Does Skeletal Muscle Loss and Sarcopenia Predispose Patients for the Development of a Paraconduit Hernia After Minimally Invasive Esophagectomy? – A Propensity Matched Case-control Study

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Abstract

Background

Paraconduit hernia is a relatively common long-term complication after esophagectomy which has the potential to cause great morbidity and even mortality. The aim of this study is to examine the relationship between sarcopenia and muscle mass loss and paraconduit hernia after minimally invasive esophagectomy in esophageal adenocarcinoma patients who have received neoadjuvant treatment.

Methods

All minimally invasive esophagectomies done for patients with neoadjuvant-treated esophageal or esophagogastric junction adenocarcinoma at our institution between 2008 and 2018 were included in this study. Propensity score matching was utilized to minimize confounding effects of retrospective data analysis. Computed tomography scans were used to measure skeletal muscle mass and to quantify sarcopenia.

Results

The incidence of paraconduit hernia was 14 out of 171 patients (8.2%). The hernia was surgically repaired in 10 (71.4%) of patients. A total of 23 (82.1%) patients in the matched group were sarcopenic before start of neoadjuvant treatments, 22 (78.6%) after neoadjuvant treatments and 24 (85.7%) at 6 months of follow-up. Skeletal muscle area, skeletal muscle index or prevalence of sarcopenia had no correlation with paraconduit hernia developement. Using the median change of skeletal muscle area between pre-neoadjuvant and 6 months follow-up visit as a threshold to divide the patients into two equal size groups yielded no significantly different survival curves using Kaplan-Meier analysis ($p = 0.6$).

Conclusion

Paraconduit hernia is a relatively common complication after minimally invasive esophagectomy for neadjuvantly treated adenocarcinoma patients. Sarcopenia and muscle mass loss are not predictive factors for paraconduit hernia.

Introduction

The incidence of esophageal adenocarcinoma is increasing in many Western countries.[1,2] Esophagectomy is the only curative treatment in advanced disease, but it is associated with a high rate of perioperative complications.[3–5] With current multimodality treatments and advanced staging methods, the 5-year survival of surgically treated esophageal adenocarcinoma has improved significantly. [3,6,7] Minimally invasive esophagectomy (MIE) has been established as a safe approach to treat esophageal cancer and is associated with less pulmonary complications and postoperative pain than open esophagectomy (OE).[3] However, the incidence of paraconduit hernia after MIE has been higher than after OE.[3,8–12]

Paraconduit hernia after esophagectomy is a rare but notable late-onset postoperative complication. It occurs when intraperitoneal contents, such as small or large bowel, herniate through the hiatal orifice and accounts for considerable morbidity due to life threatening emergencies with incarceration, strangulation and perforation of the bowel. [9,13,14] With prolonged life expectancy, an increasing number of patients suffering from paraconduit hernia will potentially need treatment in the future. A recent review found the rate of paraconduit hernia after MIE to be 4.5% and 1.0% after open esophagectomy (OE), incidence rates ranging between 0 - 26% after MIE and 0 -10% after OE.[15] Treating paraconduit hernias by minimially invasive approach has been gaining traction and seems to be safe.[8,13,16]

In the recent years, there have been numerous studies on sarcopenia, and other markers of frailty, as prognostic factors in cancers. Sarcopenia is defined as the progressive loss of muscle related to aging or disease.[17] Sarcopenia, and loss of muscle mass have been associated with worse outcomes in esophageal and esophagogastric junction cancer.[18–20] Pronounced loss of muscle mass during neoadjuvant treatments has also been indicated in poor prognosis of esophageal cancer.[20]

The aim of this trial was to explore the effects of sarcopenia and muscle loss on the development of paraconduit hernia, as well as to explore other risk factors for paraconduit hernia development. As the link between muscle loss during neoadjuvant treatments and survival has been previously established, we postulated that the same effect could also be seen in paraconduit hernia development. To avoid unnecessary heterogeneity related to different neoadjuvant treatments and tumor location, only patients with adenocarcinoma of the esophagus or esophagogastric junction were examined.

