criteria demonstrated that 40% of their cohort were predicted to have mild disease and 60% moderate to severe disease. (28) The accuracy of the Ranson criteria in predicting adverse outcomes was not evaluated in this study by Dutta.

Cappell demonstrated that the Ranson scale was a poor predictor (sensitivity 41%, PPV 53% and NPV 52%) of outcomes and that the Acute Physiology And Chronic Health Evaluation 2nd edition (APACHE II) system had a sensitivity of 73% and a specificity of 68% in predicting a severe outcome in HIV+ve patients. The PPV and NPV were 70% and 71% respectively.(31) Gan demonstrated that the maximum accuracy was achieved with a cut-off of 14 for the APACHE II score and 4 for the Glasgow and Ranson criteria.(37) In contrast the best cut-off value in HIV-ve patients are markedly lower at 8, 3 and 3 for

the APACHE II, Glasgow and Ranson criteria respectively.(38-41) What is required is a prospective comparison of the accuracy of these scoring systems in predicting adverse outcomes in HIV+ve and HIV-ve patients with acute pancreatitis.

1.1.5 Morbidity and mortality

The outcomes in HIV related acute pancreatitis vary and Gan found that 15% of 73 patients with AIDS had severe disease as defined by ICU admission, death, local complications or surgical interventions, and seven patients (10%) died. (37) There was no differences in CD4 counts, AIDS status or years since diagnosis between mild and severe disease. They also found that the incidence of severe outcomes and mortality was comparable between their HIV +ve patients and HIV-ve historical controls. (37) In a non-comparative observational study by Parithivel the mortality rate was reported as 32% in HIV+ve patients which is much higher than in reports on pancreatitis without HIV infection. (42)

Factors influencing outcomes in patients with severe HIV associated pancreatitis are unclear. Afessa and Green from the University of Florida assessed 599 HIV +ve patients admitted to ICU with critical illnesses and reported no difference in mortality between patients admitted with sepsis and patients admitted with Systemic Inflammatory Response Syndrome (SIRS) of a non-infectious aetiology. (43) They also observed that a low CD4 lymphocyte count was not associated with an increased mortality but noted that three of the four ICU admissions with acute pancreatitis died. (43) In another American study 17% of the patients with clinical pancreatitis died. (20)

1.1.6 Summary

Pancreatic enzyme elevations are common in HIV infected patients but clinical acute pancreatitis is lower. The use of total serum amylase in this population group may be unreliable as asymptomatic hyperamylasaemia is common and macroamylasaemia and the parotid fraction of total amylase have also been found to be elevated in HIV infected patients. The precise role of pancreatic isoamylase and lipase assays in this context are not defined. Despite this diagnostic dilemma, the prevalence of acute pancreatitis in HIV infected populations is higher than the general population. Although there has been a decline in HIV related pancreatitis after the introduction of HAART, there is a rising prevalence of HIV infection in pancreatitis cohorts in South Africa. In reports from regions with low HIV infection prevalence where alcohol and gallstones are responsible for the majority of cases of acute pancreatitis, the patients with HIV infection had AIDS, opportunistic infections and drugs as the more frequent causes of acute pancreatitis although alcohol and gallstone remained major aetiological considerations. There is thus a paucity of information on the spectrum of aetiologies of acute pancreatitis in areas with a high prevalence of HIV infection such as South Africa.

If pancreatitis occurs more frequently in the HIV infected community, then additional aetiological factors must exist which directly or indirectly enhance the susceptibility to acute pancreatitis. There are a large number of potential factors causing or associated with pancreatitis in HIV infected individuals and proving them as a cause of the disease is imprecise. This is pertinent since acute pancreatitis in HIV+ve patients was higher prior to the advent of HAART. This suggests the presence of additional causes of acute pancreatitis in HIV infection.

1.2 Problem statement

Despite this relevance there is a paucity of information on HIV and acute pancreatitis from South Africa. The few studies in a South African context have demonstrated an increase in the prevalence of HIV infection in patients presenting with acute pancreatitis. (17-19) (**Table 2**). These studies involved patients in whom HIV testing was not performed in all patients and are likely to have underestimated the prevalence of HIV infection in patients with acute pancreatitis.

1.3 Hypotheses

HIV infection is more prevalent in patients admitted with acute pancreatitis than in patients admitted as a result of trauma. The prognostic systems used in non-HIV associated pancreatitis are not as effective in predicting the outcomes of pancreatitis associated with HIV infection. Acute pancreatitis associated with HIV infection results in a higher morbidity and mortality than in HIV negative patients.

1.4 Research Objectives

In the context of a high HIV prevalence environment, this study therefore sought to establish a bench mark data set and was conducted to

1. Describe and compare the HIV prevalence in acute pancreatitis and trauma cohorts. The trauma cohort being representative of the general population

2. Define and compare the applicability of diagnostic and severity assessment tools in HIV related pancreatitis.

3. Determine and compare the morbidity and mortality rates in HIV+ve and HIV-ve patients with acute pancreatitis.

4. Determine the factors associated with morbidity and mortality in HIV related pancreatitis.

1.5 Methods and study period

The study was a prospective descriptive analysis of acute pancreatitis and trauma cohorts over a two year period in two regional hospitals in the Durban region of Kwazulu Natal.

1.6 Outline of study

This chapter introduced the critical aspects of our current understanding of the association between HIV and acute pancreatitis and contexualised the research objectives. The literature review presents the current understanding of the diagnosis, severity assessment, aetiopathogenesis and treatment of acute pancreatitis. Secondly a synopsis of the epidemiology and other factors pertinent to HIV infection in South Africa is presented to detail aspects of the diagnosis, management and factors that influence morbidity and mortality. A brief description of the role of acute pancreatitis in mortality in HIV infection is presented. This sets the framework to formulate the study aim that is to address the paucity of critical analysis of the relationship between HIV infection and pancreatitis in an environment with a high prevalence of HIV infection. The thesis will be structrured as follows:

Chapter 2 – Literature review

Chapter 3 – Methodology and study design

Chapter 4 – Results

Chapter 5 – Discussion

Chapter 6 – Synthesis and conclusion

Chapter 2: Literature review

Section 1: Acute pancreatitis

2.1 Clinical presentation and initial diagnosis

Acute pancreatitis is a symptom complex consisting of severe persistent epigastric pain which may be associated with nausea and vomiting and radiates to the back. The physical examination may be unrevealing in mild attacks, whilst in those with severe disease signs of peritonitis are overt and respiratory distress and hypotension are often present. The condition is usually associated with an elevated serum amylase or lipase. These symptoms and biochemical combination suffice to arrive at a diagnosis in most cases. The clinical and biochemical criteria are not specific for acute pancreatitis and other diseases such as perforated duodenal ulcer, mesenteric ischaemia and bowel obstruction can also produce enzyme elevation. In instances of diagnostic doubt CT imaging is required to confirm acute pancreatitis or evaluate for other disease processes.(44) Emergency laparotomy may be performed when doubt persists and pancreatitis is diagnosed by fat saponification and inflammation of the gland.

2.2 Enzyme elevation in the diagnosis of acute pancreatitis

Table 3 provides a summary of a number of studies investigating the diagnostic accuracy of amylase and lipase which are the routinely used diagnostic tests. (45-54) These tests have been more commonly assessed than others and most studies show lipase to be the most accurate diagnostic test. However, investigations into amylase and lipase as diagnostic aids have not been standardized. **Table 3** highlights the variation, in the analytic tests (including their isoenzyme fractions), their timing and cut-off values that make inter-study comparisons difficult.

α-Amylase is an important enzyme within the gastrointestinal tract. The main sources are the salivary gland(S-type) and the pancreas(P-type) and the untyped lesser amylase activity that is found within the small bowel, lung and skeletal muscle. The usefulness of amylase in the diagnosis of acute pancreatitis was first demonstrated in 1929. (55) Following the initial insult, the serum amylase level increases rapidly over 3 to 6 hours. With a half-life of 10-12 hours, it can remain elevated for 3 to 5 days, but may be normal with background chronic pancreatitis, when hypertriglyceridaemia is present and with delayed presentations. It is excreted by the kidneys and may be falsely elevated in renal impairment.

Serum lipase is composed of 3 subtypes which have pancreatic, hepatic and lipoprotein components with the pancreatic proportion being less than the lipoprotein and hepatic components when measured in asymptomatic subjects. (54) Serum lipase level increases in 3 to 6 hours and peaks in 24 hours. It is

more useful than amylase in delayed presentation since it can remain elevated for one to two weeks as it is reabsorbed by the kidney tubules. (56) The ratio of pancreatic lipase to total lipase subtypes was more accurate than pancreatic lipase and amylase in confirming pancreatitis diagnosed by contrast enhanced computed tomography scan at presentation. (54) (**Table 3**)

Lipase was shown to be superior to amylase as it was found to be more sensitive and specific in an institution where both tests were available. (57) The authors found that the use of lipase alone was more cost effective than using both tests for pancreatitis. Elevations in amylase and lipase greater than 3 times the upper limit of normal are uncommon in abdominal pain that is caused by extra-pancreatic diseases although a study by Hendry et al in 1987 found that 30(7%) of patients admitted with amylase levels above 1000IU/l had other abdominal conditions. (58) Ruptured aortic aneurysm, perforated duodenal ulcer, cholecystitis and intestinal obstruction were the other conditions that resulted in a markedly elevated amylase.

Table 4 summarises the less frequently investigated diagnostic tests and again illustrates the varying levels of sensitivity and specificity calculated at different cut-off values. (45-49, 51) As with amylase and lipase standardization of these tests was poor, some were measured in serum and urine without stipulating which sampling route was considered the most worthwhile and the laboratory upper limits of normal values were not provided in some instances. Currently these tests have no clinical utility over amylase or lipase and are not used in routine practice.

Despite alternatives amylase and lipase remain the most commonly used diagnostic biochemical markers because they are widely available and cost effective. Lipase has been evaluated to be superior to amylase in a number of studies and should be the preferred test. In resource constrained environments amylase is more widely available with assays of lipase performed offsite and delaying the diagnosis. However, clinicians should be aware that significant elevations in amylase may result from other medical conditions. CT imaging is required when pancreatic enzymes are normal or insignificantly elevated and if there is diagnostic doubt. On occasions when imaging is non-specific a laparotomy may be required as most alternative diseases which mimic acute pancreatitis are addressed by emergency surgery.

2.3 Aetiology and epidemiology

There has been an increase in hospital admissions for acute pancreatitis in European, American and Far Eastern settings (59, 60) with gender distribution dependent on aetiology and a mean age of 54-60 years. (2, 9, 57) In South_Africa there are no population based figures on the incidence of acute

pancreatitis and in hospital prevalence rates, acute pancreatitis represented 1% and 1.2% of all admissions to a general surgery service in two hospital populations. (15, 17)

In most settings alcohol and gallstones are associated with 80% of cases of acute pancreatitis (**Table 2)**. In South Africa alcohol has been the aetiological association in 63-83% and gallstones in 7-14% of patients with acute pancreatitis. In studies from other centres in the world alcohol has been the cause in 7-33% and gallstones in 33-69% (**Table 2**). Alcohol causes a direct toxic effect on the pancreas and gallstone migration and transient obstruction of the ampulla with bile reflux into the pancreatic duct are thought to be the mechanisms of these aetiologies. Gallstone pancreatitis is more prevalent in females (61) with small gallstones(<5mm). Gallstone-related pancreatitis increases with age and peaks after 60 years of age whereas an alcohol cause peaks at 45 to 55 years and declines thereafter. (22)

The concept of spasm of the sphincter of Oddi(SOD) as a mechanism of inducing acute pancreatitis was demonstrated in animal experiments. (62) The same authors suggested that recurrent pancreatitis after cholecystectomy in some patients could be attributed to spasm of the sphincter of Oddi. The SOD has three variants with types 1 and 11 associated with biliary dilatation and deranged liver function tests and the type 111 variant with abdominal pain. However longterm results of the of the endoscopic sphincterotomy for SOD have shown that sphincterotomy does not result in pain improvement from the type 111 variant of SOD dysfunction despite manometry revealing raised sphincter pressures.(63)

In studies by Fortson and Cameron the association between hypertriglyceridaemia and pancreatitis was investigated. Caucasians and African Americans accounted for the majority of patients with hypertriglyceridaemia and pancreatitis. (64, 65) Hypertriglyceridaemia in South Africa has an ethnic bias and is more frequently found in Caucasian and Indian racio-ethnic groups, is intermediate in those of mixed ethnicity and low in the indigenous African population. (66, 67) Pancreatitis associated with hypertriglyceridaemia was predominantly found in the Indian racio-ethnic group and was low in indigenous Africans. (66) Thirty-four percent of the admissions with acute pancreatitis in a Durban hospital had dyslipidaemia associated with pancreatitis over a 4-year period which is similar to the frequency in the series by Cameron and Buch who similarly performed routine testing for dyslipidaemia. (65, 66, 68) However only 26 (6%) had hypertriglyceridaemia greater than 10mmol/l in the Durban evaluation. (66)

Primary hyperparathyroidism may be sporadic or familial and may exist alone or in combination with other endocrine disorders. The pathology may be glandular hyperplasia or an adenoma which causes increased levels of parathyroid hormone and an elevated serum calcium. Acute pancreatitis is a rare complication of hypercalcaemia caused by primary hyperparathyroidism occurring in 2% of patients with primary hyperparathyroidism. (69) In a cohort of patients with primary hyperparathyroidism,

pancreatitis was found in 3.2% of patients with a spectrum of acute and chronic forms of the disease. Calcium levels were higher in patients with pancreatitis than in those without pancreatitis. (70)

Certain genetic disorders are associated with an increased susceptibility to acute pancreatitis. These include cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), serine protease inhibitor Kazal 1(SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR), chymotrypsinogen C(CTRC) and calcium-sensing receptor (CASR). Patients with these genes are more prone to develop pancreatitis when exposed to causes of acute pancreatitis. PRSS1, PRSS2 and SPINK1 are genes which result in the premature activation of Trypsinogen whereas CFTR, CTRC and CASR resulted in altered ductal bicarbonate levels, susceptibility to trypsin and altered calcium metabolism which increased the prevalence of acute pancreatitis in subjects with these mutations (76)

Congenital pancreatic anatomical variations (Pancreas divisum and annular pancreas) and malignant disease of the pancreas may cause acute pancreatitis. Pancreas divisum has been found in 16%, 16%, and 47% in those with idiopathic, and PRSS1, SPINK1, and CFTR mutation associated pancreatitis, suggesting that it is associted with gene mutations that cause acute pancreatitis and not a cause of the acute pancreatitis. (71)

In a Norwegian study 3% of acute pancreatitis was related to tumours and most of these patients presented with mild pancreatitis. The tumours were diagnosed at initial presentation or over a varying period thereafter. (72) In HIV associated pancreatitis 6(6%) of patients had associated cancers. (19) Hyperamylasaemia has also be associated with non-pancreatic malignancies. (73-75) These tumours included an ovarian tumour, paraganglioma and multiple myeloma.

Autoimmune pancreatitis is an uncommon cause of acute pancreatitis. The condition is due to autoantibodies cause acinar cells inflammation that usually responds to steriod therapy. It has type 1 and type 2 variants, the former being associated with raised levels Immunoglobulin 4 (IgG4) and often present with obstructive jaundice and the latter without raised levels of IgG4 and most often presenting abdominal pain. (77) Type 1 is also associated with other autoimmune conditions and type 2 has an association with inflammatory bowel disease

2.4 Determinants of Aetiology: biochemical and imaging

A variety of biochemical markers have been studied in relation to their ability to differentiate the various aetiologies to enable early interventions to prevent recurrent disease. Although there are no specific early interventions for an alcohol aetiology it is important to determine a gallstone cause of the

pancreatitis early in the disease as there are specific measures which may moderate the outcomes and prevent recurrent episodes. Although, the elevations of serum amylase and lipase are significantly lower in patients with alcoholic pancreatitis than in those with biliary pancreatitis, serum amylase and lipase concentrations do not establish the aetiology accurately. Studies have evaluated a variety of parameters against a gold standard to determine their accuracy in determining a gallstone aetiology. They are shown in (**Table 5)** (19, 57, 78-85) which illustrates the different and often multiple 'gold standards' used, the variability in the assays, their cut off levels and the temporal relationship of their measurement to the onset of symptoms. This makes comparison of these studies less than ideal. In South Africa with a low prevalence of gallstone related pancreatitis serum amylase > 1000IU/L was a predictor of biliary pancreatitis in female patients. (18) A biliary aetiology is associated with female gender in most assessments and was demonstrated to have a pre-test probability of 0.47 in females and 0.06 in males. (18) The serum lipase-amylase ratio is also unhelpful in aetiological differentiation as the ratio for alcoholic, biliary and non-biliary and non-alcoholic pancreatitis was 0.2-5.6, 0.1-7.9 and 0.1-4.4 respectively. (86) In studies which examined bilirubin, alkaline phosphatase, , a 3-fold elevation of ALT was associated with a 95% probability of gallstones as a cause of pancreatitis. (87) This was not improved by the use of other liver enzymes alone or in combination with ALT(**Table 5**).The performance of the transaminases in predicting a biliary cause may depend on the timing of the assay in relation to the onset of symptoms as ALT within 24 hours had a sensitivity, specificity and positive predictive value of 73%, 86% and 92% respectively which were significantly higher than the values of these parameters at 72 hours. However, the latter remained a valuable predictor of a biliary cause. (88)

Endoscopic ultrasound (EUS) and Magnetic Resonance Cholangiography (MRC) appear to be superior for determining a biliary aetiology (**Table 5**) but are usually used when there is diagnostic doubt of a biliary aetiology. EUS has a sensitivity of 94% - 100% and specificity of 95%-100% (89, 90) and MRC a sensitivity of 92-95% and specificity of 96%-99%. (91, 92)

They are of limited use as they are not available to most patients at initial presentation particularly in less developed environments and gender, biochemical parameters and transabdominal ultrasound remain the most widely available predictors of a biliary origin.

2.5 Summary

There exists a regional variation in the aetiological profile of acute pancreatitis but the majority of cases are related to alcohol and gallstones. In developed environments most pancreatitis is associated with gallstones whereas in South Africa the majority are associated with alcohol. Female gender is associated with a gallstone aetiology in all settings. In regions with a low prevalence of biliary

pancreatitis such as South Africa serum amylase is a predictor of a gallstone aetiology and ALT is a reliable predictor in all environments. Determining a gallstone aetiology is important as cholecystectomy and Endoscopic Retrograde CholangioPancreatography (ERCP) and sphincterotomy reduce the risk of subsequent attacks. There are a number of other possible causes and these may have an ethnic or regional association as demonstrated by pancreatitis associated with hypertriglyceridaemia where there was an ethnic bias in a study from Durban. In a low HIV prevalence environment tumours have also been associated with acute pancreatitis. This association was more frequent in a high HIV prevalent environment. The association between drugs and acute pancreatitis is determined by the temporal relationship between drug administration and acute pancreatitis and a number of drugs have been implicated. Sphincter of Oddi dysfunction is usually detected when investigating idiopathic pancreatitis.

2.6 Pathogenesis/Pathophysiology

2.6.1 Early events in the pancreas

Experimental pancreatitis has provided insight into the early events in acute pancreatitis. (93) The autodigestion theory of pancreatitis is the oldest explanation for these events. Trypsinogen and other digestive enzymes secreted by the exocrine pancreas are inactive proenzymes during their synthesis, storage and secretion into the pancreatic duct. The secretion of proenzymes by the acinar cells through exocytosis is influenced by calcium signalling pathways. Activation of proenzymes normally occurs in the small intestines by enterokinases in the mucosal brush border. At the cellular level, animal models of pancreatitis have shown that co-localization of hydrolases and zymogen granules occurs and result in the activation of digestive enzymes intracellularly which leads to autodigestion. The activation of G protein-linked receptors is followed by increased levels of Inositol 1.4.5 – triphosphatase, nicotinic acid, adenine dinucleotide phosphatase (ADP) and cyclic ADP-ribose. This results in calcium release from the endoplasmic reticulum and an increase in the cytosolic calcium. This elevated calcium induces intracellular activation of digestive enzymes. (94) Due to premature activation of trypsinogen and other digestive enzymes the pancreas becomes inflamed and at times this process progresses to necrosis. This results in extracellular events within the pancreas and systemic activation of the inflammatory response with deleterious effects on organ function. The prototype of this process is hereditary pancreatitis, where mutations in the cationic trypsinogen gene result in premature trypsinogen activation and autodigestion.

Experimental intra-acinar production of active trypsin has been shown to result in acinar death and local and systemic inflammation. (95)

Recent investigations have questioned the central and sole role of the autodigestion model. It has been demonstrated in experimental pancreatitis that the lack of trypsinogen does prevent pancreatic necrosis but does not inhibit the local and systemic inflammatory response. (96) Activation of trypsinogen takes place in membrane bound compartments when the zymogen and lysosomes co-localize with Cathepsin B activating trypsinogen in these vacuoles. In experimental pancreatitis where subjects were depleted of Cathepsin B or trypsinogen, local and systemic inflammation was found but with reduced pancreatic injury. This suggested that Trypsinogen activation was not necessary to induce acute pancreatitis and that activation of NF-kB, which parallels the trypsinogen activation is a proven alternate pathway to pancreatic inflammation. (97)

The initiating event produces changes within the acinar cells. This results in local and systemic effects of variable degree. The natural history is either a mild self-limiting course or a severe disease with organ failure in 20% of patients. (98) It would appear from these recent findings that Trypsinogen activation is an important but not the sole pathway in acute pancreatitis.

2.6.2 Gut mucosal dysfunction

In severe acute pancreatitis, retroperitoneal inflammation results in third space loss and relative hypovolaemia. Activation of the sympathetic nervous system and the renin-angiotensin pathway results in vasoconstriction of the mesenteric postcapillary venules and the afferent arterioles. This augments the systemic blood pressure at the expense of the splanchnic bed. This results in impaired gut perfusion and loss of gut barrier function. (99) The integrity of the gut barrier is also compromised by the lack of nutrients in severe cases. The ensuing microbial translocation causes activation of immune cells and the release of inflammatory mediators which is thought to drive the systemic inflammatory response and multiple organ dysfunction syndrome. (99) This increased intestinal permeability has been demonstrated in patients with severe forms of acute pancreatitis. Intestinal permeability was also greater in patients with severe disease who developed multiple organ failure or died. (100)

2.6.3 Inflammatory response in acute pancreatitis

The cytokine cascade which is initiated by the acinar cell damage is illustrated in **Figure 1**. This cascade illustrates the response in patients without HIV infection. A similar analysis has not been performed in HIV associated pancreatitis. Activation of leukocytes is key in the onset and propagation of the initial events associated with acute pancreatitis. (101) Cytokine and non-cytokine inflammatory mediators are raised in acute pancreatitis irrespective of the aetiology. (102) Interleukin (IL)-6, IL-8 and IL-10 peak early in acute pancreatitis(days 0-2) with significantly higher levels in severe disease. The response was also more sustained in cases of severe disease. (103) Acute pancreatitis alters the plasma concentrations of acute phase proteins [C - reactive protein (CRP), alpha-1 antitrypsin, transferrin]

whose plasma concentrations may increase or decrease in response to cytokines. A difference was found between gallstone and alcohol related pancreatitis in the levels of IL-8, but not in IL-6, IL-18, Tumour Necrosis Factor (TNF) -α and CRP.(65) Because plasma cytokines have short half-lives, quantification for clinical use is difficult and CRP is traditionally used as the measure of the acute phase response. The cytokine profiles associated with the cellular and humoral immunity are illustrated in **Figure 1**.

2.7 Classification

The first symposium on pancreatitis held in Marseille in 1963 defined 4 categories of pancreatitis namely acute pancreatitis, acute relapsing, chronic relapsing and chronic pancreatitis. (104) In 1984 the Cambridge international gathering revised this to 2 categories of acute and chronic. (105) The Atlanta conference in 1992 distinguished acute pancreatitis as a separate entity with mild or severe categories. The predictors of severe disease, the definitions of organ failure and local complications were defined by consensus. (106) A review of subsequent publications and a comparison with the Atlanta criteria revealed a discordance in the diagnostic criteria, definitions of organ failure and the cut-off values in the prediction of severe disease. This resulted in a review of the classification and an international consensus based re-classification in 2012. (44) During these periods, the CT criteria for local complications have also undergone a number of changes since their original classification by the Atlanta consensus. (107) The most recent consensus meeting/statement on acute pancreatitis in 2012 defined the diagnostic criteria, the predictors of severe disease and the role of organ failure, as defined by the Modified Marshall score, on outcomes (**Table 6**). Acute pancreatitis was classified into mild, moderate and severe forms and the CT scan criteria of local complications were defined. (44)(**Annexure Table 2**)

2.8 Predicting Severity

The need to prognosticate in acute pancreatitis arose from variable outcomes with about 25% of patients developing a complicated course which may be fatal. Predicting a severe outcome aids in determining the need for intensive monitoring and organ support, allows comparison of outcomes between different centres and provides endpoints for comparing established or novel therapies/interventions**.** Predicting a severe outcome is preferably done at presentation to enable early intervention and the ideal system for prognostication in acute pancreatitis should be available to medical personnel at various levels of care. It should be rapidly computed, inexpensive, compatible with district hospitals and available early in the course of the disease preferably in the first 24-hour period.

