

**UTILITY OF METHYLENE BLUE TEST IN DIAGNOSIS OF EARLY
ANASTOMOTIC LEAKS POST ONCOLOGIC ESOPHAGECTOMY**

A DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE AWARD OF MASTER
OF MEDICINE IN THORACIC AND CARDIOVASCULAR SURGERY AT THE
UNIVERSITY OF NAIROBI


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STUDENT DECLARATION

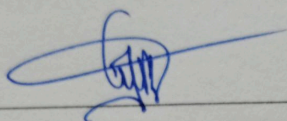
This proposal is the original work of Dr Jedida Chepkorir Kimutai , which was at a presented at a departmental meeting that was held on 15th September 2022 and thereafter approved by Kenyatta National Hospital – University of Nairobi Ethics and Research Committee

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DEPARTMENTAL APPROVAL

This is to certify that this dissertation is the original work of Dr Jedida Chepkorir Kimutai which was presented at a departmental meeting held on September 15th 2022 and thereafter approved by the Kenyatta National Hospital – University of Nairobi Ethics and Research Committee (KNH-UoN ERC).

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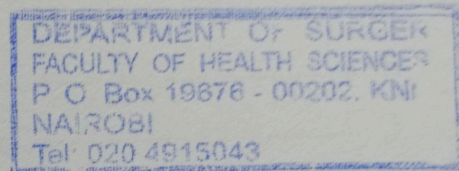


TABLE OF CONTENTS

Student Declaration.....	i
Supervisors	ii
Table of contents.....	iv
List of tables	v
List of abbreviations / acronyms.....	vi
Abstract	vii
Chapter One.....	1
1.0 INTRODUCTION.....	1
1.1 Background	1
Chapter Two	3
2.0 LITERATURE REVIEW	3
2.1 Epidemiology of anastomotic leaks	3
2.2 Diagnosis of anastomotic leak	4
2.2.2 Laboratory.....	4
2.2.3 Radiologic imaging.....	5
2.2.4 Contrast chest CT scan.....	5
2.2.5 Endoscopy.....	6
2.2.6 Bed side methylene blue test,.....	7
2.3 Statement of the problem.....	9
2.4 Justification.....	9
2.5 Conceptual framework.....	10
2.6 Study Question	11
2.7 Study Objectives	11
Broad objective	11
Specific objectives.....	11
i. To determine the sensitivity and specificity of methylene blue dye test in diagnosis of AL post esophagectomy.....	11
ii. To determine positive predictive and negative predictive values of methylene blue dye test in diagnosis of AL post oncologic esophagectomy.	11
Chapter three.....	12

3.0 METHODOLOGY.....	12
3.1 Study Design.....	12
3.2 Study site.....	12
3.3 Study Population.....	12
3.4 Study eligibility.....	12
Inclusion criteria.....	12
Exclusion criteria.....	13
3.5 Sample size determination.....	13
3.6 Sampling method.....	14
3.7 Data variables.....	14
Dependent variables.....	14
Independent variables.....	14
3.8 Ethical consideration.....	14
3.9 Data collection.....	15
3.11 Data management.....	15
3.12 Data analysis.....	15
3.14 Study limitations.....	16
CHAPTER 4.....	18
RESULTS.....	Error! Bookmark not defined.
Data analysis.....	Error! Bookmark not defined.
Discussion.....	28
REFERENCES.....	33
List of appendices.....	37
Appendix 1: Data collection tool.....	37
Appendix 2: Administrative consent to conduct the study.....	38

LIST OF TABLES

Figure 1: A histogram representing the distribution of age.....	18
Figure 2: Distribution of the Sex of the patients.....	19
Figure 3: A pie chart showing the distribution of anastomosis site.....	20
Figure 4: A histogram of post op day the MB test was done.....	21
Figure 5: Distribution of the methylene blue test results.....	22

Figure 6: A pie chart showing the distribution of clinical anastomotic leak.....23

Figure 7: The histogram shows the days of clinical manifestation.....26

Table 1: Summary of the characteristics presented by the patients who had clinical anastomotic leak**Error! Bookmark not defined.**

Table 2: Summary two way table for methylene blue dye test and AL post esophagectomy.....27

Table 3: A table for sensitivity and specificity27

Table 4: A table for negative predictive and positive predictive values28

LIST OF ABBREVIATIONS / ACRONYMS

AL	Anastomotic Leak
CRP	C-Reactive Protein
CS	Contrast Studies
ECCG	Esophagectomy Complications Consensus Group
GI	Gastrointestinal
KNH	Kenyatta National Hospital
MB	Methylene Blue
POD	Post-Operative Day
WBC	White blood cell

ABSTRACT

Background: Esophagectomy is currently the best option for treatment of resectable esophageal malignancies. Anastomotic leak (AL) is one of the most devastating post esophagectomy complication carrying high mortality, long hospital stay, poor quality of life. The high mortality is usually due to missed or delay in diagnosis. It is therefore important to make early diagnosis as this will improve outcome. At local hospital, methylene blue dye is often used to assess presence or absence of anastomotic leak prior to initiation of feeding. However, reports indicate that in a significant number of patients, the leaks occur despite a negative methylene blue dye test.

Study objective: To determine the accuracy of methylene blue dye test in diagnosis of early anastomotic leaks post oncologic esophagectomy in Kenyatta National Hospital

Methodology: A 6 year a retrospective analytical study of 265 patients who underwent esophagectomy at KNH between January 2017 and January 2023 for esophageal cancer and had methylene blue test done before post-operative day 10 was performed. . Data was collected via consecutive sampling .Of particular interest was findings of methylene blue dye test and clinical confirmation of anastomotic leak: characteristic chest drain effluent, leakage of digestive fluids; saliva and bile, food particles, pus from the cervical incision site.

Results: Out of 265 patients who were analysed, 29.45% (n=78) had clinical anastomotic leak 4.2% (n=11) patients had a positive methylene blue dye test and 95.8% (n=254) had a negative test. Sensitivity and specificity of MB test was found to be 14.1 and 100% respectively with positive predictive and negative predictive values of 100% and 73.6%

respectively. 93.6% ($n=73$) of the patients who had AL had their anastomosis on the cervical region, while 6.4% ($n=5$) had intrathoracic anastomosis. Majority of the patients who had positive test had the test done on day 5 and 6. Mean and median post-operative day when methylene blue test was carried out was found to be day 7, standard deviation of 0.8. Most common clinical features of EAL were leakage of ingested food particles and pus drainage from incision site. AL was found to occur mostly on post-operative day 10 in KNH.

