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Optimism and Survivorship after Esophageal Cancer Surgery

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By

Yangjun Liu

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Half full or half empty, that is the question.

POPULAR SCIENCE SUMMARY OF THE THESIS

What is known and what remains to be answered?

Esophageal cancer is a malignant disease which carries a poor prognosis. Among patients who are diagnosed with esophageal cancer, less than 20% survive more than 5 years after diagnosis. Surgery (i.e., esophagectomy) is the mainstay of curative treatment, which is applicable to around 25% of patients with esophageal cancer. However, esophageal cancer surgery is a major procedure, and even among patients undergoing the curatively intended surgery, less than 50% of them survive more than 5 years. Furthermore, after surgery, patients usually suffer from impaired health related quality of life (HRQL) such as pain, fatigue, eating difficulty, psychological distress, and decreased functioning.

Improving survival and HRQL after esophageal cancer surgery are important and challenging. To address this, firstly we need to understand why the prognosis varies among individuals. Previous research has found that some sociodemographic and clinical factors could predict survival and HRQL. For example, patients with advanced tumor are more likely to have shorter survival and worse HRQL. However, it has also been found that even among patients with similar sociodemographic and clinical characteristics, the prognosis still varies. Thus, there must be other factors explaining the residual variation.

The Greek philosopher Heraclitus says that “a man's character is his fate”. Also, more and more psychological studies have found that personality traits may affect our behavior and thus determine our fate to some extent. So, could personality traits explain the residual variation in the prognosis after esophageal cancer surgery? In addition, many people tend to believe that being optimistic might enhance patients’ survival chances and improve their HRQL, and caregivers sometimes encourage patients to try to be optimistic about their future even if they are facing a potentially fatal esophageal cancer. Such beliefs and actions based on folk wisdom carry a hope to improve survival and HRQL via being optimistic. However, whether optimism truly relates to the prognosis after esophageal cancer surgery remains unknown.

What has this thesis studied?

Dispositional optimism is a personality trait, which is the general expectancy that good rather than bad things would happen in the future. In this thesis, we used Swedish nationwide population-based data to examine whether higher dispositional optimism was associated with better prognosis after esophageal cancer surgery. At 1 year after surgery for esophageal cancer, we measured patients' dispositional optimism level using a self-reported scale called Life Orientation Test-Revised. At 1, 1.5, and 2 years after esophagectomy, we measured patients’ psychological status and HRQL using several self-reported scales such as the Hospital Anxiety and Depression Scale, the European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire, and Gastro-Esophageal Specific

questionnaire. We also obtained patients' mortality information from the Swedish Total Population Register.

What has this thesis found?

We found that more optimistic patients were less likely to report psychological distress (anxiety and/or depression) and were more likely to report better HRQL such as less pain, less eating difficulty, and better social function (***Study I and II***). Moreover, we also found that before the COVID-19 pandemic, among patients with early and intermediate tumor stages (pathological tumor stage Tis-II), more optimistic patients were more likely to survive longer (***Study IV***). However, this significant association was not observed among patients with advanced tumor stage (pathological tumor stage III-IV) and/or when the follow-up was during the COVID-19 pandemic (***Study IV***). In addition, we also found that psychological distress and HRQL might be causally associated (***Study III***). However, we cannot determine the causal direction. In other words, it could be that psychological distress caused worse HRQL, but it could also be the other way around (***Study III***).

What is the implication of the thesis results?

The results of this thesis support the intuition that more optimistic people have a better prognosis after surgery for esophageal cancer. Measuring dispositional optimism may help us identify vulnerable patients with potentially worse prognosis, and thus provide timely and tailored interventions to help them. In addition, given that psychological distress and worse HRQL might cause each other, in order to avoid or break the vicious circle, it is important to prevent psychological distress and provide timely interventions to improve postoperative HRQL.

ABSTRACT

Dispositional optimism is a personality trait that represents generally favorable expectations about the future. The main aim of this thesis was to examine whether higher dispositional optimism was related to better subjectively reported outcomes and better objectively measured outcomes. We used a self-reported scale, Life Orientation Test-Revised (LOT-R), to measure dispositional optimism in this thesis, with a higher LOT-R sum score representing higher dispositional optimism. Data for the four studies included in this thesis were from a prospective, Swedish nationwide, and population-based cohort entitled "Oesophageal Surgery on Cancer patients - Adaptation and Recovery (OSCAR)".

Study I and II included 192 patients who underwent surgery for esophageal cancer during January 1, 2013 and February 28, 2018 in Sweden. Patients self-reported their dispositional optimism level at 1 year after surgery. At 1, 1.5, and 2 years after esophagectomy, patients repeatedly self-reported their psychological status and health related quality of life (HRQL). Latent growth curve model and linear mixed effects model were used in these two studies. We found that higher dispositional optimism predicted a lower risk of reporting clinically significant psychological distress (anxiety and/or depression) in **study I**. The odds ratio of reporting clinically significant psychological distress was 0.56 (95% confidence interval 0.40 to 0.79) for one unit increase in the LOT-R sum score. In **Study II,** we categorized patients into four subgroups with very high, moderately high, moderately low, and very low dispositional optimism based on the quartile of the LOT-R sum score. We found that patients with very high and moderately high dispositional optimism reported better HRQL in several aspects compared to patients with lower dispositional optimism.

Study III included 180 patients who underwent surgery for esophageal cancer during January 1, 2013 and February 28, 2018 in Sweden. Patients self-reported their psychological status and HRQL repeatedly at 1, 1.5, and 2 years after esophagectomy. We used fixed effects regression model with adjustment for all time-invariant covariates and observed time-varying confounders, and found that psychological distress was associated with worse HRQL in several aspects.

Study IV included 335 patients who underwent surgery for esophageal cancer between January 1, 2013 and December 31, 2019 in Sweden. Patients were followed up until the date of death or until December 31, 2020, whichever occurred first. Cox proportional hazards regression was used. We found that among patients with early and intermediate pathological tumor stages (Tis-II) and with follow-up period before the COVID-19 pandemic, the adjusted hazard ratio for all-cause mortality was 0.89 (95% confidence interval 0.81 to 0.98) for one unit increase in the LOT-R sum score. However, this association was not statistically significant for patients with tumor pathologically staged III-IV (hazard ratio 0.99, 95% confidence interval 0.92 to 1.07) and/or during the COVID-19 pandemic (hazard ratio 1.08, 95% confidence interval 0.94 to 1.25).

In conclusion, before the COVID-19 pandemic, higher dispositional optimism was associated with less self-reported clinically significant psychological distress and better HRQL; moreover, among patients with early and intermediate pathological tumor stages, higher dispositional optimism also predicted better overall survival. Measuring dispositional optimism may help identify vulnerable patients with potentially worse prognosis after surgery for esophageal cancer, thus contributing to the development of more tailored and timely interventions to improve postoperative survivorship.

LIST OF SCIENTIFIC PAPERS

I. **Liu Y**, Pettersson E, Schandl A, Markar S, Johar A, Lagergren P.
Psychological distress after esophageal cancer surgery and the predictive effect of dispositional optimism: a nationwide population-based longitudinal study.
Supportive Care in Cancer. 2021. Epub ahead of print.

II. **Liu Y**, Pettersson E, Schandl A, Markar S, Johar A, Lagergren P.
Higher dispositional optimism predicts better health-related quality of life after esophageal cancer surgery: a nationwide population-based longitudinal study.
Annals of Surgical Oncology. 2021 Nov; 28(12): 7196-7205.

III. **Liu Y**, Schandl A, Markar S, Johar A, Lagergren P.
Psychological distress and health-related quality of life up to 2 years after oesophageal cancer surgery: nationwide population-based study.
BJS Open. 2021 Jan 8; 5(1): zraa038.

IV. **Liu Y**, Pettersson E, Schandl A, Markar S, Johar A, Lagergren P.
Dispositional optimism and all-cause mortality after esophageal cancer surgery: a nationwide population-based cohort study
Manuscript submitted

CONTENTS

LIST OF ABBREVIATIONS

CI	Confidence interval
COVID-19	Coronavirus disease 2019
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life-Core 30
EORTC QLQ-OG25	European Organization for Research and Treatment of Cancer Quality of Life-Esophago-Gastric cancer module 25
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
HRQL	Health Related Quality of Life
LOT	Life Orientation Test
LOT-R	Life Orientation Test-Revised
OSCAR	Oesophageal Surgery on Cancer patients - Adaptation and Recovery
TNM	Tumor-Node-Metastasis

1 INTRODUCTION

Esophageal cancer is an aggressive disease with a poor prognosis due to its late-onset symptoms. Surgery (esophagectomy) is the mainstay of curatively intended treatment, but the 5-year survival rate after surgery for esophageal cancer is still less than 50%. Moreover, getting a cancer diagnosis and undergoing esophagectomy are traumatic stressors to patients, which entail high prevalence of psychological distress and substantially impaired health related quality of life (HRQL). Patients' sociodemographic and clinical characteristics cannot fully explain the variations in the prognosis after esophageal cancer surgery. Whether psychological factors such as personality traits could explain the rest variations remains unknown. Dispositional optimism is a personality trait, which represents generally favorable expectations for the future. Previous studies have found that it is associated with both subjective wellbeing and objective physical health. However, whether dispositional optimism could predict prognosis after esophageal cancer surgery needs to be further explored.

This thesis aimed to investigate the potential roles of psychological factors especially dispositional optimism on the survivorship after surgery for esophageal cancer.

2 LITERATURE REVIEW

2.1 ESOPHAGEAL CANCER

2.1.1 Overview

Esophageal cancer is a malignant neoplasm with an overall 5-year survival rate of less than 20%,[1,2] The poor prognosis is partly due to the late presentation of symptoms. Clinical symptoms of esophageal cancer include dysphagia, odynophagia, involuntary and progressive weight loss, chest pain, and fatigue, which are sometimes accompanied by hoarseness, cough, vomiting, and melaena.[3,4] Owing to the muscular and expansible nature of the esophagus, early-stage cancers are rarely symptomatic. Patients usually present with symptoms when the cancer has progressed to a relatively advanced stage,[3,4] which implies a poor prognosis.

Esophageal cancer can be categorized into two main histological subtypes: esophageal squamous cell carcinoma and esophageal adenocarcinoma. Although the prognoses for these two subtypes of esophageal cancer are similar, their epidemiological and pathophysiological characteristics are divergent. In 2012, esophageal squamous cell carcinoma accounted for around 87% of the esophageal cancer cases worldwide, while esophageal adenocarcinoma accounted for around 12% of the cases.[5] In addition, most cases of esophageal squamous cell carcinoma occur in South-Eastern and Central Asia, Eastern Africa, and Southern America, while esophageal adenocarcinoma is mainly prevalent in Northern America, Northern and Western Europe, and Oceania.[5] This discrepancy in geographical distribution is partly related to different risk factors for these two subtypes of esophageal cancer. For esophageal squamous cell carcinoma, risk factors include tobacco smoking, alcohol overconsumption, low socioeconomic status, thermal injury, micronutrient deficiencies, high intake of red meat, low intake of vegetables and fruit, and genetic factors.[3,4,6-11] Some studies have found that human papillomavirus infection might also play a role in the development of esophageal squamous cell carcinoma.[12] For esophageal adenocarcinoma, the risk factors include chronic gastro-esophageal reflux, Barrett's esophagus, central obesity, tobacco smoking, male sex, high intake of red meat, low intake of vegetables and fruit, and genetic factors.[3,4,13-18] Esophageal squamous cell carcinoma and adenocarcinoma also differ in tumor location, which is partly because of the anatomical and histological features of the esophagus as well as the different risk factors for these two subtypes of cancer. In brief, esophageal squamous cell carcinoma occurs more commonly in the upper and middle thirds of the esophagus, while esophageal adenocarcinoma is more common to be found in the distal esophagus.[4]

The health burden from esophageal cancer is heavy. Esophageal cancer ranks as the 7th most commonly diagnosed cancer worldwide, and is the 6th leading cancer-specific cause of death globally.[19] Owing to the improvement of living standard and changes in the tobacco smoking, the global incidence rate for esophageal squamous cell carcinoma has decreased substantially in recent years, especially among men.[20,21] However, the incidence rate for adenocarcinoma in western countries has increased, possibly due to the increasing occurrences of reflux

disease, Barrett's esophagus, and obesity, which makes adenocarcinoma become the dominant subtype of esophageal cancer in western populations.[21,22]

