Multicenter, prospective cohort Study of Oesophageal Injuries and related Clinical outcomes (MUSOIC study)

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Mini-Abstract

The MUSOIC study is the most up-to-date and granular dataset evaluating the timeline of patients admitted with oesophageal perforation. Through this, our work updates the epidemiology of oesophageal perforation in the context of centralized tertiary centers and multi-modal treatment approaches. We have performed robust machine-learning analysis to identify the optimal management strategy, as well as predictive factors of mortality.

Structured Abstract

Objective

To identify prognostic factors associated with 90-day mortality in patients with oesophageal perforation (OP), and characterize the specific timeline from presentation to intervention, and its relation to mortality.

Background

OP is a rare gastro-intestinal surgical emergency with a high mortality rate. However, there is no updated evidence on its outcomes in the context of centralized esophago-gastric services; updated consensus guidelines; and novel non-surgical treatment strategies.

Methods

A multi-center, prospective cohort study involving eight high-volume esophago-gastric centers (January 2016 to December 2020) was undertaken. The primary outcome measure was 90-day mortality. Secondary measures included length of hospital and ICU stay, and complications requiring re-intervention or re-admission. Mortality model training was performed using random forest, support-vector machines, and logistic regression with and without elastic net regularisation. Chronological analysis was performed by examining each patient's journey timepoint with reference to symptom onset.

Results

The mortality rate for 369 patients included was 18.9%. Patients treated conservatively, endoscopically, surgically, or combined approaches had mortality rates of 24.1%, 23.7%, 8.7%, and 18.2%, respectively. The predictive variables for mortality were Charlson comorbidity index, haemoglobin count, leucocyte count, creatinine levels, cause of perforation, presence of cancer, hospital transfer, CT findings, whether a contrast swallow was performed, and intervention type. Stepwise interval model showed that time to diagnosis was the most significant contributor to mortality.

Conclusion

Non-surgical strategies have better outcomes and may be preferred in selected cohorts to manage perforations. Outcomes can be significantly improved through better risk-stratification based on afore-mentioned modifiable risk factors.

Introduction

Oesophageal perforation remains one of the most serious, albeit rare, emergent gastrointestinal conditions[1-3]. The reported in-hospital mortality from oesophageal perforation is 10% to 25% if treatment is initiated within 24 hours from onset of symptoms. However, this dramatically increases up to 60% in cases where treatment is delayed, often due to insidious and vague presentation and delays in diagnosis[4-5]. The most common cause of oesophageal perforation is iatrogenic with spontaneous perforations accounting for up to 30% of cases[6]. These different aetiologies of oesophageal perforations often have a substantially different prognosis, given the degree of mediastinal contamination seen in spontaneous perforations often driving a poorer outcome. However, given the rarity of condition, high quality evidence regarding management is severely limited and the prospect of any randomized controlled trials in the field remains unlikely.

Historically, patients have been managed based on the personal experience and preference of the treating clinician, and accordingly most patients underwent surgical management based on data from small retrospective case series[7-11]. Primary closure and wide drainage of the mediastinum was historically the treatment of choice if perforation was detected in less than 24 hours after onset of symptoms. However, recent advances in interventional endoscopy have brought less invasive therapies to the forefront[12,13]. Depending on the cause of injury, location of perforation and status of the patient, treatment options now include conservative management; endoscopy (stenting, clipping, or vacuum-based therapy); and surgery (drainage, diversion, primary repair, or esophagectomy). Recently, the World Society of Emergency Surgery (WSES) congress produced guidance on initial stratification of patients using the Pittsburgh Severity Score, diagnostic strategies, patient selection for each treatment modality, and recommendations on operative techniques[14]. However, most of these guidelines have been produced on the basis of evidence at grade 1c and below, highlighting the challenges of research in this field[13].

A previous national study utilising an administrative dataset from the UK included 2564 patients over 12 years and showed a 90-day mortality of 35-44%, with hospital volume identified as a key prognostic variable[15]. Follow-up investigations utilising the same administrative dataset, also established the prognostic importance of management of oesophageal perforation within high volume oesophageal cancer centers and by high volume oesophageal cancer surgeons[16,17]. Despite the size of the dataset, these investigations were severely limited by a lack of specific or granular data to allow more in depth understanding of the mechanism for these prognostic effects observed.

