

https://dspace.org/

Comparison of the risk factors and initial presenting symptoms to stage of disease in pancreatic ductal adenocarcinoma patients at Chris Hani Baragwanath Academic Hospital

Lahoud, Nicola

2019

https://hdl.handle.net/10539/29846

Lahoud, Nicola Ann (2019) Comparison of the risk factors and initial presenting symptoms to stage of disease in pancreatic ductal adenocarcinoma patients at Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, <http://hdl.handle.net/10539/29846>

Downloaded from a DSpace repository. https://dspace.org/

Comparison of the risk factors and initial presenting symptoms to stage of disease in Pancreatic Ductal Adenocarcinoma patients at Chris Hani Baragwanath Academic Hospital

Dr Nicola Lahoud
Student no:060062Y
MBChB
Department of General Surgery

Supervisors: Dr John WS Devar (MBBCh, FCS, Certificate in Surgical Gastroenterology)
Dr Deirdré Kruger (BSc, PGCHE, PhD)



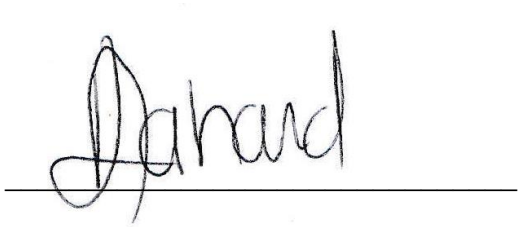
UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

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

November 2019

DECLARATION

I, Nicola Lahoud, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Surgery at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at any other University.



20th Day of November 2019 in Johannesburg

DEDICATION

To Cecilia Lahoud without your continuous support, I would not be.

PRESENTATIONS ARISING FROM THIS STUDY

- Bert Myburgh Research Forum, Department of Surgery, Wits Faculty of Health Sciences. Oral presentation. November 2017.
- IAP and HPBASA congress, 16 – 20th August 2019 in Cape Town. ePoster presented. Recipient of a young investigator award.

ABSTRACT

Background: Pancreatic adenocarcinoma (PDAC) is the second leading cause of death in the US amongst both sexes and patients often present with advanced disease. Where many studies have described the risk factors, symptoms, biochemistry and staging of the disease, none have assessed the risk factor profile and presenting symptoms according to the stage of the cancer in a black South African population.

Objectives: To assess the initial risk factor profile, presenting symptoms and biochemistry according to stage in Black South African patients with diagnosed PDAC at Chris Hani Baragwanath Academic Hospital.

Methods: A retrospective study including 71 patients with diagnosed PDAC from the Hepatobiliary unit database at CHBAH. We determined the TNM staging of each tumor from patient CT scans and correlated it to the demographic, biochemistry, risk factor and symptom data recorded in the patients file.

Results: The study population had a mean (±SD) age at presentation of 59.9 (±10.8) years with a male predominance of 56.3% males. The majority of patients had stage 2 disease (35.2%). BMI and current smoking status differed significantly across the stages. The most common symptoms were abdominal pain (67.7%), jaundice (65.6%) and weight loss (50.8%), none of which were associated with PDAC stage. Lower platelet count, high GGT and elevated CA19-9 levels were significantly associated with advanced PDAC. Platelet count showed statistical significant in each T, N and M stage, respectively. Univariate logistic regression demonstrated that platelet count, CRP and CA19-9 values are significantly associated with metastasis. In a multivariate logistic regression model lower platelet count and increased CA 19-9 are independent predictors of metastatic disease in PDAC patients with 97% specificity and 83% PPV.

Conclusion: Our data demonstrates that most risk factors or presenting symptoms show no association with PDAC stage, although it does illustrate the risk factors and clinical presentation that are prevalent in our population. Moreover, platelet count and CA19-9 are independent predictors of metastases in PDAC.

ACKNOWLEDGEMENTS

This dissertation has been made possible thanks to the encouragement, support and guidance of my supervisors Dr John Devar and Dr Deirdre Kruger.

Dr John Devar, who spent many hours of his time teaching and helping me stage the patients fully supporting me and guiding me through this dissertation and offering his superb knowledge, expertise and experience to me, he also helped proof read this dissertation.

Dr Deirdre Kruger, at every step through this dissertation guided me, supported me, helped with statistical analysis and proof read the dissertation and without her efficiency, superb abilities and exceptional expertise this dissertation would not have been possible.

The Chris Hani Baragwanath Academic Hospital Hepato-Pancreatico-Biliary Unit, without the data and patient numbers, I would not be able to finish this project.

Chris Hani Baragwanath Academic Hospital Radiology department for granting Dr John Devar and me full access to the imaging used to stage patients in this study.

TABLE OF CONTENTS

DECLARATION ii
DEDICATION iii
PRESENTATIONS ARSING FROM THIS STUDY iv
ABSTRACT v
ACKNOWLEDGEMENTS vi
LIST OF ABBREVIATIONS viii
LIST OF FIGURES ix
LIST OF TABLES x
CHAPTER 1. INTRODUCTION 1
1.1 Background 1
1.2 Risk factors 1
1.3 Symptoms 3
1.4 Diagnosis 4
1.5 Staging 5
CHAPTER 2. METHODS 6
2.1 Patient selection and data collection 6
2.2 Statistical analyses 7
CHAPTER 3. RESULTS 8
CHAPTER 4. DISCUSSION 18
4.1 Demographics and risk factors of the study population 18
4.2 Presenting symptoms of PDAC 20
4.3 Routine biochemistry and PDAC stage 20
4.4 Limitations of the study 22
CHAPTER 5. CONCLUSION 23
REFERENCES 24
APPENDIX 1: TNM staging of PDAC 27
APPENDIX 2: Approved Protocol 28
APPENDIX 3: Datasheet 37
APPENDIX 4: Ethics Clearance Certificate 38

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CEA	Carcinoembryonic antigen
CA 19-9	Carbohydrate antigen 19-9
CHBAH	Chris Hani Baragwanath Academic Hospital
CRP	C- reactive protein
ECOG	Eastern Cooperative Oncology Group
GGT	Gamma glutamyltransferase
HbA1c	Glycated hemoglobin A1c
IPMN	Intraductal Papillary Mucinous Neoplasm
LOW	Loss of weight
MCN	Mucinous Cystic Neoplasm
PANin	Pancreatic Intraepithelial Neoplasia
PDAC	Pancreatic ductal adenocarcinoma
T2DM	Type 2 Diabetes Mellitus

LIST OF FIGURES

Figure 3.1 Smoking status according to gender 10

Figure 3.2 The correlation between the Karnofsky and ECOG performance scales in our study population. 14

Figure 3.3 Platelet counts are protective against the primary tumor size in PDAC patients. 17

LIST OF TABLES

Table 1.1 Modifiable and unmodifiable risk factors for developing PDAC. 2

Table 3.1 Risk factors associated with PDCA according to stage. 11

Table 3.2 Associated symptoms in PDAC according to stage. 12

Table 3.3 Biochemical measurements according to PDAC stage. 12

Table 3.4 ECOG performance in PDAC patients according to stage. 15

Table 3.5 Variance in BMI and biochemical measurements according to separate TNM staging categories of tumor size (T), nodal disease (N) and metastases (M). 16

Table 3.6 Multivariate logistic regression analysis predicting metastasis in PDAC. 17

CHAPTER 1

INTRODUCTION

1.1 Background

Pancreatic adenocarcinoma is predicted to become the second leading cause of death due to malignancy in the US among both men and women by 2020.[1,2]The aetiology is thought to be multifactorial with various genetic mutations, environmental factors and/or other molecular abnormalities.[3] Pancreatic cancer generally refers to pancreatic ductal adenocarcinoma (PDAC) which makes up approximately 85% of all pancreatic neoplasms.[3]

Alarmingly, only approximately 9% of patients with pancreatic cancer are actually diagnosed when the tumour is still resectable.[3] As a result, median survival is poor even after surgical resection, and low resectibility rates are only part of the reason for poor survival. The mortality rate has remained unchanged over the past two decades.[2]

From the 2012 National Cancer Registry, a total of 191 males and 148 females were diagnosed with adenocarcinoma of the pancreas from our local South African population;[4] the highest incidences amongst males and females were from Caucasian ethnicity (50.3% and 54.7%, respectively). The most frequent age range of diagnosis in both males and females was 60 – 69 years. Of note, this is a pathology based registry and therefore many patients who have not confirmed pancreatic cancer were excluded from the registry and therefore the incidents would certainly be under - reported.

1.2 Risk factors

The estimated life time risk of developing PDAC is relatively low. Nevertheless, modifiable and unmodifiable factors may increase an individual's risk of developing PDAC.
These are listed below in Table 1.1.

Risk factors associated with a cancer diagnosis may differ substantially from those that modify cancer progression and survival. Furthermore, there is paucity in the literature on how specific risk factors impact progression and/or survival in different cancers. Where some data exist for breast, colon, prostate, and lung cancers,[5] the impact of specific risk factors on pancreatic cancer progression and survival have not been reported, if at all investigated.

Table 1.1. Modifiable and unmodifiable risk factors for developing PDAC.

