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Predicting Delayed Complications After Esophagectomy in the Current Era of Early Discharge and Enhanced Recovery

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Abstract

Background: Enhanced recovery protocols after esophagectomy aim to discharge patients by day 7. A small risk of delayed complications exists. We aimed to assess whether C-reactive protein (CRP) levels on day 7 could help predict delayed complications and assist safe discharge.

Methods: All consecutive esophagectomies over 3 years were retrospectively reviewed. Patients were categorized on day 7 into (1) those clinically unsafe for discharge; (2) those clinically safe for discharge; and (3) those considered safe for discharge but develop a delayed complication. CRP level on day 7 and the trend in CRP levels between days 3 and 7 were compared.

Results: A total of 140 patients underwent esophagectomy, of which 64 patients (46%) had at least one complication. On day 7, 62 (44%) patients were considered clinically unsafe for discharge; 74 (53%) were considered safe for discharge; and 4 (3%) were safe but developed a delayed complication. No patient with delayed complication had a day 7 CRP level < 84 mg/L. CRP trend did not help predict delayed complications.

Conclusions: The actual CRP level on day 7 after esophagectomy, rather than the trend, can predict delayed complications. Early discharge after esophagectomy should be desisted if the clinical picture is better than the actual blood results.

Keywords

esophagectomy, enhanced recovery, anastomotic leak, C-reactive protein

Introduction

Ivor Lewis esophagectomy remains the mainstay for curative management of esophageal cancer. Traditionally, length of hospital stay was around 14 days but more recently with enhanced recovery (ERAS) protocols, it is now as low as 7 days.[1-4] Although the length of stay (LOS) has decreased, there is still a subset of patients who cannot be discharged early due to significant complications, with a few suffering a delayed complication after discharge.[5-7] Anastomotic leak remains a significant cause of postoperative morbidity and mortality.[8] A recent multicenter Dutch study quoted the rate of anastomotic failure to be 19%[9] and an international subset of 14 high-volume centers reported a rate of 11.4%.[10] Anastomotic leak is diagnosed a median of 7 days after surgery but can occur as a late complication after day 7.[5-7,11] This could potentially put a number of patients at risk of leak after their early discharge following ERAS protocol. ERAS management after esophagectomy is often protocol driven, and discharge on the seventh day is based on clinical status, blood results, activity levels, and multidisciplinary

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management. However, most of these are subjective judgments and there are no cutoff points from blood results to predict safe discharge.

Routine blood tests such as leukocyte count, serum albumin, and C-reactive protein (CRP) in the early postoperative period and their trend have been used to predict potential in-hospital anastomotic leak.[12-15] However, no studies have determined the actual levels on the day of discharge to predict delayed postdischarge complications.

We aim to assess whether CRP levels could help the surgeon to identify patients who can safely be discharged on postoperative day 7, focusing on specific values on the day of discharge rather than an improving trend.

Methods

Clinical data from all consecutive Ivor Lewis esophagectomies for midesophageal, distal esophageal or gastroesophageal junctional adenocarcinoma or squamous cell carcinoma performed in our institution between April 2013 and March 2016 were retrospectively analyzed from a prospectively maintained database. Three-stage procedures were excluded from the study. Patient demographics, comorbidities, management, and outcomes were recorded.

All patients in the study were discussed in a multidisciplinary team meeting for treatment planning. Patients with disease greater than T2 or N1 on preoperative staging were offered neo-adjuvant chemotherapy, if deemed clinically fit for chemotherapy. Patients having neo-adjuvant chemotherapy had a minimum of 5-week recovery after finishing chemotherapy prior to the date for their surgery. All patients had a standard two-phase esophagectomy with abdominal and right thoracic approach. Stomach was mobilized preserving the right gastroepiploic artery. A feeding jejunostomy was placed as a nutritional adjunct selectively as per surgeon preference. Thoracic duct was ligated just above the diaphragm in all cases. A circular stapled anastomosis above the azygos vein was carried out. After surgery, patients were initially managed on the high-dependency unit. An informal enhanced recovery program was used in management where patients had chest physiotherapy and were mobilized on the first postoperative day. Oral intake was commenced by day 3 and patients were on soft diet on day 5 if deemed clinically safe. Early drain removal occurred at days 3 to 5, with a view to discharge on day 7 if clinically well. Routine blood tests including CRP were performed daily.

Anastomotic leakage was defined as clinically and radiologically confirmed anastomotic breakdown. Mortality was recorded as in-hospital death or death occurring within 30 days.

