Surgical Oncology 43 (2022) 101789

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Age and Charlson Comorbidity Index score are not independent risk factors for severe complications after curative esophagectomy for esophageal cancer: a Dutch population-based cohort study☆

Nikolaj Baranov *, Linda Claassen, Frans van Workum, Camiel Rosman

Department of Surgery, Radboud University Medical Center, Nijmegen, the Netherlands

ARTICLE INFO

Keywords:
Postoperative morbidity
Elderly patients
Minimally invasive esophagectomy
Open esophagectomy
Esophageal cancer
Mortality

ABSTRACT

Background: The number of older patients undergoing curative esophagectomy for esophageal cancer is increasing, and minimally invasive techniques are being increasingly used. The aim of this study is to compare postoperative outcomes after curative esophagectomy between older and younger patients.

Methods: Data was retrieved from the Dutch Upper Gastrointestinal Cancer Audit (DUCA), a national surgical outcome registry. The primary outcome was severe complications, defined as complications graded Clavien-Dindo ≥ 3. The secondary outcomes were postoperative complications, reintervention rates, length of hospital stays, and mortality. Outcomes were compared between patients aged ≥75 and < 75 years. We performed additional subgroup analyses between these age groups after totally minimally invasive esophagectomy (TMIE) and in patients with severe complications. We adjusted for the following parameters: gender, BMI, Charlson Comorbidity Index score (CCI), ASA score, histology, type of neoadjuvant therapy, and surgical technique.

Results: Of all 3775 included patients, 455 (12.1%) were aged ≥75 years and 3302 (87.9%) were aged <75 years. Overall, severe complications occurred in 184 (40.4%) older and in 1140 (34.5%) younger patients (CI = 1.009–1.080). After TMIE, severe complications occurred in 150 (42.1%) older and in 891 (35.8%) younger patients (CI = 1.007–1.088). In patients with severe complications, rates of complications, reinterventions, mortality, and ICU stays were comparable between older and younger patients. After adjustment for casemix, age and CCI score were not independent risk factors for (severe) complications and mortality.

Conclusions: Age and Charlson Comorbidity Index are not adequate predictors of postoperative morbidity and mortality after curative esophagectomy for esophageal cancer.

1. Introduction

The aging of the Western population and the increased incidence of esophageal cancer have led to an increased number of older patients with esophageal cancer [1]. Increased age is associated with increased risk of multiple comorbidities, which are associated with worse postoperative outcomes after esophagectomy for esophageal cancer [2,3]. Older patients also suffer from increased cognitive impairment and frailty, which negatively affects the postoperative course as well [4].

Several studies reported conflicting results on the relationship between patient age and postoperative outcome after esophagectomy with curative intent for esophageal cancer. One large review of mostly single-center, small sample sized studies where most patients underwent *open* esophagectomy (OE) reported that older patients suffer more from pulmonary and cardiac complications and increased mortality [5]. More recently, non-randomized cohort studies that only included patients who underwent minimally invasive esophagectomy showed no differences between postoperative complications and mortality rates between older and younger patients [6,7]. However, patients aged 75 years or older (i.e., older patients) were systematically excluded from the most prominent clinical trials: the TIME and MIRO trials [8,9]. In addition, while several large, observational studies did not exclude older patients, they were not analyzed as a separate group, and relatively few older patients were included [10–15]. Finally, while large databases do exist, such as the General Thoracic surgery Database (GTSD), no study has used entirely population-based data and adjusted for comorbidity and

☆ Accepted for ePoster presentation at the congress of International Society of Diseases of the Esophagus (ISDE) in September 2021.

* Corresponding author. Department of Surgery, Radboud University Medical Center, P.O. Box 9101, 6500 HB, Nijmegen, the Netherlands.
E-mail address: nikolaj.baranov@radboudumc.nl (N. Baranov).

https://doi.org/10.1016/j.suronc.2022.101789
Received 16 October 2021; Received in revised form 20 May 2022; Accepted 6 June 2022
Available online 21 June 2022

other confounding factors for the specific purpose of investigating the relationship between age and postoperative outcome after esophagectomy with curative intent [16–18].

The main objective of this study is to compare the rate of severe postoperative complications after esophagectomy with curative intent for esophageal cancer between patients aged 75 years or older and patients younger than 75 years. A second aim is to perform the comparison in a subgroup of totally minimally invasive esophagectomy (TMIE).

