Identifying Clusters of Curatively-Treated Esophageal Cancer Patients Using Patient-Reported Outcome Measures at Three Months from Discharge: A Secondary Analysis from a Longitudinal Single Center Study

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Rosario Caruso[1,2], Arianna Magon[1], Gianluca Conte[1], Luigi Bonavina[2,3]

[1]Health Professions Research and Development Unit, IRCCS San Donato Milanese, 20097 San Donato Milanese, Italy
[2]Department of Biomedical Sciences for Health, University of Milan, 20133 Milan, Italy
[3]Division of General and Foregut Surgery, IRCCS Policlinico San Donato, 20097 San Donato Milanese, Italy

AIM: This study aims to identify meaningful clusters based on Patient-Reported Outcome Measures (PROMs) in curatively-treated esophageal cancer patients at three months post-discharge.
METHODS: This secondary analysis of a longitudinal single-center study included 46 esophageal cancer patients who underwent curative surgery. Patients were selected based on their completion of PROMs surveys at three months post-discharge, were aged 18 years or older, and had undergone surgical resection (esophagectomy) with or without neoadjuvant chemotherapy and/or radiotherapy. The analysis utilized t-distributed Stochastic Neighbor Embedding (t-SNE) for dimensionality reduction and hierarchical clustering to analyze PROMs data collected three months post-discharge. Clustering was performed on physical, emotional, cognitive, and social functioning variables, symptom burden, and health literacy.
RESULTS: Three distinct clusters were identified: Cluster 1 (n = 24) with higher functioning and moderate symptoms, Cluster 2 (n = 14) with moderate functioning, higher symptoms, and lower health literacy, and Cluster 3 (n = 8) with the highest functioning, lowest symptoms, and highest health literacy. Significant differences between squamous cell carcinoma and adenocarcinoma subtypes were observed across several PROMs domains, including critical health literacy, general health status/quality of life, nausea and vomiting, and insomnia. These clusters provide an exploratory framework for tailoring post-operative interventions to enhance patient recovery, which necessitates further confirmatory investigations, including outcomes such as complications and mortality, in the analysis.
CONCLUSIONS: This study fills a research gap by demonstrating the utility of PROMs in identifying distinct recovery patterns in esophageal cancer patients post-surgery. The findings support the use of PROMs to guide personalized post-operative care, potentially improving patient outcomes and quality of life. Further research is needed to validate these findings in larger, diverse populations.

Keywords: esophageal cancer; Patient-Reported Outcome Measures; t-SNE; hierarchical clustering; post-operative recovery; health literacy; quality of life

Introduction

Esophageal cancer is a significant global health issue, with over 0.6 million new cases and 0.54 million deaths reported worldwide in 2020, making it one of the leading causes of cancer-related deaths [1, 2]. It predominantly affects individuals in their sixth and seventh decades of life, with a higher prevalence in men [2]. The standard treatment modalities for esophageal cancer include surgery, chemotherapy, and radiation therapy [3]. Curative treatment often involves esophagectomy, which can be performed using surgical approaches that include field techniques involving the neck, thorax, and abdomen: Ivor-Lewis, McKeown, minimally invasive Ivor-Lewis, minimally invasive McKeown, transhiatal, minimally invasive transhiatal, left transthoracic or thoracoabdominal approach with cervical anastomosis, and robotic-assisted minimally invasive esophagectomy (MIE) [4].

Recovery from surgery is critical, as it impacts patients' overall survival and quality of life [5]. Effective recovery management includes monitoring physical, emotional, and social well-being to address complications and improve long-term outcomes. In this context, Patient-Reported Outcome Measures (PROMs) are standardized tools that capture patients' perspectives on their health status, including symptoms, functional status, and overall quality of life [6]. PROMs play a crucial role in assessing the health-related quality of life (HRQoL) in cancer patients, offering insights that often remain obscured in standard clinical evaluations [7]. Existing literature highlights the significance of PROMs in tracking various aspects of HRQoL, including physical functioning, emotional well-being, and social interactions [5, 6, 7]. Studies have shown that esophageal

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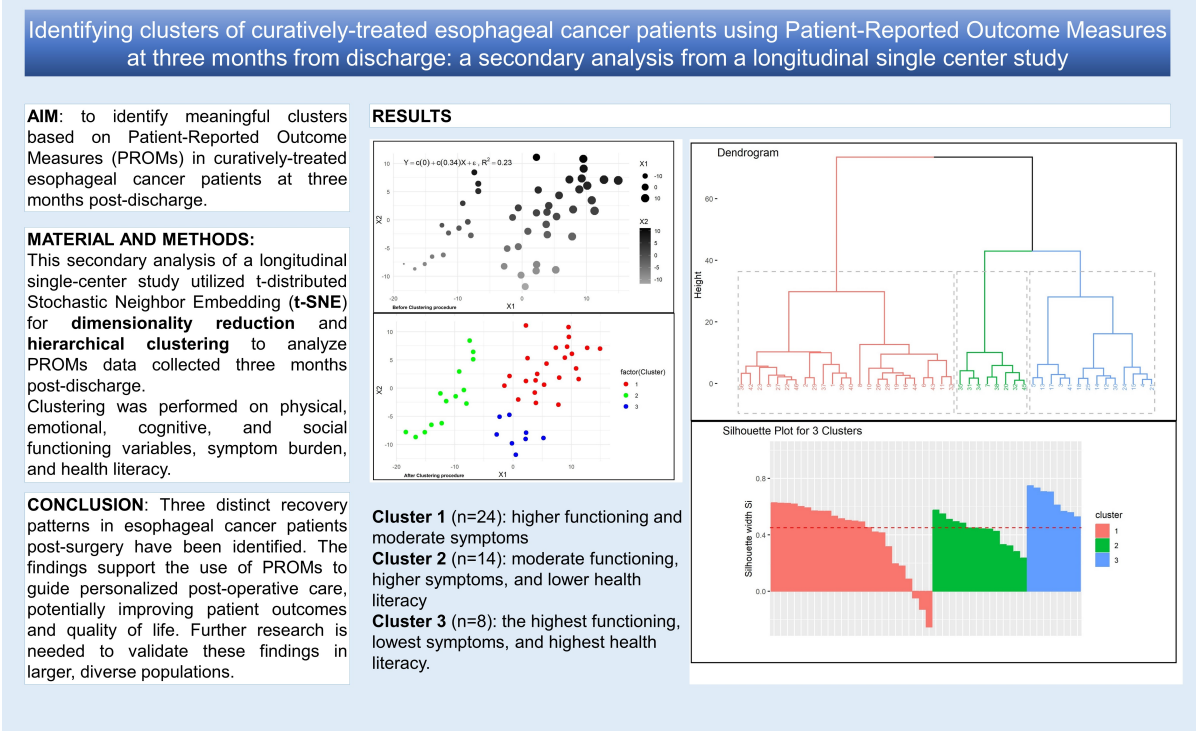
Correspondence to: Rosario Caruso, Health Professions Research and Development Unit, IRCCS San Donato Milanese, 20097 San Donato Milanese, Italy; Department of Biomedical Sciences for Health, University of Milan, 20133 Milan, Italy (e-mail: rosario.caruso@grupposandonato.it).



