Profiling Patient-Reported Symptom Recovery from Esophagectomy for Patients with Esophageal Squamous Cell Carcinoma: A Real World Longitudinal Study

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Research Article

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Abstract

Purpose: Esophageal squamous cell carcinoma (ESCC) patients have severe symptom burden after esophagectomy; however, longitudinal studies of symptom recovery after surgery are scarce. This study used longitudinal patient-reported outcome (PRO)-based symptoms to identify severe symptoms and profile symptom recovery from surgery in patients undergoing esophagectomy.

Methods: Esophageal cancer patients (N=327) underwent esophagectomy were consecutivly included between April 2019 and March 2020. Data were extracted from the Sichuan Cancer Hospital's Esophageal Cancer Case Management Registration Database. Symptom assessment time points were pre-surgery and 1, 3, 5, 7, 14, 21, 30, and 90 days post-surgery using the Chinese version of the MD Anderson Symptom Inventory. The symptom recovery trajectories were profiled using mixed-effect models and Kaplan–Meier analysis.

Results: The most-servere symptoms after esophagectomy were pain, fatigue, dry mouth, disturbed sleep, and distress. The severity of symptoms peaked on day 1 after surgery. The top two symptoms were fatigue (mean: 5.44[SD 1.88]) and pain (mean: 5.23[SD 1.29]). Fatigue was more severe 90 days after surgery than at baseline (mean: 1.77 [SD 1.47] vs 0.65 [SD 1.05]; P<.0001). Disturbed sleep and distress persisted from pre-surgery to 90 days post-surgery; average sleep recovery time was up to 20 days, and 50.58% of patients had sleep disturbances 90 days post-surgery.

Conclusions: Early postoperative pain management after esophagectomy should be considered. Characteristics and intervention strategies of postoperative fatigue, distress, and disturbed sleep in esophageal cancer patients warranty further studies.

The study was registered on ChiCTR.org.cn Web site (ChiCTR2000040780, date 12/10/2020).

Introduction

Esophageal cancer is the 6th leading cause of cancer-related death globally [1]. Approximately one-third to half of the esophageal cancer cases are diagnosed in China[2], with >90% cases being esophagus squamous cell carcinoma (ESCC), and the 5-year survival is 30.3%-52.9%[3,4]. Comprehensive treatment based on surgery is the primary treatment for esophageal cancer. The risk of above grade Ⅲ complications is 11.6%, and the incidence of surgery-related complications is 89.9% [3]. Complications are associated with impaired health-related quality of life, exacerbated symptom severity, and functional impairment[5–7].

The recovery process for esophageal carcinoma patients post-surgery is complicated and lengthy owing to surgical trauma and reconstruction of the digestive tract[8]. At 3 months post-surgery, symptom burden, especially that of fatigue, appetite loss, reflux, and eating difficulties, remains high[9]. Gastrointestinal symptoms such as reflux, eating difficulties, diarrhoea, and appetite loss can persist 10 years post-surgery[8]. Symptom persistence is related to patient prognosis. Patients who experience surgical symptoms such as reflux-cough and eating difficulties are have an increased risk of mortality[10].

Patient-reported outcomes (PROs) provide the most important information regarding operation success[11,12]. PROs are directly derived from a patient's subjective evaluation of their own health status and treatment results without the explanation of medical professionals[13]. Traditional postoperative recovery indicators are primarily objective measures, i.e., length of hospital stay, postoperative complications, and readmission rate[14,15]. However, indicators such as 'complete disappearance of symptoms' and 'return to daily life function as soon as possible' have become the main indicators for clinical medical judgement of postoperative recovery[16]. Because of the reliability, sensitivity, and feasibility of measuring patients' daily functions and symptoms, PRO has been applied in clinical research, drug approval, and enhanced recovery after surgery (ERAS) protocol evaluation in Europe and America[17–21]. Therefore, subjective measures provided by patients represent an important outcome measure.

Despite this, PRO data characterising the time course, developmental trajectory and recovery of postoperative symptoms in ESCC patients are lacking. Therefore, we analysed PRO-based symptoms reported by ESCC patients 90 days after surgery to (1) identify the most-servere symptoms; (2) describe the trajectory of these symptoms; and (3) profile symptom recovery after surgery.