Modifiable risk factors

- Cigarette smoking: relative risk of 1%, strongest exogenous risk factor associated with pancreatic cancer.[6]

  The risk increases with the number of cigarettes consumed. Excess risk decreases when one stops smoking;[7]smoking decreases the median age of presentation from 71 years in non-smokers to 56 years in smokers.[8]

- Obesity and physical inactivity:

  BMI of more than 30 kg/m^2 significantly increases the risk compared to BMI of less than 23 kg/m^2. Some propose that overweight and obese individuals develop pancreatic cancer at younger age and have a decreased survival once diagnosed.[9]

- Alcohol consumption: small association limited to heavy alcohol consumption.[10]

Unmodifiable risk factors

- Age
- Diabetes
- Familial Pancreatic cancer:

  5–10% of patients have first degree relatives with pancreatic cancer;[11] Patients present at a younger age (<50 years).[12]

- Hereditary pancreatic syndromes:

  Certain genetic syndromes are known to give rise to pancreatic cancer, with these associated genes - *BRCA2*, *p16/CDKN2A*, *STK1*, *PRSS1*, *MLH1*, *MSH2 (Lynch Syndrome)*.[4]

- Familial atypical multiple mole melanoma (FAMMM).[6]
- Peutz Jeghers Syndrome.[4,6]
- Cystic fibrosis.[6]
- Familial adenomatous polyposis.[6]
- Non-hereditary and hereditary pancreatitis:[4,6]

  Hereditary pancreatitis is a severe risk factor for pancreatic cancer, increases the risk of developing pancreatic cancer by 40 -55%.[2]

- Premalignant lesions – Intraductal Papillary Mucinous Neoplasm (IPMN), MCN, PANin.[2]

1.3 Symptoms

In most patients, with early PDAC are asymptomatic. The initial symptoms are usually vague and non-specific .The latter is one of the main reasons why patients are initially falsely reassured that their symptoms cannot be of any importance.[13] Symptoms may differ depending on the location of the tumor in the head, body or tail of the pancreas. Nevertheless, the most frequent symptoms at presentation, which are often common symptoms for many illnesses, are discussed below.[4,14]

Abdominal pain - Reported in up to 70% of patients in South Africa, the abdominal pain associated with pancreatic cancer is usually insidious in onset, and has been present for one to two months at the time of presentation. It has a typical gnawing visceral quality, and is usually epigastric, radiating to the sides and/or straight through to the back. It may be intermittent and be made worse by eating or lying supine. It is frequently worse at night. Lying in a curled or fetal position may improve the pain.

Asthenia – Asthenia, or lack of energy, is commonly reported in cancer and in pancreatic cancer it has been reported to be prevalent in 30-86% of PDAC patients.

Jaundice - Reported in 50-75% of PDAC cases, an obstructive picture may be seen in patients with a head of pancreas carcinoma, body and tail lesions are unlikely to present with jaundice due to the anatomical location of the tumor in relation to the bile duct.

Loss of weight (LOW) - Loss of a lot of weight has been reported in up to 85% of patients and is more common with cancers in the head of the pancreas.

Other common symptoms of PDAC – these include nausea (51%), diarrhea (43.7%) and vomiting (33%); steatorrhea (25%); new onset of atypical diabetes mellitus (less than 2 years) or worsening of pre-existing diabetes; pruritus (32%); acholic stools (54%).

Also, some patients may present with gastric outlet obstruction secondary to invasion of cancer into the duodenum, junction of duodenum and jejenum (ligament of Treitz). Unexplained superficial thrombophlebitis, which may be migratory (classic Trousseau's syndrome), is sometimes present and reflects the hypercoagulable state that frequently accompanies pancreatic cancer.

Pancreatic tail adenocarcinoma tends to present at a more advanced stage than pancreatic head cancers. Jaundice in these patients is a particularly poor prognostic factor, often associated with regional lymphadenopathy extending into the portal area.

Interestingly, a retrospective review of electronic patient records from a large primary care database in the UK aimed to determine the early symptom profiles of PDAC and biliary tract cancers in the two years prior to diagnosis.[15] The authors reported 11 alarm symptoms associated with PDAC through a multivariate logistic regression model: LOW, abdominal pain, nausea and vomiting, dyspepsia, new onset diabetes, change in bowel habit, lethargy, pruritus, back pain, shoulder pain and jaundice. Where some of these early symptoms overlapped for biliary tract cancers, unique features of PDAC were identified as back pain, lethargy and new onset diabetes. Similarly, a recent study from the US reported that new onset diabetes and LOW often feature together before a diagnosis of PDAC, with lethargy and depression also identified as potential precursors.[16]

Where some studies have looked at symptoms and the duration of symptoms on PDAC disease progression, resectability and survival, most of them report that these factors either have no/minimal impact or do not correlate with the stage of disease. Furthermore, clinical presentation also had no impact on the survival.[17,18] Notwithstanding, there are no studies from Sub-Saharan Africa that have investigated the association between symptoms and disease progression or prognosis in PDAC.

1.4 Diagnosis

PDAC is often undetected until it is an advanced stage. Accurate diagnosis of PDAC cannot be made on clinical presentation alone. Early diagnosis depends on the effect of the mass and this depends on the location of the tumor within the pancreas. To date there are no screening tests available to assist with the early diagnosis of PDAC, [19] and regrettably the low sensitivity and specificity of the most widely used marker, CA 19-9, renders it inadequate to use as a screening test.

Diagnosis includes taking the patient's medical history, doing a physical exam and laboratory tests. Further diagnostic work-up is then required in the form of serology and abdominal imaging. For patients with the initial presentation of jaundice and abdominal pain, the first imaging investigation would typically be a transabdominal ultrasound (US), however most often patient will require a multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI) and tissue biopsy for definite diagnosis and staging. In saying this, it is not necessarily done on all patients with suspected PDAC (eg performance

status 4, those not fit for surgery or chemotherapy, upfront patients who present with a resectible tumor and who are jaundice) [4,19,20a]

1.5 Staging

Staging of PDAC is based on the primary tumor itself, regional lymph node and distant metastases (TNM) staging system maintained by the American Joint Committee on Cancer (AJCC) (Appendix 1). The main modality used for the staging of PDAC is cross-sectional imaging MDCT/MRI, preoperatively.[20a] Another common approach used to categorize PDAC is based on the resectability of the tumor, enabling the clinician to plan the most suitable treatment strategy, be it surgery, neoadjuvant or palliative chemotherapy as well as radiotherapy that is currently being practiced in United States . [20b]

Finally, PDAC is a devastating disease with poor outcomes, despite advancements in modern medicine and technology. Cumulatively, the aforementioned review of the literature demonstrates that multiple risk factors exist for developing PDAC and numerous presenting symptoms, often common to many illnesses, delay health seeking behavior in PDAC patients resulting in advanced stage at diagnosis. Moreover, the risk factors and presenting symptoms associated with a diagnosis of PDAC may differ substantially from those that alter disease progression and survival. Identifying and understanding individual patient-related factors, risk factors and symptoms across the stages of PDAC could enable us to better target affected individuals to promote prompt health seeking behavior which, in turn, may result in an earlier diagnosis of PDAC at a resectable stage and improved survival of this devastating disease. No studies to date have identified and described the risk factors and symptoms in PDAC patients from South Africa. Thus, in black South African patients with a diagnosis of PDAC, the aim of our study was to assess the risk factor profile, presenting symptoms and routine biochemistry and determine their relationship, if any, with the stage of the cancer.

CHAPTER 2

METHODS

2.1 Patient selection and data collection

As part of a larger, ongoing study, the Hepato-Pancreatico-Biliary (HPB) Unit at Chris Hani Baragwanath Academic Hospital (CHBAH) keep an existing database of patients with diagnosed PDAC, diagnosed either by cytological or histological investigations. Our retrospective study identified Black PDAC patients from that existing database who first presented to the HPB Unit during July 2013 – May 2016. The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (clearance number M160840).

Clinical and demographic data collected included age at diagnosis, gender, risk factor data for smoking, alcohol consumption, hypertension, diabetes mellitus, vascular disease, BMI and functional performances status. Alcohol consumption and usage was recorded by means of the reliable and validated CAGE questionnaire. 'CAGE' is an acronym used for the four questions that this questionnaire asks and one point is given for each 'yes' answer. A score of two or above indicates that the possibility of alcoholism should be further investigated. The four yes/no questions are as follows: 1) Have you ever felt the need to **C**ut down on your drinking? 2) Have you ever felt **A**nnoyed by criticism of your drinking? 3) Have you ever felt **G**uilty about your drinking? 4) Have you ever felt the need to drink a morning **E**ye-opener?

Performance status scales are tools that attempt to quantify a patient's general well-being and activities of daily living. We used the Eastern Cooperative Oncology Group (ECOG) and the Karnosky scores, both of which facilitate the classification of a patient's functional impairment, effectiveness of therapies and the prognosis of the patient.

Presenting symptoms were recorded and included jaundice, LOW, abdominal pain, vomiting and ascites. Routine biochemistry data included platelet counts, C-reactive protein (CRP), total bilirubin, gamma-glutamyl transferase (GGT), and percentage glycated hemoglobin (HbA1c). Tumor markers included serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA).

Most of the patients identified had imaging for staging before and were included in the study achieved. We retrieved the abdominal CT scans from these patients to determine the TNM

stage of the cancer and correlated these findings to the demographic, risk factor and symptom data recorded.