2.8.1 History and general factors in prognostication

Prior to the 1970s, the assessment of severity was by clinical means. Clinical parameters such as tachycardia, respiratory distress, shock and signs of peritonitis are compatible with severe disease. In western environments old age has been associated with increased mortality. These clinical criteria predicted severe disease in 39% of patients with a severe attack. (108) Bruising and purple discoloration in the flanks, Grey Turner's sign, or periumbilical ecchymosis, Cullen's sign, did predict a severe attack of acute pancreatitis but took 24–48 hours to develop and were seldom present. (109)

2.8.2 Age

Advanced age has been a determinant of poorer outcome and is a factor in a number of prognostic systems. This is based on several studies analysing age alone as a predictor of mortality. A Scottish study by McKay reported on 19633 admissions of 13727 patients with acute pancreatitis between January 1984 and December 1995. The median age was 54 years and the authors demonstrated that mortality was 1-2% in those younger than 40 years and more than 18% in those older than 70 years with 59% deaths occurring in those older than 70 years (**Table 7**). (110) In a study from England in 1985 which examined 650 patients, the mean age at presentation was 60 years with a mortality rate of 20%. Age was a predictor of death with a mortality of 28% in those older than 60 years and 9% in those below that age. (111) Frey in 2006 reported on 70231 patients with acute pancreatitis. (12) They showed a 15-fold and 22-fold greater chance of dying within 2 weeks and within 91 days respectively if the age was greater than 75 years. Advancing age in Western series is a consistent predictor of outcome and justifiably a component of systems that predict poor outcome.

2.8.3 Nutritional status as a predictor of outcome in acute pancreatitis

The proportion of adults who are overweight or obese was 37% for men and 38% for women worldwide in 2013.(112) Obesity is defined by a BMI (body mass index of greater than 30) and is one of the clinical parameters that predicts a severe course of acute pancreatitis. Though lower than this worldwide average the prevalence of obesity in patients with acute pancreatitis is high and was demonstrated to be 28.9% in a Korean study and 21% and 24% in South African and Spanish cohorts. (16, 113, 114) These studies demonstrated that obesity was associated with more complications of acute pancreatitis. In a South African study, the mean(±SD) BMI of patients with severe acute pancreatitis was significantly higher than that in patients with mild disease 31.2(±5.6) versus 23.3(±5.6) kg/m2. In patients with a BMI>30, disease severity, abscess formation and mortality were demonstrated to be significantly higher. (16)

The addition of obesity (BMI>30) to the APACHE II score predicted severe acute pancreatitis with a sensitivity of 82%, specificity of 86%, positive predictive and negative predictive values of 74% and 91% respectively. (115) However, in an American study in 2006 the admission APACHE O [Area Under the Curve (AUC) 0.895] and APACHE II (AUC 0.893) demonstrated similar accuracy in predicting a severe outcome although BMI > 30 was identified as a significant risk for severe acute pancreatitis and mortality. The CRP levels and Ranson score were also significantly higher in obese patients. (116)

Further evidence was provided by Martinez in a meta-analysis of 739 patients where severe acute pancreatitis was significantly more frequent in obese patients (OR 2.9, 95% CI 1.8-4.6). (117) Obese patients also developed significantly more systemic (OR 2.3, 95% CI 1.4-3.8) and even more local complications (OR 3.8, 95% CI 2.4-6.6). The mortality rate was also higher in obese patients (OR 2.1, 95% CI 1.0-4.8)

2.8.4 Peritoneal lavage

Peritoneal lavage was superior to clinical assessment and equivalent to the Glasgow criteria in predicting a severe form of pancreatitis with sensitivities of 53%, 34% and 61% respectively. Visceral injury occurred in 2 of 253 patients (0.8%). (118) This method of prognostication has been discarded because of its invasive nature and the potential for visceral injury.

2.8.5 Multiple factor, single factor and radiological prognostication systems

Subsequent prognosticators were developed within specific populations usually from high income countries with variable patient demographics aetiological mixes and comorbidities. In this regard a number of single factor and multifactorial scoring systems have been developed. **Table 8** depicts accuracy metrics for a number of severity prediction factors in relation to their temporal use. (38-41, 119-127) The various scoring systems have been utilized over a varying period after onset of symptoms and they have shown varying sensitivities and specificities in determining a severe outcome. The APACHE II system has been shown in several comparisons to be the most reliable of these tools.

2.8.6 Multiple factor prognosticators

In 1970 Ranson developed the first of the multifactorial scoring systems. (128) The APACHE II (129) and the Glasgow (**Annexure Tables 3 and 4**) (130) joined Ranson as the most commonly used scoring systems. The Ranson and Glasgow criteria are collated over 48 hours and are not suitable for early evaluation. The Ranson criteria were developed in a cohort of acute pancreatitis with alcohol as a cause

in 75% of patients and modifications to accommodate a biliary origin were impractical as the aetiological association was frequently unknown at the initial assessment. The APACHE system was initially developed and validated in the classification of patients in intensive care units where it proved to be reliable in predicting outcomes. (131) This system made allowance for the weighting of 34 different physiological measures on a scale of 1 to 4. These provided a physiological score. The APACHE II score was a modification which reduced the physiological variables from 34 to 12 to simplify the score but added a premorbid assessment. (129, 132) The APACHE II score was found to discriminate between uncomplicated, complicated and fatal forms of acute pancreatitis. It was also of value in ongoing assessment as it revealed a worsening score in patients dying within 4 days and declining scores during the first seven days in those who survived the attack. (133) The APACHE III and later APACHE IV modifications used additional variables, expanded the disease codes to forty and remodelled the weighting of the different variables. This resulted in a possible range of scores of 0 to 299 in the APACHE III. The APACHE IV score was calculated using 129 variables and in a study of 266 patients with severe pancreatitis, an APACHE IV score of 44 or more predicted mortality in the 15(5.6%) who died. (134) The receiver operating characteristic curve for APACHE IV was 0.93 (CI, 0.88-0.97); APACHE II, 0.87 (CI, 0.80-0.94); Bedside Index for Severity in Acute Pancreatitis (BISAP), 0.86 (CI, 0.78-0.94); and Ranson criterion, 0.90 (CI, 0.94-0.96). These scores resulted in more complex calculations which were unsuitable for the primary assessment at initial presentation and was counter to trends which sought simpler prognosticators early in the disease process. In a study, further mitigating against their routine use, which compared the Ranson, APACHE II and APACHE III in 153 patients with acute pancreatitis, the Ranson criteria were equivalent to the APACHE II scores when there was a 24 - hour delay in the assessment of patients. The APACHE II and APACHE III scores had the same predictive value. (134)

BISAP is a 5-point system based on one point for each of the following parameters: Urea, Impaired mental status, Systemic Inflammatory Response Syndrome (SIRS), age and pleural effusion as detailed. (**Annexure Table 5**)(135) It was derived from data collected from 17,992 cases of acute pancreatitis from 212 hospitals in 2000-2001 and validated on data collected from 18,256 AP cases from 177 hospitals in 2004-2005. (35) The 'AUC' of BISAP was 0.82 and 0.83 for the APACHE II system. Subsequently the BISAP score has been compared to other scoring systems in differing communities. A comparison of Ranson, BISAP, APACHE II, Computerized Tomography Severity Index (CTSI) and CRP at 24 hours in predicting severe disease revealed that the APACHE II score had the highest accuracy with an area under the curve of 0.78(95% CI: 0.7-0.84) without a statistically significant difference between the scoring systems. () The BISAP score was also found to be similar to the APACHE II and Ranson scoring systems in predicting a severe outcome in a Chinese population of

497 patients. (135) The BISAP scoring system has the advantage of simplicity and use within 24 hours of presentation**.**

In HIV related pancreatitis there is limited evidence on the suitability of established prognostic systems**.** In a study by Gan, the APACHE II criteria best predicted outcome with an overall accuracy of 75% (Glasgow 69%, Ranson 48%). (37) In HIV related pancreatitis, maximal accuracy was achieved with cut-offs of 14 for APACHE II and 4 for the Glasgow and Ranson criteria.

A severe outcome is associated with a severe inflammatory cascade which results in systemic organ dysfunction and mortality. The criteria for a SIRS have been validated in large studies and include any 2 of the predefined cut-offs of the following criteria: temperature, heart rate, respiratory, arterial partial pressure of carbon dioxide and white cell count **(Annexure Table 6).** (103) Since cytokine assays are not readily available and difficult to measure because of their brief half-lives, these systemic criteria are surrogates of the cytokine response. A persistent SIRS response at 48 hours is associated with persistent organ dysfunction and mortality. (136)

Besides these scoring systems, there are others which have shown promise without wider validation. For example, the score based on specific cut-offs has been demonstrated to be equivalent to Ranson, Glasgow and APACHE II systems in predicting mortality. (137, 138)

2.8.7 The single factors prognosticators

An Erythrocyte Sedimentation Rate (ESR) value of 60mm/hr or greater had a sensitivity and specificity of 86% and 57% at 36 hours while a CRP value of 150mg/L or greater at 36 hours had a sensitivity and specificity of 86% and 87% in predicting severe acute pancreatitis. A 36-hour delay to predicting severity is inadequate for early triage and the institution of early organ support. When elevations of either ESR or CRP were used to predict severe disease at 24 hours a sensitivity and negative predictive value of 100% was achieved, and when elevation of both ESR and CRP were utilized at 24 hours the specificity and Positive Predictive Value (PPV) were 100%. (139) This study was conducted in 50 patients and would require validation in a larger cohort with appropriate statistical power to justify regular use of ESR alone or in combination with CRP.

Median concentrations of ProCalciTonin(PCT) and IL-8 were demonstrated to be significantly higher in patients with infected necrosis than in those with sterile necrosis and there was no difference in CRP in the two groups. (140) A PCT value of 3.5 ng/mL on 2 consecutive days was superior to a CRP value of 430 mg/L for predicting infected necrosis with Multiple Organ Dysfunction Syndrome (MODS) or

non-survival. The sensitivity and specificity of PCT was 93% and 88% and for CRP 40% and 100% (p=0.01). (141)

CRP is synthesized in the hepatocytes as a response to cytokine stimulation and may therefore lag behind the initial SIRS. CRP was found to be useful from day 2 to 8 with levels ≥ 210mg/L on days 2,3 and 4 and ≥120mg/L at the end of the first week when compared to other scoring systems. (142) The CRP after 24 hours was superior to the CRP at admission with an area under the curve of 0.68 and 0,52 respectively. This delayed value of CRP in prognostication was confirmed when CRP at 48 hours was superior to CRP assessment at admission, 24 hours and 72 hours in predicting severe pancreatitis, pancreatic necrosis and mortality. (143) However in a different finding, CRP at presentation and at 48 hours did not differ in predicting severe pancreatitis and mortality and CRP at presentation improved the prediction of organ failure. (144) This temporal variation of CRP makes it an inconsistent predictor of severity.

Trypsinogen activation to trypsin and the release of Trypsinogen activation peptide (TAP) is an early event in acute pancreatitis. TAP is released into the plasma, urine and peritoneum. TAP assays have been evaluated as a prognostication factor.

In a multicentre study from the USA and England which examined 139 patients with acute pancreatitis and 50 controls with other acute abdominal conditions, TAP was found to peak at 6-12 hours following admission. A TAP value of 10ng/ml obtained within 48 hours was demonstrated to have a 100% sensitivity and 85% specificity for predicting severe pancreatitis as defined by organ failure and pancreatic necrosis. (121)

In a subsequent multi-center European study of 246 patients in which 172 had acute pancreatitis and 74 were controls. A urinary TAP >35 nmol/L, 24 hours after onset of symptoms, was superior to a CRP >150 mg/L and an APACHE II ≥8 in predicting severe disease, but at 48 hours all parameters were equivalent. (122)

Trypsinogen has two major isoenzymes which are the Trypsinogen-1(cationic) and Trypsinogen-2(anionic) forms, an immunochromatographic urinary Trypsinogen-2 dipstick test has been used to measure the levels of this isoenzyme. In study from Finland the dipstick for Trypsinogen-2 had superior sensitivity and specificity to CRP >150 mg/l and APACHE II > 8 on admission but not at 24 hours. (123) TAP assays show promise as accurate predictors of severity but are not readily available and require further evaluation including cost analysis in larger patient cohorts.

Complements C3a and sC5b-9 measured daily during the first week were noted to have high sensitivity (0.93) and specificity (0.88) and high negative predictive value (0.93) and positive predictive values (0.87) for a severe outcome but require further evaluation. (145)

Poor prognosis is related to the extent of local pancreatic necrosis, the severity of the systemic SIRS and the development of organ failure. This progression is dependent on the balance between local and systemic immune responses. Proinflammatory cytokines determine the systemic response and the degree of organ failure whereas ant-inflammatory cytokines seek to limit the inflammation in the pancreas. The pro-inflammatory cytokines include IL-1β, TNF-α, IL-6, IL-8, and platelet activating factor (PAF) and the anti-inflammatory cytokines IL-10, TNF-soluble receptors and IL-1 receptor antagonist have been most frequently assessed in acute pancreatitis.

Of the cytokines, the pro-inflammatory cytokine IL-6 has been demonstrated to be most useful in predicting outcome. It induces CRP synthesis in the liver as part of the response to acute inflammation and so serum levels peak earlier than CRP. In a study of 38 patients with acute pancreatitis, IL-6, IL8, b2-microglobulin and CRP values were compared on admission and daily for five days. IL-6 had a sensitivity of 100%, with a specificity of 86% for severe pancreatitis at a value of ≥ 2.7 ng/L. (146) In a study of 80 patients with acute abdominal pain, 40 had acute pancreatitis with 15 having severe disease,
IL-6 at a value of ≥3.7 ng/l, had a sensitivity of 100% and a specificity 83% for detecting severe acute pancreatitis. (147) However, serum concentrations of IL-6 decrease rapidly and its use in clinical practice has also been limited by the complexity of the assay.(151) In a study from China on 50 patients that evaluated the median peak values on day 1 for TNF-α, IL-1-β, IL-6 and IL-8 and on day 2 for CRP, they found that IL-6 was the most useful predictor of severe disease. (149)

2.8.8. Radiological prognostication systems

Radiological imaging has developed as an important tool in the management of acute pancreatitis. Chest radiographs provide information on pleural effusions and the features of adult respiratory distress syndrome and pneumonia. CT scan provides information on the early changes in the pancreas as well as later complications. The CT scan has emerged as a reliable tool in the assessment of pancreatic pathology (150, 151) and has been shown to accurately delineate abnormalities associated with acute pancreatitis. (152) These abnormalities have been demonstrated to be predictors of outcome. Early CT scan within 5 days has been demonstrated to underestimate disease severity and should be limited to cases where there is doubt concerning the diagnosis. (153) The initial description by Balthazar graded

the morphological changes in the pancreas at CT scan into 5 grades of A to E. These emphasized fluid collections and did not recognize pancreatic necrosis which was later found to be an important determinant of outcome in severe disease. Nevertheless, the grades were associated with differing outcomes with higher morbidity and mortality in grade E. (154) In the more widely used CTSI morphological pancreatic and peripancreatic changes and the extent of necrosis are used to arrive at a score which ranges from 0 -10. A score of >6 represents severe disease. (155) The modified version of the CTSI incorporates other extrapancreatic changes such as pleural effusions, ascites, splanchnic thrombosis and other gastrointestinal changes with a score of > 6 representing severe disease. (156) There was no difference between the CTSI and modified CTSI scores in predicting severe disease when computed within one week of onset of symptoms. (157)

There are other CT based severity grading systems which include the renal rim grade (RRG) and the extra-pancreatic inflammation on computed tomography (EPIC). These have not been extensively used in severity assessment of acute pancreatitis. The renal rim grade is based on the fact that in severe pancreatic inflammation, the inflammatory changes may extend beyond Gerotas fascia which is normally a barrier against inflammatory extension. The non-inflamed perirenal fat tissue surrounded by the inflamed pararenal fat tissue with Gerota's fascia as the boundary is referred to as the renal rim. The loss of the renal rim signifies severe inflammation and is known as loss of the renal rim sign. The renal rim has three grades which are associated with the extent of inflammation: grade 1 normal pararenal and perirenal spaces, grade 2 attenuation of pararenal space without loss of renal rim sign and grade 3 loss of the renal rim sign. The renal rim grades were associated with severe disease in 3%, 48% and 89% in grades 1, 2 and 3. The mortality rate was 3%, 8% and 31% respectively in patients with the three different grades. (158)

The EPIC score considers extrapancreatic changes (pleural effusion, ascites, mesenteric and retroperitoneal changes) while discounting pancreatic necrosis within 24 hours. Values range from 0 to 7 with a score of ≥4 predicting severe disease. (159)

These CT based scoring systems are computed after 72 hours and therefore not suitable for early prognostication at presentation or in the first 24 hours. However, performing CT on all patients with acute pancreatitis is unnecessary as in the majority with mild disease this will be wasteful expenditure. CT based prediction of severity has been found to be similar to the clinical scoring systems APACHE II and BISAP. (129) This is further mitigation against the use of early CT for the purpose of assessing disease severity. CT is of greater value in assessing the complications of acute pancreatitis and guiding management. Patients with necrosis of more than 50% of the pancreas are prone to infection and multiorgan failure.

2.8.9 Organ failure and pancreatic necrosis

The development and progression of organ failure and its relationship to pancreatic necrosis are the key determinants of morbidity and mortality. However, the relationship between pancreatic necrosis and organ failure is not linear and organ failure is found in only half of patients with pancreatic necrosis. (160) In the early phase of acute pancreatitis the severity of disease is determined by the presence of organ failure and whether this is transient (less than 48 hours) or persistent (beyond 48 hours). (82) The Marshall (**Table 6**) and Sequential Organ Failure Assessment (SOFA) (**Table 9**) scoring systems allow stratification of organ failure into degrees of severity and they may be repeated daily. In the revised Atlanta criteria, the Marshall score is used to determine the respiratory, cardiovascular and renal organ failure. A Marshall score of 2 or more determines organ failure. (44) The Marshall score can be used in the initial assessment of all patients whereas the SOFA score is more applicable in an intensive care environment in patients on inotropic and ventilatory support. Pancreatic necrosis without MODS is unlikely to be associated with mortality.

Ideally, prognostication should be feasible at admission to facilitate early intervention in terms of specific measures and admission to high dependency areas for those with severe disease. The Ranson and Glasgow criteria were validated for use at 48 hours after admission and do not meet this requirement. The CRP and APACHE II at 24 hours have been demonstrated to be reliable predictors. The BISAP score may be used within 24 hours with similar benefit. However, it is not clear whether these systems provide similar benefit in HIV related pancreatitis. Despite these prognostication systems, persistent organ failure beyond 48 hours is a reliable predictor of poor outcome. Organ failure can be categorized into different severities using the Modified Marshall score and this can be performed daily to assess trends. In essence it is early physiological or single marker assessment and as the disease evolves the dynamic of organ failure becomes the most important determinant of outcome.

2.9 Management of acute pancreatitis

There is no specific treatment for acute pancreatitis. The majority of patients have self-limiting disease with resolution of symptoms and pancreatic inflammation in a few days and in these patients, identifying an aetiology and preventing recurrent disease is the main focus. There are specific therapies addressing aetiology and the prevention of recurrent episodes**.** In severe disease the management is geared toward organ support and the management of local and systemic septic complications. In patients who survive an episode of acute pancreatitis, further management is aimed at preventing recurrent disease**.**

2.9.1 Early management

In the 20% of patients with severe disease specific measures must be employed to manage the complications. It is not clear whether specific measures to address hypertriglyceridaemia (63) and hypercalcaemia moderate outcomes. In patients with pancreatic necrosis and organ failure initial therapy is organ support in high dependency areas with monitoring for infection

Fluid resuscitation

Early fluid therapy is the initial intervention as elevated or rising serum urea levels within the first 24 hours were associated with mortality. (160) Gut ischaemia has been demonstrated to play a critical role in the natural course of severe acute pancreatitis. Reversing this ischaemia early in the disease is a widely accepted therapeutic goal. Maintaining an adequate intravascular volume is essential in the management of severe forms of the disease. This early resuscitation maintains pancreatic and tissue perfusion and may limit the development and extent of pancreatic necrosis. Despite this understanding the nature of resuscitation fluid, the appropriate volumes and the timing of intervention and the targets of fluid resuscitation have not been settled. (161)

In a retrospective study of 99 patients, those who received more than 4000ml of fluid in the first 24 hours had more respiratory complications (65% vs 53%) and intensive care unit admissions (47% vs 20%) than patients who received less than 4000ml in the first 24 hours. (162) A study that used changes in haematocrit at 24 hours as a marker of fluid resuscitation, showed that all patients with inadequate fluid resuscitation (persistent haemoconcentration at 24 hours) developed pancreatic necrosis. (163)

In patients with severe acute pancreatitis presenting within 72 hours of onset of symptoms, infusion rates of 10-15 ml/kg/hour were compared to rates of 5-10 ml/kg/hour. (164) Fluid sequestration in mls (5378±2751) vs (4215 ±1998) within 4 days was higher in the first group. The APACHE II scores were also significantly higher at days 1,2 and 3 in the first group and so was the rate of mechanical ventilation (94% vs 65%). Abdominal compartment syndrome and sepsis were lower in the second group whereas survival was lower in the first group (69.4% vs 90%, $p < 0.05$). This study concluded that the higher fluid resuscitation protocol was not beneficial to patients within 72 hours of the onset of severe acute pancreatitis.

In a study by Gardner, on 45 patients presenting with severe acute pancreatitis, a comparison was made between two groups who received ≥ or ≤ 33% of their 72-hour fluid requirements within the first 24 hours. Patients with ≤ 33% fluid resuscitation regimen had a higher mortality (18% vs 0%) and a trend towards a higher rate of persistent organ failure (43% vs 35%). (165) There was no difference in the

fluid administered during the first 72 hours suggesting a benefit from more aggressive resuscitation within the first 24 hours of presentation.

The nature of fluid to be used in resuscitation is also controversial. Infusions of large volumes of normal saline are associated with hyperchloraemic acidosis. In a pilot study which compared Ringers lactate and normal saline fluids, there was a significant reduction in SIRS after 24 hours in patients resuscitated with lactated Ringer's solution (84% vs 0%). (166) In a study from Scotland which compared survivors and deaths from severe acute pancreatitis, the cumulative volume of crystalloid given at 48 hours in patients who died was less than in survivors (3331 ± 800 ml vs. 7287 ± 544 ml). Patients who died were found to have received lower fluid volumes with higher median central venous pressures of 18 mmHg (range 15-19) vs 11 mmHg (7- 14) The use of central venous pressure as a marker of adequate fluid resuscitation was found to be unreliable. (167)

Until better powered trials are completed Ringer's Lactate should be the preferred crystalloid solution for the early resuscitation of patients with acute pancreatitis. Fluid resuscitation in acute pancreatitis is pertinent in severe forms of the disease. Rather than adhering to specific volumes and rates, the fluid requirements are tailored to individual requirements utilizing a number of critical care tools such as cardiac and renal output, inotropic requirements, central venous pressure, end tidal $C0_2$ and other markers of tissue perfusion.

Early interventions in biliary, hypercalcaemia, hypertriglyceridaemia associated pancreatitis

Gallstone pancreatitis

The need for early intervention in gallstone pancreatitis with biliary decompression by ERC is controversial with a number of conflicting reports. Biliary pancreatitis is caused by migrating stones and the duration of ampullary obstruction by migrating stones beyond 48 hours is associated with more severe pancreatitis.(168,169) Common bile duct (CBD) stones were also found in 75% of patients operated on within 73 hours and 28% of those having an elective cholecystectomy after discharge in a study by Stone in 1981. (170)

The initial trials on ERCP in gallstone pancreatitis were performed non-selectively in patients with gallstone related pancreatitis with conflicting results. When ERCP within 72 hours was performed non-selectively in 55 patients with gallstone related pancreatitis, 37(67%) were demonstrated to have choledocholithiasis and choledocholithiasis was more frequent in predicted severe than predicted mild disease(57% vs 29%). (171) When ERCP was performed non-selectively within 72 hours in 59 of 121 patients with gallstone related pancreatitis, there were fewer complications and shorter hospital stay in those subjected to ERCP. (172) In a subsequent study by Fan in 1993 on 127 patients non-selective

ERCP resulted in decreased biliary sepsis but not other complications of pancreatitis. (173) The decrease in biliary sepsis was similar in mild and severe pancreatitis.