Conclusion

Methylene blue test has high specificity but very low sensitivity, making it ideal to be used as a screening test, other test should be done to confirm diagnosis.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Esophageal cancer in Kenya is second most prevalent cancers, with incidence of 17.6 per 100,000, which is one of the highest in the world (1). In Kenya a relatively young population is affected, with significant number of patients being below age of 40yrs. About 70-80%of the cases are diagnosed in stage 3 and 4. Treatment options offered include chemotherapy, radiotherapy and surgery. Esophagectomy remains the best choice for treatment of resectable tumors. Several early and late post-operative complications have been documented which include respiratory complications; (pneumonia, aspiration, pleural effusion), cardiac complications; arrhythmias, wound infections, conduit related; anastomotic leaks, conduit necrosis, anastomotic strictures(2) .Anastomotic leak is one of the most devastating and severe post esophagectomy complication carrying high mortality, long hospital stay, poor quality of life(3), and increased risk of local tumor recurrence.(4) (5) One of the major factors leading to high mortality is missed or delay in diagnosis.(4) It is therefore important to make early diagnosis as this will improve outcome. In Kenyatta National Hospital esophagectomies are done through 3 main approaches: three field esophagectomy (Mc Keown's) and Trans hiatal whereby anastomosis fashioned on the cervical region, 2 field (Ivor Lewis where intrathoracic anastomosis is done. Mostly surgical approach is dictated by location and extent of the disease and also surgeon's preference. All cases are hand sewn. Leaks can therefore occur either on the cervical incision site or intrathoracic. Intrathoracic leaks have worse outcomes than cervical because spillage into the chest causes mediastinitis, pleural effusion, and even sepsis. (6) (7).

During surgery, two-to -three drains are placed; Chest drain (if thoracotomy is done), a decompressive nasogastric tube and a feeding jejunostomy tube. Patients are kept on nil per oral until day 7-8, when the integrity of the anastomosis is tested using methylene blue dye. 10mls of methylene blue dye is diluted in 250 mls of water and patient is allowed to take orally. Chest tube drain and cervical wound dressing is observed for 1 hour. The test is said to be positive if bluish discoloration of the chest drain occurs or if the blue coloured dye is seen soiling the cervical incision dressing. (8), (9)

The role of methylene blue dye in detecting early anastomotic leak is debatable despite persistent use of the test at the Kenyatta National Hospital. Its sensitivity, specificity, positive and negative predictive values, and accuracy remain unknown. Therefore, the main objective of this test was to assess the accuracy of methylene blue dye test in detecting the anastomotic leaks post esophagectomy.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Epidemiology of anastomotic leaks

Anastomotic leak (AL) according to Esophagectomy Complications Consensus Group (ECCG) is defined as full thickness defect of the gastrointestinal tract involving esophagus, anastomosis, staple line, or conduit irrespective of clinical presentation or diagnostic method. Leak rates vary widely in different parts of the world being between 7.2 % to 48%(6), leading to mortality of up to 60%, morbidity, poor quality of life, long hospital stay and higher rates of local tumor recurrence(11), (12), (13).

In Kenyatta National Hospital, a study done by Ogendo et al published in 2005, where 201 patients who underwent esophagectomy were analysed. 67% of patients had anastomosis fashioned in the chest, 33% fashioned in the cervical region. The study found an overall leak rate of 16.4%, overall mortality rate for all oesophagectomies in-hospital was found to be 28.9%. The patients who developed anastomotic leak post operatively had in hospital mortality rate of 48.4%. Those who had no leaks had an in-hospital mortality rate of 27.2%. (14).

Study done locally by Gachara 2022(15) , 377 patients who underwent esophagectomy between 2014-2021 with a cervical esophago-gastric anastomosis were recruited into the study.

Prevalence of cervical esophageal anastomotic leaks was found to be 20%, with most leaks occurring between days 7-9. (15)

2.2 Diagnosis of anastomotic leak

Diagnosis of AL remains a challenge; currently there is no single test that is considered as a gold standard. Therefore, most centers take multimodality approach. Diagnosis can be made by physical examination, laboratory tests, radiologic imaging and endoscopy. Endoscopy has shown to have an advantage over the other diagnostic modalities

2.2.1 Clinical

Clinical presentation of AL varies widely, ranging from no signs and symptoms to severe sepsis.

Common signs include:

- i. None specific clinical signs are; presence of fever, tachycardia, arrhythmias, and
- ii. Specific clinical signs are; change in chest drain characteristics i.e. colour, quantity, smell, presence of enteric content, saliva, bile. Erythema, swelling, tenderness of the cervical incision site also drainage of saliva, pus or ingested food particles.

The none specific ones are important in raising high index of suspicion as they may be helpful in predicting early AL. The specific signs are usually diagnostic for AL.

2.2.2 Laboratory

Laboratory tests of importance in AL are; Elevated CRP, WBC count, chest drain fluid analysis for salivary amylase, microscopy, culture and sensitivity. One of the most widely used and studied is NUn score which evaluates elevation of some acute phase reactants, particularly: C-reactive protein, albumin and white cell count on postoperative day four (POD 4). This has been demonstrated to have 100% sensitivity and 57% specificity (16,17). C-reactive protein level of above 17 mg/dl from third postoperative day (POD) has been found to be of great diagnostic

importance as a predictor for leakage development (18). Presence of salivary amylase in the pleural fluid is highly diagnostic, with sensitivity of 100% and specificity of 86 % when the test is carried out from day 4-6. (19)

2.2.3 Radiologic imaging

The most relevant imaging for diagnosis of AL are; Oral water-soluble upper GI contrast studies and chest CT- scan with oral contrast.

Esophagogram with contrast is relatively safe, easily accessible and cost friendly modality to assess anastomotic integrity, status of the conduit. It also gives information on the patency of the pylorus. Anastomotic leakage is evident if extravasation of contrast material from the anastomotic site is visualized. Leakage may be seen as contained or free leaking into the chest (20). Small leaks and also contained ones may be missed. Sensitivity ranges between 33 and 52% in literature for thoracic anastomoses and lower in cervical anastomoses, Jones et al(21) (22). Limitations include the need for an expert for interpretation of results and the need of ingestion of contrast agents. Major known complication is aspiration of contrast which may cause pneumonitis. The imaging is contraindicated therefore in patients with altered swallowing mechanism or, depressed state of consciousness and those under sedation.

2.2.4 Contrast chest CT scan

CT Scan with oral contrast is of great the value as compared to plain CT scan. Presence of mediastinal air/fluid, extravasation of contrast, visualization of a fistula, esophago-gastric wall discontinuity are Ct scan features of anastomotic leak.(23),(24). CT scanning is noninvasive, and its availability currently has markedly improved. Advantages include visualization of the defect and location of the leak, also location of extra luminal fluid collections and possibility of

accessing for percutaneous drainage. It has an advantage in that other complications can be diagnosed; abscesses, pleural effusions, pneumothorax, or other pulmonary abnormalities). Applicability in critically ill patients who have limited mobility, or are mechanically ventilated may be limited. The sensitivity, specificity, are 100%, 80%, respectively.

