Role of Interleukin 6 in Prediction of Early Complications After Minimally Invasive Esophagectomy – A Pilot Study

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Abstract

INTRODUCTION:

Infectious complications following esophagectomy are associated with significant morbidity. Early prediction of these complications may mitigate significant morbidity and mortality

METHODS:

Patients undergoing minimally invasive esophagectomy for carcinoma esophagus between January 2019 to June 2020 were included in the study. All patients underwent standard preoperative investigations and preparation. Post-operative complications including infectious complications were recorded. Association of postoperative serum interleukin 6 (IL-6) levels with postoperative complications were analysed.

RESULTS:

A total of twenty-two participants were included in the study (median age; 51 years, 13(%) male). The tumor site was middle 1/3rd of esophagus in 13 (59.1 %), lower 1/3rd of esophagus in 9 (40.9 %). The tumor histology was squamous cell carcinoma in all patients. Eight (36.4 %) patients developed Major complications and five of them developed anastomotic leak. IL 6 levels was significantly higher on POD 3 in patients who developed major complications ($p = 0.009$) and anastomotic leak ($p = 0.031$). At receiver operating characteristic curve (ROC curve) analysis an IL 6 cut-off level of 36.4 pg/ml on POD 3 yielded a sensitivity of 87 % and a specificity of 79 % for the prediction of major complication and cut-off level of 44.3 pg/ml on POD 3 yielded a sensitivity of 80 % and a specificity of 82 % for the prediction of anastomotic leak.

CONCLUSION:

A high postoperative IL 6 level helps in the prediction of major complications and cervical esophagogastric anastomotic leak.

Introduction

Esophagectomy is associated with significant morbidity. Respiratory complications, anastomotic leak, systemic inflammatory response syndrome (SIRS), sepsis are the most serious complications following esophagectomy. Even though minimally invasive esophagectomy (MIE) were associated with less blood loss and decreased length of stay but pulmonary complications and anastomotic leak were comparable with open techniques¹. Early prediction of patients at high risk for developing complications helps in clinical decision making and directed therapy thereby improving their outcome.

Various markers have been investigated for their ability to predict complications after esophagectomy. Among these different markers, serum albumin, C-reactive protein and interleukin 6 (IL-6) are regarded as the most favourable prognostic markers available. Only few studies have assessed the predictive value of IL 6 for early diagnosis of postoperative systemic inflammatory response syndrome (SIRS), pneumonia, gastroesophageal anastomotic leakage, pulmonary complications²⁻⁵. These studies have heterogeneous study population, including major abdominal surgery for both oesophageal and gastric malignancies, thoracic surgeries for lung, pleura and oesophagus.

So in this prospective study, we planned to evaluate the feasibility of IL 6 as a predictive biomarker in early prediction of complications after minimally invasive esophagectomy (MIE) for oesophageal cancer.

Methods

Study design and participants

This is a single centre prospective study performed at a tertiary care institute in North India between January 2019 and June 2020. The study was approved by institutional ethical committee. All participants gave written informed consent. Consecutive patients of biopsy proven carcinoma of middle or lower third of oesophagus including gastroesophageal junction (GEJ) tumour were assessed for inclusion. Patient demographic characteristics including comorbidities were recorded for all included patients. All patients underwent upper gastrointestinal endoscopy and staging was done using contrast enhanced computed tomography (CECT) of the neck, chest and abdomen. After staging, locally advanced/ advanced cT3 N+ patients will be subjected to neoadjuvant chemoradiotherapy (NACRT) in the form of platinum/ taxane doublet + 40 Gy/ 20# over 4 weeks. The restaging was done using CECT neck, chest and abdomen, 6-8 weeks after completion of NACRT. Patients with poor performance status, unresectable disease, previous thoracic surgery, conversion to open thoracotomy and those who refused consent were excluded.

Surgical procedure

Esophagectomy was done using McKeown minimally invasive esophagectomy (MIE). First, mobilization was done via video assisted thoracoscopic surgery (VATS) – right thoracoscopic approach in the prone position. The abdominal dissection was done via laparoscopic or open approach as per the surgeons' discretion. Reconstruction was done using gastric conduit with a left cervical esophago-gastric anastomosis in all patients using hand sewn or stapled technique as per surgeon's discretion. A jejunostomy tube was placed in all patients for enteral nutrition.

