

Intraoperative hypotension is not associated with adverse short-term postoperative outcomes after esophagectomy in esophageal cancer patients

Ephraim Teffera Yeheyis (✉ ephhram@yahoo.com)

Addis Ababa University School of Medicine <https://orcid.org/0000-0003-2968-500X>

Seyoum Kassa

Addis Ababa University School of Medicine

Hiwot Yeshitila

Addis Ababa University School of Medicine

Abebe Bekele

Addis Ababa University School of Medicine

Research article

Keywords: Esophageal cancer, esophagectomy, low blood pressure, mortality, anastomotic leak

Posted Date: June 25th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-37807/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on January 2nd, 2021. See the published version at <https://doi.org/10.1186/s12893-020-01015-z>.

Abstract

Background The effect of low systolic blood pressure and its subsequent postoperative outcome during esophagectomy for esophageal cancer is not well studied. **Methods** Prospective study was conducted and data were collected on patients who underwent esophagectomy and esophagogastrectomy for esophageal cancer. Intraoperative Hypotension (IOH), defined as Systolic Blood Pressure (SBP) < 90 mm Hg lasting more than 5 minutes, was recorded. Patients' 30 days post-operative composite outcome of mortality, anastomotic leak and prolonged hospital stay were analyzed as outcome variables **Result** A total of 54 patients underwent esophagectomy for esophageal cancer during the study period. The mean age was 54 years. Mean duration of the surgery was 208 minutes. Intraoperative mean low SBP was 80mmHg while the lowest record was 55 mmHg. IOH occurred in 51.2 % (n=29) of patients; of these, 7.4% (n=4) had anastomotic leak (OR 1.2, 95% CI 0.26-6.3; p=0.76) , mortality was 5.5% (n=3) (OR 1.44, 95% CI 0.22- 9.3; p =0.7) and 33 % (n=18) had prolonged hospital stay (OR 0.53, 95% CI 0.14- 1.9; p=0.34). Over all anastomotic leak rate was 13% (n=7). The 30 days operative mortality was 9.2% and 55 % (30) of patients had prolonged hospital stay. Multivariate analysis (logistic regression model) showed SBP < 90mmHg for more than 5 minutes was not significantly associated either with individual or composite outcomes of mortality, anastomotic leak and prolonged hospital stay (AOR 1.06 ,95% CI 0.98-1.14; p=0.16) **Conclusion** In patients undergoing esophagectomy for esophageal cancer, a systolic blood pressure < 90 mm Hg for greater than 5 min during surgery has no significant statistical association either with individual or composite adverse outcomes of mortality, anastomotic leak and prolonged hospital stay.

Introduction

Globally esophageal cancer is on the rise being the 8th most common cancer and 6th most common cause of death from cancer¹. It is, particularly, increasing in Sub-Saharan Africa with higher incidence rates in Eastern and Southern African Sub-regions². It is also the leading cause of elective cardiothoracic admissions to the surgical ward for procedures performed at our University hospital³. Esophageal cancer results in severe multifaceted insults to the physiology and cardiorespiratory reserve. Not only does it cause homeostatic derangements due to cachexia as in other malignancies, but the dysphagia and subsequent dehydration further confounds their clinical status⁴. The presenting symptoms of esophageal cancer usually signify locally advanced disease, distant metastases, or both, irrespective of histologic type; even in cases with "early" diagnosis^{5,6}. Hence, patients tend to have an overall poor performance status, a state of depleted intravascular volume, and hypoalbuminemia at the time of diagnosis resulting in higher risk of postoperative morbidity and mortality.

Esophagectomy, the main stay of management in esophageal cancer, is a major and complex surgery involving the abdomen, chest, and / or neck. It is commonly associated with significant blood loss⁷⁻¹⁰. Manipulation of the mediastinum during surgery often leads to decreased preload, vagal stimulation and arrhythmia^{11,12}, thereby worsening the state of hypovolemia and hypo perfusion. It is estimated up to

75% of esophagostomies are associated with intra operative hypotension¹³. There is, however, paucity of data on the relationship of intraoperative low Systolic Blood Pressure (SBP) and postoperative outcomes during esophagectomy particularly from a low resource, high volume centers.