2.1.2 Treatment

Options of treatment for esophageal cancer include endoscopic management, esophagectomy with or without neoadjuvant chemoradiotherapy or chemotherapy, definitive chemoradiation, and palliative treatment.[4] The choice of treatment depends on the characteristics of both the patient (e.g., age, comorbidity, and nutritional status) and the tumor, mainly the tumor-node-metastasis (TNM) stage.[4] T represents the size of the primary tumor and the depth of the invasion. N describes invaded regional lymph nodes. M stands for the occurrence of distant metastasis outside the field of traditional resection.[4] The TNM classification is based on the guideline from the American Joint Council on Cancer (8th version).[23] Esophagus has four layers, which from inner to outer are: mucosa, submucosa, muscularis propria, and adventitia. Esophageal neoplasm grows from the inner surface to the outside. T1a means that tumor invades mucosa (the first layer) while T1b means that tumor invades submucosa (the second layer).[23] T2 indicates that tumor invades muscularis propria (the third layer),[23] and T3 means that tumor invades adventitia (the fourth layer).[23] T4 suggests that tumor invades adjacent structures.[23] N0 refers to no invaded regional lymph node, while N1, N2, and N3 represent that 1-2, 3-6, and ≥7 regional lymph nodes have been involved, respectively.[23] M0 indicates no distant metastasis while M1 suggests at least one distant metastasis.[23] For esophageal cancer with very early stage such as T1aN0M0, endoscopic management like endoscopic mucosa resection or endoscopic submucosal dissection could be performed.[4] In addition, for patients with tumor staged T1bN0M0 or who are unsuitable for surgery due to poor general health status, endoscopic submucosal dissection could also be attempted.[4] For tumor staged T1b or T2 with N0M0, esophagectomy alone could be considered.[3,4] However, for locally advanced tumor (T3-4 or N1-3, M0), esophagectomy together with chemoradiotherapy or chemotherapy are required.[3,4] Definitive chemoradiation is mainly recommended for esophageal squamous cell carcinoma, but it could also be considered for patients with esophageal adenocarcinoma who are ineligible for surgery.[3,4] Palliative treatment is mainly performed for patients with unresectable tumor at diagnosis or with cancer recurrence.[3,4]

Surgery (esophagectomy) with or without neoadjuvant therapy is the primarily curative way to treat esophageal cancer. Only around 25% of the patients with esophageal cancer are eligible for surgical resection.[3,4] The operation is extensive and followed by a high 30-day postoperative mortality rate, a high incidence of postoperative complications, and severely compromised health related quality of life (HRQL).[1,24-27] Moreover, the 5-year postoperative survival rate is still less than 50%.[1,24-27] There are three main surgical approaches: open esophagectomy (transthoracic or transhiatal), hybrid minimally invasive esophagectomy (laparotomy plus thoracoscopy or laparoscopy plus thoracotomy), and total minimally invasive esophagectomy (laparoscopy and/or thoracoscopy).[3,4] The choice of the surgical approach largely depends on the hospital tradition or the preference of surgeons.[28] One meta-

analysis has demonstrated that long-term survival after minimally invasive esophagectomy is comparable with or may even be better than the survival after open esophagectomy.[29] Randomized controlled trials have also found that compared with open esophageal resection, minimally invasive esophagectomy has comparable 3-year survival, decreased incidence of pulmonary complications, shorter hospital stay, and better short-term HRQL.[30-33] Moreover, a meta-analysis has shown that compared with patients receiving open esophagectomy, patients receiving minimally invasive esophagectomy report better physical function and global quality of life as well as less fatigue and pain until 3 months after surgery, but the difference does not remain at 6 and 12 months postoperatively.[34]

2.2 CANCER SURVIVORSHIP

Cancer survivors refer to patients diagnosed with cancer. Their family members, friends, and caregivers are cancer co-survivors.[35,36] The experience of cancer survivors and co-survivors from cancer diagnosis onwards is cancer survivorship,[35-37] which is defined as "living with, through, and beyond cancer".[36] Accordingly, cancer survivorship contains three phases[36,37]: (1) Acute survivorship (living with cancer): it is a treatment phase starting from cancer diagnosis and lasting until the completion of the initial treatment.[36,37] (2) Extended survivorship (living through cancer): it is a watchful waiting phase after treatment, during which patients visit their oncologists regularly and watch out for cancer recurrence.[36,37] (3) Permanent survivorship (living beyond cancer): it is a "cure" phase, where the risk of cancer recurrence is low and patients gradually return to the new "normal" life.[36,37] Improving HRQL and psychological well-being are important goals of cancer survivorship.[35,37]

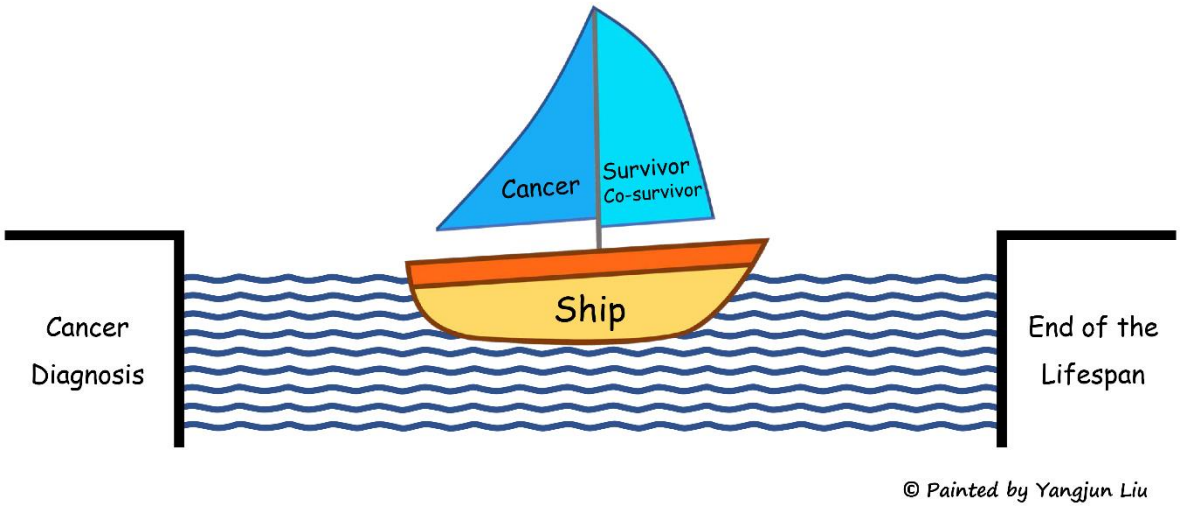

Figure 1. "Cancer Survivor Ship": a journey from cancer diagnosis to the end of the lifespan.

2.2.1 Health Related Quality of Life (HRQL)

2.2.1.1 Overview

The meaning of quality of life varies among different populations and different circumstances, and there is no universal definition regarding quality of life.[38] In medical field, HRQL is frequently used.[38] It is universally agreed that HRQL is a multidimensional construct describing subjective health status, which usually includes four dimensions: physical function, emotional function, social function, and symptoms.[38,39]

When measuring HRQL, "ask the patient" is essential.[38] Healthcare professionals and patients' relatives usually provide biased evaluations of patients' general quality of life and symptom experiences, so the core to assess HRQL is asking patients to report it by themselves.[38] Thus, HRQL is a form of patient-reported outcomes reflecting patients' opinions regarding the influences of disease and/or treatment on their daily lives.[38,39]

A sizable body of instruments have been developed to measure HRQL. These measures could be classified into three groups: generic instruments, disease-specific instruments, and aspect-specific instruments.[38,39] Generic instruments can be used irrespective of the respondent's health condition. *Medical Outcome Study 36-Item Short Form (SF-36)* and *EuroQoL (EQ-5D)* are representatives of generic instruments.[38] Disease-specific instruments focus more on the issues of a particular disease.[38] For example, *European Organization for Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30)* and *EORTC disease- or treatment-specific modules* are cancer-specific questionnaires.[38] Aspect-specific instruments evaluate specific aspects of HRQL.[38] For instance, the *Hospital Anxiety and Depression Scale (HADS)* measures psychological health. In addition, except for these standardized questionnaires, HRQL can also be assessed using study-specific instruments or interviews.[40]

2.2.1.2 HRQL after Esophageal Cancer Surgery

Curatively intended surgery improves the chance of survival but entails substantially negative impacts on HRQL, especially within the first 12 months postoperatively.[1,2,26,40-46] One study has shown that a large proportion of patients experience early satiety, fatigue, depression, and fear of metastasis and death within 1 year after esophagectomy.[47] For long-term HRQL, poor physical function, severe breathlessness, diarrhea, and reflux are reported at 3 years after surgery,[41] even though most HRQL aspects have recovered to the preoperative level.[41,44] Moreover, compared with the age- and sex-adjusted reference population, patients report worse social and role functions, and more fatigue, nausea and vomiting, diarrhea, and appetite loss at 3 years after surgery.[48] Furthermore, according to one Swedish population-based study, there is no clinically relevant improvement in any measured aspects of HRQL between 5 and 10 years after esophageal cancer surgery, and compared with the reference population, 10-year survivors have worse HRQL in all 25 measured aspects of HRQL, especially in

global quality of life, social function, role function, eating difficulty, reflux, appetite loss, and diarrhea.[49]

Recovery of HRQL is not only related to patients' subjective satisfaction with their daily life, but also associated with objective survival rate.[50] It has been found that improvements in emotional function and physical function between pre-treatment and 6 months after treatment are related to better survival,[50,51] while increased fatigue and pain are associated with higher mortality.[51] In addition, HRQL at 6 months after surgery for esophageal cancer significantly predicts all-cause mortality.[52]

A large number of studies have investigated risk factors for poor HRQL.[25,34,46,53-55] Patients with esophageal squamous cell carcinoma, with tumor located in the middle or upper esophagus, and with advanced tumor stage (III-IV) are more likely to have worse HRQL.[53] With regards to surgical approach, patients undergoing minimally invasive operation tend to have better physical function and global quality of life as well as less fatigue and pain at 3 months postoperatively compared to patients with open esophagectomy.[34] Also, transhiatal esophagectomy is associated with better activity levels and fewer physical symptoms at 3 months post-surgery compared with transthoracic esophagectomy.[46] However, no differences persist in the longer term.[34,46,56] In addition, patients receiving a cervical anastomosis have better physical function, social function and global health status as well as less reflux-related symptoms like insomnia than patients receiving a intrathoracic anastomosis.[54] Compared to patients without major postoperative complications, patients with major postoperative complications report more dyspnea, fatigue, and eating restrictions.[25] Patients with comorbidity are prone to have compromised cognitive function, appetite loss, choking, and coughing than those with stable health status from 3 to 5 years post-surgery.[55] Additionally, eating difficulty is related to worse HRQL in several aspects up to 10 years after surgery.[57]

2.2.2 Anxiety and Depression

2.2.2.1 Overview

Diagnosed with a life-threatening esophageal cancer, undergoing an extensive esophagectomy, experiencing impaired HRQL, and facing a long convalescence are traumatic stressors for patients with esophageal cancer, which could trigger strong emotional responses. Anxiety and depression are two common emotional responses to stressors. Anxiety evoked by stressors is state anxiety, which manifests as being anxious, worried, irritable, fearful, and vigilant. Anxiety is an instinctively adaptive and protective response to danger, which helps to increase arousal level and promote defensive actions.[58] However, excessive anxiety is a pathologically maladaptive response that weakens our ability to cope with the changing environment and could cause autonomic dysfunction.[58] Depression caused by stressors is called exogenous depression, which manifests as anhedonia, neurovegetative symptoms (e.g., anorexia, insomnia, fatigue, and inattention), and somatic disturbances.[58] It

usually further results in behavior disorders, like retreat from social and physical activities, diminished self-esteem, being occupied by a strong feeling of helplessness and worthlessness, or even suicide.[58]

2.2.2.2 Anxiety and Depression after Esophageal Cancer Surgery

High prevalence of anxiety and depression disorders have been found both before and after esophageal cancer surgery. A longitudinal study assessing anxiety and depression by HADS has shown that 33% of patients have anxiety disorders before esophagectomy, 28% at 6 months and 37% at 12 months postoperatively.[59] In contrast to the stable trend of anxiety, prevalence of depression disorders increases over time, from 20% prior to surgery to 27% at 6 months and 32% at 12 months after surgery.[59] One study following up patients for a median of 45 months after esophageal cancer diagnosis has found that 36% and 24% of patients have probable anxiety and depression, respectively.[60] In addition, within 1 year after esophageal cancer surgery, 13.9% of patients have recorded psychiatric diagnosis or prescription in the British hospital and primary care databases.[61] Within 2 years after esophageal cancer surgery, 32.3% of patients without psychiatric histories are newly prescribed psychotropic drugs based on the data from the Swedish nationwide health registers.[62]

