FACTORS ASSOCIATED WITH HIGH-GRADE PROSTATE CANCER DETECTION AT INITIAL BIOPSY IN PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL.

Amini M. Alexandre, (MD)

MMed (Urology) Dissertation

Muhimbili University of Health and Allied Sciences

October, 2024

Muhimbili University of Health and Allied Sciences

Department of Surgery



FACTORS ASSOCIATED WITH HIGH-GRADE PROSTATE CANCER DETECTION AT INITIAL BIOPSY IN PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL.

By

Amini Mitamo Alexandre

A Dissertation Submitted in (Partial) Fulfilment of the Requirement for the Degree of Master of Medicine in Urology at

Muhimbili University of Health and Allied Sciences

October, 2024

CERTIFICATION

The undersigned, certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation titled: **"Factors associated with high-grade prostate cancer detection at initial biopsy in patients attending Muhimbili National Hospital"** in fulfilment of the requirements for Award of the Master of Medicine in Urology of Muhimbili University of Health and Allied Sciences.

_____

Prof. Charles Mkony (Urology)

(Supervisor)

Date:_____

_____

Dr. Deogratius Emmanuel Mahenda, MD MMed (Urology)

(Co-Supervisor)

Date:_____

DECLARATION AND COPYRIGHT

I **AMINI MITAMO Alexandre** declare that this dissertation is my original work and has not been presented and will not be presented to any other Higher Learning Institution for a similar or any other degree award.

Signature: …… Date: ……..

This thesis/Dissertation is copyright material protected under the Berne Convention, the Copyright and Neighboring Right Act 1999 and other international and national enactments, on behalf, of intellectual property. It may not be reproduced by any means in full or in part, except for short extracts in fair dealings, for research or private study, critical scholarly review or discourse with an acknowledgement, without the written permission of the Director of Postgraduate Studies on behalf of both the author and the Muhimbili University of Health and Allied Sciences.

ACKNOWLEDGEMENT

First and foremost, I would like to thank God for his abundant blessings and guidance upon my life.

I would like to express my sincere gratitude to all those who contributed to the successful completion of this research project. I extend my deepest appreciation to Professor Charles Mkony and Doctor Deogratius Mahenda, my research supervisor and co-supervisor, respectively, for their invaluable guidance, unwavering support, and insightful feedback throughout every stage of this study.

I am immensely grateful to the staff and administration of Muhimbili National Hospital for providing access to resources, facilities, and necessary support, which greatly facilitated the execution of this research.

Special thanks are also due to the BEBUC Excellence Scholarship Program and the Else-Kröner-Fresenius-Stiftung for supporting my Master's training program. Their generous financial assistance has played a pivotal role in enabling me to pursue and complete this work.

I would like to extend my heartfelt appreciation to the participants of this study for their cooperation, time, and willingness to share their information, without which this research would not have been feasible.

I am indebted to my family and friends for their unwavering encouragement, understanding, and patience throughout this journey.

Finally, I acknowledge the collective efforts of all individuals who directly or indirectly contributed to this research endeavor. Their contributions are deeply appreciated and have played a significant role in the completion of this study.

DEDICATION

To my beloved parents, Mitamo Balingene and Kahindo Yvonne, my dearest wife Kavira Mwenge Pascaline, my brothers and sisters. Your constant support has been a source of strength and motivation for me.

ABSTRACT

Background: Prostate cancer (PCa) is a significant public health concern, particularly in the elderly male population. Detecting high-grade prostate cancer (HGPC) is crucial because it has a worse prognosis than low-grade PCa, necessitating aggressive treatment.

Objective: This study investigated factors associated with the detection of high-grade prostate cancer in patients undergoing initial biopsy at Muhimbili National Hospital (MNH), with a focus on the Tanzanian context.

Methods: A retrospective cross-sectional analytical design was employed, encompassing adult males aged 40 years and older who underwent prostate biopsy at MNH. Demographic, clinical, and lifestyle factors were systematically assessed, and data on prostate-specific antigen (PSA) levels, digital rectal examination (DRE) findings, prostate ultrasound and biopsy results were recorded. A Chi-square test was conducted to analyse the associations between factors of interest and high-grade prostate cancer (Gleason score ≥ 7). Multivariate analysis was employed to determine the independent factors associated with high-grade prostate cancer, controlling for confounding variables. A p value ≤ 0.05 was considered to indicate statistical significance.

Results: A total of 260 participants who underwent prostate biopsy from October 2022 to March 2024 were included in this study. The majority were aged 60-79 years (72±9), married, and self-employed. Common comorbidities included hypertension (42.7%) and diabetes (8.1%), and a positive history of smoking was reported by 38.5% of patients. The main complaint was LUTS (61.5%), and 73.5% of the studied population had abnormal findings on digital rectal examination (DRE). The median PSA level was 81.6 ng/mL (0.096-2000), with 93.8% of patients having increased PSA levels. The proportion of HGPC among the studied population was 63.08%, with Gleason patterns 8 and 9 being the most prevalent (42.1% and 26.8%, respectively). Multivariate logistic regression analysis revealed significant predictors of HGPC, including a family history of prostate cancer (AOR = 8.45, p = 0.001), cigarette smoking (AOR = 2.797, p = 0.044), abnormal DRE findings (AOR = 36.897, p < 0.001), and a PSA-Density greater or equal to 0.15 (AOR = 10.39, p = 0.044).

Conclusion: Family history of prostate cancer, cigarette smoking, abnormal DRE findings and a PSA-D greater or equal to 0.15 emerged as significant predictors of HGPC. Overall, these findings emphasize the need for individualized patient selection for prostate biopsy while targeting HGPC.

Keywords: High-grade prostate cancer, Initial biopsy, Muhimbili National Hospital

TABLE OF CONTENTS

CERTIFICATION i
DECLARATION AND COPYRIGHT ii
ACKNOWLEDGEMENT iii
DEDICATION iv
ABSTRACT v
LIST OF TABLES x
LIST OF FIGURS x
LIST OF ABBREVIATIONS xi
OPERATIONAL DEFINITIONS xii
CHAPTER ONE 1
1.0 INTRODUCTION 1
1.1 Background 1
1.2 Problem Statement 4
1.3 Rationale 4
1.4 Conceptual Framework 5
1.5 Research Questions 7
1.5.1 Primary Research Question 7
1.5.2 Secondary questions 7
1.6 Study objectives 8
1.6.1 Main objective 8
1.6.2 Specific objectives 8
CHAPTER TWO 9
2.0 LITERATURE REVIEW 9
2.1 Prevalence of prostate cancer 9
2.2 Factors associated with prostate cancer 9
2.3 Clinical factors associated with high-grade prostate cancer 11
2.4 High-grade prostate cancer and lifestyle factors 12
2.5 Prostate cancer and comorbidities 13
2.6 Histopathology and grades of prostate cancer 14

CHAPTER THREE 16
3.0 METHODOLOGY 16
3.1 Study design 16
3.2 Study area 16
3.3 Study population 17
3.4 Inclusion and Exclusion Criteria 17
3.5 Sample size and sampling technique 18
3.6 Study variables 19
3.7 Data collection techniques and tools 20
3.8 Data processing and analysis 21
3.9 Ethical considerations and approval 22
3.10 Study limitations and mitigation 23
CHAPTER FOUR 24
4.0 ANALYSIS AND RESULTS PRESENTATION 24
4.1 Sociodemographic profile of patients undergoing prostate biopsy at MNH 24
4.2 Clinical profile of patients undergoing prostate biopsy at Muhimbili National Hospital 26
4.3 Proportion of patients with high-grade prostate cancer in patients undergoing prostate biopsy at MNH 28
4.4 Factors associated with high-grade prostate cancer at initial biopsy 30
CHAPTER FIVE 35
5.0 DISCUSSION 35
5.1 Sociodemographic and clinical profile of patients undergoing prostate biopsy at Muhimbili National Hospital 35
5.2 Proportion of patients with high-grade prostate cancer among MNH patients 37
5.3 Factors associated with high-grade prostate cancer at MNH 39
CHAPTER SIX 41
6.0 CONCLUSION AND RECOMMENDATIONS 41
REFERENCES 42

APPENDICES 49
Appendix I: Informed Consent (English Version) 49
Appendix II: Informed Consent (Swahili Version) 51
Appendix III: Data Collection Tool 53
Appendix IV: Ethical Clearances 56
Appendix V: Introduction Letter 58
Appendix VI: Permission Letter 59

LIST OF TABLES

Table 1: Sociodemographic profile of patient undergoing prostate biopsy at Muhimbili National Hospital.....25

Table 2: Clinical profile of patient undergoing prostate biopsy at Muhimbili National Hospital.....27

Table 3: Distribution of Gleason pattern, score and ISUP grade among patients with high-grade prostate cancer.....29

LIST OF FIGURS

Figure 1: Conceptual Framework Illustration by the Principal Investigator.....6

Figure 2: A pie chart demonstrating the proportion of patients with high-grade prostate cancer 28

LIST OF ABBREVIATIONS

Cc	Cubic centimeters
CI	Confidence interval
DRE	Digital Rectal Examination
HGPC	High-Grade Prostate Cancer
LUTS	Lower urinary tract symptoms
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
PCa	Prostate cancer
PCPTRC	Prostate Cancer Prevention Trial Risk Calculator
PSA	Prostate-Specific Antigen
PSA-D	Prostate-Specific Antigen Density
SPSS	Statistical Package for the Social Sciences
TRUS	Transrectal Ultrasound

OPERATIONAL DEFINITIONS

Prostate cancer: a malignant tumour that originates in the prostate gland, a part of the male reproductive system.

High-grade prostate cancer: prostate cancer characterized by a higher likelihood of aggressive growth and spread, typically identified by a Gleason score of 7 or higher.

Initial biopsy involves taking for the first time a tissue sample from the prostate gland to assess for the presence of cancer.

Gleason score: a grading system used to evaluate the aggressiveness of prostate cancer based on the microscopic appearance of cancer cells in a biopsy sample.

Prostate-specific antigen (PSA): a protein produced by the prostate gland. Elevated blood PSA can indicate various prostate conditions, including prostate cancer.

Digital Rectal Examination (DRE): a physical examination where a healthcare provider inserts a gloved, lubricated finger into the patient's rectum to detect abnormalities in the prostate gland suggestive of prostate cancer.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Prostate cancer (PCa) is one of the most prevalent cancers among elderly men and has varying degrees of aggressiveness [1]. According to recent studies, PCa ranks as the second most prevalent cancer diagnosis and is fifth in terms of cancer-related mortality in men on a global scale [2]. Given the increase in elderly people worldwide, we anticipate an increase in PCa incidence and associated ailments. In response, developed and developing countries have initiated screening initiatives for early PCa detection, aiming to lower disease morbidity and mortality rates [3]. The reported age-standardized incidence ratio for prostate cancer, which is 19–24 per 100,000 people in Africa, is believed to be underestimated owing to well-documented deficits in screening, timely identification, diagnosis, access to specialized healthcare services, and accurate record-keeping [4]. According to recent studies, in Tanzania, the prevalence of PCa in adult males attending an oncology unit is 39.84%, and the majority of these patients present the high-grade variant of the disease. This poses a challenge because it restricts the range of available treatment options, emphasizing the pressing need for enhanced diagnostic and therapeutic strategies to address this prevalent and aggressive form of cancer [5].

Advanced age, ethnicity (African ancestry), and heredity are the three well-established predisposing factors for PCa [6]. This disease affects elderly men more often and therefore is a greater health concern, especially in countries with high life expectancies [7]. Aging increases the risk of PCa [8,9]. According to the autopsy data, 30% of men who reach the age of 60 exhibit microscopically detectable traces of PCa. This finding underscores the high prevalence of latent PCa in the aging male population, emphasizing the importance of selection for biopsy for patients at risk of presenting a

clinically significant cancer [10]. Genetic background may contribute to PCa risk, as suggested by associations with race, family, and specific gene variants. A man's risk of developing PCa increases twofold if he has a first-degree relative who has the condition [1,10]. Compared with men without a family history, those with two affected first-degree relatives are five times more at risk [1]. Additionally, PCa is typically detected six to seven years earlier in PCa family members than in controls [9,11]

The majority of prostate cancer variants are characterized by indolent growth patterns, often presenting either with clinical manifestations for prolonged periods or remaining asymptomatic during the initial phases of the disease [12]. Typical manifestations include micturition difficulties, nocturia, and, in advanced stages, urinary retention. Additionally, metastatic manifestations, such as spinal discomfort and paralysis, may also become evident [13]. Men with prostate cancer may experience symptoms similar to those of benign prostatic hyperplasia (BPH). Notably, concurrent enlargement of the prostate can coexist with cancerous cell growth in distinct regions of the gland [14]. PCa screening allows the detection of a large number of cancers discovered at an early stage with potentially curative treatment [9,10,15].

Two primary screening tools routinely used for PCa screening are digital rectal examination (DRE) and the measurement of prostate-specific antigen (PSA) levels. PCa was suspected when the PSA level was elevated and/or there were abnormal findings on the DRE [7,16,17]. Studies on DRE findings and PSA measurements have shown that in men aged 50 years and above, DRE or PSA levels are abnormal in 36% of men, and PCa is diagnosed by biopsy in 6.4% of men [9]. In a meta-analysis, assessed alone, DRE allowed the detection of prostate cancer (PCa) in 1% of patients, as indicated by the pooled cancer detection rate (CDR) of 0.01 (95% CI 0.01–0.02) [18]. In light of an inadequate pathologist workforce, certain medical facilities in Tanzania continue to hinge their prostate cancer diagnoses on PSA levels, a measure known for its limited specificity [5]. The serum PSA assay serves as a prevalent

diagnostic screening modality for detecting PCa. A recent randomized trial in Europe illustrated that although PCa screening led to a 20% reduction in PCa mortality, it also carried a notable risk of overdiagnosis [16]. Approximately 1.5 million men in the United States between the ages of 40 and 69 exhibit a PSA level exceeding 4.0 ng/mL, a threshold widely acknowledged as a positive test outcome [5]. In the context of men exhibiting PSA levels within the intermediate range (4 to 10 ng/mL), the prostate biopsy detection rate is approximately 25%. Within this range, PSA alone is inadequate for distinguishing between BPH and PCa due to its inherent lack of specificity [19]. Consequently, various clinical and laboratory parameters have been proposed with the aim of enhancing the accuracy and precision in identifying prostate cancer in men with intermediate PSA levels.

Individuals with high-grade prostate cancer (HGPC) have less favourable prognoses than those with low-grade prostate cancer (PCa). Accurate identification of HGPC is crucial for implementing aggressive therapeutic strategies [20]. The Gleason score, which is based on the microscopic appearance of cancer cells in a biopsy sample, distinguishes between low-grade (Gleason score 6) and high-grade (Gleason score 7-10) PCa. A Gleason score of 2 to 6 indicates slow-growing cancer, while scores of 7 to 10 signify more aggressive and rapidly growing cancer [21]. Predictive models and nomograms, pioneered by Thompson et al. and Nam et al., respectively, incorporate factors such as elevated serum PSA levels, abnormal DRE results, advanced age, ethnicity, family history, and urinary symptoms to predict the likelihood of PCa and high-grade cancer [22,23].

Notably, neither of these investigations specifically addressed the prediction of high-grade prostate cancer during initial biopsy in the African population. Additionally, there is a conspicuous absence of a similar local study in this domain. This study seeks to build upon these insights and further investigate the factors associated with high-grade prostate cancer detection at initial biopsy, ultimately contributing to improved diagnostic

accuracy and more effective management of this clinically significant cancer in the Tanzania context.

1.2 Problem Statement

The Gleason score serves as a valuable parameter for grading prostate cancer and is associated with disease progression, with higher scores being associated with more aggressive disease, which is also considered a clinically significant disease and is therefore worthy of early management. Given Tanzania's high incidence of prostate cancer, accurately predicting the presence of high-grade prostate cancer (HGPC) during initial biopsy is crucial for effectively identifying individuals at heightened risk of aggressive PCa.

Conventional screening tools for prostate cancer: PSA and DRE exhibit limitations in specificity and sensitivity for diagnosing high-grade prostate cancer, hence contributing to the challenges of overdiagnosis and underdiagnosis. In developed countries, nomograms (prostate cancer risk calculators) have been developed and validated to predict the risk of high-grade prostate cancer. Among these tools we have the Memorial Sloan Kettering Cancer Centre and Prostate Cancer Prevention Trial Risk Calculator Version 2.0. However, the PSA-DRE-based screening remains the tool in use in the African context in general, and at MNH in particular.

1.3 Rationale

This study seeks to bridge existing gaps in diagnostic methodologies, with the primary goal of enhancing the precision of detecting HGPC.

Notably, there is a lack of comprehensive literature in Africa, particularly in Tanzania, focusing on the predictive aspects of HGPC among men undergoing prostate biopsies for elevated PSA levels and/or abnormal digital rectal examination (DRE) findings.

The absence of a comparable local investigation underscores the need to explore factors associated with HGPC within the unique context of the study area. Factors such as local demographics, healthcare accessibility, and genetic considerations may introduce variations in the risk profile for HGPC, necessitating a targeted examination distinct from broader population trends.

By addressing these intricacies, this research aims to offer insights that can refine current diagnostic practices and contribute to the body of literature, advancing our understanding of HGPC detection and management, particularly among patients attending Muhimbili National Hospital.

1.4 Conceptual Framework

Independent Variables:

A. Demographic factors: This includes variables such as age, ethnicity, family history, and socioeconomic status.
B. Clinical factors: include variables such as chief complaint, PSA levels, DRE findings, prostate size and echogenicity.
C. Lifestyle and behavioural factors: smoking habits and alcohol consumption.

Dependent Variables:

High-grade prostate cancer detection via prostate biopsy

Mediating Factors:

Diagnostic Tools and Protocols: The utilization of diagnostic tools and protocols, including PSA testing (for suspicious prostate cancer), DRE, and the initial biopsy procedure (for confirming the cancer diagnosis as well as its grade), plays a mediating role in diagnosing prostate cancer.

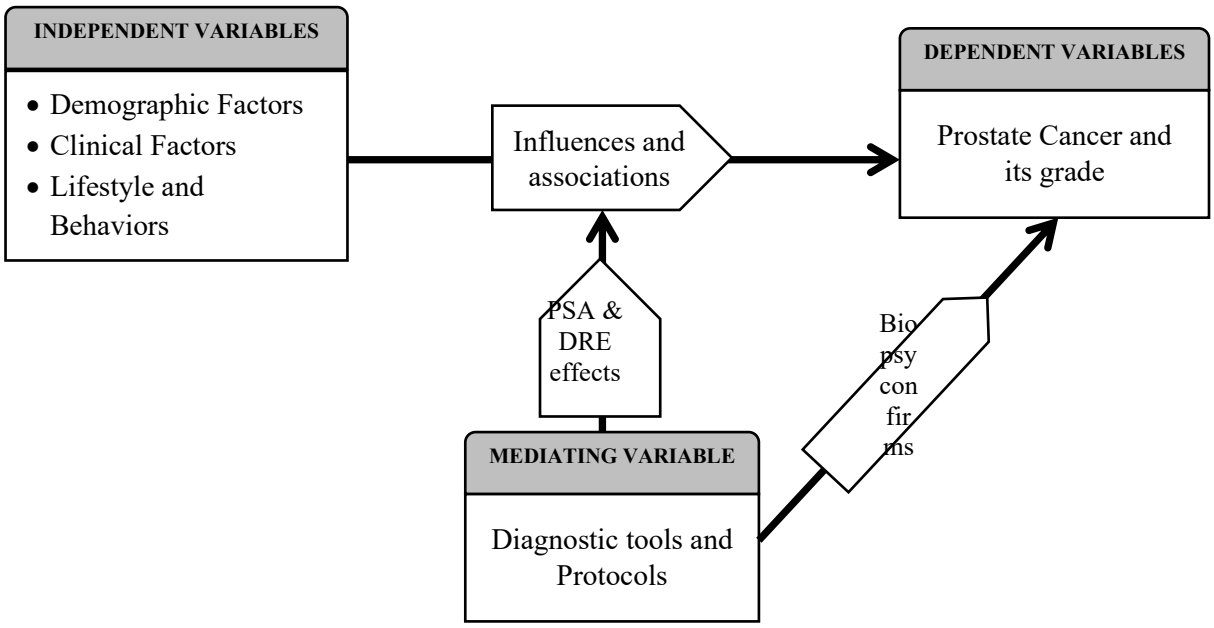


Figure 1: Conceptual Framework Illustration by the Principal Investigator

Hypotheses:

1. Demographic factors: The demographic profile of patients at MNH significantly influences the likelihood of detecting high-grade prostate cancer at initial biopsy.
2. Clinical factors hypothesis: Specific clinical factors, such as chief complaints, elevated PSA levels and abnormal DRE results, are associated with a greater probability of detecting high-grade prostate cancer among MNH patients.
3. Lifestyle and behavioural factors: lifestyle factors, such as smoking and dietary habits, influence the likelihood of high-grade prostate cancer detection.
4. Diagnostic tools and protocols hypothesis: The use of diagnostic tools and protocols, including PSA testing and biopsy procedures, will significantly impact the detection of high-grade prostate cancer.

1.5 Research Questions

1.5.1 Primary Research Question

What are the factors associated with the detection of high-grade prostate cancer at initial biopsy in patients admitted to the Urology Department at Muhimbili National Hospital (MNH)?

1.5.2 Secondary questions

1. What is the sociodemographic and clinical profile of patients undergoing prostate biopsy at MNH?
2. What proportion of patients undergoing prostate biopsy at MNH have high-grade prostate cancer?
3. What are the specific sociodemographic and clinical factors associated with a high-grade prostate cancer diagnosis among individuals attending MNH?

1.6 Study objectives

1.6.1 Main objective

To determine factors associated with the detection of high-grade prostate cancer at the initial biopsy in patients attending the Urology Clinic at MNH.

1.6.2 Specific objectives

1. To describe the sociodemographic and clinical profiles of patients undergoing prostate biopsy at MNH.
2. To determine the proportion of prostate biopsy patients with high-grade prostate cancer at initial biopsy at MNH.
3. To determine the sociodemographic and clinical factors associated with a high-grade prostate cancer diagnosis among PCa patients attending the MNH.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Prevalence of prostate cancer

According to the GLOBOCAN study conducted by Wang et al., the global landscape of prostate cancer diagnosis in 2020 revealed an astonishing tally of more than 1.4 million new cases. The crude incidence rate was 36.0 cases per 100,000 males, while the age-standardized incidence rate (ASIR) was 30.7 per 100,000 males. Europe, Latin America and the Caribbean, North America, and Oceania demonstrated ASIRs exceeding 59 cases per 100,000 males, while Africa and Asia reported notably lower rates, falling below the 30 per 100,000 males threshold. Intriguingly, the distribution of age-standardized mortality rates (ASMRs) exhibited a distinct pattern, with Africa leading the list, followed by Latin America and the Caribbean, Europe, Oceania, North America, and Asia [24].

In the Tanzanian context of prostate cancer, Katabalo et al. [5] reported that the prevalence of prostate cancer was 39.84%, which was observed in 153 out of 384 male patients. The average age of individuals diagnosed with prostate cancer was 64.85 years ± 14.59 years. Notably, two-thirds of the patients had prostate cancer graded at the time of presentation, and among these patients, 52.58% (51 out of 97) had high-grade prostate cancer, characterized by Gleason scores of 8, 9, or 10. Accordingly, Lyimo et al. highlighted prostate cancer as the most frequently identified cancer among men [25].

2.2 Factors associated with prostate cancer

Prostate cancer has a well-established association with older age, as indicated by a retrospective cohort study conducted by Siegel et al. Their research revealed that a substantial majority, approximately 66%, of prostate cancer cases are detected in individuals aged 65 years and above [26]. This finding underscores the strong

correlation between prostate cancer incidence and advancing age. Furthermore, Shah et al.'s similar study revealed the age-specific incidence of high-grade prostate cancer, particularly in men aged 70 to 80 years. This research underscores the importance of considering age as a critical factor when assessing the risk of high-grade prostate cancer within clinical practice [27]. Conversely, in a screening trial spanning from 1995 to 2009 led by Godtman and colleagues, it was revealed that there was no discernible link between age and the likelihood of receiving a Gleason score of less than 7 in prostate cancer diagnoses after 2005. Furthermore, in men who underwent PSA testing prior to 2005, age exhibited an independent correlation with the probability of receiving a prostate cancer diagnosis. Age exerted a more pronounced influence on the likelihood of being diagnosed with a GS ≥7 tumor than on the likelihood of being diagnosed with a GS <7 tumor [28]. The extensive body of research on prostate cancer and its association with age provides valuable insights that justify the need for a similar study at Muhimbili National Hospital within the Tanzanian context.

A research investigation led by DeSantis within the United States revealed a notable disparity in prostate cancer risk between African American men and their white counterparts. The findings revealed a substantially elevated incidence rate of prostate cancer among African-American men, at 208.7 cases per 100,000, in stark contrast to the rate of 123.0 cases per 100,000 observed in white men. Moreover, this discrepancy extends to prostate cancer mortality, with African-American men experiencing a higher mortality rate of 47.2 cases per 100,000, compared to the rate of 19.9 cases per 100,000 among white men. These findings underscore the critical need to address racial disparities in prostate cancer risk and outcomes [29]. Nonetheless, the forthcoming study will not focus on racial factors, given that the predominant population under examination primarily consists of individuals of Black African descent.

Additionally, Shah et al. noted that high-grade prostate cancer disproportionately affects individuals from disadvantaged socioeconomic backgrounds who tend to seek medical care only when they display symptoms. Often, by the time they seek medical

attention, the disease has already progressed to an advanced and incurable stage [27]. However, it is important to note that this observation lacks substantial supporting evidence, as no further studies have highlighted this particular aspect. Considering these insights from previous studies, conducting a similar investigation at Muhimbili National Hospital in Tanzania is imperative. The Tanzanian context may present unique demographic, healthcare, and socioeconomic factors, which could influence prostate cancer risk and detection patterns differently. Therefore, a localized study can provide more precise, context-specific guidance for prostate cancer screening and management, contributing to improved patient outcomes and healthcare practices in Tanzania.

2.3 Clinical factors associated with high-grade prostate cancer

Prostate cancer is a prevalent malignancy among men, and the detection of high-grade disease, characterized by a Gleason score of 7 or higher, is crucial for appropriate clinical management. This literature review delves into the clinical factors associated with the development and diagnosis of high-grade prostate cancer. Understanding these factors is pivotal for risk assessment, early detection, and tailored treatment strategies. Although prostate-specific antigen (PSA) testing and digital rectal examination (DRE) are fundamental for screening, their limitations and the emergence of advanced diagnostic tools have transformed the landscape of high-grade prostate cancer detection. This review seeks to explore the evolving role of clinical factors in identifying high-grade disease and their implications for clinical decision-making.

In the context of PSA levels, Shah revealed that a substantial proportion of patients, approximately 86%, exhibited PSA levels within the range of ≤ 10 ng/mL. This observation indicates that, based on their prebiopsy characteristics, the majority of these patients were categorized as not being at high risk [27]. Furthermore, in their retrospective analysis, Jeong et al. reported that the percentage of free PSA, a recognized supplementary PSA test, exhibited limited predictive efficacy within their study [30]. Their observations were in line with prior research, which indicated that the

percentage of free PSA did not offer superior specificity compared to the total PSA in Korean men under the age of 65 who presented with a nonpalpable benign prostate gland and PSA levels ranging from 4.0 to 10.0 ng/mL [31]. The results obtained from the Korean study closely mirrored those reported in Western nations. Nevertheless, the underlying reasons for this parallel between the current findings and those in Western men with typical PSA levels remain somewhat elusive. A comparative assessment between developed and developing countries, particularly Africa, is notably lacking. This research endeavours to bridge this existing gap by exploring these distinctions and commonalities in prostate cancer characteristics across diverse regions.

In their retrospective investigation, Shah and Loffe made interesting observations. They noted that because approximately half of the biopsy specimens tended to provide a lower pathologic grade than what is actually present, they postulated that the true prevalence of prostate cancer with Gleason sum scores (GSSs) in the range of 7 to 10 is likely in the vicinity of 80% to 85% when there is a positive DRE result [27]. This underscores the importance of comprehensive diagnostic approaches to accurately assess the true incidence of high-grade prostate cancer. Similarly, Thompson and colleagues reported that elevated serum PSA levels, abnormal DRE findings, older age at the time of biopsy, and African ethnicity were indicative factors associated with the occurrence of high-grade disease, characterized by a Gleason score exceeding 7 [23]. Notably, to our knowledge, to date, no study conducted within African contexts has attempted a similar investigation.

2.4 High-grade prostate cancer and lifestyle factors

Numerous modifiable factors have also been implicated in the development of prostate cancer, including three well-established nonmodifiable factors: age, race, and a positive family history of prostate cancer. The following factors were studied: alcohol intake, tobacco consumption, sexual habits, diet [32,33] and physical activity [32].

An evaluation of the relationship between tobacco use and prostate cancer revealed that smoking was associated with an increased risk of high-grade PCa. [32,33].

Regarding alcohol intake, most of the evidence in the literature affirms an association with an elevated risk of high-grade prostate cancer, but alcohol intake has a relatively smaller impact on overall risk. Specifically, the risk of high-grade prostate cancer seems to rise notably among moderate and heavy drinkers, estimated at a minimum of 10 units per week. [33]

The impact of sexual habits, physical activity, and diet on high-grade prostate cancer diagnosis is multifaceted. Research suggests that specific sexual practices and a greater frequency of sexual activity may be linked to a reduced risk of developing high-grade prostate cancer [32,33]. Regular physical activity has been associated with a lower likelihood of aggressive prostate cancer, emphasizing the potential benefits of an active lifestyle in mitigating risk. [32] Additionally, dietary factors play a role, with certain dietary patterns, such as those rich in fruits and vegetables and low in processed foods, demonstrating potential protective effects against high-grade prostate cancer. However, further investigation is needed to fully elucidate the complex interplay between these lifestyle factors and their influence on the diagnosis of high-grade prostate cancer. [32,33]

2.5 Prostate cancer and comorbidities

The connection between prostate cancer and various comorbidities has been investigated, with diabetes and hypertension emerging as the most extensively studied concurrent conditions, isolated or associated in the metabolic syndrome [34]

In a retrospective study conducted by Hong et al. examining the aggressiveness of PCa, multicore biopsy revealed that individuals with DM were notably more prone to exhibit high-grade (Gleason score ≥ 7) PCa. Conversely, the association between DM and low-grade (Gleason score 6) PCa was not statistically significant. [35] The use of

antidiabetic drugs and normalization of glucose levels has been reported to contribute to reducing the risk of PCa [33]

Other studied factors for prostate cancer, particularly HGPC, are obesity [33], hypercholesterolemia [36], male factor infertility [20] and hormonal imbalance (low testosterone) [37]

2.6 Histopathology and grades of prostate cancer

This review concentrates on the histopathological dimensions of prostate carcinoma. The determination of prostate cancer frequently relies on a tissue diagnosis of adenocarcinoma, and the fundamental method for such a diagnosis involves the microscopic examination of tissue sections stained with hematoxylin and eosin (H&E). According to Guo et al., prostate adenocarcinoma demonstrates an irregular glandular pattern, disrupting the normal relationships between benign epithelial and stromal components. These changes are most effectively observed at lower magnifications during scanning [38].

Individuals with high-grade prostate cancer (HGPC) exhibit markedly less favourable prognoses than those with low-grade PCa. Consequently, accurately anticipating the presence of HGPC is highly important for facilitating and implementing aggressive therapeutic strategies for these patients [20]. To determine whether PCa is low grade or high grade, the Gleason score is used to grade the aggressiveness of prostate cancer based on the microscopic appearance of the cancer cells in a biopsy sample. Two separate scores are assigned-the most prevalent and the second most prevalent histological pattern in the tumour- each on a scale ranging from 1 to 5. These two scores are added together to create the Gleason score, which theoretically ranges from 2 to 10, however, 6 is currently the lowest score assigned. Report of Gleason scores of 2 to 5 have virtually disappeared from current clinical practice [39]. A Gleason score of 6 is considered low-grade, indicating slow-growing cancer. Scores of 7 to 10 are considered high-grade, indicating more aggressive and rapidly growing cancer [21] . Thompson et

al. pioneered the development of a predictive model for PCa based on data from the placebo group of the Prostate Cancer Prevention Trial, revealing predictive factors such as elevated serum PSA levels, abnormal DRE results, advanced age at the time of biopsy, and African American ethnicity concerning high-grade disease (Gleason score > 7) [23]. Similarly, Nam et al. designed a nomogram to predict the likelihood of PCa as well as high-grade cancer, incorporating parameters such as age, ethnicity, family history, urinary voiding symptom scores, percent free PSA, and DRE findings [22].
Wilson et al. [40] conducted a study focusing on lifestyle factors and their association with lethal prostate cancer. They found that factors such as diet, physical activity, and obesity may play a role in the risk of developing any grade of prostate cancer. Moreover, in a study conducted by Center and colleagues, genetic variations had the potential to impact the occurrence of both less aggressive, low-grade prostate cancer and more aggressive, high-grade prostate cancer. This finding underscores the intricate role that genetics can play in the development of different prostate cancer grades [4].

While these studies provide valuable insights into factors associated with prostate cancer, a direct comparison of factors between low-grade and high-grade prostate cancer within a specific population, such as the initial biopsy of high-grade cancer, appears to be an area with potential for further research.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study design

The research employed a cross-sectional analytical design, during which data were retrospectively collected from patients who had undergone prostate biopsy at Muhimbili National Hospital, Upanga campus, from October 2022 to March 2024.

3.2 Study area

The study took place at Muhimbili National Hospital (MNH) in Dar es Salaam, a tertiary healthcare facility, on the Upanga campus. MNH operates as a teaching hospital affiliated with Muhimbili University of Health and Allied Sciences (MUHAS), facilitating the systematic collection of clinical data, patient records, and treatment outcomes for adults with prostate cancer. This study specifically focused on the Urology Department at MNH, which plays a pivotal role in the comprehensive management of prostate cancer patients.

The Department of Urology at Muhimbili National Hospital is a leading centre for the diagnosis, treatment, and management of urological conditions in Tanzania. The department offers the following services: diagnostic (advanced imaging studies, laboratory tests, and minimally invasive procedures) and medical and surgical treatment modalities. Patient care is performed utilizing a multidisciplinary approach involving the radiology, pathology, and oncology departments.

MNH has a total bed capacity of 1500, 120 of which are set apart for adult general surgery services, including the Urology Department, which is staffed by 14 urologists, 1 surgeon, 4 registrars, 14 nurses, and a variable number of residents in training.

Regarding the care of patients with prostate cancer, the department offers diagnostic services (clinical exam, biopsy, biochemical tests, and imaging), therapeutic interventions, and follow-up care.

The patient care approach is inherently multidisciplinary and involves collaboration among oncologists, urologists, radiologists, and pathologists. The department, on average, processes approximately 15 prostate biopsies monthly, as documented in hospital records, showcasing the robust staffing and services dedicated to prostate cancer care at MNH. At MNH, digitally guided transrectal prostate biopsies are performed using an eight-core sampling technique.

3.3 Study population

All patients aged 40 years and above who presented at MNH with prostate-related symptoms and who underwent prostate biopsy.

3.4 Inclusion and Exclusion Criteria

3.4.1 Inclusion criteria

All patients aged 40 years or older who attended the clinic for prostate-related concerns and who were considered for prostate biopsy by their attending urologist based on increased PSA or abnormal DRE findings were included.

3.4.2 Exclusion criteria

Individuals who were admitted for urinary retention, those who had recently undergone prostatic surgery or an endoscopic urethral procedure, those who were receiving 5-alpha reductase inhibitors, patients who were diagnosed with any other malignancy, and those whose biopsy results revealed inadequate or unrepresentative samples were excluded from the study.

3.5 Sample size and sampling technique

3.5.1 Sampling procedure

Consecutive patients who met the inclusion criteria were included in the study until the sample size was reached. A convenient sampling approach was used.

3.5.2 Sample Size Estimation

Using data from the PCPTRC study of 2014, an elevated PSA level of 6 ng/mL or higher emerged as a major predictor of high-grade prostate cancer. This study revealed that 13.33% of patients with elevated PSA levels were diagnosed with HGPC versus 3.06% of patients with PSA levels less than 6 ng/mL [41].
By incorporating these proportions into OpenEpi, version 3, an open-source calculator that uses the formulas of Kelsey et al., and Fleiss [42], we obtained the following sample size.

Sample Size: X-Sectional, Cohort, & Randomized Clinical Trials

Two-sided significance level(1-alpha):	95
Power (1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1
Percent of Unexposed with Outcome:	3.1
Percent of Exposed with Outcome:	13
Odds Ratio:	4.9
Risk/Prevalence Ratio:	4.4
Risk/Prevalence difference:	10

	Kelsey	Fleiss	Fleiss with CC
Sample Size - Exposed	112	111	130
Sample Size-Nonexposed	112	111	130
Total sample size:	224	222	260

Hence, 260 patients were recruited to participate in the study.

3.6 Study variables

3.6.1 Independent variables

A. Demographic factors:
    1. Age: age of the patients at the time when the biopsy was performed.
    2. Ethnicity: the ethnic background or cultural affiliation of the patients.
    3. Socioeconomic status: a measure of patients' economic and social standing.
    4. Education level: the highest level of education attained by the patients.
    5. Family history: included prostate cancer (yes/no) and breast cancer (yes/no), with patient having a positive history, the relative affected was categorised as first-, second- or third-degree relative.
    6. Comorbidity
B. Clinical Factors:
    1. Chief complaint: reason for the patient to seek medical consultation
    2. PSA Levels: Prostate-specific antigen levels measured in the patient's blood.
    3. DRE findings: Results of the digital rectal examination indicating abnormalities in the prostate. DRE findings were grouped into normal and abnormal (suspicious)
    4. Ultrasound results: prostate size and characteristics (homogeneous or heterogeneous, presenting hypoechoic areas)
C. Lifestyle or behavioural factors: These variables included smoking habits and alcohol consumption.

3.6.2 Dependent Variables

Prostate biopsy results: Categorical variables indicating the Gleason score, categorized as no cancer, low-grade (Gleason score < 7) or high-grade (Gleason score ≥ 7). The HGPC was also categorized according to Gleason score, Gleason pattern and grade group.

3.7 Data collection techniques and tools

The data collection was performed following these steps: First, information on the total number of patients who underwent prostate biopsy was obtained from the minor procedure log book, which provided patient file numbers. Second, with the patient file number, we obtained access to their respective files and phone numbers with the help of the hospital data manager. Information of interest were gathered from patient files, the Jeeva hospital database, and through over the phone interviews with patients for completeness of data**.** Information from 260 patients who underwent prostate biopsy at MNH between October 2022 and March 2024 were retrieved by the principal investigator with assistance from the hospital medical records manager, and the predefined structured data collection tool used is provided in Appendix I.

The following information was obtained from medical records and the Jeeva hospital system: patient file number, phone number, age, profession, marital status, education level, insurance status, comorbidity, main complaint, PSA level, DRE findings, ultrasound results, and biopsy results. The following data were obtained from patient interviews: past medical history, family history, smoking status, and alcohol consumption status.

3.7.1 Recruitment and training of research assistants

Two research assistants working at the Urology Unit at the MNH underwent a comprehensive two-day training session. They were briefed on the study's objectives, and the target population. Additionally, they received instructions on how to effectively

run the interview and accurately document patients' responses. Ethical considerations, including obtaining informed consent and maintaining confidentiality, were also covered extensively. Moreover, they were reminded of the importance of communication in addressing any concerns or issues that may arise during the data collection process.

3.7.2 Piloting tool

To assess the accuracy and consistency of the research tool, a sample of patients' medical records from MNH was used. The preliminary testing phase involved administering the checklist to 10 patient records. The responses were analysed to evaluate the validity and internal consistency of the questions, and prompt adjustments were made if inconsistencies were identified.

3.8 Data processing and analysis

3.8.1 Data Management

The data collected underwent initial processing in Microsoft Excel before being imported into SPSS software version 23 for both quality control and analysis purposes. Quality control measures included running frequencies of the variables to verify the completeness and accuracy of the collected data prior to analysis. Any missing or incorrectly recorded data were identified and addressed using patient file numbers to ensure comprehensive data integrity.

3.8.2 Data analysis

Objective 1

Descriptive statistical analysis was employed to summarize the profiles of patients who underwent prostate biopsy. Frequencies, percentages, means, medians and standard deviations (SDs) were calculated to provide a comprehensive overview of the patient population. Summary statistics and frequency tables were generated to summarize the results and presented using tables.

Objective 2

The proportion of patients with high-grade prostate cancer was calculated by dividing the number of patients diagnosed with high-grade prostate cancer by the total number of patients who underwent prostate biopsy. This proportion was expressed as a percentage, and summarized in a pie chart, and the Gleason pattern distribution shown in frequency tables.

Objective 3

Logistic regression was used to assess the association between the variables (such as patient demographics and clinical factors) and a binary outcome (HGPC or not). This was proceeded by Chi-square analysis which was conducted to examine the associations between all the factors of interest and the outcome (HGPC). All factors that were found to be significant, were subsequently assessed collectively through multiple logistic regression to control for confounding variables and determine adjusted odds ratios. A confidence interval (CI), of 95% was used, and a p-value of < 0.05 was considered significant.

3.9 Ethical considerations and approval

The study protocol was submitted to the MUHAS Senate Research and Publication Committee; ethical clearance certificate no. MUHAS-REC-03-2024-2109 was granted.

Permission to collect data at the Urology Unit, Medical Records Department, and Jeeva System of the Hospital was obtained from the MNH administration. The confidentiality of the collected data was assured. Only personnel directly involved with the research had access to the data, and the data were used only for purposes of research and results publication. Informed consent was obtained from the patients to provide extra-information that was not included in their files. Patients were contacted via phone calls and seen during their appointments a Urology clinic.

3.10 Study limitations and mitigation

The limitations of this study arise from its cross-sectional retrospective design, and its single-centre, and hospital-based nature. While efforts were undertaken to collect comprehensive data from patients and their medical records, some information were missing or incomplete, influenced by patients' recall and the quality of medical records. To address this, rigorous data checks were performed, and any patients with persistent missing information of interest were excluded from the analysis.

Additionally, despite the multivariable analysis, the presence of unmeasured or residual confounding factors may still influence the observed analysis results. For example, procedure-related information such as the number of prostate core biopsies or the experience of the individual performing the biopsy may affect the outcomes.

CHAPTER FOUR

4.0 ANALYSIS AND RESULTS PRESENTATION

4.1 Sociodemographic profile of patients undergoing prostate biopsy at MNH

Between October 2022 and March 2024, 260 patients who met the inclusion criteria among those who underwent prostate biopsy were included.

The Table 1 presents the sociodemographic characteristics of the patients undergoing prostate biopsy. The mean age of the patients undergoing prostate biopsy was 71 years, with a range from 40 to 93 years. The majority of patients (71.2%) fell within the 60-79 age group, followed by 20.8% in the 80 and above age group. Regarding marital status, the majority of patients were married (82.3%). In terms of education, the majority of patients had a primary education level (58.8%). Concerning employment status, most patients were self-employed (75.8%), followed by those who were not employed (17.3%). For insurance status, the majority of patients were insured (93.5%). Hypertension was found to be the most prevalent comorbidity (42.7%), followed by diabetes (8.1%). A notable percentage of patients had a family history of prostate cancer (27.7%), with most affected being a first-degree relative (79.1%). Additionally, a small percentage of patients had a family history of breast cancer (5.4%). Regarding lifestyle factors, alcohol consumption was prevalent among the patients, with 62.3% reporting alcohol consumption. Smoking was also common, with 38.5% reporting a history of smoking.

Table 1: Sociodemographic profile of patient undergoing prostate biopsy at Muhimbili National Hospital

Variable	Frequency (n)	Percent (%)
Age (years),		
Mean age (SD, min-max)	71(40-93)	
40-59	21	8.1
60-79	185	71.2
80-above	54	20.8
Marital status		
Married	214	82.3
Single	46	17.7
Education		
No formal education	29	11.2
Primary	153	58.8
Secondary	52	20.0
University	26	10.0
Employment status		
Employed	18	6.9
Self-employed	197	75.8
Not employed	45	17.3
Insurance status		
Insured	243	93.5
Not-insured	17	6.5
Comorbidities		
Diabetes	21	8.1
Diabetes, Hypertension	17	6.5
Hypertension	111	42.7
No comorbidity	97	37.3
Others	7	2.7
Family history of PCa		
Yes	72	27.7
No	188	72.3
Relative affected (n=72)		
First degree	57	79.2
Second degree	13	18.1
Third degree	2	2.8
Family history of breast Cancer		
Yes	14	5.4
No	246	94.6

Variable	Frequency (n)	Percent (%)
Relative affected (Breast cancer)		
First degree	6	2.3
Second degree	8	3.1
Third degree	0	0
Smoking		
Pack-years, median (Rage)	4.50 (0-21)	
Yes	100	38.5
No	160	61.5
Alcohol consumption		
Yes	162	62.3
No	98	37.7

4.2 Clinical profile of patients undergoing prostate biopsy at Muhimbili National Hospital

The table below shows the clinical characteristics of patients who underwent prostate biopsy at Muhimbili National Hospital. The reasons for admission varied among the patients, with the majority presenting with low urinary tract symptoms (58.1%), and only a small percentage of patients (0.8%) were admitted for asymptomatic health checks. Regarding digital rectal examination (DRE) findings, the majority of patients (73.5%) had abnormal findings. The median PSA level among our patients was 81.6 ng/mL, with a wide range from 0.096 to 2000 ng/mL. The majority of patients (93.8%) had increased PSA levels. Prostate echotexture was assessed in a subset of patients (n=211), with approximately equal proportions having heterogeneous (46.0%) and homogenous (54.0%) echotexture. The distribution of patients across different prostate sizes shows variability, with a substantial number having prostate volumes ranging from 40 to 99 cm^3. The median PSA density was 0.89 ng/mL/cm^3, and the majority of patients (73.1%) had a PSA density ≥ 0.15 ng/mL/ cm^3.

Table 2: Clinical profile of patient undergoing prostate biopsy at Muhimbili National Hospital

Variable	Frequency (n)	Percent (%)
Reason for admission		
Asymptomatic health check	2	0.8
Low back pain	98	37.7
Low urinary track symptoms	160	61.5
DRE findings		
Abnormal	191	73.5
Normal	69	26.5
PSA level. Median (range)	**81.6 (0.096 – 2000)**	
PSA level (Age adjusted)		
Normal	16	6.2
Raised	244	93.8
Prostate echotexture (N=211)		
Heterogenous	97	46.0
Homogenous	114	54.0
Prostate size Median (range), N=211	**65.73 (14 – 298)**	
Less than or equal to 39	47	22.3
40 – 59	53	25.1
60 – 79	23	10.9
80 – 99	33	15.6
100 and above	55	26.1
PSA Density (ng/mL/cm^3**) Median(range), N=211**	**0.89 (0.01, 47.03)**	
Less than 0.15	21	8.1
≥ 0.15	190	73.1

4.3 Proportion of patients with high-grade prostate cancer in patients undergoing prostate biopsy at MNH

The pie chart below shows that 63.08% (164) of patients had high-grade prostate cancer. Its prevalence is substantially greater than that low-grade prostate cancer (5.77%) and benign prostatic hyperplasia (31.15%).

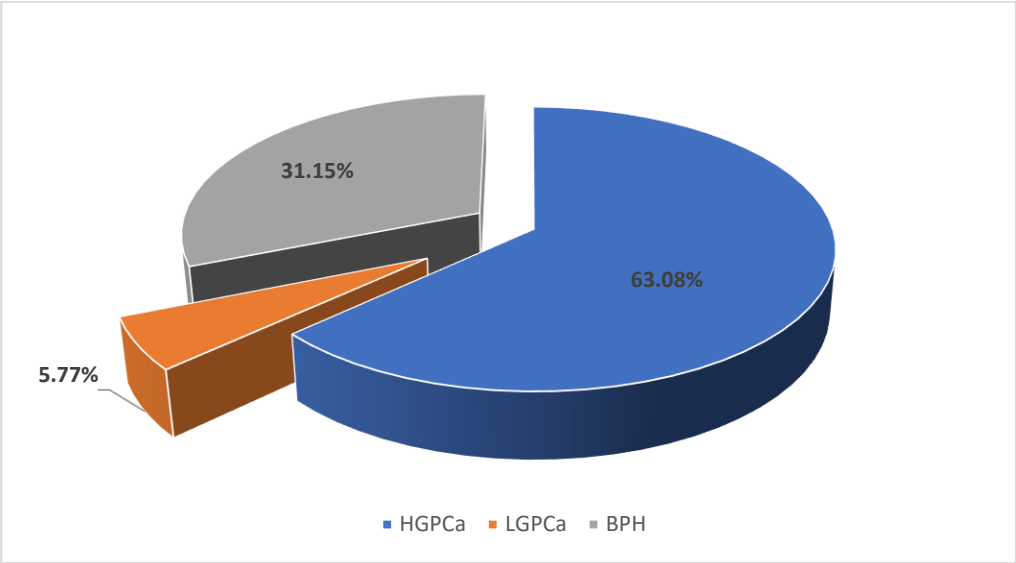


Figure 2: A pie chart demonstrating the proportion of patients with high-grade prostate cancer

Table 3 summarizes the distribution of Gleason patterns, scores, and ISUP grades among patients diagnosed with high-grade prostate cancer. Gleason pattern distribution revealed that Gleason score 8 (42.1%) was the most prevalent, followed by Gleason score 7 (28.0%) and Gleason score 9 (26.8%). Among the specific Gleason patterns, 4+4 (38.4%) was the most common, followed by 4+3 (15.9%) and 3+4 (12.2%). Furthermore, the distribution of ISUP grade groups highlights the predominance of Grade 4 (42.1%), followed by grade group 5 (29.9%).

Table 3: Distribution of Gleason pattern, score and ISUP grade among patients with high-grade prostate cancer

Variable	Frequency (n)	Percent (%)
Gleason pattern (n=164)		
Gleason 7	**46**	**28.0**
3+4	20	12.2
4+3	26	15.9
Gleason 8	**69**	**42.1**
3+5	4	2.4
4+4	63	38.4
5+3	2	1.2
Gleason 9	**44**	**26.8**
4+5	31	18.9
5+4	13	7.9
Gleason 10 (5+5)	**5**	**3.0**
ISUP Grade group (n=164)		
1*	-	-
2	20	12.2
3	26	15.9
4	69	42.1
5	49	29.9

*ISUP Grade group 1 corresponds to low-grade prostate cancer, hence, it is not included in the distribution table of high-grade prostate cancer patients.

4.4 Factors associated with high-grade prostate cancer at initial biopsy

The chi-square test results from Table 4 reveal the associations between sociodemographic and clinical factors and the detection of high-grade prostate cancer at initial biopsy. Although age group, marital status and comorbidities showed no significant associations, a family history of prostate cancer exhibited a strong correlation with high-grade disease ($p < 0.005$). Smoking ($p = 0.002$) and alcohol consumption ($p = 0.001$) displayed notable associations with higher proportions of high-grade cases. High-grade prostate cancer was also found to be associated with the complaints on admission, indicating the relevance of symptomatology ($p < 0.001$). Furthermore, abnormal findings on digital rectal examination ($p = 0.000$), increased PSA levels ($p < 0.001$), prostate echotexture ($p = 0.001$), and elevated PSA density ($p < 0.001$) were significantly associated with high-grade prostate cancer.

Table 4: High-grade prostate cancer by sociodemographic and clinical factors

	High-grade Prostate Cancer		
Variable	**Yes (%)**	**No (%)**	**p_value**
Age group			0.715
40-59	12(57.1)	9(42.9)	
60-79	116(62.7)	69(37.3)	
80 and above	36(66.7)	18(33.3)	
Marital status			0.732
Married	136(63.6)	78(36.4)	
Single	28(60.9)	18(39.1)	
Comorbidities			0.338
Diabetes	15(71.4)	6(28.6)	
Diabetes, Hypertension	11(64.7)	6(35.3)	
Hypertension	69(62.2)	42(37.8)	
HIV	2(28.6)	5(71.4)	

	High-grade Prostate Cancer		
Variable	**Yes (%)**	**No (%)**	**p_value**
No comorbidity	64(66.0)	33(34.0)	
Others	3(42.9)	4(51.1)	
Family history of PCa			**< 0.001**
Yes	64(88.9)	8(11.1)	
No	100(53.2)	88(46.8)	
Family history of breast Cancer			0.266
Yes	11(78.6)	3(21.4)	
No	153(62.2)	93(37.8)	
Smoking			**0.002**
Yes	75(75.0)	25(25.0)	
No	89(55.6)	71(44.4)	
Alcohol consumption			**0.001**
Yes	115(71.0)	47(29.0)	
No	49(50.0)	49(50.0)	
Reason for admission			**< 0.001**
Asymptomatic health check	1(50.0)	1(50.0)	
Low back pain and LLN/W	78(79.6)	20(20.4)	
LUTS	85(53.1)	75(46.9)	
DRE findings			**< 0.001**
Normal	7(11.5)	54(88.5)	
Abnormal	157(78.9)	42(21.1)	
PSA level (Age adjusted)			**< 0.001**
Normal	2(12.5)	14(87.5)	
Abnormal (Raised)	162(66.4)	82(33.6)	
Prostate echotexture			**0.001**
Homogenous	57(50.0)	57(50.0)	
Heterogenous	71(73.2)	26(26.8)	

	High-grade Prostate Cancer		
Variable	**Yes (%)**	**No (%)**	**p_value**
Prostate size Median (range)			**0.435**
Less than or equal to 39	28(59.6)	19(40.4)	
40 – 59	36(67.9)	17(32.1)	
60 – 79	14(60.9)	9(39.1)	
80 – 99	18(54.5)	15(45.5)	
100 and above	32(58.2)	23(41.8)	
PSA Density (ng/mL/cm^3**)**			**< 0.001**
Less than 0.15	2(9.5)	19(90.5)	
≥ 0.15	126(66.3)	64(33.7)	

LUTS: lower urinary tract symptoms, LLN/W: lower limb numbness or weakness

Table 5 summarizes the results of a multivariable logistic regression analysis elucidating factors associated with high-grade prostate cancer (HGPC) detection at initial biopsy. A family history of prostate cancer emerged as one of significant predictors, with individuals with such a history exhibiting substantially greater odds of HGPC (AOR = 8.45, 95% CI: 2.324-30.721, p = 0.001). Cigarette smoking also demonstrated a significant association, with smokers having greater odds of HGPC than nonsmokers did (AOR = 2.79, 95% CI: 1.028-7.611, p = 0.044). Regarding clinical factors, abnormal findings on digital rectal examination (DRE) were significantly correlated with increased odds of HGPC (AOR = 36.897, 95% CI: 10.897-125.049, p < 0.001). Additionally, individuals with a PSA-D above or equal to 0.15 had substantially greater odds of having HGPC than those with a lower PSA-D (AOR = 10.394, 95% CI: 1.060-101.916, p=0.044). Furthermore, history of alcohol consumption, chief complaint, prostate texture and echogenicity, and PSA levels (age adjusted) were associated with increased odds of HGPC, but the associations were not statistically significant (p > 0.05).

Table 5: Multivariable Logistic Regression factors associated with High Grade Prostate cancer

Variables	HGPC		AOR	95% CI		p_Value
	Yes (%)	No (%)		Lower	Upper	
Family history of Prostate cancer						
Yes	64(88.9)	8(11.1)	8.450	2.324	30.721	**0.001**
No	100(53.2)	88(46.8)	Ref.			
Cigarette smoking						
Yes	75(75.0)	25(25.0)	2.792	1.028	7.661	**0.044**
No	89(55.6)	71(44.4)	Ref.			
Alcohol consumption						
Yes	115(71.0)	47(29.0)	1.4660	0.587	3.628	0.416
No	49(50.0)	49(50.0)	Ref.			
Reason of admission						
Asymptomatic health check	1(50.0)	1(50.0)	Ref.			
Low back pain and LLN/W	78(79.6)	20(20.4)	10.397	0.359	301.456	0.173
Low urinary track symptoms	85(53.1)	75(46.9)	0.096	0.003	2.789	0.173

DRE findings						
Normal	7(11.5)	54(88.5)	Ref.			
Abnormal	157(78.9)	42(21.1)	36.897	10.887	125.049	**<0.001**
Prostate texture and echogenicity						
Homogenous	57(50.0)	57(50.0)	Ref.			
Heterogenous	71(73.2)	26(26.8)	1.933	0.844	4.423	0.119
PSA level (Age adjusted)						
Normal	2(12.5)	14(87.5)	Ref.			
Abnormal (Raised)	162(66.4)	82(33.6)	6.136	0.216	174.064	0.288
PSA-D						
Less than 0.15	2(9.5)	19(90.5)	Ref.			
≥ 0.15	126(66.3)	64(33.7)	10.394	1.060	101.916	**0.044**

CHAPTER FIVE

5.0 DISCUSSION

Despite numerous interventions and innovations to improve the early detection and management of prostate cancer, prostate cancer morbidity and mortality remain a global public health concern, especially in lower- and middle-income countries. Prostate biopsy has never been innocuous; rather, it has been associated with hazards such as unnecessary costs and the risk of infection. Thus, avoiding unnecessary biopsies and accurately predicting high-grade cancer will provide a net benefit to patients.[41] The aim of this study was to determine the factors associated with high-grade prostate cancer at initial biopsy in patients attending MNH.

5.1 Sociodemographic and clinical profile of patients undergoing prostate biopsy at Muhimbili National Hospital

The sociodemographic profile of patients undergoing prostate biopsy at Muhimbili National Hospital, as depicted in Table 1, provides valuable insights into the characteristics of the study population and aligns with the literature on prostate cancer demographics. The mean age in our study was 71 years, with patient ages ranging from 40 to 93 years. This is similar to findings from a study on patient selection for prostate biopsy conducted by Nariculam et al. These researchers reported a mean age of 67 years, ranging from 41 to 83 years old, in their study population. [43] The predominance of patients in the 60-79 age group in our study is consistent with the well-established trend of prostate cancer prevalence increasing with age, with the majority of cases diagnosed in older men. This finding underscores the importance of age as one of the three well-established risk factors for prostate cancer, together with African ancestry and heredity [6].

Among the comorbidities found in our patients, a high frequency of hypertension was observed. This finding is consistent with previous research indicating a potential association between hypertension and prostate cancer risk. Melanie and colleagues reported a comorbidity rate of 51%, among which approximately 42% had hypertension as a comorbidity [44]. In our study, hypertension was the most prevalent isolated comorbidity (42.7%). This can be explained by the older age of our patients.

The proportions of patients with a family history of prostate cancer and breast cancer were 27.7% and 5.4%, respectively, with first-degree relatives being the most represented in the two groups. The hereditary component of prostate cancer has been among the first known causes of this disease, and hereditary prostate cancer has been ranked as having the highest heritability among all major cancers in men, being most prevalent in patients of African ancestry and presenting in aggressive form and at a younger age. [45] Additionally, the prevalence of lifestyle factors such as smoking (4 patients out of 10) and alcohol (6 patients out of 10) consumption among the patient population can reveal associations between these behaviors and an increased risk of aggressive prostate cancer. Furthermore, the diverse range of education levels, employment statuses, and insurance statuses among patients underscores the complex interplay between socioeconomic factors and prostate cancer incidence, with lower socioeconomic status often associated with poorer prognosis and access to care. [46]

The clinical profile outlined in Table 2 sheds light on various aspects of patients undergoing prostate biopsy at Muhimbili National Hospital, offering insights that are consistent with the literature on prostate cancer diagnosis and risk assessment. The predominance of patients who presented with low urinary tract tract symptoms aligns with the findings of Nariculam et al., who assessed the presence or absence of LUTS among participants and reported that LUTS was observed in 51% of all patients. Since their study was population-based, no other symptoms were noted. [43] The findings from these studies highlight the significance of urinary symptoms as potential indicators of benign or malignant prostate abnormalities. In our study,

in addition to LUTS as the main complaint, our patients also presented with hematuria, lower back pain and lower limb weakness.

The high proportion of patients with abnormal DRE findings and elevated PSA levels, as revealed in this study, is in line with established diagnostic criteria for prostate cancer, emphasizing the utility of these screening modalities in identifying individuals at risk. [7,16,17].

This study revealed a variable distribution of prostate size and PSA density. This highlights the heterogeneity of prostate cancer presentations in the studied population and the importance of considering multiple factors in risk stratification and diagnosis. Both factors could play a role in the detection of high-grade prostate cancer as potential risk factors [30,47,48] or as cofounders.

Prostate echotexture assessment plays a crucial role in clinical decision-making for prostate pathology. By evaluating the echotexture of the prostate, clinicians can gain valuable insights into tissue characteristics that may indicate underlying pathology [49]. In this study, homogenous echotexture was the most prevalent, representing 54.0% of the studied population.

5.2 Proportion of patients with high-grade prostate cancer among MNH patients

The pie chart illustrating the distribution of prostate conditions underscores the prevalence of high-grade prostate cancer, which constitutes approximately 63.08% of cases, indicating a substantial burden of aggressive disease among patients admitted to Muhimbili National Hospital. This prevalence is high compared to that found in similar previous studies. A community-based study conducted in Nigeria revealed benign prostatic hyperplasia as the most prevalent histopathology finding in patients who underwent prostate biopsy, which was observed in 71.0% of patients, and prostate adenocarcinoma was found in only 12.6% of patients. [50] Most of these studies were population-based, with a defined upper limit of PSA among the inclusion criteria.[30,41] In the study by Gab Jeong et al., which included a total of 1,048 men, adenocarcinoma of the prostate was detected in 216

individuals (20.6%) upon biopsy, with the remaining 832 patients (79.4%) exhibiting no signs of cancer. Among the 216 patients diagnosed with cancer, 97 individuals (44.9%) had a Gleason score greater than 7, indicating a high-grade prostate cancer overall proportion of 9.3%. In this study, only patients with PSA levels less than 10 ng/mL were included. [30] Conversely, low-grade prostate cancer represented a smaller proportion in our cohort, accounting for only 5.77% of cases, suggesting a lower prevalence of less aggressive disease phenotypes at MNH. Benign prostatic hyperplasia (BPH), accounting for 31.15% of cases, has emerged as the second most prevalent condition. These findings, although having shown a high prevalence in high-grade prostate cancer, also revealed a high proportion of negative biopsies (benign prostatic hyperplasia) and underscored the necessity for accurate patient selection for biopsy.

The distributions of Gleason patterns, scores, and ISUP grades among patients with high-grade prostate cancer, as depicted in the study, are different from established findings in the literature. Although Gleason 8 (69%) emerged as the most prevalent pattern in our study, followed by Gleason 7 and Gleason 9, previous studies found that Gleason pattern 7 (3+4) was the most prevalent pattern. Shah et al. reported the following distributions: Gleason score 7 in 43.5%, 8 in 10%, 9 in 6.5% and 10 in 1% [51]. The Gleason score is a prognostic factor for prostate cancer, with higher scores being associated with poor prognosis. The difference in Gleason score distribution between our study and previous studies can be explained by the large number of patients who sought medical consultation when experiencing symptoms. This was not the case in previous studies, which were predominantly community-based and were mainly characterized by asymptomatic participants.

Overall, these findings underscore the high proportion of patients with higher Gleason scores at Muhimbili National Hospital, providing a better understanding of the factors associated with high-grade prostate cancer to define prevention measures and early screening protocols.

5.3 Factors associated with high-grade prostate cancer at MNH

Heredity is a well-established risk factor for prostate cancer. However, there is scarce African research focused on the impact of a family history of prostate cancer on high-grade prostate cancer, a clinically significant form associated with poor prognosis. Consistent with prior US research, a family history of prostate cancer emerged as a significant predictor of HGPCa in our study, with first-degree relatives being the most represented group, corroborating the hereditary component in prostate cancer risk. In a multicentre study in America and Europe, Matthew and colleagues reported increased odds of HGPCa in people with a positive family history of prostate cancer and breast cancer. [52] In our study, there was no evidence of an association between a positive history of breast cancer and HGPCa. This could be attributed to the low proportion (5.4%) of patients with a positive history of breast cancer in our study population.

The observed association with cigarette smoking mirrors previous studies highlighting the detrimental impact of smoking on prostate cancer aggressiveness.[32,33] Cigarette smoking increases prostate cancer risk by altering hormone levels by increasing the bioavailability of testosterone on one side and decreasing that of oestradiol on the other side, therefore promoting cell proliferation in the prostate. Additionally, cigarettes contain cadmium, which is associated with prostate carcinogenesis.[53]

Conversely, the lack of a significant association with alcohol consumption contrasts with some studies suggesting a potential link, although conflicting evidence exists. [54].

The significant correlation between abnormal DRE findings and increased odds of HGPCa underscores the clinical utility of DRE in prostate cancer diagnosis and risk assessment. A hard prostate has been one of the primary indications for prostate cancer biopsy [7,16,17], and its association with high-grade prostate cancer has been documented by O'Brien et al. They found that abnormal DRE findings were associated with 2.7-fold increased odds of high-grade prostate cancer. [55] Ankerst

D. and colleagues also found DRE findings among predictors of HGPCa, with an increased odds ratio of 1.29 higher in patients with abnormal DRE findings. [41]

Prostate size was not found to be associated with high-grade prostate cancer. This finding contrasts with previous studies that concluded that there is a negative correlation between TRUS prostate size and high-grade prostate cancer. [30,47]

On the other hand, the association between prostate echogenicity and HGPCa was not statistically significant (p=0.83). Although prostate cancer commonly presents as a region with reduced echogenicity (hypoechoic) in the peripheral zone of the gland, this presentation lacks specificity because a hypoechoic appearance has been found in other conditions, such as prostatitis and benign prostatic hyperplasia. Additionally, early-stage prostate cancer has been associated with a normal ultrasonographic appearance (isoechoic) since it is characterized by a greater proportion of normal glandular tissue. [49]

In addition to alcohol consumption, prostate size and echogenicity, and elevated PSA levels (age adjusted) were associated with increased odds of HGPC, but the associations were not statistically significant ($p > 0.05$) according to multivariate analysis. Concerning the PSA-D, this showed a significant association, with greater PSA-D being associated with increased odds of HGPC. This is in consistence with a study conducted in Israel by Yusim and colleagues who reported a statistically significant association between PSA-D and high-grade prostate cancer compared to PSA alone. In their study, they created a decision tree and found that patients with a prostate-specific antigen density (PSAD) higher than 0.19 exhibited a likelihood ranging from 30% to 60% of being diagnosed with clinically significant cancer. Conversely, individuals with a PSAD lower than 0.09 demonstrate a notably low probability (4%) of having clinically significant prostate cancer. Intriguingly, the probability of clinically significant prostate cancer in men with PSAD values falling within the "grey zone" of 0.09 to 0.19 is relatively modest at 8.5%. [48]

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

This study evaluated factors associated with high-grade prostate cancer detection at initial biopsy in patients admitted to Muhimbili National Hospital. This study revealed a high prevalence of HGPC at MNH. A positive family history of prostate cancer, a history of cigarette smoking, an abnormal DRE finding and an increased PSA-D were the established factors associated with HGPC. On the other hand, age, alcohol consumption, main complaint, PSA level (age adjusted), and prostate echotexture did not show statistically significant associations, and their roles in HGPC risk assessment warrant further investigation. Overall, these findings emphasize the need for personalized selection of patients for prostate biopsy while targeting HGPC.

6.2 Recommendations

Based on these results, several recommendations can be made to enhance HGPC detection rate. Healthcare should routinely inquire about patients' family history of prostate cancer and smoking habits during clinical assessment to identify individuals at higher risk, and to promote healthy lifestyle practices, including maintaining a healthy weight and avoiding tobacco use. Further research adopting multicentre and community-based approaches are needed to validate these findings, and explore other factors that could not be measured due to design limitation.

REFERENCES

1. Mustafa M, Salih AF, Illzam EM, Sharifa AM, Suleiman M, Hussain SS. Prostate cancer: pathophysiology, diagnosis, and prognosis. IOSR Journal of Dental and Medical Sciences. 2016;15(6):04-11.

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021 May;71(3):209-49.

3. Kocan H. Factors affecting the diagnosis of prostate cancer through 12 quadrant guided prostate biopsy. The Aging Male. 2020 Dec 4;23(5):663-8.

4. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012 Jun;61(6):1079–92.

5. Katabalo DM, Josephat J, Minja W, Mwita S, Marwa KJ, Rambau P. Prevalence, Grades and Management of Prostate Cancer among Men Attending Oncology Unit at Bugando Medical Centre Mwanza, Tanzania. Open J Epidemiol. 2022;12(02):146–57.

6. Adeloye D, David RA, Aderemi AV, Iseolorunkanmi A, Oyedokun A, Iweala EEJ, et al. An estimate of the incidence of prostate cancer in Africa: A systematic review and meta-analysis. PLoS One. 2016;11(4):1–18.

7. Al Rumaihi K, Al Jalham K, Younes N, Majzoub AA, Shokeir AA. The role of an abnormal prostate-specific antigen level and an abnormal digital rectal examination in the diagnosis of prostate cancer: a cross-sectional study in Qatar. Arab Journal of Urology. 2013 Dec 1;11(4):355-60.

8. Patel AR, Klein EA. Risk factors for prostate cancer. Nat Clin Pract Urol. 2009;6(2):87–95.

9. Crawford ED. Epidemiology of prostate cancer. Urology. 2003;62(6 SUPPL. 1):3–12.

10. Flam Thierry, Amsellem-Ouazana Delphine AA. Urologie, 4è édition. 4è. Paris: Maloine; 2011.

11. Randazzo M, Müller A, Carlsson S, Eberli D, Huber A, Grobholz R, et al. A positive family history as a risk factor for prostate cancer in a population-based study with organised prostate-specific antigen screening: Results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). BJU Int. 2016;117(4):576–83.

12. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J cancer. 2007 Oct;121(7):1571–8.

13. Hamilton W, Sharp DJ, Peters TJ, Round AP. Clinical features of prostate cancer before diagnosis: a population-based, case-control study. Br J Gen Pract. 2006 Oct;56(531):756–62.

14. Alcaraz A, Hammerer P, Tubaro A, Schröder FH, Castro R. Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. Eur Urol. 2009 Apr;55(4):864–73.

15. Vickers AJ, Cronin AM, Roobol MJ, Savage CJ, Peltola M, Pettersson K, et al. A four-kallikrein panel predicts prostate cancer in men with recent screening: Data from the european randomized study of screening for prostate cancer, Rotterdam. Clin Cancer Res. 2010;16(12):3232–9.

16. Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009 Mar;360(13):1320–8.

17. Ogunbiyi JO, Stefan DC, Rebbeck TR. African Organization for Research and Training in Cancer: position and vision for cancer research on the African Continent. Infect Agent Cancer [Internet]. 2016;11(1):1–6. Available from: http://dx.doi.org/10.1186/s13027-016-0110-9

18. Matsukawa A, Yanagisawa T, Bekku K, Parizi MK, Laukhtina E, Klemm J, Chiujdea S, Mori K, Kimura S, Fazekas T, Miszczyk M. Comparing the performance of digital rectal examination and prostate-specific antigen as a screening test for prostate cancer: a systematic review and meta-analysis. European Urology Oncology. 2024 Jan 4.

19. Ham WS, Chalfin HJ, Feng Z, Trock BJ, Epstein JI, Cheung C, Humphreys E, Partin AW, Han M. New prostate cancer grading system predicts long-term survival following surgery for Gleason score 8–10 prostate cancer. European urology. 2017 Jun 1;71(6):907-12.

20. Walsh TJ, Schembri M, Turek PJ, Chan JM, Carroll PR, Smith JF, et al. Increased risk of high-grade prostate cancer among infertile men. Cancer. 2010;116(9):2140–7.

21. Eggener SE, Berlin A, Vickers AJ, Paner GP, Wolinsky H, Cooperberg MR. Low-Grade Prostate Cancer: Time to Stop Calling It Cancer. J Clin Oncol. 2022;13(27):4–9.

22. Nam RK, Toi A, Klotz LH, Trachtenberg J, Jewett MAS, Appu S, et al. Assessing individual risk for prostate cancer. J Clin Oncol. 2007 Aug;25(24):3582–8.

23. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst. 2006 Apr;98(8):529–34.

24. Wang L, Lu B, He M, Wang Y, Wang Z, Du L. Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to

2019. Front Public Heal. 2022;10(February).

25. Lyimo EP, Rumisha SF, Mremi IR, Mangu CD, Kishamawe C, Chiduo MG, et al. Cancer Mortality Patterns in Tanzania: A Retrospective Hospital-Based Study, 2006-2015. JCO Glob Oncol. 2020 Feb;6:224–32.

26. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.

27. Shah N, Ioffe V. Frequency of Gleason score 7 to 10 in 5100 elderly prostate cancer patients. Rev Urol. 2016;18(4):181–7.

28. Arnsrud R, Stinesen K, Pihl C gustaf, Ma M, Hugosson J, Novara G, et al. The Association Between Age , Prostate Cancer Risk , and Higher Gleason Score in a Long-term Screening Program : Results from the Göteborg-1 Prostate Cancer Screening Trial. 2022;82:311–7.

29. DeSantis CE, Siegel RL, Sauer AG, Miller KD, Fedewa SA, Alcaraz KI, et al. Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. CA Cancer J Clin. 2016 Jul;66(4):290–308.

30. Jeong IG, Lim JH, Kim SC, You D, Hong JH, Ahn H, et al. Nomogram using transrectal ultrasound-derived information predicting the detection of high grade prostate cancer on initial biopsy. Prostate Int [Internet]. 2013;1(2):69–75. Available from: http://dx.doi.org/10.12954/PI.12008

31. Jeong IG, Lee KH. Percent free prostate specific antigen does not enhance the specificity of total prostate specific antigen for the detection of prostate cancer in Korean men 50 to 65 years old: a prospective multicenter study. J Urol. 2008 Jan;179(1):111–6.

32. Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: Age, location, and behavioral correlates. Clin Epidemiol. 2012;4(1):1–11.

33. Ziglioli F, Patera A, Isgrò G, Campobasso D, Guarino G, Maestroni U. Impact of modifiable lifestyle risk factors for prostate cancer prevention: a review of the literature. Front Oncol. 2023;13(September):1–13.

34. Xiang YZ, Xiong H, Cui ZL, Jiang SB, Xia QH, Zhao Y, et al. The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence. J Exp Clin Cancer Res. 2013;32(1).

35. Hong SK, Oh JJ, Byun SS, Hwang S Il, Lee HJ, Choe G, et al. Impact of diabetes mellitus on the detection of prostate cancer via contemporary multi (≥12)-core prostate biopsy. Prostate. 2012;72(1):51–7.

36. Jamnagerwalla J, Howard LE, Allott EH, Vidal AC, Moreira DM, Castro-Santamaria R, Andriole GL, Freeman MR, Freedland SJ. Serum cholesterol and risk of high-grade prostate cancer: results from the REDUCE study. Prostate cancer and prostatic diseases. 2018 Jun;21(2):252-9.

37. Schatzl G, Madersbacher S, Thurridl T, Waldmüller J, Kramer G, Haitel A, et al. High-grade prostate cancer is associated with low serum testosterone levels. Prostate. 2001;47(1):52–8.

38. Guo CC, Epstein JI. Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. Mod Pathol. 2006 Dec;19(12):1528–35.

39. Pudasaini S, Subedi N. Understanding the gleason grading system and its changes. J Pathol Nepal. 2019;9(2):1580–5.

40. Wilson KM, Giovannucci EL, Mucci LA. Lifestyle and dietary factors in the prevention of lethal prostate cancer. Asian J Androl. 2012 May;14(3):365–74.

41. Ankerst DP, Hoefler J, Bock S, Goodman PJ, Vickers A, Hernandez J, et al. Prostate cancer prevention trial risk calculator 2.0 for the prediction of low- vs

high-grade prostate cancer. Urology. 2014;83(6):1362–8.

42. Sullivan K, Soe M. Sample Size for an Unmatched Case-Control Study. Methods Obs Epidemiol [Internet]. 2013;Progiciel en ligne version 3.01. Available from: http://www.openepi.com/PDFDocs/SSCCDoc.pdf

43. Nariculam J, Shabbir M, Thomas K, le Roux PJ, Walker RM, Charig CR, et al. Patient selection for prostate biopsy: Risk-based or PSA-based? J Clin Urol [Internet]. 2012;5(3):128–33. Available from: http://dx.doi.org/10.1016/j.bjmsu.2011.08.004

44. Jefferson M, Drake RR, Lilly M, Savage SJ, Price ST, Halbert CH. Co-morbidities in a retrospective cohort of prostate cancer patients. Ethn Dis. 2020;30:185–92.

45. Vietri MT, D'elia G, Caliendo G, Resse M, Casamassimi A, Passariello L, et al. Hereditary prostate cancer: Genes related, target therapy and prevention. Int J Mol Sci. 2021;22(7).

46. Rundle A, Neckerman KM, Sheehan D, Jankowski M, Kryvenko ON, Tang D, et al. A prospective study of socioeconomic status, prostate cancer screening and incidence among men at high risk for prostate cancer. Cancer Causes Control. 2013 Feb;24(2):297–303.

47. Newton MR, Phillips S, Chang SS, Clark PE, Cookson MS, Davis R, et al. Smaller prostate size predicts high grade prostate cancer at final pathology. J Urol [Internet]. 2010;184(3):930–7. Available from: http://dx.doi.org/10.1016/j.juro.2010.04.082

48. Yusim I, Krenawi M, Mazor E, Novack V, Mabjeesh NJ. The use of prostate specific antigen density to predict clinically significant prostate cancer. Sci Rep [Internet]. 2020;10(1):1–6. Available from: https://doi.org/10.1038/s41598-020-76786-9

49. Liau J, Goldberg D, Arif-Tiwari H. Prostate Cancer Detection and Diagnosis: Role of Ultrasound with MRI Correlates. Curr Radiol Rep [Internet].

2019;7(3):7. Available from: https://doi.org/10.1007/s40134-019-0318-8

50. Ikuerowo SO, Omisanjo OA, Bioku MJ, Ajala MO, Nonyelim Mordi VP, Esho JO. Prevalence and characteristics of prostate cancer among participants of a communitybased screening in Nigeria using serum prostate specific antigen and digital rectal examination. Pan Afr Med J. 2013;15:1–7.

51. Shah N, Ioffe V. Frequency of Gleason score 7 to 10 in 5100 elderly prostate cancer patients. Reviews in Urology. 2016;18(4):181.

52. Clements MB, Vertosick EA, Guerrios-Rivera L, De Hoedt AM, Hernandez J, Liss MA, et al. Defining the Impact of Family History on Detection of High-grade Prostate Cancer in a Large Multi-institutional Cohort. Eur Urol. 2022;82(2):163–9.

53. Plaskon LA, Penson DF, Vaughan TL, Stanfordz JL. Cigarette smoking and risk of prostate cancer in middle-aged men. Cancer Epidemiol Biomarkers Prev. 2003;12(7):604–9.

54. Macke AJ, Petrosyan A. Alcohol and Prostate Cancer: Time to Draw Conclusions. Biomolecules. 2022;12(3).

55. O'Brien CA, Mongoue-Tchokote S, Collins L, Spurgeon S, Peters L, Beer TM, et al. Assessment of PSA and digital rectal examination (DRE) for the detection of Gleason ≥ 7 prostate cancer in a referral population. J Clin Oncol [Internet]. 2006 Jun 20;24(18_suppl):4633. Available from: https://doi.org/10.1200/jco.2006.24.18_suppl.4633

APPENDICES

Appendix I: Informed Consent (English Version)

Consent for Participation in Research Study Introduction

ID no_

Consent to participate in the study assessing factors associated with high-grade prostate cancer detection at initial biopsy in patients attending Muhimbili National Hospital

Greetings! My name is Dr. Amini Mitamo Alexandre, a postgraduate student at Muhimbili University of Health and Allied Sciences, School of Medicine, Department of Surgery

The purpose of the study: This research will aim to investigate the factors associated with the detection of high-grade prostate cancer during initial biopsy in patients admitted to Muhimbili National Hospital.

What participation involves: If you agree to participate in the study, of course, after having suspected prostate cancer according to the inclusion criteria, you will be asked questions concerning your demographic particulars, your medical history and your symptoms.

Subsequently, your weight and height will be measured, and your digital rectal examination findings, PSA level, prostate ultrasound and Tru-cut biopsy results will be recorded.

Confidentiality: Unique identification codes will be used instead of participants' names. All information collected on the questionnaires and the results of your tissue will be entered into a computer with an identification code previously assigned. Aggregate data will be used to prevent the identification of individual participants. The questionnaires will be handled with great secrecy, ensuring that privacy is maintained throughout the course of the study.

Risks: Participation in this study is not associated with any known risk. The study involves only recording information regarding demographic particulars, medical history, symptoms, BMI, prostate ultrasound results, DRE findings, and biopsy result.

Alterative and right to withdraw: Participation in this study is entirely voluntary. If you decide not to participate in the study, you will still receive all the regular services provided by the hospital.

Benefits: By consenting to be enrolled in this study, you will not gain any immediate advantages beyond contributing to the discovery of factors associated with high-grade prostate cancer detection, factors that will play a pivotal role in shaping the future guidelines in decision making for prostate biopsy.

Who to contact: If you have any inquiries or concerns regarding this study, you can reach out to Dr. Amini Mitamo Alexandre on +255 767591787.

If you have inquiries or concerns about your rights as participant, you may contact the office of the DVC-RC.

The Deputy Vice Chancellor - Research and Consultancy,

Muhimbili University of Health and Allied Sciences (MUHAS),

P.O. Box 65001

Dar es Salaam

Signature

I ..... have read the content of this form. My questions have been answered. I agree to participate in this study.

Signature of the participant .....

Signature of witness .....

Date of signed consent .... /…../2024

Participant agrees ___participant does agree _____

Appendix II: Informed Consent (Swahili Version)

Fomu ya Idhini kwa Ushiriki wa Utafiti

Namba ya utambulisho .....

Hati ya ukubali wa kushiriki kwenye utafiti wa kuchunguza sababu zinazoambatana na kupatikana kwa saratani ya tezi dume ya kiwango cha juu kipindi cha awali cha uchukuaji wa sampuli ya tishu kwa wagonjwa wanaopata matibabu katika Hospitali ya Taifa Muhimbili.

Salaam! Naitwa Dkt. Amini Mitamo Alexandre, mwanafunzi wa uzamili katika Chuo Kikuu cha Afya na Sayansi Shirikishi Muhimbili, Idara la Upasuaji

Lengo la utafiti

Utafiti huu utalenga kuchunguza sababu zinazohusiana na ugunduzi wa saratani ya tezi dume yenye kiwango cha juu wakati wa kipimo cha kwanza cha kuchukua nyama kwa wagonjwa wanaohudhuria Hospitali ya Taifa Muhimbili.

Ushiriki wako ni wa namna gani?

Ikiwa utakubali kushiriki katika utafiti, bila shaka baada ya kuwa na viashiria vya saratani ya tezi dume kama vigezo vya kuingia, utaulizwa maswali kuhusu taarifa zako za demografia, historia yako ya matibabu na dalili zako. Baadaye, uzito wako na urefu wako vitapimwa, na matokeo ya uchunguzi wa tezi dume kwa kutumia kidole (DRE), kiwango cha PSA, matokeo ya upimaji wa tezi dume kwa kutumia ultrasound, na matokeo ya tru-cut biopsy yatarekodiwa.

Usiri

Makala za kitambulisho maalum zitatumika badala ya kutumia majina ya washiriki. Taarifa zote zilizokusanywa kwenye maswali na matokeo ya tishu yako yataingizwa kwenye kompyuta yenye kificho cha utambulisho kilichopewa hapo awali. Takwimu za jumla zitatumika ili kuzuia kutambulika kwa washiriki binafsi. Maswali yatafanyiwa kazi kwa siri kubwa ili kuhakikisha kwamba faragha inazingatiwa kipindi chote cha utafiti.

Madhara

Kushiriki katika utafiti huu hakuhusishwi na hatari yoyote inayofahamika. Utafiti huu unajumuisha tu kurekodi taarifa kuhusu maelezo yako ya kidemografia, historia ya matibabu, dalili, BMI, matokeo ya upimaji wa tezi dume kutumia ultrasound, matokeo ya uchunguzi wa kidole kwenye tezi dume (DRE), na matokeo ya kipimo cha tishu ya tezi dume.

Mbadala na haki ya kujitoa

Ushiriki wako kwenye utafiti huu sio wa kulazimishwa. Ukiamua kutoshiriki katika utafiti, bado utaendelea kupokea huduma zote zinazotolewa na hospitali kama kawaida.

Faida

Hakuna faida ya moja kwa moja kwenye ushiriki wako katika utafiti huu zaidi ya kuchangia katika ugunduzi wa mambo yanayohusiana na ugunduzi wa saratani ya tezi dume ya kiwango cha juu. Mambo haya yatacheza jukumu muhimu katika kuunda miongozo katika kufanya maamuzi kuhusu kuchukua vipimo vya tezi dume.

Mawasiliano

Ukiwa na maswali yoyote kuhusu utafiti huu, wasiliana nami Dr. Amini Mitamo Alexandre, namba ya simu +255 767591787.

Ukiwa na maswali kuhusu haki zako kama mshiriki wa utafiti huu, wasiliana na Mkurugenzi wa Utafiti na Ushauri,

Chuo Kikuu cha afya na sayansi shirikishi Muhimbili (MUHAS),

S. L. P 65001,

Dar es Salaam

Sahihi

Mimi ..... nimekubali ushiriki utafiti huu baada ya maswali yangu yote kujibiwa.

Sahihi ya mshiriki.....

Sahihi ya shahidi.....

Tarehe ..../…./2024

Mshiriki ame kubali _____Amekataa _____

Appendix III: Data Collection Tool

Structured Questionnaire

Demographic Information:

1. No: _____
2. MR No: _____
3. Phone number: _____
4. Age: _____
5. Race/Ethnicity: _____
6. Education Level: _____
7. Marital Status: _____
8. Socioeconomic status
    a. Low [ ]
    b. Middle [ ]
    c. High [ ]

Comorbidities:

9. Do you suffer from any of the following diseases?
    a. Hypercholesterolemia [ ]
    b. HIV [ ]
    c. Diabetes [ ]
    d. Infertility [ ]
    e. Hypertension [ ]
    f. Other (to be specified) …….
10. Are you taking any medication?
    a. Yes [ ] Specify _____
    b. No [ ]

Family history:

11. Do you have a family history of prostate cancer?
    a. Yes [ ] Specify the relative affected _____
    b. No [ ]
12. Do you have a family history of breast cancer?
    a. Yes [ ] Specify the relative affected _____
    b. No [ ]

Lifestyle Factors:

13. Do you smoke?
    a. Yes [ ]
    b. No [ ]
14. If yes, please provide the following information:
    a. Age of smoking onset
    b. Number of cigarettes smoked
    c. Age at smoking cessation
15. Do you consume alcohol?
    a. Yes [ ]
    b. No [ ]

Clinical Information (To be completed by the researcher):

16. Reason for admission:
    a. Asymptomatic health check-up [ ]
    b. Low urinary tract symptoms [ ]
    c. Other [ ] Specify: ……
17. Height of the patient in cm: …….
18. Weight of the patient in kg: …….
19. What were the findings of the DRE:

……

……

……

Normal/Abnormal PSA Levels:

20. What is most recent PSA level (ng/mL)? _____
21. When was this PSA measured? (months) _____

Ultrasound (prostate) Imaging:

22. Done
    a. Yes [ ]
    b. No [ ]
23. If done
    a. Prostate size: _____cm^3
    b. Prostate texture and echogenicity:

       _____

Prostate Cancer Diagnosis (Tru-cut biopsy results):

24. Benign Prostate Enlargement [ ]
25. Prostatitis [ ]
26. Prostate cancer [ ]

    A researcher will provide the Gleason score from the Jeeva:

    _____

    a. Low-grade (Gleason score < 7) [ ]
    b. High-grade disease (Gleason score ≥ 7) [ ]

Appendix IV: Ethical Clearances

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/2109 Date: 25/03/2024

MUHAS-REC-03-2024-2109
AMINI MITAMO ALEXANDRE
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: FACTORS ASSOCIATED WITH HIGH-GRADE PROSTATE CANCER DETECTION AT INITIAL BIOPSY IN PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL

Reference is made to the above heading,

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 25/03/2024
EXPIRATION DATE OF APPROVAL: 25/03/2025

STUDY DESCRIPTION:
Purpose:

The purpose of this prospective cross-sectional study is to assess factors associated with the detection of high-grade prostate cancer at the initial biopsy in patients attending Urology clinic at MNH.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided: https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014554.pdf and in the MUHAS archives.

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain Data Transfer Agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain Material Transfer Agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country.
8. Apply for and obtain permission to publish the results from National Institute for Medical Research. The application should be before submitting to a publisher and not concurrently through the email publications@nimr.or.tz.
9. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.



Dr. Nahya Salim Masoud,

Chairperson, MUHAS Research and Ethics Committee

Appendix V: Introduction Letter

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote:
Ref. No. HD/MUH/C.276/2021 28th March, 2024

The Executive Director,
Muhimbili National Hospital-Mloganzila
P.O. Box 65000,
DAR ES SALAAM.

RE: INTRODUCTION LETTER OF AMINI MITAMO ALEXANDRE

We would like to inform you that the carrier of this letter is Amini Mitamo Alexandre with registration number HD/MUH/C.276/2021 a student in the College of Medicine in the School of Medicine at Muhimbili University of Health and Allied Science (MUHAS), pursuing MMed. Urology.

As part of his studies, he will be doing an elective research titled **"Factors Associated with High-Grade Prostate Cancer Detection to Initial Biopsy in Patients Attendign Muhimbili National Hospital".** he is being supervised by Prof. Charles Mkony from MUHAS and Dr. Hamis Juma Idd Isaka from Mloganzila.

The ethical clearance for doing the said research has been given by the University.

Kindly request your assistance and cooperation to our student.

Yours Sincerely,

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

cc: Amini Mitamo Alexandre

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

Appendix VI: Permission Letter

THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

MUHIMBILI NATIONAL HOSPITAL

In reply please quote;

Ref. No.: MNH/CRTCU/Perm/2024/162 Date: 03rd April, 2024

Head of Department,
Urology
Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH

Name Student	**Amini Mitamo Alexandre** HD/MUH/C2762021
Title	**"Factors Associated with High-Grade Prostate Cancer Detection to Initial Biopsy in Patients Attending Muhimbili National Hospital".**
Institution	Muhimbili University of Health and Allied Sciences
Supervisor	Prof. Charles Mkony (MUHAS)
Co – supervisor	Dr. Gabriel Francis Mtaturu (MNH)
Period	03rd April, 2024 to 30th July, 2024

Approval has been granted to the above principal investigators to collect data at MNH. Dissemination of study findings at MNH shall be overseen by **Dr. Gabriel Francis Mtaturu** (MNH) supervisor.

Kindly ensure the named principal investigator abide to the ethical principles and other conditions of the research approval.

Sincerely,

P.O. Box 65000 DAR-ES-SALAAM

Dr. Charles K. Pallangyo
For: Head of Clinical research, Training and Consultancy Unit

c.c DSS,
c.c Dr. Gabriel Francis Mtaturu
c.c **Amini Mitamo Alexandre**

Upanga West, Kalenga Street, Plot No. 10480/3, P.O. BOX 65000, Dar es Salaam, Tanzania.
Telephone: +255-22-2151367-9, Telephone: +255-22-2151351-2
Email: info@mnh.or.tz, Website: www.mnh.or.tz