We, therefore, prospectively studied the effect of intraoperative hypotension during esophagectomy and adverse short term postoperative outcomes among patients operated for esophageal cancer.

Patients And Methods

Study design and data collection

This is a prospective observational cohort study on patients who underwent esophagectomy for esophageal cancer from August 1, 2017 to March 30, 2020. Diagnosis was made based on clinical presentation, endoscopic evaluation, biopsy, and radiologic study (contrast x-rays and / or CT scan).

Inclusion criteria

All male and female patient's older than 18 years of age who underwent standard esophagectomy were included in the study.

Exclusion Criteria

Patients who had exploration only, patients with feeding gastrostomy or jejunostomy tube insertion without esophagectomy due to unresectable disease, patients with poor pre-operative performance status, patients with cervical esophageal cancer, and patients who had signs indicative of advanced disease state such as hoarseness of voice , malignant ascites ...etc. were excluded.

Sample size and sampling technique

The sample size was calculated using statistical software Epiinfo with power of 80 and CI of 95%. Consecutive patients were used in sampling technique.

Data collection data collection tool

Data were collected prospectively in a structured and pretested data collection format. Socio-demographics, clinical information on preoperative and intraoperative variables, as well as postoperative morbidity, mortality, and post op stay were documented. Modified Takita's grading 1 -6¹⁴ was used for the assessment of dysphagia. American Society of Anesthesiology (ASA) physical status classification system I-IV¹⁵ for preoperative anesthesiology evaluation, BMI (Body Mass Index) based on body weight and height (kg/m²), Eastern Cooperative Oncology Group (ECOG) performance classification (0-4)¹⁶, serum albumin, serum creatinine, serum electrolytes and liver enzyme tests were recorded. Preoperative

ECG, echocardiography and radiologic characteristics from barium swallow and CT studies were also recorded. AJCC 8th edition Esophageal Cancer staging was used for clinical staging¹⁷.

Definitions

As one of frequently used thresholds identified in systematic review done by Bijker et al¹⁸, SBP < 90 mmHg, and duration of more than 5 min^{18,19} was used to define Intra Operative Hypotension (IOH).

Anastomotic leak was defined by clinically diagnosed leak, and prolonged hospital stay was defined as hospital stay more than 7th post op day.

Intraoperative blood loss, intraoperative events including arrhythmias, need for blood transfusion, need for inotropic and / or vasopressor support were documented.

Trans hiatal esophagectomy was preferred for mid and distal thoracic esophageal cancers and performed in 51.0% (n=26) of cases. McKeown's esophagectomy was preferred for mid and upper thoracic esophageal cancers which are at T4 stage and performed in 15.7% (n=8) of the cases. Ivor – Lewis procedure was performed for 3.9% (n=2) patients while 29.6% (n=16) patients had Left thoracotomy approach as it was preferred for gastro esophageal junction and proximal gastric cancers. All esophago-gastric anastomosis were done via the anatomical esophageal bed and with hand sewn techniques.

End Point

The primary end point was the individual outcome variables or composite outcome of anastomotic leak, mortality of any cause, and prolonged postop hospital stay. Patients were followed for 30 days post operatively.

Data quality assurance

Data completeness was checked by reviewing data collection format and Patient medical records regularly.

Ethical Consideration

An approval from the Institutional ethics review board (*Addis Ababa University College of Health Sciences: Protocol Number 084/17/Surg.*) was acquired and written consent was obtained from the patients

Statistical Analysis

IBM SSPS 23 software package was used for statistical data analysis. Descriptive statistics was used for describing the data and results are presented in percentage and simple frequency, mean (SD) and median are used for other data. Factors with a possible influence on perioperative morbidity and mortality were

calculated using multivariate regression analysis. A p -value of <0.05 was considered statistically significant.

