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OUTCOMES OF SURGERY FOR OESOPHAGEAL CANCER WITH FOCUS ON FATIGUE

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Cover illustration: A side project in this doctoral study: a crochet blanket.
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Outcomes of surgery for oesophageal cancer with focus on fatigue

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Zhao Cheng

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“复行数十步，豁然开朗。”

“After a dozen steps, it opened into a flood of light.”

------陶渊明

ABSTRACT

Oesophageal cancer is the 6th leading cause of cancer mortality globally. Extensive surgery (oesophagectomy) with neoadjuvant chemo(radio)therapy is the backbone of curative treatment for oesophageal cancer. The thesis aimed to provide better knowledge of survivorship after oesophagectomy, focusing on cancer-related fatigue.

Study I was a population-based cohort study with 2576 patients who underwent oesophageal cancer surgery between 1987 and 2015 in Sweden. Modified Poisson regression models were used to estimate risk ratios (RR) with 95% confidence intervals (CI) comparing patients with or without comorbidity for the risk of reoperation or death within 90 days of oesophagectomy, adjusting for confounders. Patients with Charlson Comorbidity Index ≥2 were associated with 78% increased risk of reoperation or death compared with those with Charlson Comorbidity Index 0 (RR 1.78, 95% CI 1.44-2.20).

Study II was a nationwide cohort study with 331 patients operated on for oesophageal cancer between 2013 and 2018 in Sweden. Linear mixed-effect models were used to produce adjusted cancer-related fatigue scores and mean score differences (MD) with 95% CIs between patients with and without predefined postoperative complications within 30 days after oesophagectomy. Patients with any postoperative complications had increased cancer-related fatigue scores with clinical relevance (MD 5.8, 95% CI 2.6-9.0) between 1-1.5 years, and remained at the same level until 2 years after the surgery. By stratification, medical and pulmonary complications were associated with increased cancer-related fatigue.

Study III was a nationwide cohort study with 356 patients surgically treated for oesophageal cancer between 2013 and 2019 in Sweden. Longitudinal cancer-related fatigue trajectories were identified by growth mixture models. Linear and logistic regression models were fitted and showed that no associations were found between body mass index adjusted weight loss grading system and cancer-related fatigue between 1-3 years after oesophagectomy, with adjustment for confounders.

Study IV was a nationwide, longitudinal cohort study including 409 patients who underwent oesophagectomy for oesophageal cancer between 2013 and 2020 in Sweden. Growth mixture models identified 2 distinct overall cancer-related fatigue trajectories between 1-5 years after the surgery. Weighted logistic regression models were fitted to explore factors underlying such trajectories. Comorbidity, pathological tumour stage, postoperative complications, and patient-reported outcomes including anxiety, depression, and pain were associated with high levels of fatigue trajectories.

To conclude, preoperative comorbidities were associated with increased risk of reoperation or death after oesophagectomy, and patients after oesophageal cancer surgery might have distinctly different cancer-related fatigue trajectories. More comorbidities, advanced tumour stage, postoperative complications, anxiety, depression, and pain might be associated with the trajectory with higher levels of cancer-related fatigue.

LIST OF SCIENTIFIC PAPERS

I. Cheng Z, Johar A, Gottlieb-Vedi E, Nilsson M, Lagergren J, Lagergren P.

Impact of co-morbidity on reoperation or death within 90 days of surgery for oesophageal cancer.

BJS open. 2021; 5(1).

II. Cheng Z, Johar A, Nilsson M, Lagergren P.

Cancer-related fatigue after esophageal cancer surgery: impact of postoperative complications.

Ann Surg Oncol. 2022; 29:2842-2851.

III. Cheng Z, Anandavadivelan P, Nilsson M, Johar A, Lagergren P.

Body mass index-adjusted weight loss grading system and cancer-related fatigue in survivors 1 year after esophageal cancer surgery.

Ann Surg Oncol. 2022; 29:4502–4510.

IV. Cheng Z, Johar A, Nilsson M, Schandl A, Lagergren P.

Cancer-related fatigue trajectories up to 5 years in survivors after esophageal cancer surgery.

Manuscript submitted.

CONTENTS

LIST OF ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CROSS	Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study
EORTC QLQ-C30	The European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire Core 30
EORCT QLQ-FA12	The European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire, Fatigue 12
EORTC QLQ-OG25	The European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire, Oesophago-Gastric symptoms module
EBUS	Endobronchial ultrasound
ERAS	Enhanced Recovery After Surgery program
EUS	Endoscopic ultrasound
FDG	[^{18}F]2-fluoro-2-deoxy-D-glucose
FLOT	5-fluorouracil-leucovorin-oxaliplatin-docetaxel
HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamic-pituitary-adrenal
HRQL	Health-related quality of life
MD	Mean score difference
OR	Odds ratio
OSCAR	Oesophageal Surgery on Cancer patients - Adaptation and Recovery study
PET	Positron emission tomography
PRO	Patient-reported outcomes
RR	Risk ratio
SF-36	Short Form 36
WLGS	Weight loss grading system

1 INTRODUCTION

Oesophageal cancer is a leading cause of cancer incidence and mortality worldwide [1]. The mainstay of curatively intended treatment is the surgical resection of oesophagus, oesophagectomy, usually combined with neoadjuvant chemo(radio)therapy. The prognosis after the oesophagectomy is poor: less than 50% of the patients reach the 5-year survival [2], and the patients often have decreased health-related quality of life (HRQL) during the survivorship.

This thesis aimed to provide better knowledge about survivorship after oesophageal cancer surgery and to answer research questions that may facilitate early identification and targeted intervention of high-risk patients after oesophagectomy, focusing on cancer-related fatigue, which is one of the most common HRQL-related symptoms among cancer survivors. The thesis comprises four studies. Study I explored the association between preoperative comorbidity and postoperative reoperation or mortality. Study II and III compared the postoperative cancer-related fatigue level by postoperative complications and weight loss levels, respectively. Study IV explored cancer-related fatigue trajectory after oesophageal cancer surgery and the underlying factors of the identified trajectories.

2 LITERATURE REVIEW

2.1 OESOPHAGEAL CANCER

2.1.1 Epidemiology

Oesophageal cancer is a challenging disease featured by extensive treatment and poor prognosis. It ranked the 7th of cancer incidence and the 6th of cancer mortality globally, responsible for 604,000 new cases and 544,000 deaths in 2020 [1]. The overall 5-year survival of oesophageal cancer has been improving steadily in the past few decades, varying between 10-30% in different countries. The highest survival rate (36%) was reported in Japan, whereas in America, China, Australia, and some European countries, the 5-year overall survival is around 20% [3-5].

There are two major histological subtypes of oesophageal cancer: squamous cell carcinoma and adenocarcinoma, which are etiologically and epidemiologically distinct. Oesophageal squamous cell carcinoma is the predominant histological type, accounting for approximately 85% of all oesophageal cancer cases worldwide [6]. Notable geographical distribution characteristics were well established in oesophageal squamous cell carcinoma, and high-incidence areas include eastern to central Asia, eastern to southern Africa, and South America. Though adenocarcinoma represented about only 14% of all oesophageal cancer worldwide, it is the dominant histology type in North America, Oceania, and Europe [7].

2.1.2 Risk factors

In general, oesophageal cancer incidence is predominant among the elderly and male population [8-10]. Family history has been reported to increase the risk of oesophageal cancer, which comprises both familial genes and lifestyle-related factors [6].

Oesophageal squamous cell carcinoma forms when the oesophagus epithelium is damaged by physical or chemical stimuli, and furtherly develops DNA damage, forming hyperplasia, and intraepithelial neoplasia, until infiltrating carcinoma [11]. Oesophageal squamous cell carcinoma is more prevalent in less developed areas, and factors overrepresented in low socioeconomic status, such as heavy alcohol consumption, and tobacco smoking and chewing are the main risk factors for oesophageal squamous cell carcinoma [9]. Intake of vegetables and fruits seems to have a modest benefit to prevent the incidence of oesophageal squamous cell carcinoma, while pickles, red meat, and hot food or beverage are well-recognised risk factors [12], which is also consistent with the living and dietary habits in the areas with high incidence.

Oesophageal adenocarcinoma commonly origins in the distal oesophagus where the metaplastic columnar epithelium, i.e. Barrett's oesophagus, forms in response to gastroesophageal reflux disease. The strongest risk factors for oesophageal adenocarcinoma are thus gastroesophageal reflux and Barrett's oesophagus [6, 12]. Obesity is a strong risk factor for both Barrett's oesophagus and oesophageal adenocarcinoma [10]. The Helicobacter pylori

infection seems associated with decreased risk of oesophageal adenocarcinoma [13]. Tobacco smoking and low intake of fruit and vegetables increase the risk of oesophageal adenocarcinoma moderately, but no association has been found between alcohol consumption and adenocarcinoma of the oesophagus [10]. Gastroesophageal reflux and obesity are more prevalent in western countries, which partly account for the increasing incidence of oesophageal adenocarcinoma in recent decades in such areas.

2.1.3 Clinical symptoms, diagnosis, treatment and care

The clinical symptoms, diagnosis, and staging of oesophageal adenocarcinoma and squamous cell carcinoma are similar.

Tumour obstruction- and tube stricture-induced dysphagia (swallowing difficulty), odynophagia (swallowing pain), and involuntary weight loss are common symptoms at patients' first hospital visit. Nevertheless, due to the elastic structure of the oesophagus, these symptoms often become apparent at an advanced tumour stage, which leads to unfavourable prognoses in most oesophageal cancer patients [12].

Endoscopy is the gold standard for tumour detection, thereafter biopsy provides confirmative histopathological characteristics for oesophageal cancer. Staging is performed using [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)-computed positron emission tomography (PET), sometimes supplemented with endoscopic ultrasound (EUS) and if airway involvement is suspected also often bronchoscopy and endobronchial ultrasound (EBUS) [14].