Subsequent studies have been performed more selectively in patients with gallstone pancreatitis. Patients with biliary obstruction without cholangitis (bilirubin >20.52 umol/l), were randomized to urgent ERCP (within 24 hours) and early ERCP (24-72 hours). There was no differences in ERCP related complications or in hospital stay. (174)

In a 2007 study by Oria, early ERCP and papillotomy in patients with gallstone pancreatitis and biliary obstruction did not result in a lower mean organ failure score or mean CT severity index, lower incidence of local complications or mortality if there were no associated features of cholangitis. (175) A meta-analysis of three trials which included 450 patients was performed by the Dutch Pancreatitis Study Group to determine the outcomes of early ERCP in non-selected patients with acute biliary pancreatitis without cholangitis. The findings were that early ERCP was associated with a non-significant decrease in complications and a non-significant increase in mortality and these findings were not altered by analysis according to disease severity. (176) In a subsequent prospective study the same group demonstrated that complications were significantly lower and mortality insignificantly lower when ERCP was performed within 72 hours in patients with predicted severe acute pancreatitis associated with cholestasis. (177) They concluded that early ERCP is most beneficial in patients with predicted severe disease with cholestasis.

The interpretation of the most recent results has led to the current recommendations; urgent ERCP in patients with severe disease and cholangitis and ERCP at 72 hours in patients with mild disease and cholestasis. Cholecystectomy should be performed within the same admission.

Hypertriglycerideaemia

Whether early treatment to lower triglyceride levels improves clinical outcomes is not clear but there are reports suggesting that patients with severe hypertriglyceridaemia have a more severe course of acute pancreatitis with 71% having severe disease in a Dutch study.(178) The appropriate methods employed for reducing triglyceride levels > 10mmol/l and improving outcomes is controversial.(67) Measures beyond standard therapy are considered unnecessary by some authors.(179, 180) whereas others have proposed additional measures such as low dose heparin and insulin infusion (181), plasma exchange and plasmapheresis.(182) Initial local experience suggests that measures beyond initial starvation and monitoring of the reduction of levels are unnecessary.(67)

Hyperparathyroidism

Surgical treatment of hyperparathyroidism prevents reccurent pancreatitis in patients with hypercalcaemia. It has not been investigated whether therapy intended to lower the calcium levels at presentation improves outcomes in severe forms of the disease.

Nutritional interventions

Acute pancreatitis, especially the severe form, is associated with activation of systemic inflammatory pathways, complement cascade, oxygen derived radicals and arachidonic acid metabolites. These result in the production of acute phase proteins and loss of lean body mass. This is exacerbated by the lack of nutritional intake, increase in gut permeability, bacterial translocation and sepsis. Initially nutritional support in acute pancreatitis was based on the initial practice of fasting the patient in order to rest the pancreas and prevent enzyme secretion and further autolysis. This lack of nutrients to the gut wall resulted in structural and functional abnormalities with bacterial translocation and inflammation as a result. The inflammation increased the resting energy requirements and exacerbated the lean body mass loss. Parenteral nutrition served, the understanding then of, a need to rest the pancreas and counter the catabolic response. When used in all patients with acute pancreatitis, total parenteral nutrition was found to be of no benefit in reducing the days to oral intake and hospital stay or the development of complications in 54 patients randomized to the conventional therapy of fasting or total parenteral nutrition in 24 hours. (183) The improved understanding of the pathophysiology of pancreatitis resulted in the institution of early enteral nutrition. In the majority of patients with mild acute pancreatitis early enteral feeding is possible and may improve recovery but has no bearing on morbidity or mortality. (184) Early enteral nutrition using a nasojejunal feeding tube within 60 hours of onset was not associated with adverse events in predicted severe acute pancreatitis in 21 patients. (185)

Infectious complications, multiple organ failure and mortality were significantly lower in patients who received total enteral nutrition as opposed to total parenteral nutrition within 72 hours of the onset of symptoms. (186) In a randomized controlled study of patients with predicted severe disease by the APACHE II score of $\geq$8, CRP $>$ 120mg/L and Balthazar grade D or more, patients fed nasoenterally within 48 hours had fewer septic complications than patients fed by total parenteral nutrition. (187) Other complications, hospital stay and mortality did not differ. Nasoenteral feeding was also cost effective. Subsequently enteral nutrition was demonstrated to diminish the acute phase response and the disease severity when compared to parenteral nutrition. (188) However it has also been demonstrated that enteral nutrition did not improve the inflammatory response or intestinal permeability. (189) Nasogastric feeding was demonstrated to be more easily accomplished than nasojejuna feeding without worsening symptoms or negatively affecting outcomes. (190)

Modulating the nutritional content to achieve specific nutritional or immunological goals has followed on from the acceptance that early enteral nutrition is feasible and beneficial. The addition of glutamine to parenteral nutrition in acute pancreatitis was associated with a significant increase of cholinesterase, albumin and lymphocyte count and a decrease of CRP when compared to standard parenteral nutrition at day 14. Glutamine was also associated with a reduced length of parenteral nutrition [10 days {range 6–16} vs 16 days {range 10–18} ($p<0.05$)] and a trend towards reduced length of hospital stay [21 days {range14–32} vs 25 days{19–40}]. (191) Glutamine, Arginine and Omega-3 fatty acids have been shown to have immune-enhancing properties in the gut epithelium. (192) In a meta-analysis of three randomized controlled trials which included 78 patients in which Glutamine, Arginine and Omega-3 fatty acids were administered nasoenterally to 40 patients and standard nutrition to 38 patients. Infectious complications developed in 12(30%) of the immuno-nutrition group and 14(37%) of the standard enteral nutrition group without a significant reduction in the risk of infectious complications (RR 0.82; 95% CI 0.44 to 1.53),(193) Mortality between the two groups was also not significantly different (RR 0.64; 95% CI 0.20–2.07)

In patients with mild disease early feeding is possible but nutritional intervention does not affect the outcome. In severe disease, current understanding suggests that nutrition should be instituted within 48hours. The preferred route should be enteral even if only small amounts of immuno-nutrition can be delivered. Nasojejunal or nasogastric routes are equally effective. Patients with severe ileus will require parenteral feeding initially and this should be converted to an enteral route when gut function resumes.

Antimicrobials in acute pancreatitis

Advances in critical care and the use of antimicrobials resulted in a significant decline in the mortality rate of acute pancreatitis (**Figure 2**). This was as a result of management of general septic complications. Severe forms of acute pancreatitis often manifest an early significant systemic inflammatory response with capillary leak and hypovolaemia which may result in cardiorespiratory and renal complications and death. Patients who survive this initial phase in intensive care enter a later phase in which they are at risk of developing infectious complications which may include infection of the necrotic pancreas. The role of antimicrobials in preventing infection of necrotic pancreas is controversial.

Bacterial infection and the extent of pancreatic necrosis determine the incidence of organ failure independently. (194) In patients with sterile necrosis organ failure was determined by the extent of necrosis and the incidence of infection was associated with an increase in the extent of pancreatic necrosis. Infected necrosis is associated with a high incidence of organ failure. Infecting organisms in

most series are composed of Gram positive bacteria (Staphylococcus. Enterococcus, Streptococcus), Gram negative bacteria (Escherichia *coli*, Klebsiella) and Fungi (Candida, Cryptosporidium). (195, 196)

In HIV associated pancreatitis opportunistic infections such as Pneumocystis carinii and Mycobacterium avium intracellulare have been demonstrated. (24) This results in HIV patients in a larger spectrum of organisms including viruses both systemically and in the necrotic pancreas.

Selective gut decontamination was found to prevent septic complications of the pancreas and resulted in lower morbidity and the need for operation. (194) However, mortality was not significantly altered. Probiotics were an alternative therapeutic intervention based on their ability to alter the intestinal flora and reduce bacterial translocation with its attendant septic complications. An initial trial showed promise in reducing the pancreatic septic complications (197) however the subsequent Probiotics in Pancreaitis Trial (PROPATRIA) has dampened enthusiasm for this therapeutic avenue when it reported that the only mortalities were in the probiotic arm. (195)

The trials of antimicrobial agents in acute pancreatitis are summarized in **Table 10**. (13, 198-210) When examining trials which have addressed antimicrobial use; the agents used varied, the dosage and duration was not uniform and patient allocation methods and the blinding processes were unclear. In addition, two agents were used in some of the trials and the number of patients investigated were small. Beger has demonstrated that infection of the necrotic pancreas is dependent on the extent of the necrosis and the duration of necrosis with the majority of infection occurring after two weeks. (211) Some trials examined not just infection of the necrotic pancreas but also pulmonary, urinary tract and blood. (199) Antimicrobials have also been assessed in alcohol as a single aetiology group where they showed benefit. (199, 200) However it is unclear how generalizable these results are in the other common aetiology, gallstones. The study by Dellinger in 2007 did not demonstrate any benefit in the reduction of sepsis, mortality or surgical intervention when Meropenem was used in 50 of 100 patients with confirmed necrotizing pancreatitis in a multi-centre trial involving European and United States of America centres. (13)

A subsequent meta-analysis has also determined that routine antibiotic prophylaxis does not prevent septic complications or reduce mortality. (212) This review concluded that prior studies were underpowered and that Imipenem may have benefit in preventing infection in CT scan proven pancreatic necrosis. Many studies are confounded by the variable proportion of patients who die early before the pancreatic necrosis has become infected and hence the benefit of antimicrobials cannot be measured in these patients. (**Table 11**) IL-6 and PCT measured soon after hospital admission were associated with infection of pancreatic necrosis and their use to determine the need for antimicrobial therapy requires further evaluation. (213)

Routine early use of antimicrobials is not current practice. Antimicrobials are unlikely to significantly reduce mortality in the early phase as this is largely a sterile insult. Empiric antibiotics should be commenced only when there is suspicion of infection and altered to directed therapy when the offending organism is identified. In HIV related pancreatitis opportunistic and viral infections are part of the spectrum and should be considered when antimicrobial therapy is deemed necessary. A potential to improve the rational for antimicrobial therapy is better selection of patients who may benefit, using IL-6 and procalcitonin measurement soon after hospital admission.

2.8.2 Late management

The management of infected pancreatic necrosis is controversial and dependent on local expertise and experience. Intervention is contraindicated early in the process as mortality is high regardless of intervention. Pancreatic necrosis with signs of systemic sepsis indicates the need to consider the diagnosis of infected pancreatic necrosis. Infected pancreatic necrosis however diagnosed requires intervention if it is associated with organ failure. Traditionally open surgery techniques which included open packing, repeat laparotomy, closed packing and closed continuous lavage were utilised. **Table 12** (214-225) is a review of the outcomes of open surgery and demonstrates that mortality rates range between 6% and 39% and that a rate of 15% has been achieved by all techniques in experienced centres. The morbidity rate for pancreatic fistula ranged between 14% and 88% and bleeding complications between 5% and 83%.

Because of high morbidity and mortality of open surgery, minimally invasive staged necrosectomy has been utilized as initial management which may be definitive or act as a bridge to allow optimization of organ failure prior to open surgical intervention. A number of techniques have been devised utilizing percutaneous drainage with saline flushes, laparoscopic drainage, video assisted retroperitoneal debridement (VARD) and transluminal endoscopic techniques. (226, 227) The results of these approaches are evaluated in **Table 13**. (228-235, 218-219, 234-239, 225) The morbidity and mortality rates range widely between 10% and 88%, and 5% and 40% respectively due to the heterogeneity of the study populations.

Diagnosis of infected necrosis may be a challenge as these patients are frequently in high dependency environments and physiologically unstable. In many instances the clinical suspicion will guide intervention. These include non-resolving features of sepsis and clinical deterioration. There exists a need for biochemical markers of infected necrosis which can direct further evaluation. In a study to assess the predictive value of PCT and IL-8, patients with infected necrosis had significantly higher median concentrations of PCT and IL-8 than those with sterile necrosis. There was no difference in

CRP between the 2 groups. This was in patients in whom serum samples were drawn daily for 2 weeks and the diagnosis of infected necrosis was made at a median of 13.5 days from admission. (140) The aim of the study was to select patients for antimicrobial prophylaxis in those with pancreatic necrosis, serum levels of IL-6, TNF-α, CRP and PCT were assessed during the first 3 days after admission. (213) PCT and IL-6 were markedly higher and differed between patients who developed infection and those who had a negative culture when CT scan and needle aspiration of pancreatic necrosis was performed. There was no difference in the TNF- α and CRP in these 2 groups. The combined use of IL-6(<400 pg/L) and PCT (< 2 ng/L) best predicted patients not at risk for infection with sensitivity, specificity and negative predictive values of 75%, 84% and 91% respectively.

A larger cohort of 104 patients with predicted severe pancreatitis in 5 European centres were evaluated with PCT and CRP. (141) Both parameters were measured daily for 21 consecutive days and weekly thereafter. Significant elevations in PCT were associated with pancreatic infection accompanied by MODS in patients who did not survive the pancreatitis. These changes were found early after onset of symptoms. In contrast PCT elevations were moderate in pancreatic infections without MODS. CRP did not show similar changes. A PCT value of ≥3.5 ng/mL was significantly better than a CRP value of ≥ 430mg/L on the initial 2 consecutive days for determining infected necrosis with MODS or death (P < 0.01)) This difference in prediction of poor outcomes was still evident on the third and fourth days (P = 0.002) (**Table 14**).

Evolution of surgical therapy

The evolution of the management of acute pancreatitis since the first clinical description is presented in **Figure 2** and details the changes in the place of surgery and the subsequent influence of advancements in critical care, antimicrobials and minimally invasive procedures on mortality.

Initially the majority of patients were diagnosed intra-operatively and early surgical intervention was considered appropriate though only few survived surgery. In 1889, Fitz reviewed the presenting symptoms, signs, aetiological associations, local complications and different pathological classifications. (246) He set out the initial criteria for an antemortem diagnosis of acute pancreatitis. He initially considered surgery as unhelpful and later recognised some benefit in selected patients. In 1894 Werner Körte performed surgical drainage of an abscess complicating acute pancreatitis. He advocated delayed surgical intervention as early surgery was associated with poor outcome. (247) Despite these conservative recommendations, a prolonged period of the primacy of surgery in acute pancreatitis followed in the early decades of the 20th century. Moynihan was convinced that recovery was unlikely without surgical intervention despite the lack of agreement on the nature of the intervention. (248) He advocated debridement and drainage of the lesser sac. In 1927, Schmieden in

a review of 1510 cases of acute pancreatitis found a mortality rate of 51% in the 1278 patients subjected to surgery. (249) He advocated early surgical intervention despite their findings of 24% and 65% mortality rates in the oedematous and necrotizing pancreatitis respectively.

The introduction in 1929 of the biochemical marker serum amylase enabled the diagnosis of acute pancreatitis without the need for surgery. This allowed the clinical differentiation between mild and severe forms and the recognition that acute pancreatitis had a mild and self-limiting course in the majority of cases, that did not require surgery. (110) The paradigm shift from frequent surgical intervention to initial non-operative intervention was strengthened by a 1948 analysis of a series of 307 patients that revealed a surgical mortality of 45% and a non-operative mortality of 28%. (250)

A selective approach to surgical intervention became the norm with surgery reserved for those who showed clinical deterioration after the initial phase of resuscitation and cardiorespiratory support. (251) Surgery was also reserved for cases of diagnostic doubt since the clinical and biochemical parameters were not specific for pancreatitis in these patients and most of the possible differential diagnoses required a laparotomy for management. (252)

Interventions are currently restricted to patients who develop compartment syndrome, perforated bowel and infected pancreatic necrosis. Open surgical techniques for infected necrosis were practiced over decades and more recently this has been superseded by minimally invasive techniques which use a delayed step up approach using percutaneous or endoscopic techniques singly or in combination to provide staged drainage. (232, 253)

2.8.3 Mortality

At the beginning of the 20th century mortality rates in acute pancreatitis reached 60%. (254) The use of positive pressure ventilation in the 1940s resulted in a decline in mortality to 18%. (255) In the period 1969-1979 a further reduction to 7.8% was observed. (256) Subsequently in the decade from 1984 to 1995 there was a decline from 9.1% to 6.6% despite an increase in the overall number of fatalities. (5) These improvements in survival were associated with advances in respiratory, cardiac and renal support and, antimicrobial therapy in critical care settings.

Recent investigations demonstrated that death in acute pancreatitis is an early (<2 weeks) or late (>2 weeks) event. Early mortality results from a severe SIRS which may progress to multiple organ failure and death. Late mortality is a result of septic complications. (257) The management of patients in these 2 phases of the disease differs as the initial treatment is supportive with attention to organ failure and the latter may require intervention to address infected necrosis. **Table 11** (2, 4-10, 14-18, 21, 23, 139, 258) illustrates the proportion of early and late mortality in various trials and in previous studies from

South Africa most (67-79%) mortalities were early within two weeks. (3, 5-8, 14, 15, 17, 20, 22, 67, 110, 225) The global trend is towards a greater proportion of mortality within two weeks. There was no significant difference between early or late mortality in terms of age, gender distribution, aetiology, predictors of severity, BMI, comorbidity and year of admission. (14) Early deaths were associated with multiple organ failure and late deaths multiple organ failure and infected necrosis. In a large study of 13727 patients between January 1984 and December 1995, 53.7% of patients died in the first week of hospitalization with a range 61.7%- 49.1% over that period. The majority (78.4%) of early mortalities were in patients older than 60 years but the proportion of early and late mortalities was similar in all age groups. (5)

Aetiology has not been demonstrated to influence mortality in most settings but a study from Korea demonstrated that an alcohol aetiology when compared to a biliary aetiology had a more severe course with pseudocyst formation (20% vs 7%), organ failure beyond 48 hours (24% vs 1%) and a significantly higher mortality (8% vs 0%). (45)

SECTION 2: HIV INFECTION

2.9 Epidemiology of HIV infection

HIV belongs to the Retroviridae family and the Lentivirus genus. Lentiviruses cause slow, unremitting disease targeting lymphocytes and differentiated macrophages in the host. It is a retrovirus with its genetic information encoded in RNA and requires reverse-transcription into DNA by viral reverse transcriptase for replication. (253) In infected individuals, the virus is present in the blood, semen, rectal fluids, vaginal fluids and breast milk. The main routes of transmission are sexual contact, mother to child before or during birth or with breastfeeding and sharing contaminated needles for injectable substances or needle injuries in health professionals. (254) HIV infection transmission is positively influenced by viral load and associated genital ulceration. (255) Viraemia and hence transmission is higher in the 3 months after primary infection just prior to seroconversion and late in the disease before death. (256) The virus may infect a number of different cell types but the main target is CD4 T-cells. It may also infect CD4+ macrophages and dendritic cells. (257)

In a 2016 report an estimated 37 million people were living with HIV infection worldwide and 70.8% of them were in sub-Saharan Africa. (257) The age and gender distribution of HIV infection in KwaZulu Natal province is shown in **Figure 3**. In this province as in the rest of sub-Saharan Africa, the spread of the virus is predominantly by mother to child or heterosexual transmission. The world prevalence increased from 31 million in 2005 to 35.3 million in 2012 as people are living longer with treatment. This was despite a decline in the incidence of new infections from 3.3 to 2.3 million over the same period as a result of a decline in heterosexual transmission while homosexual transmission remained the same. The reduction in transmission is the result of effectively screened blood donations, increased use of HAART, perinatal HAART, male circumcision and drug infused vaginal gels. (258) Despite these measures, transmission during the acute infection phase remains problematic and cure of HIV viral infection by vaccination is hampered by the virus being inaccessible when it enters a latency phase in different cell types and its high genetic diversity. (253, 259-261) In a national survey in South Africa in 2012, 31.2 % of HIV+ve individuals were on treatment with HAART. (25)

2.10 Aetiology and pathogenesis of HIV infection

HIV has been shown to have extensive genetic heterogeneity, between individuals and within an individual. The heterogeneity is largely located in the gene encoding the envelope glycoprotein, gp 160. Genetic diversity within an individual, increases by 1% annually. (262)

HIV-1 and HIV-2 are the dominant HIV virus strains. HIV-1 is the predominant strain in South Africa and Southern Africa. HIV-2 causes a slower decline in CD4+ T-lymphocytes, longer periods of asymptomatic infection and lower mortality rates than HIV-1 infection. (263)

Primary HIV infection may range from asymptomatic seroconversion to a severe illness requiring hospitalization. (264) Symptoms which are commonly associated with primary HIV infection are fever, sore throat, fatigue, weight loss and myalgia with physical examination revealing postural hypotension, oral ulceration, exudative pharyngitis, thrush, genital or rectal ulceration, lymphadenopathy and signs of neuropathy**.** Signs and symptoms of aseptic meningitis fever, headache, photophobia and neck stiffness may also be present. As these features are not specific to HIV, the infection may be missed at this point. At the primary infection, the viral load rises and there is a rapid decline in the CD4 lymphocyte count. The immune response at seroconversion eventually contains the viral replication and the viral load will decline to levels lower than 1% of the peak levels. There follows a period of stable viral levels without symptoms. (265) There is a temporal relationship between infection and the emergence of HIV RNA P24 antigen which is shorter than the time taken to develop antibodies to the virus. P24 antigen testing has shortened but not eliminated the window period of infectivity prior to the diagnosis when sexual contacts remain vulnerable to acquiring the infection,.

Figure 4 shows the temporal relationship of the HIV diagnostic assays superimposed on a graphical depiction of the kinetics of circulating HIV RNA, p24 antigen and HIV antibodies. It shows the times to reliable positivity of the five generations of tests with the nucleic acid amplification test now being the preferred test. (266)

During the chronic phase the CD4 levels will decline to very low levels in untreated individuals rendering the host susceptible to opportunistic infections such as Mycobacterium avium, Pneumocystis, Cryptococcus neoformans, Toxoplasma gondii and Cytomegalovirus or to tumours such as Kaposi's sarcoma and B-cell lymphomas. Some patients will develop neurological dysfunction and HIV associated nephropathy. (267)

In some patients chronic inflammation persists despite undetectable viraemia and is associated with a poorer outcome. The persistent inflammation is explained by preferential depletion of the CD4+ helper cells in the gut mucosa which results in bacterial translocation and inflammation. (268) A persistently elevated CRP level (>5mg/dl) at presentation and 24 weeks after initiation of HAART was associated with disease progression when compared to persistently low levels or an isolated elevation in CRP. (269) The combination of elevated CRP(>10mg/l) and anaemia (females<12mg/dl, male<13mg/dl) prior to HAART was associated with treatment failure after initiation of HAART. Treatment failure

was defined as stage 3 (symptomatic infection with opportunistic infections), stage 4 (CD4 drops to <200 and worsening opportunistic infections) or death at 96 weeks. (270)

It is unclear which factors influence outcome in HIV infected patients who present with critical illness that requires organ support. In a study assessing HIV infected patients admitted to ICU for various diseases there was no difference in mortality between patients admitted with sepsis and patients admitted with SIRS of a non-infectious aetiology. In the same study a low CD4 lymphocyte count was not associated with an increased mortality rate, but three (75%) of the ICU admissions with pancreatitis died. (43)

2.11 Mortality in HIV infection

A survey of mortality in 78,000 HIV-infected patients from France reported 964 in 2000 and 1042 deaths in 2005. (271) AIDS related deaths accounted for 36% of deaths in 2005 and 47% of deaths in 2000. Eleven percent (2000) and 9% (2005) of patients died within 6 months of initial presentation. Non- Hodgkin Lymphoma was the most common cancer related cause of mortality in all patients. The median age of death increased from 41 years in 2000 to 47 years in 2005. The median duration of HIV infection increased from 8 to 12 years and the number on HAART was 87%, up from 86%. The mean CD4 count was 94 in 2000 and 161 in 2005. (271)

Patients with HIV infection treated with HAART have been found to have premature cardiovascular associated mortality purported to be caused by the HAART side effects of fat redistribution, dyslipidaemia and insulin resistance. (272)

In a Danish population based cohort observational study over the period 1995-2005 the median survival from 25 years of age at initial observation was 19.9 years (95% CI,18.5 to 21.3) in patients with HIV infection and 51.1 years (CI,50.9 to 51.5) in the general population. For HIV-infected patients, survival increased to 32.5 years (CI, 29.4 to 34.7) over this period illustrating the benefits from HAART. (273) In South Africa the survival times were 80-82% and 82-84% of those in HIV negative individuals for men and women respectively when calculated in individuals commencing HAART at 35 years of age with a baseline CD4 count of 200 or higher. (274) This study did not provide data on survival in HIV-ve individuals.