Results

1. Socio demographic characteristics

A total of 54 patients were included in the study. Mean age was 54 (SD ± 12.08) years and 61.1% (n=33) were females. Mean body weight of the study participants was 49.04 (SD ± 9.74) Kg and mean BMI was 18.6 (SD ± 2.85). Thirty-three (62.3%) of the patients were from rural area and 16 29.6% (n=16) of the study participants were from esophageal cancer endemic localities of the country. (Table 1)

Table 1: Socio-demographic characteristics of the study participants

Variable	Number (%)
SEX	
Male	21(38.9)
Female	33(61.1)
Residence	
Urban	20 (37.7)
Rural	34 (62.3)

2. Clinical presentation

Fifty patients (92.6 %) presented with complaint of dysphagia and the mean duration of dysphagia was 7 months (SD ± 5.2). Grade III and IV dysphagia were more common presentations than other grades of dysphagia 31.5 % (n=17) and 35.2 % (n=19) respectively. No supraclavicular lymph node was appreciated clinically in 92.6% (n=50) cases at presentation. (Table 2)

3. Preoperative risk assessment

Fifty two (96 %) of the patients were in good performance state with ECOG class 2 or less. There was no patient in ECOG class 4. Fifty percent (n=27) were in ASA class 1 classification and 88.9% (n=48) had no known comorbidity. Cardiovascular disease (mostly hypertension) was the commonest comorbidity found in 4 (7.4 %) of patients. Only 7.4% (n=4) had history of smoking.

Table 2: Clinical parameters

Variable	Number (%)
Presence of dysphagia	
Yes	50 (92.6)
No	4 (7.7)
Degree of dysphagia	
Complains but can still swallow (I)	1(1.9)
Requires liquid to swallow (II)	6(11.1)
Can swallow semisolids but not solids (III)	17(31.5)
Can swallow liquids but not semisolids (IV)	19(35.2)
Can swallow saliva but not semisolids (V)	9(16.7)
Can't even swallow saliva (VI)	2(3.8)
Presence of Supra clavicular lymph node(LN)	
Yes	2(3.8)
No	50(92.6)
Missed data	2(3.8)

4. Investigation results

Mean preoperative hematocrit was 38.41% (SD \pm 8.14) and mean WBC was 6674.2 (SD: \pm 2058). Mean serum albumin was 3.92 (SD: \pm 0.85) g/dl and median serum K⁺ was 4.00 (IQR: 3.60 -4.50) meq /L. Mean serum creatinine was 1.04 mg/dl and 88.9% (n=48) patients had no derangement of liver enzyme tests. Minor abnormal ECG was noted in 23% (n= 12) patients and 8% (n=4) cases had evidence of old ischemic changes.

CT imaging was done for 86.3% (n= 44) of the cases 23.8% (n=10) and 4.7% (n=2) had loss of fat plane between the aorta and esophagus and between the tracheobronchial tree and esophagus respectively. Mean length of malignant strictures on barium swallow study and on CT imaging was 4.94 (SD \pm 2.11) cm. Fifty two (96.3%) had upper GI Endoscopy evaluation. The mean location of tumor from incisors was at 32cm (SD: \pm 4.67). Biopsy results have revealed Squamous cell carcinoma in 72.2% (n=39).

5. Intraoperative findings and events

Thirty nine (72.2 %) patients were in clinically stage III disease and 9.2 % (n=5) patients were in stage IV. More than 90 % of the patients were found to have T3 or advanced tumor stage during surgery. Three (5.5%) patients had invasion of unresectable structures such as the aorta. All patients had lymph node involvement with N1 and N2 stage involvements being the commonest. Five patients had signs of gross metastasis. Omental wrap was used in 51.1% (n=24) of the cases.

Mean duration of surgical procedures was 208.6 minutes (SD \pm 65.89) and mean duration of anesthesia was 238 minutes (SD \pm 75.65). Mean estimated blood loss was 741ml. Mean total duration of SBP < 90mmHg was 18.3 (SD \pm 28.5) minutes. Mean low SBP below 90 mmHg was 80 mmHg (SD \pm 12.4) while the lowest record was SBP of 55 mmHg. IOH occurred in 51.2 % (n=29) of the time. Ten (18.9%) patients needed intraoperative blood transfusion and ten patients (18.9%) required intraoperative inotropic or vasopressor support. (Table 3.)