Graphical Abstract.

cancer patients often experience a range of post-surgery symptoms, such as pain, fatigue, and difficulty swallowing, which can significantly affect their quality of life [7].

Despite the recognized importance of PROMs in evaluating HRQoL for esophageal cancer patients, there is a notable lack of studies that employ clustering analysis to identify distinct subgroups of patients based on their recovery patterns. Some authors have started to identify clusters based on pre-operative data [8]. Clustering analysis, which groups patients with similar recovery trajectories, could potentially uncover meaningful patterns that are not evident in traditional analyses [9]. Identifying meaningful clusters of patients based on their PROMs could provide crucial insights into personalized care and targeted interventions. For instance, patients who experience similar symptoms and challenges during their recovery can benefit from customized support programs and treatment modifications. Furthermore, identifying clusters could aid in predicting long-term outcomes and optimizing resource allocation, ensuring that interventions are both effective and efficient. Accordingly, this study aimed to identify meaningful clusters of curatively-treated esophageal cancer patients based on their PROMs response 3 months post-discharge.

Materials and Methods

Study Design

This study represents a secondary analysis of data derived from a longitudinal single-center study aimed at evaluating the HRQoL in curatively-treated esophageal cancer patients [5]. The primary study focused on assessing PROMs over time, with the current analysis specifically examining data collected at 3 months post-discharge (the last available follow-up). The original study design included monthly follow-ups to monitor recovery patterns and complications, providing a robust dataset for secondary analysis. The reporting of this study followed the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" guidelines [10]. This study was approved by the Ethical Committee of Ospedale San Raffaele, Italy (protocol n. 136/int/2018). Written informed consent was obtained from all participating patients prior to their inclusion in the study. The study was conducted in accordance with the principles of the Helsinki Declaration.

Patients

The study population comprised 46 esophageal cancer patients who underwent curative surgery at a single medical center in 2019. To be included in the current analysis, patients had to meet the following criteria: they needed to be diagnosed with esophageal cancer and treated with curative intent, which included surgical resection (esophagectomy) with or without neoadjuvant chemotherapy and/or radiotherapy aimed at complete tumor removal and potential cure; patients have completed a PROMs survey at 3 months post-discharge, and be aged 18 years or older at the time of surgery. Exclusion criteria were patients who did not complete the PROMs survey at the specified time point and those who underwent palliative treatment or did not survive until the 3-month follow-up.

Measurements

Sociodemographic variables included sex (males, females), region (Lombardy, extra-Lombardy), and nationality (Italian, non-Italian). The TNM classification of the tumors was categorized as T1 (T1N0, T1N0M0, T1N0Mx, ypT1N2Mx), T2 (T2N0M0, T2N1Mx, T2N2M0, T2N2MX, T2N3Mx, ypT2N0), T3 (T3N0M0, T3N0Mx, T3N1, T3N1Mx, T3N2M0, T3N2Mx, T3N3Mx, ypT3N3M0), and non-specific (pT3N1Mx, T0N0Mx, TN0Mx, uT3N3Mx, uT3Nx). Histological types included squamous cell carcinoma, adenocarcinoma, and melanoma. Patients' risk factors in anamnesis were recorded as either yes or no. Age was recorded in years, and body mass index (BMI) in kg/m^2. Co-morbidities were categorized using the Charlson Comorbidity Index (CCI) into no comorbidity, mild comorbidities (one additional comorbidity), and severe comorbidities (two or three additional comorbidities, with more than three excluded). The treatment modalities included neo-adjuvant chemo/radio therapy, and surgical approaches were transhiatal esophagectomy, Ivor Lewis Procedure, minimally invasive esophagectomy, and McKeown esophagectomy. The length of hospital stay was recorded in days.

The assessment tools utilized for evaluating PROMs at the 3-month follow-up included the European Organization for Research and Treatment of Cancer (EORTC) Core quality of life questionnaire (EORTC QLQ-C30) and the EORTC quality of life questionnaire - Oesophageal Cancer Module (EORTC QLQ-OES18) [11, 12, 13]. In addition, the General self-efficacy Scale (GSE) and Health Literacy Questionnaire (HLQ) were employed to assess General self-efficacy and health literacy, respectively [14].

EORTC QLQ-C30 measures the general quality of life in cancer patients, covering physical, emotional, and social functioning. It consists of multi-item scales (five functional scales, three symptom scales, and a global health status/quality of life (QoL) scale) and single-item measures (six single items) using 4-point and 7-point Likert scales. Scores are standardized from 0 to 100, with higher scores indicating better functioning or higher symptom burden, depending on the scale [12].

EORTC QLQ-OES18 focuses on symptoms and emotional issues specific to esophageal cancer. It comprises 18 items using 4-point Likert scales, divided into four subscales (eating, reflux, pain, and dysphagia) and six single items for other symptoms. Scores are standardized from 0 to 100, with higher scores indicating better functioning or higher symptom burden [13].

GSE measures confidence in performing challenging tasks using ten items with a 4-point Likert scale. Higher scores indicate higher self-efficacy, which can be standardized 0–100 [14]. The HLQ assesses health literacy across nine subscales, corresponding to functional, communicative, and critical health literacy. It uses 44 items with 4-point and 5-point Likert scales. Higher scores indicate better health literacy. These tools have been validated in Italian and are recognized for their reliability and validity in assessing HRQoL, self-efficacy, and health literacy in cancer patients.

Data Analysis

After checking for distribution and missingness, descriptive statistics were used to summarize the data. Summaries were based on the nature of the variables and their distribution. Comparisons between PROMs from the most prevalent histological types (i.e., squamous cell carcinoma and adenocarcinoma) were performed using two-tailed Mann-Whitney U tests. To reduce the complexity of the collected information from the PROMs, the t-distributed Stochastic Neighbor Embedding (t-SNE) algorithm was employed [15]. This included the following variables: Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning, Fatigue, Nausea and vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial difficulties, general health status/quality of life (QoL), Eating difficulties, Reflux, Pain (specific to esophageal cancer), Dysphagia, Swallowing saliva, Choked swallowing, Dry mouth, Taste, Coughing, Talking difficulties, General self-efficacy, Mean health perception score, Mean health satisfaction index, Mean anxiety and mental health score, Mean social support score, Mean cognitive ability, Mean activity and energy, Mean nutrition and health status, Mean family health involvement, Mean utility and health information, Communicative health literacy, critical health literacy, Functional health literacy. The t-SNE algorithm reduced these variables into two new variables (X1 and X2) that maintained the linear and non-linear relationships of the original data. Considering the limited sample size, this data reduction technique allowed for feasible and efficient clustering. The optimal perplexity setting for t-SNE was explored, considering sample size and algorithm interpretation, where the final analysis used perplexity = 6 with seed = 42 and 1000 iterations.

Once the PROMs were reduced to the two summary variables (X1 and X2), these were used for clustering patients using the Ward technique and hierarchical approach [16]. The number of clusters was selected based on the interpretation of the clusters, silhouette analysis, and dendrogram inspection. The optimal solution identified the subgroups of patients (clusters), with each PROM described within these clusters.

Comparisons between clusters were performed using the Average Standardized Difference (ASD) for Cluster 1–2, Cluster 1–3, and Cluster 2–3 due to the limited sample size, which did not support traditional inferential comparisons such as the Kruskal-Wallis test. Thus, the comparisons should be considered exploratory. More precisely, for the standardized difference d_i for each variable i, where X values are the means of the variables in the clusters and s are standard deviations:

$$d_i = \frac{\overline{X_{1l}} - \overline{X_{2l}}}{\sqrt{\frac{s_{1i}^2 + s_{2i}^2}{2}}} \quad (1)$$

For the ASD between Cluster 1 and Cluster 2:

$$\mathrm{ASD}_{1-2} = \frac{1}{p}\sum_{i=1}^{p} |d_i| \quad (2)$$

For the ASD between Cluster 1 and Cluster 3:

$$\mathrm{ASD}_{1-3} = \frac{1}{p}\sum_{i=1}^{p} \left| \frac{\overline{X_{1i}} - \overline{X_{3l}}}{\sqrt{\frac{s_{1i}^2 + s_{3i}^2}{2}}} \right| \quad (3)$$

For the ASD between Cluster 2 and Cluster 3:

$$\mathrm{ASD}_{2-3} = \frac{1}{p}\sum_{i=1}^{p} \left| \frac{\overline{X_{2l}} - \overline{X_{3l}}}{\sqrt{\frac{s_{2i}^2 + s_{3i}^2}{2}}} \right| \quad (4)$$

All analyses were performed using R version 4.4.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.r-project.org/) with the following libraries: ggplot2, Rtsne, dplyr, tidyverse, cluster. Statistical significance was set with alfa = 5%.

Results

Sample Characteristics

As described in Table 1, 46 esophageal cancer patients who underwent curative surgery were included in the analysis. Most of the patients were male (71.74%), with females comprising 28.26% of the sample and from Lombardy (54.35%), while the rest were from regions outside Lombardy (45.65%). The vast majority of the patients were Italian (80.43%), with a smaller proportion being non-Italian (19.57%).

Regarding the TNM classification, patients were categorized as follows: 13.04% were in the T1 stage, 13.04% in the T2 stage, and 39.13% in the T3 stage. The remaining 34.78% fell into the non-specific category, which included stages such as pT3N1Mx, T0N0Mx, TN0Mx, uT3N3Mx, and uT3Nx.

Histologically, the majority of patients had adenocarcinoma (69.57%), followed by squamous cell carcinoma (28.26%), and a small proportion had melanoma (2.17%). The presence of risk factors in anamnesis was reported in 78.26% of the patients. The median age of the patients was 65.10 years, with an interquartile range (IQR) of 55.97 to 69.91 years. Co-morbidities were not present in 26.09% of the patients, and the median BMI was 24.75 kg/m^2 (IQR: 22.46–28.46 kg/m^2). Neo-adjuvant chemo/radiotherapy was administered to 60.87% of the patients. The types of surgery performed included Transhiatal Esophagectomy (6.52%), Ivor Lewis Procedure (78.26%), Minimally Invasive Esophagectomy (13.04%), and McKeown Esophagectomy (2.17%). The median length of hospital stay was 11 days, with an IQR of 10 to 13.75 days.

As described in Table 2, the baseline comparisons between patients with squamous cell carcinoma and adenocarcinoma revealed significant differences in PROMs. Patients with adenocarcinoma had significantly higher scores in critical health literacy than those with squamous cell carcinoma (p = 0.034). Additionally, patients with adenocarcinoma reported significantly better general health status/quality of life than those with squamous cell carcinoma (p = 0.033). Furthermore, patients with adenocarcinoma experienced significantly lower levels of nausea and vomiting compared to those with squamous cell carcinoma (p = 0.044). Patients with adenocarcinoma also reported significantly lower insomnia scores compared to those with squamous cell carcinoma (p = 0.010). Lastly, patients with adenocarcinoma reported higher scores of General self-efficacy (p = 0.033).

PROMs: Description at 3 Months after Discharge

The analysis of PROMs at three months post-discharge provides a comprehensive overview of the recovery and health status of esophageal cancer patients, as illustrated in Fig. 1, where the top section included variables with 0–100 metric (ordinate ranges from 0 to 100) and the bottom section included variables with 0–5 metric (ordinate ranges from 0 to 100).

The general quality of life and functioning were assessed, showing that physical functioning scores were high, with a median of 85.0 (IQR: 75.0–95.0), indicating a generally good physical recovery post-surgery. Role functioning was moderately high, with a median score of 80.0 (IQR: 60.0–100.0). Emotional well-being was also reported to be moderately high, with a median score of 70.0 (IQR: 60.0–85.0). Cognitive health scores were positive, with a median of 85.0 (IQR: 75.0–95.0), and social functioning had a median score of 75.0 (IQR: 60.0–90.0), suggesting satisfactory social interactions. The overall health status had a median score of 60.0 (IQR: 50.0–70.0), reflecting the general quality of life post-treatment (Fig. 1).

Symptom scales revealed moderate fatigue levels, with a median score of 30.0 (IQR: 20.0–40.0). Low levels of nausea and vomiting were reported, with a median score of 10.0 (IQR: 5.0–15.0), while pain was reported at moderate levels, with a median score of 20.0 (IQR: 10.0–30.0). Breathlessness was also moderate, with a median score of 15.0 (IQR: 10.0–25.0). Sleep disturbances were noted, with a median score of 25.0 (IQR: 15.0–35.0). Appetite loss was mild, with a median score of 10.0 (IQR: 5.0–15.0), and both constipation and diarrhea were reported at low levels, with

Table 1. Characteristics of patients.

Characteristics	N = 46	%
Sex		
Males	33	71.74
Females	13	28.26
Region		
Lombardy	25	54.35
Extra-Lombardy	21	45.65
Nationality		
Italian	37	80.43
Non Italian	9	19.57
TNM		
T1 (T1N0, T1N0M0, T1N0Mx, ypT1N2Mx)	6	13.04
T2 (T2N0M0, T2N1Mx, T2N2M0, T2N2MX, T2N3Mx, ypT2N0)	6	13.04
T3 (T3N0M0, T3N0Mx, T3N1, T3N1Mx, T3N2M0, T3N2Mx, T3N3Mx, ypT3N3M0)	18	39.13
Non-specific (pT3N1Mx, T0N0Mx, TN0Mx, uT3N3Mx, uT3Nx)	16	34.78
Histological type		
Squamous cell	13	28.26
Adenocarcinoma	32	69.57
Melanoma	1	2.17
Risk factors		
Yes, risk factors in anamnesis	36	78.26
Age		
Years (median; IQR; range:32–85)	65.10	55.97–69.91
Co-morbidities		
None	12	26.09
BMI		
kg/m^2 (median; IQR; range:17.11–37.50)	24.75	22.46–28.46
Neo-adjuvant		
Chemo/radiotherapy	28	60.87
Surgery		
Transhiatal esophagectomy	3	6.52
Ivor Lewis Procedure	36	78.26
Minimally invasive esophagectomy	6	13.04
McKeown esophagectomy	1	2.17
Length of hospital stay		
Days (median; IQR; range:7–55)	11	10–13.75

IQR, interquartile range; BMI, body mass index.

median scores of 5.0 (IQR: 0.0–10.0) and 10.0 (IQR: 5.0–15.0), respectively. Financial stress was moderate, with a median score of 15.0 (IQR: 10.0–20.0) (Fig. 1).

Symptom-specific scales showed that eating difficulties had a median score of 20.0 (IQR: 10.0–30.0), reflux symptoms had a median score of 10.0 (IQR: 5.0–15.0), and pain specific to esophageal cancer had a median score of 20.0 (IQR: 10.0–30.0). Difficulty in swallowing had a median score of 15.0 (IQR: 10.0–25.0), swallowing saliva had a median score of 10.0 (IQR: 5.0–15.0), and choked swallowing had a median score of 5.0 (IQR: 0.0–10.0). Dry mouth was reported with a median score of 10.0 (IQR: 5.0–15.0), taste issues were mild, with a median score of 5.0 (IQR: 0.0–10.0), coughing had a median score of 15.0 (IQR: 10.0–25.0), and difficulties in talking had a median score of 20.0 (IQR: 10.0–30.0).

Health literacy and self-efficacy were also assessed, with critical health literacy having a median score of 3.0 (IQR: 2.5–3.5), communicative health literacy having a median score of 3.5 (IQR: 3.0–4.0), and functional health literacy having a median score of 3.2 (IQR: 2.7–3.7). Self-efficacy was relatively high, with a median score of 40.0 (IQR: 35.0–45.0) (Fig. 1).

t-SNE Procedure

Fig. 2 illustrates the outcome of the t-SNE procedure. The top panel of Fig. 2 shows the scatter plot of the data points before clustering, where each point represents a patient, with the size of the points reflecting the values of X1 and the color gradient representing the values of X2. The bottom panel displays the data points after the clustering procedure, with each cluster identified by a distinct color.

Table 2. Baseline comparisons of PROMs between patients with squamous cell carcinoma and adenocarcinoma.

	Patients with squamous cell carcinoma (N = 13)			Patients with adenocarcinoma (N = 32)			Z	*p*
Score	Median	25° pct	75° pct	Median	25° pct	75° pct		
Physical functioning	93.33	80	96.67	93.33	73.33	100	0.551	0.582
Role functioning	83.33	75	100	100	66.67	100	0.191	0.848
Emotional functioning	83.33	50	91.67	75	62.5	91.67	0.097	0.923
Cognitive functioning	100	66.67	100	100	83.33	100	1.235	0.216
Social functionig	100	75	100	100	75	100	0.015	0.988
Fatigue	22.22	0	50	11.11	0	38.89	0.098	0.922
Nausea, vomiting	5.1	4.9	5.35	4.8	4.6	5	2.009	**0.044**
Pain	0	0	25	0	0	16.67	0.474	0.637
Dysponea	0	0	50	0	0	33.33	1.322	0.186
Insomnia	5.05	4.87	5.16	4.75	4.69	4.93	2.568	**0.010**
Appetite loss	0	0	66.67	0	0	58.33	0.409	0.682
Constipation	0	0	16.67	0	0	33.33	0.414	0.679
Diarrahoea	0	0	0	0	0	0	0.363	0.717
Financial difficulties	0	0	16.67	0	0	0	0.318	0.750
General health status/QoL	66	64.26	66.71	68.5	66.83	69.13	2.130	**0.033**
Eating	16.67	0	29.17	8.33	4.17	33.33	0.221	0.825
Reflux	0	0	25	0	0	0	1.557	0.119
Pain	0	0	11.11	0	0	11.11	1.147	0.251
Disfagia	55.56	38.89	88.89	66.67	30.56	80.56	0.081	0.936
Swallowing saliva	0	0	33.33	0	0	33.33	0.751	0.452
Choked swallowing	0	0	0	0	0	0	1.013	0.312
Dry mouth	0	0	0	0	0	33.33	1.497	0.136
Taste	0	0	0	0	0	16.67	1.311	0.189
Coughing	0	0	33.33	0	0	0	1.170	0.241
Talking	0	0	16.67	0	0	0	0.112	0.911
General self-efficacy	33	28	39.5	38.5	33.75	40	2.130	**0.033**
Communicative health literacy	2.97	2.79	3.31	3.39	3.06	3.68	2.120	0.034
Functional health literacy	3.13	2.86	3.46	3	2.72	3.43	1.502	0.134
Critical health literacy	2.5	2.2	2.9	3.35	3.04	3.78	2.120	**0.034**

Note: bold values are comparisons showing $p <$ alpha (0.05). Z = z-values for each comparison in the table obtained by employing Mann-Whitney U tests. PROMs, Patient-Reported Outcome Measures; QoL, quality of life.

Clustering Procedure

Fig. 3 presents the dendrogram and silhouette plot for the three-cluster solution, which was the better solution for differentiating PROMs. The dendrogram (Fig. 3, top panel) shows the hierarchical arrangement of patients into three clusters, with distinct branches representing each cluster. The silhouette plot measures how similar each patient is to their own cluster compared to others, with higher silhouette widths indicating better-defined clusters. The silhouette plot (Fig. 3, bottom panel) further supports this clustering solution, showing an overall average silhouette width of 0.45, indicating a reasonably well-defined structure. This clustering approach helped identify patient subgroups with distinct recovery patterns and PROMs profiles. Cluster 1 consists of 24 patients, Cluster 2 contains 14 patients and Cluster 3 has 8 patients.

Characteristics of the Clusters

Table 3 presents the characteristics of the clusters in terms of PROMs at three months post-discharge. Cluster 1 (n = 24) is labeled as "higher functioning with moderate symptoms", Cluster 2 (n = 14) as "moderate functioning with higher symptoms and lower health literacy", and Cluster 3 (n = 8) as "highest functioning with lowest symptoms and highest health literacy".

Cluster 1 exhibits higher median scores in physical functioning (85.0), cognitive functioning (85.0), role functioning (80.0) and social functioning (75.0), indicating relatively better functioning compared to the other clusters. The ASD between Cluster 1 and Cluster 2 for these variables are 0.45, 0.41, 0.38 and 0.36, respectively. This suggests that Cluster 1 maintains a noticeable functional advantage over Cluster 2.

Cluster 2, characterized by moderate functioning and higher symptom burden, shows lower median scores in emotional functioning (65.0) and cognitive functioning (80.0) com-

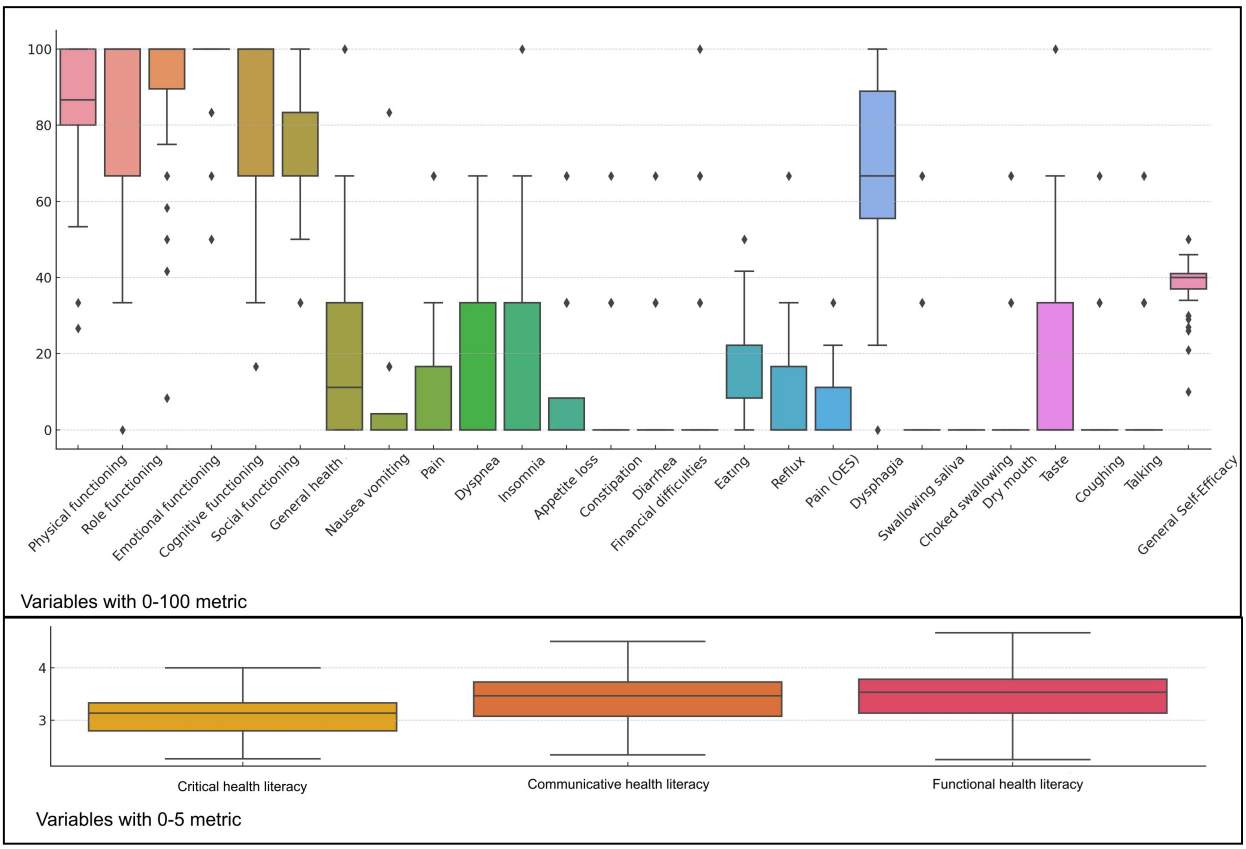


Fig. 1. Description of PROMs at three months after discharge. Note: The top section included variables with 0–100 metric (ordinate ranges from 0 to 100), and the bottom section included variables with 0–5 metric (ordinate ranges from 0 to 100). The boxes represent the interquartile range (IQR), indicating the middle 50% of the data. The whiskers extend to 1.5 times the IQR from the quartiles, showing the range of the data within this distance. OES, Oesophageal.

pared to Cluster 1. The ASD between Cluster 1 and Cluster 2 in these domains are 0.35 and 0.41, indicating significant differences. Additionally, Cluster 2 has lower health literacy scores, with critical health literacy at 2.8 and Communicative Health Literacy at 3.3, with ASDs of 0.35 and 0.41 when compared to Cluster 1, highlighting a substantial disparity in health literacy levels.

Cluster 3 stands out with the highest functioning and lowest symptom burden, exhibiting the highest median scores in physical functioning (90.0), cognitive functioning (90.0), role functioning (85.0) and General self-efficacy (42.0). The ASDs between Cluster 1 and Cluster 3 for these variables are 0.33, 0.29, 0.27 and 0.35, respectively. Cluster 3 also shows higher health literacy scores compared to both Clusters 1 and 2, with Functional Health Literacy at 3.5 and an ASD of 0.30 when compared to Cluster 1.

Discussion

This study, in an exploratory manner, contributes to addressing the paucity of research on clusters in post-operative follow-up using PROMs [17, 18]. The main novelty of this study lies in the identification of distinct patient subgroups based on their recovery patterns at three months post-discharge following curative esophageal cancer surgery. Using t-SNE for dimensionality reduction and hierarchical clustering, we identified three meaningful clusters, each characterized by unique profiles in terms of functioning, symptom burden, and health literacy.

The identification of these clusters allows clinicians to tailor possible interventions by standardizing three main approaches that reflect the distinct needs of each cluster. For patients in Cluster 1, labeled as “higher functioning with moderate symptoms”, interventions could focus on maintaining high levels of functioning while addressing moderate symptom management through regular monitoring and supportive care. For those in Cluster 2, termed “moderate functioning with higher symptoms and lower health literacy”, a more intensive approach is necessary, including enhanced symptom management and targeted health literacy interventions to improve understanding and self-management of their condition. Cluster 3, described as “highest functioning with lowest symptoms and highest health literacy”, may benefit from a maintenance approach that includes periodic check-ins and support to sustain their high level of functioning and health literacy, preventing any decline. Based on PROMs, this stratified care model

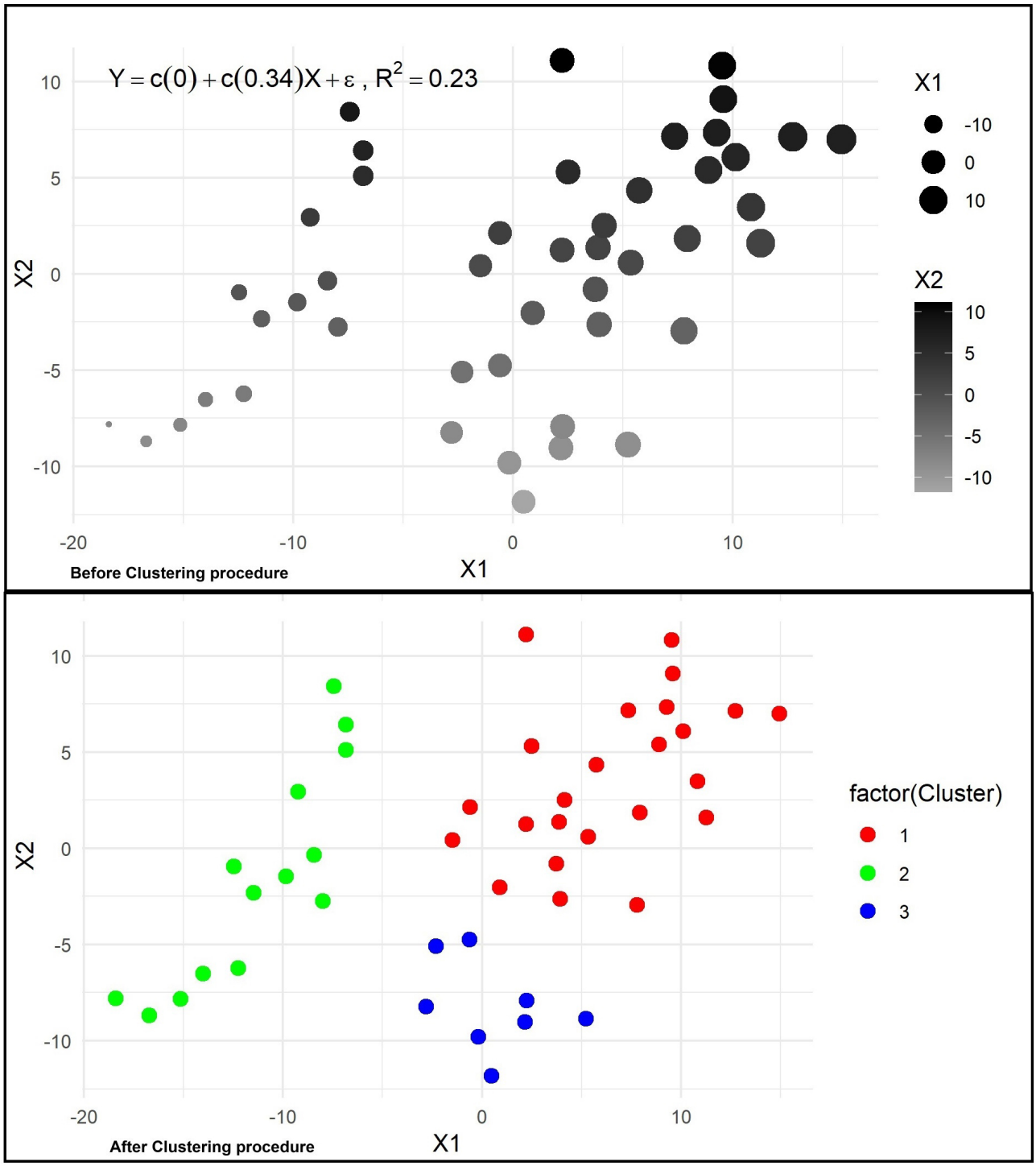


Fig. 2. t-distributed Stochastic Neighbor Embedding (t-SNE) scatterplot with and without clustering visualization.

holds the potential to improve the personalization of post-operative care, enhancing overall recovery and HRQoL for esophageal cancer patients [19, 20, 21, 22].

Our findings align with previous research that emphasizes the heterogeneity in recovery experiences among esophageal cancer patients post-surgery [19]. Previous studies have noted the variability in post-operative recovery and the importance of tailored follow-up care [19, 21]. However, the identification of specific clusters based on PROMs provides new insights into these variations and highlights the significance of personalized care approaches. This study adds to the existing literature by providing a structured method to identify and describe these patient clusters, offering a framework for future research and clinical practice in terms of described methods that could be used and practical results.

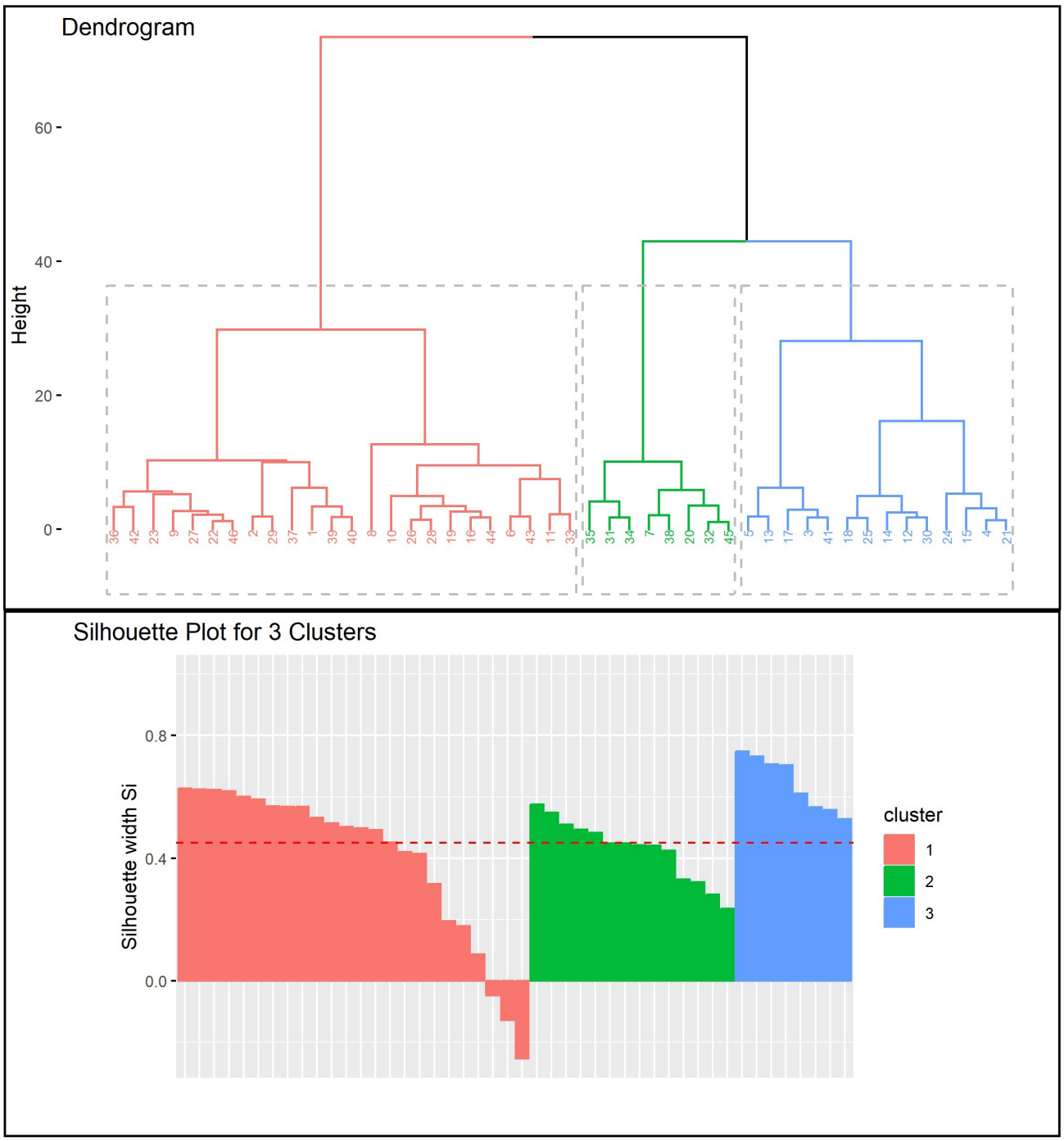


Fig. 3. Hierarchical clustering and silhouette analysis.

Future research should focus on larger, multicenter studies to validate the clusters identified in this study. Longitudinal studies are also needed to track changes in PROMs over time and understand oesophagal cancer patients' long-term recovery trajectories. Interventional studies should be conducted to test the effectiveness of tailored treatments and support programs for different patient clusters.

This study has several strengths that enhance its contribution to the field. Firstly, it utilizes a robust dataset derived from a longitudinal single-center study, ensuring comprehensive follow-up and consistent data collection. Using t-SNE for dimensionality reduction and hierarchical clustering allowed for identifying distinct patient subgroups, providing a nuanced understanding of recovery patterns at three months post-discharge. This methodological approach enables a more sophisticated analysis of PROMs, capturing both linear and non-linear relationships among the variables. Additionally, the study's findings have practical implications, allowing for tailoring interventions to specific patient needs and enhancing the personalization of

Table 3. Characteristics of PROMS accross clusters.

	Cluster 1 (n = 24)		Cluster 2 (n = 14)		Cluster 3 (n = 8)		ASD Cluster 1–2	ASD Cluster 1–3	ASD Cluster 2–3
	Higher functioning with moderate symptoms		Moderate functioning with higher symptoms and lower health literacy		Highest functioning with lowest symptoms and highest health literacy				
	median	IQR	median	IQR	median	IQR			
Physical functioning	85.0	75.0–95.0	80.0	70.0–90.0	90.0	80.0–95.0	0.45	0.33	0.15
Role functioning	80.0	60.0–100.0	75.0	55.0–90.0	85.0	70.0–100.0	0.38	0.27	0.14
Emotional functioning	70.0	60.0–85.0	65.0	50.0–80.0	75.0	60.0–90.0	0.35	0.30	0.18
Cognitive functioning	85.0	75.0–95.0	80.0	70.0–90.0	90.0	80.0–100.0	0.41	0.29	0.13
Social functioning	75.0	60.0–90.0	70.0	50.0–85.0	80.0	65.0–95.0	0.36	0.28	0.16
General health status/QoL	60.0	50.0–70.0	55.0	45.0–65.0	65.0	55.0–75.0	0.33	0.25	0.17
Fatigue	30.0	20.0–40.0	35.0	25.0–45.0	25.0	15.0–35.0	0.48	0.37	0.19
Nausea vomiting	10.0	5.0–15.0	15.0	10.0–20.0	5.0	0.0–10.0	0.50	0.40	0.22
Pain	20.0	10.0–30.0	25.0	15.0–35.0	15.0	10.0–25.0	0.44	0.35	0.18
Dyspnea	15.0	10.0–25.0	20.0	15.0–30.0	10.0	5.0–20.0	0.47	0.37	0.20
Insomnia	25.0	15.0–35.0	30.0	20.0–40.0	20.0	10.0–30.0	0.49	0.39	0.21
Appetite loss	10.0	5.0–15.0	15.0	10.0–20.0	5.0	0.0–10.0	0.52	0.41	0.23
Constipation	5.0	0.0–10.0	10.0	5.0–15.0	5.0	0.0–10.0	0.40	0.31	0.19
Diarrhea	10.0	5.0–15.0	15.0	10.0–20.0	5.0	0.0–10.0	0.45	0.35	0.21
Financial difficulties	15.0	10.0–20.0	20.0	15.0–25.0	10.0	5.0–15.0	0.46	0.36	0.23
Eating	20.0	10.0–30.0	25.0	15.0–35.0	15.0	10.0–25.0	0.50	0.40	0.24
Reflux	10.0	5.0–15.0	15.0	10.0–20.0	5.0	0.0–10.0	0.43	0.34	0.18
Pain (OES)	20.0	10.0–30.0	25.0	15.0–35.0	15.0	10.0–25.0	0.44	0.35	0.19
Dysphagia	15.0	10.0–25.0	20.0	15.0–30.0	10.0	5.0–20.0	0.46	0.36	0.21
Swallowing saliva	10.0	5.0–15.0	15.0	10.0–20.0	5.0	0.0–10.0	0.50	0.40	0.24
Choked swallowing	5.0	0.0–10.0	10.0	5.0–15.0	5.0	0.0–10.0	0.38	0.30	0.17
Dry mouth	10.0	5.0–15.0	15.0	10.0–20.0	5.0	0.0–10.0	0.49	0.39	0.22
Taste	5.0	0.0–10.0	10.0	5.0–15.0	5.0	0.0–10.0	0.36	0.28	0.16
Coughing	15.0	10.0–25.0	20.0	15.0–30.0	10.0	5.0–20.0	0.41	0.33	0.18
Talking	20.0	10.0–30.0	25.0	15.0–35.0	15.0	10.0–25.0	0.48	0.37	0.21
Critical health literacy	3.0	2.5–3.5	2.8	2.3–3.3	3.2	2.7–3.7	0.35	0.29	0.16
Communicative health literacy	3.5	3.0–4.0	3.3	2.8–3.8	3.7	3.2–4.2	0.41	0.33	0.19
Functional health literacy	3.2	2.7–3.7	3.0	2.5–3.5	3.5	3.0–4.0	0.38	0.30	0.17
General self-efficacy	40.0	35.0–45.0	38.0	33.0–43.0	42.0	37.0–47.0	0.45	0.35	0.20

Note: Pain (OES), Pain (Oesophageal); IQR, interquartile range; ASD, Absolute Standardized Difference.

post-operative care. By standardizing approaches based on cluster profiles, clinicians can improve symptom management, functioning, and health literacy, ultimately contributing to better patient outcomes.

Despite its strengths, the study has several limitations that should be acknowledged. The sample size is relatively small, which may limit the generalizability of the findings. The study's exploratory nature means that the identified clusters need to be validated in larger, more diverse populations. Additionally, using a single-center dataset may introduce center-specific biases, affecting the applicability of the results to other settings. Furthermore, the study does not account for potential confounding variables that could influence recovery patterns, such as comorbid conditions or variations in post-operative care. Lastly, the use of ASD for comparisons, while appropriate given the small sample size, indicates that the findings should be considered exploratory and hypothesis-generating rather than definitive. Moreover, while post-operative complications and survival outcomes across different subtypes of esophageal cancer are critical factors, comprehensive data on these aspects were not available in our current database. This limitation restricts our ability to analyze and elaborate on these outcomes. It highlights the need for future studies to include detailed data on post-operative complications and survival to provide a more comprehensive understanding of the differences between subtypes and their impact on patient outcomes. Future research with larger, multi-center cohorts and more rigorous statistical analyses is needed to confirm and extend these findings.

Conclusions

This study provides an exploratory analysis based on PROMs in curatively-treated esophageal cancer patients,

identifying distinct clusters based on their recovery patterns three months post-discharge. We successfully identified three meaningful clusters: patients with higher functioning with moderate symptoms, patients with moderate functioning with higher symptoms and lower health literacy, and patients with highest functioning with lowest symptoms and highest health literacy.

These clusters offer valuable insights into the diverse recovery trajectories experienced by patients. The findings emphasize the potential of using PROMs to tailor postoperative interventions, enhancing personalized care. Future studies should aim to refine these clusters and explore their implications in different clinical settings, ultimately contributing to developing targeted, effective interventions for esophageal cancer patients.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

RC: Conceptualization, Methodology, Investigation, Writing - Original Draft, Supervision, Project Administration. AM: Methodology, Validation, Formal Analysis, Data Curation, Writing - Original Draft. GC: Software, Validation, Formal Analysis, Data Curation, Visualization. LB: Conceptualization, Resources, Supervision. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethical Committee of Ospedale San Raffaele, Italy (protocol n. 136/int/2018). Written informed consent was obtained from all patients before being included in the study. All procedures performed in the study followed ethical standards, good clinical practice guidelines, and the 1964 Helsinki Declaration and its later amendments.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a Cancer Journal for Clinicians. 2021; 71: 209–249.

[2] Liu CQ, Ma YL, Qin Q, Wang PH, Luo Y, Xu PF, *et al*. Epidemiology of esophageal cancer in 2020 and projections to 2030 and 2040. Thoracic Cancer. 2023; 14: 3–11.

[3] Obermannová R, Alsina M, Cervantes A, Leong T, Lordick F, Nilsson M, *et al*. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2022; 33: 992–1004.

[4] Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, *et al*. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2019; 17: 855–883.

[5] Magon A, Caruso R, Sironi A, Mirabella S, Dellafiore F, Arrigoni C, *et al*. Trajectories of Health-Related Quality of Life, Health Literacy, and Self-Efficacy in Curatively-Treated Patients with Esophageal Cancer: A Longitudinal Single-Center Study in Italy. Journal of Patient Experience. 2021; 8: 23743735211060769.

[6] Ahmed M, Lau A, Hirpara DH, Kidane B. Choosing the right survey-patient reported outcomes in esophageal surgery. Journal of Thoracic Disease. 2020; 12: 6902–6912.

[7] Straatman J, Joosten PJM, Terwee CB, Cuesta MA, Jansma EP, van der Peet DL. Systematic review of patient-reported outcome measures in the surgical treatment of patients with esophageal cancer. Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus. 2016; 29: 760–772.

[8] Reijneveld EAE, Griekspoor M, Dronkers JJ, Kerst A, Ruurda JP, Veenhof C. Identification of subgroups of patients with oesophageal cancer based on exercise intensity during prehabilitation. Disability and Rehabilitation. 2024; 1–8.

[9] Jaeger A, Banks D. Cluster analysis: A modern statistical review. WIREs Computational Stats. 2023; 15: e1597.

[10] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of Clinical Epidemiology. 2008; 61: 344–349.

[11] Norman R, Mercieca-Bebber R, Rowen D, Brazier JE, Cella D, Pickard AS, *et al*. U.K. utility weights for the EORTC QLU-C10D. Health Economics. 2019; 28: 1385–1401.

[12] Blazeby JM, Conroy T, Hammerlid E, Fayers P, Sezer O, Koller M, *et al*. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. European Journal of Cancer (Oxford, England:

1990). 2003; 39: 1384–1394.

[13] Macefield RC, Jacobs M, Korfage IJ, Nicklin J, Whistance RN, Brookes ST, *et al*. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). Trials. 2014; 15: 49.

[14] Panadero E, Jonsson A, Botella J. Effects of self-assessment on self-regulated learning and self-efficacy: Four meta-analyses. Educational Research Review. 2017; 22: 74–98.

[15] Balamurali M. t-Distributed Stochastic Neighbor Embedding. In Daya Sagar BS, Cheng Q, McKinley J, Agterberg F (eds.) Encyclopedia of Mathematical Geosciences (pp. 1–9). Springer International Publishing: Cham. 2022.

[16] Zhang Z, Murtagh F, Van Poucke S, Lin S, Lan P. Hierarchical cluster analysis in clinical research with heterogeneous study population: highlighting its visualization with R. Annals of Translational Medicine. 2017; 5: 75.

[17] Fransen LFC, Berkelmans GHK, Asti E, van Berge Henegouwen MI, Berlth F, Bonavina L, *et al*. The Effect of Postoperative Complications After Minimally Invasive Esophagectomy on Long-term Survival: An International Multicenter Cohort Study. Annals of Surgery. 2021; 274: e1129–e1137.

[18] Li KK, Wang YJ, Liu XH, Tan QY, Jiang YG, Guo W. The effect of postoperative complications on survival of patients after minimally invasive esophagectomy for esophageal cancer. Surgical Endoscopy. 2017; 31: 3475–3482.

[19] Pape M, Vissers PAJ, Slingerland M, Haj Mohammad N, van Rossum PSN, Verhoeven RHA, *et al*. Long-term health-related quality of life in patients with advanced esophagogastric cancer receiving first-line systemic therapy. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer. 2023; 31: 520.

[20] Sun K, Goodfellow H, Konstantara E, Hill A, Lennard D, Lloyd-Dehler E, *et al*. The multidisciplinary, theory-based co-design of a new digital health intervention supporting the care of oesophageal cancer patients. Digital Health. 2021; 7: 20552076211038410.

[21] Alghamedi A, Buduhan G, Tan L, Srinathan SK, Sulman J, Darling G, *et al*. Quality of life assessment in esophagectomy patients. Annals of Translational Medicine. 2018; 6: 84.

[22] Ramsey I, Eckert M, Hutchinson AD, Marker J, Corsini N. Core outcome sets in cancer and their approaches to identifying and selecting patient-reported outcome measures: a systematic review. Journal of Patient-reported Outcomes. 2020; 4: 77.