Treatment of oesophageal adenocarcinoma and squamous cell carcinoma are similar but differ in some regards. The treatment plan is dependent on the clinical tumour stage and the patient’s general performance status [6]. Oesophagectomy, the oesophagus removal surgery, remains the curative therapy for oesophageal cancer, usually in combination with neoadjuvant oncological therapy [15]. Endoscopic resection may be the first consideration for patients with very early-stage (Tis and T1a) oesophageal lesions or cancer. For more advanced early tumour stage (T1b), surgical resection alone is often recommended with a decreased risk of cancer recurrence compared with endoscopic management, unless the patient is unfit for the surgery [16]. As to locally advanced tumours, chemotherapy or chemoradiotherapy combined with surgical resection is usually preferable [15]. The standard adjunct therapy for adenocarcinoma is either perioperative chemotherapy using the FLOT (5-fluorouracil-leucovorin-oxaliplatin-docetaxel) [17] regimen or neoadjuvant chemoradiotherapy using the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) [18] regimen. For squamous cell carcinoma, CROSS-type neoadjuvant chemoradiotherapy is the standard of care in Western countries, while neoadjuvant chemotherapy alone is used in large parts of Asia. In addition, for squamous cell carcinoma, which is more sensitive to radiotherapy, there is also an option of curing with chemoradiotherapy alone, administered in a slightly larger dose than in the neoadjuvant setting, and followed by locoregional surveillance with surgery when needed to secure locoregional control [12].

After diagnosis, about 30% of the patients are deemed as operable and available for curatively intended treatment, of which only 15-20% are eligible for curative resection after neoadjuvant therapy. The risk of recurrence is high despite curative resection and the prognosis is yet poor [12, 15]. Palliative treatment is usually the ultimate choice for the majority of patients.

In Sweden, a national care program regarding oesophageal and gastric cancer is drawn up by a national working group and updated regularly [19]. The care program defines the standardization in the investigation, treatment and follow-up of oesophageal cancer patients, and serves as a support for healthcare professionals at various levels. Briefly, each patient is assigned a contact nurse for coordinating the entire healthcare pathway and establishing an individual healthcare plan. If needed, support for smoking and alcohol cessation is provided. A counsellor will support to prevent or treat psychological distress and also provide the patients and family caregivers with information on social rights and guidance. A cancer rehabilitation plan to reduce physical, psychological, and social consequences of oesophageal cancer and the treatment is included and assessed regularly in the individual healthcare plan. After oesophagectomy, patients stay in the hospital for on average 2 weeks. Then, a discharge interview between the patients and clinicians and nurses is conducted to identify the support needed and the follow-up plan. After discharge from the hospital, the follow-up of the patients is more frequent in the first year and less frequent later. The follow-up is need-based and the patients may visit the doctor as long as there is a need. The patients may be referred to a physiotherapist, a dietician, or an occupational therapist based on the assessment during each follow-up. The Enhanced Recovery After Surgery (ERAS) program is a guideline using multimodal approaches to reduce postoperative complications and rapid recovery [20]. In Sweden, the concept of "enhanced recovery" has now been well established, but not all hospitals follow the standard ERAS for oesophageal cancer treatment.

2.2 COMPLICATIONS AFTER OESOPHAGEAL CANCER SURGERY

Oesophagectomy is recognised as a complex and extensive procedure followed by a high risk of postoperative complications. The rate of complications after esophagectomy varies between 17-74% in different scenarios from single centre databases to national registries [21, 22]. The incidence of complications after oesophagectomy mirrors factors regarding preoperative patient selection, perioperative technique, and postoperative care. Postoperative complications are known prognostic factors negatively impacting recovery, HRQL, and overall survival among oesophageal cancer patients [23-26].

2.2.1 Pulmonary complications

Pulmonary complications are the most frequent complications occurring in about 14-40% of patients who undergo oesophagectomy [21, 26-28]. Pneumonia is the most prevalent, followed by respiratory failure and pulmonary embolism [29]. Pulmonary complications are associated with

an increased risk of prolonged hospital stay, mortality, and diminished long-term survival [26, 30]. Multiple factors account for postoperative pulmonary complications, such as age, tobacco smoking, preoperative chronic pulmonary comorbidity, postoperative weak ventilation, and poor immune defence [31, 32]. The surgical approach is also found associated with the incidence of pulmonary complications after oesophagectomy. Several randomised studies have shown that minimally invasive surgery is associated with a decreased rate of pulmonary complications due to reduced surgical trauma [28, 33].

2.2.2 Atrial fibrillation

Atrial fibrillation is the second most common complication after oesophageal cancer surgery. About 10-40% of patients develop atrial fibrillation after oesophagectomy [21, 24, 34, 35]. Previous studies have found that atrial fibrillation is associated with other medical complications, such as embolism, pneumonia, and respiratory failure, but not with surgical complications, such as anastomotic leak and conduit necrosis, nor with mortality [34, 35]. Thus, very few studies focus on atrial fibrillation alone as a post-oesophagectomy complication. In most cases, atrial fibrillation was resolved and had no impact on long-term prognosis in oesophageal cancer patients [29, 34].

2.2.3 Anastomotic insufficiency

Anastomotic insufficiency, or more generally, anastomotic leakage is the most concerned surgical complication after oesophagectomy [27], occurring in about 9-15% of the patients [21, 26, 36, 37]. The rate of anastomotic insufficiency is a common measurement in studies concerning the prognosis of oesophagectomy, yet its impact needs further clarification, partly because of the diverse definitions of anastomotic insufficiency [22]. It seems to have a negative effect on short-term outcomes, including prolonged hospital stay and higher hospital costs, but the evidence of the impact on long-term prognosis is still inconsistent [26, 38-41]. Older age, overweight, comorbidity, and smoking are identified risk factors for anastomosis leak, but the influence of surgical techniques remains controversial [35, 38].

2.2.4 Death

Postoperative death is the most severe complication after oesophagectomy. Commonly reported definitions are in-hospital and 30-day mortality [27]. Postoperative short-term death within 30 days rarely occurs nowadays, especially in high-volume hospitals [34]. Due to the improvement of postoperative care, 90-day mortality is considered a necessary cut-off that could provide additional valuable information [22, 27].

2.2.5 Clavien-Dindo classification of complications

Clavien-Dindo classification is a widely accepted complication ranking system after surgery [42]. It is valid and applicable in many surgical fields [43]. Clavien-Dindo classification is a grading system based on the type of therapy needed for the complications. The severity of complications is stratified by the invasiveness and risk of treatment, which could minimize the subjective interpretations from doctors or researchers. A higher grade in Clavien-Dindo classification implies worse complications. Previous research has established that a higher Clavien-Dindo grade is associated with decreased overall survival after oesophageal cancer surgery [44, 45].

2.3 PATIENT-REPORTED OUTCOMES

Patient-reported outcomes (PRO) are different health-related statuses reported directly from the patients, such as symptoms, functions, and multi-dimensional HRQL [46]. Measurements of PROs are usually validated questionnaires completed by patients themselves [47]. Compared to the well-observed clinical responses, complicated experience accompanying the disease and treatment, e.g. fatigue, pain, and depression, is to some extent overlooked and underreported. Routinely recorded PROs can serve as a systematic tool to capture these subjective feelings and allow patients' voices to be incorporated into treatment evaluation and patient management [48].

During oesophagectomy, surgeons usually remove the tumour with most of the oesophagus and upper part of the stomach, constructing a tube of the remaining stomach to serve as a substitute for the removed oesophagus [49]. Such advanced treatment influences the general well-being in specific aspects interfering with daily life, including eating, drinking, sleeping, and socialising [50]. Comprehensive and timely information regarding postoperative survivorship is thus warranted and appreciated not only by the clinicians but also by the patients and family caregivers.

2.3.1 Health-related quality of life (HRQL)

HRQL refers to the subjective perception and experience during the disease and treatment, including disease- and treatment-related symptoms, physical function, emotional function, and social function of the patients [51, 52]. HRQL has great overlap with the dimensions in PROs, and the contents of HRQL vary in studies depending on the instruments used for measurement, which are usually standardized or self-designed questionnaires, or interviews [50]. Common questionnaires encompass three types: 1) questionnaires measuring general health conditions regardless of illness, for instance, the Short Form 36 (SF-36) which can be used on healthy people as well as people with different illnesses; 2) disease-specific questionnaires designed for disease-specific issues, for example, the well-validated European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) cancer

questionnaire [51] with site-specific modules, such as the EORTC QLQ oesophago-gastric symptoms module (EORTC QLQ-OG25), which is designed to assess problems among oesophageal, oesophago-gastric junction and gastric cancer patients [53]; and 3) aspect-specific questionnaires focusing on certain features, such as the Hospital Anxiety and Depression Scale (HADS) [54], which is a common instrument measuring anxiety and depression status.

2.3.2 HRQL among patients who underwent oesophagectomy for oesophageal cancer

For oesophageal cancer patients, the HRQL is initially undermined by symptoms related to tumour obstruction and oesophagus stricture, and later furtherly impaired by the treatment's adverse effects. The most common problems after oesophageal cancer surgery are eating difficulty, fatigue, sleep insufficiency, and anxiety [55, 56].

Patients with oesophageal squamous cell carcinoma, tumour located in the upper-middle oesophagus, advanced tumour stage, and comorbidity have an increased risk of poor HRQL [57, 58]. Cancer treatment is also associated with HRQL. Neoadjuvant therapy has been shown to reduce HRQL, especially in terms of physical and social function, fatigue, nausea and vomiting, but the symptoms are usually relieved after the therapy [59]. Dysphagia is the only dimension that alleviates during neoadjuvant therapy because of the reduced size of tumours [60]. Early postoperative complications are identified risk factors for both short and long-term HRQL in several dimensions (e.g. dysphagia, pain, and fatigue) up to fifteen years postoperatively [24, 61-63]. However, the effects of specific complications on HRQL subscales need further clarification and the mechanism of such associations remains to be elucidated.

2.3.3 Cancer-related fatigue

Cancer-related fatigue is a frequently reported, distressing sense of tiredness related to cancer and cancer treatment [64, 65]. Most cancer patients and survivors complain about incomplete role involvement and less engagement in daily activities due to the lack of energy, and the quality of life is thus undermined in most dimensions throughout cancer treatment and even the whole survivorship [65-67]. Compared to “normal” fatigue, cancer-related fatigue is more debilitating and constant, and cannot be recovered by adequate rest or sleep [68]. Not like other better-recognized symptoms such as pain and nausea, which can be manageable with medications, cancer-related fatigue is easily overlooked and deemed as a “common situation” for cancer patients.