Methods

This is a retrospective consecutive case-series of paraconduit hernia after MIE from 2008 to 2018. Only patients with esophageal or esophagogastric junction adenocarcinoma were included. This was done to minimize the confounding brought by esophageal squamous cell cancer patients, whose operation types, comorbidities and neoadjuvant treatments are different. The primary endpoint was the development of paraconduit hernia.

Data acquisition

The data was collected from the electronic medical records, after a minimum of two-year follow up after MIE. Information collected included patient age, sex, BMI, tumor characteristics, neoadjuvant- and adjuvant treatment details, co-morbidities, and symptoms. The operation reports of both the primary esophagectomy and hernia repair were studied for technical details. Follow-up reports and surveillance imaging were investigated for treatment outcomes including complications, mortality, readmissions, reoperations and hernia recurrence. The complications were graded retrospectively according to the Clavien-Dindo classification.[21]

Neoadjuvant treatment

In our institution, patients with cT2-4 & N0-2 esophageal adenocarcinoma are considered for neoadjuvant therapy in a multidisciplinary meeting. The neoadjuvant regimen used is FLOT (docetaxel, oxaliplatin, fluorouracil, and leucovorin), however other regimens can be recommended based on patient factors.[22]

Surgical treatment

Minimally invasive and open Ivor Lewis and McKeown esophagectomies are performed in our center.[23–25] In Ivor Lewis reconstruction we use a 4 cm wide gastric conduit pulled up to the thoracic cavity and anastomosed approximately at the level of the azygos vein. In general, at the end of the laparoscopic procedure the conduit is fixed with sutures to the diaphragmatic crura. If the hiatal opening appears wide, it is loosely closed after the conduit is placed in left thoracic cavity during the laparoscopic portion of the operation.

Our approach to paraconduit hernia repair is a 4-5 port laparoscopic repair, in which, the hernia contents are mobilized completely and reduced back to abdomen. The possible hernia sac is excised, and the hiatus is closed with non-absorbable sutures and if needed, reinforced with mesh. The conduit is then re-fixed to the crura with sutures. Laparotomy and/or thoracotomy incisions are used if minimally invasive repair is not feasible.

Follow-up

Patients undergo a surveillance program within our institution for up to five years postoperatively. The follow-up for esophageal cancer includes outpatient appointments at 1, 3, 6, 12, and 18 months and then annually from 2 to 5 years, including CT scans at 6 months, 18 months, and 2, 3, 4 and 5 years postoperatively. A gastroscopy is performed at 3 months, 1 year, 2 years and 4 years post operatively.

Measurement of muscle parameters & sarcopenia definition

Esophageal cancer patients undergo a full body CT scan before the start of neoadjuvant therapy, after completion of neoadjuvant therapy and at 6 months after surgery. These scans were used to measure muscle mass and define sarcopenia before neoadjuvant treatments, before surgery and at 6 months of follow-up respectively. Scans were coded in order to blind the researchers from outcome. Images were imported to Osirix® Version 12.0 (32-bit Pixmeo, Sarl, Switzerland). Abdominal musculature was delineated by use of a semi-automatic selection of region of interest tool from the level of L3. Psoas, quadratus lumborum, paraspinal, transverse abdominal, external oblique, internal oblique, and rectus abdominis muscles were included. The Hounsfield Unit threshold range for skeletal muscle was −29 to +150. The images were manually corrected, if needed, by the propulsion and brush tools in Osirix©. The cross-sectional total muscle area at the level of L3, Skeletal muscle area (SMA; unit: cm2) was divided by the square of height (m2), which produced the Skeletal Muscle Index (SMI). This method is suggested as the preferred method of measuring the muscle mass of cancer patients.[26] SMI limit for sarcopenia was < 52.4 cm2/m2 for men and < 38,5 38.5 cm2/m2 for women, based on a previous study by Prado et al.[27]

Statistics

The data was analyzed with R project (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). The risk factors for hernia were calculated using binary logistic regression. Correlation to complications with categorical variables was done by χ^2, or Fisher's exact test and with numerical variables with binary logistic regression.