There are some risk factors for developing anxiety and depression disorders after esophageal cancer surgery. Younger age, female sex, living alone, lower education level, histology of squamous cell carcinoma, postoperative complications and symptoms, and poor physical function have been found to be related to the development of anxiety and/or depression disorders.[59,62-64] Also, anxiety and depression are associated with patients' illness perception, which is an individual explanation for or perception of their illness including the timeline of the disease (chronic/acute/cyclical), personal control, treatment control, consequences, causes, and illness coherene.[60] In addition, patients with negative coping strategies are more likely to develop anxiety and depression.[60]

2.3 DISPOSITIONAL OPTIMISM

2.3.1 Overview

Dispositional optimism is individuals' generalized expectancies for their future.[65] People with higher dispositional optimism usually believe good things are going to happen, while people who are less optimistic or pessimistic expect the opposite.[65]

Dispositional optimism is a personality trait that remains relatively stable without manipulation.[66-69] Genetic influence accounts for 25-36% variation in dispositional optimism, which partly determines its stability.[70,71] Other factors especially growth experience during childhood such as parents' socioeconomic status and maternal child-rearing attitudes are

predictors of dispositional optimism,[72,73] and the unchangeable nature of these factors in adulthood also partly explains the stability. However, it is also reported that dispositional optimism increases with the accumulation of individual's social resources.[74] In addition, dispositional optimism is modifiable via psychological interventions.[75]

Until now, there is no universal agreement regarding the dimensionality of dispositional optimism. Some researchers view optimism and pessimism as one bipolar dimension, while some argue that optimism and pessimism are two separate dimensions. Practically speaking, everyone ranks in somewhere between extremely optimistic and extremely pessimistic, and there is no clear cut-off that separates people into either group.[65] Thus, the assumption of one bipolar dimension may have a stronger theory base. However, when using *Life Orientation Test (LOT)* or *Life Orientation Test-Revised (LOT-R)* to measure dispositional optimism, it has been widely reported that two dimensions existed.[76-81] The positively worded items and the negatively worded items measure different dimensions, namely, optimism and pessimism, respectively.[76-81] In addition, some studies reported dissimilar predictive effects of optimism and pessimism,[78,82] and being less pessimistic did not equal to being optimistic.[78,82] On the other hand, some researchers argued that the two observed dimensions are artificial due to the method factor related to wording.[83-89] Given that there is no consensus, researchers are encouraged to examine the structure when using LOT or LOT-R.[90]

2.3.2 Predictive Effects of Dispositional Optimism

Dispositional optimism as a personality trait is an important factor in the response to stressors. Previous studies conducted in different contexts have shown that less optimistic people are more likely to develop psychological distress and suffer from worse HRQL.[91-105] However, the associated HRQL aspects were not consistent across studies.[96,99-105] In addition, higher dispositional optimism has been found to be related to better physical health including better overall survival and lower cause-specific (e.g., cardiovascular disease, cancer, and infection) mortality among general population, elderly population, and patients with some subtypes of cancer (e.g., recurrent or metastatic cancer treated with palliative radiation, head and neck cancer, and ovarian cancer).[106-118] However, such significant associations were not observed among patients with metastatic colorectal cancer and patients with non-small cell lung cancer.[119,120] Given the absence of previous studies among patients with esophageal cancer, it remains unclear whether these predictive effects of dispositional optimism exist in this population.

3 RESEARCH AIMS

The overarching aim of this thesis was to investigate the potential roles of psychological factors especially dispositional optimism on survivorship after surgery for esophageal cancer.

The specific aims of the included four studies were to investigate:

- The potential association between dispositional optimism and postoperative psychological distress after surgery for esophageal cancer (Study I);
- The potential effect of dispositional optimism on HRQL after surgery for esophageal cancer (Study II);
- The associaiton between psychological distress and HRQL after surgery for esophageal cancer (Study III);
- The influence of dispositional optimism on survival after surgery for esophageal cancer (Study IV).

4 MATERIALS AND METHODS

4.1 OVERVIEW

Table 1. The overview of materials and methods used in studies I-IV

	Study I	**Study II**	**Study III**	**Study IV**
Design	Longitudinal study			Cohort study
Data source	A Swedish nationwide cohort entitled "Oesophageal Surgery on Cancer Patients - Adaptation and Recovery (OSCAR)". It contains patient-reported outcomes and data from medical charts and Swedish national registers.			
Population	Swedish residents undergoing surgery for esophageal cancer			
Included surgery period	Jan 1, 2013 to Feb 28, 2018			Jan 1, 2013 to Dec 31, 2019
Follow-up time points/ period	1, 1.5, and 2 years after esophageal cancer surgery			Jan 1, 2014 to Dec 31, 2020
Exposure	Dispositional optimism	Dispositional optimism	Psychological distress	Dispositional optimism
Outcome	Psychological distress	HRQL	HRQL	All-cause mortality
Covariates	Age, sex, cohabitation status, education level, histology, comorbidity, neoadjuvant therapy, tumor stage, and postoperative complication	Age, sex, cohabitation status, education level, histology, comorbidity, tumor stage, postoperative complication, postoperative weight change, and time	Postoperative weight change and assessment time points	Age, sex, cohabitation status, education level, pathological tumor stage, and the COVID-19 pandemic
Main statistical method	Latent growth curve model	Linear mixed effects model	Fixed effects regression model	Cox proportional hazards regression

HRQL: Health Related Quality of Life. Jan: January. Feb: February. Dec: December.

4.2 DATA SOURCES

Data for the four studies included in this thesis were from a prospective, Swedish nationwide, and population-based cohort study entitled "Oesophageal Surgery on Cancer patients - Adaptation and Recovery (OSCAR)".

4.2.1 The OSCAR Study

The OSCAR study includes Swedish-speaking patients without cognitive impairment who underwent curatively intended surgery for esophageal cancer between January 1, 2013 and June 30, 2020 in Sweden and had survived for 1 year after surgery. Eligible patients were identified by contacting pathology departments at eight hospitals performing esophageal cancer surgery in Sweden.[121] At around 1 year after surgery, each eligible patient's vital status was checked based on the information from the Swedish Total Population Register, which contains fundamental information such as births, domestic and foreign relocations, and death about the Swedish residents.[122] Later, the project coordinator sent the description of the OSCAR study together with an invitation letter to survivors by post followed by a telephone call.[121] If patients had agreed to participate in the OSCAR study, a research nurse visited patients and conducted a face-to-face semi-structured interview containing both predetermined questions and open-ended questions. For the predetermined self-reported questionnaires, patients completed them on a touch screen tablet computer. The whole interview followed a predefined guidebook. In addition, patients were/will be followed up further at 1.5, 2, 2.5, 3, 4, 5, 8, and 12 years after surgery. Studies included in this thesis used data from three follow-up time points, 1, 1.5, and 2 years after surgery, and the 1.5- and 2-year follow-up data were collected via mailing paper questionnaires.

Sociodemographic data such as age, sex, cohabitation status, and education level were retrieved from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies.[123] Clinical data were extracted from medical records, which were obtained from the hospitals where patients underwent surgery and oncological treatments. All medical records were reviewed by two researchers following a predefined protocol.[121] The clinical variables used in this thesis include weight, neoadjuvant therapy, histology, pathological tumor stage, resection margin status, surgical approach, postoperative complication, and comorbidity. Information on comorbidity was also collected from the Swedish Patient Register[124] and the Swedish Cancer Register[125]. Linkages of individuals' data between registers, medical records, and follow-up questionnaires were obtained through the unique personal identity number assigned to each Swedish resident at birth or immigration.

4.2.2 Questionnaires

4.2.2.1 Life Orientation Test-Revised (LOT-R)

LOT-R is a commonly used scale to measure dispositional optimism.[66] This scale consists of three positively worded items, three negatively worded items, and four filler items.[66] Respondents are asked to indicate the extent of their agreement on each five-point Likert item, ranging from 0 "Strongly disagree" to 4 "Strongly agree".[66] There is an ongoing debate about the dimensionality of the LOT-R scale. It is originally treated as a unidimensional scale,[66] where the negatively worded items are reversed prior to scoring and all items are loaded on one general factor representing dispositional optimism.[66] However, some studies have found that a two-factor model positing that positively worded items measure optimism while negatively worded items measure pessimism fit the data better.[78-81] Nevertheless, given that this scale has both positively and negatively worded items, some researchers argued that the identified two factors might be due to method effect associated with wording.[87-89]

The Swedish version of LOT-R scale consists of six items where the four filler items have been removed.[126] Given that no psychometric studies for LOT-R scale have been conducted among patients with esophageal cancer, in study I included in this thesis, we conducted a series of confirmatory factor analyses to examine the dimensionality of LOT-R scale based on the data from the OSCAR study. The model assuming one general factor on which all six items load and one method factor which includes the three negatively worded items showed the best fit. However, in this best-fit model, the loading of the first negatively worded item was negative even though its score has been reversed to account for the negative wording. Moreover, the distribution of patients' responses to this item was bimodal. These suggest that a substantial proportion of patients may have misread the wording direction. Thus, we removed the first negatively worded item and adopted the model assuming one factor (i.e., dispositional optimism) with correlated errors between the rest two negatively worded items. The McDonald's omega estimating internal reliability was 0.49 with 95% bootstrapped confidence interval (CI) 0.31-0.62.

4.2.2.2 Hospital Anxiety and Depression Scale (HADS)

HADS is a well-validated and widely used instrument.[127,128] It consists of two subscales measuring anxiety and depression respectively.[127,128] Each subscale contains seven items and each item is scored on a four-point Likert scale ranging from 0 to 3, with a higher score representing a heavier burden of anxiety or depression.[127,128] In most studies, for both subscales, a score of 7 or less is considered as non-case; a score of 8-10 is treated as borderline case and a score of 11 or more is regarded as definite case.[127] Given that anxiety and depression frequently coexist,[129] in this thesis, we regarded patients scoring 8 or more on either subscale as having clinically significant psychological distress. In addition, based on the OSCAR data, the internal reliability estimated by Cronbach's alpha for the anxiety and

depression subscales were 0.83 and 0.74, respectively. The time frame covered by the HADS is the past week.[127,128]

4.2.2.3 EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer Quality of Life-Core 30 (EORTC QLQ-C30) is a well-validated and widely used questionnaire measuring HRQL among patients with cancer in general.[130] This multidimensional questionnaire contains 30 items, which comprise five functional subscales (physical, role, emotional, social, and cognitive), three symptom subscales (fatigue, pain, and nausea/vomiting), six single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulty), and one global health status/quality of life subscale.[130] All items are scored on a four-point Likert scale ranging from 1 "Not at all" to 4 "Very much", except for the global health status/quality of life subscale, which ranges from 1 "Very poor" to 7 "Excellent".[130] The time frame for EORTC QLQ-C30 is the past week.[130]

According to the EORTC Scoring Manual, the raw score for each subscale is the mean of its component items.[131] All raw scores are transformed to a linear scale ranging from 0 to 100.[131] A higher score represents better function and global health status/quality of life or a heavier symptom burden.[131] Based on the transformed scores, a single summary score for the EORTC QLQ-C30 can be calculated by averaging all subscales and single items except for the global health status/quality of life subscale and the single item regarding financial difficulty.[132]

4.2.2.4 EORTC QLQ-OG25

The European Organization for Research and Treatment of Cancer Quality of Life-Esophago-Gastric cancer module 25 (EORTC QLQ-OG25) is a validated 25-item questionnaire measuring HRQL among patients with esophageal or gastric cancer.[133] This questionnaire includes six symptom subscales (dysphasia, eating difficulty, reflux, odynophagia, pain and discomfort, and anxiety) and ten single items (eating in front of others, dry mouth, trouble with taste, trouble with swallowing saliva, choked when swallowing, trouble with coughing, trouble with talking, worry about weight loss, self-doubt regarding body image, and hair loss).[133] Similar to the EORTC QLQ-C30, all items in the EORTC QLQ-OG25 are graded on a four-point Likert scale ranging from 1 "Not at all" to 4 "Very much",[133] and the raw score for each subscale is the mean of its component items.[131] All raw scores are transformed to a linear scale of 0-100.[131] The time frame covered by the EORTC QLQ-OG25 is the past week.[133]

4.3 STUDY DESIGN

Study I, II, and III are nationwide population-based longitudinal studies, which included patients who underwent esophageal cancer surgery between January 1, 2013 and February 28, 2018 in Sweden. Patients were followed up repeatedly at 1, 1.5, and 2 years after surgery. The processes of patient inclusion in study I, II, and III are presented in Figure 2.