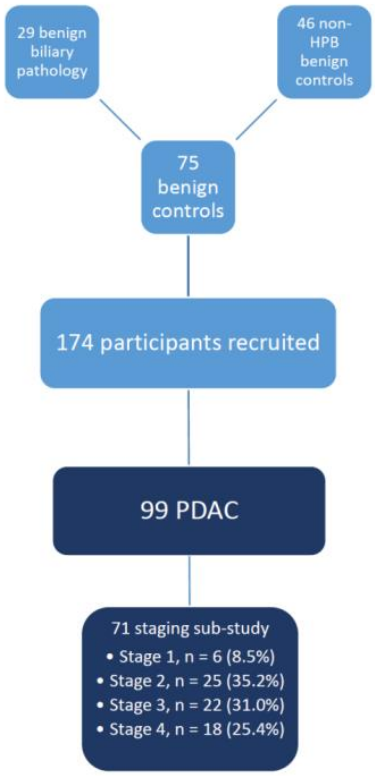
2.2 Statistical analyses

The study data was captured into Microsoft Excel and imported into the STATISTICA suite of analysis software, Version 12.7 (Statsoft Inc., Oklahoma USA). The Shapiro-Wilk W test was conducted to determine the distribution of the continuous data. Non-parametric Mann-Whitney U and Kruskal Wallis tests were used to determine the differences in clinical parameters among the different stages of PDAC. Correlations between the biochemical variables are also reported. Biochemical measurements are presented as medians and interquartile ranges. Chi-squared and Fishers' tests were used for analyses of categorical data. Bonferroni corrections were applied, where applicable, for multiple testing. The latter were expressed as absolute and relative frequencies. A value of $p \leq 0.05$ was considered statistically significant.

CHAPTER 3

RESULTS

A total of 71 patients with confirmed PDAC from the CHBAH database were included in the study and the complete TNM staging of each tumor was determined radiologically (CT or MRI). The mean (±SD) age at presentation was 59.9 (±10.8) years of age. There was male predominance with a total of 56.3% males (n = 40) versus 43.6% females (n = 31). The majority of patients had stage 2 disease (n=25, 35.2%), followed by stage 3 (n=22, 31.0%), stage 4 (n=18, 25.4%) and stage 1 (n=6, 8.5%). There were no significant differences in age between the four tumor stage groups (p = 0.50; Table 3.1).



Flowchart 3.1– demonstrates the cases assessed and those included in the study

Table 3.1 shows the risk factors present within each TNM-stage group of patients. Borderline significant differences between the BMI measurements across the TNM-stages is shown (p = 0.05). The difference in BMI was particularly significant when comparing stage 2 to stage 3 disease (p = 0.01). Only 12.5% (n = 8/64) of our PDAC patients were obese

with BMI $\geq$ 30 kg/m^2. The majority of our patients were male (56.3%) and where male predominance continues throughout stages 1 to 3, stage 4 shows female predominance.

The majority of patients were current or previous smokers (61.5%), and, overall, smoking status showed a statistically significant trend with PDAC stage ($p = 0.018$). When previous smokers were excluded, and current smokers were compared to those who have never smoked, the association between smoking status and stage becomes stronger ($p = 0.009$). Even though the majority of the non-smokers (44.4%) were stage 2 compared to the majority of the smokers (46.2%) being stage 3, the association between smoking status and stage was primarily due to differences seen between the early stages 1 and 2 (Bonferroni adjusted $p = 0.04$), and not between stage 2 and 3 (Bonferroni adjusted $p = 0.07$). There was a significant difference overall between smoking status and gender ($p < 0.0001$); specifically, only 11% of males had never smoked compared to 72% of females and all of the current smokers were of male gender ($p < 0.0001$; Figure 3.1). There was no significant difference in age at presentation based on smoking status (data not shown).

Interestingly, where the majority of PDAC patients consumed alcohol (70.8%), just over a third (34.5%) actually tested to be alcohol dependent as per the CAGE score analysis (Table 3.1). For stage 1 disease, 60% of PDAC patients had some level of alcohol dependence compared to only 25% for stage 4 disease. Overall, the prevalence of hypertension, Diabetes Mellitus and vascular disease in this PDAC study cohort was 38.5%, 24.6% and 3.1%, respectively (Table 3.1).

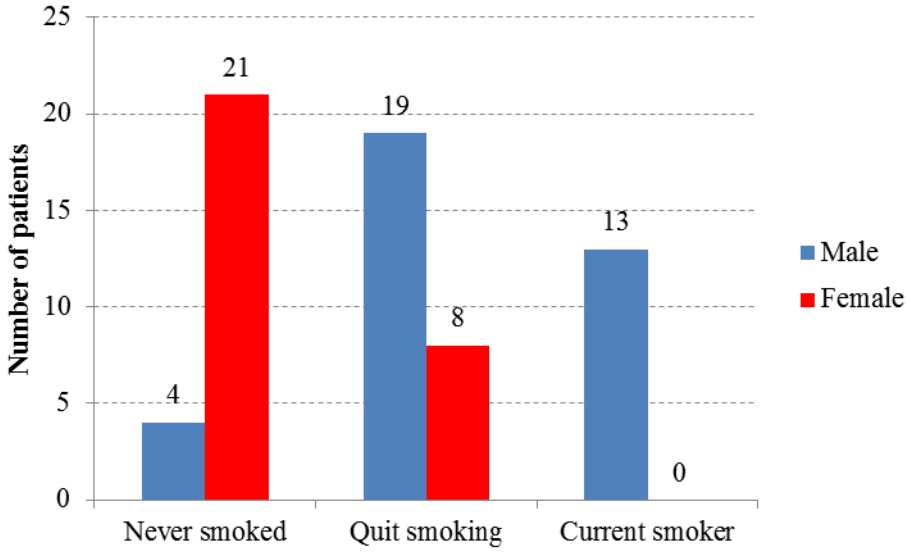


Figure 3.1. Smoking status according to gender

The presenting symptoms and signs in PDAC patients according to stage are shown in Table 3.2. The most prevalent associated symptom was abdominal pain which was present in 67.7% of all PDAC patients with even higher percentages reported for more advanced stage patients. This was followed by the presence of jaundice (65.6%), which was higher in early stage cancers, and LOW (50.8%). Vomiting and ascites was not common and only present in 21.5% and 6.2% of all PDAC patients, respectively. Ascites was only present in patients with the higher stages 3 and 4 cancers.

Table 3.1. Risk factors associated with PDCA according to stage.

Parameters	**All PDAC** (n = 71)	**Stage 1** (n = 6)	**Stage 2** (n = 25)	**Stage 3** (n = 22)	**Stage 4** (n = 18)	**p-value**
Age, years (mean ± SD)	59.9 ± 10.8	64.1 ± 11.1	61.0 ± 9.22	57.7 ± 12.1	60.7 ± 11.2	0.50[*]
BMI, kg/m^2 (median, IQR)	22.4 (18.6-25.3)	20.9 (19.2-24.3)	24.1 (21.0-27.8)	18.8 (15.8-23.6)	22.8 (19.5-24.8)	**0.05[*]**; 0.01[#]
Gender						
Male, n (%)	40 (56.3%)	5 (83.3%)	14 (56.0%)	13 (59.1%)	8 (44.4%)	0.41
	All PDAC *(n = 65)*	**Stage 1** *(n = 6)*	**Stage 2** *(n = 22)*	**Stage 3** *(n = 19)*	**Stage 4** *(n = 18)*	**p-value**
Smoking status, n (%)						
Yes, current smoker	13 (20.0%)	4 (66.7%)	1(4.6%)	6 (31.6%)	2 (11.1%)	
No, quit smoking	27 (41.5%)	2 (33.3%)	12 (54.6%)	5 (26.3%)	8 (44.4%)	**0.018[**]; 0.009[##]**
Never smoked	25 (38.5%)	0	9 (40.9%)	8 (42.1%)	8 (44.4%)	
Alcohol, n (%)						
Yes	46 (70.8%)	5 (83.8%)	14 (63.6%)	14 (73.7%)	13 (72.2%)	0.78
CAGE score, n (%)	(n = 55)	(n = 5)	(n = 20)	(n = 14)	(n = 16)	
0 – not dependent	36 (65.5%)	2 (40.0%)	12 (60.0%)	10 (71.4%)	12 (75.0%)	
1	6 (10.9%)	1 (20.0%)	0	2 (%)	3 (18.8)	
2	2 (3.6%)	0	2 (10.0%)	0	0	0.31
3	8 (14.6%)	2 (40.0%)	4 (20.0%)	1 (7.1%)	1 (6.3)	
4	3 (5.5%)	0	2 (10%)	1 (7.1%)	0	
Hypertension						
Yes, n (%)	25 (38.5%)	2 (33.3%)	10 (45.5%)	6 (31.6%)	7 (38.9%)	0.82
Diabetes Mellitus						
Yes, n (%)	16 (24.6%)	1 (16.7%)	5 (22.7%)	6 (31.6%)	4 (22.2%)	0.85
Vascular Disease						
Yes, n (%)	2 (3.1%)	0	2 (9.1%)	0	0	0.26

Abbreviations: SD, standard deviation; BMI, body mass index. [*]Kruskal-Wallis ANOVA; [#]Mann-Whitney U test comparing stage 2 to stage 3. [**]Fisher's exact for overall smoking status; [##]Fisher's exact for current smokers vs never smoked.

Table 3.2. Associated signs and symptoms in PDAC according to stage.