2.3.3.1 Mechanism, measurement, and treatment of cancer-related fatigue

The mechanism of cancer-related fatigue remains poorly understood. Proposed aetiological pathways include pro-inflammatory cytokine, hypothalamic-pituitary-adrenal (HPA) axis disruption, serotonin dysregulation, circadian rhythm modulation, etc. Among these, the

association between inflammation and cancer-related fatigue is the focus of many current studies [69, 70]. Partly due to the lack of confirmative pathophysiology evidence, the diagnosis and treatment of cancer-related fatigue are still challenging and no unanimous conclusion can be drawn.

Several instruments have been developed to measure cancer-related fatigue [71]. The well-established EORTC QLQ-C30 questionnaire comprises a three-item subscale measuring unidimensional cancer-related fatigue symptoms [51]. In conjunction with the QLQ-C30, another validated aspect-specific questionnaire named EORTC QLQ Fatigue 12 (EORTC QLQ-FA12) was designed based on a multidimensional concept, measuring 3 subscales including physical, emotional, and cognitive domains, and 2 single items, i.e. fatigue interference with daily life and social sequelae of fatigue [72]. However, the comparison and interpretation across studies focusing on fatigue are hampered by the various dimensions measured by different questionnaires.

Currently, no gold-standard treatment is available for cancer-related fatigue. Results from randomised controlled trials and systematic reviews showed that nonpharmacologic interventions, e.g. physical exercise and psychosocial therapy, are preferable recommendations to manage cancer-related fatigue [73, 74]. Pharmacologic prescriptions are mainly targeting protogenetic diseases or other treatable contributors but not directly for fatigue [67].

2.3.3.2 Factors associated with cancer-related fatigue

Cancer-related fatigue is prevalent among cancer survivors, including oesophageal cancer [55, 75-77]. In most studies, about 30-60% of cancer patients reported moderate to severe fatigue during the treatments. The symptom is usually relieved during the first year after therapy, but among about one-third of the patients, it can continue for years after successful treatment [78]. Despite the high prevalence, considerable variability might exist regarding the experience of cancer-related fatigue during survivorship [75, 79]. But whether such distinct experience trajectories exist among oesophageal cancer patients is unknown, and the identification of patients who are at particular risk for severe and persistent fatigue is important for advancing the potential intervention [75, 78, 79].

During the previous decade, studies have begun to explore factors associated with cancer-related fatigue. The genetic component is one of the growing areas of interest, especially the genetic factors influencing inflammatory activities [78]. Early fatigue level (e.g. at diagnosis, immediately after treatment) is a surrogate of many implicit host characteristics and is recognised as one of the strong and consistent predictors for post-treatment fatigue [75, 78]. Some of the psychological symptoms are usually correlated with cancer-related fatigue, including depression, anxiety, and pain [69, 78, 80]. However, currently, the causality in-between such factors is difficult to disentangle. Sleep disturbance influences daytime activity and thus aggravate cancer-related fatigue symptom, but patients cannot get fully recovered by simply adequate sleep, indicating that sleep quality is only one of the multiple factors [78, 80]. Physical inactivity is associated with cancer-related fatigue, and one of the promising interventions for cancer-

related fatigue is appropriate physical exercise [77]. Disease and treatment factors might also account for a considerable share of variability in fatigue, especially those associated with elevated inflammation levels, such as comorbidity and complications [24, 58]. Besides, the reported fatigue level is also affected by the response shift (recalibration, reprioritization, reconceptualization, and changes in appraisal), which is difficult to account for in reality [81].

Although studies have now identified potential risk factors for cancer-related fatigue, few studies have been conducted among oesophageal cancer patients, and evidence from longitudinal studies is still lacking.

3 RESEARCH AIMS

The overall aim of the thesis was to provide knowledge that can improve outcomes and survivorship in patients who underwent curatively intended surgical treatment for oesophageal cancer.

The specific aims of the four included studies were:

1) To assess the association between preoperative comorbidity and the risk of reoperation or mortality within 90 days of surgery for oesophageal cancer.

2) To estimate the association between postoperative complications and cancer-related fatigue after oesophageal cancer surgery.

3) To explore the influence of weight loss on cancer-related fatigue among oesophageal cancer survivors.

4) To identify the potentially distinct trajectories of cancer-related fatigue and factors underlying such trajectories among oesophageal cancer survivors.

4 MATERIALS AND METHODS

4.1 OVERVIEW

Table 1. Overview of the study methods

	Study I	Study II	Study III	Study IV
Short title	Comorbidity and reoperation or death	Postoperative complications and cancer-related fatigue	Weight loss and cancer-related fatigue	Cancer-related fatigue trajectory and underlying factors
Design	Cohort study	Longitudinal cohort study		
Population	Oesophageal cancer patients who had oesophagectomy in Sweden			
Study period	1987-2015	2013-May, 2019	2013-Dec, 2019	2013-Jun, 2020
Follow-up	90 days	2 years	3 years	5 years
Data source	National Cancer Register, Patient Register, Cause of Death Register, LISA[1], medical records	Interviews and questionnaires, National Register of the Total Population, Patient Register, LISA[1], medical records		
Study size	2576	331	356	409
Main exposure	Comorbidity	Postoperative complications	WLGS[2]	-
Main outcome	Reoperation or all-cause death	Cancer-related fatigue		
Covariates	Age, sex, education, tumour histology, neoadjuvant therapy, tumour stage, hospital volume, calendar period	Age, sex, education, proxy baseline fatigue, comorbidity, tumour histology, neoadjuvant therapy, tumour stage, weight change	Age, sex, comorbidity, tumour histology, neoadjuvant therapy, tumour stage, postoperative complications	Age, sex, education, proxy baseline fatigue, comorbidity, tumour histology, neoadjuvant therapy, tumour stage, postoperative complications, anxiety, depression, pain, insomnia, WLGS[2], physical activity
Main analysis	Modified Poisson regression models	Linear mixed-effects models	Growth mixture models, linear and logistic regression models	Growth mixture models, weighted logistic regression models

[1] LISA: the longitudinal integrated database for health insurance and labour market studies.
[2] WLGS: body mass index-adjusted weight loss grading system.

4.2 DATA SOURCE

All studies in the thesis were based on data extracted from Swedish national registers and review of medical records, while Study II-IV were also based on information collected from interviews and mailed questionnaires. Linkages of data from different sources were enabled by the unique Swedish personal identity number [82].

4.2.1 The Swedish national registers

4.2.1.1 National Cancer Register

The Swedish National Cancer Register was established in 1958 and registers cancer diagnoses covering the whole Swedish population [83]. The update frequency is once per year. The coverage of oesophagus and cardia cancer in the register is about 98% [84]. Oesophageal cancer patients in Study I were identified from the National Cancer Register. Oesophageal cancer diagnosis in Study II-IV was validated in this register.

4.2.1.2 National Patient Register

The Swedish National Patient Register contains information on inpatient care since 1964 and information on specialized outpatient care since 2001 in Sweden [85]. The update frequency is once per month. Information on oesophagectomy and comorbidity was retrieved from the National Patient Register. The positive predictive value of oesophagectomy records is more than 99% in this register [86].

4.2.1.3 National Cause of Death Register

The Swedish National Cause of Death Register was founded in 1952 and collects data on deaths of all Swedish residents (both in and outside Sweden). Additionally, all deaths that occurred in Sweden for non-Swedish residents were also recorded since 2012 [87]. The update frequency is once per year for the cause of death, and continuously for the death date. Information on mortality in Study I was retrieved from this registry with 100% completeness [87].

4.2.1.4 National Register of the Total Population

The Swedish National Register of the Total Population was started in 1968 and contains data on life events (birth, death, marital status, family relationships, migration, etc) of the whole population in Sweden [88]. The update frequency is once per day. Patients' vital status was checked from this register in Study II-IV before each follow-up.

4.2.1.5 The longitudinal integrated database for health insurance and labour market studies (LISA)

LISA contains data on the socioeconomic characteristics of the adult Swedish population since 1990. The update frequency is once per year [89]. Data on the highest formal education level of

the study participants were extracted from this register, which has more than 98% coverage and an accuracy of 85%.

4.2.2 Medical records

Medical records of all study participants were retrieved from the corresponding hospitals, including histopathology reports, examination results, operation charts, hospital discharge notes, etc. All medical records were reviewed by two researchers according to a predefined protocol for good consistency and uniformity. Data on calendar period of oesophagectomy, hospital volume, comorbidity, postoperative complications, treatment, and tumour characteristics were provided by review of the medical records.

4.2.3 Interview and questionnaire

Study II-IV were based on an ongoing Swedish nationwide and longitudinal cohort named "Oesophageal Surgery on Cancer patients - Adaptation and Recovery (OSCAR) study" [55], enrolling all oesophageal cancer patients who underwent oesophagectomy between January 1, 2013, and June 30, 2020, in Sweden and following them up until 12 years after the surgery. Patients were identified by a network of pathological departments in all 8 hospitals conducting oesophagectomies in Sweden. After the study invitation, a pre-interview questionnaire pack was sent to the patient and a home visit interview was arranged by a research nurse 1 year after the oesophageal cancer surgery. During the interview, the research nurse obtained consent, facilitated the patients in filling in the PRO questionnaires, and collected physical measurement data. Follow-up of PRO questionnaires is conducted at 1.5, 2, 2.5, 3, 4, 5, 8 and 12 years postoperatively. Between 1.5-4 and 8-12 years, PRO questionnaires are sent by mail. At 5 years, another interview is conducted by the research nurse.

The proxy baseline fatigue in Study II and IV was obtained from a sample of the Swedish population [90]. In total, 6969 random individuals were selected from the National Register of the Total Population, which was frequency-matched to reflect the age and sex distribution of oesophageal cancer patients. EORTC QLQ-C30 questionnaire was sent, and 4910 (70.5%) people participated. Every patient in OSCAR was matched to >50 individuals of this reference sample by age, sex, education level, and comorbidity (diabetes, cardiac, respiratory, renal, or other specified conditions). The proxy baseline fatigue score for the study participants was calculated based on the QLQ-C30 questionnaires from the matched individuals.

4.3 STUDY DESIGN

4.3.1 Study I

4.3.1.1 Study cohort

This nationwide, population-based cohort study included 98% of all patients who underwent oesophagectomy for oesophageal cancer between 1987 and 2015 in Sweden.