Materials And Methods

Patients, Settings, and Study Procedures

This real world longitudinal study included consecutive esophageal cancer patients who underwent esophagectomy at Sichuan Cancer Hospital between April 2019 and March 2020. The study was approved by the Medical Ethics Committee and Clinical Trial Review Committee of the Sichuan Cancer Hospital (SCCHEC-02-2020-036). In this department, symptom severity was assessed for all patients undergoing esophagectomy as a clinical routine, so the informed consent was waived. The study was registered on ChiCTR.org.cn Web site (ChiCTR2000040780). For the current analysis, patients were excluded if they (1) had postoperative pathological non-squamous carcinoma; (2) underwent palliative esophagectomy; (3) had esophageal and gastric junction carcinoma; or (4) ≥4 times symptoms data missing.

Data Collection

Demographic and Clinical Characteristics

Demographic characteristics and clinical information were collected from medical records. Demographic characteristics included age, sex, and marital status; clinical information included cancer location, neoadjuvant therapy, type of surgery, TNM classification, Eastern Cooperative Oncology Group performance status (ECOG PS), Patient-Generated Subjective Global Assessment (PG-SGA) scores, postoperative hospital stay, and comorbid conditions.

Symptom Data

Symptom data were obtained from the Sichuan Cancer Hospital's Case Management Registration Database based on REDCap (http://125.71.214.100:888/

redcap). Symptom data were collected at pre-surgery (baseline) and on days 1, 3, 5, 7, 14, 21, 30, and 90 after surgery. Symptoms were assessed using the Chinese version of the MD Anderson Symptom Inventory (MDASI-C). MDASI-C is a brief measure of 13 common cancer-related symptoms, and each symptom was rated on an 11-point scale, with 0 being 'not present' and 10 being 'as bad as you can imagine'[22] .We defined mild symptom as 1-3, moderate symptom as 4-6, and severe symptom as 7-10[22]. MDASI-C is well-established validity and reliability in cancer patients[23], and can be used for postoperative high-frequency symptom collection by assessing the previous 24 hours symptoms[24].

Statistical Analyses

Data are summarised as means (±standard deviation [SD]), medians (quantiles), or frequencies (percentages), as appropriate. We used the percentage of the moderate-severe level (score ≥4) on day 1 after surgery to identify the 5 most-severe symptoms and profile symptom recovery from surgery.

Mixed-effect models with the maximum likelihood method were used to compare symptom scores at each postoperative time point with preoperative levels of the symptoms. Because the random effect of timepoints was estimated to be zero, the random effect of intercepts was included in all models. The fixed effects of all independent variables were age, sex, marital status, ECOG PS, neoadjuvant therapy, surgery type, comorbid conditions, PG-SGA scores, cancer location, and the interaction between time and length of hospitalisation. In the models, we considered time as a categorical variable. Variance structure types, such as unstructured, simple, first-order auto-regressive, and compound symmetric, were compared via Bayesian information criterion (BIC). The model with least BIC was preferred.

We defined 'postoperative recovery' as symptom recovery to the mild level; i.e., after surgery, the patient-reported MDAS-C symptom scores ≤3 at one measurement. Median and mean recovery days and 95% confidence intervals (CIs) were estimated using Kaplan–Meier analysis.

All tests were two sided, with 5% as the significance level. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Sample Population

Overall, 327 esophageal cancer patients undergoing surgery were enrolled. Fifty-two patients were excluded from the study. **Figure 1** shows the inclusion and exclusion of patients in the study.

Table 1. shows the demographic and clinical characteristics of the enrolled patients. Approximately 91% of patients were treated with minimally invasive McKeown and 63% were treated with neoadjuvant therapy. The cancer location was the upper (9%), middle (58%), and lower (31%) esophagus. The absence of data

from nine consecutive symptom assessments in 275 patients is shown in **Table S1**. The highest rate of missing data was 7.64% on day 90 after surgery.

Major Postoperative Symptoms

Table 2. shows the 5 most-severe symptoms after esophagectomy were pain (88.36%), fatigue (83.64%), dry mouth (72.36%), disturbed sleep (69.45%), and distress (51.64%). **Figure 2** shows the proportions of none (0), mild (1-3), moderate (4-6), and severe (7-10) levels of the symptoms at each time point. Before surgery, the most-severe symptoms were disturbed sleep (19.63%) and distress (18.55%). The percentage of patients who reported moderate-to-severe symptoms gradually declined after surgery, although fatigue increased from 30.15% on day 7 to 39.27% on day 14 and subsequently decreased to 25.82%, 18.68%, and 9.85% on days 21, 30, and 90, respectively. One month after surgery, the most-severe symptoms were disturbed sleep (28.20%), fatigue (18.68%), and distress (17.22%). Three months after surgery, the most-severe symptoms were disturbed sleep (15.57%), fatigue (9.85%), and distress (9.84%).

The severity of symptoms peaked on day 1 after surgery. The top two symptoms were fatigue (mean: 5.44[SD 1.88]) and pain (mean: 5.23[SD 1.29]). The symptoms that remained more severe at 30 days after surgery than at pre-operation were pain (mean: 1.89 [SD 1.12] vs 0.44 [SD 0.78], P<.0001); fatigue (mean: 2.42 [SD 1.54] vs 0.65 [SD 1.05], P<.0001). Fatigue was more severe 90 days after surgery than at baseline (mean: 1.77 [SD 1.47] vs 0.65 [SD 1.05]; P<.0001) (**Figure 3, Table S2**).

Profiling the Postoperative Recovery Time Course using Symptom Outcomes

Figure 4 shows Kaplan–Meier curves of the time to recover to a none/mild level of symptoms during the 3-month period immediately after surgery for the 5 most-servere symptoms. **Table S3** presents the median and mean time course of recovery to none/mild symptom ratings (≤3 on a 0–10 scale). Disturbed sleep exhibited a slower recovery to none/mild severity than did the other four symptoms (mean: 20 vs 5–10 days), and the recovery probability is the lowest (94.2%).

Discussion

To our knowledge, this study is the first to use a validated PRO tool to longitudinally profile symptom trajectories over the course of recovery from esophagectomy in ESCC patients. The most-servere symptoms were pain, fatigue, dry mouth, disturbed sleep, and distress. The incidence of moderate-servere pain was 88.36% on day 1 after esophagectomy. Fatigue was more severe 90 days after surgery than at baseline, and the incidence of fatigue gradually decreased but had a rebound trend from 7 to 14 days after surgery. Distress and disturbed sleep were persisted before surgery to 90 days after surgery, and the average recovery time for sleep was up to 20 days.

High incidence and Long Recovery Time of Pain after Surgery

Postoperative pain is the most prominent symptom that affects the quality of life of cancer patients[25-27]. Our results showed that the severity of pain after esophagectomy peaked on day 1 after surgery. The

incidence of moderate-servere pain on day 1 was 88.36%, and the mean score was 5.23. The peak time and mean score is consistent with previous studies[27,28]. Although strong opioids were used, pain was not fully controlled within 7 days of surgery. Postoperative early effective pain management is essential for patient comfort, early recovery, low surgical morbidity, and short hospitalisation[26]. Our findings regarding the longitudinal changes in pain and the recovery trend after esophagectomy also support the importance of early postoperative pain management.

Rebound and Persistence of Fatigue

Our findings show that the incidence of fatigue initially gradually decreased but had a rebound trend from 7 to 14 days after surgery. A similar study of postoperative self-reports of lung cancer patients did not find a similar trend [24]. One reason for this could be that esophageal cancer patients had inadequate nutritional support after discharge from hospital; previous studies have shown that nutritional support can significantly improve cancer-related fatigue[29-31]. However, cancer-related fatigue is multifactorial[32]. Therefore, the mechanisms and transitional management of postoperative fatigue in esophageal cancer patients deserve further exploration. Additionally, we found that the proportion of patients with moderate-to-severe fatigue was higher 90 days after surgery than at baseline. Previous studies have also reported that fatigue is the most severe and common symptom 3 months after surgery[8,33]. Overall, fatigue in esophageal cancer patients is a concern both in the early postoperative period and subsequent long term. Many studies focusing on interventions for cancer-related fatigue have shown that exercise (i.e. aerobic and resistance training, yoga, and Tai-Chi), psychological interventions, and some other non-pharmaceutical interventions are effective for reducing fatigue [34-36]. Therefore, based on the clinical characteristics of postoperative fatigue in esophageal cancer patients, fatigue intervention strategies should be further explored.

Persistence of Disturbed Sleep and Distress

Distress and disturbed sleep are two common persistent symptoms[37,38], and higher psychological distress can predict sleep disturbances[39,40]. Our results revealed that although the peak scores for sleep and psychological symptoms were not particularly high, distress and disturbed sleep persisted before surgery to 90 days after surgery; at 90 days after surgery, approximately 50.58% of patients still reported sleep disturbances. A previous study similarly showed that the prevalence of disturbed sleep was 46.8%[8]. We found that postoperative sleep recovery time was the longest, and the average recovery time for sleep was up to 20 days. To our knowledge, there are no relevant data on the recovery time of disturbed sleep in esophageal cancer patients; however, this result also indicates that the long-term symptoms of sleep disturbance affect patients' quality of life, which is worthy of in-depth study to develop targeted symptom management measures.

Strengths and Limitations

The key strengths of this study were the longitudinal design with baseline measures of symptoms after esophagectomy, large number of participants, use of the validated PRO tool for symptom rating, high

response rate, consecutive inclusion, and homogeneous sample that included only ESCC patients. And this is, to the best of our knowledge, the first study to use PRO-based symptom data to describe the most severe postoperative symptoms and the symptom recovery for ESCC patients.

However, this study had some limitations. First, this study was performed in a single centre, the results may be biased by sampling. Second, the MDASI assesses the 13 symptoms that are common in cancer patients; an MDASI version that is specific to perioperative assessment after esophagectomy has not yet been produced and psychometrically validated. Furthermore, some ESCC-specific symptoms, such as being unable to eat, reflux, and hoarseness, were not assessed. Third, we did not collect symptom data with discharge as a starting point; thus, our results may not completely reflect the characteristics of symptoms during the transition period from discharge to home.

Conclusions

Our study demonstrated that pain, fatigue, dry mouth, disturbed sleep, and distress were 5 most-servere symptoms after esophagectomy. Although strong opioids were used, pain was not completely controlled within 7 days of surgery. Early postoperative pain management after esophagectomy must be considered. Fatigue initially gradually decreased but rebounded 14 days after surgery. Distress and disturbed sleep were persistent symptoms, indicating that patients had a prominent level of psychological stress. Therefore, characteristics and intervention strategies regarding perioperative fatigue, distress, and disturbed sleep in esophageal cancer patients deserve further studies.

Declarations

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Conflict of interest: The Chinese version of the MD Anderson Symptom Inventory is copyrighted and licensed by The University of Texas MD Anderson Cancer Center. The authors report no other conflicts of interest in this work.

Availability of data and material: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Code availability: Data were analysed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA)

Author Contributions: Conceptualization: [Qiuling Shi]; Formal analysis and investigation: [Xi Luo, Qin Xie, Yan Miao, Hong Yin, Qingsong Yu, Hongfan Yu]; Writing - original draft preparation: [Xi Luo]; Writing - review and editing: [Qiuling Shi, Xi Luo]; Funding acquisition: [Xuefeng Leng]; Resources: [Yongtao Han, Hong Zhou]; Supervision: [Hong Zhou].

Compliance with ethical standards: The study was approved by the Medical Ethics Committee and Clinical Trial Review Committee of the Sichuan Cancer Hospital (SCCHEC-02-2020-036).

Consent to participate: As this was a retrospective review of ideidentified data, the requirement for informed consent was waived.

Consent for publication: Not applicable.

Research involving human participants and/or animals: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Tables

Table 1 Demographic and clinical characteristics of esophageal squamous cell carcinoma patients (n=275)

Characteristics	n	%
Age (years)		
M (SD): 62.40 (8.09)		
Median (range): 63 (41–84)		
<65	154	56.00
≥65	121	44.00
Sex		
Male	229	83.27
Female	46	16.73
Marital status		
Married	259	94.18
All others	16	5.82
Location		
Upper	27	9.82
Middle	162	58.91
Lower	86	31.27
Neoadjuvant therapy		
Yes	174	63.27
No	101	36.73
Type of surgery		
Minimally invasive McKeown	252	91.64
Ivor-Lewis	15	5.45
Open McKeown	8	2.91
8th TNM stage		
□	98	35.64
□	82	29.82
□	95	34.55
Preoperative ECOG PS		
Good (0–1)	273	99.27

Poor (2–4)	2	0.73
Preoperative PG-SGA		
<4	139	50.55
≥4	136	49.45
Postoperative hospital stay (days)		
M (SD): 12.83 (9.89)		
Median (range):10 (6–97)		
≤10	154	56.00
>10	121	44.00
Comorbid conditions		
Yes	60	21.82
No	215	78.18

M= mean; SD=standard deviation; TNM= tumor node metastasis; ECOG PS=Eastern Cooperative Oncology Group performance status; PG-SGA= Patient-Generated Subjective Global Assessment.

Table 2 Percentage of moderate-severe symptoms in patients with esophageal squamous cell carcinoma 1 day after surgery (n=275)

Symptoms	Missing		None		Mild		Moderate		Severe		Moderate-severe
	n	%	n	%	n	%	n	%	n	%	%
pain	12	4.36	0	0.00	20	7.27	204	74.18	39	14.18	88.36
fatigue	12	4.36	6	2.18	27	9.82	147	53.45	83	30.18	83.64
drymouth	12	4.36	8	2.91	56	20.36	122	44.36	77	28.00	72.36
sleep	12	4.36	6	2.18	65	23.64	121	44.00	70	25.45	69.45
distress	12	4.36	9	3.27	112	40.73	139	50.55	3	1.09	51.64
drowsy	12	4.36	3	1.09	129	46.91	126	45.82	5	1.82	47.64
Appetite loss	13	4.73	28	10.18	121	44.00	110	40.00	3	1.09	41.09
sad	12	4.36	18	6.55	192	69.82	51	18.55	2	0.73	19.27
shortbreath	12	4.36	148	53.82	94	34.18	20	7.27	1	0.36	7.64
nausea	12	4.36	247	89.82	13	4.73	1	0.36	2	0.73	1.09
remenber	12	4.36	206	74.91	56	20.36	1	0.36	0	0.00	0.36
numbness	12	4.36	240	87.27	22	8.00	1	0.36	0	0.00	0.36
vomiting	12	4.36	257	93.45	6	2.18	0	0.00	0	0.00	0.00

Figures

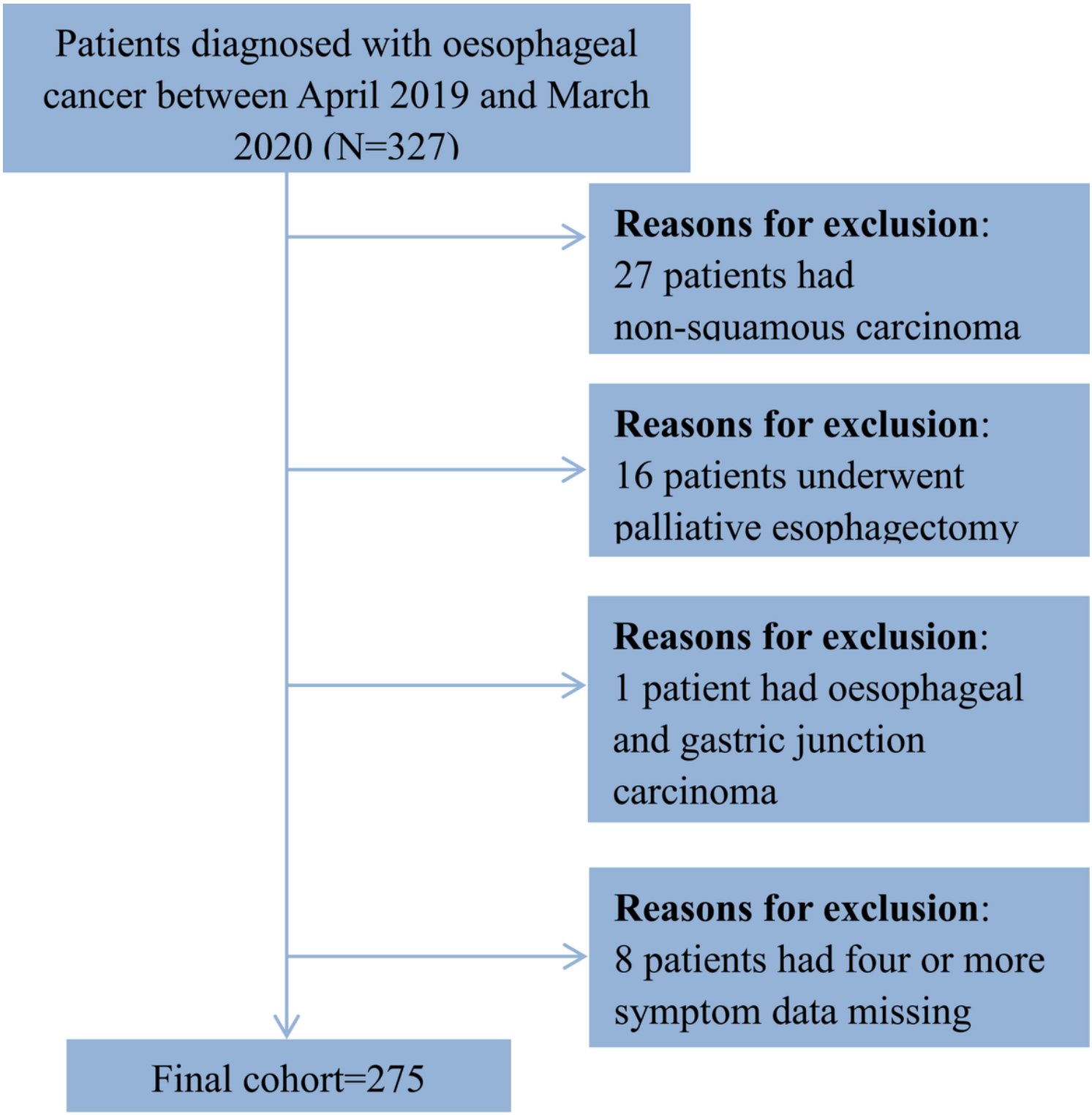

Figure 1

Flowchart of patients enrolled in the study.

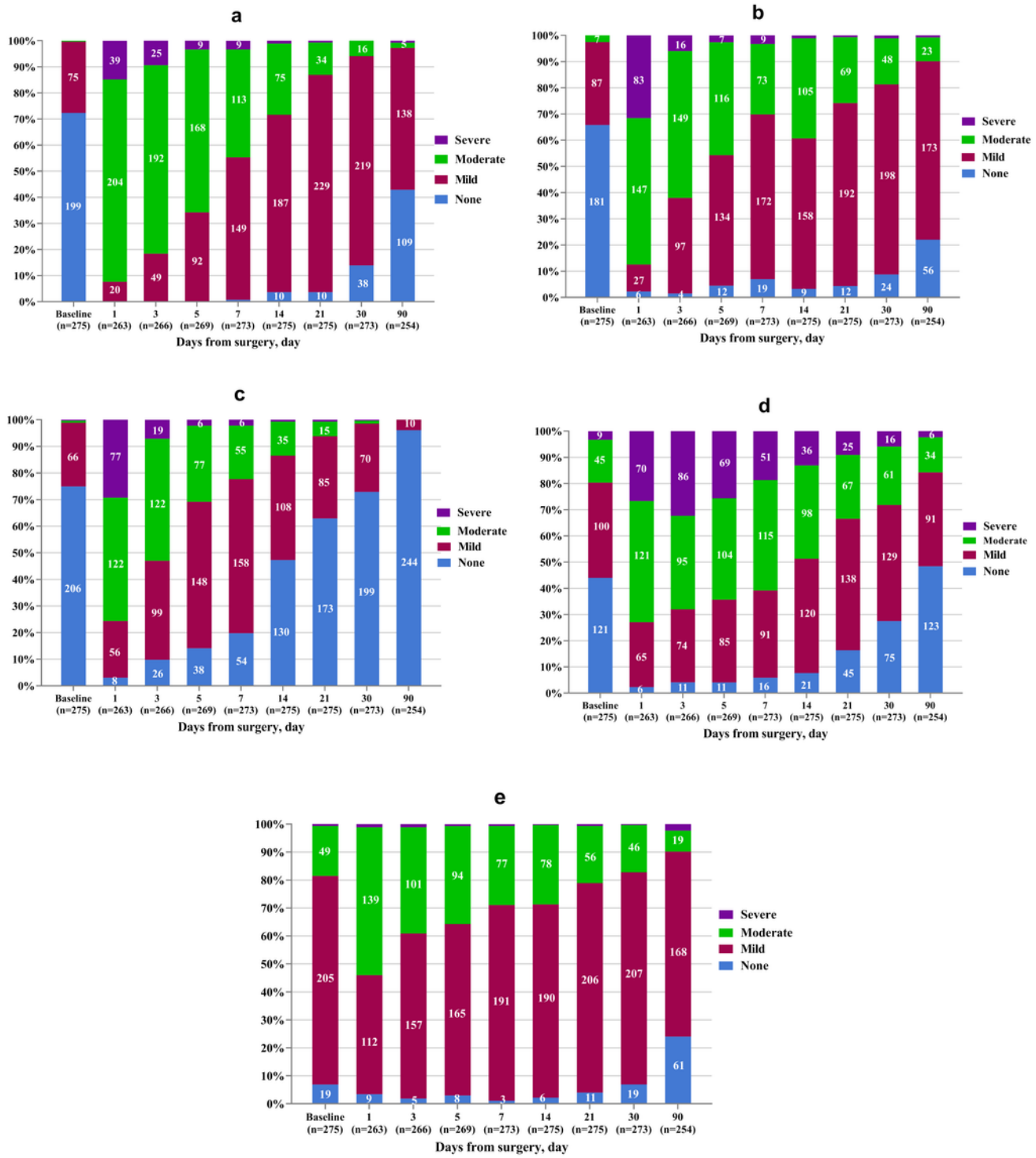

Figure 2

(a) The proportion (%) of patients reporting pain at each time point. (b) The proportion (%) of patients reporting fatigue at each time point. (c) The proportion (%) of patients reporting dry mouth at each time point. (d) The proportion (%) of patients reporting disturbed sleep at each time point. (e) The proportion (%) of patients reporting distress at each time point.

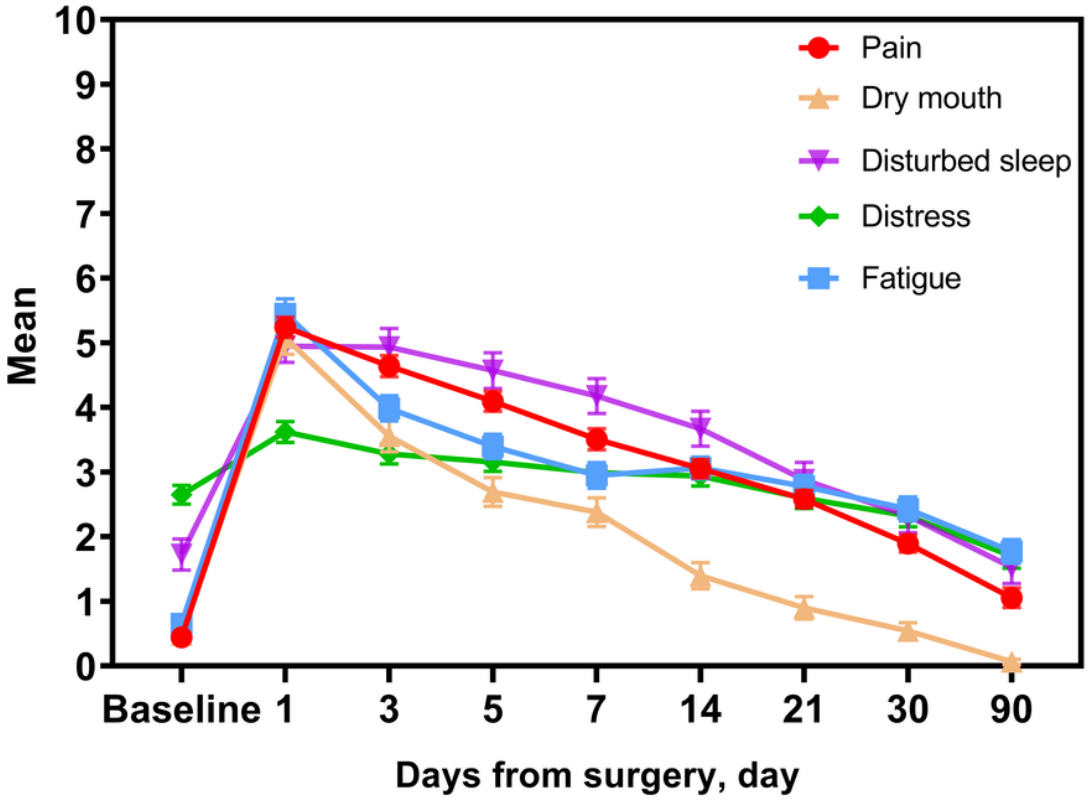

Figure 3

Symptom severity over time for the core symptoms after surgery

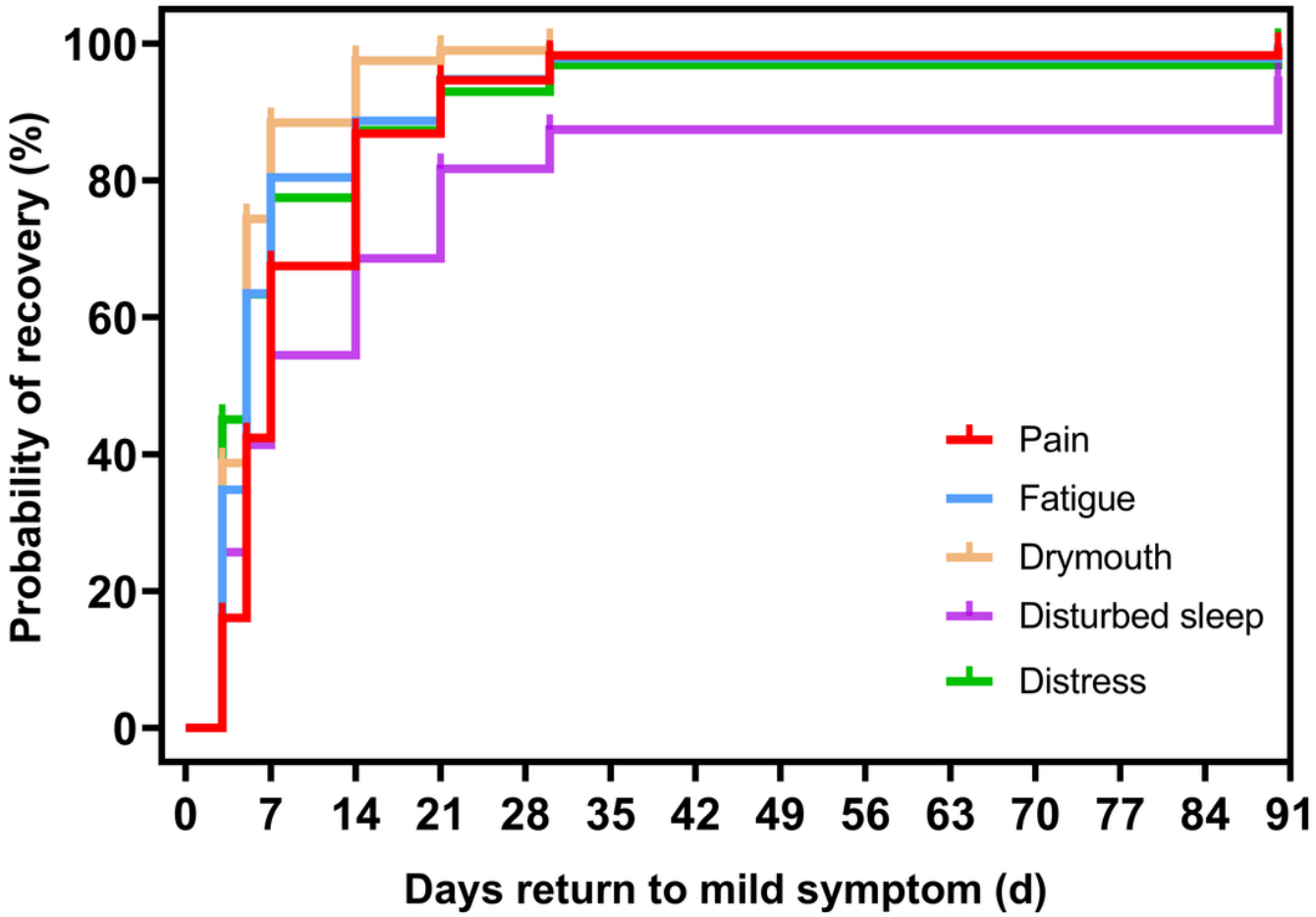

Figure 4

Kaplan–Meier curves for the core symptoms overall.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.docx