Parameters	All PDAC	Stage 1	Stage 2	Stage 3	Stage 4	p-value
Jaundice, n (%)						
Yes	42 (65.6%)	5 (83.3%)	15 (71.4%)	10 (52.6%)	12 (66.7%)	0.46
Loss of weight, n (%)						
Yes	33 (50.8%)	3 (50.0%)	11 (50.0%)	9 (47.4%)	10 (55.6%)	0.97
Abdominal pain, n (%)						
Yes	44 (67.7%)	3 (50.0%)	14 (63.6%)	14 (73.7%)	13 (72.2%)	0.68
Vomiting, n (%)						
Yes	14 (21.5%)	1 (16.7%)	5 (22.7%)	3 (15.8%)	5 (27.8%)	0.83
Ascites, n (%)						
Yes	4 (6.2%)	0	0	2 (10.5%)	2 (11.1%)	0.36

Table 3.3. Biochemical measurements according to PDAC stage.

Parameters	All PDAC	Stage 1	Stage 2	Stage 3	Stage 4	p-value*
Platelet count (10^9/L)	313.5 (249.0 – 398.0)	357.5 (324.0 -507.0)	320.5 (264.5 – 389.0)	314.5 (250.0 – 470.0)	248.5 (208.0 – 316.0)	**0.026**
CRP (mg/L)	52.5 (18.5-116.0)	101.5 (69.0 – 134.0)	29.0 (12.0 -75.0)	49.0 (13.0 – 116.0)	106.0 (30.0 – 150.0)	**0.038**
Total bilirubin (µmol/L)	136.0 (29.0- 312.0)	301.0 (212.0- 426.0)	118.0 (31.5 – 359.0)	96.5 (10.0 – 269.0)	218.5 (36.0 – 307.0)	0.11
GGT (units/L)	441.0 (137.0 – 779.0)	473.0 (441.0- 1183.0)	251.0 (91.5 – 470.5)	471.0 (136.0 – 845.5)	555.0 (383.0 – 942.0)	**0.040**
HbA1c (%)	5.9 (4.9 -7.3)	4.9 (4.6- 9.3)	6.3 (4.8 – 8.5)	6.2 (4.6 – 7.7)	5.7 (5.3 – 5.9)	0.85
CA19-9 (U/mL)	403.0 (37.5 - 5660.0)	1614.5 (34.0- 214185)	97.2 (32.0 – 198)	1303.8 (9.9 – 13102)	5660 (403 – 13408)	**0.039**
CEA (ng/mL)	6.2 (3.1 -12.9)	4.6 (3.3- 5.9)	6.0 (3.0 – 9.1)	16.8 (7.2 – 41.3)	4.3 (2.9 – 10.3)	0.15

Values are presented as median (interquartile range [IQR]); *Kruskal-Wallis ANOVA. *Abbreviations*: CA19-9, carbohydrate or cancer antigen 19-9; CEA, carcinoembryonic antigen; CRP, ***C-reactive protein***; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c.

Table 3.3 shows the biochemical measurements according to PDAC stage. A significantly lower platelet count, albeit within the normal range, is associated with advanced PDAC. Specifically, platelet counts were significantly lower in stage 4 PDAC patients when compared to those in stage 1 ($p = 0.01$), stage 2 ($p = 0.02$) or stage 3 ($p = 0.04$) with Mann-Whitney U tests. CRP levels were significantly different across the stages, with specific and significantly higher CRP values in stage 4 PDAC patients compared to stage 2 ($p = 0.005$, Mann-Whitney U test). Even though there was no significant difference for total bilirubin levels across all the stages, median values for stage 1 disease were significantly higher when compared to stage 3 disease specifically ($p = 0.02$, Mann-Whitney U test). This is in keeping with the higher prevalence of jaundice in stage 1 compared to stage 3 disease at 83.3% and 52.6%, respectively (Table 3.2). GGT, is a ductal liver enzyme, is significantly raised with advanced PDAC in this study population ($p = 0.04$). The significance of the elevated GGT levels, which is highest in those with stage 4 disease, becomes even stronger when stage 4 patients are compared to stage 2 patients alone ($p = 0.006$, Mann-Whitney U test). HbA1C levels are found to be within normal limits throughout all the stages even though Diabetes Mellitus is present in a quarter of our study patients. However, we did not take treatment in this latter group of patients into account. The tumor marker CA19-9 was elevated in advanced PDAC disease with the highest levels in those with stage 4 disease.

Both the Karnofsky and ECOG performance scales were used to determine the functional status of our PDAC study patients. Figure 3.2 shows how these scales are significantly correlated to each other ($r = -0.77$, $p < 0.0001$), hence no scale is superior above the other and either the Karnofsky or the ECOG performance scale is sufficient. In our institution we routinely use the ECOG performance scale and we therefore subsequently analyzed functional status according to PDAC stage using the ECOG scale alone (Table 3.4). There were no significant differences between the ECOG scores and the stage of the disease ($p = 0.48$). Overall the majority of PDAC patients in our study had an ECOG score of 1, i.e. they were symptomatic, yet ambulatory and able to do light work. This held true at each stage of the cancer. Interestingly, only two patients had the highest ECOG score of 3 (capable of limited self-care and confined to the bed for more than 50% of waking hours) in our population and they were at stage 2 and 3. The latter, demonstrates that those in the more advanced stages do not necessary present moribund. Notably, both these patients with ECOG scores of 3 had raised CRP levels.

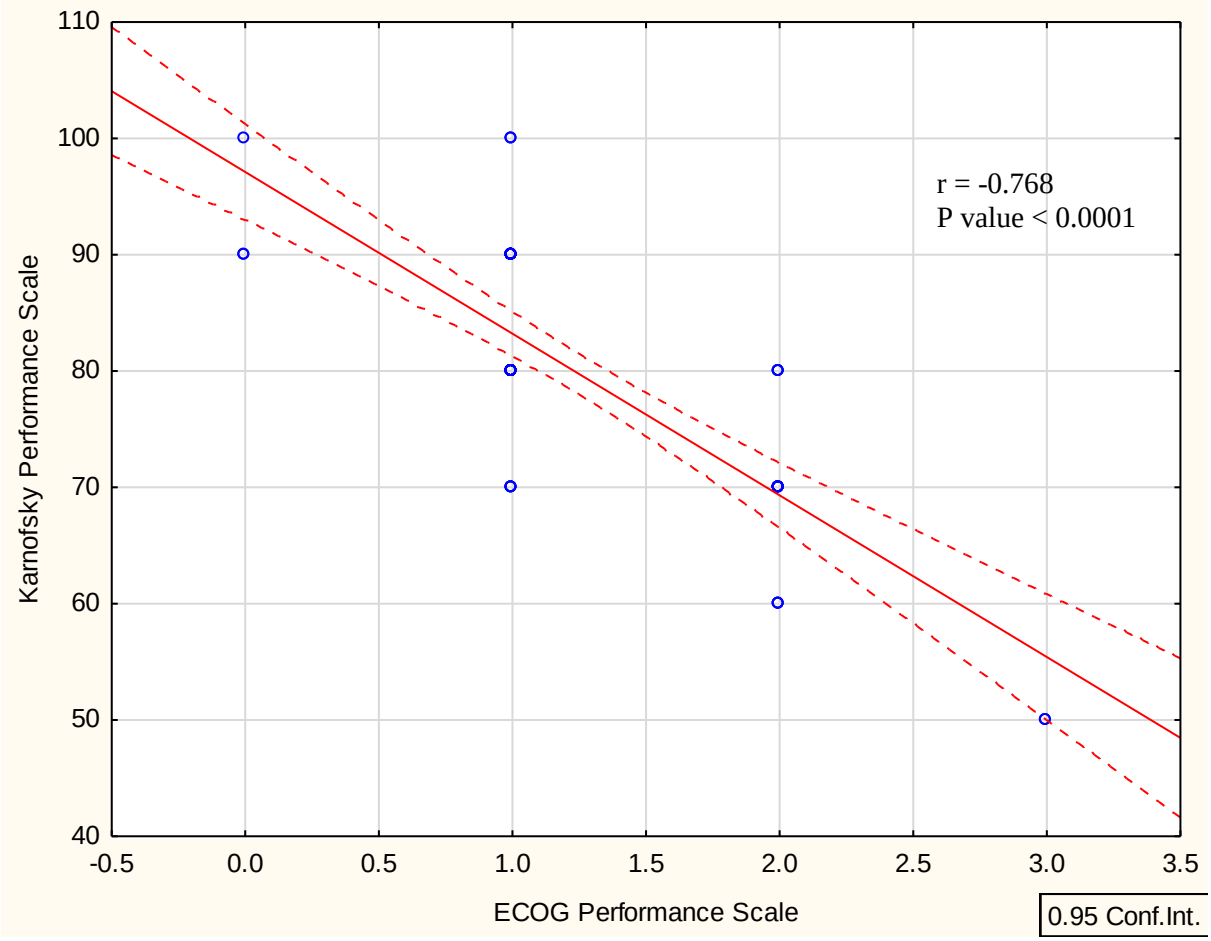


Figure 3.2. The correlation between the Karnofsky and ECOG performance scales in our study population.

In addition to analyzing our data according to TNM stage, we also investigated the significance, if any, of the presenting symptoms, risk factors and initial biochemical measurements on the PDAC tumor size (T), involvement of nodes (N) and metastatic spread (M) classifications alone. Where no associations between presenting symptoms or risk factors were found with these three staging modalities (data not shown), the biochemical data shows independent predictors.