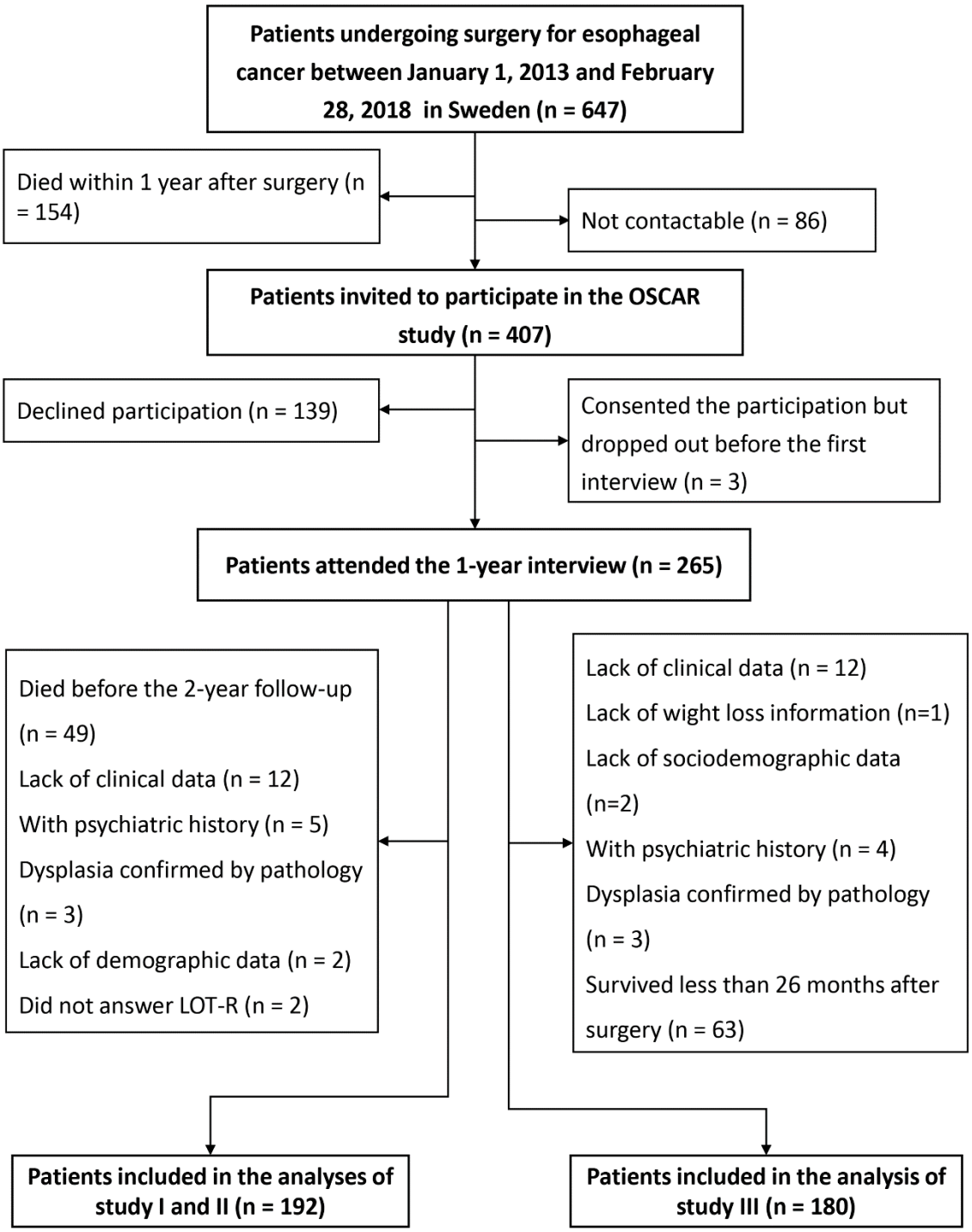

Figure 2. Flowchart of patient inclusion process in Study I, II, and III.

Study IV is a nationwide population-based prospective cohort study, which included patients who underwent esophageal cancer surgery between January 1, 2013 and December 31, 2019 in Sweden. Patients were followed up until the date of death or until December 31, 2020, whichever occurred first. Figure 3 shows the process of patient inclusion in study IV.

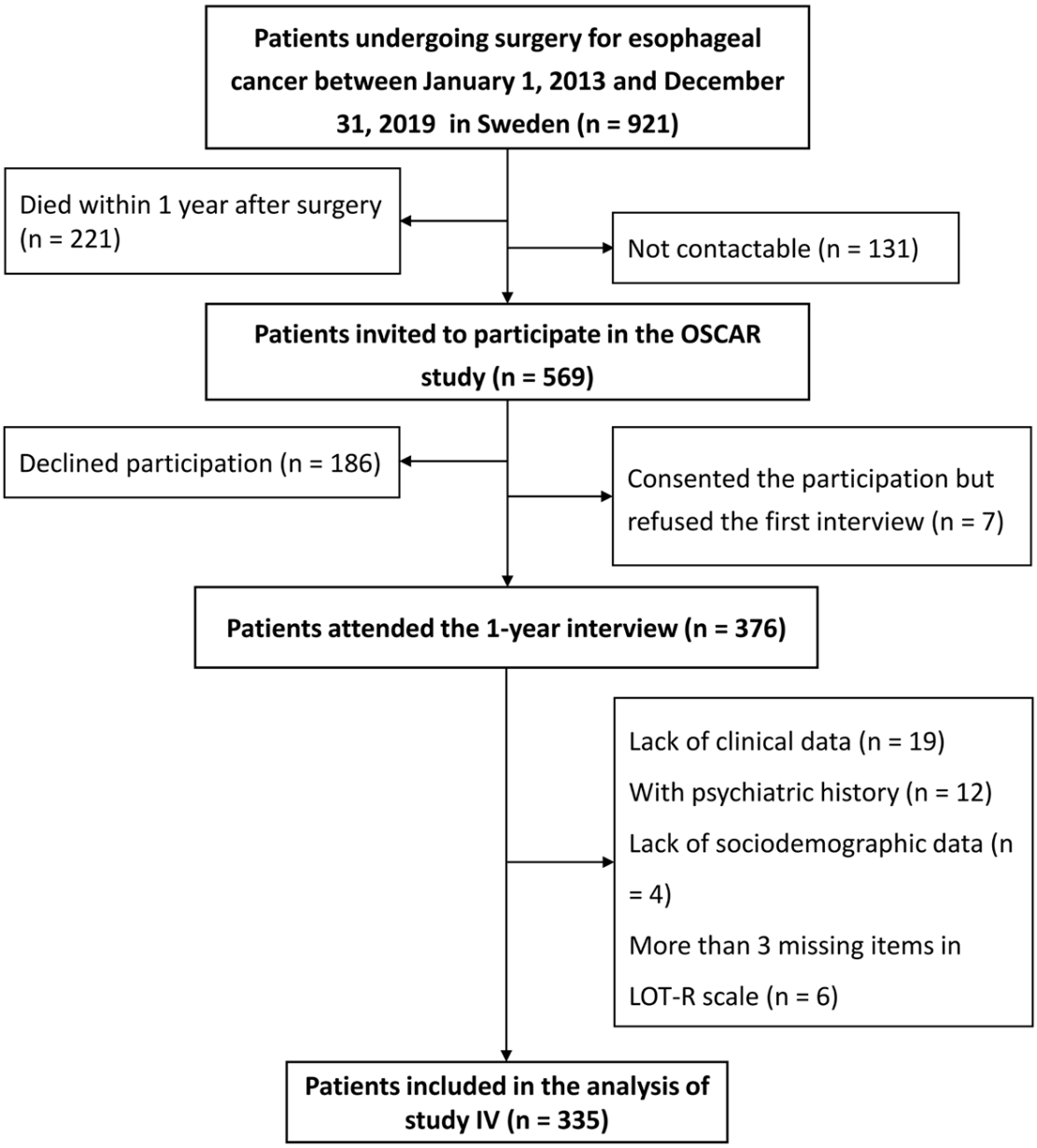

Figure 3. Flowchart of patient inclusion process in Study IV.

4.3.1 Study I

4.3.1.1 Study aims and cohort

This longitudinal study investigated the trajectory of clinically significant psychological distress from 1 to 2 years after surgery for esophageal cancer and examined whether dispositional optimism predicted this trajectory. Patients who underwent esophageal cancer surgery between January 1, 2013 and February 28, 2018 in Sweden and were alive at 1 year postoperatively were eligible to be included. Patients lacking valid contact information, died within 2 years after surgery, with psychiatric history, diagnosed as dysplasia by pathological examination, and with missing data in the independent variable (LOT-R scale) or covariates were excluded.

4.3.1.2 Exposure and outcome

Dispositional optimism was assessed at 1 year after surgery using the LOT-R scale. Psychological distress was measured at 1, 1.5, and 2 years after esophageal cancer surgery using the HADS. Patients scoring 8 or more on either the anxiety or the depression subscale were regarded as having clinically significant psychological distress.

4.3.1.3 Statistical analysis

The LOT-R sum score between patients with different characteristics were compared using Student's t-test or ANOVA. The outcome, clinically significant psychological distress, was treated as a binary variable. Latent growth curve model with maximum likelihood estimator and logit link was used to investigate the trajectory of postoperative psychological distress and to examine the predictive effect of dispositional optimism. Random intercept model with linear slope was chosen because it fit the data best. When examining the predictive effect of dispositional optimism. Three nested models with adjustment for covariates were used. The first model was a crude model. The second model adjusted for previously identified confounders including age, sex, cohabitation status, and education level. The third model further adjusted for potential but unidentified confounders including comorbidity, neoadjuvant therapy, tumor stage, histology, and postoperative complications. The second and the third model were compared using the likelihood ratio test. In the main analysis, dispositional optimism was represented by the LOT-R sum score, and in the sensitivity analysis, it was represented by a latent (i.e., error free) factor.

4.3.2 Study II

4.3.2.1 Study aims and cohort

This longitudinal study examined whether higher dispositional optimism predicted better HRQL after surgery for esophageal cancer. Patients who underwent esophageal cancer

surgery between January 1, 2013 and February 28, 2018 in Sweden and were alive at 1 year postoperatively were eligible to be included. Patients who were uncontactable, died before the 2-year follow-up, had histories of psychiatric disorders, with dysplasia diagnosed by pathological examination, and with missing data in the independent variable (LOT-R sum score) or covariates were excluded.

4.3.2.2 Exposure and outcome

The exposure was dispositional optimism, which was measured at 1 year after surgery using the LOT-R scale. A higher sum score of LOT-R represents higher dispositional optimism. The outcome was HRQL, which was measured repeatedly at 1, 1.5, and 2 years after surgery using the EORTC QLQ-C30 and EORTC QLQ-OG25. All HRQL scores were transformed to a linear score of 0-100.

4.3.2.3 Statistical analysis

The sum score of LOT-R scale between patients with different sociodemographic and clinical characteristics were compared using Student's t-test or ANOVA. Based on the quartile of the LOT-R sum score, patients were classified into four subgroups with hierarchical dispositional optimism level: very low, moderately low, moderately high, and very high dispositional optimism. Linear mixed effects model was used to compare the mean score difference of HRQL between the four patient subgroups. Ten covariates were included in the model: assessment time point, age, sex, cohabitation status, education level, comorbidity, tumor stage, histology, postoperative complications, and weight change after surgery. In addition, an interaction between the exposure (dispositional optimism) and assessment time point was included in the model and was tested by the Wald test.

Given that the outcome (HRQL) contains several aspects, in order to minimize the type I error (false positive), the significance testing for the adjusted mean score difference of HRQL was performed only if the difference had clinical relevance. With regards to clinical relevance, the mean score difference for subscales and single items included in the EORTC QLQ-C30 has four grades:[134] (1) *trivial*: circumstances unlikely to have any clinical relevance or where there was no difference, (2) *small*: subtle but clinically relevant, (3) *medium*: likely to be clinically relevant but to a lesser extent, and (4) *large*: unequivocal clinical relevance.[134] In this study, we only considered medium and large differences as clinically relevant. For emotional function, summary score of the EORTC QLQ-C30, and all aspects in the EORTC QLQ-OG25, the adjusted mean score difference of 10 or more was regarded as clinically relevant.[135]

4.3.3 Study III

4.3.3.1 Study aims and cohort

This longitudinal study examined the potential association between clinically significant psychological distress and HRQL after surgery for esophageal cancer. Patients who underwent esophageal cancer surgery between January 1, 2013 and February 28, 2018 in Sweden and were alive at 1 year postoperatively were eligible to be included. Patients who were not contactable, survived less than 26 months after surgery, with histories of psychiatric disorders, with dysplasia diagnosed by pathological examination, and with missing data in the sociodemographic or clinical information were excluded.

