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The effect of surgical complications on long-term prognosis following oesophagectomy

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ABSTRACT

Introduction: Complications are frequent after oesophagectomy, and there is evidence these adversely impact long-term prognosis. However, the effect of multiple complications, and the absolute magnitude of effect on survival is unclear. This study aimed to examine these effects in a single high-volume UK unit.
Methods: Patients undergoing oesophagectomy for cancer and who survived to 90 days post-oesophagectomy were analysed. Complications were graded according to the Clavien-Dindo (CD) classification and the Comprehensive Complication Index (CCI). The effect and magnitude of effect of complications on survival were assessed using multivariable cox regression and the risk-adjusted population attributable fraction.
Results: In total, 380 patients were included. Complications occurred in 251 (66.1%). Suffering ≥3 complications (HR 1.89, 95%CI 1.13–3.16, p = 0.015) or an unplanned escalation in care (HR 2.22, 95%CI 1.43–3.45, p < 0.001) significantly reduced survival whereas pulmonary complications and anastomotic leak did not. Patients with a CCI>30 had worse overall survival (HR 1.91, 95%CI 1.32–2.76, p < 0.001) and CCI>30 due to multiple minor complications gave a worse prognosis compared to CCI>30 due to major complications (HR 2.44, 95%CI 1.14–5.20, p = 0.022). An estimated 9.1% (95%CI 3.4–14.4%) of deaths at 5 years were attributable to a CCI>30.
Conclusion: Long-term survival following oesophagectomy for cancer is significantly affected by complications and the cumulative effect of multiple complications. Interestingly, multiple minor complications had a worse effect on survival than major complications. The absolute magnitude of effect is substantial: minimising all types of postoperative complications could have significant benefit to overall outcomes.

1. Introduction

For patients with oesophageal cancer, oesophagectomy with or without neoadjuvant treatment provides the best chance of cure [1–3]. Oesophagectomy carries significant risk of morbidity and mortality [4–6], and there is increasing evidence that postoperative complications and other adverse events are important factors influencing both perioperative and long-term survival [4,6,7]. The sophageal Complications Consensus Group (ECCG), reported that up to 59% of patients experience postoperative complications, with 56.7% of those experiencing multiple complications [8].

A recent meta-analysis of over 11,000 patients found that postoperative complications (HR 1.16, 95%CI 1.06–1.26, p = 0.001), particularly anastomotic leak (HR 1.20, 95%CI 1.10–1.30, p < 0.001) and pulmonary complications (HR 1.37, 95%CI 1.16–1.62, p < 0.001), significantly decreased overall survival [4]. They concluded that long-term survival was influenced both directly by increasing postoperative mortality, and indirectly, through patient deconditioning and the inability to receive postoperative cancer treatments which may have offered additional survival advantage [9]. A similar trend was seen for disease-free survival [4]. This meta-analysis is supported by additional, recent evidence [7], acknowledging the impact of specific complications [10,11]. These results are not universal, with some smaller studies finding no association between postoperative complications and prognosis [12,13], including that

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re-escalation to an intensive care setting has no impact on long-term survival [14].

Most historic studies have focussed on complications as single-entities, sometimes with severity graded according to worst Clavien-Dindo classification grade. There is limited evidence of the effect of multiple complications on long-term survival [15,16], and it is unclear if the apparent deleterious effect of complications is dependent on complication type, severity, overall complication burden or an interaction of these factors. Furthermore, the absolute magnitude of effect of complications on survival has not been described. The population attributable fraction (PAF) has been of growing interest in addressing this problem, where through incorporating the frequency of a specified factor of interest the absolute proportion of cases of an outcome attributable to that factor can be calculated. It has been applied to several surgical fields, including oesophageal, colorectal, and vascular, mainly to calculate the effect of complications on binary short-term outcomes [10,17,18]. The magnitude of effect on long-term survival has not been established.

In this study of cancer patients who underwent curative oesophagectomy, the relationship between postoperative complications and long-term survival, considering the effect of cumulative complication burden and absolute magnitude of effect of complications on survival was explored.