We propensity matched patients with paraconduit hernia 1:1 to a control group without a paraconduit hernia. We calculated the propensity scores using generalized linear model with age, sex, preoperative stent insertion, preoperative radiotherapy, graft saturation to crura and major postoperative complications as the dependent covariables. We performed propensity score matching with R package "MatchIt" by nearest propensity score method.[28] We calculated standardised differences between the unmatched SEMS insertion group and the control group and compared them to the standardised differences of the matched groups. We then performed statistical analysis on the newly formed case cohort to identify any statistically significant differences between the groups.

The study was approved by the Helsinki University Institutional Review Board (IRB) as part of the rare hernias study (HUS/60/2019).

Results

A total of 466 esophagectomies for esophageal cancer were performed in our center between 2008 and 2018. Of these, 335 cases were operated with MIE and 131 OE approach. Of these patients, 171 had adenocarcinoma of the esopahgus or gastroesophageal junction, underwent neoadjuvant treatment and were operated on with MIE. Of these patients, 5.9% (n=10) went through chemoradiotherapy with paclitaxel and carboplatin, 93.6% chemotherapy alone (n=160) and 0.6% (n=1) radiotherapy alone. The most used regimen for chemotherapy was 3 rounds of EOX (epirubicin, oxaliplatin, capecitabin; n=116, 67.8%). Other regimens included XELOX (oxaliplatin and capecitabin; 4.1%, n=7), FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel; 2.9%, n=5), SOX (S-1 and oxaliplatin; 0.6%, n=1) and FOLFOX (folinic acid, fluorouracil, and oxaliplatin; 0.6%, N=1). The used regimen was not specified in 17.5% (n=30).

Paraconduit hernia was found in 14 (8,2%) patients after MIE for esophageal adenocarcinoma, the median time from operation to the diagnosis of paraconduit hernia was 17 months (range 0-113 months). (Table 1). At 3 years the incidence of paraconduit hernia in the surviving patients was 11.4% and at 5 years 13.6%. The cumulative hazard of paraconduit hernia after minimally invasive esophagectomy for esophageal and esophagogastric junction adenocarcinoma is shown in Figure 1.

Table 1
Demographics of patients who underwent MIE after neoadjuvant treatment for esophageal and esophagogastric junction adenocarcinoma

		All	Paraconduit hernia
		n (%)	
Sex	Female	32 (18.7)	1 (7.1)
	Male	139 (81.3)	13 (92.9)
Age	mean (SD)	63.8 (9.4)	64.3 (9.4)
BMI	mean (SD)	25.3 (4.8)	22.2 (2.9)
ECOG	0	122 (71.3)	11 (78.6)
	1	48 (28.1)	3 (21.4)
Location	Middle esophagus	2 (1.2)	0 (0)
	Distal esophagus	57 (33.3)	4 (28.6)
	GE-juction/cardia	112 (65.5)	10 (71.4)
Preoperative treatment	Chemotherapy	160 (93.6)	10 (71.4)
	Chemoradiotherapy	10 (5.8)	3 (21.4)
	Radiotherapy	1 (0.6)	1 (7.1)
Operation type	Ivor Lewis	166 (97.1)	13 (92.9)
	McKeown	3 (1.8)	1 (7.1)
	Transhiatal	1 (0.6)	0 (0)
	Roux-en-Y	1 (0.6)	0 (0)
Approach	MIE	160 (93.6)	14 (100)
	Hybrid	10 (5.8)	0 (0)
	Laparoscopic transhiatal	1 (0.6)	0 (0)
Conversion		15 (8.8)	0 (0)
Major complication		44 (25.7)	2 (14.3)
Lymph nodes	mean (SD)	20.7 (10.3)	20.5 (8.7)
Preoperative hernia		37 (21.6)	1 (2.7)
Preoperative esophagus stent	52 (30.4)	7 (50)	

The paraconduit hernia was operatively repaired in 71% of cases (n = 10). The overall rate of paraconduit hernia requiring operative repair in the study population was 5.8%. The median time from esophagectomy to hernia repair was 14 months (range 0-113 months). Laparoscopic approach was used in 90% (n = 9) of the hernia repairs, and 30% (n = 3) were operated on in urgent or emergent basis. The median operating time was 100 minutes (SD = 52 minutes). The details related to paraconduit repairs can be appreciated in Table 2. There was one (10%) mortality after repair of paraconduit hernia. The patient in question had peritoneal tumor implants and presented with a week of symptoms from acute small bowel obstruction. Laparotomy was performed a in a life-threatening situation with vital indication. The patient suffered from multiple organ failure and died on postoperative day 8.