Table 3: Intraoperative findings and events

Variable	Number (%)
Clinical (Intra Operative) Tumor Staging	
T stage	
T1 (invasion of Submucosa)	0(0)
T2 (invasion of Muscularis propria)	5(9.2)
T3 (invasion of adventitia)	25(46.3)
T4A (invasion of resectable adjacent Structures)	21(38.8)
T4B (invasion of unresectable adjacent Structures)	3(5.5)
N Stage	
N0 (No LN invasion)	0(0)
N1 (1-2 regional LN involvement)	19(35.2)
N2 (3-6 regional LN involvement)	23(42.6)
N3 (≥ 7 regional LN involvement)	12(22.2)
M stage	
M0 (No Metastasis)	49(90.7)
M1 (Distant Metastasis)	5 (9.2)
Ascites	2 (3.7)
Liver metastasis	2 (3.7)
Lung metastasis	1 (1.8)
Clinical Stage	
I	0(0)
II	10 (18.5)
III	39 (72.2)
IV	5 (9.2)
Omental Wrap Use	
Yes	24(44.4)
No	23(42.6)

Missing data	7 (12.9)
Operative Complications*	
Tumor Perforations	3 (5.5)
Part of Tumor Left over	3 (5.5)
Chylothorax	1(1.8)
Recurrent laryngeal Nerve Injury	1(1.8)
Others~	4(7.4)
No Complication	42(77.7)
Need for intraoperative blood transfusion	
Yes	10(18.9)
No	43(81.1)
Missing data	1(1.8)
Need for intraoperative inotropic support	
Yes	15(27.7)
No	32(59.2)
Missing data	7(3.9)

*: Includes complications observed both intra op and Post op

~: includes Persistent air leak from Right, pleural breach, Pyothorax, Splenic injury (splenectomy) GB injury (cholecystectomy)

Table 4: Postoperative care and outcomes

Variable	Number (%)
Need for postoperative blood transfusion	
Yes	15(27.7)
No	37 (68.5)
Missing data	2 (3.7)
Need for Postop Inotropic/vasopressor Support	
Yes	5(9.2)
No	47(87)
Missing data	2(3.7)
Anastomotic leak	
Yes	7(13)
No	47(87)
Reoperation for complication	
Yes	6(11.1)
No	48(88.8)
30 days Mortality	6 (11.1)
In hospital	5 (9.2)
Post discharge, within 30 days post op	1 (1.8)
Probable cause of death attributed to anastomotic leak	2 (3.7)
Probable cause of death not attributed to anastomotic leak	
MI	1 (1.8)
Stroke	1 (1.8)
Chylothorax (sepsis , hypotension)	1 (1.8)
ECOG Performance status 30th Postoperative day	
0: Fully active	2 (3.7)
1: Restricted in physically strenuous activity but ambulatory	10(18.5)
2: Ambulatory and capable of all self-care but unable carry out	19(35.1)
any work activities; up and about > 50% of waking hours	

3: Capable of only limited self-care; confined to bed or chair > 50% of waking hours	18(33.3)
4 :Completely disabled; cannot carry on any Self-care; totally confined to bed or chair	0(0)
Missing data*	4(7.4)

*excluding one death post discharge

6. Postoperative care and outcomes

The 30 days operative mortality was 9.2% (n= 5). Among the in hospital deaths, 3.7% (n=2) were attributed to anastomotic leak. One (1.8%) patient died after discharge within the study period of 30 post op day form unknown cause. There were 12.9% (n=7) cases of anastomotic leak. Six (12.2%) patients underwent reoperations such as feeding jejunostomy tube insertion for complications (anastomotic leak). Mean post op hospital stay was 12 days. Thirty (55 %) of patients had prolonged hospital stay. Fifteen (28.8%) and 5(9.6%) patients needed postoperative blood transfusion and postoperative inotropic support respectively. On 30th day post op 57.4 %(n=31) of the patients were ambulatory in more than 50% of waking hours and capable of all self-care (ECOG 3). (Table 4)