2.2.5 Endoscopy.

Early endoscopy is currently gaining grounds. It is unmatched in direct visualization of the leak, location, size, characteristics of the mucosa, nature of the conduit, and suitability for therapeutic intervention. Endoscopy can also be used as the first diagnostic modality in patients who are unable to undergo other radiologic tests or MB test, such as mechanically ventilated patients. It has high sensitivity and specificity of about 95% and 98% respectively (25),(26) for intrathoracic leaks and sensitivity of 56% in cervical leaks(27) (28). It is an invasive procedure that requires experienced specialist to undertake, and there have been controversies on the timing. It has been believed that insufflation of air may disrupt the anastomosis if done early (within 72 hours), because at this time anastomosis is still unstable. However, it has been demonstrated by recent studies that in order to disrupt an esophago-gastric anastomosis intraluminal pressure greater than 80 cm H₂O need to have been used during insufflation. Therefore, during Endoscopy the physician need to always be gentle and use the lowest pressure possible, currently maximum intraluminal pressure at the anastomosis does not usually increase beyond 9 cm H₂O during insufflation, this ensures minimal interruption of blood flow in the conduit(28). There is therefore no consensus on the timing, however in many centers it done as a second line test after other tests have been done. If routinely done, it is carried out on day 5-7 because this is the time when most leaks are likely to occur. (29)

2.2.6 Bed side methylene blue test,

Methylene blue test is one of the cheapest and easily available, non-invasive diagnostic modality that is used in many centers for screening and early diagnosis of AL, However data has shown varying results.(30) (8) Mostly sensitivity and specificity has been shown to be low. False negative results lead to delay in intervention and hence poor outcomes.

In a study done in the UK by Rotundo et al, AL was diagnosed in 10.6% of patients, MB test done on post-operative day 5 yielded positive results in 66% of patients, all of which had clinically significant leaks while contrast studies (CS) diagnosed 100% of the leaks including those who had sub clinical course(8). Anastomotic integrity was tested using both methylene blue and contrast esophagogram. 100mls of water soluble contrast was used in the contrast studies. 10mls of methylene blue in 200mls of water was given orally and patients were observed. Methylene blue test was considered positive when discoloration of the chest drain occurred within 30 minutes.

In a study by Juntang Guo et al 2014, 1867 patients who underwent esophagectomy were analyzed. Overall leak rate was 1.8%, Anastomotic leakage occurred in average of 9.7 days from the time of esophagectomy. Diagnostic accuracy of methylene test was 30.1% while that of contrast CT Scan was 89% (9). In this study 5mls of methylene blue dye diluted in 100mls of water was administered on day 7 post op. The test was considered positive if discoloration of the chest drain was observed in 1 hour from the time of administration of the dye.

In KNH MB test is usually done on day 7 or 8 before oral feeds are initiated and the chest drain is observed for 1 hour. However the test can be done earlier on in patients exhibiting signs and symptoms of AL earlier. Late administration of the dye can lead to higher false negative results

as adhesions formed around the anastomosis can contain the dye, masking the leakage. Currently placement of chest drain close to the anastomosis has been used to improve efficacy of the dye test.

2.2.7 Timing of test.

The timing of early diagnosis or investigations that can help in suspecting possibility of a leak is yet to be agreed upon. It is a topic that raises a lot of debate, because the period of the manifestation and symptoms and signs of AL vary considerably.(22). The clinical observation during the postoperative course of the patient is widely adopted, together with laboratory tests: WBC count, inflammatory markers and, in some centers, salivary amylase drain levels. This is called the on-demand approach that is prevalent in most centers. Imaging investigations are used to confirm diagnosis in patients exhibiting clinical signs of AL and/or derrayed laboratory test results. In general, there is cost implication and the question of exposure to radiation in patients who have no clinical symptoms. Higher incidence of AL is found in symptomatic patients (33%) as compared to asymptomatic patients (12%)(31) further supports the on demand approach of diagnosis.

Methylene blue test is done in KNH before day 10 because Several studies are showing that median time of occurrence of AL is day 7-9.(32). Secondly about seven day period is required for re epithelialization of the anastomosis.

2.2.8 Biochemistry and pharmacodynamics

Methylene blue dye is a thiazine cationic dye, which is soluble in water and has deep blue colour, and it is due to these properties that it is widely used to test for integrity of gastrointestinal anastomosis intra and post operatively. MB has established safety profile, toxicity occurs if used at doses higher than 4mg/kg/day. About 75% of an oral dose of methylene blue is excreted in the urine in form of leucomethylene blue, a small proportion of which is the unchanged drug, while some is excreted via the bile (33) (34). Potential limitation of methylene blue dye use orally is the capability of GI bacteria (especially coliformes and enterococci) to reduce it to leucomethylene, a colourless form of MB (35).

2.3 Statement of the problem

Despite increased usage of MB test for assessing AL, its sensitivity and specificity remain unknown and may not clearly inform on patients who develop late anastomotic leaks.

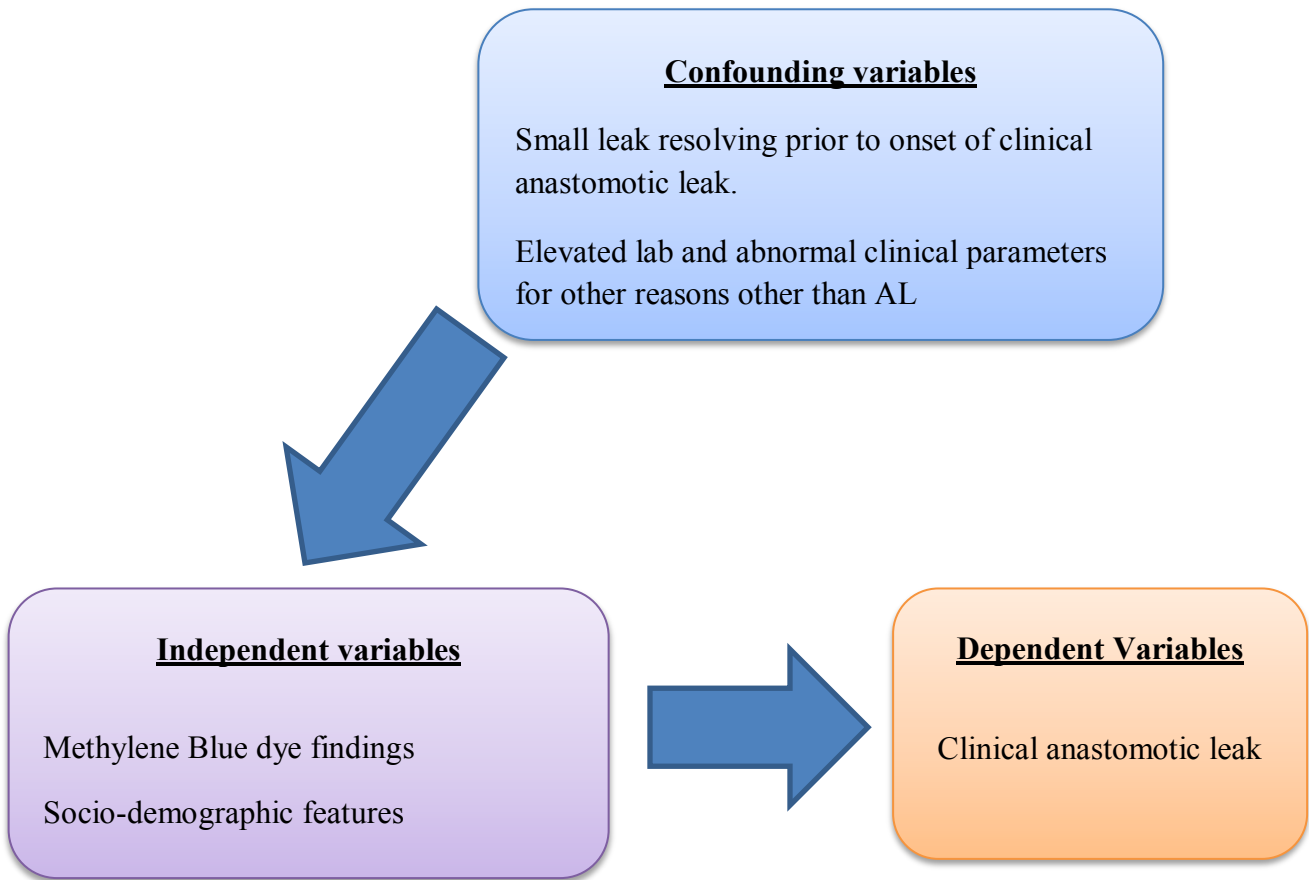
Adoption of more advanced methods of assessing AL may be needed.