In an American cohort of 4241 HIV infected participants evaluated from 1990 to 2003, 1224 (28.9%) deaths occurred with 987 deaths prior to HAART and 237 in the HAART era. The 237 deaths included 159 deaths in the early HAART era (1997–1999) and 78 in the late HAART era (2000–2003). There was an 80% decrease in deaths from 1990 to 2003. In this period AIDS defining causes of death declined from 80% to 56% and non HIV related causes of death increased from 9% to 32% and death

as a result of opportunistic infections declined from 59% to 24%. Liver disease as the primary cause of death increased from 0.2% to 3.7%. The number of deaths associated with CD4 cell counts of less than 200 cell/mm^3 declined from 93% to 61% in the same period. (275)

These observations demonstrate a benefit in survival from HAART and although acute pancreatitis is frequently associated with HIV infection it is not among the commonest causes of mortality. HAART has resulted in increased CD4 counts and a decline in AIDS defining causes of death.

Section 3: Overall summary of chapter

Amylase and lipase are enzymes that are most frequently used adjuncts to confirm the clinical diagnosis of acute pancreatitis. Lipase has been demonstrated to more useful because of a higher specificity than amylase. Establishing the aetiology and severity of the disease is key to effective management. Gallstone pancreatitis can be reliably diagnosed and managed effectively to prevent recurrence. Severity assessment allows patients to be identified to allow appropriate organ support and further assessment for the presence and extent of pancreatic necrosis and guides further management. Infected pancreatic necrosis with organ failure requires interventional management to reduce mortality. These management principles are well elucidated in HIV-ve patients but not in HIV+ve patients

HIV infection is associated with both asymptomatic and symptomatic elevations in amylase. This draws into question whether these enzymes are effective diagnostic adjuncts in HIV infected cohorts. In South Africa, over the past decade, there has been a rise in acute pancreatitis cohorts of HIV+ve patients but there is no information on the incidence of acute pancreatitis in both the general and HIV populations. Although most cases of acute pancreatitis are associated with gallstones and alcohol, in HIV infection there are many potential additional aetiological associations which include drug therapy, opportunistic infections and malignancies. In reports from regions with HIV infection prevalence rates of less than 1% there was a decline in the acute pancreatitis incidence in HIV infected individuals although this remains higher than in the general population.

Early prognostication is crucial in the management of acute pancreatitis to facilitate the identification of severe disease which may result in morbidity or death. The APACHE II score has been demonstrated to be effective and the BISAP score simple and applicable to lower levels of care. These have been studies conducted in countries with a low HIV prevalence. Since HIV infection and antiretroviral

medication is associated with deranged liver function tests, altered immunity and white cell counts, it has not been established whether the prognostic markers are suitable for use in HIV infected cohorts with acute pancreatitis which may have varying degrees of alteration in inflammatory markers and other biochemical and haematological parameters.

Since HIV infection is associated with opportunistic infections and these have been demonstrated in the pancreas in post-mortem investigations, it is not clear from previous studies whether opportunistic infections are a major factor in determining outcomes in HIV associated pancreatitis. There is no clear picture of outcomes in HIV associated pancreatitis with some demonstrating worse outcomes and others not demonstrating any differences with HIV-ve related pancreatitis.

This study aims to address these deficiencies by directly comparing the hospital prevalence of acute pancreatitis and the rate of associated HIV infection.

A study into the aetiological association between HIV infection and acute pancreatitis is highly pertinent and appropriate to South African clinical practice where the prevalence of HIV in the 15-49 year old population group is 19.2%. The few studies in a South African context have demonstrated an increase in the prevalence of HIV infection in patients presenting with acute pancreatitis. However, these studies involved patients in whom HIV testing was not performed in all patients and hence they are likely to have underestimated the prevalence of HIV infection in patients with acute pancreatitis. Theses deficits set the frame work to formulate the study aim that seeks to address the paucity of critical analysis of the relationship between HIV infection and pancreatitis in an environment with a high prevalence of HIV infection.

CHAPTER 3: METHODS

3.1 Design

The study is a prospective descriptive analysis of acute pancreatitis and trauma cohorts with universal counselling for HIV infection testing. The hypotheses to be tested are detailed in Chapter 1.

3.2 Study location and period

Prince Mshiyeni Memorial and Addington Hospitals in Durban over 2 years for data collection and analysis.

3.3 Study population

Patients were sourced from the emergency departments at Addington and Prince Mshiyeni Memorial hospitals within the Durban metropolitan functional region of the KZN Province. Addington hospital has a mixed racio-ethnic referral base derived from its urban and peri-urban population in the central and northern parts of the metropole. Prince Mshiyeni Memorial hospital has a largely indigenous African referral base serving the urban, peri-urban and rural population in the south of the metropole and the province. Racio-ethnic analysis was also included due to the marked variation in the prevalence rates of HIV infection with these designations. Racio-ethnic groups were self-declared in the study.

3.4 Data collection and tools

Patients included in the study were 18 years and older. Data related to demographics, biochemical investigations, aetiology, imaging, endoscopic procedures, surgery and outcomes were collected directly into a password protected spread sheet using Microsoft excel.

Patients were included in the study sample if they presented with the typical symptoms of sudden onset of epigastric pain and an elevated serum amylase or lipase of at least 3 times the upper limit of normal, or a urine amylase >1000 IU/L. Biochemical, haematological and clinical parameters used in assessing predictors of severity were assessed within 24 hours of presentation (SIRS, Glasgow, APACHE II, CRP and BISAP). This was temporal assement was choosen because of the interest to make the earliest prognosticalion possible as this as this would allow more accurate triage at an earlier stage. The scoring systems were assessed for their accuracy in stratifying patients into mild, moderate and severe disease according to the revised Atlanta criteria. (48) Alcohol use was sought in the history(daily consumption or binge drinking) and transabdominal ultrasound examination was used to determine gallstones as the cause of pancreatitis. All trauma and acute pancreatitis patients were counselled for HIV testing if their status was not declared and verified to be correct. Known HIV+ve patients were asked whether they

were receiving HAART and if so, what drugs they were receiving. Chest and abdominal x-rays and ultrasound were used at presentation to screen for other pathological conditions with similar presentations to acute pancreatitis. CT was used to assess for complications of acute pancreatitis in patients who did not show improvement in the first week or had severe disease. A pancreas protocol was performed in three phases. An initial non contrast scan was performed from the diaphragm to the Iliac creast. Three cups of water were given orally every 10-15 minutes prior to commencing the scan. Contrast (100ml Omnipaque) was injected intravenously at 3mls/second. Parenchymal and portal-venous phases were then acquired at 40 seconds and 80 seconds after contrast injection by scanning from the diaphragm to the Pubic symphysis. Renal function requirements for contrast administration are urea > 12mmol/l, creatinine <130 mmol/l and a glomerular filtration rate > 45. Patient with renal function worse than the presets will require periprocedural dialysis on a non contrasted Magnet Resonance Imaging (MRI). MRI was not performed in this group of patients. Antimicrobials were not prescribed routinely and were prescribed empirically when infection was suspected or using specific directed antimicrobial therapy when an organism was identified or cultured.

HIV was diagnosed by the use of 2 serial rapid third generation tests. An Enzyme-Linked Immunosorbent Assay (ELISA) was used when the tests were discordant or weakly positive. The Advanced Quality Rapid Anti-HIV Test was used as the initial test. It has been found to have a 100% sensitivity and specificity when compared to Enzyme linked immunoassay (EIA) and Western Blot as reference points. The HIV 1/2/0 Tri-line Rapid test was used as the second confirmatory test. When compared to ELISA and the Western Blot it was found to have a sensitivity of 99.9% (99.4-100%), specificity of 99.8% (99.5-99.9%) and relative accuracy of 99.8% (99.6-99.9%).

3.4.1 Patients

Inclusion / exclusion criteria

Epigastric pain associated with one of the following: an elevated serum amylase or lipase greater than 3 times the upper limit of the normal or an ultrasound or CT with features of pancreatitis or findings of pancreatitis at laparotomy.

Patients admitted with trauma of all grades were assessed and compared with the pancreatitis group in terms of age, gender, racio-ethnic proportions and the prevalence of HIV. Continuous variables will be expressed as mean and standard deviation (no outliers) or median and interquartile range (outliers) and categorical variables as numbers. Students t test or the Mann-Whitney test were used to compare medians between groups and Pearson chi-squared ($\chi 2$) test or Fishers exact tests were used to compare proportions.

Acute pancreatitis

Demographic information was evaluated, a history of regular alcohol consumption was used for an alcohol aetiology. A gallstones aetiology was determined by transabdominal ultrasound, endoscopic ultrasound and endoscopic retrograde cholangiopancreatography. A drug related cause was determined by history.

Trauma

The trauma cohort was chosen as the group which most closely mirrors the general adult population at admission as there is an assumption of absence of disease prior to admission.

Consecutive patients admitted for trauma were assessed for the extent of injury and HIV status. The patients were recruited at the commencement of the study until 90 have been accumulated. The second 90 patients were accumulated when half the required number of patients with acute pancreatitis had been recruited. The trauma cohort had their injury severity recorded. The severity was assessed initially using the abbreviated injury scale (AIS). The AIS is an anatomically-based, consensus-derived, global severity scoring system that classifies each injury by body region (head, face, chest, abdomen, extremities and skin) according to its relative severity on a 6 point ordinal scale. 1 – Minor, 2 – Moderate, 3 – Serious, 4 – Severe, 5 – Critical and 6 – Maximal. The NISS is defined as the sum of the squares of the AIS scores of each of a patient's three most severe AIS injuries regardless of the body region in which they occur. The scores range from 0 to 75.

3.4.2 Data collected

1. HIV status
2. Antiretroviral medication
3. Duration of symptoms
4. Amylase, urine amylase and lipase
5. Criteria for assessing SIRS, Glasgow score, BISAP and APACHE II scores (Annexure Tables 1 to 4)
6. CT imaging in those with predicted severe disease or failure to improve after 1 week of admission.
7. Complications and in hospital mortality during the same admission. Complications were defined as grade 1 to 5 according to the Clavien-Dindo Classification. (267)
8. In patients with gallstone related pancreatitis cholestasis were defined as elevation of the cholestatic enzymes (alkaline phosphatase: > 121 U/L, gamma-glutamyl transferase:> 64 U/L and bilirubin >21 μmol/L), Sepsis were defined as any 2 of temperature(>38˚C), white cell(>$11\times10^{12/L}$) count and tachycardia (>90 beats/minute).

3.5 Data analysis

3.5.1 Sample size

The prevalence of HIV infection in the general population in KZN is 16% and 26% in the 15 – 49 year age group more prone to acute pancreatitis. Previous prospective trials of outcomes in acute pancreatitis in this region have demonstrated morbidity and mortality of 15% and 32%, and mortality of 8% and 8% respectively. (19, 21)

These values were used to determine the pre-test probabilities of 10% and 20% for mortality and morbidity. A mortality endpoint calculation based on a hypothesized doubling of death frequency to 20% in the HIV+ve patients in comparison to the HIV-ve patients would have required a sample sizes of 219 in each group. This was based on a power of 0.80, a beta set at 0.20 and alpha to detect a difference between the group proportions of 0.1000. The proportion in group one (HIV+ve) was assumed to be 0.1000 under the null hypothesis and 0.2000 under the alternative hypothesis. The proportion in group two (HIV-ve) is 0.1000. The test statistic used was the two-sided Fisher's Exact test. The significance level of the test was targeted at p=0.05.

A recruitment target of this magnitude was not achievable given that a pancreatitis dataset to study the association with dyslipidaemia, took 10 years to accrue 600 patients at a busy regional hospital. Based on this recruitment rate it would require 6 years to accumulate 438 patients a time frame not feasible for the project. It was decided that a composite(morbidty and mortality) morbidity endpoint calculation would be more feasible. If morbidity hypothesized a doubling to 40% in the HIV+ve patients, the sample size of each group would be 90 to achieve 80% power to detect a difference between the group proportions of 0.2000. The proportion in group one (HIV+ve) is assumed to be 0.2000 under the null hypothesis and 0.4000 under the alternative hypothesis. The proportion in group two (HIV-ve) is 0.2000. The test statistic used is the two-sided Fisher's Exact test. The significance level of the test was targeted at p=0.05.

To be feasible within 3 years the study the end point must be based on morbidity which entails assessing differences in combined moderate and severe disease on the composite morbidity endpoint of complication frequency, organ failure and mortality.

3.5.2 Statistical analysis

Variables to assign groups were HIV status (HIV +ve and HIV-ve). Continuous variables were expressed as a mean with a standard deviation (SD) and categorical variables as numbers. The ability of selected severity scores to correlate with the composite severity endpoint {the frequency of local complications (pancreatic necrosis, pseudocysts, ascites, vascular complications, pancreatic abscess), organ failure and mortality during the index admission} will be evaluated by the use of 2 by 2

contingency tables and computing sensitivity and specificity. Receiver operating characteristic curves (ROC) will be calculated for the ability of each scoring system to determine disease severity. The predictive accuracy of each system will be assessed by determining the area under the curve (AUC) with 95% confidence intervals. An AUC of 0.60-0.69 will be interpreted as poor, 0.70-0.79 as fair, 0.80-0.89 as good and 0.90-1 as excellent.

Potential outcome confounders associated with HIV infection, in particular malignancy, tuberculosis and opportunistic infections were assessed.

3.5.3 Acute pancreatitis severity assessment modalities

The Glasgow criteria at 24 hours, CRP at 24hours, BISAP and APACHE II scores at 24 hours were used to predict outcomes (Annexure 1) A Glasgow score of more than 2, CRP > 150mg/l, APACHE score > 7 and a BISAP score ≥ 2 were the cut off levels used to predict a severe outcome. Organ failure was assessed and defined as a score of ≥2 for at least one of the systems for determining the Marshall score (**Table 8**).

SIRS was classified as 2 or more of the following criteria for > 48 hours: pulse > 90 beats/minute, temperature of <36˚C or >38˚C, white blood count <4000 or > 12000 per mm^3 and respiration >20/minute or PCO_2 < 32mmHg.

3.5.4 Acute pancreatitis grading of severity, modified Atlanta criteria

The pancreatitis was allocated to one of 3 grades **(Annexure Table 8).** Pancreatitis has two clinical phases, the early within the first week and the late in subsequent weeks. Severe disease in the early phase is based on the presence of organ failure and in the late phase on local complications or persistent organ failure.

3.6 Ethics

Ethical approval was provided by the Biomedical Ethics research committee of the University of Kwazulu Natal, with a bioethics number of BE222/11.

3.7 Summary

The study was conducted as a prospective evaluation of consecutive admissions with acute pancreatitis and trauma victims to 2 regional hospitals in the Durban region. The prevalence of HIV infection in acute pancreatitis was compared to that of a trauma cohort admitted to surgical wards. Diagnosis of acute pancreatitis was based on serum amylase primarily with lipase and urine amylase as the alternative modalities. Prognostication on the outcomes of acute pancreatitis was by the SIRS, Glasgow

criteria, CRP, APACHE II and BISAP scores. CD4 counts were evaluated in HIV infected patients and outcomes were determined in relation to a CD4 count of above or less than 200 cells/mm^3. Infectious complications were evaluated with a microbiological spectrum and related to HIV status. The outcomes in HIV-ve and HIV +ve patients were compared in relation to demographic profile, aetiology, prognostication, morbidity and mortality during the index admission.

CHAPTER 4: RESULTS

4.1 Description and comparison of the pancreatitis and trauma cohorts

The study was conducted from August 2013 to October 2015 and during this period 238 patients were admitted with acute pancreatitis and 181 consecutive trauma patients were evaluated as a comparison group for the prevalence of HIV infection in a hospital population. Sixty eight per cent of patients with pancreatitis were admitted to Addington hospital and 32% to PMMH. Pancreatitis was found in 0.01% of admissions to Addington hospital and in 0.002% of surgery admissions in PMMH (**Table 15**). In the pancreatitis cohort, the prevalence of HIV infection in indigenous African patients was 32(23%) and 6(7%) in the other racio-ethnic groups.

One hundred and eighty one patients were admitted with trauma. The NISS ranged from 1 to 39 with median score of 9(IQR 4-17). Forty seven (26%) had a NISS score, that represents major trauma, greater than 15. The gender proportions were significantly different in the trauma and pancreatitis cohorts with significantly more females in the pancreatitis cohort and more males in the trauma cohort. The proportion of indigenous Africans was significantly higher in the trauma cohort and those of Indian descent significantly higher in the pancreatitis cohort. Self declared mixed and white racio-ethnic groups were similar (3% vs 3% and 3% vs 2%) in the two cohorts. The prevalence of HIV infection in the indigenous African trauma patients was 28(18%) and 1(5%) in other racio-ethnic groups. The patients with pancreatitis had a 2.4 times higher prevalence of HIV and were significantly older {40(±12.3) vs 33(±11.8) years} than the trauma victims (p=0.001). (**Table 16**) A significantly higher number of patients in the trauma cohort (29% vs 9%) declined testing for HIV infection(p=0.001). Fifty nine percent of patients were on HAART in the trauma and pancreatitis cohorts. (Table 16).

HIV infection was more prevalent in females across all the age groups in the trauma and pancreatitis cohorts. In both females and males, the peak in HIV infection was in the 35-44 year age range. (**Figure 5**)

4.2 Detailed description of the entire pancreatitis cohort

In the pancreatitis cohort 58% of the patients were male with a mean age (±SD) of 40 years (±12) and 49% had alcohol as the aetiology. Drugs were the only association in 24% of the patients. The APACHE II, SIRS and Glasgow criteria were completely assessed in 97%, 97% and 90% of patients respectively. The BISAP score was completely assessed in 99% and CRP in 89% of patients. CT assessment was performed in 34(14%) and 10(4%) had features of severe disease as defined by CTSI. Organ dysfunction was present in 46 patients (19%) at admission and had resolved at 48 hours in 31. Organ failure developed in a further 13(5%) after admission. Thirty three patients (14%) had local complications and 32(13%) had pancreatic ascites which was the most common complication. When classified according to the Clavien-Dindo system, 20(61%), 1(3%), 3(9%), 1(3%), 1(3%) and 7(21%) were graded 1-5 respectively. Pancreatic necrosis was found in 11(5%) of patients, none had established infected pancreatic necrosis, and 5 died. Six of the patients with pancreatic necrosis had antimicrobial therapy and sepsis was identified in the blood in 3 patients and one had a chest infection. Twelve (5%) of the patients with acute pancreatitis died (**Table 17**).

4.3 Analysis of pancreatitis cohort based on HIV status

Ninety (38%) of the patients with pancreatitis were HIV+ve. The proportion of 50 -74 year age group (28% HIV-ve vs 9% HIV+ve) was significantly higher in the HIV-ve patients (p=0.002) and the difference was insignificant in the other age groups. The proportion of female patients (53**%** vs 35**%)** (p=0.02) and indigenous Africans (93% vs 50%) (p<0.001) were significantly higher in the HIV+ve patients than in the HIV-ve patients. In 22(9%) patients the HIV status was not known as patients declined testing for HIV infection (**Table 18**).

The assessment of aetiological patterns revealed that the prevalence of gallstone (27% vs 30%) and alcohol (41% vs 52%) aetiologies were similar between HIV+ve and HIV-ve patients and a drug related aetiology was more prevalent in HIV+ve related pancreatitis (24% vs 0%). Lamivudine, Isoniazid and Trimethoprim-Sulfamethoxazole were the drugs associated with pancreatitis in the HIV+ve group. One HIV+ve patient had Kaposi sarcoma of the ampulla of Vater as a possible cause of the acute pancreatitis. Diabetes (14% vs 3%) (p=0.026**)** and hypertension (22% vs 8%) (p=0.015) were more prevalent in HIV-ve patients. Amylase was measured in 234 (98%) patients, lipase in 169(71%) patients and urine amylase in 133(56%). There was no difference in the mean values of the diagnostic tests in HIV+ve and HIV-ve patients. Two patients in the HIV+ve patients had normal pancreatic

enzymes and the diagnosis was made at laparotomy and in 2 HIV-ve patients the diagnosis was made by CT imaging (**Table 19**).

Serum amylase as the primary diagnostic enzyme supported a diagnosis of acute pancreatitis in 179(75%) of the patients. In the 55(25%) not diagnosed by serum amylase, 33(60%) were diagnosed with aid of urinary amylase and the remaining 22 were diagnosed using serum lipase. **(Table 20)** There was no difference in the patients primarily diagnosed with serum amylase in the HIV-ve (79%) and HIV+ve (71%) patients.

Fifty three (59%) of HIV+ve patients were on HAART. Their treatment with 1st line drug regimens are detailed in **Table 21**. The mean CD4 count(±SD) was 335 cells/mm^3(±246) and 27(30%) had a CD4 count less than 200 cells/mm^3. There was no difference (p=0.46) in the mean CD4 counts of patients not receiving HAART 298 cells/mm^3 (±301) and those receiving HAART 348 cells/mm^3 (±197).

4.4 Disease severity assessment in HIV+ve and HIV-ve pancreatitis

Subsequent analysis of scoring systems were performed on the ability to predict the composite endpoint, organ failure (persistent beyond 48 hours), local complications and mortality. In predicting outcomes, the scorings systems were computed with and without age and the mean scores compared in the HIV-ve and HIV+ve patients. There was a significantly greater proportion of HIV+ve patients with an APACHE II score ≥ 8(62% vs 31%) (p = <0.001). A BISAP score >2 was marginally higher (45% vs 38%) in HIV+ve patients (p = 0.041). CRP, organ failure and the Glasgow score were similar in the 2 groups of patients. CT assessment was performed with similar frequency in the 2 groups (13% vs 14%). (**Table 22**)

There was a significantly higher proportion of HIV-ve (64% vs 46%) patients with positive SIRS criteria. None of the HIV+ve patients had three or four SIRS criteria (**Table 27**). The evaluation of severity assessment parameters is detailed in **Tables 28 and 29 and Figures 7-10**. SIRS and CRP were the least effective (AUC) in predicting a moderate/severe outcome in all the pancreatitis patients with AUC of 0.66 and 0.68 respectively. BISAP, Glasgow and the APACHE systems were more effective with AUC between 0.71 and 0.80. There was an improvement in the performance of the BISAP and Glasgow scores when age was omitted in computing the scores (BISAP 2 and Glasgow 2). The same was not observed with the APACHE II score (**Table 28**). Pairwise comparisons assessed the closeness of two scoring systems and these were interpreted according to the following values: 0.3=weak, 0.5=moderate and 0.7=strong. The analysis is shown in **Table 29** and there was a strong correlation between BISAP, Glasgow and APACHE II when these were paired with each other whereas SIRS and CRP had a strong association between the two.

When HIV-ve patients were assessed all the scoring systems other than SIRS had performances that exceeded an AUC of 0.7(**Figure. 7**). All the scoring systems showed marginal improvement when age was omitted from the computation. The APACHE II system was the best predictor of poor outcome (**Table 30**).

The APACHE II was also the best predictor of a severe outcome in HIV+ve patients with AUC of 0.89(**Fig. 8**). CRP was a poor predictor in HIV+ve patients with AUC of 0.59. In HIV+ve patients BISAP, Glasgow and APACHE II scores had AUC exceeding 0.7 and all improved when age was omitted (**Table 30**).

4.5 Comparison of morbidity and mortality in HIV +ve and HIV -ve patients

Assessment of outcomes revealed that there was no difference in the organ failure (17% vs 19%), morbidity (13% vs 14%), hospital stay (10 ± 8 vs 10 ±8) and mortality rates between the HIV-ve and HIV+ve patients (6% vs 4%) (**Table 23 and 24**). Sepsis was found in 20(8%) of the patients, 16(13%) were HIV-ve and 4(4.4%) HIV+ve (**Table 25**). Most 16(80%) of the infections were diagnosed within 2 weeks. The one tuberculosis and one CMV infection were found in two different HIV+ve patients. Sepsis of pancreatic necrosis was not demonstrated. Three of the patients with sepsis died, one was HIV+ve with tuberculosis and the other two were HIV-ve patients.

4.6 Outcomes in gallstone related pancreatitis with and without HIV infection

Twenty four (27%) of HIV+ve patients and 38(30%) of HIV-ve patients had gallstone related pancreatitis (**Table 26**). There was no difference in the gender distribution between the HIV+ve and HIV-ve patients in this sub-group. The HIV+ve patients were significantly younger with a mean age (±SD) of 35 years (±8.3) vs 45 years (±15) (p=0.003). CRP values were insignificantly lower in the HIV+ve patients (25% vs 18%) and the APACHE II ≥ 8 was significantly higher in HIV+ve patients (79% vs 7%)($p<0.001$). More HIV+ve patients had cholestasis,{22(92%) vs 26(68%)} p=0.059 and more had ERCP, {10(42% vs 4(11 %)} p=0.004. In patients with gallstone pancreatitis, there was a trend in the HIV+ve compared to the HIV-ve patients towards increased morbidity (17% vs 5%) and mortality (8% vs 2%).