4.3.3.2 Exposure and outcome

Psychological distress was measured by the HADS at 1, 1.5, and 2 years after surgery. It was treated as a binary variable where patients scoring 8 or more on either the anxiety or the depression subscale were regarded as having clinically significant psychological distress. HRQL was measured by the EORTC QLQ-C30 and EORTC QLQ-OG25 at 1, 1.5, and 2 years after surgery. Raw scores for all HRQL aspects were transformed to a linear scale ranging from 0 to 100.

4.3.3.3 Statistical analysis

For each follow-up time point, the characteristics of patients with and without clinically significant psychological distress were compared using Fisher's exact test. Fixed effects regression model and random effects model were used to examine the association between psychological distress and HRQL after surgery. Psychological distress was treated as a time-varying independent variable. Follow-up time point and postoperative weight change were adjusted in both the fixed and the random effects models as time-varying covariates. An interaction between psychological distress and time was also included and was examined by the Wald test. In addition, several observed time-invariant covariates were adjusted in the random effects model, which included age at surgery, sex, cohabitation status, education level, comorbidity, tumor stage, histology, and postoperative complications.

4.3.4 Study IV

4.3.4.1 Study aims and cohort

This prospective cohort study investigated whether higher dispositional optimism predicted lower all-cause mortality after surgery for esophageal cancer, and whether this association was modified by the pathological tumor stage and the COVID-19 pandemic. Patients who underwent esophageal cancer surgery between January 1, 2013 and December 31, 2019 in Sweden and had survived for 1 year after surgery were eligible. Patients who were

uncontactable, with psychiatric history, or with missing data were excluded. All patients were followed up until the date of death or until December 31, 2020, whichever occurred first.

4.3.4.2 Exposure and outcome

The exposure, dispositional optimism, was measured by the LOT-R scale at 1 year post-surgery, and a higher sum score of LOT-R represents higher dispositional optimism. The outcome was all-cause mortality after surgery, and this information was obtained from the Swedish Total Population Register.

4.3.4.3 Statistical analysis

Multivariable cox proportional hazards regression was used to analyze the association between disposition optimism and postoperative all-cause mortality, and we calculated the hazard ratio (HR) with 95% CI for the all-cause mortality with one unit increase in the LOT-R sum score. The time scale was time since surgery. Age at surgery, sex, education level, and cohabitation status were adjusted in the model because they are confirmed confounders. Seven factors including pathological tumor stage, comorbidity, neoadjuvant therapy, histology, postoperative complication, resection margin status, and surgical approach were considered as potential but unproven confounders. We selected these seven covariates based on stepwise forward selection. Only variables causing at least 10% change in the estimated HR for the exposure were included in the final multivariable cox model. However, none of them met this inclusion criteria.

To assess the potential effect modification by pathological tumor stage and the COVID-19 pandemic, we first added an interaction between the exposure (dispositional optimism) and each potential effect modifier (pathological tumor stage or the COVID-19 pandemic) separately into the multivariable cox regression model. Given that the results suggested that both factors could be effect modifiers, interactions among dispositional optimism, pathological tumor stage, and the COVID-19 pandemic were added. Furthermore, we conducted a subgroup analysis which limited the follow-up before the COVID-19 pandemic occurrence in Sweden (i.e., March 1, 2020), and examined the effect modification by pathological tumor stage via adding an interaction term between dispositional optimism and pathological tumor stage into the corresponding multivariable cox model.

In addition, in order to account for the potential reverse causality that imminent death might affect dispositional optimism, we conducted a sensitivity analysis excluding patients who survived less than 2 months after the measurement of dispositional optimism, and all cox models were re-estimated. The proportionality assumption was tested in all cox models using Schoenfeld residuals and this assumption was met for all cox models.

4.4 ETHICAL CONSIDERATIONS

Data for all studies included in this thesis were from the OSCAR study. The OSCAR study has been approved by the Regional Ethical Review Board in Stockholm, Sweden (diary number 2013/844–31/1) before its initiation. The description of the OSCAR study was sent to all eligible patients who were contactable, and signed written consent was collected before enrolling patient into the study. In addition, all patients were informed that they have rights and freedoms to withdraw their consents or drop out the study at any time without any risk of getting any punishment. After the enrollment, each participant was assigned a unique research number to make their personal identity number encrypted, so they cannot be identified by researchers and readers via scientific research work including study protocol, data analysis, and study results. Moreover, results generated from this thesis project were presented at an aggregate level rather than individual level, which further makes the individual identification impossible. In addition, data from Swedish registers were completely de-identified, and informed consent is not required for the register-based data according to the Swedish regulation. The original data of OSCAR study are stored in safe servers at Karolinska Institutet, and only the principal investigator and the data collection team have access to them. The electronic datasets are protected by passwords and only the data manager and researchers involved in data analysis have access to them.

5 RESULTS

Study I, II, III, and IV included 192, 192, 180, and 335 patients, respectively. Table 2 presents the characteristics of patients included in these four studies.

Table 2. Characteristics of patients included in studies I-IV

	Study I and II	Study III	Study IV
Age			
Mean ± Standard deviation	66.3 ± 8.5	66.4 ± 8.5	67.4 ± 8.2
Range	[38.2, 83.7]	[38.2, 83.7]	[34.9, 83.7]
Sex			
Female	28 (14.6)	26 (14.4)	31 (9.3)
Male	164 (85.4)	154 (85.6)	304 (90.8)
Cohabitation status			
Non-cohabitating	44 (22.9)	42 (23.3)	79 (23.6)
Cohabitating	148 (77.1)	138 (76.7)	256 (76.4)
Education level			
Nine-year compulsory school	48 (25.0)	44 (24.4)	82 (24.5)
Upper secondary school	85 (44.3)	81 (45.0)	159 (47.5)
Higher education	59 (30.7)	55 (30.6)	94 (28.1)
Neoadjuvant therapy			
Yes	158 (82.3)	33 (18.3)	265 (79.1)
No	34 (17.7)	147 (81.7)	70 (20.9)
Surgical approach			
Total minimally invasive esophagectomy	52 (27.1)	50 (27.8)	115 (34.3)
Hybrid minimally invasive esophagectomy	63 (32.8)	59 (32.8)	119 (35.5)
Open esophagectomy	77 (40.1)	71 (39.4)	101 (30.2)
Pathological tumor stage			
Tis–II	133 (69.3)	126 (70.0)	219 (65.4)
III–IV	59 (30.7)	54 (30.0)	116 (34.6)
Tumor histology			
Adenocarcinoma	163 (84.9)	151 (83.9)	279 (83.3)
Squamous cell carcinoma	29 (15.1)	29 (16.1)	51 (15.2)
Dysplasia	0 (0)	0 (0)	5 (1.5)
Postoperative complications (Clavien–Dindo grade)			
No complication	69 (35.9)	65 (36.1)	113 (33.7)
I–II	54 (28.1)	50 (27.8)	94 (28.1)
III–IV	69 (35.9)	65 (36.1)	128 (38.2)
Charlson comorbidity index			
0	94 (49.0)	87 (48.3)	142 (42.4)
1	60 (31.3)	55 (30.6)	112 (33.4)
≥2	38 (19.8)	38 (21.1)	81 (24.2)

Note. *All values are numbers (percentages %) unless otherwise stated.*

5.1 STUDY I

Study I included 192 patients. Of these, 164 (85.4%) patients were male, and 148 (77.1%) patients were married/cohabitating. The age at surgery ranged from 38.2 to 83.7 years with a mean value of 66.3 years and a standard deviation of 8.5 years. The observed LOT-R sum score ranged from 6 to 20 with a mean value of 15.2 and a standard deviation of 3.0. LOT-R sum scores were comparable between patients with different characteristics.

Among the included 192 patients, 170 patients filled in the 1.5-year follow-up questionnaires, and 156 patients filled in the 2-year follow-up questionnaires. At 1, 1.5, and 2 years after esophagectomy for cancer, 11.5% (22 out of 192), 18.8% (32 out of 170), and 25.0% (39 out of 156) patients reported clinically significant psychological distress, respectively (Figure 4).

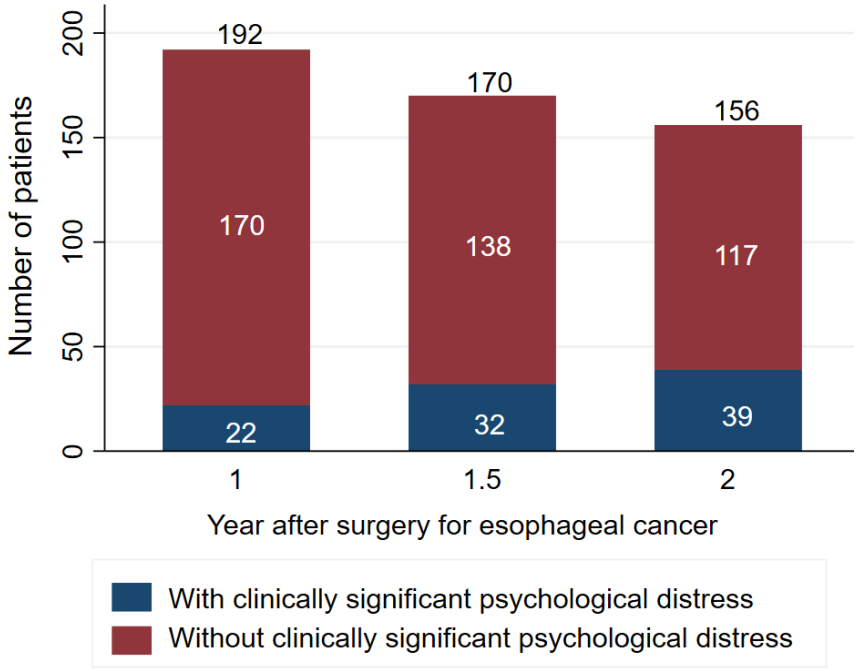

Figure 4. Number of patients with and without clinically significant psychological distress at 1, 1.5, and 2 years after surgery for esophageal cancer.

The association between dispositional optimism and postoperative psychological distress was not modified by the assessment time point, and higher dispositional optimism at 1 year post-surgery predicted a lower risk of reporting clinically significant psychological distress at 1, 1.5, and 2 years after surgery for esophageal cancer (Figure 5). The results generated from the three nested models with hierarchical adjustments were similar (Table 3). The second model with adjustment for sociodemographic covariates might be the best model based on prior knowledge and the likelihood ratio test. Odds ratio of reporting clinically significant psychological distress was 0.56 (95% CI 0.40 to 0.79) for one unit increase in the LOT-R sum score (Table 3).

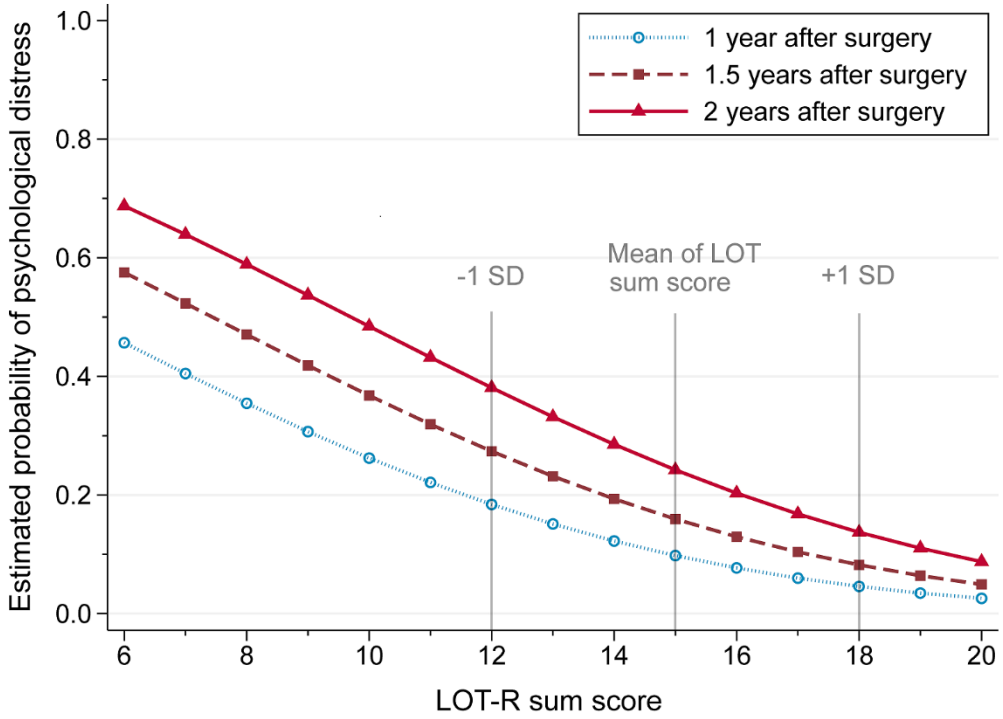

Figure 5. Estimated probability of reporting clinically significant psychological distress as a function of LOT-R sum score for three assessment time points after surgery for esophageal cancer.