2.4 Justification

The findings of this study was expected to inform on the utility of the MB test in detecting anastomotic leaks in our set – up. This may further inform local practice guidelines.

2.5 Conceptual framework

Figure 1: Conceptual framework showing interaction between various study variables.



2.6 Study Question

How accurate is methylene blue dye test in early diagnosis of AL post esophagectomy?

2.7 Study Objectives

Broad objective

To determine the accuracy of methylene blue dye test in diagnosis of AL post esophagectomy

Specific objectives **i. To determine the sensitivity and specificity of methylene blue dye test in diagnosis of AL post esophagectomy.**

ii. To determine positive predictive and negative predictive values of methylene blue dye test in diagnosis of AL post oncologic esophagectomy.

CHAPTER THREE

3.0 METHODOLOGY.

3.1 Study Design.

A retrospective analytical study design was used.

3.2 Study site

The study was carried out at Kenyatta National Hospital (KNH) which is a national teaching and referral hospital located 4 kilometers away from the Central Business District in Nairobi. The hospital serves both children and adults from all over the country and neighboring countries.

The hospital being a national referral hospital handles early and advanced cases of esophageal cancer owing to availability of specialist services to handle such cases. Esophagectomy patients in KNH are managed at The Cardiothoracic unit, Ward 4B and followed up at the Surgical outpatient clinic. Medical records of post esophagectomy patients were obtained from the records department from which data will be extracted.

3.3 Study Population.

All Patients who had oncologic esophagectomy done in KNH between 2017 – January 2023 and had methylene blue test done before day 10 post operatively.

3.4 Study eligibility

Inclusion criteria

1. Patients who underwent esophagectomy for esophageal cancer and had a methylene blue test performed before day 10.

Exclusion criteria

1. Mortality prior to establishment of presence of anastomotic leak.
2. Patients who had other thoracic surgeries/injuries prior to esophagectomy.
3. Patients who underwent esophageal resection for other causes other than malignant tumors.

3.5 Sample size determination

Formula (two sided binomial test) for calculating 95% confidence interval for sensitivity:

$$95\% \text{ confidence interval} = \text{sensitivity} \pm 1.96 (\text{SE sensitivity})$$

Where SE sensitivity = square root $[\text{sensitivity} - (1-\text{sensitivity})]/n$ sensitivity)

Formula for calculating 95% confidence interval for specificity:

$$95\% \text{ confidence interval} = \text{specificity} \pm 1.96 (\text{SE specificity})$$

Where SE specificity = square root $[\text{specificity} - (1-\text{specificity})]/n$ specificity)

From Robert M. Hamm, PhD;

Thus using a sensitivity of 33% and a specificity of 52% as based on previous research, and a prevalence of 20% for anastomotic leaks

The desired sample size was 265 patients

3.6 Sampling method

The patients who were admitted with a diagnosis of esophageal cancer and underwent esophagectomy from 1st January 2016 to January 2023 were recruited in this study through a consecutive sampling approach, whereby every patient meeting the inclusion criteria was added to the study until the sample size was met.

3.7 Data variables

Dependent variables

Clinical Anastomotic leak

Independent variables

Methylene blue dye test positivity

Socio-demographic features

Clinical features – Change in chest drain effluent, or leakage of saliva, food particles from the cervical incision site.

3.8 Ethical consideration

The institutional consent and approval were sought from the KNH-UoN Ethics and Research Committee.

The authorization to conduct the study was also obtained from KNH administration.

The participants remained anonymous and unique identification numbers were used thereby observing confidentiality and privacy throughout the duration of the study.

The data collected was used for research purposes only and the hard copies were stored in a lockable vault while the soft copies of data were password protected.

3.9 Data collection

Data collection was conducted at The KNH Records' Department. Using existing records, files of patients who underwent oncologic esophagectomy, and fit into the inclusion criteria were sampled.

A structured data collection tool was used to compile data.

Data sources for this study were the patients' files. Doctors' notes, theatre notes, nursing cardex were examined to determine post op course for these patients.

Data was collected on the socio-demographic features of the patients, the outcomes and timing of methylene blue dye test, whether positive for anastomotic leak or negative and clinical features defining the presence or absence of anastomotic leak i.e. change in chest drain effluent in terms of presence of pus, saliva, ingested food particles, bile, or swelling, erythema, pus, saliva drainage from the cervical incision site

3.11 Data management

Once data is collected, it shall be entered into the Microsoft Excel 2010 software for cleaning.

It shall then be stored in a password protected data sheet for analysis.

3.12 Data analysis

SPSS version 26 was used for data analysis.

To describe characteristics of the study participants, mean, median, standard deviation and ranges were used for continuous variables, while proportions and percentages were used for continuous variables.

To assess the sensitivity of methylene blue test for assessing anastomotic leak, the gold standard for methylene blue test to be compared with is the clinical parameter which is defined by a characteristic effluent from the chest tube, erythema, pus, saliva drainage from cervical incision site.

Therefore, to assess the methylene blue test, sensitivity, specificity and accuracy of the test against the clinical gold standard shall be used. Positive and negative predictive values have been computed to assess the performance of the methylene blue test.

Results of the study are displayed in frequency tables, pie charts and bar graphs,

3.13 Data dissemination

The study findings will be available in UoN Repository and will be shared in conferences, KNH Management, local departmental meetings. This will be done through the Head of Unit, Cardiothoracic Surgery to the hospital management

A manuscript shall be prepared and sent to a peer reviewed journal for publication.

3.14 Study limitations

Missing files and records – since the study is using file records to collate information, missing files and poor records may impact the study findings. However, the principal researcher shall ensure only records which are well collected are used for this study. Research assistants shall

also be adequately trained and their input supervised and counterchecked to ensure it meets the threshold for data collection.

CHAPTER 4

RESULTS

A total of 265 patients who underwent esophagectomy for malignant diseases and met inclusion criteria were analysed

Social Demographic characteristics

The mean age of the participants was 56 years and a standard deviation of 11.8 within a range of 28 to 85, the median age of the participants was 55 years (Figure 1).