4.7 Asessment of disease severity in patients with CD4 counts less than or greater than 200 cells/mm^3

Evaluation based on CD4 counts in HIV+ve patients revealed that significantly more females, 31(78%) than males, 15(47%)(p=0.01) had CD4 counts greater than 200 cells/mm^3. The age, length of hospital stay and severe outcomes did not differ between the groups based on the CD4 cut off level (**Table 31**).

SIRS and CRP scores were of no value in predicting severe disease in patients with CD4 counts < 200 cells/mm^3 with AUC of 0.51 and 0.46 respectively. In patients with CD4 counts > 200 cells/mm^3 CRP had an AUC of 0.73 and SIRS 0.83. The BISAP score with or without the age factor fared poorly in those with CD4 counts <200 cells/mm^3 and was best at AUC of 0.90 in predicting severe disease in those with CD4 counts > 200 cells/mm^3. The Glasgow and APACHE II scores performed similarly in the 2 groups with AUC greater than 0.8 (**Figures 9 and 10)**. SIRS and BISAP scores are affected by the significant number of patients with a score of zero having a severe outcome (**Table 32**). There is a similar trend of improved performance of the scores when age is excluded.

4.8 Factors associated with severe disease in HIV related pancreatitis

In the pancreatitis cohort of 238 patients, 29 (12%) had severe forms of the disease. Most of the severe disease was found in the 31- 40 year age group. There was no trend toward an increasing severity with age and three (10%) episodes of severe disease were in the patients > 60 years old (**Figure 6**). In HIV related pancreatitis there was no difference in the age of those with mild, 37 (SD±8) and severe disease, 35 (SD±9). The number of patients with CD4 counts less than 200 cells/mm^3 also did not differ between mild (20%) and severe disease forms (26%). The number of patients on HAART was also similar in the two groups (57% vs 62%). Of the haematological and biochemical tests performed in the evaluation of acute pancreatitis, urea and creatinine values of > 7.1 mmol/l (p = 0.000) and > 90 umol/l (p = 0.004) respectively were associated with severe disease in HIV related pancreatitis. Although there was no difference in morbidity and mortality between HIV+ve and HIV-ve pancreatitis, the mortality rate differed between those with CD4 counts less than 200 cells/mm^3(15%) and those with CD4 counts more than 200 cells/mm^3(2%) (p=0.035).

4.9 Summary

These results demonstrate a higher prevalence of HIV+ve patients in the pancreatitis cohort than in the trauma cohort. The patients with acute pancreatitis were significantly older than the trauma patients and there were significantly more females in the acute pancreatitis cohort. Serum amylase was not adequate for supporting the diagnosis of acute pancreatitis in this cohort and required the addition of

urine amylase and serum lipase. The rate of infection was not higher in the HIV+ve cohort but did include tuberculosis and Cytomegalvirus. In gallstone pancreatitis associated with HIV infection, cholestasis was more frequent and there was a trend toward an increased performance of ERCP. The currently widely used markers of severe disease are applicable to HIV+ve patients whose CD4 counts are not < 200 cells/mm^3 and the Glasgow and APACHE II are specifically useful in patients with a CD4 count less than 200 cells/mm^3. Despite these differences morbidity is similar in HIV+ve and HIV-ve patients with acute pancreatitis in this cohort and between patients with CD4 counts less than or greater than 200. Most of the mortality is in patients with CD4 counts less than 200 cells/mm^3.

CHAPTER 5: DISCUSSION

5.1 HIV prevalence in acute pancreatitis and trauma cohorts

Previous studies on acute pancreatitis in which HIV infection was not routinely tested at a regional hospital setting in Durban demonstrated that 5% in 2008 and 11% in 2012 of patients diagnosed with acute pancreatitis were associated with HIV infection. (17, 19) The 38% prevalence in this study represents a 3.4 fold increase over the 2012 reported prevalence. To put this in context we used a trauma cohort as a comparator for the prevalence of HIV infection in the hospital population. The trauma cohort with a median NISS score of 9(IQR 4-17) and 26% having a score greater than 15 was considered generally representative of the range of trauma severity as in comparison to another institution in the Kwazulu Natal (KZN) Province which had a similar distribution of injury severity with a NISS of 12(IQR 6.7-23.2) with 25% having a score greater than 15. (276) The prevalence of HIV infection was 2.4 times higher in patients with acute pancreatitis than in those admitted with trauma. The HIV infection rate in the trauma cohort of 16% is consistent with the HIV+ve prevalence recently reported as 17% in a KZN Province population based study (25) and less than half the prevalence in the acute pancreatitis cohort. The prevalence of HIV infection in the indigenous African trauma patients was 28(18%) and 1(5%) in other racio-ethnic groups. In the pancreatitis cohort, the prevalence of HIV infection in indigenous African patients was 32(23%) and 6(7%) in other racio-ethnic groups. When the trauma and pancreatitis cohorts, matched for age, gender and ethnicity were compared, the HIV infection prevalence increased to 53% in the acute pancreatitis cohort and to 23% in the trauma cohort.

There was a difference in the admissions with acute pancreatitis in the 2 hospitals. The hospital of predominant indigenous African patients had a 5-fold lower prevalence of acute pancreatitis than the hospital with a higher Indian ethnic group admission rate (**Table 20**). The 42% female gender distribution in the pancreatitis cohort is lower than other series where females accounted for 49% and 54% of acute pancreatitis admissions. (11, 98) This may be as a result of the lower contribution of gallstones as an aetiology association in this study where gallstones and alcohol accounted for 28% and 48% of cases respectively and differed from international studies where gallstones are predominant (34 - 69%) and alcohol has a lesser frequency of 7 - 33 %. (12-15) The mean age of 40 years in this cohort is also significantly lower than the majority of studies reporting a mean age range of 51-56 years. (2, 9, 12, 277)

5.2 Diagnosis and severity assessment tools in HIV related pancreatitis

Despite previous reports of asymptomatic elevation in serum amylase in HIV infected patients, the serum amylase was equally effective in diagnosisng acute pancreatitis in HIV-ve and HIV+ve patients. (23, 26)

The number of HIV+ve patients in both groups receiving HAART(59%) is nearly double the national figure in 2012 of 31%. (25) This increased use of HAART may partially explain the increased prevalence of HIV infection in the pancreatitis cohort as the treatment of HIV infection includes prophylactic therapy with Isoniazid and Trimethoprim-Sulfamethoxazole, both of which are implicated in drug induced pancreatitis. This is supported by the report by Trivedi where drug induced acute pancreatitis was more prevalent(as high as 40%) in the HIV infected population as opposed to the general population(2%). (278) In this study 24% of patients had drugs as the most probable aetiological association in HIV+ve patients whereas the study by Gan had drugs as a possible cause in 46% of patients. (37) The drug combinations are listed in **Table 21** and 34% were treated with Lamivudine and 59% with Trimethoprim Sulfamethoxazole. Among the antimicrobials commonly used in patients with HIV infection, Sulfamethoxazole, Isoniazid, Trimethoprim-Sulfamethoxazole and Rifampicin have been linked to acute pancreatitis. The appropriate response when drugs are considered to be a cause of pancreatitis depends on the severity of the attack. Patients recovering from a mild attack of acute pancreatitis require alternative drug therapy it there are recurrent attacks. Patients surviving a severe attack will require alternative therapy if the drug therapy (type Ia likelihood see annexure) is perceived as the cause of the pancreatitis.

Drugs however may not be the sole explanation for the increased prevalence of pancreatitis in HIV+ve patients as in some of the initial reports on HIV+ve patients reporting a high prevalence of acute pancreatitis, patients were not on therapy with HAART and had low CD4 counts. These observations are supported by the findings reported by Dowell where pancreatitis was associated with advanced disease (AIDS) (279) and in the study by Trivedi where 84% of patients with HIV related pancreatitis had AIDS(CD4 counts < 200 cells/mm^3). (278) In another American study 57% had CD4 counts < 200 cells/mm^3 with a median count of 160 cells/mm^3. The majority (80) were African-American and female (OR 2.58; 95% CI {1.58, 4.24} and 55% were on HAART. (280) The trend toward a low CD4 count and a racio-enthnic bias was also seen in the study by Parithivel where 89% had CD4 counts below 200 cells/mm^3 and 61% were African American. (42) The findings reported here show a median CD4 count of 298cells/mm^3 (±231) and a CD4 count of <200 cells/mm^3 in 22%. This improvement in CD4 counts over these previous studies is most likely due to the high number of patients on HAART.

As eluded to in the introduction an infective cause of acute pancreatitis is difficult to prove. In this study Cytomegalovirus was the only infection to which a probable cause could be attributed. In HIV-ve patients the spectrum of infecting organisms is similar to previous studies with Gram positive and negative bacteria and fungal organisms. (195, 196) In HIV+ve patients these included Cytomegalovirus and Tuberculosis. The patient with Tuberculosis died. In high HIV prevalent environments it may be prudent to routinely test for HIV infection in patients with severe acute pancreatitis as this may trigger a search for treatable opportunistic infections.

The patients with HIV+ve gallstone pancreatitis were younger than HIV-ve patients (35 ±8 vs 45 ±15). The age difference between HIV-ve and HIV+ve patients with gallstone pancreatitis has not been previously reported. More of the HIV+ve patients had cholestasis (92% vs 68%) but the rate of cholangitis was similar (29% vs 21%). Although jaundice (bilirubin >51umol/l) was found with similar frequency in HIV+ve and HIV-ve patients with gallstone related pancreatitis (33% vs 26%), the rate of ERCP was higher (42% vs 11%) in HIV+ve patients as was the yield of bile duct stones (25% vs 8%) (**Table 27**).

Ideally, prognostication in acute pancreatitis should be feasible at admission to facilitate early intervention in terms of specific measures and admission to high dependency areas for those with severe disease. The Ranson and Glasgow criteria were validated for use at 48 hours after admission in a HIV-ve population. (281) The complications of acute pancreatitis and organ failure are related to time from onset of symptoms and time from admission to health care. The effectiveness of the different systems in predicting severe outcomes may be limited by these temporal relationships. In this study prognostic scores were computed within 24hours of admission as the symptom interval was variable and difficult to use. The Ranson criteria were therefore not computed and the Glasgow criteria were used at 24 hours.

The appropriate timing of the use of CRP in severity assessment of acute pancreatitis is controversial. CRP is synthesized in the hepatocytes as a response to cytokine stimulation and may therefore lag behind the initial SIRS. The CRP after 24 hours was superior to the CRP at admission with an area under the curve of 0.68 and 0.52 respectively both of which are poor levels of accuracy. (41) In the study by Lawson CRP was more useful if the assessment was delayed to 48 hours in predicting severe acute pancreatitis. (245)

In HIV+ve patients, CRP levels were found to negatively correlate with CD4 counts in 119 HIV+ve patients and were the highest in those with CD4 counts less than 200 cells/mm^3. (282) In an American study over 5 years the CRP level was ≥3mg/L in 34% of 922 HIV+ve patients enrolled in the study of Fat Redistribution and Metabolic Change in HIV infection (FRAM). The mortality rate in patients with

CRP >3 mg/L, 1–3 mg/L and CRP <1 mg/L was 19%, 14% and 7% respectively. (283) These two reports suggested that CRP is elevated in HIV+ve patients without pancreatitis and questions the suitability of CRP in severity assessment of acute pancreatitis HIV+ve patients. I found that the benefit of CRP is dependent on the HIV status as well as the CD4 count as CRP at 24 hours was more effective in predicting severe disease in HIV-ve patients (AUC= 0.75) than in HIV+ve patients (AUC= 0.59) , and in patients with a CD4 count of ≥ 200 cells/mm^3 (AUC=0.73) than in patients with CD4 counts below 200 cells/mm^3 (AUC= 0.46).

The BISAP scoring system was derived from 17,992 cases of acute pancreatitis in 212 hospitals in the period 2000-2001 and validated from 18,256 acute pancreatitis cases from 177 hospitals in 2004-2005. The AUC of BISAP was 0.82 and 0.83 for APACHE II system. This is a better outcome than the present study where the BISAP system performed with AUC of 0.73, 0.71 and 0.74 for the entire cohort, HIV-ve and HIV+ve patients respectively.

The Glasgow score was useful in HIV+ve(AUC = 0.78) and HIV-ve patients(AUC=0.72) and better in patients with CD4 count < 200 cells/mm^3(AUC=0.83) and CD4 count ≥ 200 cells/mm^3(AUC=0.81).

The APACHE II score was positive for severe outcomes in 62% (≥8) of HIV+ve patients and it predicted a severe outcome in both HIV-ve and HIV+ve patients with AUC of >0.8 and in both CD4 count ranges with AUC > 0.80. The APACHE II score was the best predictor of poor outcome in this study.

Previous studies which assessed these prognostication systems did not demonstrate equivalent results to this study. In Cappell's study, 61% had CD4 counts less than 200 cells/mm^3 and the Glasgow and Ransons criteria were poor predictors of a severe outcome with sensitivities and specificities lower than 50%. The APACHE II score was a better prognosticator with a sensitivity and specificity of 73% and 68% respectively. (31) In a previous American report, the majority of patients (89%) had CD4 counts less than 200 cells/mm^3 and criteria applicable in the APACHE II and Ranson's criteria were unhelpful in predicting a severe outcome. They had a mortality rate of 32% (42). In a similar setting, 84% of patients had CD4 counts less than 200 cells/mm^3 and the Ranson, Glasgow and APACHE II scores had accuracies of 48%, 69% and 75% respectively.(37)

In the present study when age was removed from the scoring systems there was a marginal improvement in the ability to predict a moderate to severe disease outcome. These improvements were evident in HIV-ve and HIV+ve patients.

5.3 Morbidity and mortality rates in HIV related pancreatitis

The overall mortality rate of 5% does not differ from other studies where the rate was 6%-9%. (5, 284) Mortality was not associated with advancing age and the mean age of pancreatitis in HIV+ve and HIV-ve patients is a decade lower than that reported in western studies. This younger patient population is part of the explanation for the low mortality.

The mortality rate in HIV+ve patients in this study (6%) is less than the 10% reported by Gan (37) They did not find a difference in the mortality between HIV+ve patients and HIV-ve historical controls. Although the current cohort was not sufficiently powered to detect a difference in mortality based on HIV status, there are trends around mortality and CD4 counts which may partially explain the lower than expected morbidity and mortality. In two American studies the mortality rate was 5.9% (286) and 32% (46) in HIV+ve patients with sample sizes of 5970 and 54 patients respectively. The differences in mortality in these studies can be partially explained by the 58% vs 89% rate of CD4 count < 200 cells/mm^3 and the pre-existing liver and renal disease in the cohort with a larger mortality rate. In the present study where 29% of patients had a CD4 < 200 cells/mm^3, 4 of the 5 HIV+ve patients who died had CD4 < 200 cells/mm^3. The mortality of 15% in those with CD4 counts <200 cells/mm^3 was greater than the 2% in those patients with CD4 counts > 200 cells/mm^3($p=0.035$). This suggests that treatment with HAART and keeping CD4 counts above 200 cells/mm^3 may reduce mortality in HIV associated pancreatitis.

5.4 Factors associated with morbidty and mortality in HIV related pancreatitis

The age was similar in those with mild and severe HIV related pancreatitis. Although the CD4 counts were similar in those with mild and severe HIV related pancreatitis the majority of those who died in this group had CD4 counts less than 200 cells/mm^3. A urea of more than 7.1 mmol/l(44% vs 6%)($p = 0.000$) and a creatinine value more than 90 umol/l(44% vs 16%)($p = 0.004$) were also associated with severe HIV related pancreatitis. One of the patients with an opportunistic infection, Tuberculosis, died.

Chapter 6: Conclusions

6.1 Introduction

In relation to the primary hypothesis we can conclude that HIV infection is more prevalent in a pancreatitis cohort than in a trauma cohort or the general population in this region of South Africa. The spectrum of aetiologies is similar except for a drug aetiology being more common in the HIV+ve cohort and the only malignant cause was in the HIV+ve group of patients. The study partially refutes the hypothesis that the scoring systems are not effective in predicting severe disease in HIV related pancreatitis as the APACHE II score was effective in predicting severe disease in the HIV-ve and HIV+ve patients with acute pancreatitis. The other scoring systems were not as accurate in patients with CD4 counts < 200 cells/mm^3. This study has also refuted the hypothesis that outcomes are poorer in HIV associated pancreatitis as there was no difference in moderate to severe pancreatitis between the two groups of patients.

6.2 Limitations

Demonstrating differences in disease severity between HIV-ve and HIV+ve acute pancreatitis will be unlikely, given the low levels of morbidity and especially mortality demonstrated in this study, unless a much larger cohort from multiple centres can be recruited. These low levels of morbidity are at least partly attributable to the younger patient profile of this cohort as compared to reports from international series (15, 102). This is more pertinent as advancing age was not associated with poorer outcomes and that the HIV+ve patients were younger than HIV-ve patients. The second explanation is the proportion of patients with a CD4 count of less than 200 cells/mm^3 is lower than previous studies conducted prior to the advent of HAART when most patients had low CD4 counts. This is pertinent as the mortality rate in the current study was seven times higher in those with a low CD4 count.

6.3 Significance and recommendations

In an environment where serum amylase remains the primary biochemical marker of acute pancreatitis, serum amylase was sufficient in establishing the diagnosis in only 75% of patients and in the remaining patients, confirmation of the diagnosis required urine amylase or lipase. In four patients imaging by CT and laparotomy were required to confirm the diagnosis. This necessitates a shift to the use of serum lipase which has been demonstrated to be the preferred biochemical confirmatory test for acute pancreatitis in a number of studies.

When all categories of patients were considered (HIV-ve, HIV+ve and CD4 < or > 200 cells/mm^3), the APACHE II scoring system was the most accurate in predicting a severe outcome and the Glasgow systems can be used at 24 hours in a South African context in both HIV-ve and HIV+ patients with a fair AUC.

As the spectrum of infecting organisms in HIV+ve patients included CMV and tuberculosis which are not usually associated with septic complications in acute pancreatitis, it is prudent to test for HIV infection in areas of high HIV prevalence as the presence of HIV infection in acute pancreatitis will be a trigger to seek opportunistic infections.

In HIV associated pancreatitis without an attributable cause the further elucidation of the aetio-pathogenesis lies between the HIV disease itself, the drugs used to restore immune competency or prevent opportunist infection and opportunist infections themselves. Temporal association with the drugs is the best predictor of causality but this is often absent. Similarly, without direct sampling of the pancreas by invasive means, ERP or EUS it is difficult to prove that the infective causes demonstrated by post mortem studies are present in vivo.

The sample size calculation based on the older literature on the subject resulted in an overestimation of the complications and mortality rates utilized in the sample size calculation for this study.

6.4 Conclusion

This study however does provide a reference point for future studies in sub -Saharan Africa and reveals that outcomes are similar in pancreatitis in HIV-ve patients and HIV+ve patients and that in HIV+ve patients mortality is related to their CD4 count. As there are advances in the therapy of HIV infection and a decline in the numbers of those with CD4 counts less than 200 cells/mm^3, the mortality in HIV related pancreatitis is likely to approach that in HIV negative patients. This finding can assist in planning future research and further investigation into the relationship between acute pancreatitis and HIV infection in high HIV infected areas.

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TABLES INTRODUCTION

Table 1: Acute pancreatitis: spectrum of aetiologies

Causes in 80% Alcohol Biliary	**Examples** Gallstones Microlithiasis
Causes in 20% Idiopathic Metabolic	 Hypertriglyceridaemia Hypercalcaemia
Obstructive	Periampullary tumours Intraduct Papillary Mucinous Neoplasm
Drugs	Azathioprine, Didanosine, Isoniazid, Trimethoprim-Sulfamethoxazole, Rifampicin, Isoniazid,
ERCP Post-operative Congenital	Pancreas divisum Annular pancreas Long common channel Sphincter of Oddi dysfunction
Autoimmune Hereditary	Autoimmune type 2, familial pancreatitis

Table 2: Variations in the frequency of the main aetiologies of acute pancreatitis by country

Author	Year	Origin	Number	Alcohol	Gallstones	Idiopathic	HIV
				Per cent			
International							
Thomson [2]	1987	Scotland	378	25	75	NS	NS
Mann[3]	1994	England	631	30	29	NS	NS
Lowham [4]	1999	England	105	25	48	23	NS
Gloor [5]	2001	Switzerland	106	35	45	20	NS
Appelros [6]	2001	Sweden	883	32	38	23	NS
Ashley [7]	2001	USA	99	26	40	NS	NS
Ricci [8]	2002	Italy	125	33	76	0	NS
Mofidi [9]	2007	Scotland	759	33	47	13	NS
Bai [10]	2007	China	1976	9	59	25	NS
Carnovale [11]	2005	Italy	1150	7	68	12	NS
Frey [12]	2006	USA	70 231	20	33	37	NS
Dellinger [13]	2007	Multicentre	100	44	34	NS	NS
Bumbasirevic [14]	2009	Serbia	110	0	36	20	NS
South African							
John [15]	1997	S. Africa	136	83	7	7	NS
Funnell [16]	1993	S. Africa	99	74	14	7	NS
Anderson [17]	2008	S. Africa	322	62	14	7	5
Moolla [18]	2013	S. Africa	464	59	17	4	11
Anderson [19]	2017	S. Africa	627	61	19	NS	17
NS = Not stated							

Table 3: Diagnostic accuracy of amylase and lipase in acute pancreatitis

Study	Enzyme	Cut-off level	Sens	Spec	PPV	NPV	PLR	PTP	Accuracy	ROC
Steinberg [45]	Amylase	225U/l	95	89	NS	NS	NS	NS	NS	NS
	Amylase	600U/L	95	86	NS	NS	NS	NS	NS	NS
	Lipase	75U/L	87	90	NS	NS	NS	NS	NS	NS
Ventrucci [46]	Lipase latex test	200 pg/L	83	86	42	98	NS	NS	NS	NS
	Lipase ELISA	62 +g/L	92	85	42	99	NS	NS	NS	NS
	Total amylase	377 U/L	92	78	36	99	NS	NS	NS	NS
Kylänpää-Bäck [47]	Lipase	200U/L	79	88	49	97	7	24	NS	NS
		600U/L	55	99	84	94	55	45	NS	NS
Chen [48]	Lipase	570U/L	94	93	90	96	NS	NS	93	NS
	Amylase	570U/L	79	95	91	87	NS	NS	89	NS
Sáez [49]	Lipase	>180 U/L	84	86	93	72	6	93	NS	NS
	Amylase	>330 U/L	74	86	93	59	5	92	NS	NS
Smith [50]	pancreatic lipase	NS	90	93	NS	NS	NS	NS	NS	95
	serum amylase	NS	79	93	NS	NS	NS	NS	NS	91
Wilson [51]	Lipase (all)	>570 U/L	100	99	97	100	NS	NS	99	NS
	Amylase	>324 U/L	63	99	95	93	NS	NS	94	NS
	Lipase (<48hours)	>570 U/L	100	99	96	100	NS	NS	99	NS
	Amylase	>324 U/L	63	99	94	94	NS	NS	94	NS
	Lipase (>48hours)	>570 U/L	100	100	100	100	NS	NS	100	NS
	Amylase	>324 U/L	67	100	100	99	NS	NS	99	NS
Petrov [52]	Lipase	>180U/L	77	95	89	87	NS	NS	NS	96
	Amylase	>300U/L	92	94	89	95	NS	NS	NS	91
Gomez [53]	Amylase	NS	79	99	NS	NS	NS	NS	NS	NS
	Lipase	NS	97	99	NS	NS	NS	NS	NS	NS
Bang [54]	FPL/total lipase	0.0027	83	64	NS	NS	2	NS	NS	72
	Hepatic lipase	NS	NS	NS	NS	NS	NS	NS	NS	67
	Pancreatic lipase	NS	NS	NS	NS	NS	NS	NS	NS	65
	Lipoprotein lipase	NS	NS	NS	NS	NS	NS	NS	NS	62
	Endothelial lipase	NS	NS	NS	NS	NS	NS	NS	NS	56
	Serum lipase	NS	NS	NS	NS	NS	NS	NS	NS	58
	Serum amylase	NS	NS	NS	NS	NS	NS	NS	NS	54

FPL: fraction pancreatic lipase. NS: not stated.TAP: Trypsinogen activating peptide
NPV- negative predictive value PLR- positive likelihood ratio PTP- Posttest probability
ROC- Receiver operating characteristic Sens: sensitivity Spec: specificity
PPV- positive predictive value