Table 3.4. ECOG performance in PDAC patients according to stage.

ECOG scale	All PDAC	Stage 1	Stage 2	Stage 3	Stage 4	p-value
0 – asymptomatic, fully functional	3 (4.8%)	0	2 (9.1%)	0	1 (5.6%)	0.48*
1 – symptomatic but ambulatory, able to do light work	43 (68.3%)	3 (50.0%)	13 (59.1%)	13 (76.5%)	14 (77.8%)	
2 – capable of selfcare, unable to work, <50% of day in bed	15 (23.8%)	3 (50.0%)	6 (27.3%)	3 (17.6%)	3 (16.7%)	
3– limited selfcare only, >50% of day in bed	2 (3.2%)	0	1 (4.5%)	1 (5.9%)	0	

Abbreviations: ECOG, Eastern Cooperative Oncology Group. *Kruskal-Wallis ANOVA.

Table 3.5 Variance in BMI and biochemical measurements according to separate TNM staging categories of tumor size (T), nodal disease (N) and metastases (M).

Parameters	Tumor size (T) staging		Nodal disease (N) staging		Metastasis (M) staging	
	Chi^{2*}	P value	Z-value[#]	P value	Z-value[#]	P value
BMI	4.58	0.20	0.857	0.40	0.457	0.65
Platelet count (10^9/L)	8.79	**0.03**	-2.005	**0.04**	-2.776	**0.004**
CRP (mg/L)	2.48	0.48	-0.463	0.64	2.080	**0.036**
Total bilirubin (µmol/L)	0.71	0.87	-1.209	0.23	0.490	0.63
GGT (units/L)	2.84	0.42	-0.619	0.54	1.814	**0.07**
HbA1c (%)	1.76	0.62	-0.417	0.68	-0.632	0.53
CA19-9 (U/mL)	5.49	0.14	-0.754	0.46	2.352	**0.017**
CEA (ng/mL)	4.78	0.19	-0.680	0.51	-1.060	0.29

[*]Kruskal-Wallis Median Test. [#]Mann Whitney U Test.

Table 3.5 illustrates the statistical significance of the tumor, involvement of nodes and metastatic spread on biochemical markers in patients with PDAC. The platelet count is protective and statistically significant in each of the T-, N- and M-staging categories. Figure 3.3 shows the breakdown of the median platelet counts for each primary tumor T-stage category. Importantly from Table 3.5, CRP, GGT and CA19–9 are risk factors for metastatic disease and this was supported by a univariate logistic regression analysis demonstrating that that specifically platelet count, CRP and CA19-9 values are significantly associated with metastasis (data not shown). Furthermore, none of the patients with low CRP levels of <5 mg/L had metastasis, compared to 93.3% of the patients with high CRP levels ≥20 mg/L having metastasis (data not shown). We then considered platelet count, CRP and CA 19-9 in a multivariate logistic regression model (Table 3.6) which shows that decreased platelet counts and elevated CA19-9 levels are independent predictors of metastasis in PDAC. From ROC curve analyses, optimum cut-off levels for these markers were determined at a platelet count of ≤290 10^9/L and CA19-9 of ≥3600 U/mL. Using these cut-off values as a combined marker for metastasis in PDAC has a specificity of 97%, sensitivity of 46%, PPV of 83% and NPV of 83% in our study.

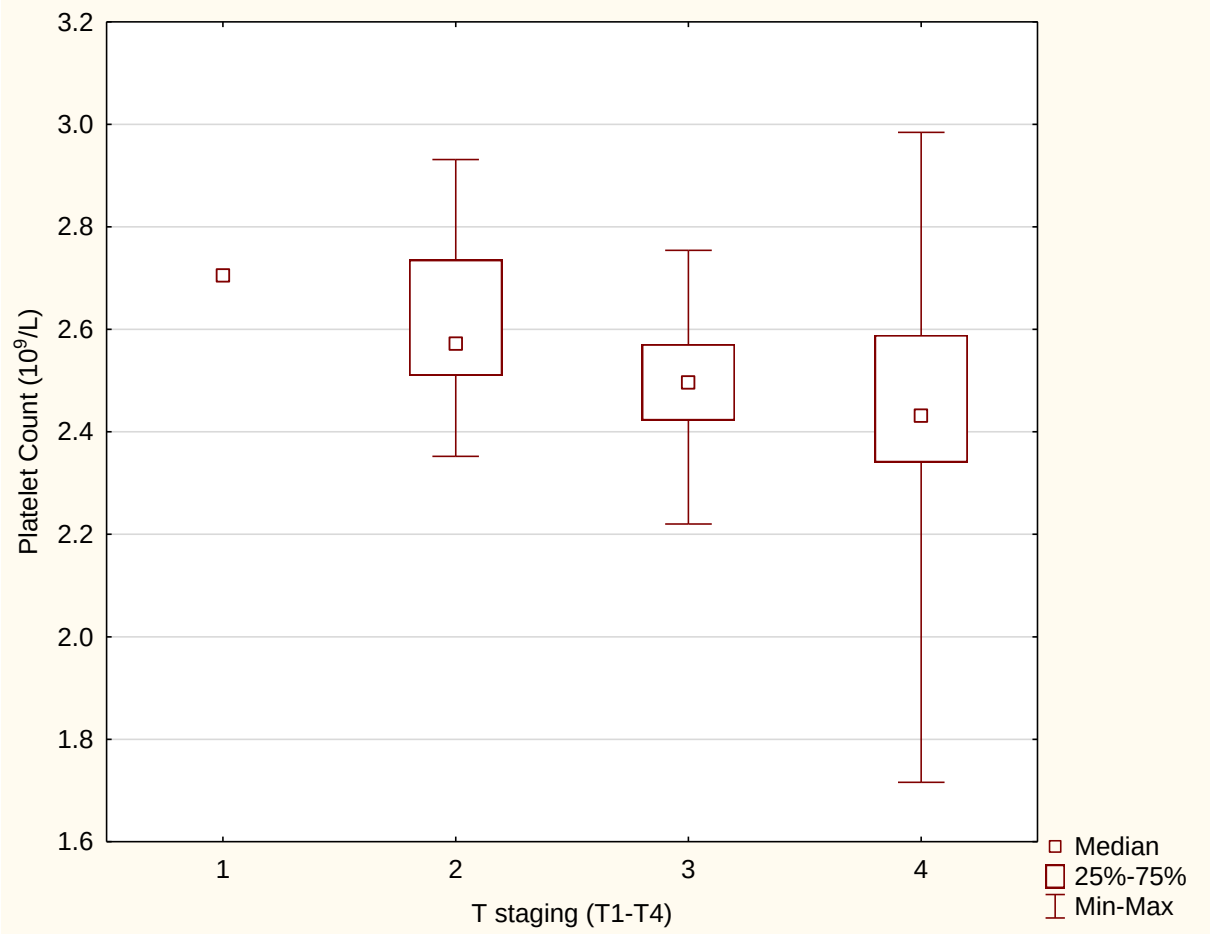


Figure 3.3. Lower Platelet counts were associated with increasing stage with regards to the primary tumour size in PDAC patients.

Table 3.6 Multivariate logistic regression analysis predicting metastasis in PDAC.

Effect	Odds Ratio*	95% Confidence Interval	P-value
Platelet count (10^9/L)	0.021	0.000 – 0.994	0.049
CA19-9 (U/mL)	1.872	1.016 – 3.451	0.044

*Modelled probability that the patient has metastasis. Statistics were conducted on log transformed values.

CHAPTER 4

DISCUSSION

This retrospective study investigates and describes the risk factors, symptoms and biochemical markers associated with PDAC and correlates these factors to the TNM stages of the disease. This study is a first in its kind in South African patients with PDAC.

4.1 Demographics and risk factors of the study population

PDAC is an aggressive cancer and the fast progression of the disease, in addition to the late presentation of patients, renders a poor prognosis.

Age: Patients affected are mainly of advanced age (seventh decade of life and upwards). In this study of 71 PDAC patients, the average age (±SD) at presentation was 59.9 (±10.8) years and no differences in age were found between the different PDAC stages. This mean age is slightly younger than that has been reported from national data,[4] and is in contrast to data from the United States that report a median age at diagnosis of 71 years, with early stage PDAC patients being approximately two years younger than advanced stage disease patients.[21] There was no association between age and stage of PDAC.

Gender: Male gender is a recognized risk factor for PDAC and PDAC is approximately 30% more common in males than females.[21] Where several studies have hypothesized that this may be due to the protective nature of female hormone exposure, consensus was made following a systematic review that these reproductive factors are not associated with the development of PDAC in women.[22] Thus, environmental factors may be more likely responsible for gender differences in PDAC, such as smoking. From our study, we report a male predominance of 56.3% versus 43.7% in females. Interestingly, all of the current smokers in our study were male and significantly fewer males had never smoked compared to females (11% versus 72%, respectively). Male gender is a risk factor for developing PDAC in our population too, although notably, the majority of patients with stage 4 disease in this study were females.

Obesity: is defined as a BMI of ≥ 30 kg/m^2 and is also a risk factor for PDAC. In our study, 12.5% of PDAC patients were obese. We assessed whether BMI levels differed according to TNM stage and, where medians for BMI were normal at each stage, there was a significant difference in BMI in stage 2 disease patients compared to stage 3 disease at 24.1 kg/m^2 and 18.8kg/m^2, respectively ($p = 0.01$). As we only had BMI levels at presentation, we are

unable to report on the effect of PDAC on BMI over the course of onset to presentation and therefore are unable to report on whether obesity is a risk factor for PDAC in our population.