A review of case notes was performed by two individual assessors (AT and AC) to identify the patients' clinical condition on day 7 by focusing on vital parameters and their trends, general recorded clinical condition, dietician input and record of nutritional intake, and physiotherapy input and mobility. The two assessors did not see the blood results during this process. Based on the review, patients were stratified into three groups: (1) those clinically unsafe for discharge due to an ongoing complication/clinical concerns; (2) those with no complications and deemed safe for discharge; and (3) those considered safe for discharge on day 7 but who developed a serious delayed complication.

A delayed complication was defined as a complication occurring after day 7 in patients who were clinically well on day 7.

CRP levels on each day were recorded for all the three groups. The level of CRP on day 7 was of particular focus. We also looked at the trend in CRP levels in all three groups. A reducing trend was defined as values sequentially reducing from day 3 to day 7. An increasing trend was defined as values sequentially increasing between day 3 and day 7, and a swinging trend was defined when the CRP values did not follow a consistent reducing or increasing trend in that timescale.

Day 7 CRP level was also compared between the three groups by performing Kruskal-Wallis test using GraphPad Prism version 8.3.1 for Windows, GraphPad Software, San Diego, CA, USA, www.graphpad.com.

Results

Demographics

A total of 140 patients underwent an Ivor Lewis esophagectomy during the study period. Median age was 65 (range 34-84) years; 26 patients were female and 114 were male. Seventy-seven patients (55%) had American Society of Anesthesiologists physical status grade I or II. Median body mass index of the group was 27 (range 17-44). Eleven patients (8%) had chronic kidney disease and one patient developed acute kidney injury during neo-adjuvant chemotherapy. Two of the patients with venous thromboembolism required an inferior vena cava filter preoperatively. Seventy-six patients (54%) had cardiovascular disease, 34 patients (24%) had respiratory comorbidity and 38 patients (27%) were active smokers at the time of their treatment.

Management

Ninety-seven patients had neo-adjuvant chemotherapy (69%). A total of 104 patients had a feeding jejunostomy (74%).

Table 1. Outcomes.

	All patients, n (%) (N = 140)
Morbidity	46
Anastomotic leak	16 (11)
Chyle leak	14 (10)
Major	8 (6)
Minor	6 (4)
Respiratory tract infection	64 (46)
Pulmonary embolism	2 (1)
Cardiac complication	17 (12)
Complication from jejunostomy tube (*n* = 104)	11 (9)
Pyloric obstruction	2 (1)
Wound complication	2 (1)
Renal failure	7 (5)
Reoperation	
1	17 (12)
2	2 (3)
30 day readmission	1 (1)
Mortality	
In-hospital /30 day	3 (2)

Outcomes

Overall, 64 patients (46%) had at least one complication of some description. These are detailed in Table 1. On grading complications by severity, 28 patients (20%) were classed to have minor complications (Clavien-Dindo grade I or II), while 21 patients (15%) had major complications (Clavien-Dindo grade III). Twelve patients (8.5%) developed life-threatening complications (Clavien-Dindo grade IV). Mortality rate was 2%. Of the three mortalities, one patient died of sepsis secondary to leak, one of a myocardial infarction, and one of a pulmonary embolism. Median LOS was 11 days (range 7-97 days). The distribution of LOS is depicted in Figure 1.

Whereas 62 (44%) patients were considered clinically unsafe for discharge on day 7, 74 (53%) were safe for discharge and 4 (3%) were classified as safe for discharge but developed a delayed complication (three anastomotic leaks, one chyle leak). There were no inconsistencies between the two assessors.

The median CRP level was 148 mg/L in patients unfit for discharge on day 7, 62 mg/L in patients fit for discharge, and 108 mg/L in patients deemed fit for discharge but who went on to develop delayed complications. Statistical comparison between the three groups demonstrated that the medians were significantly varied ($P < .0001$) as shown in Figure 2.

Trends in the CRP levels between days 3 and 7 were compared for the three groups and are shown in Table 2.

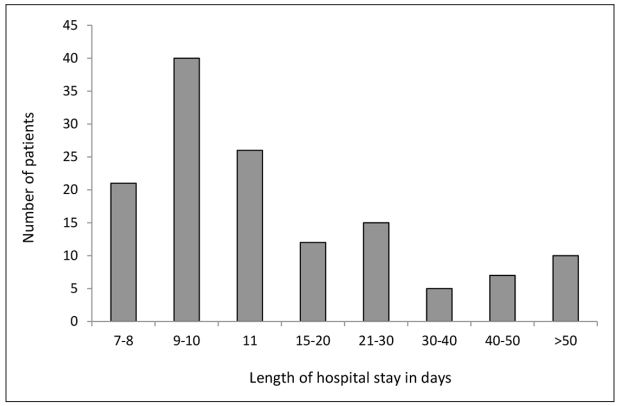

Figure 1. Length of hospital stay.

Trend in CRP was variable in all groups, with 13.5% of patients who were safe for discharge on day 7 having an increasing trend and 53% of patients who were clinically unsafe for discharge having a reducing trend. In the patients deemed fit for discharge but developed a delayed complication, 75% had a reducing trend in CRP.

Discussion

This study was distinct because it focused on the actual values of CRP on day 7 as a guide to predict delayed complication after potential discharge on day 7. Clearly, this will become increasingly important as more and more patients get discharged early with wider implementation of ERAS pathways. In our experience with ERAS protocol, patients are mobilizing earlier, eating earlier, and clinically appear very well on day 7. However, in our study, we found a few patients who then went on to have serious delayed complications. In our series, we had one patient who, having been discharged on day 7, represented with a significant delayed leak on day 10 requiring readmission and reoperation and resulting in mortality. This patient at the time of initial discharge was clinically deemed safe for discharge on all parameters and with an improving trend in blood results. This emphasizes the need to have a reliable marker on top of clinical status and improving trend of inflammatory markers to allow safe discharge.

There are a number of studies that have attempted to use blood test results in the postoperative period to predict complications.[12-14,16] Noble et al[12] introduced a scoring system (NUn) describing detection of anastomotic leaks using CRP, white cell count, and albumin levels on postoperative day 4, using a cutoff score of 10. However, external validation of this scoring system has not yet been achieved.[17,18] Veeramootoo et al[13] found that all patients undergoing minimally invasive esophagectomy demonstrated a transient abnormal rise in CRP until the third

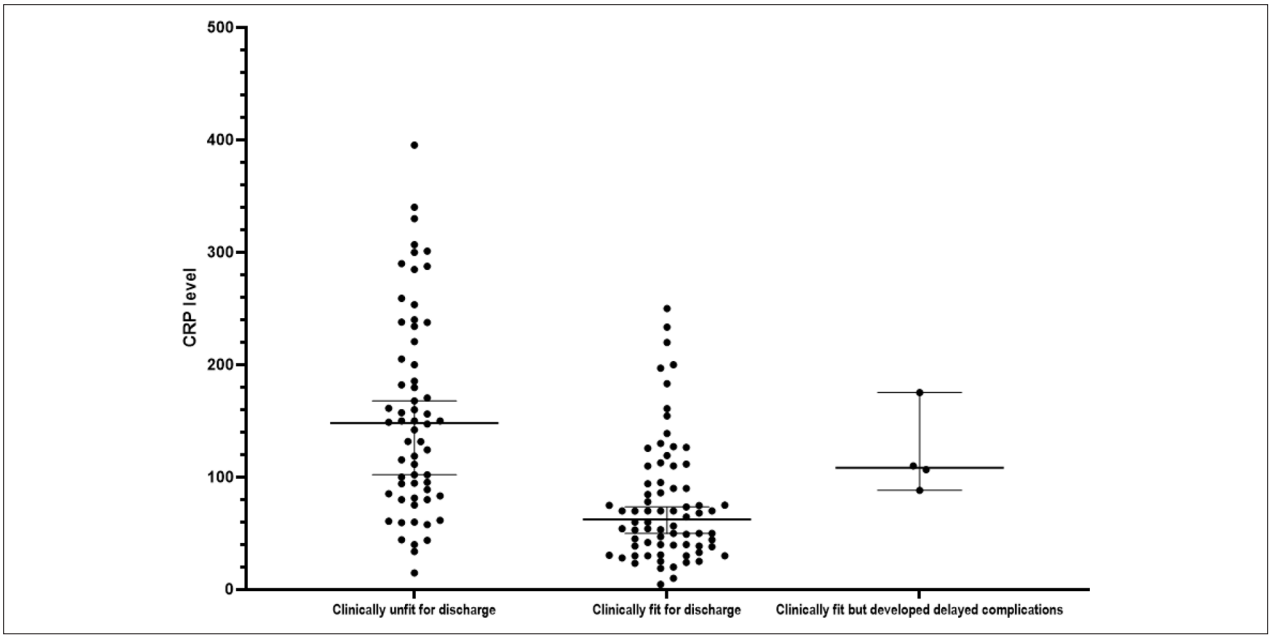

Figure 2. Scatter plot with medians + 95% confidence intervals comparing the day 7 CRP level between the three groups using Kruskal-Wallis test. ($P < .0001$). CRP, C-reactive protein.

Table 2. Trend in CRP Level for Patients in the Three Different Discharge Categories.

	Reducing trend	Increasing trend	Swinging trend
Safe to discharge n/N (%)	64/74 (86.5)	10/74 (13.5)	0
Unsafe to discharge, n/N (%)	33/62 (53.3)	11/62 (17.7)	18/62 (29)
Safe to discharge but late complication, n/N (%)	3/4 (75)	1/4 (25)	0

Abbreviation: CRP, C-reactive protein.

postoperative day. In their study, for patients with a complication the CRP levels remained significantly elevated and in those with gastric conduit failure this trend was more exaggerated.[13] CRP measured on postoperative days 2, 3, and 6 after esophageal and gastric resections was found to be a helpful negative predictive test for the development of anastomotic leak in a study performed by Gordon and colleagues.[14] In their study, the median time to diagnosis of an anastomotic leak was 6 days. CRP level cutoff points were 209, 190, and 154 mg/L on days 2, 3, and 6, respectively. Although these studies have demonstrated a link between abnormal inflammatory markers and anastomotic failure, they have essentially looked at results in the early postoperative period and hence may not be useful in identifying delayed complications.

This study highlights the importance of actual value of CRP on day 7 as opposed to the trend of CRP levels. Our results have shown that 75% of patients who developed delayed complications had a reducing trend of CRP. Equally, of the patients deemed clinically safe for discharge on day 7 and who did not have delayed complications, 13.5% had an increasing trend of CRP. Trend of CRP in isolation cannot be used to predict delayed complications.

As an alternative, a contrast swallow/esophagogram could be performed on the seventh postoperative day to exclude anastomotic leak and facilitate early, safe discharge. Hu et al[5] and Cools-Lartigue et al[11] looked at the use of esophagogram done routinely about day 7 after esophagectomy. Both of these studies show that there were a substantial number of false-negative results with an esophagogram. In the study by Cools-Lartigue et al, of the 30 patients with an anastomotic leak, 12 had a false-negative barium esophagogram.[11] Hu et al[5] reported a false-negative rate of 47.8% in detection of anastomotic leak with a barium swallow done routinely after esophagectomy. A meta-analysis by Yonis and colleagues[6] concluded that given its poor sensitivity and inability to detect leaks, oral contrast studies should be used selectively and in combination with other diagnostic tests. These indicate that contrast esophagogram done routinely on day will fail to exclude delayed anastomotic

complications.[6] This implies that there is value in focusing on the blood results to predict delayed complications.

Our study was retrospective. This meant that the clinical status on day 7 was determined on the basis of recorded notes. However, we had two authors independently review clinical entries, observation charts, specialist nurse reviews, physiotherapy, and dietician reviews to determine the clinical status on day 7 to ensure accuracy of assessment. Their assessment was consistent in all patients for fitness to discharge on day 7. Doing such a study prospectively and discharging patients with very high CRP level on day 7 may not meet a clinical equipoise.

Our unit did run an informal ERAS protocol at the time of this study but the approach was very conservative and patients often stayed over 7 days despite being clinically ready for discharge. The unit covers a wide geographical area and caters to varied socioeconomic groups. This meant that social care input was often needed to allow discharge, which resulted in delayed discharges. Since the study has been completed the 7-day safe discharge rate has significantly improved with a rigorous ERAS protocol being followed.

In our study, 97 patients had neo-adjuvant chemotherapy (69%). There is no evidence in literature that this influences the postoperative CRP levels. All patients who had chemotherapy were given a minimum 5 weeks window prior to surgery to allow physiological recovery. We do not feel that having chemotherapy would alter the inference of this study.

We had no other serious delayed complications such as pulmonary embolus, myocardial infarction, hiatus hernia, or bowel obstruction. We cannot necessarily apply this rule to these types of complications. It does, however, appear to be of use in predicting safe day 7 discharge without the risk of delayed anastomotic leaks. We do not wish to be dogmatic with regard to a certain CRP level for excluding delayed complications. We acknowledge that CRP levels may differ in different patient populations and clinical laboratories, and may vary when minimally invasive esophagectomy is performed. We want our study to highlight that focusing on day 7 CRP level will help with safe early discharge by predicting delayed complications.

In conclusion, clinicians should exercise caution at the time of early discharge after esophagectomy if the clinical picture is better than the actual blood results.

Declaration of Conflicting Interests

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