Table 4: Diagnostic accuracy of isoenzymes and other enzymes in acute pancreatitis

Study	Year	Enzyme	Cut off level	Sens	Spec	PPV	NPV	PLR	PTP
Steinberg [46]	1985	Serum Trypsinogen	85ηg/ml	97	83	NS	NS	NS	NS
		Pancreatic amylase	375U/L	92	85	NS	NS	NS	NS
Ventrucci [47]	1986	Pancreatic-Isoamylase	220 U/L	100	84	46	100	NS	NS
Kylänpää-Bäck [48]	2001	Urine trypsinogen-2	NS	93	92	NS	99	NS	NS
Sáez [49]	2005	TAP urine	NS	69	40	73	35	1	72
		Urine Trypsinogen-2	NS	69	86	91	54	5	92
Chen [50]	2005	Urine Trypsinogen-2	50 mg/L	97	86	81	92	NS	NS
Wilson [52]	2005	Elastase	2.5 ηg/mL	80	96	80	96	NS	NS
		Elastase(<48hours)	2.5 ηg/mL	75	97	78	96	NS	NS
		Elastase(>48hours)	2.5 ηg/mL	100	96	55	100	NS	NS

TAP: Trypsinogen activating peptide
Sens: sensitivity Spec: specificity, PTP: pretest probablity; PTP: Posttest probability
PPV: positive predictive value, NPV: negative predictive value
PLR: positive likelihood ratio, NS: not stated

Table 5: Markers of a biliary aetiology

Series	Diagnostic standard	Year	Biochemical marker or imaging procedure	Timing	sens	spec	PPV	NPV
Goodman [78]	AUS, ERCP, surgery	1985	1 or more +ve	admission	73	94	97	57
			ALP > 225iu/l ALT >75iu/l,BR>40umols/l					
Davidson [79]	NS	1988	ALT	48 hours	75	74	78	69
			ALT + ALP+ bilirubin		74	78	81	70
			ALT + ALP + gender+ age + amylase		62	80	80	62
Sugiyama [80]	AUS, CT scan,	1998	ERCP	24-72 hours	100	100	NS	NS
	BR>41.04 umol/l, ALT>60u/l		EUS		100	100	NS	NS
Chak [81]	AUS, ERCP, surgery	1999	EUS	<72	91	100	100	95
Ammori [82]	AUS, EUS,	2003	AUS		86	1	1	80
	postmortem		ALT≥80 iu/L		91	1	1	86
			AUS+LFT		98	1	1	96
Liu [83]	Surgey, IOC, ERCP	2005	EUS	<24	100	NS	NS	NS
Levy [84]	EUS	2005	Age >50		73	65	NS	NS
			ALT>2×ULN		74	84	NS	NS
Anderson [85]	AUS, CT scan or MRI	2010	Female	48 hours	58	54	59	52
			Age > 50 years		67	49	60	56
			ALT > 100 units/l		66	79	79	67
			ALT > 150 units/l		59	84	81	64
Gungor [86]	MRCP, ERCP and IOC	2010	ALP > 246 U/L	?	62	60	81	38
			BR>20.53 umol/l		65	67	84	43
			Direct bilirubin>3.42 umol/l		60	65	82	38
			Amylase>970u/l		61	57	79	36
			Lipase>1400u/l		61	60	80	38
Moolla [18]	AUS	2013	Amylase (1,000 U/l, normal:	24 hours	63	75	35	90
			ALT (150 U/l)		51	97	80	90
			Combined		36	97	85	87

AUS: Transabdominal ultrasound, EUS: Endoscopic ultrasound, MRI: Magnetic resonant imaging, ERCP: Endoscopic retrograde cholangiopancreatography, Intraoperative cholangiogram: IOC, Bilirubin : BR, Magnetic resonce cholangiopancreatography: MRCP, Computerised Tomography: CT, ALT: Alanine transaminase,
ULN:Upper limit of normal, ALP: Alkaline phosphatase, LFT: Liver function test, AST: Aspartate transaminase, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative p \redictive value

Table 6: Parameters to define organ failure in the modified Marshall score

Organ system	**Score**				
	0	1	2	3	4
Respiratory	>400	301-400	201-300	101-200	≤101
(PaO2/FiO2)					
Renal					
(serum creatinine, µmol/l)	<134	134-169	170-310	311-439	>439
Cardiovascular					
Systolic blood pressure, (mmHg)	>90	<90,fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2
Calculation for FiO2 in non-ventilated patients					
Oxygen (l/min)	FiO2				
Room air	21				
2	25				
4	30				
6 to 8	40				
9 to 10	50				
Criteria for organ failure: Score of >2 for each organ					

Table 7: Variation in mortality related to age in acute pancreatitis

Age	Mortality per 100,000
<30	1.0
30-40	1.4
40-50	2.9
50-60	4.4
60-70	8.6
>70	18.8

Table 8a: Series of markers of disease severity in acute pancreatitis 1993-2000

Study	Year	No	Timing	Endpoints	Test and cut-off	Sen	Spec	PPV	NPV	Accuracy	AUC
Gudgeon [38]	1990	55	Day 0	Complications	TAP≥ 2nmol/l	80	90	NS	NS	NS	NS
				Death	CRP≥ 20mg/l	53	55	NS	NS	NS	NS
			24 hrs		TAP≥2nmol/l	80	85	NS	NS	NS	NS
					CRP≥100mg/l	60	75	NS	NS	NS	NS
			48hrs		Glasgow	60	93	NS	NS	NS	NS
			5 days		CRP≥200mg/l	73	75	NS	NS	NS	NS
Dominguez-Munoz [39]	1993	182	24-48 hrs	Complications: local and systemic	Glasgow 48hrs	84	77	NS	NS	78	NS
					APACHE II 24hrs	70	79	NS	NS	77	NS
					APACHE II 48hrs	69	77	NS	NS	76	NS
					SAPS 24hrs	67	79	NS	NS	77	NS
					SAPS 48hrs	73	69	NS	NS	70	NS
Tenner [40]	1997	139	48 hrs	Pancreatic necrosis, organ failure	TAP 5ng/ml	100	75	45	100	NS	NS
					TAP 10ng/ml	100	85	60	100	NS	NS
					TAP 15ng/ml	89	95	80	98	NS	NS
					TAP20ng/ml	67	95	75	94	NS	NS
Neoptolemos[41]	2000	246	24hrs	Local or systemic complications	TAP>35nmol/l	68	74	NS	NS	73	NS
				Death	CRP>150mg/l	47	82	NS	NS	74	NS
					APACHE II ≥8	63	73	NS	NS	71	NS
			48hrs		TAP>35nmol/l	83	72	NS	NS	74	NS
					CRP>150mg/l	86	61	NS	NS	66	NS
					APACHE II ≥8	56	64	NS	NS	63	NS
					Glasgow ≥ 3	75	75	NS	NS	76	NS
					Ranson ≥ 3	89	64	NS	NS	69	NS

Study	Year	No	Timing	Endpoints	Test and cut-off	Sen	Spec	PPV	NPV	Accuracy	AUC
Lempinen [110]	2001	150	Ad	Pancreatic necrosis, organ failure	U. tryp -2 dipstick	62	87	65	85	NS	NS
				Death	CRP > 150mg/l	38	90	59	79	NS	NS
					APACHE II > 8	52	87	61	82	NS	NS
			24 hrs		U. tryp -2 dipstick	62	85	62	85	NS	NS
					CRP > 150 mg/l	83	70	52	91	NS	NS
					APACHE II > 8	45	86	56	80	NS	NS
Kylänpää-Bäck [111]	2001	57	Day 0	Organ failure	APACHE II ≥8	56	80	NS	NS	NS	NS
					CRP>150mg/L	50	83	NS	NS	NS	NS
					PCT>0.4ng/ml	69	78	NS	NS	NS	NS
					sIL-2R>1000U/mL	50	78	NS	NS	NS	NS
			12hrs		CRP >150mg/L	56	76	NS	NS	NS	NS
					PCT >0.4ng/ml	75	78	NS	NS	NS	NS
					sIL-2R>1000U/mL	81	71	NS	NS	NS	NS
			24hrs		APACHE II ≥8	56	71	NS	NS	NS	NS
					CRP ≥150mg/L	69	54	NS	NS	NS	NS
					PCT >0.4ng/ml	94	73	NS	NS	NS	NS
					sIL-2R>1000U/mL	81	68	NS	NS	NS	NS
			48hrs		Ranson≥3	88	44	NS	NS	NS	NS

TAP- Trypsinogen Activating Peptide
U.Tryp- Urinary trypsinogen
CRP - C-reactive protein
SAPS - Simplified Acute Physiology Score
PCT - Procalcitonin
sIL-2R - soluble interleukin-2 receptor
APACHE II - Acute Physiology and chronic Health evaluation
NS: not stated

Table 8b: Series of markers of disease severity in acute pancreatitis 2001-2015

Study	Year	No	Timing	Endpoints	test and cut-off	Sen	Spec	PPV	NPV	AUC
Kylänpää-Bäck [112]	2001	162	day0	Organ failure	PCT-Q strip	71	84	NS	NS	NS
			day0	Mortality	CRP>150mg/l	37	88	NS	NS	NS
			day0		APACHE II≥8	61	82	NS	NS	NS
			day1		PCT-Q strip	92	84	NS	NS	NS
			day1		CRP>150mg/l	71	68	NS	NS	NS
			day1		APACHE II	47	78	NS	NS	NS
			day 0 or 1		PCT-Q strip	95	78	NS	NS	NS
			day 0 or 1		CRP>150mg/l	74	65	NS	NS	NS
			day 0 or 1		APACHE II	71	73	NS	NS	NS
			48hours		Ranson≥3	45	98	NS	NS	NS
Chatzicostas [113]	2002	153	48hours	Organ failure	Ransons≥3	82	74	NS	NS	0,82
			24hours	Local complication	APACHE II≥10	58	78	NS	NS	0,62
					APACHE III≥42	56	86	NS	NS	0,68
Chatzicostas [114]	2003	78	72hours	Organ failure	CTSI >3	76	93	89	83	0,95
			48hours	Local complication	Ranson >2	82	65	65	82	0,78
			24hours		APACHE II >10	55	86	76	71	0,62
			24hours		APACHE III >41	50	86	73	69	0,68
Johnson [115]	2004	186	24hours	Complications	APACHE II-O>8	82	86	74	91	NS
Wu[116]	2008	17992	24 hours	Mortality	BISAP>2	NS	NS	NS	NS	0,82
					APACHE II	NS	NS	NS	NS	0,83
Koziel[117]	2015	944	24 hours(death)	Mortality	BISAP>2	NS	NS	NS	NS	0,71
					Ranson≥2	NS	NS	NS	NS	0,68

Study	Year	No	Timing	Endpoints	test and cut-off	Sen	Spec	PPV	NPV	AUC
					APACHE II≥8	NS	NS	NS	NS	0,73
					Panc 3≥2	NS	NS	NS	NS	0,57
			24 hours (severe)	Organ failure	BISAP≥2	NS	NS	NS	NS	0,69
					Ransons≥3	NS	NS	NS	NS	0,63
					APACHE II≥8	NS	NS	NS	NS	0,72
					Panc 3≥2	NS	NS	NS	NS	0,63
Cho [118]	2015	161	48 hours	Persistent organ failure	Ranson≥3	86	44	19	95	0,69
			24 hours		BISAP≥2	62	72	25	93	0,74
			24 hours		APACHE II≥8	81	66	26	96	0,78
			24 hours		CRP≥21.4	53	94	67	90	0,68
			NS		CTSI≥3	67	67	23	93	0,69

PCT-Q: Procalcitonin strip test, CRP- C-reactive protein, CTSI-Computerized Tomography Severity Index
APACHE II-Acute Physiology and Chronic Health Evaluation, BISAP - Bedside Index of Severity
Panc: Presence of Haematocrit (>44%), BMI(>30kg/m2) and Pleural effusion predict severe disease
NS: not stated

Table 9: Parameters to calculate the SOFA score

Parameters	**Score**				
	0	1	2	3	4
Respiration					
PaO2/FIO2	>400	<400	<300	<200	<100
SaO2/FIO2	?	221–301	142–220	67–141	<67
Coagulation: Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver: Bilirubin (umol/l)	<20.52	20.52–32.49	34.2–100.89	102.6–203.49	>205.2
Cardiovascular: Hypotension	Normotensive	MAP <70	Dopamine </=5 or	Dopamine >5 or	Dopamine >15 or
			Dobutamine (any)	Norepinephrine </=0.1	norepinephrine >0.1
CNS: Glasgow Coma Score	15	13–14	10–12	6–9	<6

Scores and probability of mortality	
Score	Percent mortality
0 - 6	<10
7 - 9	15-20
10 - 12	40-50
13 - 14	56-60
15	>80
16 - 24	>90

Table 10: Outcomes of antimicrobial therapy RCT'S in acute pancreatitis

Author	Year	Antimicrobial	Concealed	Blinding	A	P	Infection		RR(95% CI)	Mortality		RR (95%CI)
			Allocation				A	P		A	P	
					Number					Number		
Pederzoli [198]	1993	Imipenem	Unclear	No	41	33	5	10	0.40[0.15,1.06]	3	4	0.6[0.15,2.51]
Sainio [199]	1995	Cefuroxime	Yes	No	30	30	9	12	0.75[0.37,1.51]	1	7	0.14[0.02,1.09]
Delcenserie [200]	1996	Ceftazidime + A + M	Unclear	No	11	12	0	3	0.15[0.01,2.70]	1	3	0.36[0.04,3.00]
Schwarz [201]	1997	Ofloxacin + M	Unclear	No	13	13	8	7	1.14[0.59,2.22]	0	2	0.2[0.01,3,80]
Nordback [202]	2001	Imipenem	Unclear	No	25	33	1	6	0.22[0.03,1.71]	2	5	0.53[0.11,2.50]
Spicak [203]	2002	Ciprofloxacin + M	Unclear	No	33	30	1	0	2.74[0.12,64.69]	5	3	1.52[0.40,5.81]
Spicak [204]	2003	Meropenem	Unclear	No	20	21	3	6	0.53[0.15, 1.82]	4	5	0.84[0.26,2.69]
Isenmann [205]	2004	Ciprofloxacin + M	Yes	Yes	58	56	7	5	1.35[0.46, 4.01]	3	4	0.72[0.17,3.09]
Røkke [206]	2007	Imipenem	Unclear	No	36	37	3	6	0.51[0.14, 1.90]	3	4	0.77[0.19,3.20]
Dellinger [13]	2007	Meropenem	Yes	Yes	50	50	9	6	1.50[0.58, 3.90]	10	9	1.11[0.49,2.50]
Barreda [207]	2009	Imipenem	Unclear	No	24	34	3	2	2.13[0.38,11.76]	0	0	NE
Garcia-Barrasa [208]	2009	Ciprobay	Yes	Yes	22	19	8	8	0.86[0.40, 1.85]	4	2	1.73[0.35,8.41]
Xue [209]	2009	Imipenem	Unclear	No	29	27	8	10	0.74[0.35, 1.61]	3	4	0.7[0.17,2.84]
Yang [210]	2009	Imipenem	Unclear	No	28	26	6	8	0.70[0.18, 1.74]	2	3	0.62[0.11,3.41]
Total					420	421	71	89	0.78[0.60,1.02]	41	55	0,74
Percent							17	21		10	13	

RCT: randomized controlled trials, NE not estimable, RR: relative risk, CI: confidence interval
M = Metronidazole A = Amikacin A = Antimicrobials P = Placebo

Table 11: Patterns of mortality in series of acute pancreatitis

Author	Year	Origin	Number	Deaths		Early	Late
				No	%	% of deaths	
Renner[211]	1985	USA	405	100	25	76	24
Mann[3]	1994	England	631	57	9	44	56
McKay[98]	1999	Scotland	13727	1030	8	54	46
Lowham[4]	1999	England	105	6	6	100	0
Mutinga[212]	2000	USA	805	17	2	47	53
Ashley[7]	2001	USA	99	14	14	29	71
Gloor[5]	2001	Switzerland	106	10	9	0	100
Appelros[6]	2001	Sweden	883	21	2	62	38
Carnovale[11]	2005	Italy	1150	55	5	51	49
Frey[12]	2006	USA	70231	4227	6	30	70
Mofidi[9]	2006	Scotland	759	45	6	51	49
Fu[213]	2007	Taiwan	643	105	16	42	58
Bai[10]	2007	China	1976	233	12	79	21
Dellinger[13]	2007	Multicentre	100	19	19	42	58
Bumbasirevic[14]	2009	Serbia	110	59	54	25	75
Overall			**76752**	**4746**	**9**	**43**	**57**
Anderson[17]	2008	South Africa	322	28	9	79	21
Anderson[19]	2017	South Africa	627	42	7	67	33
South Africa			**949**	**70**	**8**	**73**	**27**
Total			**77701**	**4816**	**9**	**58**	**42**

Table 12: Outcomes of surgery in infected pancreatic necrosis

Procedure				**Fistula (%)**				
Open laparotomy	**Year**	**No**	**Infection (%)**	**Pancreatic**	**Enteric**	**Total**	**Haemorhage (%)**	**Mortality (%)**
Beger[214]	1988	95	42	NS	NS	NS	NS	8
Fernandez-del Castillo [215]	1998	64	56	53	16	69	5	6
Branum[216]	1998	50	84	72	16	88	ns	12
Bosscha[217]	1998	28	100	NS	NS	25	50	39
Raraty[218]	2010	52	72	8	10	18	17	38
Pupelis[219]	2013	36	44	22	22	44	83	19
Wronski[220]	2017	22	77	32	36	68	29	27
Planned re-laparotomies								
Sarr[221]	1991	23	75	26	52	78	26	17
Tsiotos[222]	1998	72	79	19	27	35	18	25
Closed continuous lavage								
Farkas[223]	1996	123	100	13	1	14	2	7
Farkas[224]	2006	220	100	NS	NS	NS	NS	8
Surgical step-up approach								
van Brunschot[225]	2018	47	98	32	17	49	21	13

Table 13: Series of minimally invasive necrosectomy reporting outcomes

Procedure	Year	No	Infected	Procedure completed	Sepsis ↓	Morbidity	Mortality
Percutaneous			%				
Freeny[228]	1998	34	100	47	74	0	12
Echenique[229]	1998	20	100	100	NS	50	0
Gouzi[230]	1999	32	81	65	NS	59	15
Retroperitoneal laparostomy							
Fagniez[231]	1989	40	97	NS	NS	50	33
Villazon[232]	1991	18	100	NS	NS	38	22
Nakasaki[233]	1999	8	100	NS	NS	65	25
Raraty[218]	2010	137	64	86	NS	55	19
Pupelis[219]	2013	22	64	NS	71	45	5
Laparoscopy							
Zhu[234]	2001	10	0	90	NS	NS	10
Retroperiteonoscopy							
Gambiez[235]	1998	20	65	75		65	10
Carter[236]	2000	10	100	80	NS	28	20
Castellanos[237]	2002	15	100	NS	NS	20	27
Connor[238]	2003	24	100	87	NS	88	25
Bakker[239]	2012	10	90	100	NS	90	40
van Brunschot[225]	2018	47	98	100	NS	32	13
Endoscopic							
Bakker[239]	2012	10	100	100	NS	10	10
van Brunschot[225]	2018	51	90	100	NS	25	18

Sepsis ↓: % decline in sepsis

Table 14: Accuracy of serological predictors of infected pancreatic necrosis

Author	Year	Test	Duration assay	Sens %	Spec %	PPV %	NPV %
Rau[140]	1997	PCT (1.8 ng/ml)	1st 2 days	94	91	NS	NS
		IL-8 (112 pg/ml)		72	75	NS	NS
Riche[213]	2003	IL-6 (< 400 pg/l) + PCT (< 2 ng/l)	1st 3 days	75	84	60	91
Rau[141]	2007	PCT≥3.5 ng/ml	1st 2 days	93	88	NS	NS
		CRP ≥430 mg/l		40	100	NS	NS
		PCT≥3.5 ng/ml	3rd and 4th day	79	93	NS	NS
		CRP ≥430 mg/l		36	97	NS	NS

PCT: Procalcitonin. IL: Interleukin, CRP: C-reactive protein, Sens: sensitivity, Spec : specificity, PPV : positive predictive value, NPV : negative predictive value, NS: not stated

Table 15: Admissions: Addington and Prince Mshiyeni Memorial hospitals showing numbers and ethnic distribution

Periods	Addington	PMMH	p-value
	n	n	
General surgery hospital admissions			
Aug 2013- July 2014	5370	12775	
Aug 2014- July 2015	5874	14141	
Aug 2015- Oct 2015	1558	4079	
Total	12802	30995	
Trauma admissions: n=181(%)	76(42)	105(58)	
Age: mean(±SD)	33(±13)	33(±11)	
Gender: male (%)	67(88)	93(89)	
female (%)	9(12)	12(11)	
Ethnicity: n(%)			
African	62(82)	101(96)	0.0019
Mixed	4(5)	1(1)	
White	6(8)	2(2)	
Indian	4(5)	1(1)	
Pancreatitis admissions: n(%)	161(0.01)	77(0.002)	
Age: mean(±SD)	40(±13)	35(±11)	0.0017
Gender: female (%)	64(40)	36(39)	
male (%)	97(60)	41(51)	
Ethnicity: n (%)			
African	82(51)	75(97)	0.0001
Mixed	8(5)	0	
White	4(2)	1(1)	
Indian	67(42)	1(1)	0.0001
Complications: n(%)			
pancreatic ascites	10(6)	7(9)	
pancreatic fluid collections	8(5)	8(10)	
portal vein thrombosis	1(1)	2(3)	
abscess	1(1)	3(4)	
pancreatic necrosis	5(3)	8(10)	0.0240
Mortality	6(4)	6(8)	0.0046
PMMH = Prince Mshiyeni Memorial Hospital			

Table 16: Patient demographics, ethnicity and HIV status in trauma and pancreatitis cohorts

	Trauma		**Pancreatitis**		
	No		**No**		**p-value**
Total	181		238		
Characteristic		SD		SD	
Age: mean (±SD)	33	±11.8	40	±12.3	<0.001
Gender		%		%	
Female	22	12	100	42	<0.001
Male	159	88	138	58	
Ethnicity					
African	157	87	157	66	<0.001
Mixed	6	3	8	3	
Indian	12	7	68	29	
White	6	3	5	2	
HIV status					
1	99	55	126	53	<0.001
2	29	16	90	38	
3	53	29	22	9	<0.001
On HAART	**17**	59	**53**	59	
1: HIVnegative 2: Tested positive or known 3: Declined testing					

Table 17 General characteristics, severity markers and outcomes of the pancreatitis cohort

Total		238	
Parameter		**Mean**	**SD**
Age (years)		40	±12.3
		No	Percent
Gender	Female	100	42
	Male	138	58
Ethnicity	African	157	66
	Mixed	8	3
	Indian	68	29
	White	5	2
Aetiology	Alcohol	117	49
	Gallstones	66	28
	Dyslipidaemia	6	3
	Drugs	24	10
	Idiopathic	25	11
CRP>150mg/l	Evaluated in 213(89%)	83	39
BISAP ≥ 2	Evaluated in 238(100%)	40	17
Glasgow ≥ 3	Evaluation based on 9 factors in 225(95%) & 8 factors in 13(5%)	55	23
APACHE 2 ≥ 8	Evaluation based on 14 factors in 233(98%) & 12 factors:5(2%)	105	44
SIRS ≥ 2	Evaluation based on 5 factors in 231(97%) & 4 factors:7(3%)	128	54
CTSI	Mild	12	5
	Moderate	12	5
	Severe	10	4
Organ failure	Transient 31(67%), persistent 15(33%)	46	19
Local complications	Ascites (32), Sepsis (20), Pseudocyst (12), Abscess (4), PVT (3), PN (11)	33	14
Mortality	Early (≤14 days): 6		
	Late (>14 days): 6	12	5

CRP: C- reactive protein, BISAP : Bedside Index of Severity in Acute Pancreatitis, SD-standard deviation, APACHE : Acute Physiology And Chronic Health Evaluation,

SIRS : Systemic Inflammatory Response Syndrome, PVT: portal vein thrombosis,

PN: pancreatic necrosis, CTSI: CT scan severity index

Table 18: HIV Status by age range, gender and ethnicity of the pancreatitis cohort

	HIV Status						Total	p value
	Negative		Positive		Unknown			
Age group	n	%	n	%	n	%	n	0.002
< 30	26	21	25	28	2	9	53	
30-49	65	52	57	63	12	55	134	
50-74	35	28	8	9	8	36	51	
Total	**126**	**100%**	**90**	**100%**	**22**	**100%**	**238**	
Gender								
Female	44	35	48	53	8	36	100	0.02
Male	82	65	42	47	14	64	138	
Total	**126**	**100%**	**90**	**100%**	**22**	**100%**	**238**	
Ethnic								
African	63	50	84	93	10	45	157	< 0.001
Mixed	7	6	1	1	0	0	8	
Indian	51	40	5	6	12	55	68	
White	5	4	0	0	0	0	5	
Total	**126**	**100%**	**90**	**100%**	**22**	**100%**	**238**	
HIV : Human immunodeficiency virus								

Table 19: Comparisons of the spectrum of aetiologies, comorbidities and diagnostic modalities in HIV+ve and HIV-ve pancreatitis cohorts

Characteristic		HIV Status						p-value
		HIV-ve (n=126)		HIV+ve (n=90)		Unknown (n=22)		
		n	Percent	n	Percent	n	Percent	
Aetiology	Alcohol	66	52	37	41	14	64	0.14
	Gallstones	38	30	24	27	4	18	0.48
	Dyslipidaemia	4	3	0	0	2	9	0,03
	Drug related	0	0	24	27	0	0	<0.001
	Idiopathic	18	14	4	6	2	9	0.09
	Tumour	0	0	1	1	0	0	
Comorbidity	Diabetes	18	14	3	3	3	14	0.03
	Hypertension	28	22	7	8	5	23	0.02
	IHD	4	3	1	1	0	0	0.64
	Renal	2	2	1	1	0	0	1
Diagnosis	Imaging	2	2	0	0	0	0	0.32
	Laparotomy	0	0	2	2	0	0	0.60
		Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	
	Amylase(n=234)	1106	968	1011	10326	1185	933	0.19
	Lipase(n=185)	809	1345	1106	1768	802	1228	0.42
	Urine Amylase (147)	10794	20251	9124	18254	16311	24789	0.65

SD: standard deviation; i: Pearson chi-squared ($\chi 2$) test or Fishers exact,

HIV : Human immunodeficiency virus, IHD : ischaemic heart disease

Table 20 Diagnosis of acute pancreatitis utilizing amylase and lipase at ≥3 times upper limit and urine amylase at ≥1000 u/l.