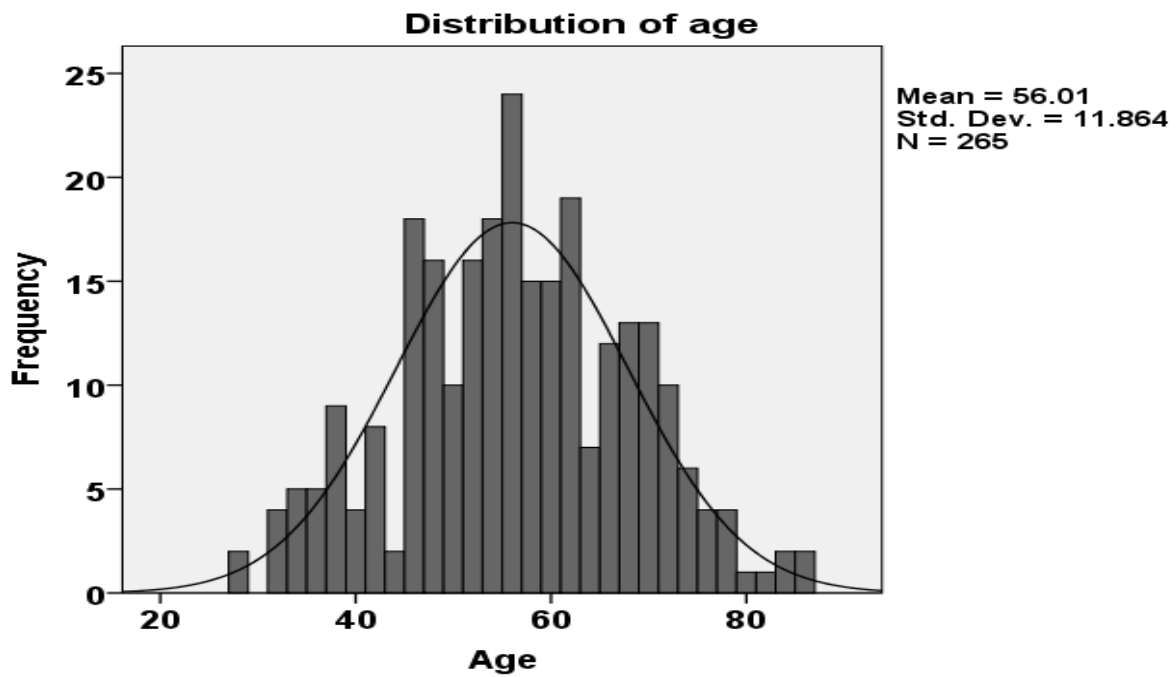


Figure 1: A histogram representing the distribution of age

The results of the demographic characteristics of the patients indicated that 140 (54%) of the patients were male, while 120 (46%) of them were female. (Figure 2)

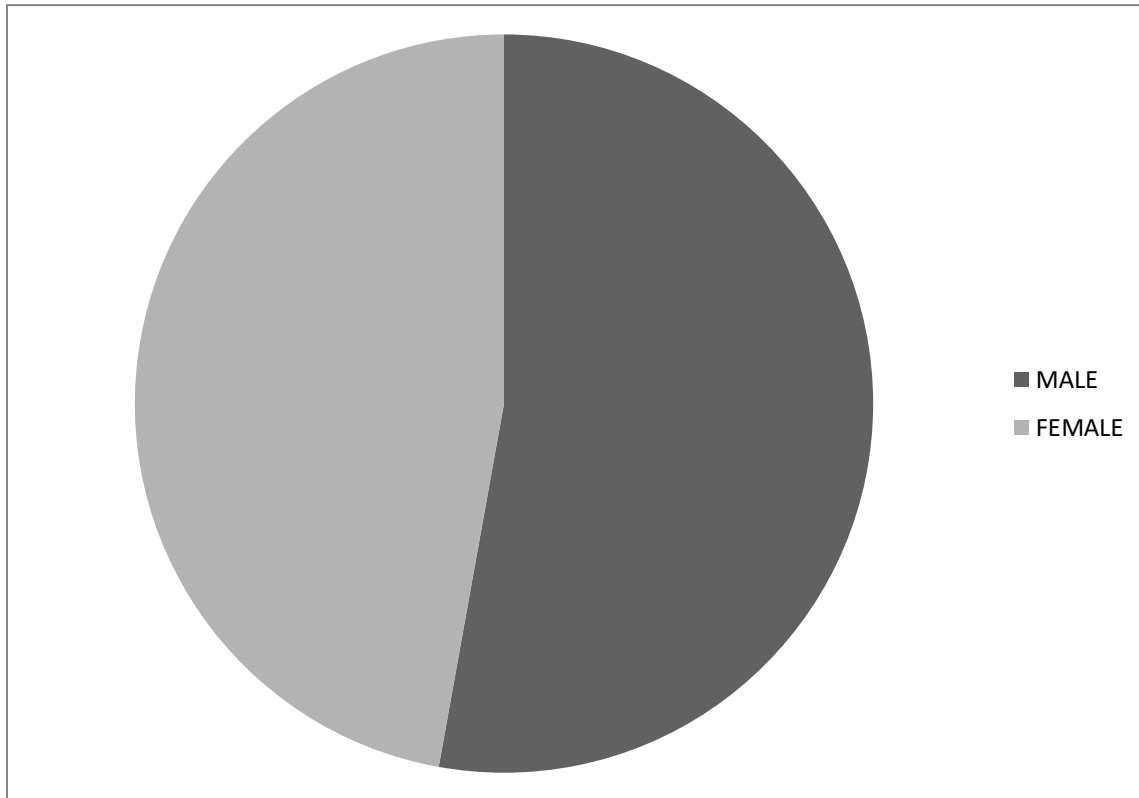


Figure 2: Distribution of the Sex of the patients

Anastomosis site distribution.

A total of 218(82.3%) anastomoses were fashioned on the cervical region, while those who had intrathoracic anastomosis were 47(17.7%) (Figure 3).

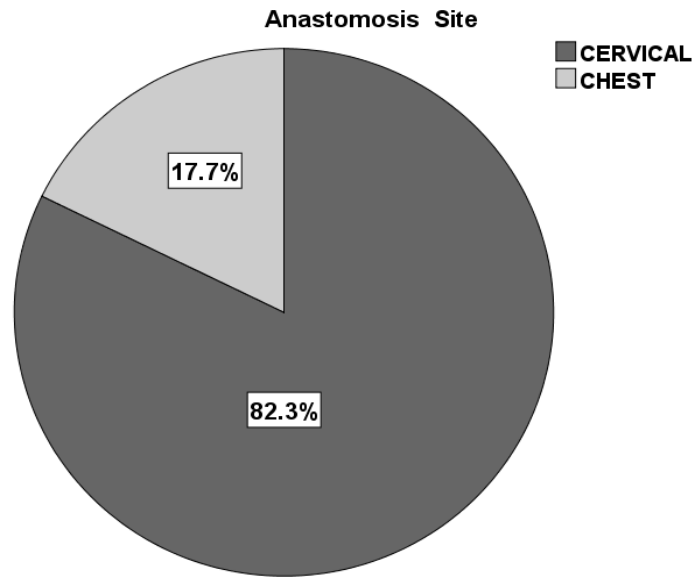


Figure 3: A pie chart showing the distribution of anastomosis site

	Clinical AL	No Clinical AL	Total
Cervical anastomosis	73(93.6%)	145	218
Intrathoracic anastomosis	5(6.4%)	42	47
Total	78	187	265

Table 1 Distribution of anastomotic leaks as per anastomotic site.