Table 5: Intraoperative hypotension and Outcome variables

End point		No Intraop hypotension N (%)	Intraop hypotension N (%)	OR 95% CI	P value
Hospital stay	≤7 days	5(9.2)	7(12.9)	0.53 (0.14-1.9)	p=0.34
	>7 days	24(44.4)	18(33.3)		
Anastomotic leak	Yes	3(5.5)	4(7.4)	1.28 (0.26-6.3)	p=0.76
	No	23(42.6)	24(44.4)		
Death	Yes	2(3.7)	3(5.5)	1.44 (0.22-9.3)	p=0.70
	No	24(44.4)	25(46.2)		

7. Outcome of patients and associated factors

Four (7.4%) patients with anastomotic leak (OR 1.2, 95% CI 0.26- 6.3; $p=0.76$), 3(5.5%) patients who died (OR 1.44, 95% CI 0.22- 9.3; $p=0.7$) and 18(33 %) with prolonged hospital stay (OR 0.53, 95% CI 0.14,-1.9 $p=0.34$) had experienced IOH. (Table 5)

Multivariable binary logistic regression analysis showed SBP < 90mmHG for > 5 min was not significantly associated with composite outcomes of anastomotic leak, mortality and prolonged hospital stay (AOR 1.06, 95% CI 0.98-1.14; $p=0.16$).

Patients who had N3 (≥ 7 LN) clinical intraoperative tumor stage were 96% less likely to have good composite outcome compared to those patients who had N1 (<3 LN) clinical intraoperative tumor stage (AOR 0.04, 95% CI 0.01-0.97; $p=0.048$). (Table 6)

Table 6: Composite Out comes and Perioperative factors

Variables	COR (95% CI)	p-value	AOR (95% CI)	p-value
N Stage				
N1 (<3 LN)	1		1	
N2 (3-7 LN)	0.53 (0.13, 2.23)	0.388	0.27 (0.05, 1.43)	0.125
N3 (>7 LN)	0.13 (0.12, 1.01)	0.051	0.04 (0.01, 0.97)	0.048*
SBP <90mmHg >5 min	1.06 (0.99, 1.12)	0.056	1.06 (0.98, 1.14)	0.160
SBP <90mmHg	2.36 (0.7, 7.93)	0.166	1.07(0.16,6.99)	0.945
Lowest SBP	0.96 (0.91, 1.01)	0.135	0.98 (0.93, 1.03)	0.423
Pre op ECOG performance				
Level 0 and 1	0.41 (0.11, 1.51)	0.181	0.46 (0.08, 2.73)	0.394
Level 2 and 3	1		1	

*statistically significant

Discussion

The rates of morbidity and mortality following esophagectomy for esophageal cancer are improving ⁽²⁰⁾. In a 1980 review article, operative mortality for esophageal resection was 29 %²⁰. In mid 2000s operative mortality decreased to 10-11 %^{9,21,22}. While multiple literatures suggested tumor stage, histologic sub

type, performance status, age, type of surgical approach, intraoperative blood loss and blood transfusion as risk factors, few have clearly addressed the effect of intraoperative hypotension on postoperative morbidity and mortality of patients undergoing esophagectomy for esophageal ca^{9,10,21-27}. Furthermore lack of agreed upon definitions of intraoperative hypotension (IOH) during surgical procedures, including esophageal resections has confounded the association between blood pressure deviations during surgery and mortality^{15,18}. The paucity of such studies makes comparison with our study challenging.