Parameter	No	median	IQR
serum amylase	234	711	1030
urine amylase	147	3861	6641
Lipase	185	350	748
	n	**%**	
n=238: serum amylase ≥375	179	75	serum amylase 75% diagnostic
<375	55	23	
n=55: urine amylase ≥1000	33	60	urine amylase diagnostic in 60% misdiagnosed by amylase
<1000	22	40	
n=22: serum lipase ≥180	22	100	lipase diagnostic in all missed by amylases
IQR: measured as the difference between the first and fourth quartiles			

Table 21: HAART regimens in HIV+ve patients in the acute pancreatitis cohort

	CD4 mean(±SD)	
Not on HAART	298(±301)	p=0.8181
On HAART	348(±301)	
HAART regimens	No	%
Lamivudine†, Tenofovir†, Efavirenz*	25	47
Tenofovir†, Emtricitabine†, Efavirenz*	22	42
Lamivudine†, Tenofovir†, Nevirapine*	6	11
HAART: highly active antiretroviral therapy Nucleoside reverse transcriptase inhibitors (NRTI) † Non-nucleoside reverse transcriptase inhibitors (NNRTI) *		

Table 22 Proportion of positive prognostication markers in relation to HIV status

Characteristic	Criteria	HIV-ve(n=126)		HIV+ve(n=90)		Unknown (n=22)		p-value
		n	Percent	n	Percent	n	Percent	
CRP	<150	64	50	55	43	10	8	0.52
	≥150	47	57	29	35	8	10	
Glasgow	<3	100	55	67	37	15	8	0.44
	≥3	26	46	23	41	7	13	
APACHE II	<8	92	71	23	18	14	11	<0.001
	≥8	34	31	67	62	8	7	
BISAP	<2	111	56	72	36	15	8	0.04
	≥2	15	38	18	45	7	18	
Organ failure	No	104	54	73	38	15	8	0.29
	Yes	22	48	17	37	7	15	
CT scan:		18	14	12	13	0	0	0.17

CRP : C-reactive protein, APACHE : Acute Physiology And Chronic Health Evaluation,
BISAP : Bedside Index of Severity in Acute Pancreatitis, CT : Computerised Tomography,
HIV : Human Immunodeficiency Virus

Table 23: Acute pancreatitis outcomes in relation to the HIV status

Parameter	HIV Status						p-value
	HIV-ve(n=126)		HIV+ve(n=90)		Unknown (n=22)		
	n	Percent	n	Percent	n	Percent	
Local complications							
Pancreatic ascites	14	11	17	19	1	5	0.15
Pancreaticfluid collection	7	6	5	6	0	0	0.82
Pancreatic abscess	2	2	2	2	0	0	1
Portal vein thrombosis	2	2	1	1	0	0	1
Pancreatic necrosis	6	5	5	6	0	0	0.73
Mortality	7	6	5	6	0	0	0.66
	Mean	±SD	Mean	±SD	Mean	±SD	
Hospital stay (days)	10	8	10	8	7	4	0.223
SD: standard deviation, i: Pearson chi-squared ($\chi 2$) test or Fishers, HIV : Human Immunodeficiency Virus							

Table 24 Categorical assessment of severe disease parameters in relation to the HIV status

Parameter	HIV status								p value
	HIV -ve		HIV+ve		Unknown		Total		
	n	%	n	%	n	%	n	%	
Organ failure									
Yes	22	17	17	19	7	32	46	19	
No	104	83	73	81	15	68	192	81	0.3
Total	126	100	90	100	22	100	238	100	
Local complications									
Yes	17	13	13	14	1	5	31	13	
No	109	87	77	86	21	95	207	87	0.4
Total	126	100	90	100	22	100	238	100	
Mortality									
Yes	7	6	4	4	1	5	12	5	
No	119	94	86	96	21	95	226	95	0.8
Total	126	100	90	100	22	100	238	100	
Severity									
Not severe	100	79	72	80	14	64	186	78	
Severe	26	21	18	20	8	36	52	22	0.3
Total	126	100	90	100	22	100	238	100	
HIV : Human Immunodeficiency Virus									

Table 25: Temporal relation of sepsis site and micro-organisms to HIV status

HIV Status		**Organisms**	
	Site	**0 - 14days**	**>14 days**
HIV-ve	Blood	Staphylococcus Aureus	
		Staphylococcus Aureus	
			Staphylococcus Aureus
	Catheter tip	Enterococcus	
	Sputum	Candida Albicans	
		Pseudomonas	
		Candida Albicans	
			Enterobacter
		Pseudomonas	
		Haemophilus	
		Candida Albicans	
	Urine	Candida Albicans	
		Escherichia Coli	
			Candida Albicans
	Ascites	Staphylococcus Aureus	Enterobacter
		Candida Albicans	
HIV+ve	Respiratory		Tuberculosis
	Blood	Escherichia Coli	
		Cytomegalovirus	
		Staphlococcus Aureus	
HIV : Human Immunodeficiency Virus			

Table 26. Demographics, severity assessment and outcomes in patients with gallstone related pancreatitis in relation to HIV Status

Variable		**HIV-ve**		**HIV+ve**		
		No	%	No	%	
Gender	Female	26	68	22	92	0.059
	Male	12	32	2	8	
Ethnicity	African	20	53	24	100	<0.001
	Mixed	1	3	0	0	
	Indian	15	39	0	0	
	White	2	5	0	0	
Staging	CRP	18	47	6	25	0.058
	Glasgow	12	32	7	29	0.841
	APACHE II	7	18	19	79	<0.001
	BISAP	5	13	5	21	0.423
	Organ failure	6	16	5	21	0.613
	CT scan	6	16	1	4	0.232
	Cholangitis	8	21	7	29	0.467
	Cholestasis	26	68	22	92	0.059
Jaundice	Jaundice	10	26	8	33	0.553
	ERCP	4	11	10	42	0.004
	BD stones	3	8	6	25	0.077
Morbidity	Local complications	5	5	4	17	0.725
	Pancreatic ascites	4	4	2	8	1
	Pancreatic fluid collections	3	3	2	8	1
	Pancreatic abscess	1	1	1	4	1
	Portal vein thrombosis	1	1	0	0	1
	Pancreatic necrosis	2	2	2	8	0.637
Mortality		2	2	2	8	0.637

ALT: Cholestasis: Alanine transaminase, BD: bile duct, jaundice: bilirubin ≥51um/l, CRP : C-reactive protein, APACHE: Acute physiology And Chronic Health Evaluation, BISAP : Bedside Index of Severity in Acute Pancreatitis, ERCP : Endoscopic Retrograde Cholagiopancreatography, Cholestasis: cholestasis will be defined as elevation of the cholestatic enzymes (alkaline phosphatase: > 121 U/L, gamma-glutamyl transferase:> 64 U/L and bilirubin >21 μmol/L), Cholangitis: Cholestasis + any 2 of temperature(>38˚C), white cell(>11×1012/L) count and tachycardia (>90 beats/minute).

Table 27. Spectrum of the SIRS response in HIV-ve and HIV+ve pancreatitis cohorts

	HIV Status								
	HIV-ve		**HIV+ve**		**Unknown**		**Total**		**P value**
	n	**%**	**n**	**%**	**n**	**%**	**No**	**%**	
SIRS Grade									
0	10	8	13	14	2	9	25	10	
1	39	31	36	40	9	43	85	36	
2	39	31	41	46	11	48	91	38	0,0003
3	27	21	0	0	0	0	27	11	
4	11	9	0	0	0	0	11	5	
Total	**126**	**100%**	**90**	**100%**	**22**	**100%**	**238**	**100%**	
SIRS: Systemic Inflammatory Response Syndrome									

Table 28: Pancreatitis severity assessment in the entire pancreatitis cohort

Scoring System **ROC**

	No	**AUC**	**95% Conf. Interval**		**Sens**	**Spec**	**PPV**	**NPV**
			Upper limit	**Lower Limit**	%(95% CI)	%(95% CI)	%(95% CI)	5(95% CI)
SIRS≥2	213	0.66	0.58	0.75	77(63-87)	52(45-60)	31(23-40)	89(82-94)
CRP≥150mg/dl	213	0.68	0.59	0.77	63(48-77)	68(60-70)	35(25-46)	87(80-92)
BISAP≥2	213	0.74	0.66	0.82	44(30-59)	90(85-94)	56(40-72)	85(80-90)
BISAP [2]≥2	213	0.76	0.68	0.83	40(27-55)	92(87-95)	58(41-74)	85(79-90)
Glasgow≥3	213	0.76	0.68	0.83	48(34-62)	84(78-89)	46(32-59)	85(79-90)
Glagow [2]≥3	213	0.78	0.70	0.85	44(30-59)	88(83-92)	51(36-66)	85(79-89)
APACHE II≥8	213	0.79	0.72	0.87	79(65-89)	63(56-70)	37(28-47)	92(85-96)
APACHE II [2]≥8	213	0.79	0.71	0.86	64(49-76)	70(63-77)	37(27-48)	87(81-92)

AUC Interpretation	0.50-0.60 fails as discriminator 0.61-0.70 is a poor discriminator 0.71-0.80 is a fair discriminator 0.81-0.90 is a good discriminator 0.91-1 is excellent discriminator

[2]: scores computed excluding age, ROC : Receiver operating characteristic, AUC : Area under the curve, Sens,: sensitivity, Spec.: specificity, PPV : positive predictive value, NPV : negative predictive value, SIRS : Systemic Inflammatory Response Syndrome, CRP : C-preactive protein, APACHE: Acute physiology And Chronic Health Evaluation, BISAP : Bedside Index of Severity in Acute Pancreatitis, CI : confidence interval

Table 29 Pairwise comparison of the AUC of the Scoring systems

Scoring system	**SIRS**	**CRP**	**BISAP**	**Glasgow**	**BISAP 2**	**Glasgow 2**	**APACHE II**	**APACHE II 2**
SIRS≥2	X	**0.8**	0.049	0.1	0.04	0.11	0.09	0.03
CRP≥150mg/dl		X	0.25	0.09	0.11	0.037	0.09	0.053
BISAP≥2			X	**0.83**	**0.86**	**0.82**	**0.63**	0.31
Glasgow≥3				X	**0.87**	**0.92**	**0.75**	0.36
BISAP ^{2}≥2					X	NS	NS	NS
Glasgow ^{2}≥3						X	NS	NS
APACHE II ≥8							X	NS
APACHE II ^{2}≥8								X

SIRS : Systemic Inflammatory Response Syndrome, CRP : C-preactive protein, APACHE: Acute physiology And Chronic Health Evaluation, BISAP : Bedside Index of Severity in Acute Pancreatitis
NS = not significant
Correlation is interpreted as 0.3 = weak, 0.5=moderate and 0.7=strong
Highlighted are strong correlations, ^{2}: scores computed excluding age

Table 30: Severity assessment in the pancreatitis cohort patients in relation to HIV status

Scoring System		No	AUC	Standard. Error	95% Conf. Interval	
					Upper limit	Lower limit
CRP >150mg/	HIV-ve	110	0,75	0,05	0.66	0.85
	HIV+ve	84	0,59	0,07	0.45	0.74
BISAP≥2	HIV-ve	110	0,71	0,06	0.60	0.82
	HIV+ve	84	0,74	0,07	0.61	0.88
BISAP [2]≥2	HIV-ve	110	0,72	0,05	0.62	0.83
	HIV+ve	84	0,77	0,06	0.64	0.89
SIRS≥2	HIV-ve	110	0,68	0,07	0.55	0.81
	HIV+ve	84	0,69	0,07	0.56	0.82
Glasgow≥3	HIV-ve	110	0,72	0,05	0.61	0.82
	HIV+ve	84	0,78	0,07	0.65	0.91
Glasgow [2]≥3	HIV-ve	110	0,74	0,05	0.63	0.84
	HIV+ve	84	0,79	0,07	0.66	0.92
APACHE II≥8	HIV-ve	110	0,81	0,06	0.69	0.92
	HIV+ve	84	0,88	0,04	0.80	0.95
APACHE II [2]≥8	HIV-ve	110	0,84	0,05	0.73	0.94
	HIV+ve	84	0,89	0,03	0.83	0.96

AUC Interpretation	0.50-0.60 fails as discriminator 0.61-0.70 is a poor discriminator 0.71-0.80 is a fair discriminator 0.81-0.90 is a good discriminator 0.91-1 is excellent discriminator

[2]: scores computed excluding age, ROC : Receiver operating characteristic, AUC : Area under the curve, Sens,: sensitivity, Spec.: specificity, PPV : positive predictive value, NPV : negative predictive value, SIRS : Systemic Inflammatory Response Syndrome, CRP : C-preactive protein, APACHE: Acute physiology And Chronic Health Evaluation, BISAP : Bedside Index of Severity in Acute Pancreatitis, CI : confidence interval

Table 31: Patient demographics and outcomes in HIV+ve patients

	CD4				Total	p value
	< 200		≥200			
	No	%	No	%	No	
Age group						
< 30	6	30	14	70	20	0.1
30-49	15	33	30	67	45	
50-74	5	71	2	29	7	
Gender						
Female	9	23	31	78	40	0.01
Male	17	53	15	47	32	
Ethnicity						
African	25	38	41	62	66	0.5
Mixed	0	0	1	100	1	
Indian	1	20	4	80	5	
White	0		0		0	
Length of stay						
< 7 days	10	38	16	62	26	0.3
7-13 days	5	24	16	76	21	
14-55 days	11	44	14	56	25	
Disease severity						
Severe	6	50	6	50	12	0.3
Not severe	20	33	40	67	60	

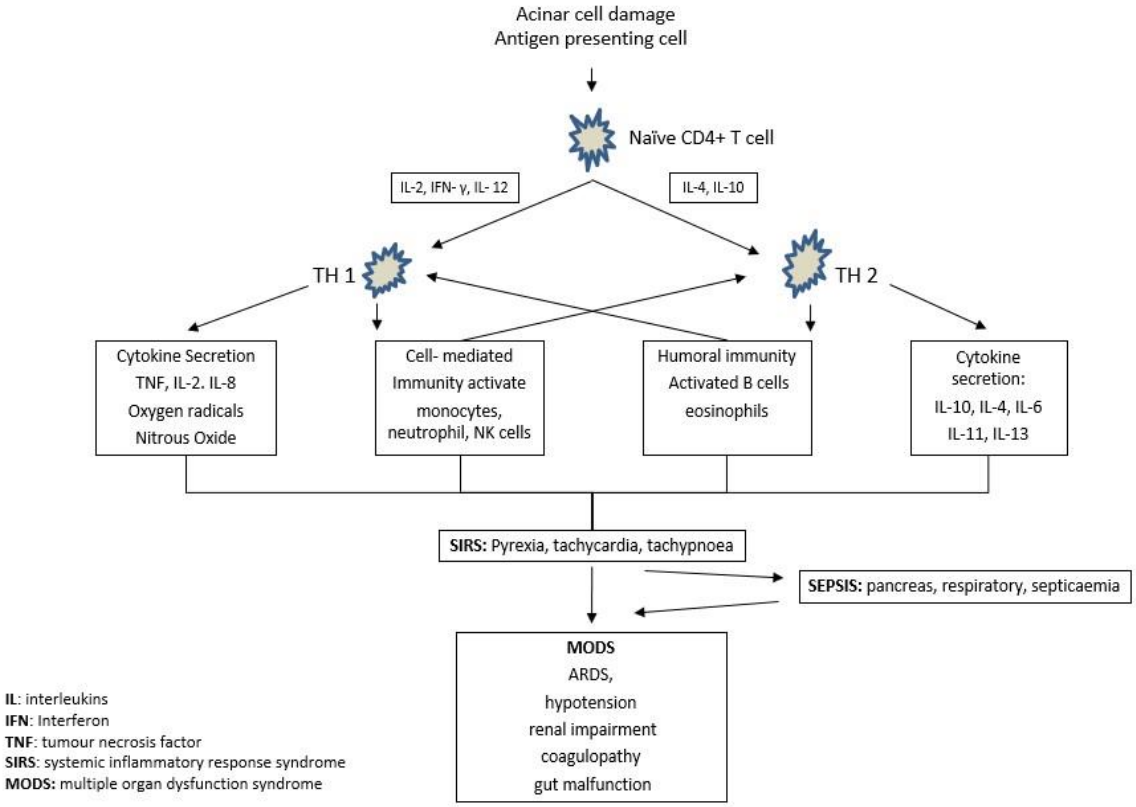
Table 32: Scoring systems and the relationship to CD4 count in HIV+ve patients with acute

Score	CD 4 <200					CD4 > 200				
				95% CI					95% CI	
	No	AUC	SE	lower	upper	No	AUC	SE	lower	upper
SIRS≥2	26	0,51	0,16	0,20	0,82	42	0,83	0,04	0,76	0,91
CRP≥150mg/dl	26	0,46	0,13	0,21	0,71	42	0,73	0,16	0,42	1,00
BISAP≥2	26	0,62	0,15	0,33	0,91	42	0,90	0,05	0,79	1,00
Glasgow≥3	26	0,83	0,08	0,68	0,98	42	0,81	0,13	0,55	1,00
BISAP[2]≥2	26	0,62	0,15	0,33	0,91	42	0,90	0,05	0,79	1,00
Glagow[2]≥3	26	0,88	0,07	0,75	1,00	42	0,81	0,13	0,55	1,00
APACHE II≥8	26	0,80	0,09	0,62	0,98	42	0,87	0,06	0,76	0,98
APACHE II[2]≥8	26	0,82	0,08	0,65	0,98	42	0,90	0,05	0,80	0,99
AUC Interpretation:	0.50-0.60 fails as discriminator 0.61-0.70 is a poor discriminator 0.71-0.80 is a fair discriminator 0.81-0.90 is a good discriminator 0.91-1 is excellent discriminator									

[2]: scores computed excluding age, SIRS : Systemic Inflammatory Response Syndrome, CRP : C-preactive protein, APACHE: Acute physiology And Chronic Health Evaluation, BISAP : Bedside Index of Severity in Acute Pancreatitis, AUC : Area under the curve, CI : confidence interval, SE : standard error

FIGURES INTRODUCTION

Figure 1: Immune regulation pathways in acute pancreatitis



ARDS: Adult respiratory distress sundrome
NK : natural killer

Figure 2: Factors influencing the mortality rate of acute pancreatitis over a century

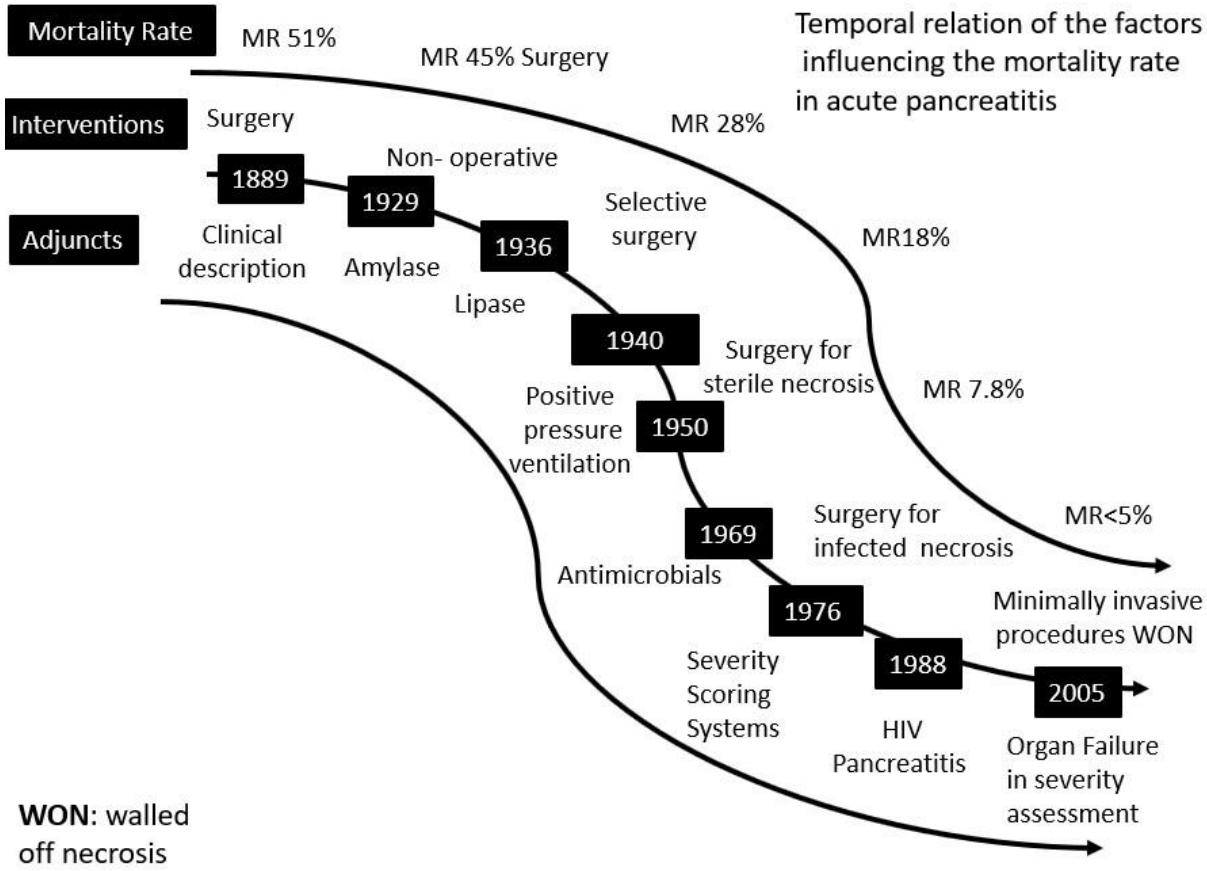
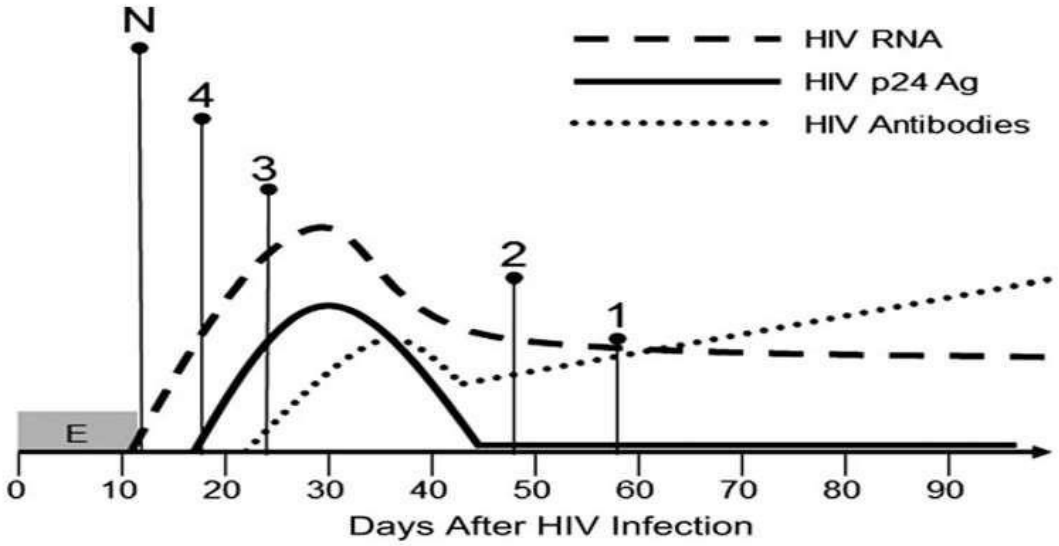


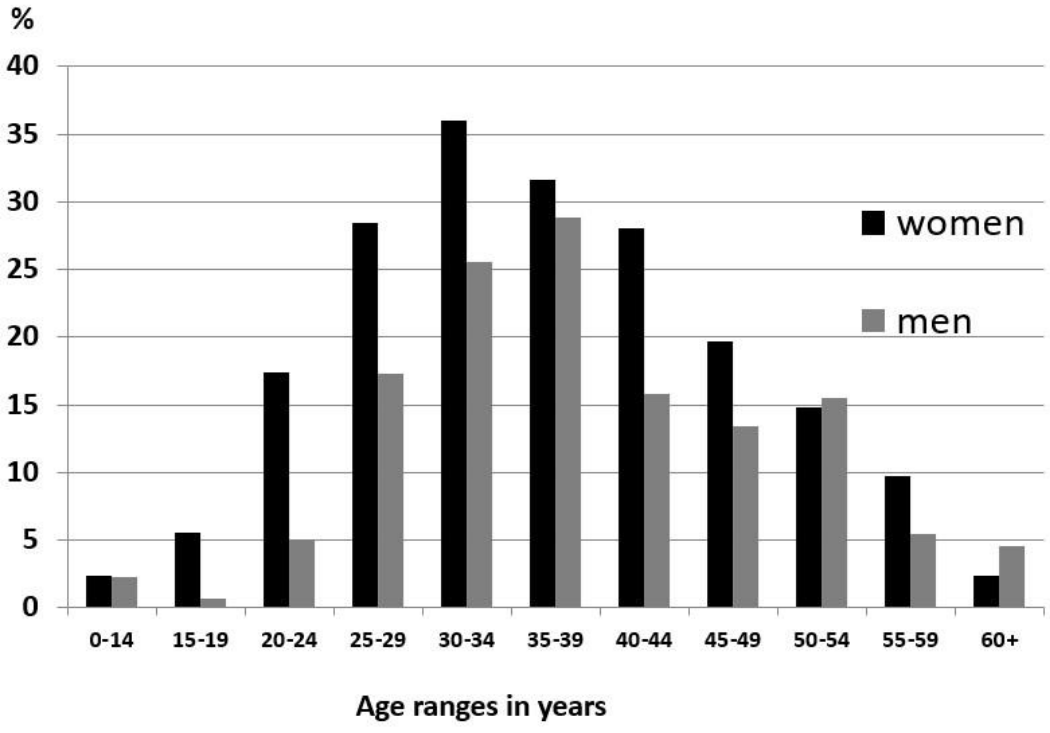
Figure 3: Temporal relation of diagnostic markers of HIV infection



Ag-antigen, E- eclipse period, RNA – ribonucleic acid.