Smoking: The literature highlights that just the fact that an individual smokes is in itself a major risk factor for developing PDAC and that the pattern of smoking duration or time since quitting, is more relevant than the smoking intensity.[21,23] The majority of our PDAC patients (61.5%) were either current or previous smokers, and we report an overall significant trend of smoking status with PDAC stage. The percentage of current smokers declined from 66.7% in stage 1 compared to 11.1% in stage 4 disease. Specifically, all our patients with stage 1 disease were current or previous smokers, suggesting that smokers present earlier in our population. Although none of the presenting symptoms differed depending on smoking status, other unidentified or unmeasured symptoms or co-morbidities may have resulted in the smokers presenting earlier. This would have to be investigated further. Also, our data on smoking duration and time since quitting was limited in this study.

Alcohol: The majority of our PDAC patients consumed alcohol at 70.8%. The highest percentage of patients who consumed alcohol was 83.8% in stage 1 disease and lowest at 63.6% in stage 2 disease, thus showing no significant association between alcohol users and cancer stage. From the CAGE questionnaire to determine alcohol dependence, two thirds of PDAC patients (65.4%) did not demonstrate alcohol dependence. There was a trend for an increase in patients not alcohol dependent with advancing PDAC stage, although this did not reach statistical significance. The level of alcohol consumption was not quantified in our study and therefore high daily consumptions of >40 grams per day could not be assessed.[3]

Hypertension: The prevalence of hypertension in South Africans aged between 40 and 60 years has been reported as over 40.0%.[24] Specifically, the prevalence in the local Johannesburg population of Soweto is 54.1%. In our study, hypertension was prevalent in 38.5% of PDAC patients and this did not differ depending on stage of the disease.

Type II Diabetes Mellitus (T2DM): The association between PDAC and T2DM has been widely reported in the literature.[6,25] Moreover, the prevalence of PDAC is significantly higher in patients with new-onset T2DM than that in the general population.[25] In our study, 24.6% of patients with PDAC had T2DM, which is much higher than the 14% prevalence reported for this local Johannesburg population.[26] Stage 3 disease patients had the highest

prevalence of T2DM at 31.6%, although rates were not significantly different across the stages of the cancer. Unfortunately, our study is limited in that we are unable to report on the duration of T2DM, and thus on new-onset T2DM in these patients.

Vascular disease: Only 2 patients in our study had vascular disease and both were stage 2 PDAC. Hence, this was not a major presenting risk factor, nor was it associated with stage.

4.2 Presenting symptoms of PDAC

The most common presenting symptoms recorded in our study population were abdominal pain (67.7%), jaundice (65.5%) and LOW (50.8%). All of the associated symptoms investigated were unrelated to stage of PDAC in our study.

Abdominal pain: The majority of patients presented with abdominal pain at 67.7%, which is in line with what is reported in the literature of 70% of PDAC patients.[4] Even though there was a trend for increased abdominal pain with increased PDAC stage, this was not significant. This may be linked to the sizes of the tumor that the bigger the tumor the worse pain and invasion of surrounding structures.

Jaundice: In line with the literature, jaundice was prevalent in 65.5% of PDAC patients in our study, with the highest prevalence in stages 1 and 2 of 83.3% and 74.1%, respectively.

Loss of weight: we report LOW at presentation in approximately half of our PDAC patients, with the highest reported LOW in stage 4 disease of 55.6%. Although reported prevalence of LOW varies widely, this is lower than reported elsewhere, [14] and was not associated with having T2DM in our population.

Other: Vomiting was prevalent in 21.5% of patients with the highest rates reported for stage 4 disease (27.8%) and ascites was not common (6.2%) and only reported in more advanced disease patients.

4.3 Routine biochemistry and PDAC stage

Platelet count: In our study, the platelet count was significantly protective against advanced stage disease and remained significant in each of the individual T-, N- and M-staging categories. The contribution of platelet counts and thrombocytosis to pancreatic cancer is

controversial.[27] Pre-operative platelet counts of greater than 300–400 x 10^9/L have been reported to have a poorer prognosis, however PDAC patients might present with a thrombocytopenia caused by occlusion of the splenic vein from tumor invasion leading to a splenomegaly mediated thrombocytopenia. Another reason is that extremely aggressive pancreatic cancer might metastasize to the bone marrow leading to a thrombocytopenia.[27] Platelet counts in our study, albeit within normal ranges, may be a prognostic factor of the stage of disease. Specifically, from multivariate analyses, we report that a decreased platelet count is an independent predictor of metastasis in PDAC.

CRP: CRP levels have been used to predict survival in patients with different cancers and evidence exists for CRP as an indicator of the aggressiveness of advanced PDAC.[28] Specifically, a higher concentration of CRP is associated with poorer outcomes, lower functional activity, abnormal metabolism, hypoalbuminemia and more extensive disease. In our study, CRP was an independent predictor of metastasis in PDAC and the vast majority of patients with high CRP levels had metastasis, compared to none of the patients with low CRP levels. In addition, both patients in our study with limited functional performance had high CRP levels, in line with the literature.[28]

GGT: The strength of the association between elevated GGT levels and risk of developing different cancers vary and the role of GGT as an indicator of PDAC risk is weak.[29] The highest GGT levels were in stage 4 disease PDAC patients in our study and, as a result, GGT was significantly associated with metastatic disease in our cohort.

CA 19–9: As CA 19-9 may be elevated in benign disease associated with other hepatobiliary diseases and biliary obstruction; it is not considered a specific tumor marker. In PDAC, another problem with CA 19–9 as a diagnostic aid is the high portion of false positives in patients who are jaundiced and, as discussed above, up to 75% of PDAC patients are jaundiced. In our study, CA 19-9 levels were highest in stage 4 disease patients and, from multivariate analyses, we report CA 19-9 to be an independent predictor of metastasis in PDAC.

Finally, we report a combined biomarker for metastasis in PDAC, including cut-off values of a platelet count of ≤290 10^9/L and CA 19-9 of ≥3600 U/mL, with a specificity of 97% and PPV of 83%

4.4 Limitations of the study

This retrospective study is limited as only parameters at presentation were recorded. We cannot comment on the longitudinal affect that many factors have on PDAC, such as hypertension and DM, or the affect that PDAC has on many variables, such as BMI. Furthermore, we were unable to quantify many categorical variables recorded, in terms of quantifying amount of alcohol ingested daily, the years patients have stopped smoking, the onset and new onset of diabetes mellitus, patients BMI prior to diagnosis of PDAC which limited us in obtaining more accurate results in our study. Our data has also not taken cholangitis into account. Lastly, the CA 19-9 levels were done at the time of initial presentation. We are unsure if the CA 19-9 levels were elevated secondary to the patients having obstructive jaundice with no biliary drainage or due to metastatic disease. This will need to be assessed in a prospective study looking at CA 19-9 levels pre- and post-biliary drainage in those with metastatic disease.

CHAPTER 5

CONCLUSION

PDAC is a devastating disease and this retrospective study, being the first in its kind for a black South African population, gave us the opportunity to assess its effect on our population. We found the mean age of onset was 59.9 (+/-10.8) years. And the PDAC affects 56.3% males expect in those patients with stage 4 disease. Smoking, ethanol consumption, hypertension and Type 2 Diabetes Mellitus are risk factors in our population. The most common symptoms found were abdominal pain (67%), jaundice (65.5%) and LOW (50.8%). Our data demonstrates that most risk factors or presenting symptoms show no association with PDAC stage. The most interesting outcome was that a decreased platelet count of $\leq 290\ 10^9$/L and increased CA 19-9, of ≥ 3600 U/mL were independent predictors of metastatic disease in our population with a specificity of 97% and PPV of 83%.

REFERENCES

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. Cancer research 2014.
2. Kolodecik T, Shugrue C, Ashat M, Thrower EC. Risk factors for pancreatic cancer: underlying mechanisms and potential targets. Frontiers in physiology 2013;4:415.
3. He XY, Yuan YZ. Advances in pancreatic cancer research: moving towards early detection. World journal of gastroenterology 2014;20:11241-8.
4. Factsheet on Pancreatic Cancer. 2012. (Accessed 27 June, 2018, at http://www.cansa.org.za/files/2017/07/Fact-Sheet-Pancreatic-Cancer-NCR-2012-web-July-2017.pdf.)
5. Wei EK, Wolin KY, Colditz GA. Time course of risk factors in cancer etiology and progression. J Clin Oncol 2010;28:4052-7.
6. Camara SN, Yin T, Yang M, et al. High risk factors of pancreatic carcinoma. Journal of Huazhong University of Science and Technology Medical sciences = Hua zhong ke ji da xue xue bao Yi xue Ying De wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban 2016;36:295-304.
7. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. Archives of internal medicine 1996;156:2255-60.
8. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2004;2:252-61.
9. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. Jama 2001;286:921-9.
10. Michaud DS, Vrieling A, Jiao L, et al. Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). Cancer causes & control : CCC 2010;21:1213-25.
11. McWilliams RR, Rabe KG, Olswold C, De Andrade M, Petersen GM. Risk of malignancy in first-degree relatives of patients with pancreatic carcinoma. Cancer 2005;104:388-94.
12. Brune KA, Lau B, Palmisano E, et al. Importance of age of onset in pancreatic cancer kindreds. Journal of the National Cancer Institute 2010;102:119-26.