Post-operative management and outcome assessment

Patients were encouraged for early ambulation and chest physiotherapy. They were started on enteral nutrition via jejunostomy tube on first post-operative day (POD 1). Daily chest drain output volume and character were monitored and recorded. Chest drain was removed when output was < 50 ml/day.

Patients are examined for infectious and anastomotic leak complications and the findings were recorded.

The complications occurring during the hospitalization or within 30 days of the surgery were graded as per Clavien-Dindo classification into minor (Grade I and II) or major (III and above)⁶.

Biochemical IL-6 analyses

Blood sample were collected from the patient in a EDTA vial 3 ml before surgery on admission (preoperative) and then post operatively on the morning of POD 1 and POD 3. Samples centrifuged and plasma were transferred to a polypropylene tube and stored in freezer at - 82° C. The assays were performed in duplicate using human IL 6 ELISA kit.

STATISTICAL ANALYSIS:

Data obtained from the study including all the demographic, operative and tumour characteristics, post-operative complications, Clavien-Dindo classification, preoperative, POD 1 and POD 3 values of IL 6 values were entered directly into the SPSS for analysis.

Statistical analysis was performed using SPSS, version 26 for Windows (SPSS Inc., Chicago, IL). Data for the clinical characteristics of patients (age, BMI, operative time, blood loss, serum albumin, CRP and IL 6) are expressed as median (IQR). Chi square test was performed to determine the association between categorical variables. The clinical characteristics of the patients were compared using the Mann-Whitney U test according to the variable type and the data distribution. The Mann-Whitney U test was performed for two independent groups. The ROC analysis was performed to evaluate the diagnostic accuracy of IL 6. The cut-offs were determined along with sensitivity and specificity. Area under the curve (AUC) was computed and 95% confidence interval (CI) was estimated. $P < 0.05$ was taken as statistical significance for all the analysis.

Results

Patient demographic and Tumour characteristics

A total of 29 patients were evaluated for inclusion. One patient with poor performance status, one patient with conversion to open thoracotomy, two patients with unresectable disease on thoracoscopy and three patients with technical errors on sample storage were excluded. Thus a total of 22 patients were included in the final analysis. The demographic and tumour characteristics are summarised in Table 1. The median (IQR) age was 51 (45,60) years. The tumour site was middle 1/3rd in 13 (59.1 %), lower 1/3rd of oesophagus in 9 (40.9 %). The tumour histology was squamous cell carcinoma in all patients.

Table 1
Clinical Demographic, Operative and Tumour characteristics

Variables	
Age, Median (IQR), years	51 (45,60)
BMI, Median (IQR), kg/m ²	20.38 (19.16,22)
Grade of dysphagia, n (%)	0
Grade 1	6 (28.6)
Grade 2	4 (19)
Grade 3	2 (9.5)
Grade 4	2 (9.5)
Grade 5	0
Grade 6	
History of smoking, n (%)	9 (40.9)
Weight loss (%)	19 (86.4)
Blood loss, Median (IQR), ml	125 (100,300)
Operative time, Median (IQR), min	270 (240,300)
Blood transfusion, n (%)	6 (27.3)
Tumour location, n (%)	13 (59.1)
Middle 1/3rd	9 (40.9)
Lower 1/3rd	
Resection margin, n (%)	20 (90.9)
R0 resection	2 (9.1)
R1 resection	
BMI – Body mass index, IQR – Inter Quartile Range, min – minutes, ml – millilitre	

Table 2
Post-operative Complications

Post-operative Complications	Frequency n (%)
Anastomotic leak	5 (22.7)
Conduit necrosis & Mediastinitis	4 (18.18)
Diaphragmatic hernia with conduit perforation	1 (4.54)
Chyle leak	1 (4.54)
Pleural effusion	3 (13.63)
Vocal cord paresis	3 (13.63)
Pneumonia	3 (13.63)
Pneumothorax	2 (9)
SSI	1 (4.54)
Atrial fibrillation	1 (4.54)
SSI – Surgical site infection	

Intraoperative Characteristics

Total of 13 patients underwent totally minimally invasive esophagectomy (TMIE) and 9 patients underwent hybrid minimally invasive esophagectomy (HMIE) where abdominal dissection was done by open approach. The median (IQR) operative time was 270 min (240,300) and operative blood loss was 125 ml (100,300) (Table 1).

Post-operative Outcome

Twelve patients developed postoperative complications and 8 patients had major Clavien – Dindo complications (Table 3). The cervical esophagogastric anastomotic leak occurred in 5 (22.7%) patients. There was one post-operative mortality on POD 9 due to conduit perforation. Four patients underwent re-exploration. The median (IQR) post-operative hospital stay was 22 (19,30) days.

Table 3
Proinflammatory markers compared with Major complication and Anastomotic leak group

	Major complication	No major complication	P value [†]	Anastomotic leak	No Anastomotic leak	P value [†]
Preoperative IL 6, Median (IQR), pg/ml	3.13 (1.03,6.74)	1.66 (1.09,4.27)	0.441	3.15 (3.11,6.07)	1.5 (0.79,4.27)	0.218
POD 1 IL6, Median (IQR), pg/ml	77.8 (58.39,121.44)	71.43 (52.43,85.43)	0.413	73.77 (51.78,95.34)	74.59 (54.07,85.43)	0.784
POD 3 IL6, Median (IQR), pg/ml	46.88 (41.67,115.49)	15.34 (10.37,29.21)	0.009	48.28 (45.48,91.70)	19.4 (13.55,40.13)	0.031
Preoperative CRP, Median (IQR), mg/L	1.84 (0.83,3.11)	1.87 (1.54,3.11)	0.402	2.72 (1.28,5.88)	1.84 (1.33,3.11)	0.649
POD 1 CRP, Median (IQR), mg/L	86.2 (76.3,103.83)	104.5 (82.7,134.25)	0.533	88.3 (82.2,103.83)	102 (66.69,143.5)	0.949
POD 3 CRP, Median (IQR), mg/L	112.45 (53.5,288)	109.2 (71.55,182.39)	0.903	163 (61.9,273)	104 (60,189.78)	0.644
Preoperative Serum Albumin, Median (IQR), gm/dl	4.40 (4.25,4.57)	4.20 (4.07,4.37)	0.441	4.34 (4.25,4.57)	4.2 (4.05,4.47)	0.595
POD 1 Serum Albumin, Median (IQR), gm/dl	3.25 (2.68,3.4)	3.12 (2.89,3.46)	0.777	3.31 (2.9,3.4)	3.11 (2.87,3.55)	0.726
POD 3 Serum Albumin, Median (IQR), gm/dl	2.98 (2.52,3.3)	3.20 (2.97,3.5)	0.061	2.94 (2.52,3.3)	3.1 (2.94,3.5)	0.152
IQR – Inter Quartile Range, IL 6 – Interleukin 6, CRP – C reactive protein, pg – pictogram, gm – gram, dl – decilitre, L - litre						
† Mann-Whitney U test						

Proinflammatory Markers And Complications

The relation of proinflammatory markers with postoperative complications and anastomotic leak is summarised in Table 3. Preoperative levels of IL 6, CRP and serum albumin were similar among no major complication and major complication group. The median level of IL6 were significantly higher in major complication group on POD 3 (46.88 pg/mL vs 15.34 pg/mL; $p = 0.009$) (Fig. 1A). The median IL 6 levels in patients who developed cervical anastomotic leak were significantly higher on POD3 compared to no anastomotic leak group on POD 3 (48.28 pg/mL vs 19.4 pg/mL; $p = 0.031$) (Fig. 1B). Using an ROC curve, an IL 6 cut-off level of 36.4 pg/ml on POD 3 yielded a sensitivity of 87 % and a specificity of 79 % for the prediction of major complication (AUC: 0.839; 95% CI: 0.64-1.0) (Fig. 2A). An IL 6 cut-off level of 44.3 pg/ml on POD 3 yielded a sensitivity of 80 % and a specificity of 82 % for the prediction of cervical anastomotic leak (AUC: 0.824; 95% CI: 0.642-1.0) (Fig. 2B).

Discussion

In our prospective observational study, we evaluated the role of IL 6 in predicting the complication after MIE for carcinoma oesophagus. In our study, Major complications (Grade III – V) have been reported in nine patients (40.9 %) and cervical anastomotic leak in five patients (22.7 %). The raised IL 6 level on POD 3 helped in predicting major complications and cervical anastomotic leak.

There is paucity of studies using proinflammatory markers as predictor of complications after oesophageal resection for carcinoma oesophagus and most of these are retrospective studies. Therefore, in the present study we evaluated the role of proinflammatory markers in predicting the complications after MIE for carcinoma oesophagus prospectively. Despite improvements in patient selection, preoperative staging, surgery and perioperative care, significant number of patients develops complication after esophagectomy. There is overproduction of inflammatory mediators in the perioperative period which has been shown to predict the development of post-operative complications.

Various proinflammatory markers like serum albumin, CRP, procalcitonin and IL 6 have been studied in predicting complications after esophagectomy with ambiguous results^{2, 7-9}. Only few studies were able to predict post-operative complications. The ambivalent nature of these results paved the way for further research into these proinflammatory markers.

Serum IL 6 response to surgical trauma has been characterized extensively. Surgical stress induces a rise in circulating IL 6 within hours of surgery and may remain elevated upto 72 hours in uncomplicated cases¹⁰. In one study, serum IL 6 value of 310 pg/ml on POD 1 showed a sensitivity of 90 % and specificity of 58 % in diagnosing post-operative sepsis¹¹. In another study, they did sequential measurements of serum IL 6 levels in patients who had undergone surgical resection of the oesophagus to differentiate between sepsis and post-operative SIRS. Persistently elevated serum IL 6 levels until POD 5 were used to predict and differentiate sepsis from post-operative SIRS¹². In another study, high IL 6 levels on POD 1 recognised high risk patients for complications even before changes in CRP levels².

In our study, IL 6 level on POD 3 were statistically higher in complication group. To establish a threshold for the relationship between IL 6 and the development of major complications and cervical anastomotic leak after MIE, receiver operator characteristics (ROC) curve were plotted. A threshold value of IL 6 levels to predict major complications (36.4 pg/ml) providing a sensitivity (87 %) and specificity (79 %) with a diagnostic accuracy of 0.839 and cervical anastomotic leak (44.3 pg/ml) providing a sensitivity (80 %) and specificity (82 %) with a diagnostic accuracy of 0.824. The early detection of complications is clinically important for the initiation of early goal directed therapy to improve the patients' outcome. Elevated IL 6 levels on POD 3 alarms further evaluation for detection and management of complications.

Though the study is limited by small number of study population and single centre, but showed significant association of IL 6 level in predicting early complication in minimally invasive esophagectomy. Early initiation of directed therapy in these high risk patients might help in improving clinical outcomes. However, a multicentre study with a large sample size is required to validate our results.

Declarations

Funding – Funding was taken from institute Research Grant

Conflict of interest/ Competing interest – None

Availability of data and material – Available

Code availability – NA

Ethical approval – Taken from institute ethical committee

Consent to participate – Taken from participant

Consent for publication- Taken from participant

Authors contribution –

Study conception and design: HS,SK,

Acquisition of data: HS,SK,HK,VS,HM,SR

Analysis and interpretation of data: HS,SK,HK,VS,HM,SR

Drafting of manuscript: HS,SK,HK,VS,HM

Critical revision: HS,SK,HK,VS,HM

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Figures

Figure 1

IL 6 levels before surgery and on POD 1 & 3 dependent on the occurrence of major complications (A) and Anastomotic leak (B)

Figure 2

Receiver Operate Characteristics (ROC) curve of IL 6 on POD 3 in prediction of major complications with AUC: 0.839 (A) and Anastomotic leak with AUC: 0.824 (B)