4.3.1.2 Exposure

The study exposure was comorbidity recorded before oesophageal cancer surgery and based on the diseases included in the recently validated version of Charlson comorbidity index [91], excluding oesophageal cancer. Charlson comorbidity index is a widely used comorbidity scoring system calculating the number of coexisting and chronic disease categories. In total, 14 disease categories were included: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, liver disease, diabetes, hemiplegia/paraplegia, renal disease, malignancy, metastatic tumours, and acquired immune deficiency syndromes (AIDS). In study I, comorbidity was analysed as:

1) Charlson comorbidity index (0, 1 or ≥2);
2) Charlson comorbidity index as a discrete variable;
3) Pulmonary disease (no or yes), defined by any records of chronic bronchitis, emphysema, chronic obstructive pulmonary disorder, asthma, bronchiectasis, pneumoconiosis and chronic lung manifestations caused by chemicals, gases, smoke or radiation;
4) Cardiac disease (no or yes), defined by any records of myocardial infarction and congestive heart failure;
5) Diabetes (no or yes);
6) Cerebral disease (no or yes), defined by any records of cerebrovascular disease, dementia, hemiplegia or paraplegia;
7) Other malignancy (no or yes), defined by any records of malignant lymphoma, leukaemia and solid malignant tumours, excluding oesophageal cancer and non-melanoma skin cancer.

4.3.1.3 Outcome

The study outcome was a composite of reoperation or all-cause death within 90 days of oesophagectomy (no or yes).

4.3.1.4 Statistical analysis

Modified Poisson regression was used to estimate risk ratios (RRs) with 95% confidence intervals (CI) for associations between exposures and outcome, adjusting for 8 covariates: age at surgery (continuous variable), sex (male or female), education (<9, 9-12, or >12 years of formal education), tumour histology (adenocarcinoma or squamous cell carcinoma),

neoadjuvant therapy (no or yes), pathological tumour stage (0-I, II, III-IV), annual hospital volume (<10 or ≥10 operations/year), and calendar period of oesophagectomy (continuous variable). Other comorbidities (no or yes) were also adjusted in the model when analysing the specific comorbidity exposures, defined by whether additional comorbidities existed except for the analysed ones. In separate models, the interactions between pulmonary and cardiac disease were also tested.

Stratified analyses were conducted by: 1) median age at surgery (≤60 and >60 years); 2) annual hospital volume (<10 and ≥10 operations/year); 3) tumour histology (adenocarcinoma and squamous cell carcinoma); 4) calendar period of surgery (1987-1999 and 2000-2015).

4.3.2 Study II

4.3.2.1 Study cohort

This nationwide, longitudinal cohort study included oesophageal cancer survivors who underwent oesophagectomy between January 2013 and May 2019 in Sweden. Patients who survived 1 year after the surgery were enrolled.

4.3.2.2 Exposure

The study exposure was postoperative complications within 30 days of oesophagectomy, including postoperative bleeding, anastomotic insufficiency, substitute necrosis, intra-abdominal abscess, intrathoracic abscess or empyema, sepsis, wound infection, wound dehiscence, renal failure, respiratory insufficiency, hepatic insufficiency, recurrent laryngeal nerve paralysis, pneumonia, pulmonary embolism, other embolisms, deep venous thrombosis, ileus, thoracic ductus injury, myocardial infarction, atrial fibrillation, cerebral infarction, strictures in anastomosis, gastric perforation, and other complications. The complications were analysed as:

1) Occurrence of any complications (no or yes);
2) Clavien-Dindo classification (0-I, II-IIIa, or IIIb-IV) [42];
3) Surgical complication (no or yes), defined by any records of postoperative bleeding, anastomotic insufficiency, substitute necrosis, thoracic ductus injury, intrathoracic abscess or empyema, intra-abdominal abscess, wound infection, wound dehiscence, ileus, gastric perforation, recurrent laryngeal nerve paralysis, or strictures in anastomosis;
4) Medical complication (no or yes), defined by any records of sepsis, pneumonia, hepatic insufficiency, renal failure, deep venous thrombosis, pulmonary embolism, other embolisms, myocardial infarction, atrial fibrillation, cerebral infarction, or respiratory insufficiency;
5) Pulmonary complication (no or yes), defined by any records of respiratory insufficiency or pneumonia;

6) Cardiac complication (no or yes), defined by any records of myocardial infarction or atrial fibrillation.

4.3.2.3 Outcome

The study outcome was cancer-related fatigue measured at 1, 1.5, and 2 years after oesophageal cancer surgery by EORTC QLQ-C30 and QLQ-FA12.

Throughout the thesis, the fatigue measurements were transformed into 0-100 scores. Higher scores indicate higher levels of cancer-related fatigue. Missing data were handled in line with the EORTC scoring manual [92].

In this study, cancer-related fatigue was analysed as continuous variables for:

1) QLQ-C30 fatigue scores;
2) QLQ-FA12 overall fatigue scores;
3) QLQ-FA12 physical fatigue scores;
4) QLQ-FA12 emotional fatigue scores;
5) QLQ-FA12 cognitive fatigue scores.

4.3.2.4 Statistical analysis

Linear mixed-effect models were used to estimate mean scores and mean score differences (MD) with 95% CIs of cancer-related fatigue by postoperative complications, adjusting for age at surgery (continuous variable), sex (male or female), education (<9, 9-12, or ≥12 years of formal education), proxy baseline QLQ-C30 fatigue score (continuous variable), Charlson comorbidity index (0, 1 or ≥2), tumour histology (adenocarcinoma or squamous cell carcinoma), neoadjuvant therapy (no or yes), pathological tumour stage (0-I, II, III-IV), weight change 1 year after the surgery (continuous variable). MD ≥5 indicated potential clinical relevance throughout the thesis [93, 94].

Sensitivity analyses were conducted: 1) furtherly adjusted for the preoperative weight change (between average weight as an adult and weight at surgery); 2) excluding fatigue measurements of patients who died within 2 months of the follow-up.

4.3.3 Study III

4.3.3.1 Study cohort

This nationwide, longitudinal cohort study included oesophageal cancer survivors who underwent oesophagectomy between January 2013 and December 2019 in Sweden. Patients who survived 1 year after the surgery were enrolled.

4.3.3.2 Exposure

The study exposure was weight loss defined by body mass index (BMI) adjusted weight loss grading system (WLGS) [95]. WLGS is a newly proposed classification of cancer-associated weight loss, incorporating both body habitus (BMI) and weight change (Table 2). WLGS 0 represents the least-risk patient group with the highest BMI and least weight loss, while higher grades are assigned to patients with higher risk, i.e. patients with lower BMI and more weight loss. In Study III, the WLGS was analysed as:

1) Preoperative WLGS (categorical variable: 0, 1, 2, 3, or 4), defined by BMI at surgery and weight loss between average weight as an adult and at the time of surgery;
2) Postoperative WLGS (categorical variable: 0, 1, 2, 3, or 4), defined by BMI at six months after surgery and weight loss between weight at surgery and six months after surgery;
3) Cumulative WLGS (categorical variable: 0, 1, 2, 3, or 4), defined by BMI at six months after surgery and weight loss between average weight as an adult and weight at six months after surgery.

Table 2. Body mass index adjusted weight loss grading system (WLGS, 0-4)

	Body mass index (kg/m^2)				
Weight loss (%)	≥ 28	25-28	22-25	20-22	<20
<2.5	0	0	1	1	3
2.5-6	1	2	2	2	3
6-11	2	3	3	3	4
11-15	3	3	3	4	4
≥ 15	3	4	4	4	4

4.3.3.3 Outcome

The study outcome was cancer-related fatigue measured at 1, 1.5, 2, 2.5, and 3 years after oesophageal cancer surgery by EORTC QLQ-C30 and QLQ-FA12. The scores of QLQ-C30, QLQ-FA12 overall, QLQ-FA12 physical, QLQ-FA12 emotional, and QLQ-FA12 cognitive fatigue were calculated, and analysed as:

1) Cancer-related fatigue score at 1 year after oesophagectomy (continuous variable);
2) Cancer-related fatigue trajectories between 1 and 3 years after oesophagectomy (categorical variable).

4.3.3.4 Statistical analysis

Growth mixture models were used to identify the latent cancer-related fatigue trajectories. Patients were categorised to the trajectory with the highest posterior probability. Linear regression was used to calculate the mean score and MDs with 95% CIs of cancer-related fatigue at 1 year after the surgery by WLGS, adjusting for age at surgery (continuous variable), sex (male or female), Charlson comorbidity index (0, 1 or ≥2), tumour histology (adenocarcinoma or squamous cell carcinoma), neoadjuvant therapy (no or yes), pathological

tumour stage (0-I, II, III-IV). For the analyses regarding postoperative or cumulative WLGS, 30-day Clavien-Dindo classification (0-I, II-IIIa, or IIIb-IV) was also included in the model as a covariate. Logistic regression was fitted to estimate odds ratios (OR) with 95% CIs for the association between WLGS and caner-related fatigue trajectories, adjusting for the same covariates mentioned above.

Sensitivity analyses were conducted: 1) among patients with dumping syndrome; 2) among patients in the ERAS program [20].

In post-hoc analyses, instead of WLGS, BMI and weight loss were included in the linear and logistic regression to explore the association between weight change and cancer-related fatigue.

4.3.4 Study IV

4.3.4.1 Study cohort

This nationwide, longitudinal cohort study included oesophageal cancer survivors who underwent oesophagectomy between January 2013 and June 2020 in Sweden. Patients who survived 1 year after the surgery were enrolled.