The MUSOIC study group designed a multi-center UK study including eight high volume esophago-gastric centers, with the aim of developing a highly granular, valid, and updated dataset that seeks to address these deficits in previous evidence. The primary objective of the MUSOIC study was to identify key patient, oesophageal perforation specific, hospital and treatment prognostic factors associated with 90-day mortality. The secondary objective was to map the specific timeline from presentation through diagnosis and to intervention for patients with oesophageal perforation and how this relates to mortality.

Methods

Design

A multi-center cohort study was designed (data from January 2016 to December 2020) to examine the prognostic factors associated with 90-day mortality following oesophageal perforation (MUSOIC dataset). The majority of participating centers (six out of eight) had prospectively maintained databases to facilitate inclusion in this study however several additional data points were needed that required a retrospective review of patient notes by a clinical member of the team. Local ethical approval was obtained from each participating site for the inclusion of anonymized patient data into the MUSOIC dataset. Study data were collected and managed using REDCap electronic data capture tools hosted at Imperial College London[18].

Cohort

Participating centers were all high volume esophago-gastric centers (based on annual major upper gastrointestinal case volume) experienced in the management of oesophageal perforation (supplemental table S1).

Inclusion criteria:

- Adult patients managed as an inpatient for more than 24 hours with a radiological or endoscopic diagnosis of oesophageal perforation.
- Patients admitted between January 2016 to December 2020 to one of the eight participating hospitals.

Exclusion criteria:

- Patients under 18 years of age
- Patients with anastomotic leak or conduit necrosis following esophagectomy
- Patients with incomplete data concerning 90-day mortality (n=1)

Intervention definition

Classification of intervention used in these patients was based upon the primary treatment approach. Surgery included thoracotomy or thoracoscopy with mediastinal drainage, management of perforation with primary closure or external drainage, nutritional access including gastrostomy or jejunostomy. Endoscopy included nasogastric tube placement for drainage, vacuum therapy, oesophageal stenting, and endoscopic clips. Combined intervention referred to surgical and endoscopic intervention performed together for example endoscopic vacuum therapy with thoracoscopic mediastinal drainage. Conservative management included all patients not managed with any of the above interventions, and thus management largely consisted of antibiotics and nil by mouth.

Outcome

Primary outcome: 90-day mortality

Secondary outcome measures: Complications including re-intervention and re-admission, length of hospital and ICU stay.

Statistical analysis

Descriptive statistics were used for primary and secondary outcome measures. Propensity score matching was performed using optimal pair matching on selected clinically relevant variables most likely to influence choice of intervention, including comorbidity, age, estimated degree of thoracic contamination on CT scan and cause of perforation[19]. For mortality prediction, raw data were pre-processed as follows (summarized in supplemental Figure S1): variables with greater than 10% missing data were removed, patients with incomplete mortality data were excluded, and then random forest imputation used to complete the dataset[20]. Backward selection was performed with logistic regression using the Akaike Information Criterion to identify the most informative variables, and these were assessed for collinearity with Pearson correlation coefficients, keeping variables with a correlation coefficient -0·5 to 0·5. Data were then split into a train and test sets in a ratio of 3:1. Model training was performed using random forest, support-vector machines, and logistic regression with and without elastic net regularisation[21]. Model performance was assessed on test data sets using receiver operating characteristics (ROC) and area under the curve (AUC)[22]. To assess model stability, repeated random subsampling validation was performed (1000 iterations). Chronological analysis was performed by examining each patient journey timepoint as determined from the clinical notes with reference to patient reported symptom onset (time zero). Intervention and surgery timepoints were collapsed into a single time point (intervention), and times to referral and transfer were excluded due to insufficiently robust or missing data, based on clinical notes review. Remaining timepoints were symptom onset, hospital visit, diagnosis, and intervention. Patients were then excluded that did not have any intervention, or who had greater than two missing time points. Uniform manifold approximation and projection (UMAP) dimensionality reduction was used to visualise chronology data in two dimensions, and outcome measures overlaid. Specific time points were then modelled with logistic regression with reference to outcomes measures which showed a visually assessed pattern in dimensionality reduction. All analysis was performed in R (v4.2) with code available.

Role of the funding source

No funding was required for this work, and thus there was no role for it in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication.

Results

Baseline characteristics of presentation, diagnosis and treatment

Data were collected for 369 patients and key demographic details are summarized in Tables 1 (ensemble) and 2 (by intervention type). Most perforations were confirmed on CT (93.6%), with perforations diagnosed by endoscopy and contrast swallow without CT in 3.25% and 3.52%, respectively. Overall, 46.0% and 34.3% of patients had an endoscopy or swallow, respectively (supplemental Table S2). Most patients treated with surgery had thoracotomy and laparotomy (63% and 70%, respectively), and most endoscopically treated patients had stents or endoscopic vacuum therapy (53% and 32%, respectively) (supplemental Table S3).

Clinical outcomes from treatment

Overall 90-day mortality was 18·9%. Patients treated without intervention, endoscopically, surgically, or with combined approaches had 90-day mortalities of 24·1%, 23·7%, 8·7%, and 18·2%, respectively, with a significantly lower mortality in surgically treated patients as compared to conservative, endoscopically, or combination treated patients (p=0·004). Complications occurred in 73·3% of patients, with Clavien-Dindo grade III or higher complications in 55·2%. Complications were more common and more severe in surgically treated patients (90·2% vs 61·0%, p=4·51e-08; 67·9% vs 46·1% Clavien-Dindo III and above, p=0·0002). Reintervention rates within 90 days were 15·2%, with the most common being radiological interventions after surgery (61·9%). From 333 patients with relevant complete data, the 90-day readmission rate was 17·7% with most readmissions occurring after surgical intervention (30·0%, p=0·002; compared to 8·99% and 22·9% in conservatively and endoscopically treated patients, respectively). Median length of stay (LOS) was 25·5 days (interquartile range (IQR) 10-51 days), with significantly longer LOS in patients treated by surgery (40 days, IQR 25-61 days), or combined interventions (74 days, IQR 46-97 days; p<0.001). Median ICU stay was 4 days (IQR 0-14 days), which was significantly higher in surgically treated patients (10 days, IQR 4-18 days; p<0·001). Since surgery was associated with lower mortality, and there is likely to be a significant selection bias by treatment type, propensity score matching was performed between surgery and endoscopically treated patients (n=76), and surgery and conservatively treated patients (n=230), respectively. The survival advantage observed in surgically treated patients was maintained after matching on age, Charlson comorbidity index, CT findings, and cause of perforation in both comparisons, though only to significance in conservatively treated patients (surgery vs endoscopic: 10·5% vs 23·4%, p=0·22; surgery vs conservative: 8·7% vs 26%, p=0·00079; supplemental Table S4a and S4b and supplemental Figure S2a and S2b). When conservatively treated patients who died within three days were excluded from analysis, to identify patients who were not treated with curative-intent, a significant difference in mortality between conservatively and surgically treated patients remained (17.6% vs 8.7%, p=0.025).

Defect size has been associated with poorer outcomes. Data were available for absolute oesophageal defect size in 49 patients, and no significant differences were identified by defect size for mortality (p=0.7), intervention type (p=0.083), or cause of perforation (p=0.90) (supplemental Figure S3). 20mm has previously been used to discriminate small from large oesophageal defect size. These data were available for a total of 58 patients, and logistic regression also did not reveal any significant differences in mortality, intervention type, or cause of perforation (supplemental Table S5).

Mortality prediction

After data pre-processing (see statistical methods and supplemental Figure S1), mortality prediction was possible with a high area under the curve (>0·8) with several modelling methodologies (Figure 1a and 1b). Logistic regression generally performed well in comparison to random forest and support-vector machines, with little benefit from elastic net regularisation or model tuning, and therefore logistic regression was preferred due to its simplicity and the transparency of variable relevance (supplemental Table S6). The predictive variables for mortality after selection were Charlson comorbidity index, haemoglobin count, leucocyte count, creatinine levels, cause of perforation, presence of cancer, type 2 diabetes mellitus, hospital transfer, CT findings, whether a pre-intervention contrast swallow was performed, and the intervention type (Table 3 and Figure 2). Interestingly, the logistic regression model performed strongly even without American Society of Anesthesiologists physiological status, despite a clear impact on mortality, which was excluded due to the confines of the data pre-processing (supplemental Figure S4), and when variables which might not be feasible to include in a more generalized setting were removed (hospital transfer and intervention type; Figure 1c and 1d). Whilst currently unvalidated, this model is made freely available for use.

Chronological analysis

Detailed chronological records were available for 150 patients who underwent intervention, allowing timings to be mapped on a per-patient basis (Figure 3a and 3b). Patients who were transferred to a different unit for intervention had no worse mortality, length of stay or complication rate than those treated within the admitting hospital. To better understand whether the intervals between symptom onset, hospital attendance, diagnosis, referral to treating hospital, transfer to treating hospital, intervention and surgery had any impact on the primary and secondary outcomes, data were first processed as described in the statistical methods, leaving 150 patients with sufficient data for imputation (<10% missing data for each timepoint), then plotted using dimensionality reduction methods to explore whether the pattern of chronological variables showed any influence on outcomes (Figure 3c). Visual inspection suggests mortality was influenced by overall chronology, and not by other outcomes such as length of stay in hospital or intensive care (Figure 3c, lower plots). Logistic regression showed interval from symptom onset to hospital visit had a significant association with mortality (p=0·028, Table 4a). To avoid issues of collinearity from cumulative interval timings, a similar analysis was performed using intervals from each time point to the next. This stepwise interval model showed that time to diagnosis was the most significant contributor to mortality, with a borderline significance (p=0·053, Table 4b, supplemental Figure S5a and S5b).

Discussion

The MUSOIC study included 369 patients from eight high volume esophago-gastric surgical centers with highly granular data collected from 2016 to 2020, representing a modern cohort of patients presenting with oesophageal perforation. The 90-day mortality was 18·9%, which compares well with the 38·8% mortality identified in a previous publication from a nationwide UK cohort study in 2012 based on the hospital episode statistic dataset[15]. Systematic review of 53 small retrospective studies (median study size of 28 patients) has shown a substantially lower mortality of 13·3% in the 39 studies that recorded mortality, but measures of central tendency were not reported making it difficult to see how consistently these low mortality rates were observed in this mixed cohort[23]. Surgery as primary treatment approach was seen to reduce 90-day mortality (8·7%) compared to endoscopic (24%) or conservative management (24%). However, surgical intervention was seen to increase complications and reinterventions when compared to other treatment approaches. Key factors including Charlson comorbidity index, haemoglobin count, leucocyte count, creatinine levels, cause of perforation, presence of cancer, hospital transfer, CT findings, whether a contrast swallow was performed, and the intervention type, when combined into risk prediction models were able to consistently identify patients at risk of 90-day mortality. Removal of factors which could not be determined at the onset of clinical management did not overly impact the performance of the model, meaning clinical application is feasible with further model validation. Importantly, the granularity of the dataset allowed examination of the timeline of patients with oesophageal perforation and established the prognostic importance of time to diagnosis in this cohort.

One of the major findings of the study was that surgical intervention was associated with a significantly reduced 90-day mortality. Oesophageal perforation is a complex gastrointestinal condition, with a recent rise in potential available treatment options including vacuum therapy, covered stenting, and endoscopic clips[14,23]. Specifically endoscopic vacuum therapy either with the esosponge or VAC stent, is gaining greater adoption across Europe in more recent years, with promising results seen[24]. Given the breadth of treatment options available, there is a need for careful multidisciplinary discussion regarding each patient where feasible and development of a pathology- and patient--tailored treatment approach, such as that established within MUSOIC study centers. Centralization of esophageal perforation to high volume centers, will also facilitate the implementation of standardized clinical pathways and protocols that may further facilitate the improved outcomes seen in these higher volume centers.[3,24] Crucially, the prognostic importance of surgery highlighted within the current study illustrates the need for specialized oesophageal surgeons to be at the core of the multi-disciplinary process, in order to have the available surgical skillset and be able utilise a surgical approach when required and available.

A novel aspect of this multi-center study was the time-line analysis provided within a centralized model for the management of patients with oesophageal perforation. This established that the most prognostically important time interval for these patients was time to diagnosis. Given the design of this study it is not possible to identify the nature of the delays to diagnosis that led to an adverse clinical outcome. However, this result does identify the need for access to timely radiological investigation once a clinical suspicion of oesophageal perforation has been identified. More broadly the time-line analysis highlights the time-sensitive nature of this condition in terms of diagnosis, but less so in time to intervention. The importance of intervention being undertaken in the most appropriate environment, in centers with esophago-gastric surgical expertise has previously clearly been demonstrated[16-17].

The 90-day mortality risk prediction model that was developed showed good accuracy overall with an area under the curve of >0·8. This is the first mortality risk prediction model developed within a multi-center study for oesophageal perforation and is freely available. The combination of baseline patient data, with biochemical measures, aetiology, imaging findings and treatment, establishes the importance of all these factors in patients' mortality from oesophageal perforation. Prior to clinical implementation, there is a need for further validation of this model, both internally within a planned further investigation in the United Kingdom and externally through open access and use of the model by international collaborators.

It is important to consider the limitations of this study in view of the findings identified. Firstly, this study includes eight high volume esophago-gastric surgical centers and is representative of a centralized practice in the management of oesophageal perforation. This is in direct comparison to our previously published national cohort study, and thus does have an inherent selection bias given the design of the study[15]. Importantly, the present study represents an analysis of the effects of centralizing the management of oesophageal perforation to high volume esophago-gastric surgical centers to optimise care. While this is likely to enhance the internal validity of treatment decisions between centers, we accept that the generalisability of the results is reduced and makes historical outcome comparisons difficult. Further, given the observational nature of the study design, causation cannot be established, especially when considering the association of reduced 90-day mortality seen with surgical intervention. This may be the result of an inherent selection bias, whereby patients deemed physiologically fit for surgery are escalated to centralized care and thus more likely to undergo major interventions, however this was not captured within the parameters adjusted for in the analysis. Given the detailed nature of the data requested on every patient there were patients with missing data, especially in the timeline analyses, which may have led to this analysis being underpowered and introduce bias due to non-random missing data and imputation.

In conclusion, this large multi-center study including eight high volume esophago-gastric surgical centers was able to establish with a centralized service for the management of oesophageal perforation the 90-day mortality is 18·9%. Key patient, biochemical, aetiological, radiological and treatment factors can be combined into a risk model that accurately identifies patients at risk of mortality from oesophageal perforation. Surgical intervention and time to diagnosis were determined to be key prognostic factors associated with reduced mortality. Future investigation must seek to validate this mortality predictive risk model, and to identify key areas for change that may reduce 90-day mortality further.

Reporting: This manuscript is reported with strobe checklist (supplementary table S7).

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Data sharing statement

Will individual participant data be available?	Yes
What data will be shared?	Processed data files with all the individual participant data analyzed in this study, after de-identification
What other documents will be available?	Analytic code
When will data be available (start and end dates)?	Immediately following publication; no end date
With whom?	Data curated from the raw data will be available to anyone. Complete raw data will be granted subject to review by a data access committee*.
For what types of analyses?	Any purpose
By what mechanism will data be made available?	Data are available indefinitely in Mendeley Data (DOI: 10.17632/by6rthpwb8.1)

*Raw data access requests should be made to the corresponding author with a clear description of planned analysis. Access will be grated after a discussion with the data access committee (DAC). The DAC will be constituting a minimum of three of the authors including, but not limited to, the first author and the corresponding author.

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Figure 1: Mortality prediction models and performance. A – Receiver operator characteristic curves showing the performance of the modelling techniques used with the area under curve values for each method printed within the plot. B – Box plots showing the area under curve values over 50 iterations of repeated random subsampling validation. C – As in A but with hospital transfer and intervention type variables removed. D – As in B, applied to C. (tpr – true positive rate; fpr – false positive rate; AUC – area under curve; EN – logistic regression with elastic net regularisation; LR – logistic regression; RF – random forest; SVM – support-vector machines.)

Figure 2: Boxplots (upper plots) and proportional bar charts (bottom row) showing the differences in mortality from oesophageal perforation for a selection of significant variables (red=alive, turquoise=deceased/dead). Asterisks above the boxplots denote p value (*<0·05, **<0·01, ***<0·001).

Figure 3: Chronology mapping and dimensional reduction. A – Example of patient journey chronology across key timepoints of symptom onset, time to hospital visit, time to diagnosis, time to transfer to treating hospital (where relevant) and time to intervention. B – Summary of first ten patient journey chronologies. C – Uniform manifold approximation and projection plots of all patient journey chronologies. The upper plots show intervals from symptoms onset, and the lower plots show the main outcomes of mortality (bottom left, patient deaths highlighted in larger orange points with grey arrow to indicate visual interpretation of higher density of mortality), length of stay (bottom middle) and intensive care stay. (los – length of stay; icu – intensive care unit).