Note. *LOT-R: Life Orientation Test-Revised.*

Table 3. Odds ratio of reporting clinically significant psychological distress for each unit increase in the LOT-R sum score among patients with esophageal cancer surgery

	Crude model	Model adjusted for previously identified confounders	Model adjusted for both identified confounders and potential but unidentified confounders
Odds ratio with 95% CI	0.56 (0.40, 0.80)	0.56 (0.40, 0.79)	0.55 (0.39, 0.78)

Note. *LOT-R: Life Orientation Test-Revised. CI: confidence interval. Previously identified confounders include age, sex, cohabitation status, and education level. Potential but unidentified confounders include comorbidity, neoadjuvant therapy, tumor stage, histology, and postoperative complications.*

5.2 STUDY II

Study II included 192 patients with surgery for esophageal cancer. Of these, 170 patients filled in the 1.5-year follow-up questionnaires for HRQL, and 156 patients filled in the 2-year follow-up questionnaires for HRQL. The observed range of LOT-R sum score was 6 to 20, with a mean value of 15.2 and a standard deviation of 3.0. LOT-R sum scores were comparable between patients with different characteristics. Based on the quartile of LOT-R sum score, the included 192 patients were divided into four subgroups (Table 4).

Table 4. LOT-R sum score for four patient subgroups with hierarchical dispositional optimism levels

	Dispositional optimism level			
	Very low (n = 48)	Moderately low (n = 51)	Moderately high (n = 45)	Very high (n = 48)
LOT-R sum score				
Range	[6, 13]	[14, 15]	[16, 17]	[18, 20]
Mean ± SD	11.3 ± 1.6	14.5 ± 0.5	16.5 ± 0.5	18.9 ± 0.9

Note. *LOT-R: Life Orientation Test-Revised. SD: standard deviation.*

Over the three assessment time points, patients with moderately low dispositional optimism did not report clinically different HRQL in any aspects compared to patients with very low dispositional optimism. However, time-invariant, clinically relevant, and statistically significant differences were found in global health status/quality of life (adjusted mean score difference 10, 95% CI 4 to 17) and diarrhea (adjusted mean score difference -9, 95% CI -18 to -1) between patients with moderately high dispositional optimism and patients with lower (moderately low and very low) dispositional optimism.

Patients with very high optimism reported clinically relevantly better HRQL in several aspects including global health status/quality of life, emotional function, social function, pain, dyspnea, diarrhea, anxiety, dry mouth, trouble with taste, worry about weight loss, self-doubt about body image, and eating difficulty compared to patients with lower (moderately high, moderately low, and very low) dispositional optimism (Figure 6). Only the adjusted mean score difference in eating difficulty varied over the three assessment time points, while the adjusted mean score differences in other aspects were not modified by time.

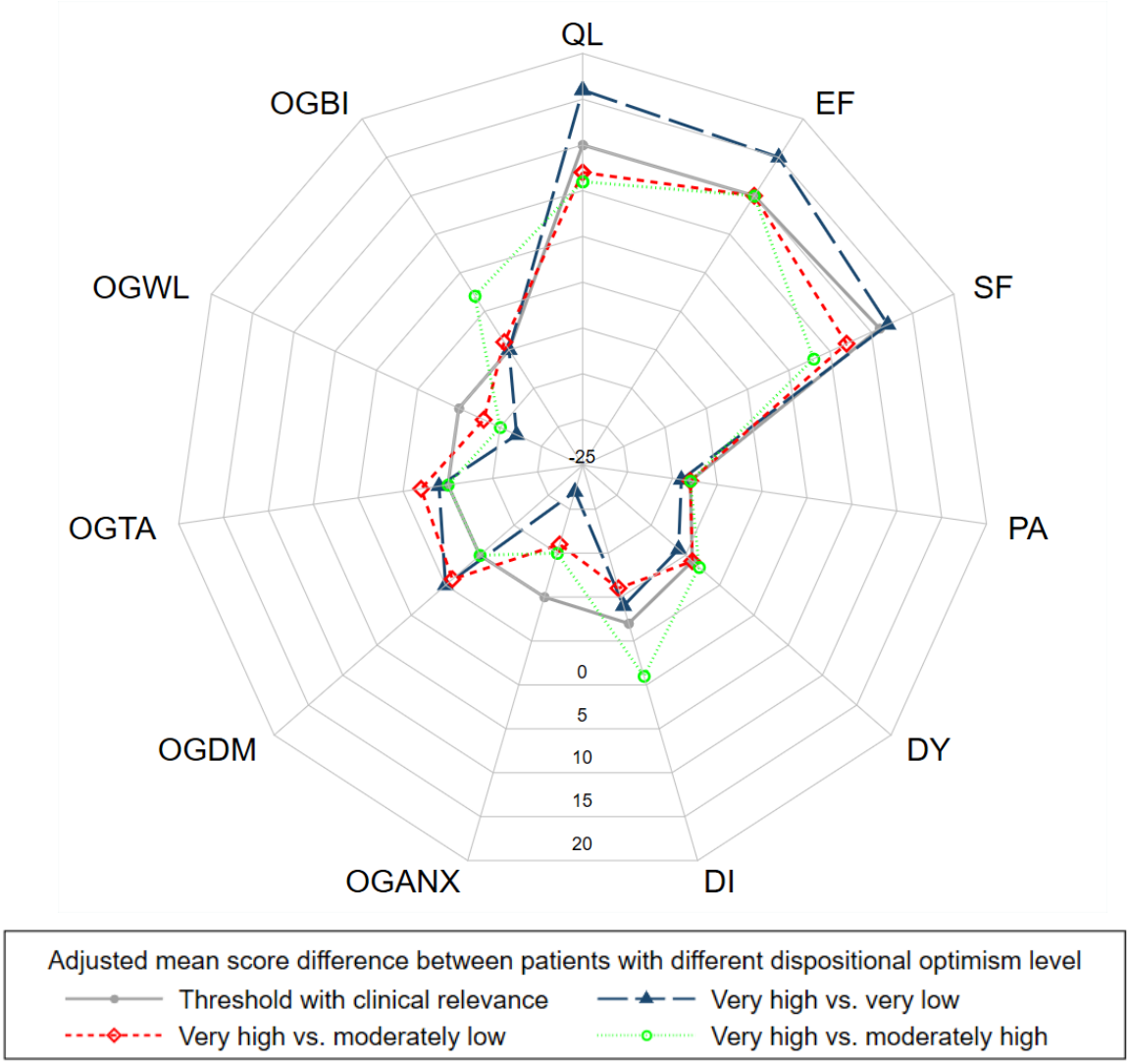

Figure 6. Health related quality of life aspects with time-invariant and clinically relevant mean score differences between patients with very high dispositional optimism and patients with lower (very low/moderately low/moderately high) dispositional optimism over the three assessment time points (1, 1.5, and 2 years after surgery for esophageal cancer).

Note. *QL: global health status/quality of life; EF: emotional function; SF: social function; PA: pain; DY: dyspnea; DI: diarrhea; OGANX: anxiety; OGDM: dry mouth; OGTA: trouble with taste; OGWL: worry about weight loss; OGBI: self-doubt regarding body image.*

5.3 STUDY III

Study III included 180 patients who underwent surgery for esophageal cancer and attended the interview at 1 year post-surgery. Of these, 154 (85.6%) patients were male, and 138 (76.7%) patients were married/cohabitating. The age at surgery ranged from 38.2 to 83.7 years with a mean value of 66.4 years and a standard deviation of 8.5 years. During the

follow-ups, 157 patients filled in the 1.5-year follow-up questionnaires, and 151 patients filled in the 2-year follow-up questionnaires. The proportions of patients who reported clinically significant psychological distress at 1, 1.5, and 2 years postoperatively were 10.6% (19 out of 180), 17.2% (27 out of 157), and 23.2% (35 out of 151), respectively. At each assessment time point, patients' sociodemographic and clinical characteristics were comparable between those reporting clinically significant psychological distress and those without clinically significant psychological distress.

Results from random effects models with adjustments for observed confounders showed that compared with patients having clinically significant psychological distress, patients without clinically significant psychological distress reported clinically relevant and statistically significant better HRQL in most aspects. However, after further adjusting for unmeasured time-invariant confounders via fixed effects regression model, mean score differences with clinical relevance and statistical significance were found in fewer aspects, which included emotional function, social function, cognitive function, global health status/quality of life, summary score of EORTC QLQ-C30, dyspnea, appetite loss, anxiety, eating difficulty, eating in front of others, trouble with taste, worry about weight loss, and self-doubt about body image. Among these aspects, the adjusted mean score differences in cognitive function, global health status/quality of life, EORTC QLQ-C30 summary score, appetite loss, trouble with taste, and self-doubt about body image varied over time (Table 5), while the adjusted mean score differences in other aspects were not modified by time (Figure 7).

Table 5. Health related quality of life aspects with time-varying adjusted mean score differences between patients with clinically significant psychological distress and patients without clinically significant psychological distress

	Adjusted mean score difference (95% CI)		
	1 year	1.5 years	2 years
Cognitive function	-7 (-14, -0)	-3 (-9, 3)	**-11 (-17, -6)**
Global health status/quality of life	-5 (-15, 4)	**-13 (-22, 5)**	**-20 (-28, -13)**
EORTC QLQ-C30 summary score	-8 (-13, -3)	-8 (-12, -4)	**-14 (-18, -10)**
Appetite loss	6 (-6, 18)	7 (-3, 17)	**26 (17, 35)**
Trouble with taste	-4 (-15, 7)	**13 (3, 23)**	5 (-4, 13)
Self-doubt about body image	**28 (17, 38)**	**23 (14, 32)**	**13 (5, 21)**

Note. *Values are adjusted mean score differences with 95% confidence intervals (CIs) in parentheses, rounded up to the nearest integer. Values in bold have clinical relevance and statistical significance. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30.*

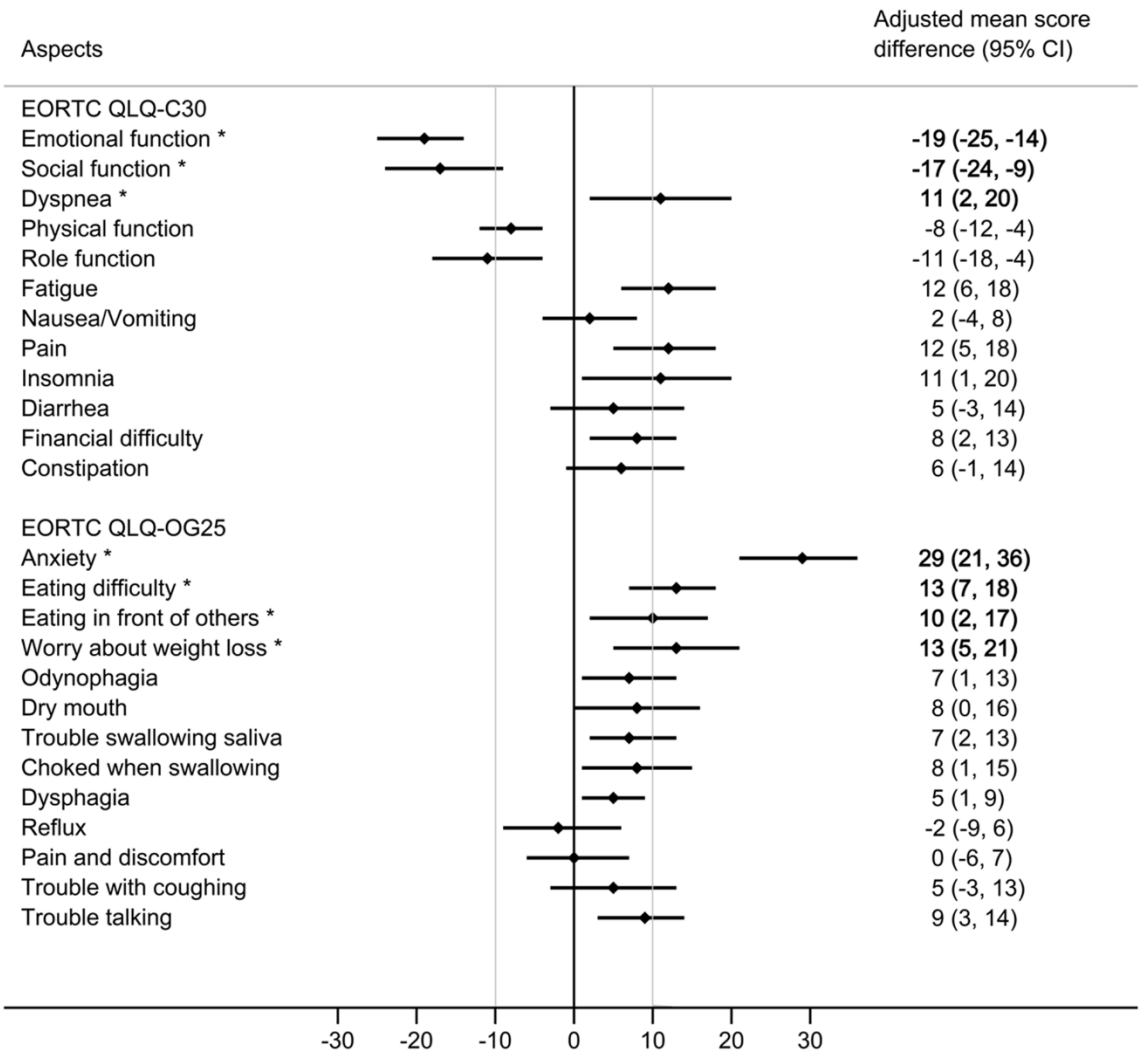

Figure 7. Health related quality of life aspects with time-invariant adjusted mean score difference between patients with clinically significant psychological distress and patients without clinically significant psychological distress.