4.3.4.2 Outcome

The study outcome was cancer-related fatigue measured at 1, 1.5, 2, 2.5, 3, 4, and 5 years after oesophageal cancer surgery by EORTC QLQ-C30 and QLQ-FA12. Cancer-related fatigue trajectories were analysed as categorical variables for:

1) QLQ-C30 fatigue;
2) QLQ-FA12 overall fatigue;
3) QLQ-FA12 physical fatigue;
4) QLQ-FA12 emotional fatigue;
5) QLQ-FA12 cognitive fatigue;
6) QLQ-FA12 fatigue interference with daily life;
7) QLQ-FA12 social sequelae of fatigue;

4.3.4.3 Factors

This study included predefined factors that might influence cancer-related fatigue trajectories:

- Sociodemographic and clinical factors: age at surgery (continuous variable), sex (male or female), education (<9, 9-12, or >12 years of formal education), proxy baseline QLQ-C30 fatigue score (continuous variable), Charlson comorbidity index (0, 1 or ≥2), tumour histology (squamous cell carcinoma or adenocarcinoma), neoadjuvant therapy (no or yes), pathological tumour stage (0-I, II, III-IV), 30-day Clavien-Dindo classification (0-I, II-IIIa, or IIIb-IV);

- PRO factors: anxiety (Hospital Anxiety and Depression Scale [HADS] score ≥8: no or yes) [54], depression (HADS score ≥8: no or yes), pain score (QLQ-C30 pain subscale, continuous variable), insomnia score (QLQ-C30 insomnia subscale, continuous variable), preoperative WLGS (categorized by BMI at surgery and weight loss between average weight as an adult and at the time of surgery: 0, 1, 2, 3 or 4) [95], and physical activity measured at 1 year after oesophagectomy (International Physical Activity Questionnaire [IPAQ]: low, moderate, and high level) [96].

4.3.4.4 Statistical analysis

Growth mixture models were used to identify the latent cancer-related fatigue trajectories. Patients were categorised to the trajectory with the highest posterior probability. Weighted logistic regression was used to provide ORs with 95% CIs for the associations between predefined factors and cancer-related fatigue trajectories. The posterior probabilities were used as weights in the logistic regression models.

The models were analysed by: 1) only including sociodemographic and clinical factors; 2) including sociodemographic, clinical, and PRO (anxiety, depression, pain, and insomnia) factors; 3) including sociodemographic, clinical, and all PRO factors.

5 RESULTS

5.1 STUDY I

Among the 2576 patients who underwent oesophagectomy for oesophageal cancer during 1987-2015, 1553 (60.3%) had a Charlson comorbidity index ≥1. Regarding the outcome, 195 (7.6%) underwent a reoperation, 184 (7.1%) died with no reoperation record, and 67 (2.6%) died with a reoperation record. Table 3 presents the main characteristics of the 2576 patients by the Charlson comorbidity index.

Table 3. Characteristics of 2576 patients included in Study I

	Charlson comorbidity index		
	0	1	≥2
	Number (%)	Number (%)	Number (%)
Total	1023 (39.7)	922 (35.8)	631 (24.5)
Mean age ± standard deviation	63.8 ± 9.9	65.7 ± 9.1	67.1 ± 8.9
Sex			
Male	791 (77.3)	691 (75.0)	494 (78.3)
Female	232 (22.7)	231 (25.1)	137 (21.7)
Tumour histology			
Adenocarcinoma	575 (56.2)	462 (50.1)	356 (56.4)
Squamous cell carcinoma	444 (43.4)	458 (49.7)	272 (43.1)
Missing	4 (0.4)	2 (0.2)	3 (0.5)
Pathological tumour stage			
0-I	234 (22.9)	185 (20.1)	143 (22.7)
II	316 (30.9)	303 (32.9)	216 (34.2)
III	339 (33.1)	316 (34.3)	200 (31.7)
IV	63 (6.2)	59 (6.4)	42 (6.7)
Missing	71 (6.9)	59 (6.4)	30 (4.8)

Charlson comorbidity index ≥2 was associated with an increased risk of reoperation or death after oesophagectomy (RR 1.78, 95% CI 1.44-2.20) (Table 4). Pulmonary disease, cardiac disease, diabetes, and cerebral disease were also associated with reoperation or death within 90 days after the surgery.

In stratified analyses, the risk of outcome by Charlson comorbidity index or other specific comorbidity groups was mostly similar across the age, annual hospital volume, tumour histology, and calendar period groups.

Table 4. Comorbidity and risk of reoperation or death within 90 days of oesophagectomy

	Reoperation or death		
	Number (%)	Crude RR (95% CI)	Adjusted RR (95% CI)[1]
Charlson comorbidity index			
0	138 (13.5)	1.00 (Reference)	1.00 (Reference)
1	148 (16.1)	1.19 (0.96-1.47)	1.04 (0.83-1.30)
≥2	160 (25.4)	**1.88 (1.53-2.31)**	**1.78 (1.44-2.20)**
Charlson comorbidity index[2]	-	**1.28 (1.20-1.38)**	**1.27 (1.18-1.37)**
Pulmonary disease			
No	349 (15.9)	1.00 (Reference)	1.00 (Reference)
Yes	97 (25.1)	**1.58 (1.29-1.92)**	**1.66 (1.36-2.04)**
Cardiac disease			
No	379 (16.7)	1.00 (Reference)	1.00 (Reference)
Yes	67 (21.8)	**1.30 (1.03-1.64)**	**1.37 (1.08-1.73)**
Diabetes			
No	397 (17.0)	1.00 (Reference)	1.00 (Reference)
Yes	49 (20.6)	1.21 (0.93-1.58)	**1.50 (1.14-1.99)**
Cerebral disease			
No	400 (16.8)	1.00 (Reference)	1.00 (Reference)
Yes	46 (24.0)	**1.43 (1.09-1.87)**	**1.40 (1.06-1.85)**
Other malignancy			
No	342 (17.0)	1.00 (Reference)	1.00 (Reference)
Yes	104 (18.5)	1.09 (0.90-1.33)	1.19 (0.97-1.47)

[1] Adjusted for age, sex, education, tumour histology, neoadjuvant therapy, pathological tumour stage, annual hospital volume, and calendar period.
[2] Analysed as a discrete variable to evaluate the linear trend.

5.2 STUDY II

During the study period, 522 patients were eligible for inclusion in Study II. Among these, 331 (63.4%) were included in the study with 1-year measurement of cancer-related fatigue. The follow-up response rates at 1.5 and 2 years were 75.5% and 70.3%, respectively. The main patient characteristics are presented in Table 5.

Table 5. Characteristics of 331 patients included in Study II

	Complication	
	No	Yes
	Number (%)	Number (%)
Total	120 (36.3)	211 (63.7)
Mean age ± standard deviation	66.5 (8.0)	67.3 (8.6)
Sex		
Male	14 (11.7)	20 (9.5)
Female	106 (88.3)	191 (90.5)
Tumour histology		
Adenocarcinoma	105 (87.5)	172 (81.5)
Squamous cell carcinoma	15 (12.5)	39 (18.5)
Pathological tumour stage		
0-I	42 (35.0)	69 (32.7)
II	40 (33.3)	68 (32.3)
III-IV	38 (31.7)	72 (34.1)
Missing	0 (0.0)	2 (0.9)

Compared with patients who had no complications, an increase in cancer-related fatigue scores was found among those with complications (QLQ-C30 fatigue: MD 5.8, 95% CI 2.6 to 9.0; QLQ-FA12 overall fatigue: MD 7.2, 95% CI 4.9 to 9.5), especially among the patients with medical complications (QLQ-C30 fatigue: MD 6.9, 95% CI 3.0 to 10.7; QLQ-FA12 overall fatigue: MD 8.2, 95% CI 5.5 to 10.9) between 1 and 1.5 years, and remained stable until 2 years after oesophagectomy (Figure 1). Pulmonary complications were also associated with increased levels of postoperative cancer-related fatigue with clinical relevance. Regarding cancer-related fatigue subscales, similar changing patterns were also seen in physical and emotional fatigue, but not cognitive fatigue.

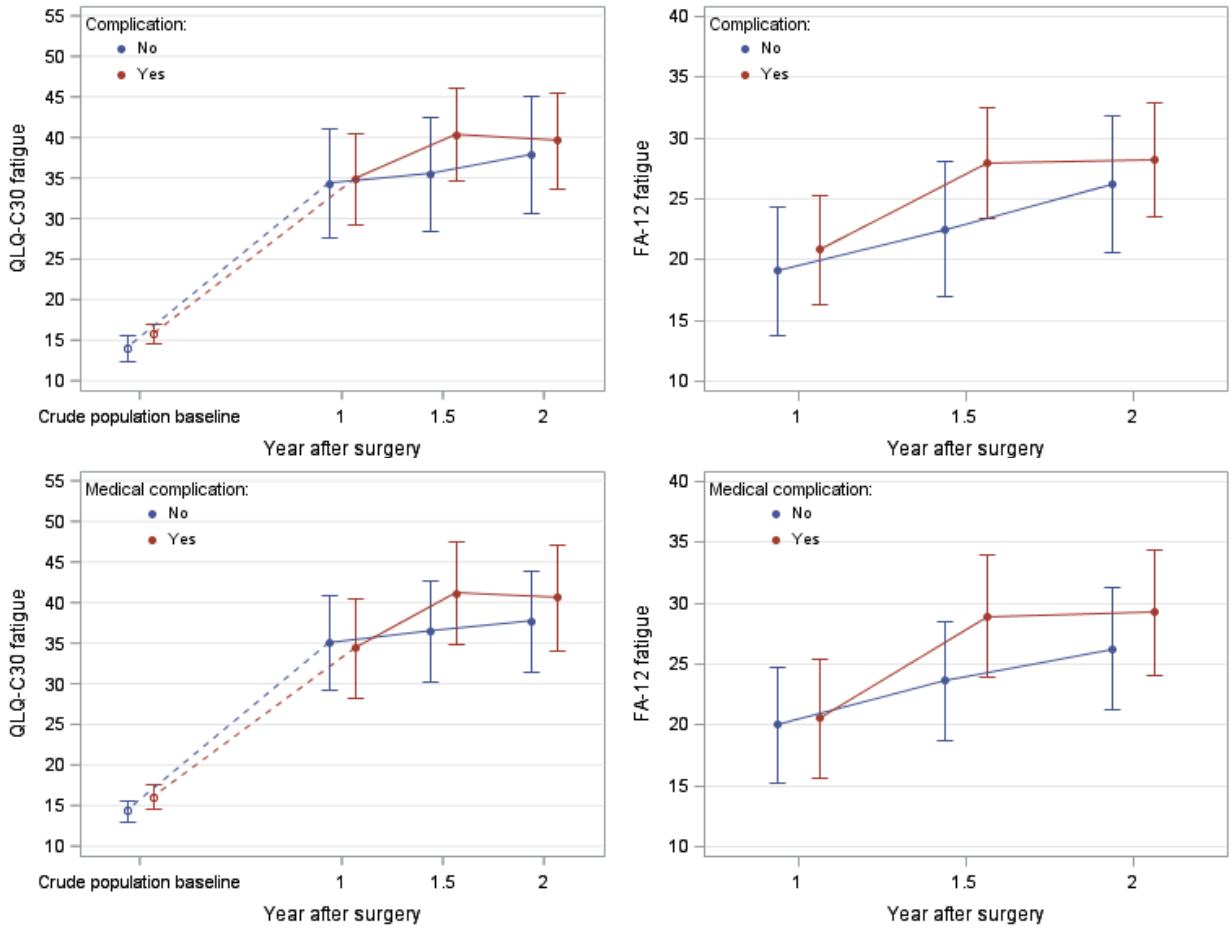

Figure 1. Cancer-related fatigue between patients with and without postoperative complications

5.3 STUDY III

During 2013-2019, 569 patients were eligible for study inclusion in Study III. Among these, 356 (62.6%) completed the 1-year measurement of cancer-related fatigue. The follow-up response rates during the follow-up were 82.6%, 76.6%, 67.5% and 68.1% at 1.5, 2, 2.5, and 3 years, respectively. The main patient characteristics are presented in Table 6.