In our study we found that neither intraoperative hypotension, SBP < 90mm Hg for more than 5 min (OR 1.06, 95%CI 0.98- 1.14; $p= 0.160$) nor the lowest SBP (OR 1.07, 95 % CI 0.16- 6.99; $p= 0.945$) were associated with adverse composite out comes of mortality, anastomotic leak or prolonged hospital stay. The overall mortality was 9.2 %. This was similar to post esophagectomy mortality rates of 3-16 % reported by multiple studies^{9,10,21-23,25}. In this study mortality adjusted for Trans Hiatal Esophagectomy (THE) only, was 10% which was less than the 18.7 % reported in a 2012 study for THE in the same institution but not statistically significant ($p=0.34$).⁷

IOH was not found to be associated with an increased perioperative mortality (5.5% vs 3.3%; OR 1.44 (0.22, 9.3) $p=0.7$). This finding aligns with the retrospective cohort study on combined intraoperative blood pressure data by Monk et al¹⁹ which identified Systolic BP < 70 mm Hg, not higher, for ≥ 5 min to be associated with increased 30-day operative mortality in non-cardiac surgery. A study by Fujisawa, A et al²⁶ found that patients with intraoperative hypotension showed significantly lower 1 year cancer specific survival than patients without hypotensive episodes ($p=0.0002$). They, however, defined intraoperative hypotension as SBP < 70mmHg and did not describe short term outcome.

The anastomotic leak we found in this study is had no significant statistical association with intraoperative hypotension (5.5 % Vs 7.4 %; $p=0.76$). This is in contrast to the finding by Fumagalli U. et al²⁷ where leaks were significantly more common in patients with intra-operative hypotensive episodes ($p= 0.02$). Their study involved larger patient number (84), defined hypotensive episodes as SBP decreasing more than 30 % of the basal value for more than 5 min, and had procedures performed in prone position. Unlike their study, none of our study patients were operated in prone position.

Our anastomotic leaks accounted for 2(33.3%), of the deaths and had a 2/7 (28.5 %) mortality which is comparatively higher than a 12 % mortality from anastomotic leak found in a systematic review done by Verstege et al²⁸ and other recent data³⁰ but comparable to the 37 % mortality reported by Turkyilmaz A et al²⁹

Even though Gockel and colleagues⁹ in their study involving 424 patients suggested that tumor characteristics, e.g. TNM classification, were of no influence on the postoperative course our study, however, found that N3 stage, hence stage III disease, is significantly associated with adverse short term postoperative out comes (AOR 0.04 (0.01- 0.97 $p= 0.048$). This result is in agreement with other risk analysis studies which suggest that those with stage III or IV disease have a higher postoperative mortality^{30,31}

Limitations And Recommendations

In this study, we have identified certain limitations. It has a small sample size and has some missing data. The study also hasn't addressed the effect of sustained and non-sustained IOH. Additionally, IOH was not defined and analyzed in terms of mean arterial and diastolic blood pressure on short term post op outcomes. Moreover, the study did not analyze the association and outcome of IOH with stage sub types, different esophagectomy approaches, and histologic subtypes. Furthermore, the study has not addressed other secondary end points such as wound infection, pulmonary complications...etc.

Conclusion

In this study, we found that a systolic blood pressure < 90 mm Hg for greater than 5 min during surgery has no significant statistical association either with individual or composite adverse outcomes of mortality, anastomotic leak and prolonged hospital stay.

Abbreviations

AJCC : American Joint Committee on Cancer

AOR : American Society of Anesthesiology

BMI : Body Mass Index

CI : Confidence interval

COR : Crude Odds Ratio

ECG : Electrocardiogram

ECOG : Eastern Cooperative Oncology Group

IOH : Intra operative hypotension

LN : Lymph Node

OR : Odds Ratio

RBBB : Right Bundle Branch Block

SBP : Systolic Blood Pressure

TNM : Tumor Lymph node Metastasis

THE : Trans hiatal Esophagectomy

Declarations

Ethics approval and consent to participate

- An approval from the Institutional ethics review board (*Addis Ababa University College of Health Sciences: Protocol Number 084/17/Surg.*) was acquired and written consent was obtained from the patients

Consent for publication

- *Not applicable*

Availability of data and materials

- *The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request*

Competing interests

- *The authors have no conflict of interest to declare*

Funding

- *The funding for the study was granted from the junior Scholars fellowship Program of Medical Education Partnership Initiative program of Addis Ababa University School of Medicine*