First (1), second (2), third (3), and fourth (4) generation and nucleic acid amplification test (N) HIV diagnostic assays superimposed on a graphical depiction of the kinetics of circulating HIV RNA, p24 antigen, and HIV antibodies..

Figure 4: Age and gender distribution of HIV prevalence in KwaZulu Natal in 2012



RESULTS FIGURES

Figure 5: Age and gender distribution of HIV infection in the trauma and acute pancreatitis cohorts

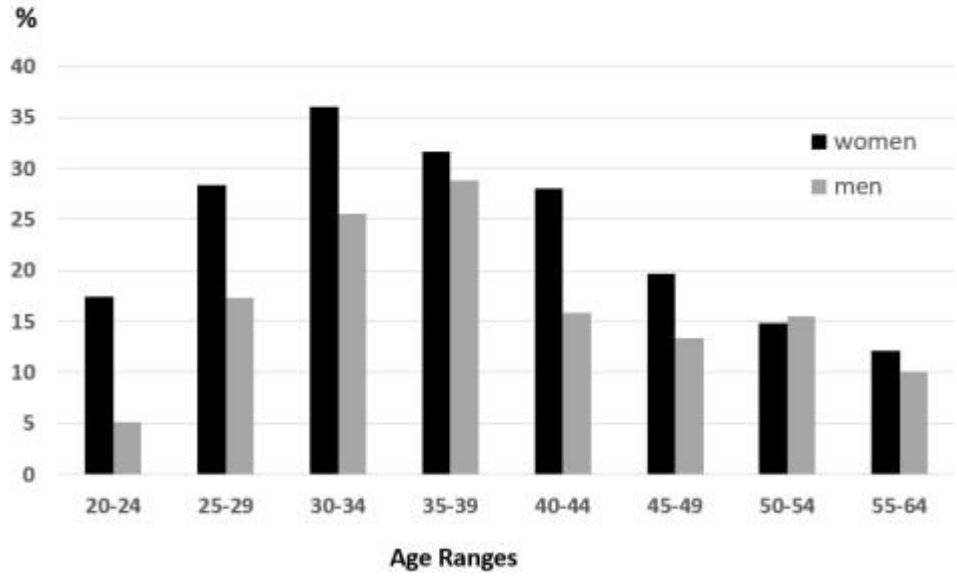


Figure 6: Severe disease in age brackets in relation to HIV status

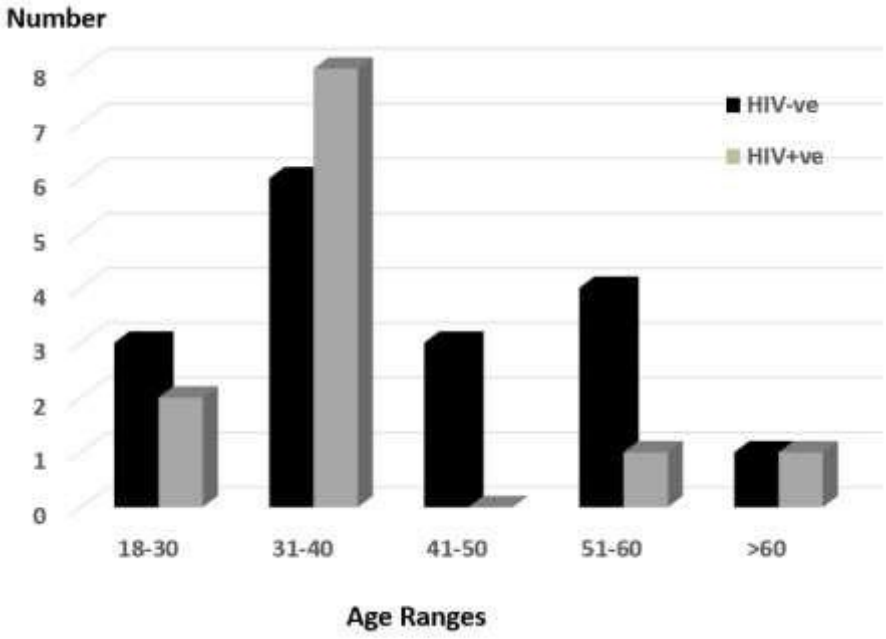


Figure 7: ROC graph of scoring systems to detect severe disease in HIV-ve patients

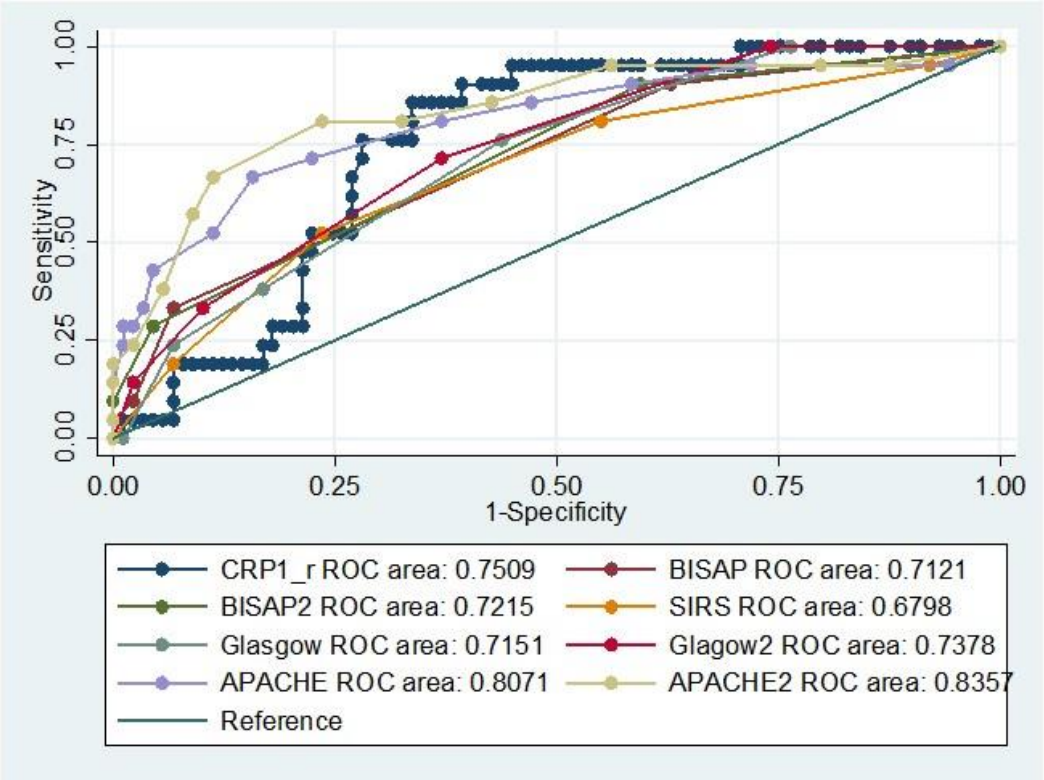


Figure 8: ROC graphs of scoring systems to detect severe disease in HIV+ve patients

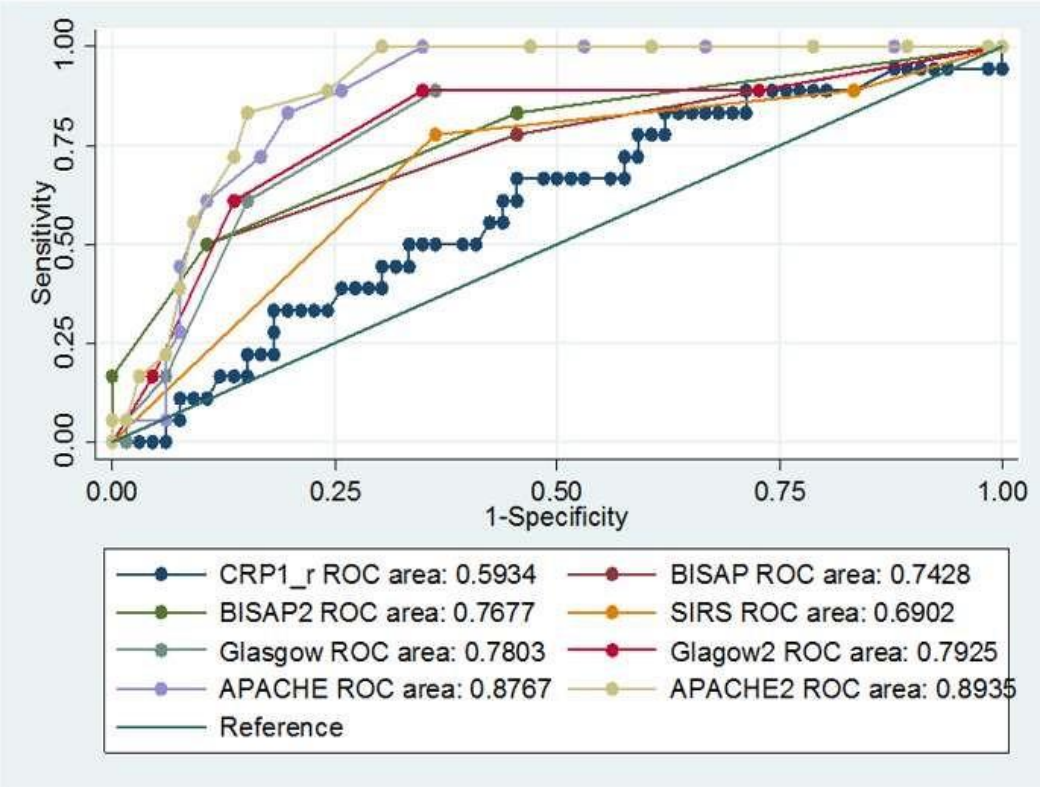


Figure 9: ROC graph to detect severe disease in HIV +ve patients with CD4 count more than 200

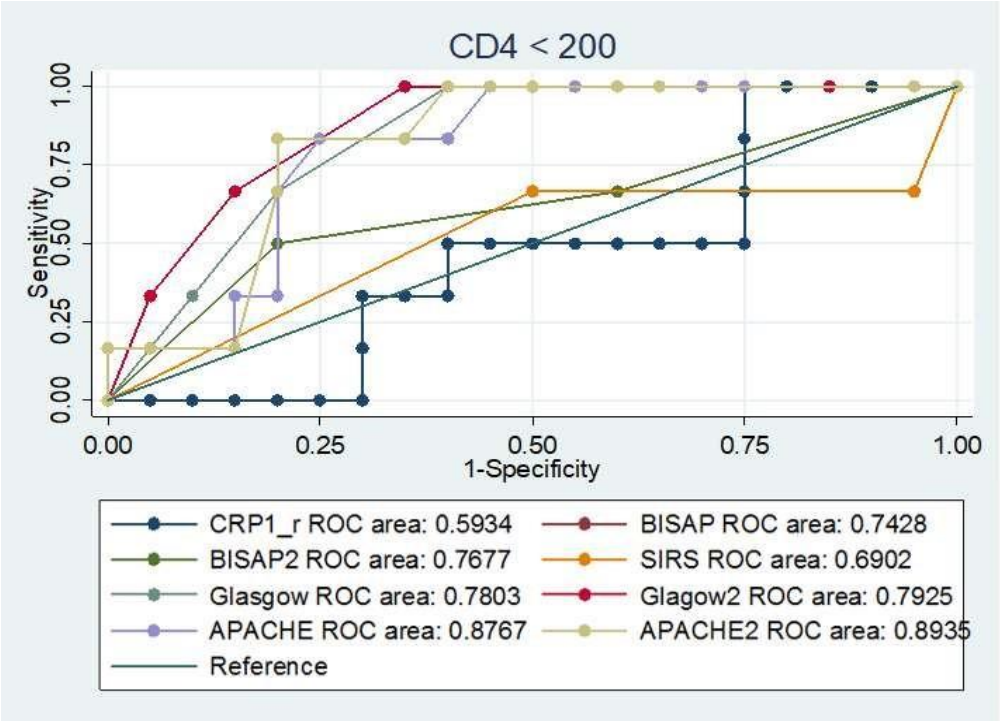
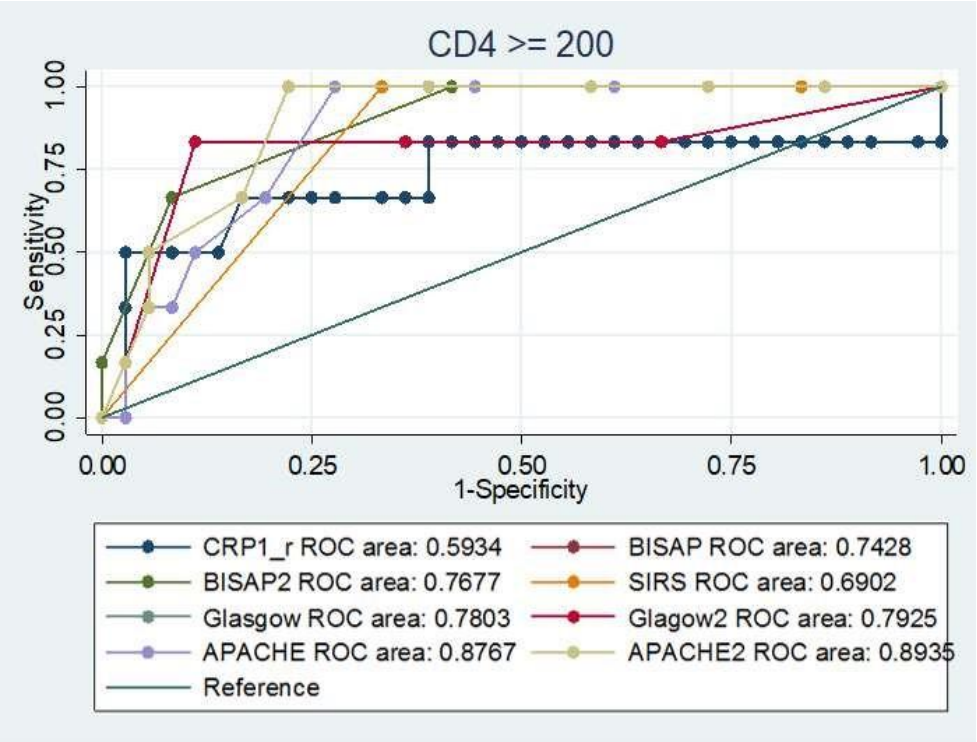


Figure 10: ROC graph to detect severe disease in HIV +ve patients with CD4 count less than 200



ANNEXURE TABLES

Table 1: Risk category of likelihood of drug related pancreatitis

Category	**Criteria**	Likeilihood
Ia	1 case report with positive re-challenge, other causes excluded	Highly probable
1b	1 case report with positive re-challenge, other causes were not ruled out	Probable
II	At least 4 cases reported, consistent latency in ≥ 75% cases	Likely
III	At least 2 cases reported, no consistent latency or re-challenge	Less likely
IV	1 case report without re-challenge	Least Likely

Table 2: Acute pancreatitis grading using revised Atlanta criteria

Grade	**Criteria**
Mild	No organ failure or local and systemic complications
Moderate	Organ failure resolving at 48hours after admission
	or Local complications*
Severe	Organ failure** persisting for more than 48hours
	or Mortality during index admission
Local Complications *pancreatic necrosis, pancreatic fluid collections, vascular complications, pancreatic abscess pancreatic ascites. Organ failure: ** defined by the Marshall score	

Table 3: Criteria for the APACHE II scoring system

1. Age < 44: 0 points
2. Heart rate 70-109 beats per minute: 0 points
3.Respiratory rate 12-24 breaths per minute: 0 points
4.Mean arterial pressure 70-90 mmHg: 0 points
5.Temperature 36-38.4 °C: 0 points
6.Creatinine 62-115 µmol/L: 0 points
7.Ph 7.33-7.49: 0 points
8.Sodium 130-149 mmol/L: 0 points
9.Potassium 3.5- 5.4 mmol/L: 0 points
10.Haematocrit 30- 45.9: 0 points
11.White blood cell count 3- 10.7 cells $\times 10^9$: 0 points
12.Glasgow coma score 15: 0 points
13.PaO2(depending on FiO2) or A-a gradient Po2
14.Chronic organ insufficiency or immuno-compromise

Range of normal values are provided which do not attract points are provided
Each factor is accorded 1 point and 8 or more points is a marker of severe disease

Table 4: Criteria for the Glasgow score

1. Age	> 55
2. Arterial partial pressure oxygen	< 60mmHg
3. White blood cell count	>15 $\times 10^9$ /L
4. Serum calcium	< 2 mmol/l
5. Blood urea nitrogen	> 16 mmol/L
6. Blood glucose	>10 mmol/L
7. Serum Albumen	< 32 g/L
8. Lactate dehydrogenase	> 600 U/L
Each positive factor is awarded 1 point and ≥ 3 points predicts severe disease	

Table 5: Criteria for Bedside Index for Severity in Acute Pancreatitis (BISAP)

1. Urea > 9mmol/l
2. Impaired mental status (Glasgow coma score <15)
3. SIRS (Table 1)
4. > 60 years of age
5. Pleural effusion

Each of the five criteria score one point and a score of greater than 2 defines severe disease.

Table 6: Diagnostic criteria for Systemic Inflammatory Response Syndrome

1. Heart Rate: >90/minute
2. Respiratory rate: > 20/minute or $PaCO^2$ <30 mmHg
3. Temperature: >38°C or <36°C
4. White cell count >12.0 × 10^9 /L or < 4.0 × 10^9 /L + >10% bands

SIRS is defined by the presence of 2 or more of these clinical factors.

Table 4: Criteria for the APACHE O scoring system

1. Age < 44: 0 points
2. Heart rate 70-109 beats per minute: 0 points
3.Respiratory rate 12-24 breaths per minute: 0 points
4.Mean arterial pressure 70-90 mmHg: 0 points
5.Temperature 36-38.4 °C: 0 points
6.Creatinine 62-115 µmol/L: 0 points
7.Ph 7.33-7.49: 0 points
8.Sodium 130-149 mmol/L: 0 points
9.Potassium 3.5- 5.4 mmol/L: 0 points
10.Haematocrit 30- 45.9: 0 points
11.White blood cell count 3- 10.7 cells ×109 : 0 points
12.Glasgow coma score 15: 0 points
13.PaO2(depending on FiO2) or A-a gradient Po2
14.chronic organ insufficiency or Immuno-compromise
Points allocated to BMI
BMI < 26 = 0 BMI 26 - 30 = 1
Range of normal values are provided which do not attract points are provided
Each factor is awarded 1 point and 8 or more points is a marker of severe disease

Table 6: Criteria for CT Severity Index (CTSI) score

Pancreatic inflammation	**Points**
Normal pancreas	0
Focal or diffuse enlargement of pancreas	1
Peripancreatic inflammation	2
Single acute fluid collection	3
Two or more acute fluid collections	4
Pancreatic parenchymal necrosis	
None	0
< 30%	2
Between 30% - 50%	4
> 50%	6
The score is the sum of the scores of pancreatic inflammation and necrosis - maximum score of 10 Mild: 0-3, Moderate 4-6, Severe 7-10	

Annexure 7: INFORMED CONSENT FOR INCLUSION IN PANCREATITIS AND HIV STUDY

Patient Information

You have been diagnosed with pancreatitis. Gallstones and alcohol are the commonest causes. HIV infection may be a cause of the disease and may also determine the severity of the disease. We wish to find out if your attack is related to HIV infection. All information gathered will be regarded as confidential. Testing for HIV will benefit you as you will know your HIV status and you will be referred for appropriate counselling and treatment. Your HIV status will not affect the treatment you receive for pancreatitis. You do not have to agree to HIV testing and this will not effect the treatment you receive.

I agree to be tested for HIV infection

Subject

Signed: Date:

Researcher

Signed: Date:

Witness

Signed: Date:

If you have any questions contact me on the following number: 0762621940

IMVUME YOKUBANDAKANYWA KUCWANINGO NGEGKIWANE LESANDULELA NGULAZA KANYE NOKUVUVUKALO KWAMANYIKWE

Odokotela bathe uma bekuhlola, bathola ukhuthi amanyikwe akho avuvukele. Imbangela kungaba amatshe akheke esikhwameni senyongo, ukuphuza kakhulu utshwala, kanye negciwane lesandulelo ngculaza. Igciwane lesandulela ngculaza lona lingakwenza kudlange lokukufa. Ngakhoke sifuna ukwenza isiqiniseko ukuthi akulona yini igciwane lesandulela ngculaza elenza ugule ngaloluhlobo. Lonke ulwazi esiyoluthola luyoba imfihlo yethu nawe. Ukuhlolela leligciwane lesandulela ngculaza kuyokusiza nawe uzazi ukuthi ukuliphi bese welashwa ngendlela, efanele.

Uma kutholakala ukuthi unalo igciwane, noma futhi ungenalo lokho akusho lutho ngoba indlela yokukwelapha ukuvuvuka kwamanyikwe iyefana. Nokho ke awuphoqelekile ukuba uhlole ngoba lokho akuzuphazamisa esizokwelapha ngayo indlela.

NGIYAVUMA UKUHLOLELA IGCIWANE LESANDULELA NGCULAZA.

SIGNATURE: DATE (USUKU):

UMCINANINGI: USUKU:
SIGNATURE:

UMFAKAZI: USUKU:
SIGNATURE:

Uma unemibuzo shayela Kulenombolo 0762621940