Odds ratio (OR) of 4.23, 95%CI (1.605,11.14), (P- 0.0035)

93.6% of anastomotic leaks occurred in patients who had cervical anastomosis. 0.64% occurred in patients who had intrathoracic anastomosis.

Mean post op day of the MB test

The mean post op day of the MB test was 7.1 and a standard deviation of 0.8 with a median of 7 and a range of 5 to 10 (Figure 4).

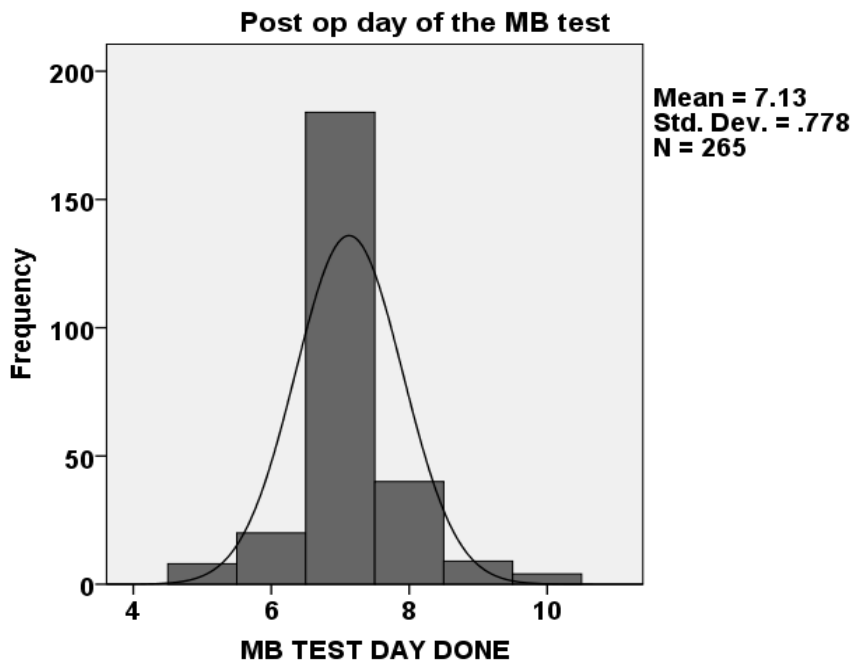


Figure 4: A histogram of post op day the MB test was done.

Methylene blue test results

Methylene blue test results turned positive for 11(4.2%) of the patients. Negative methylene blue for 254(95.8%) of the patients (Figure 5).

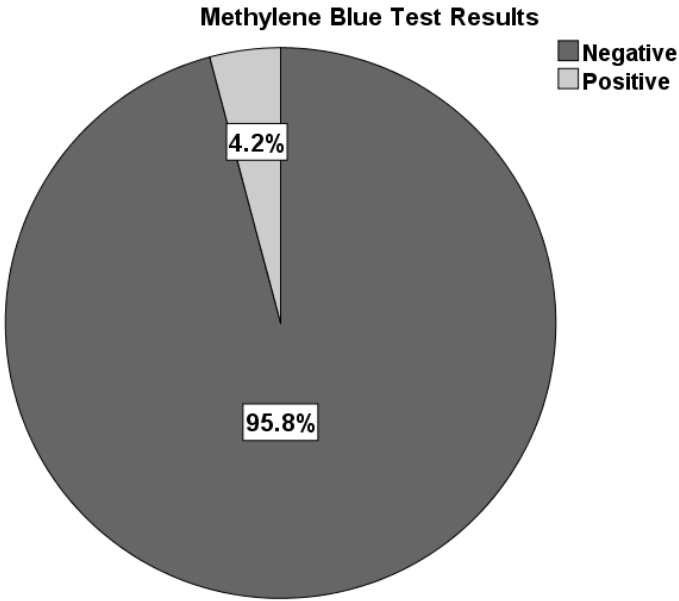


Figure 5: Distribution of the methylene blue test results

Clinical anastomotic leak was present in 78 (29.4%) and absent in 187 (70.6%) of the patients (Figure 6).

All the cases that had a positive methylene blue test had their anastomoses on the cervical region. Mean post-operative day when methylene blue test was done in this group was day 6.

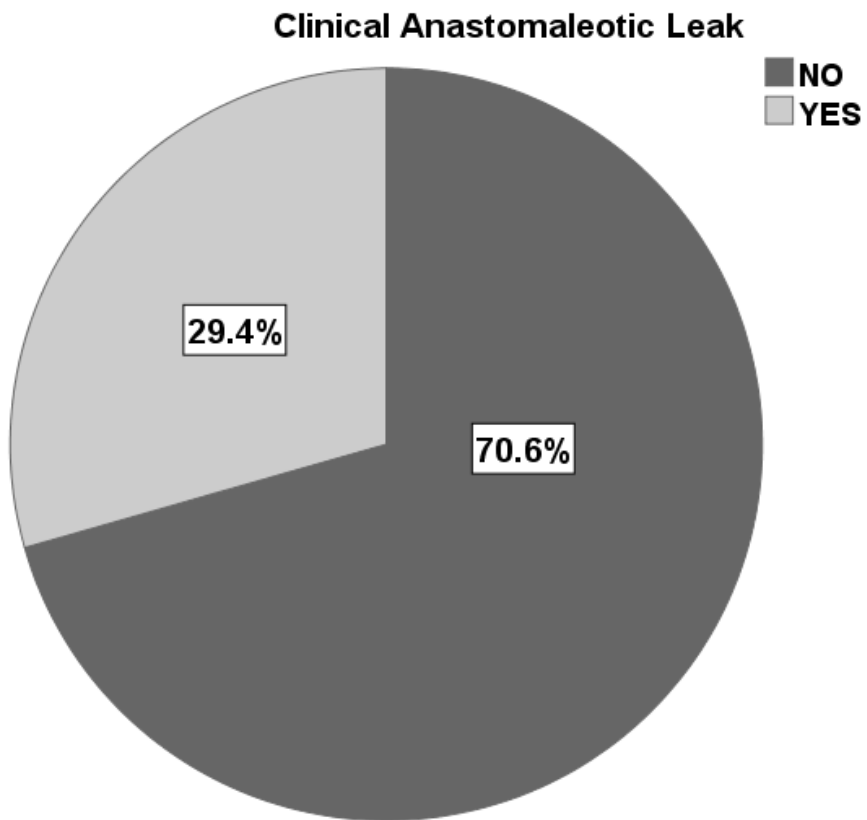


Figure 6: A pie chart showing the distribution of clinical anastomotic leak

Prevalence of AL amongst patients with cervical anastomosis was found to be 33%, while amongst those with intrathoracic anastomosis was 10.6%.