Note. *Values are adjusted mean score differences with 95% confidence intervals (CIs) in parentheses, rounded up to the nearest integer. Values in bold and the aspects marked by * have clinical relevance and statistical significance. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30; EORTC QLQ-OG25, European Organization for Research and Treatment of Cancer Quality of Life-Esophago-Gastric cancer module 25.*

5.4 STUDY IV

Study IV included 335 patients. Of these, 304 (90.8%) patients were male, and 256 (76.4%) patients were married/cohabitating. The age at surgery ranged from 34.9 to 83.7 years with a mean value of 67.4 years and a standard deviation of 8.2 years. Most patients (89.6%) were enrolled in the study before the COVID-19 pandemic in Sweden, and 65.4% of patients had

esophageal tumor with pathological stage Tis-II. The observed LOT-R sum score ranged from 6 to 20 with a mean value of 15.2 and a standard deviation of 3.0. LOT-R sum scores were comparable between patients with different characteristics.

Both pathological tumor stage and the COVID-19 pandemic potentially modified the association between dispositional optimism and all-cause mortality. The adjusted HR of all-cause mortality was 0.89 (95% CI 0.81 to 0.98) for one unit increase in the LOT-R sum score among patients with early and intermediate tumor stage (Tis-II) and with follow-up period before the COVID-19 pandemic (Figure 8). However, this association was not statistically significant for patients with advanced tumor stage (III-IV) and/or during the COVID-19 pandemic (Figure 8). The subgroup analysis limiting the follow-up before the COVID-19 pandemic generated similar results as the analysis using the whole cohort, and higher dispositional optimism predicted lower all-cause mortality in patients with tumor staged Tis-II (HR 0.89, 95% CI 0.81 to 0.98) but not in patients with tumor staged III-IV (HR 0.99, 95% CI 0.92 to 1.07). The sensitivity analysis excluding patients who died within 2 months after dispositional optimism measurement generated almost unchanged results as the main analysis.

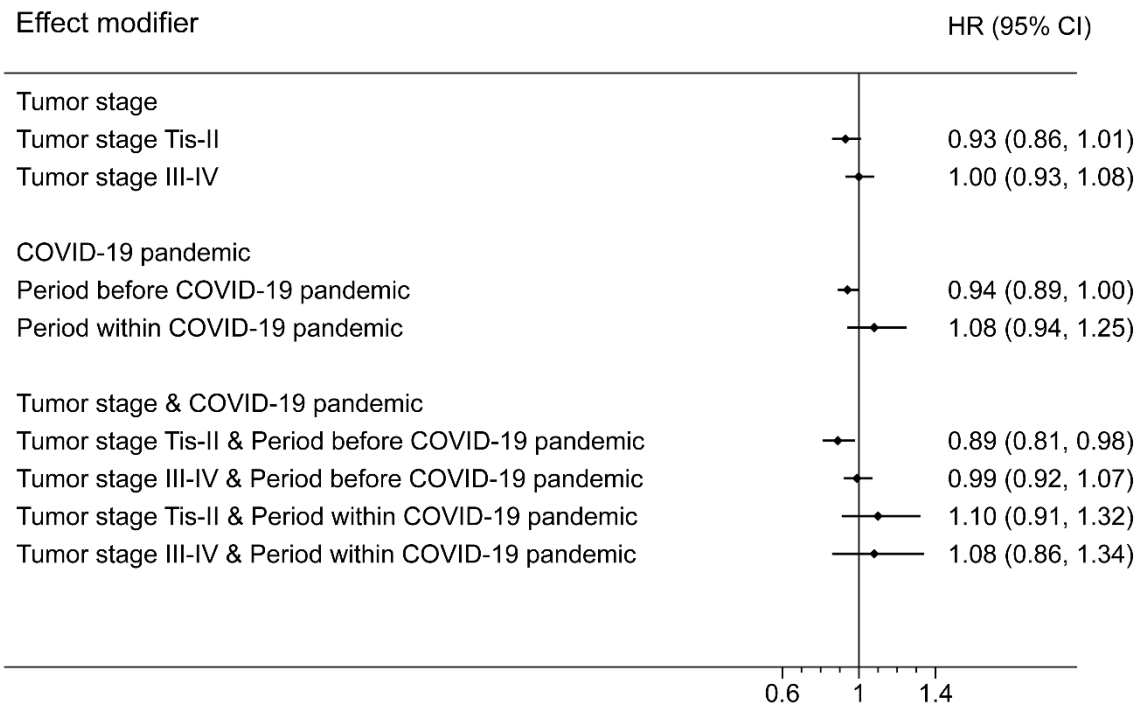

Figure 8. Hazard ratio (HR) and 95% confidence interval (CI) of all-cause mortality for one unit increase in the sum score of Life Orientation Test-Revised (LOT-R), with pathological tumor stage and the COVID-19 pandemic as effect modifiers.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study Design

Studies included in this thesis were observational population-based longitudinal studies based on a nationwide and prospectively collected cohort. In general, the quality of evidence of cohort studies is weaker than meta-analyses, systematic reviews, and randomized controlled trials.[136] Given that no original studies on the topics covered by this thesis have been conducted previously in patients with esophageal cancer, it was impossible to conduct a meta-analysis or systemic review focusing on this patient population. However, few studies on these topics have been performed among patients with other subtypes of cancer, and in the future, with the accumulation of original studies, systematic reviews or meta-analyses focusing on a wide range of cancers may be worth being conducted. A randomized controlled trial is usually more robust to make causal inference because, theoretically, an ideal randomization process will break the association between the exposure and potential confounders. However, the strict experimental setting in randomized controlled trials reduces the generalizability of the study findings. Furthermore, for the topics covered by this thesis, randomized controlled trials might be either difficult or unethical to be implemented; therefore, observational studies might be the optimal choice to start with.

6.1.2 Internal Validity

Internal validity refers to whether the inference is true for the source population (the population from which the study sample was drawn).[137] The most common violations of internal validity include selection bias, information bias, and confounding.[137]

6.1.2.1 Selection bias

Selection bias can occur at the participant recruitment stage and/or due to loss to follow-up.[137] It implies that the association observed in the study sample is not the true association in the source population.[137] It is also recognized as "collider bias" resulting from conditioning on the common effect of the exposure (or variables associated with the exposure) and the outcome (or variables associated with the outcome).[138] It is difficult to use statistical methods to control for or quantify the selection bias, so it is important to think through potential selection bias during the study design phase and try to avoid it.

The studies included in this thesis were population-based. We aimed to invite and include all 1-year survivors who underwent esophageal cancer surgery during the specified time period in Sweden. This strategy reduced the risk of selection bias. However, not all invited patients agreed to participate in the study, and the association between exposure and outcome observed in the participants might be different from the corresponding association among the

non-participants, which threatens the validity. For example, patients with lower dispositional optimism and worse HRQL might tend to reject the study invitation, and this could lead to an underestimation of the observed association. However, the outcomes in this thesis were measured repeatedly after patient enrollment, which decreased the risk of selection bias caused by non-participation because it was less likely that future outcomes affected the choice of participation.

Loss to follow-up may be the principal cause for potential selection bias in this thesis. Study I, II, and III were longitudinal studies, and dropouts happened during the follow-up, which caused missing data. In the analyses, we used maximum likelihood estimation assuming that missing data caused by dropouts or intermittent attendance were missing at random. However, it is possible that this missingness is actually missing not at random, which could lead to biased estimates. For example, patients with lower dispositional optimism and worse HRQL might be prone to skip the follow-up questionnaires or drop out the study, which could make the observed association underestimated. It is difficult to address the issue caused by missing not at random, and usually auxiliary data (such as variables correlated with reasons for dropout) and more complicated statistical models (such as joint models) are required.[139,140] In study IV, information about the outcome, all-cause mortality, was collected from the Swedish Total Population Register, which has complete ascertainment of death.[122] Such complete follow-up minimized the risk of selection bias in this study.

6.1.2.2 Information bias

Bias resulted from measurement errors is called information bias.[137] For discrete variables, measurement error is also called misclassification or classification error.[137] When the misclassification of one variable (e.g., exposure, outcome, or confounder) does not depend on other variables, it is called nondifferential misclassification. Otherwise it is called differential misclassification.[137] Most measurement errors in this thesis were likely to be nondifferential.

In this thesis, one major concern regarding information bias is the measurement error in the LOT-R scale. We used LOT-R to measure dispositional optimism and treated it as a continuous exposure in study I and as a categorical exposure in study II. Random measurement errors in the continuous exposure could dilute the real association.[141] In study I, except for using the observed sum score of LOT-R to present dispositional optimism, we also used a latent (i.e., error free) factor to represent it. Such a strategy helped to quantify the bias caused by this measurement error, and the standardized effect size was truly increased after removing the measurement error. However, when the exposure is a categorical variable, the direction of the potential bias resulted from measurement error is hard to be predicted.[142] Therefore, it is difficult to evaluate the potential effects caused by measurement errors in LOT-R in study II.

In addition, we used HADS to measure psychological distress and treated it as a binary outcome in study I and as a binary exposure in Study III. The HADS is estimated to have

good reliability (i.e., low measurement error). Moreover, nondifferential misclassification of the binary exposure tends to bias the observed estimate towards the null,[137] and nondifferential misclassification of the binary outcome usually biases the estimate towards to the null or increases the standard error of the estimate.[137,141] Therefore, measurement errors in HADS cannot explain the observed significant associations but might explain those observed nonsignificant associations. In study II and III, we used EORTC QLQ-C30 and EORTC QLQ-OG25 to measure HRQL and treated HRQL as continuous outcome. Random measurement errors in the continuous outcome usually do not bias the point estimate but increase the standard error of the estimate.[141] For the mean score difference in HRQL between different exposure groups, we emphasized its clinical relevance rather than its statistical significance, which alleviated the effects of measurement errors in HRQL measurements in these two studies. The outcome in study IV was all-cause mortality, and we obtained this information from the Swedish Total Population Register that has high validity and completeness. Thus, it was less likely that this information contained measurement errors. In addition, measurement errors could also exist in confounders. Independent nondifferential measurement errors in confounders could lead to residual confounding or even worse distorted effect modification.[137] In this thesis, we collected sociodemographic and clinical covariates from national registers and medical charts that were reviewed by two clinicians independently, which minimized the risk of measurement errors to a large extent.

6.1.2.3 Confounding

Confounding is the bias that arises from the presence of the common cause of exposure and outcome.[138] Confounders are factors that could help remove confounding.[138] Failure to adjust for potential confounders could lead to a spurious observed association between the exposure and the outcome.[137,138]

Residual confounding is an important issue that needs to be considered especially in observational studies.[137] While selection bias and information bias can only be avoided via study design, confounding bias can be controlled via both study design and statistical analysis.[137] In the four studies included in this thesis, we used multivariable statistical analysis to control for observed potential confounders. In study III, we took the advantage of longitudinal study design and used fixed effects regression model, which further adjusted for unmeasured time-invariant confounders.[143] Overall, the relatively comprehensive data collected in the OSCAR study have enabled adjustments for most important confounders in this thesis. However, there is still a risk of residual confounding due to unmeasured confounders (e.g., genetic factors) and due to potential measurement errors in measured confounders.