Table 6. Characteristics of 356 patients included in Study III

	Postoperative WLGS [1]				
	0	1	2	3	4
	Number (%)				
Total	20 (5.6)	28 (7.7)	41 (11.5)	141 (39.6)	114 (32.0)
Mean age ± standard deviation	67.6 (9.3)	66.4 (8.7)	66.5 (11.0)	67.3 (7.7)	67.5 (8.2)
Sex					
Male	16 (80.0)	22 (78.6)	40 (97.6)	131 (92.9)	102 (89.5)
Female	4 (20.0)	6 (21.4)	1 (2.4)	10 (7.1)	12 (10.5)
Tumour histological type					
Adenocarcinoma	16 (80.0)	19 (67.9)	35 (85.4)	124 (87.9)	98 (86.0)
Squamous cell carcinoma	4 (20.0)	9 (32.1)	6 (14.6)	17 (12.1)	16 (14.0)
Pathological tumour stage					
0-I	5 (25.0)	9 (32.1)	9 (22.0)	51 (36.2)	42 (36.8)
II	7 (35.0)	11 (39.3)	13 (31.7)	39 (27.7)	34 (29.8)
III-IV	8 (40.0)	8 (28.6)	19 (46.3)	51 (36.2)	38 (33.3)

[1] WLGS: Body mass index adjusted weight loss grading system.

There were 3 trajectories identified: low, moderate, and severe levels of cancer-related fatigue (Figure 2). Among the 356 patients, 19.9% and 10.5% of them had a severe and persistent fatigue trajectory regarding QLQ-C30 and QLQ-FA12, respectively. Similar persistent trajectories were also identified in QLQ-FA12 physical, emotional, and cognitive fatigue.

No association was found between WLGS and cancer-related fatigue score 1 year after oesophagectomy (Table 7). Further, WLGS was not associated with cancer-related fatigue trajectories between 1 and 3 years postoperatively either (Table 7).

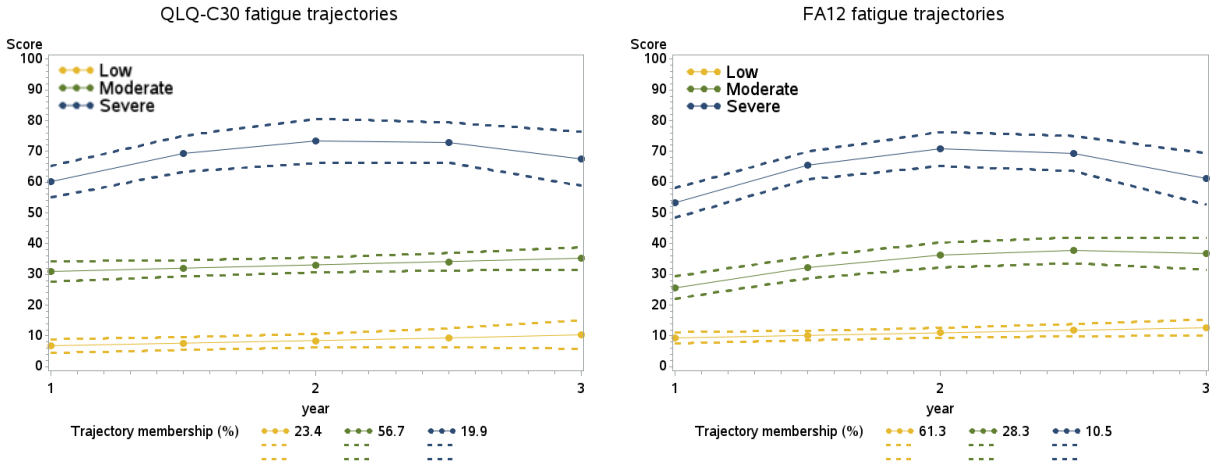

Figure 2. Cancer-related fatigue trajectories between 1 and 3 years after oesophageal cancer surgery

[1] Solid lines represent mean scores. Dotted lines represent 95% CIs.

Table 7. Cancer-related fatigue comparing different levels of body mass index adjusted weight loss grading system (WLGS)

	QLQ-C30 fatigue		QLQ-FA12 overall fatigue	
	Fatigue score at 1 year	Severe fatigue trajectory	Fatigue score at 1 year	Severe fatigue trajectory
	MD (95% CI)	OR (95% CI)	MD (95% CI)	OR (95% CI)
Preoperative WLGS[1]				
0	35.9 (29.9-41.8)	1.0 (Reference)	21.5 (17.1-25.9)	1.0 (Reference)
1 vs 0	-5.3 (-15.2-4.7)	0.93 (0.37-2.34)	1.1 (-6.2-8.5)	1.78 (0.60-5.29)
2 vs 0	2.3 (-6.5-11.1)	0.75 (0.31-1.78)	1.1 (-5.5-7.7)	1.51 (0.53-4.32)
3 vs 0	-3.1 (-11.7-5.5)	1.03 (0.47-2.29)	-2.1 (-8.5-4.3)	0.70 (0.21-2.42)
4 vs 0	2.8 (-8.5-14.1)	0.93 (0.33-2.61)	-0.7 (-9.1-7.7)	1.79 (0.52-6.21)
Postoperative WLGS[1,2]				
0	28.8 (18.3-39.4)	1.0 (Reference)	24.3 (16.4-32.2)	1.0 (Reference)
1 vs 0	7.9 (-7.8-23.6)	1.87 (0.31-11.27)	-4.1 (-15.9-7.7)	1.08 (0.14-8.26)
2 vs 0	1.9 (-12.9-16.7)	1.48 (0.26-8.62)	-4.3 (-15.4-6.8)	0.84 (0.11-6.30)
3 vs 0	7.4 (-5.6-20.4)	2.76 (0.58-13.16)	-2.6 (-12.3-7.2)	1.52 (0.28-8.24)
4 vs 0	5.0 (-8.1-18.1)	1.90 (0.39-9.24)	-2.1 (-11.9-7.8)	1.81 (0.33-9.76)
Cumulative WLGS[1,2]				
0	36.7 (25.9-47.5)	1.0 (Reference)	26.2 (18.2-34.3)	1.0 (Reference)
1 vs 0	-0.3 (-17.4-16.8)	2.03 (0.38-10.78)	-3.2 (-16.0-9.5)	2.23 (0.29-17.41)
2 vs 0	-0.4 (-16.0-15.2)	2.76 (0.61-12.45)	-3.8 (-15.5-7.8)	1.73 (0.26-11.56)
3 vs 0	-4.8 (-18.0-8.4)	0.90 (0.22-3.73)	-7.6 (-17.4-2.3)	0.62 (0.10-3.83)
4 vs 0	-2.1 (-14.9-10.7)	1.23 (0.32-4.72)	-5.4 (-14.9-4.2)	1.22 (0.23-6.48)

[1] Adjusted for age at surgery, sex, Charlson comorbidity index, tumour histology, pathological tumour stage, and neoadjuvant therapy.
[2] Further adjusted for Clavien-Dindo classification.

5.4 STUDY IV

In total, 617 patients were eligible for study inclusion during the study period. Among these, 418 (67.7%) patients participated in Study IV. There were 2 trajectories of cancer-related fatigue identified: low and high levels of cancer-related fatigue (Figure 3). About 36% of the patients were categorised with high levels of QLQ-C30 and QLQ-FA12 overall fatigue trajectory. Distinctly different trajectories were also identified regarding QLQ-FA12 physical fatigue, emotion fatigue, and fatigue inference with daily life subscale. The main patient characteristics across cancer-related fatigue trajectories are described in Table 8.

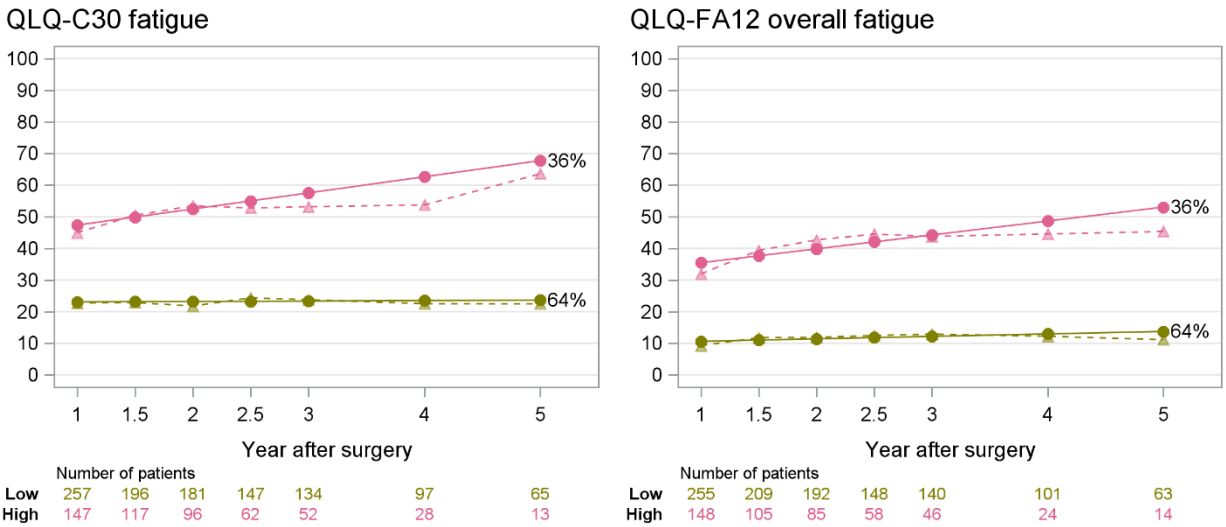

Figure 3. Cancer-related fatigue trajectories between 1 and 5 years after oesophageal cancer surgery

[1] Solid lines represent estimated means. Dotted lines represent sample means.

[2] The percentage after each trajectory is the final patient proportion for the trajectory category based on the most likely trajectory membership.

Table 8. Characteristics of 409 patients included in Study IV

	QLQ-C30 fatigue trajectory		QLQ-FA12 overall fatigue trajectory	
	Low	High	Low	High
	Number (%)	Number (%)	Number (%)	Number (%)
Total	261 (63.8)	148 (36.2)	260 (63.6)	148 (36.2)
Mean age ± standard deviation	67.9 (7.4)	66.0 (9.6)	68.0 (7.3)	66.0 (9.7)
Sex				
Female	20 (7.7)	14 (9.5)	20 (7.7)	14 (9.5)
Male	241 (92.3)	134 (90.5)	240 (92.3)	134 (90.5)
Tumour histology				
Squamous cell carcinoma	33 (12.6)	23 (15.5)	36 (13.8)	20 (13.5)
Adenocarcinoma	228 (87.4)	124 (83.8)	223 (85.8)	128 (86.5)
Missing	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)
Pathological tumour stage				
0-I	98 (37.5)	39 (26.4)	99 (38.1)	38 (25.7)
II	80 (30.7)	45 (30.4)	85 (32.7)	40 (27.0)
III-IV	81 (31.0)	61 (41.2)	73 (28.1)	69 (46.6)
Missing	2 (0.8)	3 (2.0)	3 (1.2)	1 (0.7)

Pathological tumour stage III-IV (OR 2.16, 95% CI 1.16-4.01), depression (OR 5.22, 95% CI 1.98-13.76), pain (OR 1.02, 95% CI 1.01-1.03), and insomnia (OR 1.01, 95% CI 1.00-1.02) were associated with a higher level of QLQ-C30 fatigue trajectory (Table 9). Besides, comorbidity, postoperative complications, and anxiety were also found associated with QLQ-FA12 overall and subscale trajectories.

Table 9. Associations between predefined factors and cancer-related fatigue trajectories after surgery for oesophageal cancer

	High level of QLQ-C30 fatigue [2]	High level of QLQ-FA12 overall fatigue [3]
	OR (95% CI)	OR (95% CI)
Age		
Continuous	1.00 (0.97-1.03)	1.00 (0.97-1.04)
Sex		
Female	1.00 (Reference)	1.00 (Reference)
Male	1.07 (0.41-2.79)	1.54 (0.53-4.53)
Education level (years)		
<9	1.00 (Reference)	1.00 (Reference)
9-12	0.95 (0.47-1.92)	1.25 (0.59-2.66)
>12	0.81 (0.43-1.53)	1.24 (0.62-2.45)
Proxy baseline QLQ-C30 fatigue		
Continuous	1.00 (0.96-1.05)	0.98 (0.93-1.03)
Charlson comorbidity index		
0	1.00 (Reference)	1.00 (Reference)
1	0.97 (0.51-1.84)	0.97 (0.49-1.92)
≥2	1.39 (0.61-3.14)	**2.52 (1.07-5.94)**
Tumour histology		
Squamous cell carcinoma	1.00 (Reference)	1.00 (Reference)
Adenocarcinoma	0.97 (0.45-2.09)	1.41 (0.61-3.27)
Neoadjuvant therapy		
No	1.00 (Reference)	1.00 (Reference)
Yes	1.04 (0.54-2.02)	1.43 (0.70-2.92)
Pathological tumour stage		
0-I	1.00 (Reference)	1.00 (Reference)
II	1.61 (0.85-3.07)	1.24 (0.63-2.45)
III-IV	**2.16 (1.16-4.01)**	**2.52 (1.33-4.77)**
Clavien–Dindo classification		
0–I	1.00 (Reference)	1.00 (Reference)
II–IIIa	1.45 (0.80-2.61)	1.56 (0.84-2.90)
IIIb–IV	1.90 (0.99-3.67)	1.64 (0.82-3.27)
HADS anxiety [1]		
No	1.00 (Reference)	1.00 (Reference)
Yes	1.58 (0.60-4.14)	**7.58 (2.20-26.17)**
HADS depression [1]		
No	1.00 (Reference)	1.00 (Reference)
Yes	**5.22 (1.98-13.76)**	**15.90 (4.44-56.93)**
QLQ-C30 pain		
Continuous	**1.02 (1.01-1.03)**	**1.02 (1.01-1.04)**
QLQ-C30 insomnia		
Continuous	**1.01 (1.00-1.02)**	1.01 (1.00-1.02)

[1] HADS: Hospital Anxiety and Depression Scale.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

In this thesis, all four studies use cohort designs and Study II-IV are longitudinal cohorts with repeated observations at different time points during the follow-up.

In cohort studies, a group of predefined people with different levels of exposure are followed up regarding different outcomes during the study period. The study base of the included studies in this thesis is oesophageal cancer patients who underwent oesophagectomy in Sweden during the study period with different follow-up times as summarized in Table 1. The preoperative exposure records and the incidence of postoperative outcomes in Study I naturally formed the temporality and the prospective cohort design. However, in Study II-IV, the outcome (cancer-related fatigue) by definition can happen at any time after the tumour develops, and the chronological order between some of the exposures (e.g. postoperative complications) and the incident outcome is unknown. In such cases, the study's interest is to assess the natural course of cancer-related fatigue over time, and the association between exposures measured at an earlier time point and the outcomes measured at a later period, which are still prospective cohort studies.

After conducting a study, internal and external validity need to be considered when interpreting the study results. In epidemiological studies, internal validity is affected by two types of errors, namely random error, and systematic error. Generally, systematic errors comprise selection bias, information bias, and confounding. These considerations regarding the studies in this thesis are discussed below.

6.1.2 Internal validity

6.1.2.1 Random error

The random error comes from the variability of data after accounting for the system errors. Statistically, confidence interval and P values can be used to indicate the random error. A 95% confidence interval is a common way to reflect random error, defined as the range of values that would include the correct estimate of measurement if a test is repeated infinitely and free of bias 95% of the time. P value stands for the “probability” of observing a current or even stronger association, conditional on the null hypothesis being true. However, in practice, not all theoretical assumptions are met in the statistical model, and the P value is in most cases not a meaningful probability but can be seen as a measure of consistency between the null hypothesis and the estimated result. Random error is also inevitable in epidemiological studies but can be reduced by avoiding multiple testing to reduce the risk of Type I error (acceptance of a false positive hypothesis) and increasing the sample size to lower the risk of Type II error (acceptance of a false negative hypothesis).

Study I had a relatively bigger sample size, and was at a lower risk of random error. But in the stratified analyses and Study II-IV, the sample size might be underpowered for testing some mild effects. Multiple testing is less of a concern in the thesis because all studies were conducted based on predefined protocols with clearly defined hypotheses, and all the results were presented without selection.

6.1.2.2 Selection bias

Selection bias occurs when the study participants cannot represent the source population during the study period. It can arise not only at the study inclusion but also when there is loss-to-follow-up. Study I in this thesis identified patients from the national registry with complete (98%) inclusion and follow-up, selection bias is less of a concern in this study. Study II-IV had around 30% of the patients who did not participate due to "too sick", "unwilling to participate", or "lack of information". And the study results were at risk of selection bias since the characteristics of patients who did not participate were unknown, and the direction of the bias remained unclear. It is possible the patients who were too sick or unwilling may be the patients with the worst physical status and therefore had poor levels of exposure and severe fatigue, hence the potential associations might be diluted. Besides, though some of the patients dropped out because of death or cancer recurrence, the response rates were on average over 70% during the follow-up, which is considered acceptable in such longitudinal study designs.

6.1.2.3 Information bias

Information bias refers to the measurement error that occurs when the data is not correctly or accurately collected in the study. Misclassification is one type of information bias, comprising 2 types: it is nondifferential when the misclassification is not associated with other study variables, while differential misclassification occurs when such association exists. The bias is of special concern when it happens in exposure or outcome. The data quality in the national registry and medical records reviewed according to a predefined protocol is considered high, though minor misclassification errors might be difficult to rule out completely. And such misclassification should be nondifferential, and could mostly dilute the associations towards null, not explaining it.

Cancer-related fatigue was measured by 2 validated questionnaires. The reason for using 2 questionnaires was to have a more comprehensive measure of this abstract symptom and to help interpret the results with each other. Recall bias could occur since the questionnaire asked about the experience in the previous week. The trajectories of cancer-related fatigue were identified by growth mixture models in Study III and IV. Growth mixture models allow empirically identifying latent groups of patients with similar fatigue trajectories. In the output of the model, patients' probabilities of being assigned to each trajectory were estimated. And patients were assigned to the trajectory with the highest probability estimation. By doing this assignment, there was a risk of misclassification [97], which might also bias the results. Whether such misclassification was differential or not is unknown, and this can become a concern for

patients whose probability estimations were similar among the identified trajectories (i.e. lead to more uncertainty when doing the patient assignment).

6.1.2.4 Confounding

Confounding is the mixing of exposure effects caused by the imbalance distribution of a confounder, which is a variable that is associated with both exposure and outcome, but not in the causal pathway. A recognised and measured confounder can be dealt with by randomization, restriction, matching, or statistical adjustment. In all four studies included in this thesis, multivariable regression models were used with adjustment of the important covariates. Stratification and sensitivity analyses conducted among patients with selected characteristics were also applied to relieve the concern of confounding. The selection of covariates in the thesis was based on prior knowledge and data availability. However, residual confounding is inevitable in the observational designs. In these studies, potential unmeasured confounders, such as data on lifestyle or tumour recurrence, might still distort the observed association to some degree.