Table 2
Characteristics of paraconduit hernia repair operations

		n	**(%)**
Time from primary operation	< 90 days	1	(10.0)
	90-365 days	2	(20.0)
	> 365 days	7	(70.0)
Symptomatic		5	(50.0)
Technique	Laparoscopy	9	(90.0)
	Conversion	1	(11.1)
	Laparotomy	1	(10.0)
Urgency	Elective	7	(70.0)
	Emergency	3	(30.0)
Repair	Hiatoplasty and fixation	4	(40.0)
	Hiatoplasty	1	(10.0)
	Fixation of graft	1	(10.0)
	Mesh	4	(40.0)
Hernia Type	Colon	7	(70.0)
	Small bowel	2	(20.0)
	Colon and small bowel	1	(10.0)
Bowel resection		0	(0.0)
Complication		1	(10.0)
90-day mortality		1	(10.0)

Using multivariate binomial logistic regression model, preoperative radiotherapy (OR = 9.62; 95% CI = 1.33-71.46, p = 0.0220) and a BMI less than 25 (OR = 9.59, 95% CI = 1.48-194.26, p = 0.0464) were found to be strong risk factors for paraconduit hernia development in the unmatched group, as shown in Table 3.

Table 3
Risk factors for paraconduit hernia, unmatched group

	OR	**95% CI**	***p***
Age	0.96	0.89-1.04	0.2965
Male sex	0.56	0.03-4.08	0.6218
BMI under 25	9.59	1.48-194.26	0.0464
Major Complication	0.45	0.06-2.28	0.3813
Preoperative stent	2.56	0.58-12.77	0.2240
Conduit sutured to crura	0.34	0.04-3.05	0.2878
Preoperative radiotherapy	9.62	1.33-71.46	0.0220

Total of 14 patients without paraconduit hernia were propensity matched with the paraconduit hernia group (N = 14). The demographics of the propensity score matched groups can be seen in *Table 4* and the Love plot of standardized mean differences of covariates in Figure 2. All of the covariates showed improved balance after matching, although some of the covariates still had residual differences, as shown by the SMD values > 0.1 in Figure 2. The measured skeletal muscle parameters for both of these groups can be seen in Table 5. A total of 23 (82.1%) patients in the matched group were sarcopenic before start of neoadjuvant treatments, 22 (78.6%) after neoadjuvant treatments and 24 (85.7%) at 6 months of follow-up. None of the skeletal muscle parameters were statistically significantly different between the groups. We then used median change of skeletal muscle area (ΔSMA) between pre-neoadjuvant and 6 months follow-up visit to divide the patients into two equal size groups. With these groups, a Kaplan-Meier survival analysis of freedom from hernia was done, shown in Figure 3. This yielded no statistically significant difference between the groups (p = 0.6).

Table 4 Demographics of the propensity matched groups

		Paraconduit Hernia		No paraconduit hernia	
		(N= 14)		(N = 14)	
Age (Years)					
	Mean (SD)	64.3	(9.44)	63.8	(8.48)
Sex					
	Male	13	(92.9%)	14	(100.0%)
	Female	1	(7.1%)	0	(0%)
Major Complications		12	(85.7%)	11	(78.6%)
Preoperative stent		7	(50.0%)	7	(50.0%)
Conduit fixation		3	(21.4%)	2	(14.3%)
Preoperative radiotherapy		10	(71.4%)	10	(71.4%)

Table 5
Muscle measurements between patients with paraconduit hernia and no paraconduit hernia