13. Evans J, Chapple A, Salisbury H, Corrie P, Ziebland S. "It can't be very important because it comes and goes"--patients' accounts of intermittent symptoms preceding a pancreatic cancer diagnosis: a qualitative study. BMJ open 2014;4:e004215.
14. Porta M, Fabregat X, Malats N, et al. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 2005;7:189-97.
15. Keane MG, Horsfall L, Rait G, Pereira SP. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. BMJ open 2014;4:e005720.
16. Olson SH, Xu Y, Herzog K, et al. Weight Loss, Diabetes, Fatigue, and Depression Preceding Pancreatic Cancer. Pancreas 2016;45:986-91.
17. Almadi MA, Alharbi O, Azzam N, et al. Clinical predictors of resectability of pancreatic adenocarcinoma. Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association 2013;19:278-85.
18. Raptis DA, Fessas C, Belasyse-Smith P, Kurzawinski TR. Clinical presentation and waiting time targets do not affect prognosis in patients with pancreatic cancer. Surgeon 2010;8:239-46.
19. Delbeke D, Pinson CW. Pancreatic tumors: role of imaging in the diagnosis, staging, and treatment. Journal of hepato-biliary-pancreatic surgery 2004;11:4-10.
20a. Kinney T. Evidence-based imaging of pancreatic malignancies. The Surgical clinics of North America 2010;90:235-49.
20b. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A (Et al). Fluorouracil-based chemoradiation with either gemcitabine or flurorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5 yar analysis of the U.S. Intergrouo/RTOG 9704 phase III trial. Ann Surg Oncol,2011 May 18(5): 1319-26.
21. Midha S, Chawla S, Garg PK. Modifiable and non-modifiable risk factors for pancreatic cancer: A review. Cancer letters 2016;381:269-77.
22. Wahi MM, Shah N, Schrock CE, Rosemurgy AS, 2nd, Goldin SB. Reproductive factors and risk of pancreatic cancer in women: a review of the literature. Annals of epidemiology 2009;19:103-11.
23. Schulte A, Pandeya N, Tran B, et al. Cigarette smoking and pancreatic cancer risk: more to the story than just pack-years. European journal of cancer (Oxford, England : 1990) 2014;50:997-1003.

24. Gomez-Olive FX, Ali SA, Made F, et al. Regional and Sex Differences in the Prevalence and Awareness of Hypertension: An H3Africa AWI-Gen Study Across 6 Sites in Sub-Saharan Africa. Global heart 2017;12:81-90.
25. Illes D, Terzin V, Holzinger G, et al. New-onset type 2 diabetes mellitus--A high-risk group suitable for the screening of pancreatic cancer? Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al] 2016;16:266-71.
26. Crowther NJ, Norris SA. The current waist circumference cut point used for the diagnosis of metabolic syndrome in sub-Saharan African women is not appropriate. PloS one 2012;7:e48883.
27. Miyamoto R, Oda T, Hashimoto S, et al. Platelet x CRP Multiplier Value as an Indicator of Poor Prognosis in Patients With Resectable Pancreatic Cancer. Pancreas 2017;46:35-41.
28. Mitsunaga S, Ikeda M, Shimizu S, et al. C-Reactive Protein Level Is an Indicator of the Aggressiveness of Advanced Pancreatic Cancer. Pancreas 2016;45:110-6.
29. Van Hemelrijck M, Jassem W, Walldius G, et al. Gamma-glutamyltransferase and risk of cancer in a cohort of 545,460 persons - the Swedish AMORIS study. European journal of cancer (Oxford, England : 1990) 2011;47:2033-41.

APPENDIX 1: TNM staging of PDAC

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ[a]
T1	Tumor limited to the pancreas, ≤ 2 cm in diameter
T2	Tumor limited to the pancreas, > 2 cm in diameter
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node(s) metastasis
N1	Regional lymph node(s) metastasis

Distant metastasis (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1–3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

[a] This also includes the "PanINIII" classification

From Edge SP, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

Available from: http://www.cancernetwork.com/cancer-management/pancreatic-neuroendocrine-gi-and-adrenal-cancers/page/0/2

APPENDIX 2: Approved Protocol

Comparison of the risk factors and initial presenting symptoms to stage of disease in pancreatic ductal adenocarcinoma patients at Chris Hani Baragwanath Academic Hospital

Dr Nicola Lahoud
Student number: 0600062Y
MMED Surgery

Supervisors:

Dr John Devar (MBChB, FCS, Certificate in Surgical Gastroenterology)
Dr Deirdré Kruger (BSc, PGCHE, PhD)

1. BACKGROUND

Pancreatic adenocarcinoma is the fourth leading cause of death due to malignancy in the US among both men and woman (1, 2). Although the exact cause is not known, it is believed to develop over decades as a result of a combination of specific genetic mutations, environmental factors and/or other molecular abnormalities (3). Pancreatic cancer usually refers to ductal adenocarcinoma which makes up approximately 85% of all pancreatic neoplasm. (3) Pre-clinical data suggests that pancreatic adenocarcinoma may have the ability to metastasise when invasive foci measure in the 'sub clinical range'. Numerically speaking, by the time the tumour reaches 1 mm3 in diameter, it has probably had over 20 doublings over the course of 5 years (3). As such early cases may have a high risk of recurrence, even after complete marginal resection.

Approximately 9% of patients with pancreatic cancer are actually diagnosed when the tumour is still localised and resectable (3).Median survival is less than 1 year and the mortality rate has remained unchanged over the past 2 decades (1, 2). Radical surgery offers the only potential for curable treatment, but unfortunately most patients present with advanced disease resulting in only a few being eligible candidates for surgery. Five year survival after pancreaticoduodenectomy is about 25 to 30 percent for node-negative and 10 percent for node-positive disease (4, 5).

From the 2008 Cancer registry, a total of 121 males and 103 females were diagnosed with adenocarcinoma of the pancreas from our local South African population (6); the highest incidence amongst males was from Caucasian ethnicity (45%) and that amongst females was from African ethnicity (44%). The most frequent age range of diagnosis in both males and females was 60 – 69 years. To our knowledge, no further publications from any South African population exist (6).

Risk factors

The estimated life time risk of developing pancreatic adenocarcinoma is relatively low. Nevertheless, certain modifiable and unmodifiable factors may increase an individual's risk of developing pancreatic adenocarcinoma. These are listed below in Table 1. No data exists from a South African population on the main contributing risk factors in our local setting.

TABLE 1 Modifiable and unmodifiable risk factors for developing pancreatic adenocarcinoma

Modifiable risk factors

- Cigarette smoking: relative risk of 1%.

  The risk increases with the amount of cigarette's consumed. Excess risk decreases when one stops smoking. (5,3) lower's the median age of presentation from 71 years in non-smokers to 56 years in smokers (2)
- Obesity and physical inactivity:

  BMI of more than 30kg/m ^{2} significantly increases the risk compared to BMI of less than 23kg/m^2. Some propose that overweight and obese individuals develop pancreatic cancer at younger age and have a decreased survival once diagnosed. (5)
- Alcohol consumption: association with heavy alcohol consumption. (5,3)

Unmodifiable risk factors

- Age
- Diabetes
- Familial Pancreatic cancer:

  5–10% of patients have first degree relatives with pancreatic cancer. Patients present at a younger age <50 years. (5)
- Hereditary pancreatic syndromes:

  Certain germ mutations are known to give rise to pancreatic cancer, BRCA2, p16, STK11/LKBI, PRSSI (7)
- Familial atypical multiple mole melanoma (FAMMM) (7)
- Non-hereditary and hereditary pancreatitis (5,7)

  Hereditary pancreatitis is a severe risk factor for pancreatic cancer, increases the risk of developing pancreatic cancer by 40 -55% (2).

Symptoms

In most patients, noticeable symptoms are lacking early on for pancreatic adenocarcinoma. Moreover, where symptoms are present in such patients, they are often less specific and are rather part of 'the systemic tumour syndrome' (3). Having said that, head of the pancreas lesions usually present with jaundice, pruritus and exocrine insufficiency secondary to bile duct or pancreatic duct obstruction (4). Other symptoms may include the following listed and discussed below:

- Jaundice (75%) – usually an obstructive picture but can present differently (4).
- Abdominal pain (39%) – the abdominal pain associated with pancreatic cancer is usually insidious in onset, and has been present for one to two months at the time of presentation. It has a typical gnawing visceral quality, and is usually epigastric, radiating to the sides and/or straight through to the back. It may be intermittent and be made worse by eating or lying supine. It is frequently worse at night. Lying in a curled or fetal position may improve the pain (4).
- Loss of weight (15%)
- Nausea and vomiting (13%)
- Steatorrhea.
- New onset of atypical diabetes mellitus or worsening of pre-existing diabetes.
- Pruritus (11%)
- Acholic stools
- Some patients may present with gastric outlet obstruction secondary to invasion of cancer into the duodenum, junction of duodenum and jejenum (ligament of Treitz) (4).
- Unexplained superficial thrombophlebitis, which may be migratory (classic Trousseau's syndrome), is sometimes present and reflects the hypercoagulable state that frequently accompanies pancreatic cancer (4).