Authors' contributions

- *T. Yeheyis: conceived, designed and conducted and coordinated the study, operated cases, collected data, and wrote the manuscript*
- *Kassa: conducted the study, operated cases and collected data*
- *Yeshitla: conducted the study and collected data.*
- *Bekele: Mentorship, operating cases and data collection, revised and edited the manuscript*

Acknowledgements

The authors would like to acknowledge Abebe Bezabih (MD), Birhanu Nega (MD), Ayalew Tizazu (MD), Mahlet Tesfaye (MD) operated cases and Messafint Abeje (BSc, MPH) in entry and data analysis

Authors' information

Ephraim Teffera Yeheyis, MD¹ephhrain@yahoo.com

Assistatnt Prpofessor oF Surgery Division of Cardiothoracic and Vascular Surger Department

References

1. https://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
2. Rabson Kachala Systematic review: epidemiology of Oesophageal Cancer in Sub Saharan Africa. Malawi Medical Journal; Sept 2010 22(3): 65-70 doi: 10.4314/mmj.v22i3.62190.
3. Ephraim T, Seyoum K, Adem A, Patterns Of Cardiothoracic Admissions at A Tertiary Hospital In Ethiopia East and Central African Journal of Surgery. July/August; 2013 18 (2):126-131
4. Poorna A, Pernilla L. Cachexia in patients with oesophageal cancer. Nat Rev Clin Oncol 2016 Mar13 (3):185-98. doi: 10.1038/nrclinonc.2015.200.
5. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy for treatment of benign and malignant esophageal disease. World J Surg 2001 Feb; 25(2):196-203.
6. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun M et al. Cancer statistics, 2003. CJan-Feb 2003; 53(1):5-26. doi: 10.3322/canjclin.53.1.5.
7. B.N. Alemu, A. Ali, D. Gulilat, S. Kassa, A. Bekele Outcome of Trans hiatal Esophagectomy Done for Advanced Oesophageal Cancer. East and Central African Journal of Surgery. November/December 2012 Volume 17 (3) 43- 55.
8. Orringer MB , Marshall B, Chang A, Lee J, Pickens A, Lau C.L. Two thousand transhiatal esophagectomies changing trends, lessons learned. Ann Surg 2007 Sep; 246(3):363-72; discussion 372-4. doi: 10.1097/SLA.0b013e31814697f2. .
9. Gockel I, Exner C, Junginger T. Morbidity and mortality after esophagectomy for esophageal carcinoma: A risk analysis World Journal of Surgical Oncology 2005, 3:37 doi: 10.1186/1477-7819-3-37.
10. Whooley B, Law S, Murthy S, Alexandrou Wong J. Analysis of Reduced Death and Complication Rates After Esophageal Resection Ann Surg. 2001 Mar; 233(3): 338–344. doi: 10.1097/00000658-200103000-00006.
11. Sepesi B, Swisher SG, Walsh GL, Correa A, Mehran RJ, Rice D, et al . Omental reinforcement of the thoracic esophagogastric anastomosis: An analysis of leak and reintervention rates in patients undergoing planned and salvage esophagectomy J Thorac Cardiovasc Surg. 2012 Nov; 144(5):1146-50. doi: 10.1016/j.jtcvs.2012.07.085.
12. J M Daly 1, L H Karnell, H R Menck. National cancer database report on esophageal carcinoma. Cancer. 1996 Oct 15; 78(8):1820-8. doi: 10.1002/ (sici) 1097-0142(19961015)78:8 <1820: aid-cncr25>3.0.co; 2-z.
13. Nikbakhsh N, Amri P, Shakeri A, Shakeri A, Changes in blood pressure and heart rhythm during transhiatal esophagectomy Caspian J Intern Med 2012; 3(4):541-545.
14. Takita H, R. Vincent R, and Caicedo V, Gutierrez A, Squamous cell carcinoma of the esophagus: A study of 153 cases J Surg Onc. 1977 Vol 9(6): 547-554.