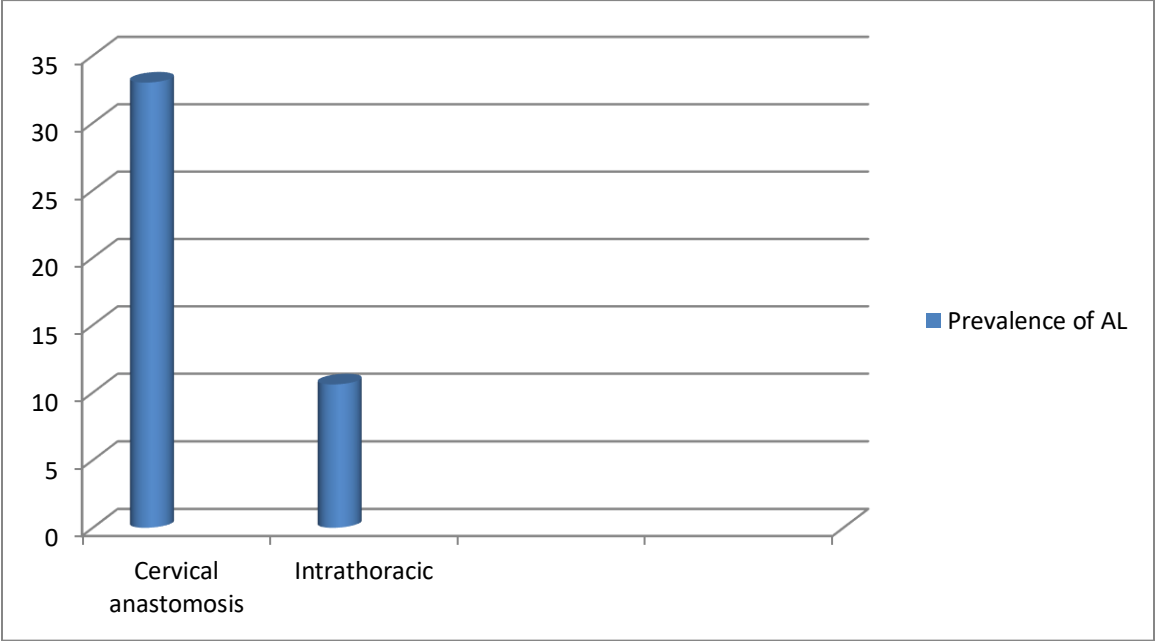


Figure 7; Prevalence of AL in cervical vs intrathoracic anastomosis groups

Table below shows comparison of MB test positivity in patients with clinical AL, as per anastomotic site. All the 11 cases of positive MB test had anastomosis in the cervical region.

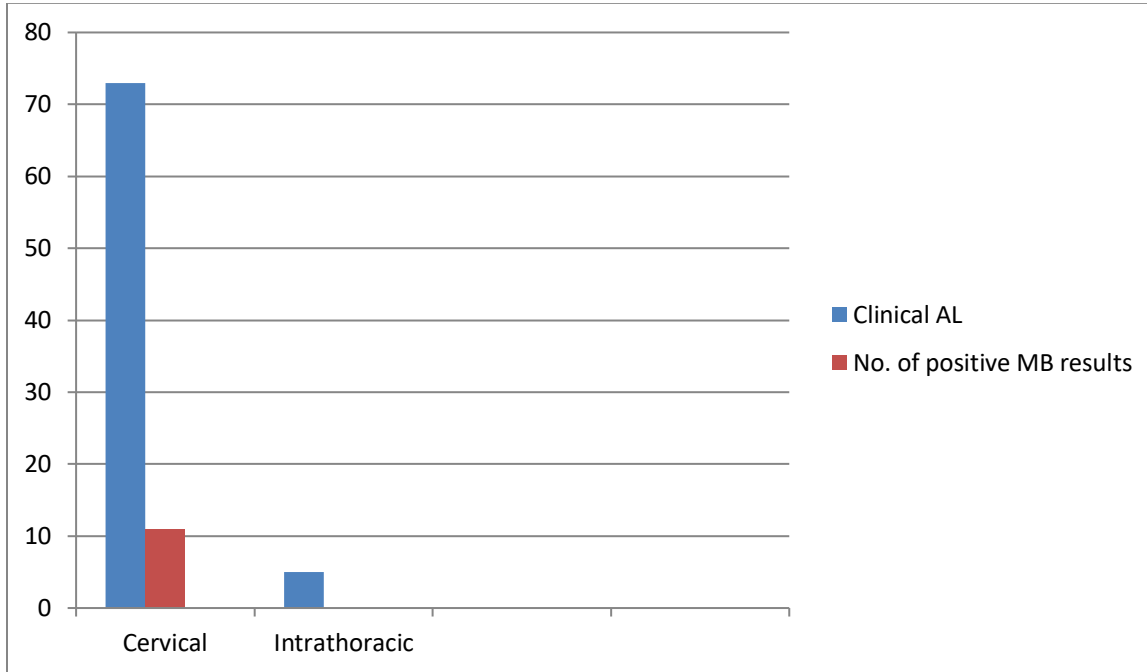


Table 2 above shows MB positivity amongst the two groups of patients

Presence of ingested food particles in the chest drain and cervical incision site was the most common clinical characteristic amongst patients who had clinical AL 33(42.4%) (Table 1)

Table 3: The table below is a summary of the characteristics presented by the patients who had clinical anastomotic leak

Characteristics	Count	Percentage	
Ingested food	33	42.4	
Pus	31	39.7	
Swelling/erythema	10	12.8	

Saliva	7	9.0	
Empyema	6	7.7	

Day of clinical manifestation

The mean day of clinical manifestation was 9 and a standard deviation 1.6. The median was 10 with a range of 7 to 13 (Figure 7).

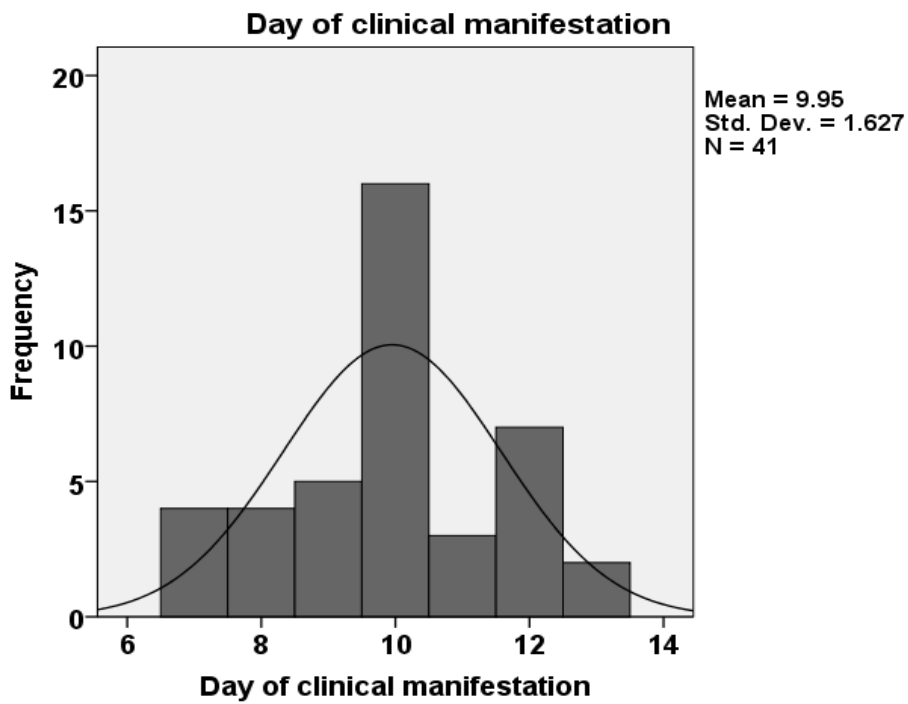


Figure 8: The histogram shows the days of clinical manifestation

Objective 1

To determine the sensitivity and specificity of methylene blue dye test in diagnosis of AL post esophagectomy.