	Paraconduit hernia		**No paraconduit hernia**		***p***
	(N = 14)		(N = 14)		
Preneoadjuvant					
SMA, mean (SD)	138	(25)	142	(34)	0.722
SMI, mean (SD)	42	(7)	46	(9)	0.301
Sarcopenia, N (%)	12	(85.7)	11	(78.6)	1.000
Preoperative					
SMA, mean (SD)	131	(25)	130	(31)	0.958
SMI, mean (SD)	41	(8)	42	(8)	0.801
Sarcopenia, N (%)	12	(85.7)	10	(71.4)	0.645
6 months follow-up					
SMA, mean (SD)	132	(24)	131	(31)	0.884
SMI, mean (SD)	42	(6)	42	(9)	0.915
Sarcopenia, N (%)	13	(92.9)	11	(78.6)	0.589
Preoperative BMI, mean (SD)	22	(4)	21	(3)	0.624
SMA = Skeletal muscle area at the level of L3, unit = cm2					
SMI = Skeletal muscle index i.e. SMA standardized to patients height, unit = cm2/m2					
BMI = Body mass index, unit = kg/m2					

Discussion

Paraconduit hernia is a relatively common long-term complication after esophagectomy for distal esophageal and gastroesophageal junction adenocarcinoma with an incidence of 8.1%. It can be repaired safely with laparoscopic approach in experienced centers, with a complication rate of 10% in our series. Neither sarcopenia nor muscle loss during treatments was correlated with paraconduit hernia formation in our series.

Patients with or without paraconduit hernia did not have differing skeletal muscle measurements before neoadjuvant treaments, preoperatively or after 6 months of follow-up, as seen in Table 5. Kaplan-Meier survival curves did not differ between the group who had less pronounced muscle loss between preneoadjuvant state and 6 months follow-up compared to those who had pronounced muscle loss during this time period. These results indicate that sarcopenia or progressing muscle loss are not related to paraconduit hernia formation. To our knowledge, this study is the first to examine this relationship. Previous studies have, however established a strong link with loss of muscle mass during neoadjuvant treatments, sarcopenia in general, and worsened overall survival.[18–20]

Preoperative radiotherapy was linked to a higher risk of paraconduit hernia, as has been seen in previous studies, which is logical as the effects radiation most likely weaken the crura and the crural repairs.[12] A BMI under 25 was also associated with increased risk of paraconduit hernia, however this effect was not apparent after matching (Table 5*)*, suggesting confounding variables to be responsible for this effect. Other factors, including hiatal hernia at the time of esophagectomy or stenting before esophagectomy were not associated with paraconduit hernia.

In our study, the incidence of paraconduit hernia (8.1%) is in line with previous reports.[3,8] Rate of paraconduit hernia repair after MIE for esophageal or esophagogastric junction adenocarcinoma was 5.8% ,which is also similar to earlier reports.[3,8,13] Laparoscopic repair was used in 90% of paraconduit hernia repair. Only one conversion to laparotomy was necessary, and this patient had peritoneal carcinosis and was in extremis from small bowel obstruction. Apart from the single patient whose prognosis was very grim related to the carcinomatosis of the peritoneal space, there were no mortality or complications related to the hernia repairs. In previous review by Oor et al, the pooled morbidity rate was 25% (range: 0% – 60%).[15]

The majority (71.4%, N = 10) of the paraconduit hernias in this study were diagnosed more than one year after the esophagectomy, and only one case within 3 months. To prevent early paraconduit hernia in our institution, the graft is sutured to the crura in addition to a hiatoplasty as needed. We believe that this prevents paraconduit hernia formation in the immediate postoperative period. However, no comparative data on the effect of this maneuver exists. In previous studies, the hernias that appeared early after esophagectomy were associated with high morbidity.[29]

The strength of this study was that even though it is a retrospective study, there was good follow-up data available due to standard follow-up protocols after esophagectomy for esophageal cancer. We also utilized propensity matching to somewhat diminish the potential biases that a retrospective study design inherently contains. Additionally, Finland has a centralized archive for medical records, so that data on complications can be achieved even if they are treated at another institution.

However, there are some limitations. There is a chance for selection and information bias. As esophageal cancer is a disease with high mortality, there is considerable mortality in follow-up. We included only patients with adenocarcinoma of the distal esophagus and gastroesophageal junction, who had received neoadjuvant therapy in order to maximize homogeneity. This means the results can not automatically be generalized to all esophagectomy patients.

According to our study, paraconduit hernia is a relatively common complication in patients undergoing minimally invasive esophagectomy for esophageal- or esophagogastric junction cancer after neoadjuvant treatments. However, no association between paraconduit hernia formation and sarcopenia or muscle mass loss during neoadjuvant treatments could be established.

Declarations

Ethics approval and Consent to Participate

all methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved was approved by the Helsinki University Hospital study committee. As a retrospective study without individual level data published, ethics committee approval and informed consent was waived by Helsinki University Hospital study review board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to involvement of data that makes identification of patients possible but are available in an anonymized form from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

HH and TJ collected and analyzed the data, performed statistical testing, wrote the initial manuscript and the revisions. TJ, II and JR revised and commented on the manuscript. All authors read, commented on, and approved the final manuscript.

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Figures

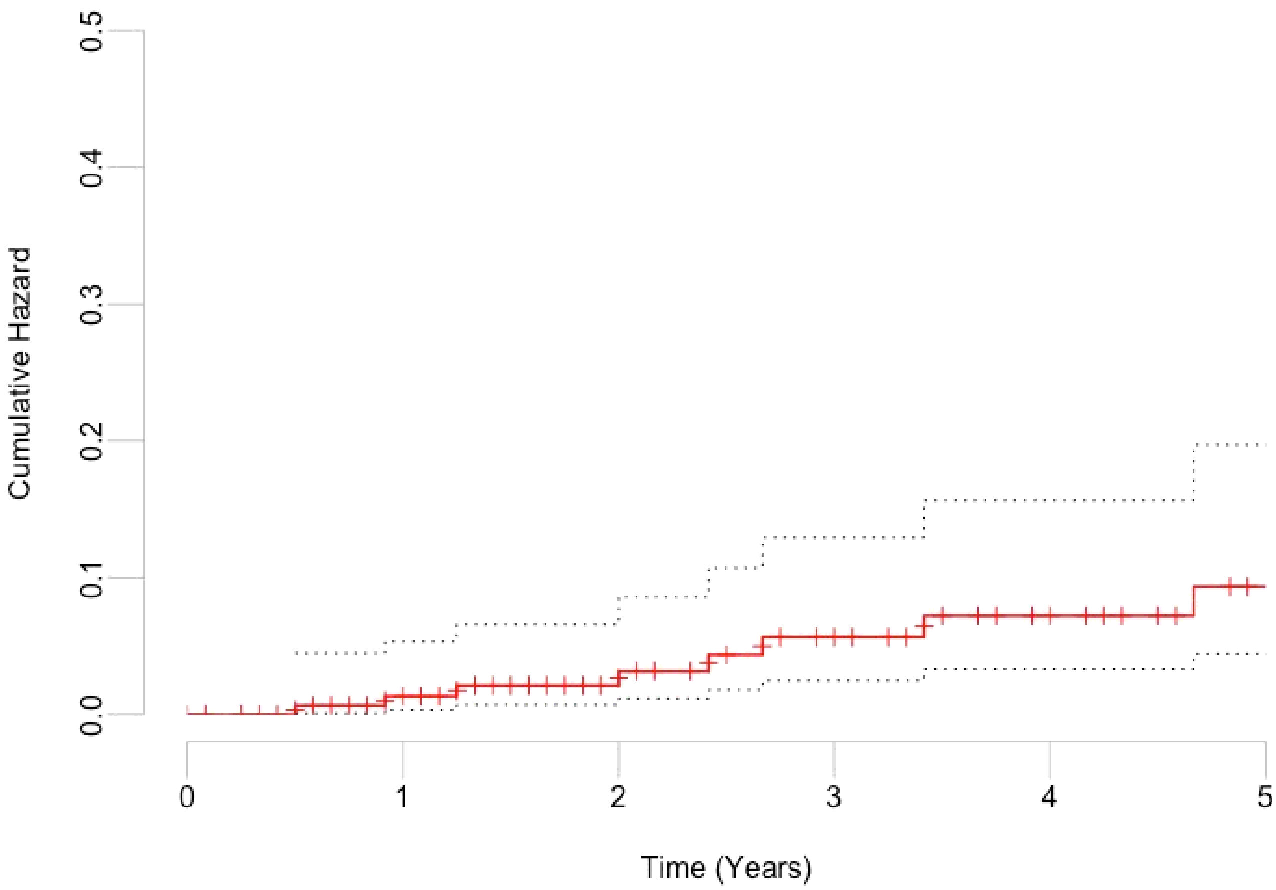

Figure 1

Cumulative hazard of paraconduit hernia after minimally invasive esophagectomy for esophageal and esophagogastric junction adenocarcinoma