2. Materials and methods

A comparative cohort study was performed comparing the rates of postoperative complications, mortality, and length of hospital stay between two groups of patients based on their age at primary surgery: a group of patients aged 75 years or older (the older group) and a group of patients aged younger than 75 years (the younger group). Because large clinical trials excluded patients of 75 years and older for this study, the age limit was set at 75 years prior to performing statistical analysis [8,9,19]. Subgroup analyses were performed in patients that underwent TMIE and patients that had a severely complicated (Clavien-Dindo 3 and higher) postoperative course.

2.1. Setting

Patient data was retrieved from the Dutch Upper Gastrointestinal Cancer Audit (DUCA), a national surgical outcome registry that includes all patients with esophageal, junctional, or gastric cancer undergoing surgery in the Netherlands. Patients who do not undergo surgery are not included in the DUCA. Participation in the DUCA is obligatory, so all hospitals in the Netherlands performing esophagogastric surgery for cancer are included. Case ascertainment for the DUCA in 2013 was estimated at 97.8% of all primary esophageal and junctional cancer resections, as registered in the Netherlands Cancer Registry [20]. No ethical approval or informed consent was required for this study under Dutch law.

2.2. Participants

All patients diagnosed with primary esophageal cancer or primary junctional cancer (e.g., cT1b-4a N0-3 M0) who underwent transthoracic esophagectomy with curative intent in an elective setting, registered in the DUCA between January 1, 2011 and January 1, 2019 were included. Patients younger than 18 years at time of primary surgery were excluded.

Preoperative work-up was in accordance with local hospital protocol. The seventh edition of the American Joint Committee on Cancer TNM classification was used for tumor staging, and preoperative risk was assessed using the American Society of Anesthesiologists (ASA) physical status classification [21]. The surgical techniques varied and were defined as follows. OE was defined as a primary laparotomy with thoracotomy. Hybrid minimally invasive esophagectomy (HMIE) was defined as a combination of either primary laparotomy with thoracoscopy or primary laparoscopy with thoracotomy and was only included in the primary analysis. TMIE was defined as a primary laparoscopy with thoracoscopy. All outcome parameters were registered during initial hospital stay or within 30 days after initial operation.

2.3. Variables; outcome parameters and definitions

The primary outcome parameter was severe complications, defined as any complication graded ≥3 according to the Clavien-Dindo classification of surgical complications [22].

The secondary outcomes were: overall complications; clinically or radiologically proven anastomotic/staple line leakage or conduit necrosis; pulmonary complications, defined as clinically proven pneumonia, pleural effusion leading to *percutaneous drainage of or placing of a chest tube within the pleural cavity*, pleural empyema, acute respiratory distress syndrome, or reintubation; postoperative wound infection; damage to the recurrent laryngeal nerve; chyle leakage; postoperative hemorrhage requiring transfusion or reintervention; permanent injury as a consequence of a complication; reintervention rate (radiologic, endoscopic, or surgical); initial length of hospital stay *excluding duration of stay after readmission*; in-hospital mortality, mortality within 30 days postoperatively, and mortality within 90 days postoperatively.

Preoperative parameters registered at or around the time of surgery were: gender; body-mass index (BMI), calculated from length and weight; types of comorbidity converted to the Charlson Comorbidity Index (CCI) scores for each patient [23]; ASA score; histology type; tumor site; type of neoadjuvant therapy; surgical approach; type of reconstruction, and presence of lymphadenectomy. Gender, BMI, CCI score, ASA score, type of neoadjuvant therapy, and surgical technique were considered as potential confounders.

2.4. Statistical methods

All analyses were performed using the statistical software program R version 4.0.2 [24]. To adjust for the potential confounders, adjusted relative risk ratios (RR) and p-values for dichotomous outcomes were calculated using Poisson regression with robust standard errors to estimate confidence intervals (CI) were obtained separately using the R packages “lmtest” version 0.9–38 and “sandwich” version 3.0–0 [25–28].

Continuous, non-normally distributed outcomes were described using medians, inter-quartile ranges, lower and upper boundaries, and p-values were obtained using the Mann-Whitney *U* test. Continuous, normally distributed outcomes were described using means and standard deviations, and p-values were obtained using the Student’s *t*-test. Continuous outcomes were not adjusted for potential confounders and were not analyzed in the multiple imputed datasets (2.5 Missing data). Adjusted RRs and CIs from the *original* data are presented in the text, unless specified otherwise.