Table 4: Summary two way table for methylene blue dye test and AL post esophagectomy

MB test results	Present Clinical anastomotic leak.	Absent Clinical anastomotic leak	Total
Positive	11	0	11
Negative	67	187	254
Total	78	187	265

Table 5: A table for sensitivity and specificity

measure	value	95% confidence interval	
Sensitivity	14.1%	7.3	23.8
Specificity	100%	98.1	100

Objective 2

To determine the Negative predictive and positive predictive values of methylene blue dye test in diagnosis of AL post esophagectomy

Table 6: A table for negative predictive and positive predictive values

measure	Value (%)	95% confidence interval	
Positive predictive value	100	71.5	100
Negative predictive value	73.6	68.2	78.9
Prevalence	29.4	23.9	34.9
Accuracy	74.7	69.1	79.8

Discussion. Methylene blue test is widely used as a bed side diagnostic modality for esophageal anastomotic leaks. This is due to the fact that it is cheap, easy to administer and has a well-established safety profile. Accuracy of this test has remained unknown locally.

The purpose of this study was to determine the accuracy of methylene blue dye test in diagnosis of AL post esophagectomy. Sensitivity and specificity, negative predictive and positive predictive values of methylene blue dye test in diagnosis of AL post esophagectomy were calculated. Results of methylene blue dye test were compared to a gold standard, which in this study is the presence of clinical anastomotic leaks, which is characterized by the presence of characteristic chest drain effluent: the presence of pus, ingested food particles, digestive fluid (saliva, bile), and erythema, pus, presence of ingested food particle, saliva on the cervical surgical wound.

The mean age of the participants was 56 years and a standard deviation of 11.8 within a range of 28 to 85, the median age of the participants was 55 years

This study demonstrated a sensitivity of 14.1% and a specificity of 100%, with negative and positive predictive values of 73.6% and 100%, respectively, and a diagnostic accuracy of 74.7%.

Clinical anastomotic leak was diagnosed in 29.4% (n = 78) of the patients. This falls within the range published by many authors worldwide, which is between 7.4 and 48% (6).

Majority of the patients, 93.6% (n-73), who had clinical anastomotic leaks, had their anastomoses done in the cervical region, and 6.4% (n-5) had intrathoracic anastomosis.

In a study done in the UK by Rotundo et al. (3), AL was diagnosed in 10.6% of patients; MB test done on post-operative day 5 yielded positive results in 66% of patients, all of which had clinically significant leaks; while contrast studies (CS) diagnosed 100% of the leaks, including those who had a subclinical course (3). Anastomotic integrity was tested using both methylene blue and contrast esophagography.

In a study by Juntang Guo et al. (4), 1867 patients who underwent esophagectomy were analyzed. Overall leak rate was 1.8%. Anastomotic leakage occurred in an average of 9.7 days from the time of esophagectomy. The diagnostic accuracy of methylene test was 30.1%, while that of contrast CT scan was 89% (4).

In comparison with above two studies, results of this study show a higher diagnostic accuracy of MB test.

The mean post-operative day when MB dye test was done as per this study was 7.1 with a standard deviation of 0.8, a median of 7, and a range of 5 to 10 days. This is within the bracket time when the dye test is done in different centers, as demonstrated by the two studies above. In KNH, MB dye test is done on post-op day 7 because several studies show that the median time of occurrence of AL is days 7-9. Secondly, a seven-day period is required for re epithelialization of the anastomosis. However, majority of the patients who tested positive had their tests done on days 5 and 6 (54%). This particular group of patients had other non-specific symptoms of AL, such as fever and elevated WBCs, and therefore the test was carried out earlier than day 7.

In this study, the mean time of occurrence of clinical anastomotic leakage was day 9, with a standard deviation of 1.6. The median was 10, with a range of 7 to 13, which is like in most centers, where the mean time for the occurrence of clinical signs of anastomotic leak is day 9.

Pus drainage from the neck incision and the presence of ingested food particles in the chest or cervical incision sites were the most common presenting signs of AL.

An ideal diagnostic test, though it doesn't exist, would have a sensitivity and specificity of 100%. Different diagnostic tests can usually have high sensitivity and low specificity, and vice versa. A highly specific test will usually sacrifice sensitivity by having a high false-negative rate. This makes a highly sensitive test ideal for a screening examination, whereas highly specific tests are good for confirming a diagnosis. From this analysis methylene blue test can be used as a screening test, and other tests e.g. upper GI contrast studies, contrast CT scans, and early endoscopy to confirm diagnosis.

Conclusion

Methylene blue test has high specificity but low sensitivity, making it ideal for use as a screening test. The test also has shown to have a good negative predictive value (73%), based on the prevalence of the disease in our set up (29.4%) This is useful because it shows that true negatives in our setup will be low if MB test is negative. Results of this study have demonstrated that methylene blue test done earlier than day 7 could yield better results and is more useful in patients with cervical anastomotic leaks. This study can therefore be used as a basis to compare the accuracy of methylene blue test with other diagnostic methods used in our setup, e.g., upper GI contrast studies.

Limitations of the Study

The study relied on data from a single center; a multicenter study would be more representative and offer clearer and more acceptable results. As a retrospective study it has an inferior level of evidence compared with prospective studies.

Recommendations

Methylene blue test to be used as a screening test, but other tests: Contrast upper GI studies, CT scan upper GI endoscopy to be used as confirmatory tests in symptomatic patients and those with derrayed laboratory results.

Further studies to be conducted to compare MB test with other frequently used diagnostic modalities.

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LIST OF APPENDICES

Appendix 1: Data collection tool

Form number: _____

- Age (years):
- Sex:
 - Male
 - Female
- Anastomosis site;
 - i. Cervical
 - ii. Intrathoracic
- Post op day of the MB test
- Methylene Blue test results:
 - i. Positive
 - ii. Negative
- Clinical anastomotic leak: Yes / No
- i. Pleural fluid changes: Pus
 - Bile
 - Saliva
 - ii. Cervical incision site changes; Erythema
 - Swelling

Pus drainage

Presence of food particles

Presence of saliva

Appendix 2: Administrative consent to conduct the study

I Dr. Jedidah Chepkorir, a registrar in the THORACIC AND CARDIOVASCULAR SURGERY Unit of Department of Surgery, University of Nairobi, would like to seek consent from the Research and Administration department/Office of the Kenyatta National Hospital to Conduct a research study entitled, **UTILITY OF METHYLENE BLUE TEST IN DIAGNOSIS OF ANASTOMOTIC LEAKS POST ESOPHAGECTOMY FOR MALIGNANT DISEASES.**

This study entails using patients’ files to assess the role of methylene blue dye in detecting anastomotic leaks after esophagectomy.

Information derived from this study will help to inform clinicians on role of the test and whether it adds any diagnostic value in patients undergoing this procedure.

No patient identifying information will be collected.

Results of this study shall be shared with the stakeholders to help improve local policies and guidelines on management of patients undergoing esophagectomy.

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Hospital representative

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Principal Investigator