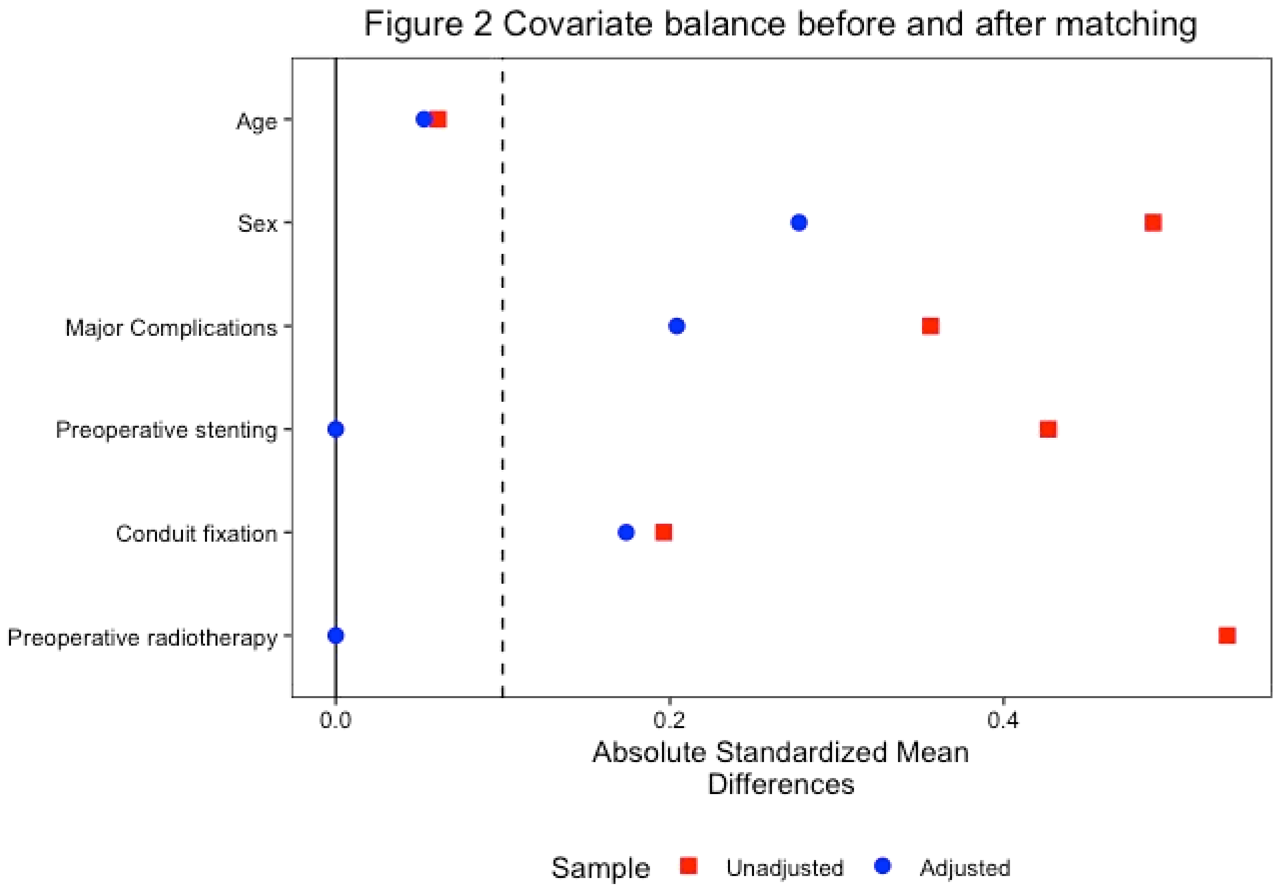

Figure 2

Love plot of standardized mean differences between patient groups with and without paraconduit hernia before propensity matching (red square) and after matching (blue circle)