Non Specific signs and symptoms may be seen in patients with pancreatic tail carcinoma: abdominal pain, back pain, loss of weight, nausea and vomiting. If jaundice is seen in this group, it is a poor prognostic factor as it indicates that there is regional lymphadenopathy which extends into the portal area and could be obstructing the extrahepatic ducts (4).

Diagnosis

Understandably clinical suspicion alone, be it based on risk factors or presenting symptoms, does not provide an accurate diagnosis. Early diagnosis depends on the effect of the mass and this depends on the location of the tumour within the pancreas. To date there are also no screening tests available to assist with the early diagnosis of pancreatic adenocarcinoma (9),

and regrettably the low sensitivity and specificity of the most widely used marker, carbohydrate antigen (CA) 19-9, renders it inadequate to detect pancreatic adenocarcinoma early on.

Further diagnostic work-up is required in the form of serology and abdominal imaging (4). For patients with the initial presentation of jaundice and abdominal pain, the first imaging study would typically be a transabdominal ultrasound (US) however all patient's need MDCT/MRI, which is the gold standard for diagnosis and staging (6, 9,10).

Staging

Staging of pancreatic adenocarcinoma is based on the Primary tumour, Nodal and Distant metastases (TNM) staging system maintained by the American Joint Committee on Cancer (AJCC) (Table 2). The AJCC evaluates local extent of the primary tumour, lymph node involvement and presence of distant metastasis to classify disease according to stage and ultimately give a prognosis. The main modality used is cross sectional imaging MDCT/MRI; this depends on the institution and availability. Imaging is the primary modality used for staging of pancreatic adenocarcinoma (10, 11). To date there are no studies which assess the correlation between the amount of risk factors and symptoms to staging.

TABLE 2 TNM staging of pancreatic adenocarcinoma

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ[a]
T1	Tumor limited to the pancreas, ≤ 2 cm in diameter
T2	Tumor limited to the pancreas, > 2 cm in diameter
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node(s) metastasis
N1	Regional lymph node(s) metastasis

Distant metastasis (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1–3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

[a] This also includes the "PanINIII" classification

From Edge SP, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

Reference: http://www.cancernetwork.com/cancer-management/pancreatic-neuroendocrine-gi-and-adrenal-cancers/page/0/2

Finally, pancreatic adenocarcinoma is a devastating disease with known poor outcomes, despite advancements in modern medicine and technology. No studies to date have described the risk factors and/or symptoms in patients with pancreatic adenocarcinoma from South Africa or correlated it to staging. Only such a study could potentially identify whether we have environmental or inherited predispositions in developing this devastating disease. Our study hopes to identify, from the onset, the risk factors and symptoms in a South African population and correlate it to the staging, drawing our basis from international populations and literature.

2. AIM & STUDY OBJECTIVES

The aim of this study is to assess the initial presenting risk factors and symptoms of patient's with diagnosed adenocarcinoma of the pancreas at Chris Hani Baragwanath Academic Hospital and see if these have any effect on the stage of the disease.

Study Objectives

In patients with a diagnosis of pancreatic ductal adenocarcinoma (PDAC) at Chris Hani Baragwaneth Academic Hospital (CHBAH), this study's objectives are:

- To describe the risk factors
- To determine whether the presence of certain risk factors correlate to the staging of disease?
- To describe the symptoms.
- To assess how the presenting symptoms correlate to the stage of the disease.

3. METHODS

Research paradigm

A cross-sectional, retrospective analysis of a database from an ongoing study within the Pancreatic Research Thrust within the Department of Surgery, Wits.

Patient Population

The Hepatobiliary Unit at CHBAH has a database of patient's with diagnosed adenocarcinoma of the pancreas. For each patient presenting; symptoms were recorded in the patients file as well as a full medical history which identifies risk factors for each patient. Not all the patient's may have actual pre-operative staging however all do have imaging and from there we will analyse staging and correlate the risk factors and symptoms to the staging.

Study Sample

The study sample will include patients with documented PDAC that presented to the hepatobiliary unit at CHBAH. The study will commence once ethics approval for this sub study has been granted and will continue until 50 -100 patients have been sampled.

Inclusion criteria: patient's with confirmed PDAC, whether done by imaging or actual histology.

Exclusion criteria: patient's will be excluded from subgroup analyses if risk factors and presenting symptoms are not available

Data Collection

A collection of data from patient's records and the existing database of those already diagnosed with adenocarcinoma of pancreas. A data collection sheet will be used (attached as an appendix) to capture presenting symptoms and risk factors and data will be captured

on a excel spreadsheet. Under the supervision of Dr Devar, I will stage each patient's cancer according to TNM staging.

4. DATA ANALYSIS AND STATISTICS

Excel spreadsheet with captured data will be imported into STATISTICA for analyses. Descriptive statistics will be used to describe the contributing risk factors and initial presenting symptoms from patients with pancreatic ductal adenocarcinoma.

The Chi-squared or Fishers' exact test will test associations between risk factors, symptoms and the staging of the disease. Non-parametric Mann-Whitney or Kruskal-Wallis tests will be used to determine any associations between numerical data, such as age, and the staging of the disease.

5. ETHICS

An application for Ethics approval for this sub-study will be made to the University of the Witwatersrand Human Research Ethics Committee [(HREC)-Medical] in January 2016.

6. TIMING

	2015					2016			
Month of the Year	**Jun**	**Jul**	**Aug**	**Sept**	**Oct**	**Nov – Jan**	**Feb – May**	**Jun**	**Jul**
Literature search									
Reading literature									
Summarising literature									
Preparing Protocol									
Protocol Assessment									
Ethics application									
Collecting data									
Data analysis									
Writing up thesis									
Submit: marking									
Writing up paper									

7. BUDGET

Funding will not be needed as the study is retrospective in nature and will only require access to the various databases.

8. ANTICIPATED PROBLEMS

Retrospective nature of study may yield some missing data.

1. Riker A, Libutti SK, Bartlett DC. Advances in the early detection and staging of pancreatic cancer. Surg Onc. 1998; 6(3): 157-169
2. Kolodecik T, Shugruie C, Ashat M, Thrower EC. Risk factors for pancreatic cancer: underlying mechanism and potential targets. Frontiersin.org. 2014 Jan 16; 4.
3. He XY, Yuan YZ. Advances in pancreatic cancer research: Moving toward early detection. World J Gastroenterol.2014 Aug 28; 20 (32): 11241-11248
4. Castillo CF, Jimenez RE, Tanabe KK, Savarese D. Clinical manifestations, diagnosis and staging of exocrine pancreatic cancer. UpToDate. 2015 May 11.
5. Castillo CF, Jimenez RE, Tanabe KK, Savarese D. Epidemiology and Risk factors for exocrine pancreatic cancer. UpToDate. 2015 Mar 26.
6. Professor Herbest MC. Fact sheet on Pancreatic cancer. CANSA. Jan '15
7. Pietryga JA. Morgan DE. Imaging preoperatively for pancreatic adenocarcinoma. J Gastrointest Oncol. 2015 Jan 22; 6(4): 343-357
8. Klapman J. Malafa M. Early detection of pancreatic cancer: why, who and how to screen. Cancer Control. 2008 Oct; 4: 280-287
9. Delbeke D. Pinson CW. Pancreatic tumours: role of imaging in the diagnosis, staging and treatment. J hepatobiliary Pancreat Surg.2004;11: 4 – 10
10. Kinney T. Evidenced Based Imaging of Pancreatic Malignancies. Surg Clin N Am. 2010; 90: 235 -249
11. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. Version 1.2013.**http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf** (22/10/2015)
12. van der Gaag N. Castro SMM. Raus E. Bruno M. Eijok C. Kuipers E, et al. Preoperative biliary drainage for periampullary tumours causing obstructive jaundice: Drainage vs (direct) Operation (DROP trial). BMC Surg. 2007 March 12;7:3

APPENDIX 3: Datasheet

"Assessment of risk factors and initial presentation of symptoms in patients with adenocarcinoma of pancreas.

- **Study Participant Number:** ☐

- **Admission Criteria**

- Diagnosed with adenocarcinoma of pancreas Y ☐ N ☐
- Gender: Male ☐ Female ☐

• Risk Factors:

- Age (years) _____
- Cigarette smoking previous ☐ current ☐
- Diabetes Mellitus new onset ☐ pre existing ☐
- Alcohol consumption _____
  - Age score _____
- BMI _____
- • Co-Morbid Disease:
  _____

- Initial presenting symptoms

  - Jaundice Y ☐ N ☐

    Bilirubin level < 250umol/l ☐ >250umol/l ☐

As per 'DROP trial' (12)

  - Abdominal pain Y ☐ N ☐
  - Loss of weight Y ☐ N ☐
    - < 10 Kg ☐ >10kg ☐
  - Nausea and vomiting Y ☐ N ☐
  - Ascites Y ☐ N ☐

- Stage of disease _____

APPENDIX 4: Ethics Clearance Certificate

R14/49 Dr Nicola Lahoud et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160840

NAME: (Principal Investigator)	Dr Nicola Lahoud et al
DEPARTMENT:	Surgery Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Comparison of the Risk Factors and Initial Presenting Symptoms to Stage of Disease in Pancreatic Ductal Adenocarcinoma Patients at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	26/08/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Deidre Kruger
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/05/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review August and will therefore be due in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES