COLPOSCOPIC AND HISTOPATHOLOGIC COMPARATIVE INTERPRETATIONS AMONG PATIENTS UNDERGOING EVALUATION FOR CERVICAL DYSPLASIA IN WESTERN KENYA.

BY

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DECLARATION

Student declaration

This thesis is my original work and has not been presented for a degree or any other award in any College or University.

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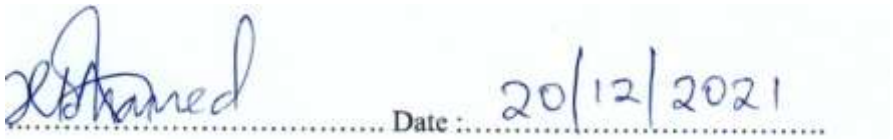
Signature :  Date : 20/12/2021

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LIST OF ABBREVIATIONS

CIN	Cervical Intraepithelial Neoplasia
CIS	Carcinoma In Situ
DNA	Deoxyribonucleic Acid
HPV	Human Papilloma Virus
IREC	Institutional Research Ethics Committee
LEEP	Loop Electrical Excision Procedure
MTRH	Moi Teaching and Referral Hospital
RCI	Reid's Colposcopic Index
SCJ	Squamo-Columnar Junction
VIA	Visual Inspection with Acetic Acid
AIS	Adenocarcinoma In Situ

DEFINITION OF TERMS

Cancer	Cancer is a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/ or spread to other organs.
Cervical Cancer screening	involves applying simple tests or procedures across a healthy population inorder to identify unrecognized cancer disease or pre-cancerous lesions in individuals before they develop any symptoms of the cancer.
Colposcopy	the examination of the epithelia of the cervix, lower genital tract, and anogenital area using magnified illumination after the application of specific solutions to detect abnormal appearances consistent with dysplasia/neoplasia, or to affirm normality.
Dysplasia	is a precancerous condition in which abnormal cell growth occurs on the surface lining of the cervix or endocervical canal, the opening between the uterus and the vagina. It is also called cervical intraepithelial neoplasia (CIN).
Metaplasia	is the conversion of a mature differentiated cell into another form of a mature cell type, often following injury or insult.
Sensitivity	the ability of a test to correctly identify those with the disease (true positive rate)
Specificity	the ability of the test to correctly identify those without the disease (true negative rate)
Leucorrhoea	a whitish or yellowish vaginal discharge
Frank Lesion	fungating growth on the cervix.

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COLPOSCOPIC AND HISTOPATHOLOGIC COMPARATIVE INTERPRETATIONS AMONG PATIENTS UNDERGOING EVALUATION FOR CERVICAL DYSPLASIA IN WESTERN KENYA.

ABSTRACT

Background: Cervical cancer has high morbidity and mortality and in Kenya its second in prevalence and first cause of cancer related mortality. Cervical cancer starts as cervical dysplasia (cervical intraepithelial neoplasia (CIN)) which transform to invasion with time. Early diagnosis of cervical dysplasia utilizes both colposcopy and histopathology. Although histopathology is the gold standard for diagnosing cervical cancer, its access and utility is limited due to both cost and limited expertise. There is also paucity of data on sensitivity and specificity of colposcopy locally.

Objective: To determine the correlation between colposcopic and final histopathologic results amongst patients undergoing a colposcopic evaluation in cervical dysplasia clinics in Western Kenya.

Methods: This was a Cross sectional comparative diagnostic study conducted among 164 women undergoing Colposcopic evaluation across several cervical dysplasia clinics in Western Kenya between august 2019 and august 2020. Institutional ethical approval was sought and informed consent obtained from each participants. A colposcope was used to examine the cervix and findings graded using the modified Reid's colposcopic index. A colposcopy guided punch biopsy was then taken for histopathological evaluation when abnormal area was sited. Descriptive statistical analysis of mean (with corresponding standard deviation) for continuous variables and frequencies (with corresponding proportions) for categorical variables was calculated to determine whether differences across groups were statistically significant ($p \leq 0.05$). Bayesian theorem model was used to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with corresponding 95% confidence interval. A Receiver Operating Characteristics (ROC) curve was plotted as sensitivity against 1-specificity and the area under the curve (AUC) computed. An overall Kappa value was calculated as an estimate of the strength of correlation between colposcopy and histopathology.

Results: Mean age of the study participants was 40.6 years with 64.6% being HIV negative and 134 (81.7%) were premenopausal. Modified Reid's index classified 20.7%, 40.2% and 39.1% as having low grade, intermediate and high-grade cervical dysplasia, respectively. Colposcopy classified 0.6%, 38.4% and 60.1% as normal, CIN 1 and CIN 2/3 respectively. Histopathology classified 16.5%, 26.2%, 53.3% and 3% as having Normal, CIN 1, CIN 2/3, Carcinoma in situ, respectively. Sensitivity of colposcopy with histology as gold standard was 85.3%, specificity was 69.7% and diagnostic accuracy was 80.3%, Positive predictive value (PPV) was 85.3% and Negative predictive value (NPV) was 69.7%. The empirical ROC plot revealed an area under the curve with Optimal Youden's index value of 0.7758. The estimated strength of correlation between colposcopy and biopsy was relatively strong with kappa=0.55.

Conclusions: There were nearly equal proportions of intermediate and high-grade cervical dysplasia when Modified Reid's index was used to classify colposcopy findings whereas histopathology had more than half of all the findings classified as high grade disease (CIN2/3). There is an association between the discriminatory powers of colposcopy and histology but colposcopy had a lower specificity when compared to histopathology.

Recommendations: The study recommends that colposcopy is important in directing biopsy, and histopathology should continue as a gold-standard for cervical cancer diagnosis.Further studies to validate the findings especially controlling for the interobserver variability are recommended.

CHAPTER ONE

1.0 Introduction

1.1Background

Cervical cancer is a consequence of long-term infection with human papillomavirus (HPV). It is ranked 4th in both incidence and cancer-related mortality amongst women with an estimated 569,847 new cases new cases and 311,365 deaths annually globally. This accounts for 13.1% of all new female cancers world-wide. In Eastern Africa, cervical cancer remains the most common cancer in women with estimated age standardized incidence and mortality rates of 40.1 and 30.0 per 100,000 respectively (GLOBOCAN, 2018).

Cervical cancer contributes 5,250 (12.9%) of the new cancer cases annually and 3,286 (11.84%) of all cancer deaths annually in Kenya. It is the leading cause of cancer related deaths in Kenya and the 2nd most common cancer among females. (GLOBOCAN, 2018).

In the year 2018, the World Health Organization developed its global its strategy to accelerate the elimination of cervical cancer as a public health problem. This strategy is made up of three key targets, the 90-70-90 targets to be reached by the year 2030: -

90% of girls to be fully vaccinated with the HPV vaccine by the of 15 years

70% of women to be screened with a high-performance test by 35 years of age and again by 45 years of age.

90% of women identified with cervical disease to receive treatment (90% of women with pre-cancer to be treated and 90% of women with invasive cancer to be managed.)

Cervical cancer is one of the types of cancers that originates in the epithelium of the cervix and that manifests initially through precursor lesions of slow and progressive evolution, these can happen in stages from dysplasia to carcinoma in situ (circumscribed to the epithelial surface) and finally to invasive cancer when the lesion crosses the basement membrane (Barut et al., 2015). Cervical cancer caused by specific strains of Human papilloma virus (HPV) has a global death burden of over 300,000 and is the second cause of cancer mortality among the known types of cancers (de Freitas, Coimbra, & Leitão, 2014).

Cervical cancer screening is the process of detecting abnormal tissue or cells in the cervix before cervical cancer develops (Quinn, Babb, Jones, & Allen, 1999). By aiming to detect and treat cervical neoplasia early on, cervical cancer screening aims at secondary prevention of cervical cancer (Bornstein et al., 2012). There are several methods for screening cervical cancer, which include; cytology/Pap smear test (conventional cytology and liquid based cytology), the HPV DNA testing, and the visual inspection (with acetic acid or with lugols iodine)) (Lee et al., 1997). Cytology have been effectively used in diminishing incidence and mortality rates of cervical cancer in developed countries but not in developing countries (Lee et al., 1997). Prospective screening methods that can be used in low-resource areas in the developing countries are the HPV DNA testing and the visual inspection (Denny et al., 2000). Histopathology or cervical biopsy is a surgical procedure in which a small amount of tissue is removed from the cervix.

The cervix is the lower, narrow end of the uterus located at the end of the vagina (Denny, Quinn, & Sankaranarayanan, 2006). Histopathology/cervical biopsy is done after abnormalities (such as the presence of certain types of HPV(oncogenic subtypes)

which puts one at risk for developing cervical cancer or cells that are precancerous) has been detected during a normal exam or Pap smear (Lee et al., 1997). Histopathology, which involves the examination of biopsy, determines treatment of cancer and precancer by categorizing the patterns of microscopic organization of cells in tissue sections from biopsy or surgical specimens (Vidyadhar et al., 2017). Histopathology remains important as the most widely used clinical endpoints by which the performance of new techniques for cervical cancer prevention are currently evaluated.

Colposcopy on the other hand is the examination of the epithelia of the cervix, lower genital tract, and anogenital area using magnified illumination after the application of specific solutions to detect abnormal appearances consistent with dysplasia or neoplasia, or to affirm normality. Integral to the procedure is targeting biopsies to areas of greatest abnormality (Bornstein et al., 2012).

There are four basic colposcopic diagnoses: (i) Normal (ii) low-grade disease (HPV infection/CIN 1), (iii) (major) high-grade disease (CIN 2 or CIN 3), (iv) Invasive cancer (Mayrand et al., 2007). Colposcopic grading systems e.g. Reid and Swede have been developed to provide an objective, accurate, reproducible, and clinically meaningful prediction of the severity of CIN lesions based on discriminatory analysis of specific colposcopic signs (Reid, Stanhope, Herschman, Crum, & Agronow, 1984). Colposcopy and if needed directed biopsy will pick up the maximum number of cases of premalignant lesions & thus will help to reduce the disease related mortality and morbidity. Colposcopic grading using modified Reid's index makes colposcopy less subjective as it relies on critical analysis rather than pattern recall serving as a meaningful guide to histopathological severity. The biopsy specimen obtained during colposcopy are all submitted for histopathological interpretation. Over time, some

well-defined precursor lesions may develop into cervical cancer. This implies that the detection of precancerous lesions is of maximum importance when it comes to the prevention and treatment of cervical cancer. However, statistics have identified that over 570,000 women all over the world were diagnosed with cancer in 2018, where cervical cancer claimed over 6.6% of the total findings (Barut et al., 2015).

At the MTRH cervical dysplasia clinic and its satellite clinics in Western Kenya, colposcopy is usually performed when the patient had already undergone cervical cancer screening and had a positive screening results, either a positive aceto-white lesion upon performing visual inspection with acetic acid or had been referred from facilities with positive cytology results. Some patients are also referred to the clinic with unexplained, persistent vaginal discharge with a strong odor smell for assessment by colposcopy to exclude a neoplastic cause. Other indications include vulvar or vaginal neoplasia, or condylomata acuminata. Therefore, the aim of this study was to determine the colposcopic-histologic correlation among patients undergoing a colposcopic evaluation at Moi Teaching and Referral Hospital (MTRH) cervical dysplasia clinic.

1.2 Problem Statement

Cervical cancer has high morbidity and mortality and in kenya its second in prevalence and first cause of cancer related mortality (GLOBOCAN 2020). Cervical cancer has a long latent phase and can be prevented and cured if detected early. The primary method for cervical cancer prevention is through vaccination against Human Papillomavirus (HPV), while the secondary method of cervical cancer prevention is through cervical cancer screening (kaban 2015). Cervical cancer initially presents as cervical dysplasia which may transform into cervical cancer. The diagnosis of cervical

dysplasia utilizes both colposcopy and histopathology to inform patient management. Although histopathology is the gold standard for diagnosing cervical cancer, its access and utility is limited due to both cost and limited expertise. There is also paucity of data on the sensitivity and specificity of Colposcopy locally. Hence the need to determine the Sensitivity and Specificity of Colposcopy.

1.3 Justification of the Study

Colposcopy and Histopathology serves as a diagnostic tool following cervical cancer screening. The colposcope consists of a stereoscopic viewing system with magnification and high intensity halogen light. Colposcopy allows examination of the lower genital tract and anus to further evaluate abnormal findings gotten from screening meaning methods. Colposcopy guided punch biopsies are taken upon siting of an abnormal area which are then taken for histopathology to confirm absence or presence of a disease (Verma, 2018). The study was conducted among women undergoing colposcopy and histopathology in several cervical dysplasia clinics in western Kenya under the AMPATH Cervical Cancer Program. In Western Kenya, majority of the facilities performing cervical cancer screening do have a functioning colposcope. The findings from this study will inform on the sensitivity and specificity of colposcopy in western Kenya. This will help in improving in the screening and diagnosis of cervical dysplasia and cervical cancer. In resource limited areas like in Western Kenya, it is important to implement an appropriate cervical cancer screening and diagnosis program. Determining the sensitivity and specificity of colposcopy will further strengthen to implement the recommended detect-and-treat strategy as per W.H.O plan to eliminate Cervical cancer by 2030. Hence the main aim of this study was to determine the correlation between colposcopic and final histopathologic result

amongst patients undergoing a colposcopic evaluation in western Kenya cervical dysplasia clinic.

1.4 Research Questions

i. What are the findings of the colposcopy tests carried out?

ii. What are the findings of histology tests carried out?

iii. How sensitive and specific is the colposcopy screening using the Modified Reid's Index.

1.5 Objectives

1.5.1 General objective

To determine the correlation between colposcopic and final histopathologic result amongst patients undergoing a colposcopic evaluation in western Kenya cervical dysplasia clinic.

1.5.2 Specific Objectives

i. To describe the colposcopy findings using modified Reid's index among patients undergoing colposcopy in western Kenya cervical dysplasia clinic.

ii. To describe the histopathological findings among patients undergoing colposcopy and biopsy in western Kenya cervical dysplasia clinic.

iii. To determine the sensitivity, specificity, diagnostic accuracy, positive and negative predictive value of colposcopy findings among patients undergoing colposcopy and biopsy in western Kenya cervical dysplasia clinic.

CHAPTER TWO

2.0 Literature Review

2.1Introduction

In Kenya, Screening programmes continue to have a vital role, it allows for early detection and treatment in order to achieve a maximal impact on cervical cancer prevention. The natural history of cervical cancer is many years to decades, with a long precancerous, preclinical phase, allowing for testing (screening) for precancerous lesions and cancer. When screening detects precancerous lesions, these can easily be treated and cancer avoided. Screening can also detect cancer at an early stage, enabling women to receive treatment when it is highly effective (WHO, 2014). The increasing availability of HPV vaccination for girls and the potential for reduction of the possibility of developing cervical cancer later in life, however, does not eliminate the need for regular screening when women get older.

The success of a screening programme in reaching its aims is dependent on achieving adequate coverage. While the screening programme will be introduced incrementally depending on health service capacity, the ultimate goal is to screen at least 70% of women, nationally, within the target age group within 10 years of initiating the programme (Sonali et al, 2014.)

Colposcopy is an outpatient procedure that is simple, quick, and well-tolerated. It allows examination of the lower genital tract and anus with a microscope to further evaluate abnormal Pap test results and visible epithelial abnormalities. This allows identification and management of premalignant lesions. Colposcopic examination of the cervix remains the clinical standard in the evaluation of patients with abnormal cervical cytology. However, its sensitivity, interobserver agreement, and reproducibility have recently come into question (Kaban, 2015).

There are many styles of colposcopes, but they all operate similarly. The colposcope consists of a stereoscopic viewing system with magnification settings ranging from three- to 40-fold attached to a freely moveable stand. A high-intensity halogen light provides illumination. Use of a green (red-free) light filter emphasizes contrast by causing the color red to appear black, aiding the examination of vascular patterns (Vidyadhar et al., 2017).

2.2 Cervical cancer

Cervical cancer has been identified to be the second most common type of gynecologic cancer and it accounts for as much as 13% of all female cancer infections in developing countries (Anand et al., 2008). Among the reasons that have contributed to a higher number of cervical cancer infections among the developing countries include the higher rates of poverty (Bosch & de Sanjosé, 2007). This implies that individuals from these nations have inadequate resources that are required in the diagnosis and treatment of the disease. Other reasons for the increased cases are lack of effective and convenient programs for screening purposes as well as poorly managed and organized health systems (Koutsky et al., 1992). This makes the detection of the precancerous condition before it progresses into invasive cancer almost impossible.

Human papillomavirus infection (HPV) causes more than 90% of cases, most people who have had HPV infections, however, do not develop cervical cancer (Bast Jr et al., 2017). Smoking, weak immune system, use of birth control pills, early sexual debut, and having many sexual partners are some of the risk factors, but seems to be less important. Cervical cancer typically develops from precancerous changes over 10 to 20 years (Dunne & Park, 2013). Over 90% of cervical cancer cases are as a result of uncontrolled growth of abnormal cervical cells, whereas 10% is attributed to

adenocarcinoma and a small number are other types. Diagnosis of this type of cancer is through cervical screening to check for any changes in the cervix followed by a biopsy. Medical imaging is then done to determine whether or not the cancer has spread (Anand et al., 2008; Tran et al., 2014).

HPV vaccines protect against between two and seven high-risk strains of this family of viruses and may prevent up to 90% of cervical cancers (Tran et al., 2014). Because the risk of cancer exists, it is recommended that women of reproductive age to undergo continuous regular Pap tests. Having few or no sexual partners and the use of condoms are some of the ways in which transmission of HPV can be reduced, eventually reducing the burden of cervical cancer. Cervical cancer test such as the Pap test or acetic acid screening can identify precancerous changes in the cervix. When detected early, treatment can prevent the development of cancer. Treatment of cervical cancer may consist of some combination of surgery, chemotherapy, and radiation therapy (Karimi-zarchi et al., 2015).

2.3 Methods of screening for cervical cancers

Cervical screening is the process of detecting and removing abnormal tissue or cells in the cervix before cervical cancer develops (Agyemang-Yeboah et al., 2017). By aiming to detect and treat precancerous cells early on, cervical screening aims at secondary prevention of cervical cancer. There are several methods which are used to detect cancer of the cervix. The methods include: Pap test (also known as Pap smear) which includes conventional cytology and liquid-based cytology, the HPV DNA testing and the visual inspection with acetic acid (Boicea et al., 2012). The first two methods (Conventional cytology and liquid-based cytology) have been effective in detecting precancerous cells diminishing incidence and mortality rates of cervical

cancer in developed countries (Quinn et al., 1999). In the developing countries (low-resource areas), screening methods that can be used include; HPV DNA testing, Cytology and visual inspection.

2.3.1Conventional cytology

This type involves collecting cell smears from the cervix. The smears are then fixed on a microscopic glass slide before sending them for evaluation in the laboratory (Bornstein et al., 2012). This method is commonly referred to as pap smear. This method has a sensitivity and specificity of 72% and 94% respectively (Parvin, Alam, Talukder, & Alam, 2018). Since early 1950s, Papanicolaou (pap smear) tests have been effectively used in detecting cervical cancer due to its cost-effectiveness. Since its invention, it has significantly reduced the mortality of cancer among women as it could be detected early enough before the cancer cells spreads (de Freitas et al., 2014; Karimi-zarchi et al., 2015). Ever since its development, the test has managed to decrease the rate of cervical cancer by approximately 79%. This has, in turn, helped to reduce the rates of mortality cases that are related to cervical cancer by as much as 70%. The sensitivity of the Pap test has been identified to be 51% (Barut et al., 2015). In addition, the sensitivity and specificity of this test in detecting high-grade lesions has been shown to be approximately 55.4% and 96.8% for CIN II and CIN III respectively (Massad & Collins, 2003). However, the sensitivity and specificity of pap smear is low as it could miss some cases during diagnosis. The incidences of cervical cancer were reported in patients who were undergoing frequent pap smear tests (Koutsky et al., 1992). In the diagnosis and treatment of cervical cancer, high percentages of sensitivity and specificity in colposcopy reflect a higher degree of accuracy (Boicea et al., 2012). Therefore, it becomes easier to determine the presence or absence of the infestation, which in turn, facilitates the treatment of the same. This

disadvantage calls for a more rapid and sensitive test in detection of the HPV oncoproteins.

2.3.2 Liquid-based monolayer cytology

There are two of the types of monolayer cytology the are currently used: Sure-Path (TriPath Imaging) and Thin-Prep (Cytyc Corp) (Karimi-zarchi et al., 2015), Sure-Path uses ethanol-based media whereas ThinPrep uses methanol media preparations. The principle behind these techniques are based on placing the sample into a vial containing a liquid medium that preserves the cells have been increasingly used (Massad & Collins, 2003). These liquid sample preparations has the advantage of being suitable for high-risk HPV testing with an eventuality of reducing unsatisfactory specimens from 4.1% to 2.6% (Dunne & Park, 2013). For a higher accuracy of the test, it is of paramount importance to have proper sample acquisition, as a cell that is not in the sample cannot be evaluated. This technique has a sensitivity and specificity of 61%- 66% and 82%- 91% respectively (Bast Jr et al., 2017).

2.3.3Visual Inspection Methods

Visual Inspection with acetic acid (VIA) is a visual examination of the uterine cervix after application of 3-5% acetic acid (Ajenifuja et al., 2013). Whenever the cervical epithelium contains an abnormal/irregular load of cellular proteins, it will result in coagulation of acetic acid with the proteins, forming an opaque and white aspect of the concerned area (Almonte et al., 2007). A precancerous lesion is known to have higher protein content when compared to normal epithelium. As a result, it becomes white/acetowhite (VIA positive) (Ajenifuja et al., 2013).

Visual Inspection with Lugol's iodine (VILI) is a visual examination which is generally performed after the VIA test and requires the application of Lugol's iodine, a compound that reacts with glycogen resulting in a brown or black coloration (Sankaranarayanan et al., 2003). The normal mature squamous epithelium contains glycogen, resulting into a black formation when in contact with Lugol's iodine, whereas precancerous lesions and cancer contain little or no glycogen thus turning yellow after Lugol application (VILI positive) (Almonte et al., 2007).

2.3.4 Human papillomavirus DNA testing

Human papillomavirus (HPV) infection is the primary cause of nearly all cases of cervical cancer with only specific virus which produce oncogenic proteins which are necessary for the abnormal growth of cells in the cervix, resulting into cancer if not detected and treated early (Bosch & de Sanjosé, 2007). Similar to some other groups of viruses, most women will successfully clear HPV infections in less than 2 years. Not all HPV viruses results into cancer, some are benign (do not produce oncogenic proteins) such as those which cause genital warts (type 6 and 11) (Bosch & de Sanjosé, 2007). It is thought that a prolonged infection with a high-risk type (e.g. types 16, 18, 31, 45) are more likely to develop precancerous, due to the effects that HPV has on DNA (Bosch & de Sanjosé, 2007). HPV triage is currently being used in majority of the western countries in its screening program, if the first/initial screening test shows borderline results or low-grade abnormal cells, a further test for HPV is recommended on the sample (Manos et al., 1999). Whenever HPV is present, the patient is requested for a further examination as a tie-breaker. If the test turns negative for HPV, the patient resumes the usual screening schedule as if no abnormalities had been found. Studies conducted on this method have a shown a sensitivity and specificity of 88% - 91% and 97% respectively (Mayrand et al., 2007).

2.3.5 Colposcopy

Colposcopic examinations include: Direct examination of cervix with green filter and saline application; Examination of the cervix after test with 3% acetic acid, seeing the junction of squamous cell, erosion, papillary lesions, aceto-white areas and vascular design; Examination of the cervix after Lugol test in which normal squamous epithelium, which contains glycogen, it turns brown (Reid & Scalzi, 1985). The colposcopic findings are classified into non-malignant and malignant categories. The non-malignant category includes: normal findings or viral wart changes, and the malignant category will be divided into five groups: CIN I, CIN II, CIN III, micro-invasive carcinoma and CIS (Reid et al., 1984).

Studies have found out that the performance as well as the accuracy of colposcopy mainly depends on the training and experience and the screening skills that the colposcopist possesses. As a result, the sensitivity and the specificity of the tests vary from one region to the other depending on the skills of the colposcopist (Boicea et al., 2012). In a number of meta-analysis, the researchers, Mitchell and his colleagues, carried out a study with the aim of distinguishing normal cervix from the rest of other diagnosis. They found the individual approximation of the sensitivity of the colposcopy diagnostic screens whereby the highest sensitivity ranges were identified to be 87%-99% while the lower specificities were observed to be 23%-87% (Mitchell, Schottenfeld, Tortolero-Luna, Cantor, & Richards-Kortum, 1998). It is estimated that in every 4 out of 10 women that undergo colposcopy do have a normal result (Karimi-zarchi et al., 2015). This indicates that no abnormal cells are found in the cervix during the colposcopy. This implies that one does not require immediate treatment. Other similar studies were also conducted with the aim of distinguishing normal cervix and atypia. Here, the highest sensitivity in the diagnostic colposcopy was found

to range from 64% to 99% while those of specificity fell between 30 to 93%. In their research, Masaad and Collins found out that the sensitivity of colposcopy was 89% but it could also fall to the level of 56% upon the raising of a high-grade result (Massad & Collins, 2003).

Colposcopy provides results that are of higher accuracy which is easily confirmed by their percentages (Barut et al., 2015; Karimi-zarchi et al., 2015). Considering that colposcopy is a subjective assessment, in most cases, not all abnormalities may have distinctive appearances. The greatest challenge when using colposcopy often arises when differentiating between CIN II and III (Mayrand et al., 2007). However, considering all options, the specificity of screening and diagnosis by colposcopy can only be termed to be of secondary significance. This is because, in most cases, any patient who gets screened and is found to be malignant is further advised to undergo a biopsy where she is given the relevant and appropriate treatment regardless of the different inaccuracies in the categorization of the cancer infection. Women who come from low-income developing countries are referred to colposcopy based on the visual screening methods which possess a higher rate of positivity since they are highly economical, hence affordable (Vidyadhar et al., 2017). There are various side effects that are associated with the process. They include bleeding, abdominal pains, and one can also get an infection from the process. These side effects are easy to manage. This, therefore proofs that colposcopy is rather beneficial compared to other screening methods. Having the process conducted by a well-trained colposcopist is important as he/she will know on how to mitigate the side effects. The colposcopist should be able to understand the concerns of the patient and advice the patient on the best procedure to undertake if the risk of complications and side effects are high on the patient. The colposcopist should also provide the patient with various instructions that she needs to

follow after the procedure, especially on having sexual intercourse. This will reduce the chances of an infection and reduce pains after the procedure.

A prospective cross sectional study on Evaluation of Reid's Combined Colposcopic Index as a predictor of cervical intraepithelial lesion that was conducted adult married women attending gynae OPD in MDOH, Ludhiana, Punjab, India, concluded that Predictive accuracy of colposcopy increased with increasing severity of disease. Doing colposcopy as a primary screening modality can be helpful in low recourse settings and developing countries where the patient compliance is poor. Using a scoring system like RCI can help us in studying the different changes in the cervix. The study recommended that recommend colposcopic evaluation of suspicious cervix found on clinical examination and do the directed biopsy to reach the final diagnosis (Verma et al, 2018).

In a study on role of colposcopy using modified reid's index in screening of cervical cancer in women with abnormal cervix on naked eye examination carried in government medical college & hospital, Aurangabad from November 2011 to November 2012, it was concluded that colposcopy with high sensitivity & specificity is a good screening tool in cervical cancer especially in high grade lesions but comparatively low specificity in low grade histological lesions will cause overestimation of diagnosis. Also the limiting factor is that the accuracy of the method is directly related to the expertise of its operator (Sonali et al, 2014).

A prospective comparative study titled Comparison of Diagnostic Accuracy of Colposcopic Findings Using Modified Reid Colposcopic Index with Histopathology in Cervical Lesions carried out in the Department of Pathology, K.V.G Medical College, Sullia, D.K, from January 2015 to June 2016, This study demonstrated high accuracy and correlation between colposcopy and histopathology. There were cases of

under and over diagnosis, so the benefit of colposcopy and directed biopsy is helpful to avoid over treatment of low-grade lesion and under treatment of high-grade lesion (Navya et al, 2016.

In a prospective clinical study “Colposcopic evaluation of unhealthy cervix and its correlation with Papanicolau smear in cervical cancer screening” done at Government Medical College, Aurangabad, Maharashtra, India from May 2012 to Nov 2014 on 100 women with unhealthy cervix on naked eye examination and abnormal symptoms, it was noted that Both PAP smear and colposcopy can be used reliably to screen women having abnormal symptoms for diagnosing premalignant lesions. Critical evaluation of the statistical analysis says that colposcopy can be used as a better tool than PAP smear for diagnosis of precursors of carcinoma of cervix. However, the accuracy of colposcopy is dependent on the training, expertise and skill of the Operator with emphasizes proper training, certification and experience of Colposcopist. Colposcopy eliminates the need for repeated follow up as in PAP smear which has low sensitivity. As the number of cases studied is less, more cases should be studied for better conclusions. Histo-pathology of suspected lesion remains gold standard for final diagnosis of precancerous lesions, in view of the false positive and false negative cases in this study (Kalyankar et. al, 2017).

A prospective study to evaluate the correlation between Reid Colposcopic impression and biopsy histology conducted at Vali-e-Asr university hospital in Tehran, Iran, between March 2004 and October 2005 on a sample of 344 women, it was noted that the investigations performed have shown good correlation between colposcopic impression and histological diagnosis. Hence, further study is required to identify clinical situation in which discrepancies between colposcopy and biopsy are most

likely to occur, to determine the most appropriate role for colposcopic grading in patient management (Mousavi, 2007).

In a study on the agreement between colposcopy results using the Reid Colposcopic index and histopathology using a sample of 105 women, a prospective cross-sectional study conducted between June 2011 and September 2011 at the colposcopy unit of the obstetrics and gynaecology clinic of the Bakirkoy Dr Sadi Konuk Training and Research Hospital, it was concluded that Colposcopy is an essential tool for identifying precancerous lesions. High compliance between histopathology and screening using RCI enables every Gynaecologist to use this method, which can easily be integrated into colposcopy clinics. At present, colposcopy is widely used as a secondary diagnostic tool to identify pre-invasive and invasive cervical diseases in women with positive pap smear results, but not as the primary screening tool. Colposcopy is important for estimating suspicious areas of the cervix in order to provide histologic evidence. However, it has no diagnostic value to replace histologic evaluation. Although colposcopy is proven secondary diagnostic modality, it has many limitations, and its value depends upon the experience and the skill of the colposcopist. The use of a scoring system may improve the quality of colposcopy, yet fast and reliable criteria are needed to make biopsies a daily practice in the most critical areas (Kaban et al, 2015).

CHAPTER THREE

3.0 METHODOLOGY

3.1Study site

The study was conducted at the Chandaria Cancer and Chronic Disease Center at Moi Teaching and Referral Hospital and its satellite cervical dysplasia clinics in western Kenya (Busia Referral Hospital, Chulaimbo Sub County Hospital, Webuye Sub County Hospital and Kitale County Referral Hospital). AMPATH Cervical Cancer Program (ACCP) clinic is based at the cancer centre and screens approximately 350-400 women per month. Out of these, 33 undergo colposcopic evaluation and after which colposcopic guided biopsies are performed. The clinic began in 2010 at AMPATH. The clinic was then shifted to the cancer centre at Chandaria in 2015 upon completion of the Chandaria Cancer and Chronic Disease Centre. The department had two nurses and two research assistants at the time of this study. The two nurses had been well trained in doing screening for cervical cancer, taking biopsies and performing LEEPs. The satellite clinics located in western Kenya still ran under the AMPATH Cervical Cancer Program and each had atleast a nurse and research assistant.

3.2 Study design

This is a cross sectional study design which was conducted at the Cervical Cancer Screening Clinic located within Chandaria Cancer and Chronic Disease Center in Moi Teaching and Referral Hospital (MTRH), in Eldoret, Kenya and its satellite cervical dysplasia clinics in western Kenya.

3.3 Study population

The study population involved women who had been scheduled for Colposcopic evaluation at MTRH cervical dysplasia clinic and its satellite cervical dysplasia clinics in western kenya because of the following reasons; acetopositivity on visual inspection with acetic acid (VIA), suspicious looking cervix (suspicious for malignancy), CIN1/CIN2/CIN3 on cytology, invasive carcinoma on cytology, persistent CIN1 for more than 12-18 months on cytology, persistent leucorrhoea and postcoital bleeding.

3.4 Sample size

The computation of the number of subjects required for this study was based on the prevalence of cervical cancer in the population, expected sensitivity of colposcopy and the expected marginal error of the estimate. There was no locally documented evidence of the prevalence, sensitivity and specificity of colposcopy as a diagnostic approach to cervical cancer hence the estimation of sensitivity and specificity was computed through calculation of the mean specificity and sensitivity obtained from the following three studies:

1. Comparison of Diagnostic Accuracy of Colposcopic Findings Using Modified Reid Colposcopic Index with Histopathology in Cervical Lesions by Dr. Navya BN 1, Dr.Rashmi B2 , Dr.Ravikanth Go3 and Dr. Sathyavathi R Alva (Sensitivity = 92.0%, Specificity = 90.48%)

2.A prospective study to evaluate correlation between Reid's Colposcopic Index impression and biopsy histology by Sonal Kulshreshtha1, Richa Chouksey2 and Pratibha Garg3 (Sensitivity = 43.2%, Specificity = 95.2%)

3.Evaluation of Reid's Combined Colposcopic Index as a predictor of cervical intraepithelial lesion by Indu Verma, Pratibha Pundhir, Tejinder Kaur, Veena Jain and Dinesh Sood (Sensitivity = 50.0%, Specificity = 100.0%)

The total sample size was computed based on the Hurley's formula.

$$n^{Se} = \frac{(Z_{\frac{\alpha}{2}})^2 * \text{Se}\,(1 - \text{Se})}{\text{d}^2 * (1 - \text{Prevalence})}$$

$$n^{Sp} = \frac{(Z_{\frac{\alpha}{2}})^2 * \text{Sp}\,(1 - \text{Sp})}{\text{d}^2 * (1 - \text{Prevalence})}$$

The mean sensitivity and specificity from the three studies was 61.7% and 95.23% respectively. The margin of error for sensitivity and specificity was obtained through calculation of the standard deviations associated with the computed means. These were 21.58% and 4.62% respectively. The margin of error was therefore approximated at 20% and 5% respectively as shown in the equations below.

$$n^{Se} = \frac{(1.96)^2 * 0.617\,(1 - 0.617)}{0.20^2(1 - 0.5)} = 45\ \text{Subjects}$$

$$n^{Se} = \frac{(1.96)^2 * 0.952\,(1 - 0.952)}{0.0482^2(1 - 0.5)} = 165\ \text{Subjects}$$

The sample size required to perform a specificity and sensitivity analysis would be 45 and 165 subjects respectively. A larger value of 165 subjects was therefore adopted for this study since it involved both sensitivity and specificity.

3.5 Eligibility criteria

3.5.1 Inclusion Criteria

- Women who were scheduled for Colposcopy

3.5.2Exclusion Criteria

- Women who bled at the time of examination
- Women who had Frank lesion
- Women who were previously treated for carcinoma cervix, who have had procedures like LEEP, cryotherapy and radiotherapy
- Women who were pregnant at the time of the study

3.6 Study procedures

The potential study subjects were reassessed to ascertain that they qualified for the study as per the inclusion and exclusion criteria in the eligibility criteria section. The subjects were then provided with all the relevant information pertaining to the study in either English or Swahili language. All the subjects in the study understood English, Swahili or both hence there was no incident where a translator was needed. Subsequent to this, each subject was given a chance to ask any question and front comments on any issue that was not clear. The subjects who met the eligibility criteria were then requested to express their decision to participate in the study by signing an informed consent form. An informed consent was considered to have been duly signed if and only if a subject appended his signature or the left hand thumb print to it. Only the subjects who had met the eligibility criteria and signed the consent form were enrolled into the study. This sequence of events was replicated in all subjects until the requisite sample size was attained.

Client recruitment was done by consecutive sampling. All eligible clients were enrolled during the study period until the desired sample size of 165 was attained.

This minimized selection bias by consecutively recruiting any client who met the inclusion criteria. Upon fulfilling the inclusion criteria, the patient underwent colposcopy. The patient was made to lie in lithotomy position on the examination table. A speculum was then placed in the vagina to help visualize the cervix. The Gyn Oncologists or the clinical fellow doctor used a Colposcope to examine the cervix and the findings recorded using the Modified Reid's Index. The Modified Reid's Index gave a systematic and objective method of grading the severity of premalignant cervical lesions through four colposcopic signs: lesion margin, color of aceto whitening, blood vessels, and iodine staining. Colposcopic diagnosis was made based on RCI. The total score for detecting the lesion were as follows: 0–2, low grade lesion (likely to be CIN 1): 3–4, intermediate grade (likely to be CIN 1 or CIN 2): 5–8, high grade lesion (likely to be CIN 2 or CIN 3) (Reid et al., 1984). The colposcope consists of a stereoscopic viewing system with magnification settings ranging from three to-fourty fold attached to a freely moveable stand. A high intensity halogen light provided illumination. Use of a green (red-free) light filter empahasizes contrast by causing the colour red to appear black, aiding the examination of vascular patterns. Colposcopic examinations included: Direct examination of cervix with green filter and saline application; Examination of the cervix after test with 3% acetic acid, seeing the junction of squamous cell, erosion, papillary lesions, aceto-white areas and vascular design; Examination of the cervix after Lugol test in which normal squamous epithelium cells, which contains glycogen, turned brown. The colposcopic findings were classified into non-malignant and malignant categories. The non-malignant category included normal findings or viral wart changes. The malignant category was divided into five groups namely CIN I, CIN II, CIN III, micro-invasive carcinoma and CIS. A biopsy (removal of a small piece of tissue) was done if an abnormal area was

sighted. The tissue would then be sent to the MTRH laboratory for examination under a microscope. A biopsy served as the gold standard in determining if an abnormal area was a pre-cancer, a true cancer, or neither. Normal looking cervix on colposcopy was not subjected to biopsy.

3.7 Data Variables

The main outcome of interest in this study was the cervical cancer classification as per colposcopy results. The main exposure of interest was the cervical precancerous classification as per histology results. Colposcopy was the test and histology the disease. The combination of the two into a 2 x 2 table yielded a confusion matrix of True Positives, False Positives, False Negatives and True Negatives which was then used to compute measures of accuracy and effectiveness that were earlier stated in the research design section. Other variables of interest were the socio-demographic parameters.

3.8 Data Collection Procedure

This was a sensitivity specificity study that aimed to compare colposcopy assessment technique to histology as the standard technique. After enrolment into the study, the socio-demographic characteristics of the patient were recorded. This included the age, last menstrual period, menopausal status, parity, and gravidity. Further information on colposcopy and histology assessment was collected and recorded as per the data collection form in the Appendix section. Grading of colposcopy results was based on the Modified Reid's Colposcopic index/ Score (RCI). The index gave a systematic and objective method of grading the severity of premalignant cervical lesions through four colposcopic signs: lesion margin, color of ace to whitening, blood vessels, and iodine staining.

3.9 Data Quality Assurance

Data was collected by trained research assistants. Their task involved ensuring that the data collection form was fully filled and that all the relevant information was collected. The research assistants were subjected to a two-week-long data collection test run to ascertain that they were conversant with all that was expected from them. This was done under the close guidance and supervision of the principal investigator to ensure quality data was collected. Moreover, designing of the data collection form, the actual data collection and data entry process were all designed and conducted electronically using EpiData Version 3.1 software. This ensured that relevant data was collected by raising pop-up alerts whenever a wrong entry was made.

3.10 Data Management and Analysis

The accuracy and effectiveness of colposcopy as the test method against histology as the standard method was done via computation of the measures of accuracy namely apparent prevalence, true prevalence, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio test and negative likelihood ratio test. These measures were computed from the resultant true positives, false positives, true negatives and false negatives that had been obtained from the results of colposcopy and histology as per the equations stated below.

- True Positive (TP) = Number of Positives for both Colposcopy and Histology
- False Positive (FP) = Number of Positives for Colposcopy but Negative for Histology
- True Negative (TN) = Number of Negatives for both Colposcopy and Histology
- False Negative (FN) = Number of Negatives for Colposcopy but Positive for Histology

$$\text{Apparent Prevalence} = \text{Prevalence as per Test Resuts}$$

$$= \frac{(\text{TP} + \text{FP})}{\text{Total no. of Subjects}}$$

$$\text{True Prevalence} = \text{Prevalence as per Test Resuts} = \frac{(\text{TP} + \text{FN})}{\text{Total no. of Subjects}}$$

$$\text{Sensitivity (Se)} = \text{Colpo} + \text{ve}|\ \text{Histo} + \text{ve} = \frac{(\text{TP})}{(\text{TP} + \text{FN})}$$

$$\text{Specificity (Sp)} = \text{Colpo} - \text{ve}|\ \text{Histo} - \text{ve} = \frac{(\text{TN})}{(\text{FP} + \text{TN})}$$

$$\text{Positive Predictive Value (PPV)} = \text{Histo} + \text{ve}|\ \text{Colpo} + \text{ve} = \frac{(\text{TP})}{(\text{TP} + \text{FP})}$$

$$\text{Negative Predictive Value (PPV)} = \text{Histo} - \text{ve}|\ \text{Colpo} - \text{ve} = \frac{(\text{TN})}{(\text{FN} + \text{FP})}$$

$$\text{Positive Likelihood Ratio (PLR)} = \frac{(\text{Colpo} + \text{ve}|\ \text{Histo} + \text{ve})}{(\text{Colpo} + \text{ve}|\ \text{Histo} - \text{ve})} = \frac{(\text{Se})}{(1 - \text{Sp})}$$

$$\text{Negative Likelihood Ratio (NLR)} = \frac{(\text{Colpo} - \text{ve}|\ \text{Histo} + \text{ve})}{(\text{Colpo} - \text{ve}|\ \text{Histo} - \text{ve})} = \frac{(1 - \text{Se})}{(\text{Sp})}$$

Association between results obtained from colposcopy as the method under evaluation and histology as the standard diagnosis method was estimated through computation of odds ratios, their confidence interval and p-values. Analysis was computed in R Studio version 1.2.1335 statistical software. Statistical significance was determined at 95% confidence interval and critical p-value of 0.05.

3.11 Control of Biases and Errors

All the research subjects were assigned a unique code to conceal their identity. The research assistants were then given the results of colposcopy examination after which the samples for biopsy were obtained from the subjects. A second unique identity that matched the first one was assigned to each biopsy sample. Nevertheless, to control

bias, it is only the principal investigator who knew the colposcopy result that matched each biopsy. It was therefore the responsibility of the principal investigator, and not the research assistants, to match the results of histology to colposcopy. The statistician was blinded in all these processes and only came in at the point of data cleaning and analysis. Errors were controlled by training the research assistants on data collection and entry. Data was also collected electronically with pop up alerts included whenever a wrong entry was made. Lastly, the research assistants underwent a two-week-long data collection test run to ascertain their data collection capability.

3.12 Pilot study

Prior to commencement of this study, a pilot study was conducted to validate the data collection tools and also to compare results from colposcopic and histopathologic interpretations among patients udergoing screening for cervical dysplasia at MTRH. Five women were recruited for the pilot study.

3.13 Ethical consideration

Ethical approval was sought and obtained from IREC before commencing the study. Duly signed informed consent were obtained from the patients before they were included in the study. Participation in the study was voluntary and the participant reserved the right to withdraw their participation at any stage of the interview. The names of the patient were not included on the sample collected. The samples were identified only by the code and date of collection. Written documents for the study were kept in locked offices while any data stored on computers was assigned a security code. Only the research team and service provider had access to client's name and the study results. Publications and/or presentations that resulted from this study concealed the identity of the client's name.

CHAPTER FOUR

4.0 RESULTS

4.1 Socio – Demographic Characteristics

The pie chart below depicts the distribution of patients among Western Kenya clinics.

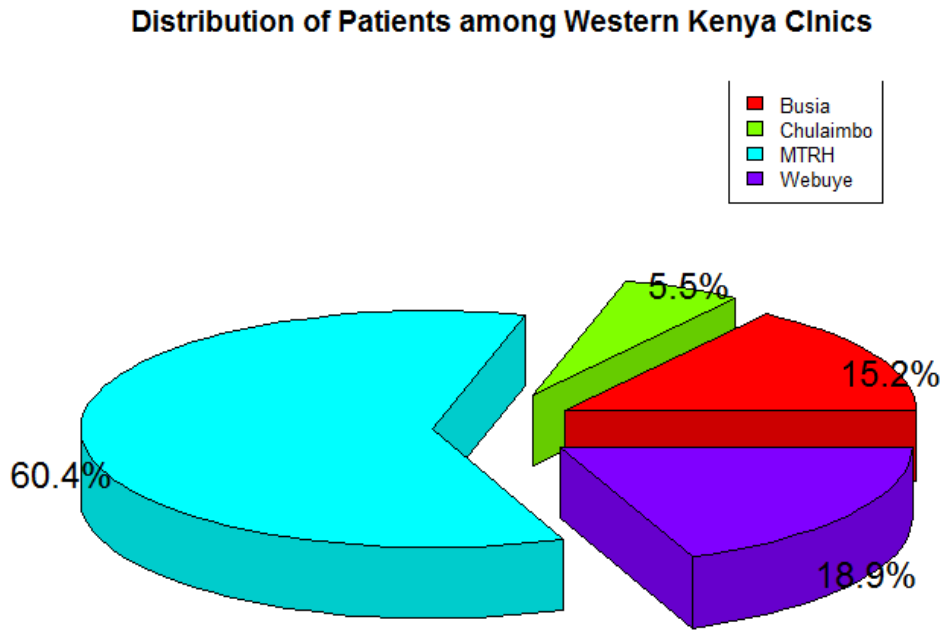

Figure 1: Distribution of patients among Western Kenya Clinics

This study involved 164 patients with a mean age of 40.6 years. Majority, 99 (60.4 %), were screened at MTRH while the rest 25 (15.2%), 9 (5.5%), 99 (60.4 %) and 31 (18.9%) were screened from Busia, Chulaimbo, MTRH and Webuye hospitals in that order.

Table 1 below summarizes the information on socio-demographic characteristics of the study patients.

Table 1: Socio – Demographic Characteristics of the Study Participants

Characteristic	Category	Freq, n = 164 (%)
Marital Status	Single Married Divorced	27 (16.5) 131 (79.9) 6 (3.6)
Education	Primary Secondary Tertiary	85 (51.8) 38 (23.2) 41 (25.0)
Visit	New Revisit	156 (95.1) 6 (3.7)
Post Menopausal	Yes No	30 (18.3) 134 (81.7)
HIV Status	Yes No Unknown	43 (26.2) 106 (64.6) 14 (8.5)
Age in Years	Mean (SD)	40.6 (11.4)

Missing entries: Visit 2 (1.2%), HIV Status 1 (0.6%)

A total of156 (95.1%) patients had visited the hospital for the first time while 6 (3.7%) were revisiting. A total of 131 (79.9) patients were married, 27 (16.5) were single while the remaining 6 (3.6%) were divorced. In relation to the level of education attained by the patients, 85 (51.8%) had studied to primary level, 38 (23.2%) had studied to secondary school level while 41(25.0%) had attained tertiary education. Thirty (18.3%) had attained menopause while 134 (81.7%) were premenopausal. Fourteen (8.5%) patients never knew their HIV status. There were 106 (64.6%) and 43 (26.2%) negative and positive cases for HIV respectively. Two (1.2%) patients had missing data on visit while only one (0.6%) had missing data on HIV status.

Objective 1: To describe the Colposcopy findings using Modified Reid's Index among patients undergoing colposcopy in Western Kenya Cervical Dysplasia Clinic.

Patients were subjected to both Colposcopy and Biopsy diagnostic techniques to compare the effectiveness of the former in approximating the results obtained by biopsy. Table 2 summarizes this information.

Table 2: Classification by Colposcopy Impression

Colposcopy	Frequency (n=164)	Percentage Freq (%)
Normal	1	0.6
CIN 1	63	38.4
CIN 2/3	100	61.0

Colposcopy results showed that 1 (0.6%) patient had a normal cervix, 63 (38.4%) patients had CIN1 while 100 (61.0%) had CIN2/3. In this study, colposcopy technique was not used to diagnose carcinoma due to our inclusion and exclusion criteria.

Modified REID's colposcopic index classified 34 (20.7%) patients as likely to be CIN I with a score between 0 and 2 (Low grade disease). It also classified 66 (40.2%) as likely to be CIN I-II with a score between 3 and 5 (Intermediate grade disease). The remaining 64 (39.1%) patients were classified as likely CIN II-III with a score between 6 and 8 (High grade disease). Table 3 below summarizes this information.

Table 3: Classification by Modified Reid's Colposcopic Index

Modified Reid Index	Frequency (n=164)	Percentage Freq (%)
0 - 2 (Likely to be CIN I)	34	20.7
3 - 5 (Likely to be CIN I – II)	66	40.2
6 - 8 (Likely to be CIN II – III)	64	39.1

Objective 2: To describe the histopathological findings among patients undergoing colposcopy and biopsy in Western Kenya Cervical Dysplasia Clinic.

Results obtained from biopsy acted as the gold standard in this sensitivity – specificity study. The results revealed that 27 (16.5%) patients had a normal cervix, 43 (26.2%) patients had CIN1, and 89 (54.3) patients had CIN2/3 while 5 (3.0%) patients had a carcinoma. Table 4 below summarizes this information.

Table 4: Histopathological classification on colposcopy-driven biopsy

Biopsy	Frequency (n=164)	Percentage Freq (%)
Normal	27	16.5
CIN 1	43	26.2
CIN 2/3	89	54.3
Carcinoma	5	3.0

Objective 3: To determine the sensitivity and specificity of colposcopy findings among patients undergoing colposcopy and biopsy in Western Kenya Cervical Dysplasia Clinic.

The roadmap to the final confusion matrix for the specificity-sensitivity analysis involved several steps. A total of 27 subjects whose biopsy turned normal were dropped from the sensitivity-specificity analysis. This was necessary because patients who had initially been classified as normal by colposcopy were never subjected to a biopsy hence there was no way of comparing the results with that of the gold standard. Likewise, a total of 5 subjects whose biopsy revealed a carcinoma were also dropped from the sensitivity-specificity analysis. Colposcopy was not used to diagnose a carcinoma due to our inclusion and exclusion criteria hence there was no results to be compared to that of the biopsy.

Having dropped 32 patients from the sensitivity specificity analysis, a total of 132 subjects were therefore used to determine the effectiveness of colposcopy in discriminating CIN2/3 (Disease positive (+)) from CIN1 (Disease Negative (-)). The 2 by 2 matrix shown in Table 5 was adopted as the final confusion matrix for determining the efficiency of colposcopy as a diagnostic alternative for biopsy method.

Biopsy results showed that, out of 132 patients, 89 had CIN2/3 while 43 had CIN1. Likewise, colposcopy results also showed that 89 patients had CIN2/3 while 43 had CIN1. Furthermore, colposcopy showed 76 true positives for CIN2/3 and 13 false positives. It also gave 30 true negatives for CIN2/3 and 13 false negatives as shown in Table 5 below.

Table 5: Confusion matrix of Colposcopy against Biopsy

Colposcopy	**Biopsy (Histopathology)**		**Total**
	CIN2/3 (+) DISEASE (+)	**CIN1 DISEASE (-)**	
CIN2/3 (+) DISEASE (+)	76	13	89
CIN1 DISEASE (-)	13	30	43
Total	89	43	132

The true prevalence of CIN2/3 of cervical cancer, as shown by results from biopsy, was 67.4%. Likewise, the apparent prevalence of CIN2/3 as shown by results obtained from colposcopy was 67.4%. Colposcopy correctly diagnosed 76 CIN2/3 out of the possible 89 cases. It therefore had a sensitivity of 85.3%. It also correctly diagnosed 30 CIN1 cases out of the possible 43 cases. It therefore had a specificity of 69.7% for diagnosing CIN2/3.

The diagnostic accuracy of colposcopy was computed by summing up the true positives and true negatives as a percentage of the total number of patients. It had a diagnostic accuracy of 80.3%. On the contrary, diagnostic inaccuracy of colposcopy was computed by summing up the false positives and false negatives as a percentage of the total number of patients. Colposcopy had a diagnostic inaccuracy of 19.7%.

The number needed to diagnose (NND) was computed as a reciprocal of the Youden's Index (J). Colposcopy had a Youden's index of 0.551 hence an NND of 1.812. The higher the value of the Youden's index the better the test. On the other hand, the lower the number needed to diagnose the better.

Colposcopy had a positive predictive value (PPV) of 85.3%. This was computed as a conditional probability of colposcopy correctly detecting CIN2/3 given that actually the patient is in CIN2/3 stage of cervical cancer. Moreover, it had a negative predictive value (NPV) of 20.9%. This was computed as a conditional probability of

colposcopy to correctly detect CIN1 given that the patient is actually in CIN1 stage of cervical cancer.

Likelihood ratio of a positive test (PLR) for CIN2/3 was computed as a ratio of the conditional probability that colposcopy correctly diagnoses CIN2/3 given that the patient actually has CIN2/3 to that of the conditional probability that colposcopy wrongly diagnoses CIN2/3 given that the patient has CIN1. Colposcopy had a PLR of 2.824.

Likelihood ratio of a negative test (NLR) for CIN2/3 was computed as a ratio of the conditional probability of that colposcopy wrongly diagnoses CIN1 given that the patient actually has CIN2/3 to that of the conditional probability that colposcopy correctly diagnoses CIN1 given that the patient actually has CIN1. Colposcopy had a NLR of 0.209.

Proportion of subjects with the outcome ruled out (PRO) for colposcopy was computed as a proportion of CIN1. Colposcopy classified 43 cases as CIN1 (ruled out CIN2/3) hence it had a PLO of 32.5%. Proportion of subjects with the outcome ruled in (PRI) for colposcopy was computed as a proportion of CIN2/3. Colposcopy classified 89 patients as CIN2/3 (ruled in CIN2/3) hence it had a PLO of 67.5%.

Proportion of false positive (PFP) for colposcopy with respect to CIN2/3 was computed as a proportion of CIN2/3 as classified by colposcopy to that of true CIN1 as classified by biopsy. Colposcopy had a PFP of 30.2% with respect to CIN2/3. Proportion of false negative (PFN) for colposcopy with respect to CIN2/3 was computed as a proportion of CIN1 as classified by colposcopy to that of true CIN2/3 as classified by biopsy. Colposcopy had a PFP of 14.6% with respect to CIN2/3.

Table 6: Sensitivity analysis of colposcopy as a diagnostic alternative to biopsy

Abbreviation	Parameter	Estimate (95 % CI)
aprev	Apparent Prevalence	0.674 (0.587, 0.753)
tprev	True Prevalence	0.674 (0.587, 0.753)
se	Sensitivity	0.853 (0.763, 0.919)
sp	Specificity	0.697 (0.538, 0.828)
diag.acc	Diagnostic Accuracy	0.803 (0.724, 0.867)
diag.or	Diagnostic Odds Ratio	13.491 (5.611, 32.436)
nnd	Number needed to diagnose	1.812 (1.336, 3.312)
youden	Youden's Index (J)	0.551 (0.301, 0.748)
ppv	Positive Predictive Value	0.853 (0.763, 0.919)
npv	Negative Predictive Value	0.697 (0.538, 0.828)
plr	Positive Likelihood Ratio	2.824 (1.779, 4.483)
nlr	Negative Likelihood Ratio	0.209 (0.122, 0.359)
pro	Proportion of subjects with their outcome ruled out	0.325 (0.246, 0.412)
pri	Proportion of subjects with their outcome ruled in	0.674 (0.587, 0.753)
pfp	Proportion of false positive	0.302 (0.171, 0.461)
pfn	Proportion of false negative	0.146 (0.080, 0.236)

Optimal Youden's Index Point

The optimal youden's index point for colposcopy as a diagnostic alternative to biopsy in discriminating CIN2/3 from CIN1 was derived empirically in RStudio. The optimal point featured a true positive rate of 69.8 % and a false positive rate of 14.6 %. The empirical ROC plot revealed an area under the curve (optimal youden's index) value of 0.7758. The plot below gives a diagrammatic presentation of this information. Data analysis was done in RStudio version 1.0.136 using Bayesian theorem and Bayesian statistics.

Empirical ROC plot and Youden's Index

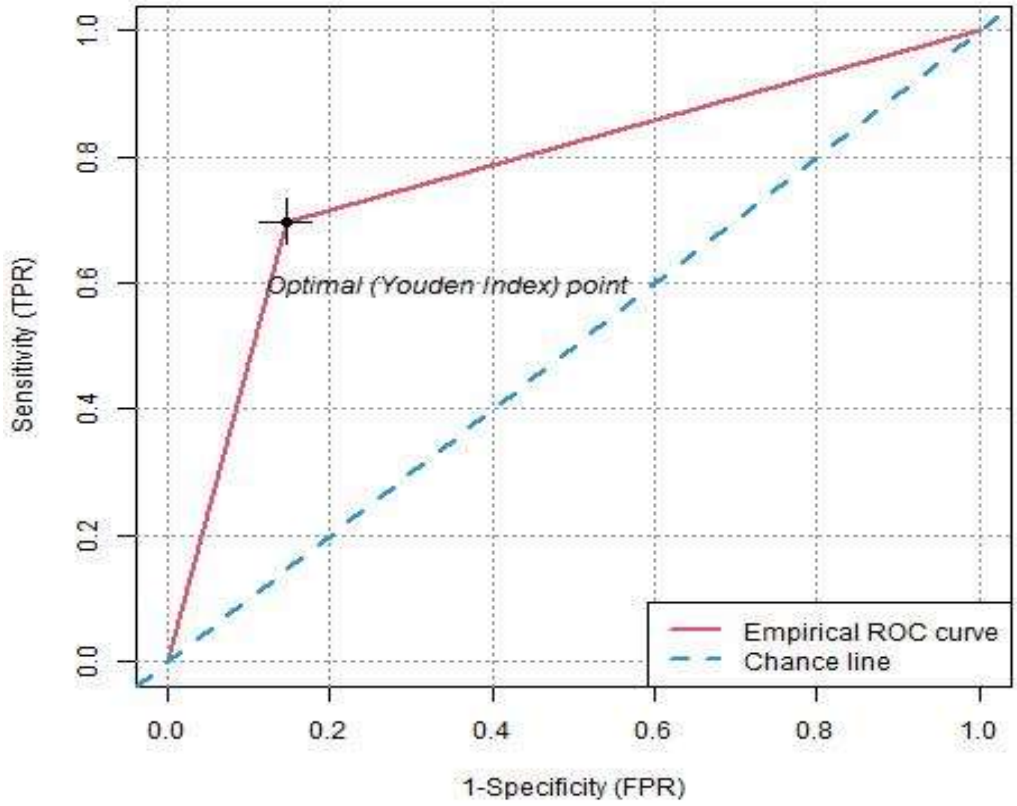

Figure 2: Empirical ROC plot and Youden's Index

CHAPTER FIVE

DISCUSSION

This study involved 164 patients who were subjected to both Colposcopy and Biopsy diagnostic techniques to compare the effectiveness of the former in approximating the results obtained by biopsy. Results from biopsy were considered as the gold standard in this sensitivity – specificity study. A total of 32 subjects were dropped from the analysis. This was necessary because histopathology results classified 27 patients as having a normal cervix. On the contrary, patients who had normal colposcopy results were never subjected to histopathology examination. Comparing the two methods based on this category would have introduced bias by design. Likewise, histopathology results classified 5 patients as having a carcinoma. On the contrary, colposcopy was never used to determine carcinoma. Comparing the two diagnostic methods based on this category would have introduced design bias too.

Objective 1: To describe the colposcopy findings using Modified Reid's Index among patients who underwent colposcopy in Western Kenya Cervical Dysplasia Clinic.

Results of colposcopy findings, using modified Reid's index, among patients who underwent colposcopy in western Kenya cervical dysplasia clinic showed that 1 (0.6%) patient had a normal cervix, 63 (38.4%) patients had CIN1 while 100 (61.0%) patients had CIN2/3. A study on the role of colposcopy using modified Reid's Index in diagnosing dysplasia in women with abnormal cervix on naked eye examination using a sample of 384 patients classified 278 (76.6%), 56 (15.6%) and 28 (7.8%) patients as CIN1, CIN 2 and CIN 3 respectively (Sonali et al, 2014). CIN2/3 therefore constituted 84 (23.3%) of the total number of patients. This proportion is much lower than 61.0% obtained in this study. The proportion of CIN1 (76.6%) estimated by

Sonali et al, 2014 was approximately twice that which was estimated by this study (38.4%). This could have been due to inclusion of normal looking cervix into their study and also a larger sample size compared to the current study.

A prospective comparative study carried out in the Department of Pathology, K.V.G Medical College, Sullia, D.K, from January 2015 to June 2016. A total of 50 women who met the selection criteria were included in the study. According to Reid colposcopic index, there were 54% benign cases, 18% women were diagnosed as CIN I, 16 % CIN II and 12% as CIN III. (DR. Navya et al, 2016) compared to the current study this proportion is way lower. This could have been due to a smaller sample size compared to the current study.

A prospective cross sectional study on Evaluation of Reid's Combined Colposcopic Index as a predictor of cervical intraepithelial lesion that was conducted adult married women attending gynae OPD in MDOH, Ludhiana, Punjab, India. Out of 125 women enrolled in the study, 47 (37.60%) of them had low grade disease, 11 (8.80%) intermediate and 4 (3.20%) high grade disease. Colposcopy was suggestive of invasive carcinoma in one subject. The colposcopy score was however not given. RCI could not be allotted due to unsatisfactory colposcopy in 6 subjects (Verma et al, 2018). In comparison to our study, Modified REID's colposcopic index classified 34 (20.7%) patients as likely to be CIN I with a score between 0 and 2 (Low grade disease). It also classified 66 (40.2%) as likely to be CIN I-II with a score between 3 and 5 (Intermediate grade disease). The remaining 64 (39.1%) patients were classified as likely CIN II-III with a score between 6 and 8 (High grade disease). Compared to the current study, the proportion of intermediate grade and high grade disease was very low. This could have been due to inclusion of normal cervix in their study.

In a prospective clinical study done at Government Medical College, Aurangabad, Maharashtra, India from May 2012 to Nov 2014 on 100 women with unhealthy cervix on naked eye examination and abnormal symptoms, amongst 41 patients with abnormal colposcopic findings, 13 (23.63%) were likely to be CIN I, 25 (45.45%) were likely to be CIN I-II, 3 (5.45%) were likely to be CIN II -III according to Modified Reid's Index (Kalyankar et. al, 2017). The results for low grade and intermediate disease were almost similar at 20.7% and 40.2% respectively to the ones estimated by this study. The result for high grade disease was almost 8 times higher at 39.1%.

A prospective study to evaluate the correlation between Reid Colposcopic impression and biopsy histology conducted at Vali-e-Asr university hospital in Tehran, Iran, between March 2004 and October 2005 on a sample of 344 women, colposcopy graded 204 (59.1%) women as having normal cervix, 86 (24.9%) women as having CIN 1 and 54 (15.7%) women as having CIN2/3 (Mousavi, 2007). In the current study, normal cervix was very low at 0.6% and CIN 2/3 was almost three times higher at 61%. This could have been due to inclusion of normal in the study by Mousavi.

A study on the agreement between colposcopy results using the Reid Colposcopic index and histopathology using a sample of 105 women, colposcopy graded 63 (60%) women as having normal cervix, 29 (27.6%) as having CIN 1 and 13 (12.4%) as having CIN 2/3 (Kaban, 2015). In the current study, normal cervix was very low at 0.6%, CIN 2/3 was almost five times higher at 61%. This could have been due to inclusion of normal in the study by Kaban.

Objective 2: To describe the histopathological findings among patients who underwent colposcopy and biopsy in Western Kenya Cervical Dysplasia Clinic.

Histopathology findings revealed that 27 (16.5%) patients had a normal cervix, 43 (26.2%) patients had CIN1, and 89 (54.3) patients had CIN2/3 while 5 (3.0%) patients had a carcinoma. Like in colposcopy, using a sample of 384 patients, Sonali et al, 2014 classified 264 (68.8%), 36 (9.4%), 16 (4.2%) and 8 (2.1%) patients as CIN1, CIN 2, CIN 3 and invasive cervical cancer in that order. CIN2/3 therefore constituted 52 (13.53%) of the total number of patients. This proportion is less than half of the proportion of CIN2/3 (38.4%) in this study. The proportion of CIN1 (68.8%) estimated by Somali et al, 2014. was much higher than that which was estimated by this study (26.2%). This study estimated a higher proportion of invasive cervical cancer (3.0%) compared to Sonali et al, 2014 (2.1%). This could have been due to inclusion of normal cervix in their study.

In the prospective comparative study carried out in the Department of Pathology, K.V.G Medical College, histopathological correlation 58% were benign showing chronic erosive cervicitis, where as 12%, 16%, 14% were diagnosed as CIN I (mild dysplasia), CIN II (moderate dysplasia), CIN III (severe dysplasia) respectively. CIN 2/3 therefore constituted 30%. (DR. Navya et al, 2016). This proportion is way lower compared to our findings. This could have been due to inclusion of normal cervix in their study as well as having a larger sample size.

According to Verma et al, 2018, all women with suspicious colposcopy findings 89.86% (62), unsatisfactory colposcopy 8.70% (6) and those colposcopic findings suggestive of the presence of invasive carcinoma underwent cervical biopsy. All women with unsatisfactory colposcopy also underwent ECC. Chronic cervicitis was the most common diagnosis, 57.97% (40). Low grade CIN was diagnosed on cervical

biopsy in 9 (7.2%) women, HPV related CIN in 2 (1.6%), CIN2/3, micro invasive squamous carcinoma and non-keratinizing poorly differentiated squamous cell carcinoma, one each 0.8% was also confirmed on cervical biopsy. In six women with unsatisfactory colposcopy, no pre invasive or invasive pathology was detected on cervical biopsy and ECC was negative. Compared to our study, the proportion of chronic cervicitis in this study was 3 times higher. Nevertheless, the proportion of CIN 1, CIN 2/3 and Carcinoma in situ were very low compared to the current study. This could have been due inclusion normal cervix in their study.

A prospective study to evaluate the correlation between Reid Colposcopic impression and biopsy histology conducted at Vali-e-Asr university hospital in Tehran, Iran, between March 2004 and October 2005 on a sample of 344 women, Histopathology graded 210 (68.9%) women as having normal cervix, 91 (29.8%) women as having CIN 1 and 52 (14.7%) women as having CIN2/3 (Mousavi, 2007). In the current study, normal cervix was very low at 16.5%, CIN 1 was similar at 26.2% and CIN 2/3 was almost four times higher at 54.3%. This could have been due to inclusion of normal in the study by Mousavi.

A study on the agreement between colposcopy results using the Reid Colposcopic index and histopathology using a sample of 105 women, Histopathology graded 66 (62.9%) women as having normal cervix, 27 (25.7%) as having CIN 1 and 12 (11.4%) as having CIN 2/3 (Kaban, 2015). In the current study, normal cervix was very low at 16.5%, CIN 1 was similar at 26.2%, while CIN 2/3 was almost five times higher at 54.3%. This could have been due to inclusion of normal in the study by Kaban.

Objective 3: To determine sensitivity and specificity of colposcopy findings among patients who underwent colposcopy and biopsy in Western Kenya Cervical Dysplasia Clinic.

Sensitivity analysis for colposcopy as a diagnostic method was based on its ability to discriminate CIN2/3 from CIN1. A Chi square test conducted on the outcome from 132 patients revealed a highly significant association between colposcopy and biopsy in discriminating CIN2/3 from CIN1, $p<0.0001$ (chi = 37.7, df = 1). There was a fairly strong resemblance in the results from colposcopy and biopsy diagnostic techniques, kappa = 0.55 (95% CI, 0.40 to 0.70), $p < 0.0001$. Aue-Aungkul and Suprasert compared the results obtained from Reid Colposcopic Index Evaluation and biopsy results. Their study involved comparison of diagnoses done by general and oncologic gynecologists. They estimated the strength of the correlation (Kappa) between colposcopy impression and biopsy results on diagnoses done by the oncologic gynecologists group to be equal to 0.34 while that of the general gynecologist group was equal to 0.22 (Aue-Aungkul & Suprasert). In both cases, the estimated strength of correlation was weaker than that which was obtained in this study (Kappa = 0.55).

Colposcopy had sensitivity and specificity of 85.3% and 69.7%, respectively. A prospective cross sectional study on correlation of colposcopy using REID colposcopic index and histopathology (Durdi et al, 2009) yielded comparable results on sensitivity. It had a sensitivity of 88.5% with CIN1 as a disease threshold and 85.2% with CIN2 as a disease threshold. It had a relatively high specificity of 76.2% with CIN1 as a disease threshold and 99.6% with CIN2 as a disease threshold. The study was conducted in the colposcopy clinic at KLES Dr Prabhakar Kore Hospital & Medical Research Center Belgaum between Jan 2008 and June 2009 with a sample

size of 268. Aue-Aungkul and Suprasert estimated a comparable specificity of 70.2% in their study on Reid Colposcopic Index Evaluation: Comparison of General and Oncologic Gynecologists with a sample size of 125 patients (Aue-Aungkul & Suprasert). Our study has shown that there is a probability of approximately 85.3% that colposcopy test will return a positive CIN2/3 result among a population suffering from CIN2/3. Our study also shows that colposcopy has a 69.7% chance of returning CIN1 among a population suffering from CIN1.

The PPV and NPV for colposcopy in discriminating CIN2/3 from CIN1 was 85.3% and 69.7% in that order. Durdi et al, 2009 estimated a PPV of 77.0% and 95.8% with CIN1 and CIN2 as disease thresholds respectively. These estimates were relatively comparable especially when CIN2 was applied as the disease threshold. On the contrary, the study yielded higher negative predictive values of 93.5% and 98.5% respectively. Aue-Aungkul and Suprasert estimated higher PPV and NPV of 89.0% and 86.0% respectively. Our study estimates that following a positive colposcopic classification of CIN2/3 on a patient, there is an 85.3% chance that indeed that patient is in CIN2/3 stage. It further estimates that given a colposcopic classification of CIN1 on a patient, there is a 69.7% chance that indeed that patient is in CIN1 stage of cervical cancer. This revelation is in agreement with the conclusion from a prospective cross sectional trial on Evaluation of Reid's Combined Colposcopic Index as a predictor of cervical intraepithelial lesion. Using a sample of 125 women aged above 20 years and scheduled for a colposcopy at Chiang Mai University Hospital between August, 2008 and May, 2014, the study concluded that the predictive accuracy of colposcopy increased with the increasing severity of the disease (Verma et al, 2018).

Verma et al, 2018 also estimated the diagnostic accuracy of colposcopy using Reid's combined colposcopic index to be 98.4%. This is much higher compared to 80.3% which is the estimated diagnostic accuracy of colposcopy in discriminating CIN2/3 from CIN1 in this study. Our study showed that colposcopy had 80.3% chance of correctly classifying CIN2/3 and CIN1. This also means that it had a 19.7% chance of either misclassifying CIN2/3 as CIN1 and vice versa. The odd of a positive CIN2/3 test in those with disease was 13.491 times that of the odd of a positive CIN2/3 test in those without disease. This further confirms that colposcopy has a higher chance of returning a positive CIN2/3 among patients with CIN2/3 as opposed to those who were not in that stage.

The Youden's index associated with colposcopy using Reid's colposcopic index to discriminate between CIN2/3 and CIN1 was 0.551 (0.301, 0.748). This was relatively fair because the Youden's index can only take values between 0 and 1 signifying poor and good diagnostic tests respectively. The number needed by colposcopy to differentiate between CIN2/3 and CIN1 was 1.182. Our study therefore showed that colposcopy needed utmost two patients for it to correctly discriminate CIN2/3 from CIN1. This is relatively a good performance for a diagnostic test. This study also estimated an Optimal Youden's index value of 0.776 with a true positive rate of 69.8 % and a false positive rate of 14.6 %. This is synonymous to a sensitivity and specificity of 69.8% and specificity of 85.4%. This also means that in a situation where an investigator deems both sensitivity and specificity as diagnostically important and desirable, the best performance of colposcopy would be noticed at these specificity and sensitivity thresholds respectively.

This study also estimated a positive and negative likelihood ratio of 2.824 (1.779, 4.483) and 0.209 (0.122, 0.359) in that order. The PLR is an important estimate in diagnostics because it gives the change in odds of having a diagnosis in patients with a positive test. This study revealed that there was a 2.824-times increase in the odds of having CIN2/3 in a patient who was classified as having CIN2/3 by colposcopy technique. This odd shows that colposcopy has some discriminating ability on CIN2/3 and CIN1 hence it is informative. A PLR of 1 would mean the odds of a patient having CIN2/3 does not change whether colposcopy classifies them as CIN2/3 or CIN1.

On the other hand, the NLR defines the change in odds of having a diagnosis in patients with a negative test. The NLR of 0.122 indicate an 8.3-times decrease in the odds of having CIN2/3 in a patient who has been classified as having CIN1 by colposcopy technique. The smaller the value of the NLR, the more informative the test is. A NLR of 0.122 further shows that colposcopy is an informative diagnostic alternative for biopsy.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusion

1. There were nearly equal proportions of intermediate and high grade disease when Modified Reid's index was used to classify colposcopy findings.
2. Histopahology reported more than half of all the findings were high grade disease (CIN 2/ CIN 3).
3. This study reports that there is an association between the discriminatory power of the two methods, however, colposcopy had a lower specificity when compared to histopathology.

6.2 Study Limitations

Normal cervix on colposcopy were not subjected to biopsy and also cervix that had frank lesion on colposcopy were not included in the study.

6.3 Recommendations

The study recommends that colposcopy is important in directing biopsy, and histopathology should continue as a gold-standard for cervical cancer diagnosis.

Further studies to validate the findings are recommended.

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APPENDICES

Appendix 1: Consent form
PATIENT STUDY ID: _____SCREENING DATE: __ __ / __ __ / __

PROJECT TITLE: Comparison of Colposcopic and Histopathologic Interpretations among Patients Undergoing Screening for Cervical Cancer in western kenya Cervical dysplasia clinic

Principal investigator

Dr. MOHAMED ALI HASSAN (SM/PGRH/03/17), Institute ……., email address……phone no: ……

What you should know about this research study:

- We give you this informed consent document so that you may read about the purpose, risks, and benefits of this research study.
- You have the right to refuse to take part or agree to take part now and change your mind later.
- Please review this consent form carefully. Ask any questions before you make a decision.
- Your participation is voluntary.

PURPOSE

To determine the colposcopic-histologic correlation among patients undergoing a colposcopic evaluation at Moi Teaching and Referral Hospital (MTRH) cervical dysplasia clinic

RISKS AND DISCOMFORTS

Undergoing cervical cancer screening can cause worry or concern, regardless of the test results. For this reason, both before and after you have these tests done, we will give you counselling about the meaning of the results. Cervical cancer screening and diagnosis might cause mild physical discomfort as the test involves a pelvic examination and biopsy. We will inform you of what to expect at each step of the examination.

BENEFITS AND/OR COMPENSATION

The benefit to you of cervical cancer screening and diagnosis is that we can diagnose pre-cancer in the cervix and prevent cervical cancer. You will be referred for further evaluation if you need it. There is no cost to you for participation in this study. There is no compensation for this study.

CONFIDENTIALITY

Your name will not be placed on the sample we collect from you; it will be identified only by a code and date of collection. Written documents for the study will be kept at locked offices. Any data stored on computers will have a security code. Only the research team and your provider will have access to your name and the study results. The research team and your provider may have access to study data and records to monitor the study. Publications and/or presentations that result from this study will not identify you by name.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. If you decide not to participate in this study, your decision will not affect your care, and you can still seek cervical cancer screening at MTRH. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without penalty. Withdrawal from

the study will not affect your care. Any refusal to observe and meet appointments agreed upon with the Principal investigator will be considered as implicit withdrawal and therefore will terminate your participation in the investigation without your prior request. If you believe you are injured as a direct result of your participation in this study or should you have questions about the study and your rights as a research participant, contact the Investigators at the top of this consent.

AUTHORIZATION

You are making a decision whether or not to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to participate.

Name of Research Participant (please print) Date_____

Signature of Staff Obtaining Consent Date

(Optional)

FUTURE CONTACT

Do you agree to be contacted in the future regarding participation in future research related to cervical cancer screening and treatment?

☐ Yes Signature_____ Phone number_____

☐ No

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research participant; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact **Dr. MOHAMED ALI HASSAN (SM/PGRH/03/17), Phone no: 07…… e mail address:…….**

Appendix 2: Questionnaire

Dysplasia Form		
First Name	Second name	Last name
AMPATH ID:	New ☐ Revisit ☐ Scheduled ☐	Unscheduled ☐
Age ……..	Clinic ……. Module 1 ☐ 2 ☐ 3 ☐ 4	
1. Last menstrual period ☐ …... Postmenopausal Parity ……. Gravida ……...		
(if LMP > days do Pregnancy Test) Pregnancy Test Results Positive ☐ Negative ☐		
2. HIV status ☐ unknown ☐ Positive ☐ Negative Latest CD4 Count…… Date ……..		
3.Prior dysplasia test Yes ☐ No ☐ if yes fill below Prior VIA results Yes ☐ No ☐ Date ……. Prior pap smear results Normal ☐ ASCUS ☐ AGUS ☐ LSIL ☐ Squamous CA ☐ Adeno CA ☐ Prior colpo results Normal ☐ CIN 1 ☐ CIN 2 ☐ CIN 3 ☐ Carcinoma ☐ Date ……... Other biopsy results ……..		
4. **Prior Treatment** Cryotherapy ☐ LEEP ☐ Surgery ☐ Other ☐ Date ……. Pathology ……	**Prior Treatment** Cryotherapy ☐ LEEP ☐ Surgery ☐ Other ☐ Date ……. Pathology ……	**Prior Treatment** Cryotherapy ☐ LEEP ☐ Surgery ☐ Other ☐ Date ……. Pathology ……

5. Modified Reid's Colposcopic index/ Score (RCI)

Colposcopy sign	Score 0	Score 1	Score 2
Margin	Condylomatous or micropapillary contour. Flocculated or feathered, jagged, angular, satellite lesion, AWA beyond original squamo-columnar junction	Regular lesion with smooth indistinct borders	Rolled, peeling edges, sharp margins
Colour	Shiny, snow white, areas of faint (semi-transparent) whitening	Intermediate shade (shiny but grey white	Dull, oyster grey
Vessels	Uniform, fine calibre non-dilated capillary loops fine punctuation or mosaic	Absence if surface vessels	Definite, coarse punctuation or mosaic
Iodine staining	Any lesion staining mahagony brown, mustard yellow stains by a minor lesion (by the first 3 criteria)	Partial iodine uptake (mottled pattern)	Mustard yellow staining of a significant lesion (an acetowhite

			area scoring 3 or more points by the first 3 criteria
☐ 0 – 2 Likely to be CIN I ☐ 3-5 Likely to be CIN 1-II ☐ 6-8 Likely to be CIN II-III			
6. Visual Impression: **Cervix:** ☐ Normal ☐ CIN 1 ☐ CIN 2/3 ☐ Carcinoma	Vulva ☐ Normal ☐ Condyloma ☐ VIN 2/3		Vagina ☐ Normal ☐ VAIN 1 ☐ VAIN 2/3
7. **Pathology Results** **Cervix:** ☐ Normal ☐ CIN 1 ☐ CIN 2/3 ☐ Carcinoma	**Vulva** ☐ Normal ☐ Condyloma ☐ VIN 2/3		**Vagina** ☐ Normal ☐ VAIN 1 ☐ VAIN 2/3
8. Plan ☐ Biopsy done (list sites) ……. ☐ ECC done ☐ Routine yearly VIA ☐ Pap smear in 6 months ☐ VIA in 6 months		☐ Repeat colposcopy in …… months ☐ Cryotherapy done ☐ LEEP done (Number of specimens……..) ☐ Wide local excision/ vulva ☐ Hysterectomy ☐ Others	
Comments …… ……..... …… …….			

Appendix 3: Budget

Item	Cost per item	Total
Biostatistician	30,000	30,000
Research Assistant	@15,000	30,000
Internet and computer	15,000	15,000
Printing costs	50,000	50,000
Miscellaneous costs	20,000	20,000
Consent printing	7,500	7,500
Total		**152,500**

Appendix 4: Work Plan

Activity/Time	April 2019	May - Sep, 2019	Sep – Dec, 2019	Dec – March, 2020	April – May, 2020
Preparation and submission of project's research proposal					
Making corrections					
Data collection at MTRH Cancer centre					
Compiling of research report					
Defence, Binding and submission of the research report					

Appendix 5: IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

27th February, 2020

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
27 FEB 2020
APPROVED
P. O. Box 4606 - 30100 ELDORET

Reference: IREC/2019/86
Approval Number:0003383

Dr. Mohamed Ali Hassan,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Hassan,

COLPOSCOPIC AND HISTOPATHOLOGIC COMPARATIVE INTERPRETATIONS AMONG PATIENTS UNDERGOING SCREENING FOR CERVICAL DYSPLASIA IN WESTERN KENYA

This is to inform you that ***MU/MTRH-IREC*** has reviewed and approved your above research proposal. Your application approval number is ***FAN:0003383.*** The approval period is ***27th February, 2020 – 26th February, 2021.***

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MU/MTRH-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MU/MTRH-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MU/MTRH-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MU/MTRH-IREC.***

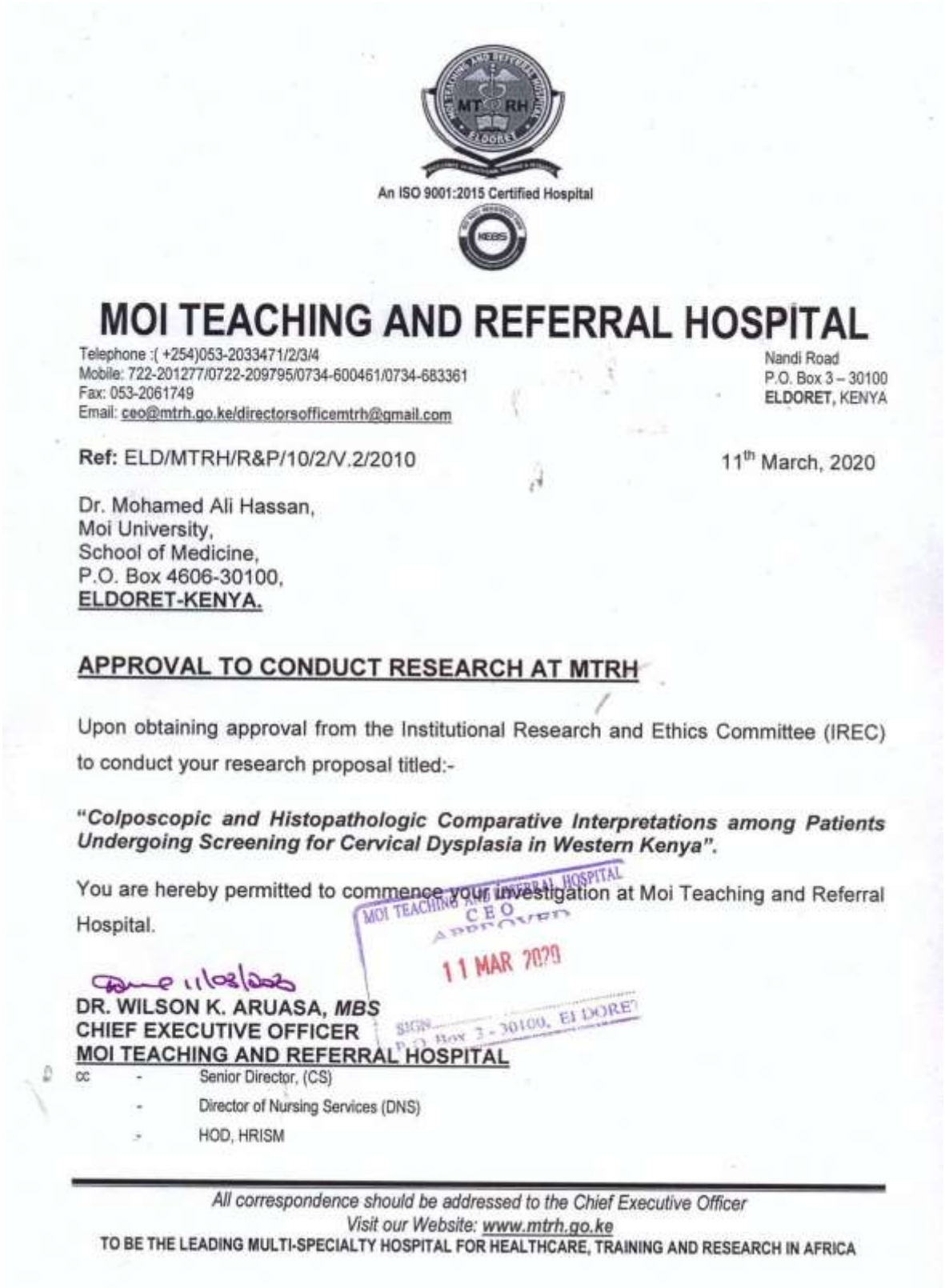
Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and also obtain other clearances needed.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 6: Hospital Approval (MTRH)



An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

11th March, 2020

Dr. Mohamed Ali Hassan,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Colposcopic and Histopathologic Comparative Interpretations among Patients Undergoing Screening for Cervical Dysplasia in Western Kenya".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITAL
CEO
APPROVED
11 MAR 2020
SIGN
P.O Box 3 - 30100, ELDORET

11/03/2020

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM

All correspondence should be addressed to the Chief Executive Officer
Visit our Website: www.mtrh.go.ke
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