6.1.3 External validity

External validity is the generalizability of a study finding to another population or setting. Conditional on good internal validity, the external validity of any epidemiological studies must be interpreted cautiously. One can argue that a nationwide or population-based study design is a guarantee of good external validity, but external interpretations can only be drawn considering the distribution of all relevant characteristics among the study and targeted populations are similar. For example, even within the same country, cities could have different distributions of relevant characteristics, such as socioeconomic status or environmental factors, and the estimated association on a nationwide level is an "average" of the associations that would be estimated at the city level. And to generalize a nationwide level estimation to a specific city needs to take important covariates distribution into account. Stratification and regression modelling can be used to facilitate external extrapolation [98]. In the studies included in this thesis, both methods were used to estimate the conditional effects of study exposures. However, to generalize the current results to other populations need to consider the distribution differences of other unmeasured or unadjusted relevant factors, e.g. psychological and lifestyle factors between the study and the targeted population.

6.2 GENERAL DISCUSSION

6.2.1 Study I

Study I showed that preoperative comorbidities, specifically pulmonary disease, cardiac disease, diabetes, and cerebral disease, were associated with an increased risk of postoperative adverse outcomes in terms of death or reoperation within 90 days of oesophagectomy.

This study is merited by the nationwide registry-based cohort design and high-quality data with complete inclusion and follow-up, counteracting the risk of selection and information bias. Residual or unmeasured confounding might be limited since established and important covariates were controlled in the analyses. The outcome used a composite of reoperation or death as a proxy of severe adverse outcomes postoperatively, which also dealt with the competing risk of death if analysing the reoperation rate alone. However, not all severe postoperative complications needed reoperations and those that only required intensive care were recorded with poor quality and thus not included in the study outcome. But such misclassifications could only bias the result towards null, not explaining it. Besides, due to patient selection for oesophagectomy, the numbers of patients with high Charlson comorbidity index or with some specific comorbidities were small, which restricted the power of stratified analyses.

Compared to previous studies, Study I provided updated evidence by using 90-day instead of 30-day for short-term postoperative outcomes. Previous studies have found that a higher Charlson comorbidity index was associated with an increased risk of 30-day postoperative complications or death [99-101], which was also proved in this study. But conclusions regarding cardiorespiratory comorbidity [102, 103], and diabetes[104, 105] were still contradictory. Positive associations were found in this study between these comorbid diseases and reoperation or death within 90 days of oesophagectomy. Patients with preoperative cardiac or pulmonary disease might be prone to have postoperative atrial fibrillation or pneumonia, which are the most common postoperative complications after oesophagectomy, and causes 50% of in-hospital death [24, 106, 107]. Patients with preoperative diabetes carry a higher risk of microvascular diseases and the wound might not heal properly with hyperglycaemia, which also increases the risk of adverse postoperative outcomes.

6.2.2 Study II

Study II indicated that post-oesophagectomy complications, especially medical and pulmonary complications, were associated with increasing and higher levels of cancer-related fatigue.

Strengths of this study include the nationwide and longitudinal cohort design, reliable data sources from validated questionnaires, national registers, and careful review of medical records, reducing the concern of information bias. However, due to nonparticipation and loss-to-follow-up, there is a risk of selection bias. For example, patients who have severe cognitive fatigue might not be able to join the study and the lack of association need to be interpreted cautiously. Although selected covariates were adjusted in the analyses, residual and unmeasured confounders might still exist, such as the true baseline fatigue level and psychological factors. Besides, the estimated score differences of fatigue were just around the minimal threshold of clinical relevance (small deteriorations) [93], and some of the analyses might be at risk of underpowering. This was solved by the predefined grouping of the exposures, and the sample

size was large enough to detect the differences between exposure groups. A larger sample size is needed if the interest is the effect of a specific complication.

Study II is, to the best of our knowledge, the first longitudinal cohort study focusing on cancer-related fatigue regarding postoperative complications after oesophagectomy for oesophageal cancer. Previous studies have shown higher levels of cancer-related fatigue after treatment compared to baseline measurements in other cancer types [108-110], which was also seen in Study II. It is generally accepted that the fatigue level increases greatly during cancer therapy and continues increasing until 6 months to 1 year after the treatment, but whether the level of fatigue could recover to pre-treatment level or remains high in the long-term was unsure [75, 109, 111]. In Study II, the fatigue score increased, especially among patients with medical complications, between 1-1.5 years and remained at the 1.5-year level until 2 years after the surgery. Patients experienced increased cancer-related fatigue because of the side effects of extensive cancer treatment and multiple symptoms to recover or cope with during the treatment and acute recovery period. But even after 1 year postoperatively, the fatigue level kept increasing and remaining, which was found associated with medical complications in this study. Postoperative complications were usually controlled shortly, and the long-lasting effect on cancer-related fatigue might be due to the activation of inflammatory response persists, or probably also due to the patients with medical complications were those at higher risk of other chronic diseases or poor physical conditions. This explained the long-term effect to some extent, but the effect found in this study remained after adjusting for preoperative comorbidities, indicating the need of uncovering other underlying factors.

6.2.3 Study III

Study III showed that weight loss seemed not to be associated with cancer-related fatigue after oesophageal cancer surgery.

Among the strengths of this study are the longitudinal cohort design and robust measurements of exposures, outcomes, and covariates, which minimized information bias. The use of BMI-adjusted WLGS is another merit of Study III. WLGS was proposed in 2015, providing diagnostic criteria for the classification of cancer-associated weight loss. Study III is the first study estimating the association between WLGS and cancer-related fatigue among oesophageal cancer patients, a group of patients suffering from unintentional weight loss [95]. However, WLGS incorporates only BMI and weight change, and the effect of body composition cannot be assessed, which might be a crucial role in influencing cancer-related fatigue. Same as in Study II, Study III also has selection bias due to nonparticipation and loss-to-follow-up. Unmeasured confounding, such as changes in lifestyle or psychological factors, might influence the results. But based on the results from Study IV which adjusted for anxiety and depression, the confounding from such factors may be minor in Study III. Another weakness was the underpower after categorization by different WLGS groups, with very few patients

having severe preoperative or minor postoperative weight loss in this cohort, and the interpretation of the results should be cautious.

Two explanations were proposed to explain the negative association found in Study III: First, weight loss in oesophageal cancer patients is mostly caused by dysphagia due to the tumour and eating habits adaptation after the treatment [6, 112], which might not directly lead to the fatigue-related inflammation, and thus not causing cancer-related fatigue. Second, despite the adjustment of BMI in WLGS, the proportion of muscle loss within the weight change was unknown, and considering about 64% of the oesophageal cancer patients were overweight (BMI $\geq$25 kg/m^2) at surgery in this cohort, the loss of weight might not well account for the muscle loss.

6.2.4 Study IV

Study IV showed that distinctly different longitudinal cancer-related fatigue trajectories exist among oesophageal cancer survivors after oesophagectomy. Comorbidity, advanced tumour stage, postoperative complications, and PROs including anxiety, depression and pain were found associated with higher levels of fatigue trajectories.

Strengths of this study included the nationwide cohort study design with repeated follow-up measurements for up to 5 years, and the ability to include not only data from national registries and review of medical records but also several PROs measured by validated questionnaires. Same as in Study II and III, with nonparticipation and loss-to-follow-up, there was a risk of selection bias. Besides, some of the patients did not reach the latter follow-up when the study was conducted (e.g. patients who had oesophagectomy in 2020 had not reached the 5-year follow-up). This was dealt with by using growth mixture models using all available data, and providing robust estimates given the missing is at random. No targeted adjustment of confounding was conducted in Study IV since the nature of the study was exploratory and a large number of factors were included in the analyses, assumed to be confounders for each other. Patients were assigned to the identified trajectories by the posterior probabilities output from growth mixture models. Such uncertainty could be a source of misclassification and was accounted for by using the posterior probabilities as weight in the logistic regression.

To the best of our knowledge, Study IV is the first study identifying cancer-related fatigue trajectories up to 5 years among oesophageal cancer survivors. The identified trajectories were rather stable during the follow-up, indicating the potential of using earlier measurements to identify patients with a higher risk of persistent cancer-related fatigue. The proxy fatigue score before cancer diagnosis did not associate with the identified fatigue trajectory, while other studies found the fatigue measurement after diagnosis associated with the longitudinal fatigue trajectory [75, 108, 113], suggesting the timing of baseline measurements needs to be considered. Comorbidity, advanced tumour stage, and postoperative complications were found associated with fatigue development, which has also been seen in previous studies [24, 79, 108, 114]. Besides, Study IV found that some PROs, including anxiety, depression, and pain, were associated with

cancer-related fatigue. Considering there is no targeted treatment for cancer-related fatigue currently, established interventions regarding such clustered symptoms may help alleviate the persistent fatigue, as well as improve the overall survivorship.

7 CONCLUSIONS

Among patients who underwent oesophagectomy for oesophageal cancer:

1) Preoperative comorbidities were associated with an increased risk of reoperation or death within 90 days of surgery, particularly pulmonary disease, cardiac disease, diabetes, and cerebral disease.

2) Postoperative complications were associated with increasing and higher levels of cancer-related fatigue, particularly medical and pulmonary complications.

3) Weight loss was not associated with postoperative cancer-related fatigue.

4) Cancer-related fatigue developed distinctly after the surgery. Comorbidity, advanced tumour stage, postoperative complications, and PROs including anxiety, depression, and pain were found associated with higher levels of fatigue trajectories.

8 POINTS OF PERSPECTIVE

Despite the advances achieved in treating oesophageal cancer, the survivorship of the patients is still underreported and understudied. This thesis provided knowledge regarding cancer-related fatigue and the underlying factors.

Study I emphasized the need for careful assessment of comorbidities before oesophagectomy to achieve better postoperative outcomes. Future studies may focus on the controversial comorbidity groups and the effect of potential targeted preoperative optimization or postoperative support.

Study II provided evidence of the association between postoperative complications and cancer-related fatigue among oesophageal cancer survivors. Future studies may focus on the underlying factors associated with either postoperative complications or cancer-related fatigue with longer follow-ups.

Study III did not support the association between weight loss and cancer-related fatigue after oesophagectomy. Future studies may explore the effect of changing body composition in relation to cancer-related fatigue.

Study IV indicated the existence of distinct cancer-related fatigue trajectories among oesophageal cancer patients. Future studies may explore the effects of baseline measurements measured at different times after diagnosis for efficient early patient identification.

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