15. <https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system>.
16. <https://ecog-acrin.org/resources/ecog-performance-status>.
17. Rice T, Patil D.T. Blackstone E. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice *Ann Cardiothorac Surg*. 2017 Mar; 6(2): 119–130.
18. Bijker J , van Klei W, Kappen T, Wolfswinkel L, Moons K, Kalkman C Incidence of Intraoperative Hypotension as a Function of the Chosen Definition: Literature Definitions Applied to a Retrospective Cohort Using Automated Data Collection *Anesthesiology*, 2007 Aug;107(2):213-20.
19. Monk T, Bronsert M, Henderson W, Mangione M, SumPing ST. et al Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery *Anesthesiology* 2015, 123(8); 307-319.
20. Earlam R, Cunha-Melo Jr - Esophageal squamous cell carcinoma. A critical review of surgery. *Br J Surg*. 1980 Jun; 67 (6):381-90.doi:10.1002/bjs.1800670602.
21. Thomas A. D'Amico Outcomes after Surgery for Esophageal Cancer *Gastrointestinal Cancer Gastrointest Cancer Res*. 2007 Sep-Oct; 1(5): 188–196.
22. Atkins BZ, Shah AS, Hutcheson KA, Mangum J, Pappas T, Harpole Jr D, et al: Reducing hospital morbidity and mortality following esophagectomy. *Ann Thorac Surg* 2004 Oct 78(4):1170–1176.doi: 10.1016/j.athoracsur.2004.02.034.
23. Bailey S, Bull D, Harpole D, Rentz J, Neumayer L, Pappas T, et al Outcomes after Esophagectomy *Ann Thorac surg* 2003(75):217–22.
24. Law SYK, Fok M, Wong J: Risk analysis in resection of squamous cell carcinoma of the esophagus. *World J Surg* 1994, 18:339-346.
25. Mariette C, Taillier G, Seuning I.V. Triboulet J.P. et al. Factors Affecting Postoperative Course and Survival after En Bloc Resection for Esophageal Carcinoma .*Ann Thorac Surg* 2004 Oct; 78 (4):1177-83. doi: 10.1016/j.athoracsur.2004.02.068. .
26. Fujisawa A., Yamauchi-Satomoto M., Uchida T., Miyawaki Y., Kawano T., Makita K. Potential influence of intraoperative hypotensive episodes on postoperative recurrence and survival in patients with complete resection of esophageal cancer *European Journal of Anaesthesiology*: 2012 June 29(27).
27. Fumagalli U , Melis A , Balazova J , Lascari V , Morengi E, Riccardo Rosati R. Intra-operative Hypotensive Episodes May Be Associated With Post-Operative Esophageal Anastomotic Leak, *Updates Surg*. 2016 Jun; 68(2):185-90.
28. Verstegen M , Bouwense S, van Workum F, ten Broek R, Siersema P, Rovers M, Rosman C et al Management of intrathoracic and cervical anastomotic leakage after esophagectomy for esophageal cancer: a systematic review *World Journal of Emergency Surgery* 2019 14:17 .doi.org/10.1186/s13017-019-0235-4.
29. Turkyilmaz A, A Eroglu, Y Aydin, C Tekinbas, M Muharrem Erol, N Karaoglanoglu . The management of esophagogastric anastomotic leak after esophagectomy for esophageal carcinoma. *Dis Esophagus* 2009; 22(2):119-26. doi: 10.1111/j.1442-2050.2008.00866.

30. Lund O, Kimose HH, Aagaard MT, Hasenkam JM, Erlandsen M: Risk stratification and long-term results after surgical treatment of carcinomas of the thoracic esophagus and cardia. *J Thorac Cardiovasc Surg* 1990, 99:200-209.
31. Shao-bin Chen, et al Prognostic Factors and Outcome for Patients with Esophageal Squamous Cell Carcinoma Underwent Surgical Resection Alone. *J Thorac Oncol.* 2013; 8:495-501.