6.1.3 Random Error

Except for the systematic errors (selection bias, information bias, and confounding) that have been discussed above, another type of error damaging the accuracy of an estimate is random error.[137] Significance testing is used to decide whether the observed association is solely due to random error.[137] A computed quantity called *P*-value is compared with the predefined cutoff point called alpha (α) level.[137] The alpha level is usually set at 0.05 by convention. The *P*-value is the probability of obtaining results equal to or more extreme than the results observed when the null hypothesis is true.[137] If $P < \alpha$, we say that the test is statistically significant at level α and reject the null hypothesis.[137] Type I error (i.e., alpha error) occurs if the true null hypothesis is incorrectly rejected.[137] In this thesis, the outcomes in study II and III were HRQL that contains many aspects, and thus multiple testing was required, which boosted the likelihood of type I error. To minimize the type I error, we only conducted significance testing for the aspects in which mean score difference had clinical relevance. In addition, type II error (i.e., beta error) occurs if the false null hypothesis is not rejected.[137] When the sample size is small, the risk of type II error becomes high because the study may have low power to detect the truly existed effect. In study I, II, and III, although the number of included patients were not many, each patient was measured repeatedly over time, which increased the total number of observations and thus boosted the statistical power. In study IV, we incorporated interaction terms in statistical models, and this study might be underpowered to detect interaction effects given that such an analysis requires large sample size.[144] However, in this study, we evaluated the interaction based on effect size instead of *P*-value, which minimized the risk of type II error. In addition, compared with *P*-value, it is more recommended to use confidence interval to account for random error. Confidence interval with 1-alpha (e.g., 95%) confidence level is a range of parameter values whose *P*-values exceed the specified alpha level (e.g., 0.05).[137] We used 95% confidence interval throughout studies included in this thesis.

6.1.4 External Validity

External validity or generalizability refers to how well the inference could be generalized to other populations or settings.[137] Internal validity is the prerequisite for external validity.[137] Studies included in this thesis are qualified for the evaluation of external validity given their overall good internal validity as discussed above. The four studies included in this thesis were Swedish nationwide population-based studies, which facilitate the generalizability. However, eligible patients in these four studies were those having survived at least 1 year after esophageal cancer surgery, and findings from this thesis should be generalized with great caution to patients surviving less than 1 year after surgery for esophageal cancer.

6.2 GENERAL DISCUSSION

6.2.1 Study I, II, and IV

Study I found that the proportion of patients self-reporting clinically significant psychological distress increased from 1 to 2 years after surgery for esophageal cancer and that more optimistic patients were less likely to report clinically significant psychological distress. Study II found that more optimistic patients reported better HRQL after surgery for esophageal cancer. Study IV further found that more optimistic patients had a better overall survival, but this association was only significant among patients with esophageal cancer staged Tis-II and when the follow-up was before the COVID-19 pandemic.

In study I, 11.5% and 25.0% of patients reported clinically significant psychological distress at 1 and 2 years post-surgery, respectively. These proportions were similar with but a bit lower than the proportions presented by two previous studies with large sample sizes.[61,62] One study based on the data from the British hospital and primary care databases has found that 13.9% of patients had psychiatric diagnosis or prescription within 1 year after surgery for esophageal cancer,[61] and the other study based on the data from the Swedish nationwide health registers has found that 32.3% of patients were newly prescribed psychotropic drugs within 2 years after esophageal cancer surgery.[62] Several reasons might explain the minor inconsistencies between study I and previous studies. First, some patients refused to participate in the OSCAR study, and non-participants might suffer more from psychiatric disorders, which could result in underestimations of these proportions in study I. Second, study I only assessed anxiety and depression using the self-reported questionnaire HADS, while the previous two studies used comprehensive psychiatric diagnoses and/or prescriptions to identify psychiatric disorders. Also, the risk of misclassification might be higher when categorizing patients only based on self-reporting compared with based on clinical diagnosis and/or prescription, and most likely self-reporting would lead to underestimation.[145] Moreover, psychiatric drugs could be prescribed for purposes other than treating psychiatric disorders (e.g., antidepressants can be used for cancer pain),[146] which could result in overestimation in previous studies. In addition, the previous two studies assessed cumulative incidences of psychiatric disorders within 1 and 2 years after esophageal cancer surgery, while Study I in this thesis assessed psychological distress at 1 and 2 years after surgery. However, the longitudinal trajectories found by study I and previous studies were the same, and that is that psychiatric disorders after esophageal cancer surgery increased over time.

The increasing proportion of patients with clinically significant psychological distress over time suggests unmet needs for early detection and timely psychological support. Esophageal cancer surgery is a major procedure which removes part of or all esophagus and then reconstructs the digestive tract. Recovery and adaptation after esophageal cancer surgery is a long process. Postoperative symptoms and compromised functioning could exist until 10 years after surgery.[49] Moreover, patients may further develop new comorbidities due to increasing age and pre-existed risk factors related to esophageal cancer.[4] Constantly exposed

to these stressors could lead to changes in glucocorticoid signalling and brain structure,[147,148] and thus further make patients vulnerable to psychological distress.[148]

There are several potential mechanisms explaining the observed predictive effects of dispositional optimism on postoperative psychological distress, HRQL, and survival. Given that these results were from observational studies, residual confounding such as genetic factors[70,149,150] and early life experience[151] might cause spurious observed associations. However, these observed associations might also be causal, and several potential pathways could be involved. Previous studies have found that more optimistic people tend to adopt more effective coping strategies, adjust goals more efficiently, and receive more social support.[152-159] Effective coping strategies are associated with less psychological distress and better HRQL.[160-162] After esophageal cancer diagnosis and surgery, the feasibility of previously set goals may change, and efficient goal adjustments could help patients focus more on achievable goals and rapidly disengage from unattainable goals, thus leading to less psychological distress and better HRQL.[163-165] Higher social support has been found to be related to better mental health, better HRQL, and better overall survival.[166-168] Furthermore, more optimistic people are prone to have healthier lifestyles including smoking less, exercise more, and eat healthier,[169] and thus might be less likely to develop comorbidities and more likely to have a better recovery after esophageal cancer surgery. In addition, people with higher dispositional optimism tend to have healthier levels in several aging-related biomarkers (e.g., telomere, interleukin-6, fibrinogen, homocysteine, and lipid profile) compared with less optimistic people,[170-172] and thus might have a lower risk of dying from aging-related diseases and be more likely to have better overall survival. Additionally, given that psychological comorbidities and poor HRQL are risk factors for poor survival after esophageal cancer surgery,[50-52,62] one potential pathway could also be that higher dispositional optimism led to less psychological distress and better HRQ, and the latter further contributed to better overall survival.

In study I and II, we followed up patients who underwent surgery between January 1, 2013 and February 28, 2018 in Sweden for two years, so the included follow-up periods ended approximately on February 29, 2020, while in study IV, the included follow-up period were until December 31, 2020. Given that only two cases of COVID-19 were reported in January and February, 2020 in Sweden,[173] it is less likely that the COVID-19 pandemic had effects on the results of study I and II, and whether the results from these two studies could be generalized to the periods with and after the COVID-19 pandemic needs further investigation. In study IV, we examined the potential effect modification by the COVID-19 pandemic, and found that the association between dispositional optimism and all-cause mortality was not statistically significant during the COVID-19 pandemic. However, given the rather small sample size and relatively short follow-up period during the COVID-19 pandemic, this result was of low precision, and should be interpreted cautiously and examined further by studies with larger sample sizes. Nevertheless, it made conceptual sense that higher dispositional optimism no longer had protective effects on survival during the COVID-19 pandemic. Patients with cancer have higher risks for COVID-19 infection and its

adverse outcomes including death.[174-176] Moreover, the postponements of routine health care and scheduled surgery during the COVID-19 pandemic[173] may have further decreased the controllability of esophageal cancer, and thus patients could hardly prolong their lives via being optimistic. In addition, in study IV, we also found that the association between dispositional optimism and all-cause mortality was close to the null among patients with advanced tumor stage. This might also be because the prognosis for advanced esophageal cancer is much less controllable with 5-year survival rate less than 15%.[2]

The observed predictive effects of dispositional optimism on postoperative psychological distress, HRQL, and survival may assist in identifying vulnerable patients with worse prognosis after surgery for esophageal cancer, thus contributing to the development of more tailored and timely interventions to improve postoperative survivorship. In addition, given that dispositional optimism is modifiable via psychological interventions including Best Possible Self exercise and cognitive behavior therapy,[75] enhancing dispositional optimism may help improve prognosis after esophageal cancer surgery.

6.2.2 Study III

Study III found that clinically significant psychological distress was associated with worse HRQL after surgery for esophageal cancer. In this study, we used fixed effects regression model to control for all time-invariant covariates (no matter they were measured or not) and observed time-varying confounders.[143] This method takes the advantage of longitudinal study design and, in essence, compares patients with themselves (i.e., compares patients' status at later time points with their own status at earlier time points). Therefore, it removes the confounding due to time-invariant confounders, which enhances causal inference. However, there is still a risk of residual confounding resulted from unmeasured time-varying confounders. Furthermore, given that the independent variable (psychological distress) and the dependent variable (HRQL) were measured repeatedly at the same time points in this study, it is difficult to ascertain the direction of the potential causation between psychological distress and HRQL.

In this study, after adjusting for all time-invariant covariates and observed time-varying confounders, we found that clinically significant psychological distress was associated with worse emotional function and social function, and more dyspnea, anxiety, eating difficulty, trouble with eating in front of others, and worry about weight loss. Given that these associations were not modified by time, the potential bias caused by time-varying confounders might not sufficiently explain these observed associations. In other words, these observed associations might be causal, even though we cannot determine the potential causal direction. It might be that clinically significant psychological distress caused worse emotional function and social function, and more worry about weight loss. However, it could also be that severe postoperative symptoms such as eating difficulty caused clinically significant psychological distress.

We also found time-varying associations between clinically significant psychological distress and cognitive function, global health status/quality of life, EORTC QLQ-C30 summary score, appetite loss, trouble with taste, and self-doubt about body image. Residual time-varying confounders such as cancer recurrence and postoperative adaptation might be potential explanations for these observed time-varying associations. In addition, the adjusted mean score difference in most of these aspects increased over time, from clinically irrelevant to clinically relevant. The increased associations might be because patients developed more severe psychological distress over time, and thus led to further deteriorated HRQL. However, it might also be the other way around, and that is that patients with constantly deteriorated HRQL were more likely to suffer from psychological distress.

This study highlights the importance of timely and effective interventions to prevent psychological distress and to improve HRQL after esophageal cancer surgery, given that clinically significant psychological distress and worse HRQL might cause each other. In other words, if one of them occurred, it might lead to a cascade of adverse outcomes.

7 CONCLUSIONS

- From 1 year to 2 years after surgery for esophageal cancer, self-reported clinically significant psychological distress increased over time.

- Higher dispositional optimism predicted better HRQL and a lower risk of reporting clinically significant psychological distress after surgery for esophageal cancer.

- Postoperative psychological distress and HRQL were potentially causally associated, but the direction of the potential causation was uncertain.

- Higher dispositional optimism predicted better overall survial among patients with early and intermediate esophageal cancer before the COVID-19 pandemic.

8 POINTS OF PERSPECTIVE

The predictive effects of dispositional optimism on postoperative psychological distress, HRQL and survival among patients with esophageal cancer surgery may help update the prognostic model and contribute to the development of personalized health care. Future studies with larger sample sizes are required to further validate these predictive effects. In addition, whether these predictive effects could be generalized to other populations is largely unknow, and related studies are warranted.

Given that the observed predictive effects might be explained by residual confounding, whether these associations are causal or not need to be examined further in the future. If these associations are causal, it may be worth investigating the underlying mechanisms or pathways and especially identifying those easily modifiable mediators. In addition, given that dispositional optimism is potentially modifiable via psychological interventions,[75] studies exploring whether increasing dispositional optimism could improve postoperative prognosis are also warranted.

This thesis also found that postoperative psychological distress and worse HRQL might be causally associated. However, this potential causation identified in this thesis was cross-sectional, and we cannot determine the direction of the potential causation. In the future, longitudinal studies using more complicated statistical models such as cross-lagged panel model might be useful to examine the potential causal direction. In addition, time-varying confounding is a threat to the potential causation identified in this thesis, and future studies are suggested to adjust for more potential time-varying confounders.

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