2.5. Missing data

Most missing values concern postoperative complication variables, and reasons for absence may vary considerably since this dataset is derived from a nationwide hospital registration. We used multiple imputation and assumed missing data were missing completely at random, with a maximum of 30 iterations to create and analyze 5 multiple imputed datasets [29,30]. Incomplete variables were imputed under fully conditional specification, using the default settings of the R package “mice” version 3.12.0 [31]. The parameters of interest were estimated in each imputed dataset separately and combined using Rubin’s rules.

3. Results

6210 patients with esophageal or junctional cancer were included in the original database. After exclusion Fig. 1), 3757 patients were deemed eligible for statistical analysis, of which 3302 (87.9%) were younger than 75 years (younger patients), and 455 (12.1%) were 75 years or older (older patients). Analyses of multiple imputation data did not change the results and were therefore only included as supplementary files. Additional sensitivity analyses including patients who did not undergo lymphadenectomy did not change the results and were therefore excluded from the primary analysis.

Patient demographics are presented in Table 1 and supplementary Table 1. Overall, baseline characteristics were comparable between older and younger patients. The median age in the older age group was 77 (IQR = 3) and 64 years (IQR = 11) in the younger age group. Regarding comorbidities, older patients suffered more frequently from prior myocardial infarction, cerebrovascular disease, dementia,

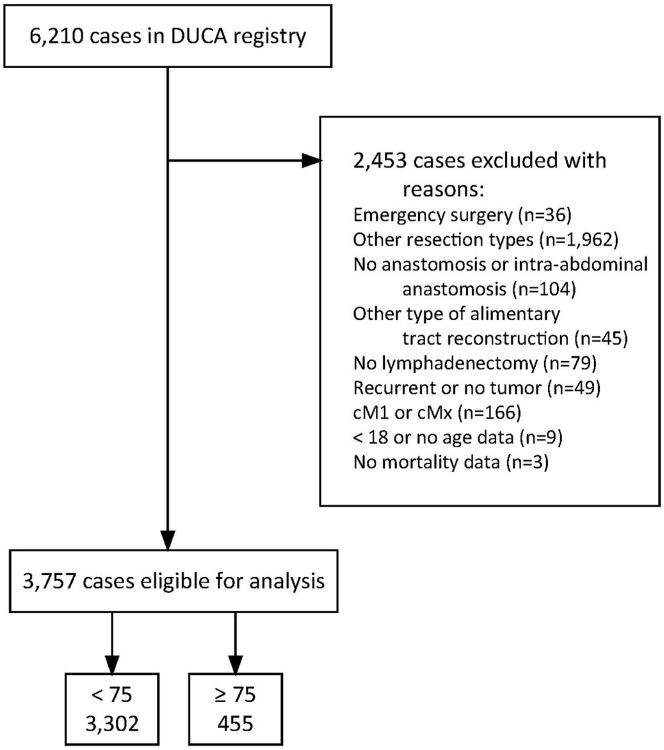

Fig. 1. Inclusion and exclusion flowchart
Flowchart depicting the case inclusion and exclusion process.

rheumatologic disease, and diabetes than younger patients. Overall, 62.2% had ASA score II and chemoradiotherapy was given to 88.6% of all patients. TMIE was the dominant surgical approach (75.7%), with more thoracic anastomoses than cervical anastomoses (54.7% vs. 45.3% respectively).

3.1. Primary outcome

Older patients suffered from severe complications significantly more frequently compared with younger patients (40.4% vs. 34.5%, CI = 1.009–1.080). After adjustment for the potential confounders, the result was no longer significant (CI = 0.991–1.062; Table 2). Multivariable analysis of risk factors for a severe complication are presented in supplementary Table 2. Older age was not an independent risk factor for severe complications. Increased ASA score and TMIE were significantly associated with increased risk of severe complications while neoadjuvant chemotherapy was associated with decreased risk.

3.2. Secondary outcome

Overall, complication rates were comparable between older and younger patients (Table 2). The median hospital length of stay in older patients was 14 days (IQR = 13), and 12 days (IQR = 11) in younger patients ($p < 0.001$). Mortality rates during hospital stay, within 30 and 90 days postoperatively, were similar for both age groups.

3.2.1. Sub-group analyses of patients that underwent TMIE (Table 3)

Overall, 356 older and 2488 younger patients underwent TMIE. A severe complication occurred in 150 (42.1%) older patients and in 891 (35.8%) younger patients (RR = 1.047, CI = 1.007–1.088). After adjustment for the potential confounders, the result was no longer significant (RR = 1.034, CI = 0.995–1.075). Overall complication rates, mortality rates, and reintervention rates were comparable between older and younger patients. Length of hospital stay was longer for older patients than for younger patients (14 days, IQR = 14 vs. 11 days, IQR = 9, $p < 0.001$).