2. Methods

2.1. Data collection

Consecutive oesophagectomies from a prospectively maintained database between 01/01/2010 and 31/12/2020 at a single high-volume tertiary centre in the UK (University Hospital Southampton) were examined to analyse the relationship between in-hospital events within 30 days of oesophagectomy and overall survival. All patients had adenocarcinoma or squamous cell carcinoma (SCC) of the oesophagus or gastro-oesophageal junction and underwent a planned curative oesophagectomy. As the purpose was to analyse the effect of complications on overall (long-term) survival, we excluded patients who died during admission or within 90 days of surgery ($n = 18$), or for whom follow-up data was unavailable ($n = 13$). Data completeness was >95% for all variables. Data collection and analysis was approved by the local ethics committee (ERGO number 45334).

All treatment decisions were made by consensus following multidisciplinary team discussion. Triple-phase computerised tomography and position emission tomography were used for pre-treatment staging. Neoadjuvant treatment preferences changed during the study period, from a dominance of chemotherapy to chemoradiotherapy, partly following the publication of the CROSS trial [3]. Where chemotherapy was given this was mainly epirubicin, oxaliplatin and capcitabine (EOX) or epirubicin, cisplatin and fluoruracil/capcitabine (ECF/ECX), with increasing use of fluoruacil, leucovorin, oxaliplatin and docetaxel in recent years. Neoadjuvant treatment was offered to patients with locally advanced disease (T2-4, N1/2). Adjuvant treatment was not used routinely.

Surgical approach (minimally invasive/hybrid/open) was decided on an individual basis. Minimally invasive oesophagectomy was adopted in 2010 (at the beginning of this study period) and comparative rates of approach remained broadly stable throughout the study period. All operations were performed by 5 expert surgeons. Procedure was Ivor Lewis (2-stage) with 2-field lymphadenectomy in >95% of cases. A significant change in surgical practice during the study period was the introduction of an enhanced recovery after oesophagectomy (EROS) protocol in 2013 as has been detailed previously [19]. Briefly, this comprised a standardised programme of postoperative mobilisation, early removal of nasogastric tubes and intercostal drains with a target discharge of postoperative day 8.

Complications were recorded at the time of occurrence and defined as per international benchmarks for complication outcomes following oesophagectomy [8]. Patients were followed up post-discharge by telephone by a dedicated nurse practitioner twice in the first week and seen in the surgical outpatient clinic at 2 weeks. All complications occurring within 30 days of surgery were recorded, in line with the ECCG criteria. Primary outcome measures were overall survival (OS) and disease-free survival (DFS). Secondary outcomes were the effect of cumulative complication burden on survival and population attributable fraction (PAF).

2.2. Complication classification

All postoperative complications (any complication, surgical or medical, which occurred within 30 days following oesophagectomy, including when patients were readmitted following discharge) were classified according to ECCG criteria and the Clavien-Dindo (CD) classification [20]. Patients were categorised according to their highest CD complication. Complications were further grouped as “major” ($CD \geq 3b$), “minor” (CD1, CD2 and CD3a) or “none” (CD0) [21,22].

The CCI is a relatively novel tool for assessing the cumulative effect of postoperative complications, providing a more global view of complication burden than a CD grade which considers single worst complication only. This is particularly important in oesophageal surgery as multiple complications are common. The CCI ranges from 0 (no complication) to 100 (death), integrating the severity (CD grade) and frequency of complications [23]. It has previously been used to compare complication rates in the CROSS trial [24]. The CCI score was calculated from the CD grades of all complications a patient suffered using an online calculator (https://www.assessurgery.com/; [25]). We determined the most discriminatory value of CCI on OS by finding the minimal log-rank p-value, from testing each integer value of the CCI (and hence the CCI value that most differentiated prognosis).

An unplanned escalation of care was any change in care level, for example from ward to HDU or ITU, when the patient had already been deescalated from that setting. Patient survival was calculated from the date of oesophagectomy to the date of death or last known follow-up, updated in May 2021.

2.3. Statistics

OS and DFS were estimated using the Kaplan Meier method with differences between groups assessed using the Log-Rank test. To establish the effect size of complications independently of known predictors of survival, multivariable cox regressions were trained containing patient, disease and treatment factors known to affect survival in addition to the specified variable of interest [26,27]. P values < 0.050 were considered statistically significant.

The absolute magnitude of effect on survival was calculated using the population attributable fraction (PAF) extended to the survival setting, using the methods described by Chen et al. [28,29] We adjusted for patient, disease and treatment factors known to affect survival. Data analysis was conducted using R (Version 4.0.4, The R Foundation for Statistical Computing). Attributable fraction was determined using the *paf* [30] and *AF* [31] packages available at https://CRAN.R-project.org/.

3. Results

Following exclusions, 380 patients were included for analysis. Clinicopathological characteristics of the cohort are shown in

Supplementary Table 1. All patients underwent curative oesophagectomy for cancer. Preoperative treatment given was chemotherapy (platinum-based triplet) for 167, chemoradiotherapy (CROSS) for 120, and 93 patients had immediate surgery. Following oesophagectomy, pathological analysis revealed most patients had adenocarcinoma (83.7%), most commonly pathological tumour stage 3 (46.8%), with nodal stage 0 in the majority (52.1%). An R0 resection was achieved in 323 (85%) patients. Complications occurred in 66.1% of patients, with major complications (CD 3b–4b) in 78 patients (20.5%). Of those who experienced complications, 113 (45%) suffered multiple complications.

3.1. Overall survival

Median OS was 62.0 months, with 50.5% of patients who were still alive 90 days following oesophagectomy surviving to 5 years (Fig. 1). The median follow-up time was 66.0 months (IQR 28.0–94.0). Survival estimates of 85.8% at 12 months, 58.9% at 36 months, and 50.5% at 60 months were observed.

Median DFS was 39 months, with 46.2% of patients alive and free from disease recurrence at 5 years following oesophagectomy.

3.2. Postoperative complications

Postoperative complications occurred in 251 (66.1%) patients. There was no significant difference in the baseline characteristics of patients who did and did not develop complications (Supplementary Table 1). Complications were most commonly pulmonary (134 patients, 35.3%): post-operative pneumonia occurred in 96 (71.6%) of these patients. Other complications included anastomotic leak (28, 7.4%), atrial dysrhythmia requiring intervention (97, 25.5%) and chyle leak (20, 5.3%). Reintubation due to respiratory failure was required in 19 patients (5.0%). The maximum number of recorded complications an individual suffered was 5 (6 patients, 1.6%). Most patients had one complication (137, 36.1%); 64 (16.8%) two complications; 34 (8.9%) three complications; and 9 (2.4%) four complications.

3.3. Effect of complications on survival

After adjustment for known prognostic factors [27], OS was significantly worse for patients suffering three or more complications of any severity; and in those who had an unplanned re-escalation in care (Table 1). A similar pattern was observed with DFS.

3.4. Comprehensive Complication Index

The CCI value which maximally differentiated OS was 30 (Supplementary Fig. 1). Table 2 demonstrates example combinations of which complications equate in combination to CCI scores above and below 30.

The median CCI amongst all patients was 20.9 (IQR 0.0–33.5). When limited to those who suffered complications only, the median CCI was 29.6 (IQR 20.9–42.4). Median survival in patients with CCI>30 was significantly less than in patients with CCI≤30 (31 vs 80 months, $p < 0.001$; Fig. 1). A CCI>30 conveyed a HR of 1.91 for worse OS (95%CI 1.32–2.76, $p < 0.001$). Of the 100 patients with CCI>30, 78 had at least one major complication (≥CD3b) and 22 had multiple minor complications (≤CD3a) totaling a CCI of 30 or more. Patients with CCI>30 due to multiple minor complications had a worse prognosis in comparison to those with CCI>30 due to major complications (HR 2.44, 95%CI 1.14–5.20, $p = 0.022$).

DFS was also reduced with a CCI>30 (HR 1.68, 95%CI 1.20–2.36, $p = 0.003$, median DFS 21 vs 61 months, $p = 0.001$; Fig. 2). Patients with CCI>30 due to multiple minor complications had significantly worse DFS than those with CCI>30 due to major complications (HR 2.72, 95%CI 1.32–5.62, $p = 0.007$).

Major complications were associated with a significantly longer length of stay (22.5 days, IQR 11.25–40.75) compared to minor (10 days, IQR 9–14) or no complications (8 days, IQR 7–10, $p < 0.001$). CCI>30 resulted in a significantly longer length of stay of 19 days (IQR 11.00–31.25) compared to 9 days (IQR 8.00–12.00) in those with CCI≤30 ($p < 0.001$).

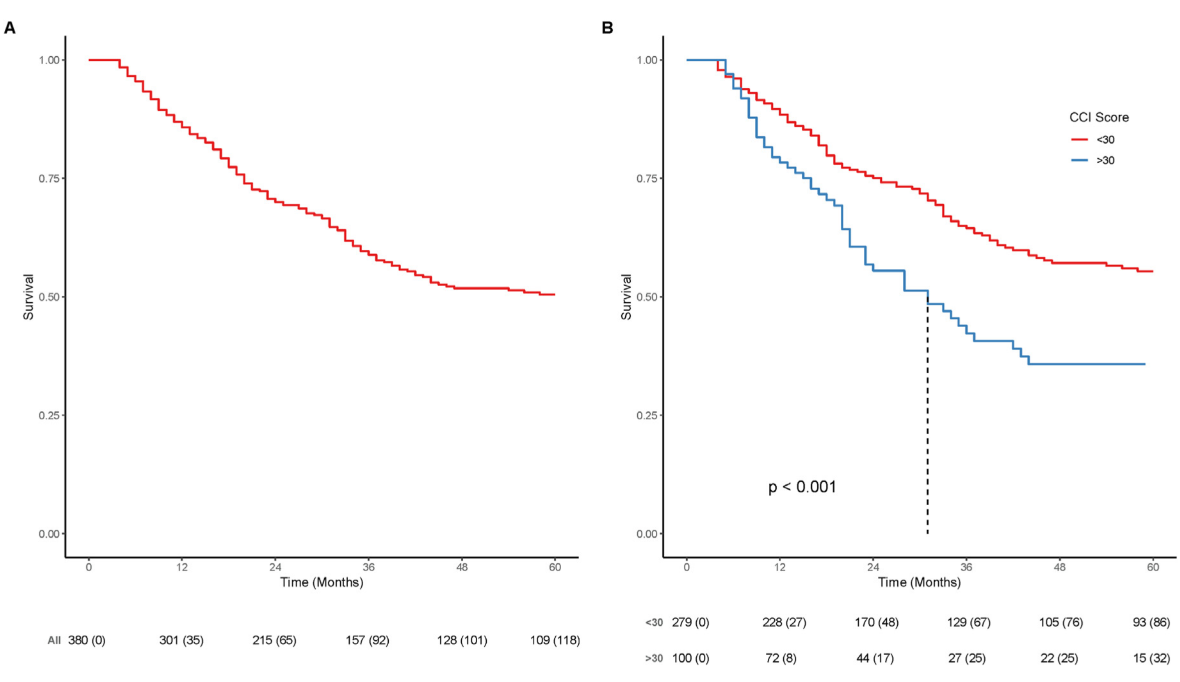

Fig. 1. Overall survival for (A) Entire Cohort and (B) when stratified by CCI score. Where reached, median survival is indicated by vertical dashed line (31 months for CCI>30).

Table 1
Complication and associated adjusted hazard ratios.

Complication	Overall Survival		Disease-Free Survival	
	Adjusted Hazard Ratio [95% CI]*	P value	Adjusted Hazard Ratio [95% CI]*	P value
Any Complication	1.28 [0.91–1.80]	0.150	1.22 [0.89–1.68]	0.218
Major complications	1.57 [1.00–2.45]	**0.050**	1.39 [0.92–2.12]	0.121
Minor Complications	1.18 [0.82–1.70]	0.374	1.15 [0.82–1.63]	0.411
1 or 2 Complications	1.18 [0.83–1.69]	0.361	1.13 [0.81–1.58]	0.472
≥3 Complications	1.89 [1.13–3.16]	**0.015****	1.75 [1.07–2.85]	**0.025****
Anastomotic Leak	0.72 [0.37–1.40]	0.332	0.65 [0.35–1.22]	0.182
Pulmonary Complications	1.32 [0.94–1.86]	0.108	1.21 [0.88–1.66]	0.241
Pneumonia	1.34 [0.94–1.91]	0.111	1.21 [0.87–1.70]	0.258
Reoperation	1.46 [0.85–2.50]	0.168	1.28 [0.76–2.14]	0.352
Unplanned Escalation in Care Level	2.22 [1.43–3.45]	**<0.001****	1.94 [1.27–2.95]	**0.002****

*Multivariate analysis adjusted for patient gender, age, performance status, ASA grade, pre-operative treatment, tumour location, histology, pathological tumour and nodal staging, surgical resection margin, tumour grade of differentiation and lymphovascular invasion. **p < 0.05.

Table 2
Example combinations of complications and their corresponding CCI scores [25].

Combination of complications categorised by Clavien-Dindo classification grade	Example Complication(s)	Comprehensive Complication Index score
Single 3a complication	Postoperative endoscopy; Interventional radiology (IR) procedure; surgical intervention not under general anaesthetic (GA)	26.2
Single 3a complication and one or two grade 1 complications	Endoscopy/IR procedure/surgery not under GA plus wound opened at bedside	27.6 or 28.9
Two grade 2 complications	Pneumonia; blood transfusion; atrial fibrillation etc	29.6
Two grade 2 complications and one grade 1 complication	Pneumonia; blood transfusion; atrial fibrillation etc plus wound opened at bedside	30.8
Single 3a complication and single grade 2 complication	Endoscopy/IR procedure/surgery not under GA plus pneumonia; blood transfusion; atrial fibrillation etc	33.5
Single 3b complication	Endoscopy/IR procedure/Surgery under GA	33.7

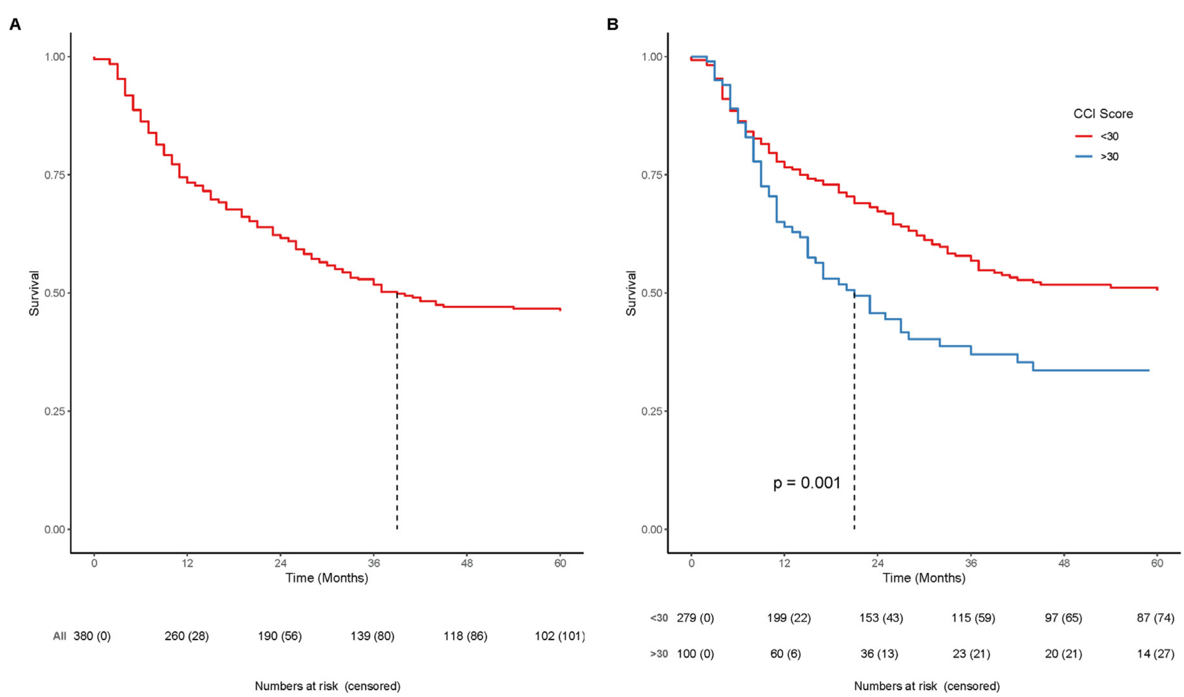

Fig. 2. Disease free survival for (A) Entire Cohort and (B) when stratified by CCI score. Median survival is indicated by vertical dashed line (39 months for entire cohort; 21 months for those with CCI>30 vs 61 months CCI≤30).

3.5. Population attributable fraction

The PAF for survival over time based on CCI>30 vs CCI≤30, adjusted for clinicopathological features known to effect outcome is shown in Supplementary Fig. 2 [27]. If all patients were limited to a CCI≤30, this would prevent 15.8% of deaths at 12 months (95%CI 5.6–24.9%, p = 0.001), 10.7% of deaths at 36 months (95%CI 4.0–17.0%, p = 0.001) and 9.1% of deaths at 60 months (95%CI 3.4–14.4%, p = 0.001). A similar, although reduced effect is seen on DFS, with an improvement of 10.9% (95%CI 3.1–18.2%, p = 0.004) at

12 months, 7.6% (95%CI 2.3−12.6%, p = 0.004) at 36 months and 6.7% (2.0−11.1%, p = 0.004) at 60 months estimated. In comparison, using the same methodology, eliminating positive resection margins and positive lymph nodes at resection are estimated to yield a 3.2% (95%CI 0.6−5.7%) and 20.7% (95%CI 8.4−31.4%) increase in survival at 5 years respectively.

4. Discussion

This study provides novel insight into the important role of cumulative complication burden as a determinant of both disease-free and overall survival following oesophagectomy for cancer. This impact is further quantified through the population attributable fraction, demonstrating the absolute magnitude of effect that post-operative complications have on survival.

Our study found 66.1% of patients had at least one surgical complication within thirty days of their oesophagectomy, consistent with international benchmarks for complication incidence following oesophagectomy [8]. Multiple complications reduced OS: both ≥3 complications of any severity, and a CCI>30 derived from multiple minor complications were associated with decreased OS, demonstrating that cumulative complication burden is an independent predictor of poor prognosis.

There are multiple hypotheses for why complications affect survival following oesophagectomy. The physiological stress of additional invasive procedures may increase inflammation: there is growing evidence that high inflammatory markers post-oesophagectomy are associated with poor prognosis [32,33]. Local inflammatory responses induced by surgical trauma may accelerate the growth of residual disease, or micro-metastases [34], which may predispose these patients to disease recurrence. Moreover, complications may worsen patient condition following oesophagectomy such that they may not tolerate adjuvant treatments, which could provide additional survival benefit [9]. This study suggests that cumulative complications may predispose to disease recurrence more than single major complications, however few patients had multiple minor complications totaling a CCI>30 (22, 5.8%) and over half of these had suffered CD3a complications (12 patients). The detrimental effect of multiple minor complications on OS may have been due to the above-described inflammatory responses promoting disease recurrence; deterioration in patient condition and resulting sarcopenia (which has also previously been associated with significantly reduced survival [35]); or a result of small group size in our cohort.

The risk-adjusted PAF enabled us to quantify the absolute effect of complications on survival, by determining what proportion of deaths would be avoided if all patients had a CCI≤30 [10,28,29]. Table 2 demonstrates example combinations of complications which may result in CCI>30 − although this commonly includes as least one > CD3a complication, it can be achieved through the accumulation of multiple minor complications alone: for example, postoperative pneumonia combined with blood transfusion and a wound infection. These types of complication in isolation may seem clinically insignificant, however, we have shown that, in combination, they may play a significant detriment to long-term survival. At five-years, 9.1% of deaths were calculated as attributable to complications totaling a CCI>30, exceeding that from a positive resection margin and almost half the magnitude due to lymph node involvement. Hence, postoperative complications play a meaningful role in long-term outcomes following oesophagectomy for cancer. Strategies to prevent complications should therefore be prioritised − enhanced recovery after oesophageal surgery (EROS) has already been associated with a low incidence of major complications [19], and patient optimisation prior to surgery, including fitness to undergo surgery [36], may also reduce complication development, however there is limited evidence for this. This may be because factors such as BMI and comorbidities, which may influence survival, are often incompletely recorded (including in our dataset), meaning their impact on survival cannot be accounted for as cofounding factors.

The most common complications were pulmonary complications. In literature, these are associated with worsened prognosis [4]. Our cohort had a high incidence of postoperative pneumonia compared to national data (25.3% vs 14.6%) [8], however, contrasting to previous research, pulmonary complications did not significantly impact OS (HR 1.32, 95%CI 0.94−1.86, p = 0.108). This may be due to timely initiation of antibiotics, thus more rapidly treating pneumonia and reducing inflammatory responses. Anastomotic leaks are also known to be associated with poor prognosis [4,11,15]. Anastomotic leak was not significantly associated with reduced OS (HR 0.72, 95%CI 0.37−1.40, p = 0.332) in this study. This may reflect the relatively low incidence of anastomotic leak in our population (28 patients, 7.4%) compared to benchmarking figures for anastomotic leak following oesophagectomy (11.4%) [8].

We have not examined the role of individual complications as an attributable fraction to OS, however previous research suggests that pulmonary complications (adjusted PAF 44.1%) and anastomotic leakage (adjusted PAF 30.4%) have the greatest impact on short-term outcomes [10]. Given that neither of these complications were associated with reduced survival, their role as attributable fractions to OS is also uncertain in our cohort and is an area for further research.

An unplanned re-escalation in care level during admission was independently associated with significantly reduced OS (HR 2.22, 95%CI 1.43−3.45, p < 0.001). This was required for 56 patients. This included, but was not limited to, some of the 28 patients who required reoperation, although reoperation was not independently associated with reduced OS (HR 1.46, 95%CI 0.85−2.50, p = 0.168). The additional patients requiring escalation in care may have needed this due to severe postoperative pulmonary complications, such as respiratory failure, necessitating the need for non-invasive or invasive ventilatory support. The requirement to transfer to an intensive care setting, and the associated morbidity that comes with an intensive care admission, may have led to patient deconditioning, increased length of stay and recovery time, and ultimately may have reduced their survival. Major complications (22.5 days, IQR 11.25−40.75, p < 0.001) and CCI>30 (19 days, IQR 11.00−31.25, p < 0.001) were both associated with significantly longer lengths of stay.

This was an observational study: preoperative treatments and patient treatment escalation were not controlled and may have introduced bias. Our trust also implemented an upper-GI-specific enhanced recovery after oesophagogastric surgery (EROS) programme in 2013 which is applied to all patients undergoing major upper GI surgery [19], and may have introduced variability in treatment pathways before and after introduction. CRT was used increasingly during the cohort timeframe following the CROSS trial (2012) therefore this may have independently improved survival in patients undergoing oesophagectomy from 2013 onwards [3]. Furthermore, recent chemotherapy changes to the FLOT4 regimen may also have positively influenced survival [2]. Whilst therapeutic progress plays an important role in improving OS from oesophageal cancer, we have shown the clinically meaningful role of post-operative complications in long-term survival which should remain an ongoing consideration for all oesophagectomy centres.

Our study adds new insight into the role of multiple complications as a determinant of OS, suggesting the important role of multiple complications and cumulative complication burden. Expanding upon previous research, which suggests that specific types of complication (anastomotic leak and pulmonary complications) negatively influence survival [4,10,11,15], our study finds that it is not only the type of complication, but number of complications that influences long-term outcomes. We add novel insight into the absolute magnitude of effect of complications on OS with the risk-adjusted PAF, which highlights that a significant proportion of deaths could be prevented if all patients had a CCI≤30.

5. Conclusions

Postoperative complications following oesophagectomy for cancer have a substantial lasting impact on patient mortality. We have shown that the cumulative burden of multiple complications is significantly detrimental to oesophagectomy patient survival using the CCI. In the theoretical scenario that complication load could be reduced such that all patients had a CCI <30, this may prevent over 9% of deaths at five years. This highlights the value of strategies such as centralisation of services and other approaches to reduce postoperative complications to improve overall outcomes for those undergoing oesophagectomy for cancer.

Author contributions

A Broadbent and S Rahman: study concepts, study design, data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation.

B Grace: data acquisition, quality control of data and algorithms, manuscript editing & review

R Walker, F Noble, J Kelly & J Byrne: data acquisition, manuscript editing & review

T Underwood: study concepts, study design, data acquisition, manuscript editing & review, supervision.

Declaration of competing interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.05.005.

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