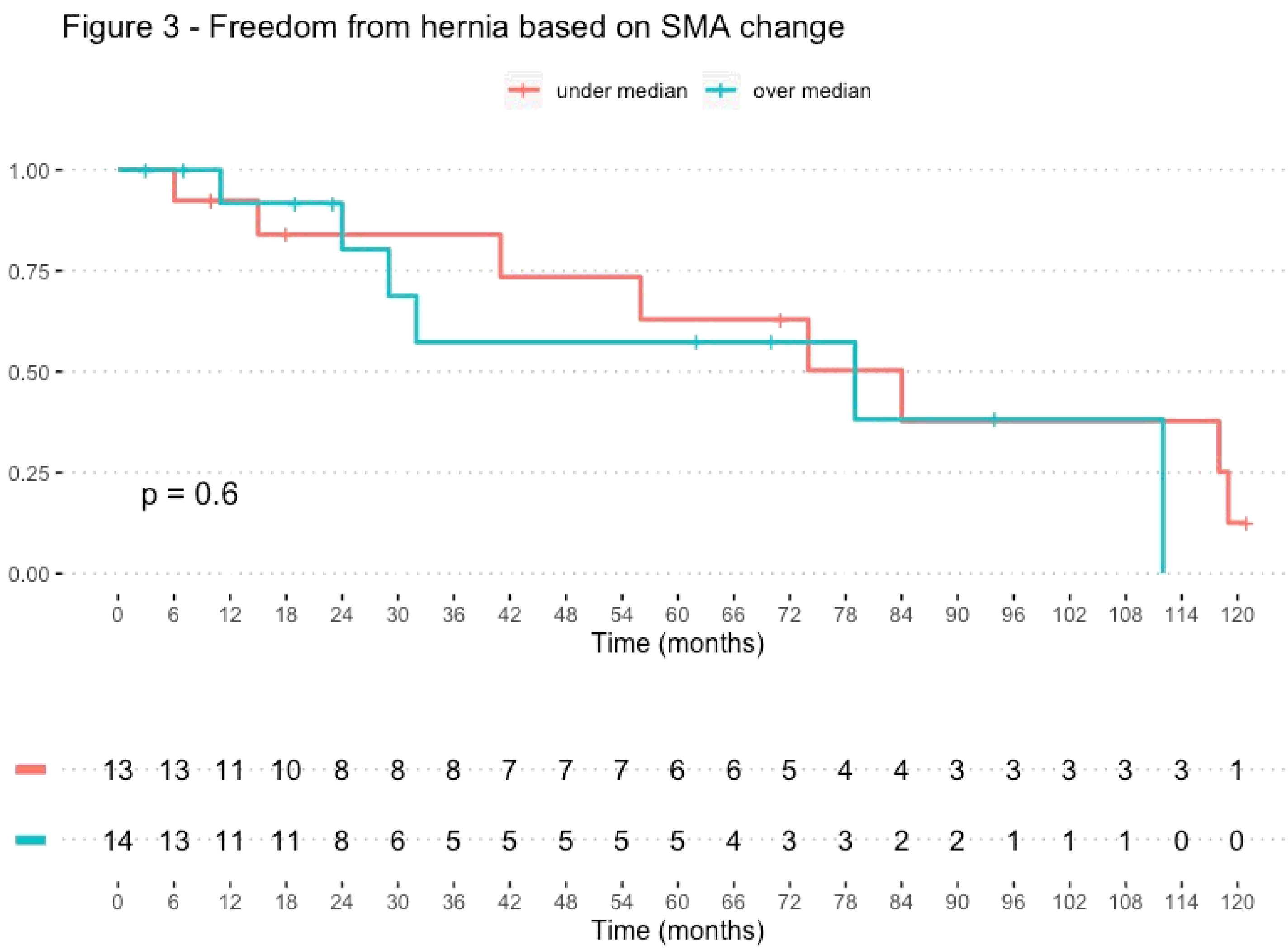

Figure 3

Kaplan-Meier survival plot of the propensity matched group, dividing the groups into two using the median of skeletal muscle change between preneoadjuvant and 6 months follow-up visit as a threshold.