3.2.2. Sub-group analyses of patients that had a severely complicated postoperative course (Table 4)

In order to investigate whether severe complications had a higher impact in older patients compared to younger patients, we investigated the outcome in a subgroup with severe complications. An anastomotic leak occurred in 77 (41.8%) older patients and in 542 (47.5%) younger patients (RR = 0.965, CI = 0.913–1.020). Pulmonary complications occurred in 109 (59.2%) older patients and in 647 (56.8%) younger patients (RR = 1.001, CI = 0.953–1.052), and chyle leakage occurred in 25 (13.6%) older patients and in 173 (15.2%) younger patients (RR = 0.989, CI = 0.944–1.037). Reintervention rates did not differ significantly. Older patients most often received an endoscopic reintervention, and younger patients a surgical reintervention. There were 43 (23.4%) older patients who had a prolonged ICU stay or ICU readmission, and 265 (23.2%) younger patients (RR = 1.001, CI = 0.963–1.041). Median ICU stay length was longer in older patients compared with younger patients, but not significantly so (5 days, IQR = 10, vs 4 days, IQR = 10, $p = 0.066$). Length of hospital stay was significantly longer in older patients compared with younger patients (26 days, IQR = 31, vs. 23 days, IQR = 28, $p = 0.005$). Mortality rates were comparable between older and younger patients.

3.2.2.1. Sensitivity analysis using three age groups (Supplementary File). The differences in baseline characteristics and comorbidities were similar to the primary analysis.

Compared with patients under 65 years, age 65–75 years was an independent risk factor of 30-day, 90-day and in-hospital mortality rate.

4. Discussion

This study showed that severe complications after esophagectomy with curative intent for esophageal cancer occurred more frequently in older patients compared with younger patients. After adjusting for confounders, we found that age and CCI score were not independent risk factors for severe complications. In addition, increased ASA score and TMIE were shown to be independent risk factors for severe complications. Furthermore, in sub-group analyses, rates of postoperative morbidity and mortality after TMIE did not significantly differ between older and younger patients, and neither did the rates of postoperative morbidity and mortality in patients with severe complications. Sensitivity analysis using three age groups, however, showed that age 65–75 was an independent risk factor of postoperative mortality.Lastly, in the primary analysis and sub-group analyses, older patients had significantly longer hospital stays than younger patients.

The major strength of our study is its nationwide character and the inclusion of all patients undergoing esophageal resection with curative intent in the Netherlands. Extensive information on comorbidities and other relevant variables provided an important opportunity to adjust for potential confounding factors. Some limitations should also be discussed. First, due to the retrospective design of this study selection bias must be considered. Some patients with several comorbidities may have been excluded from surgical treatment or recommended definitive chemoradiation therapy. Since, in general, older patients have more comorbidities, it is most likely that relatively older patients did not undergo esophagectomy compared to younger patients, and were therefore not included in this study. Since the DUCA registry only contains patients who underwent surgery, this could not be accounted for. Second, the national database comprises detailed data on hospital admission, but does not include long-term complications and data on functional outcomes, which are essential for optimally informing older patients about prognoses and impact quality of life. In addition, even though the outcomes were adjusted for several potential confounders, the possibility for residual confounding factors (e.g., frailty, nutritional

Table 1
Demographic characteristics.

		<75		≥75		Overall		RR	L	U	*p*
		N	%	N	%	N	%				
Total		3302	100	455	100	3757	100				
Age [1]	Median. IQR	64	11	77	3	66	11				<0.001
	Boundaries	19	74	75	86	19	86				
Gender	Men	2543	77.0	342	75.2	2885	76.8	0.976	0.923	1.032	0.395
	Women	758	23.0	112	24.6	870	23.2	1.072	0.902	1.274	0.428
	Unknown	1	0.0	1	0.2	2	0.1	7.257	0.454	115.908	0.161
BMI [1]	Median. IQR	25.47	5.40	25.32	4.61	25.45	5.27				0.282
	Boundaries	13.15	50.18	15.78	38.76	13.15	50.18				
CCI score	0	1726	52.3	189	41.5	1915	51.0	0.795	0.709	0.890	<0.001
	1	915	27.7	141	31.0	1056	28.1	1.118	0.965	1.296	0.138
	≥2	661	20.0	125	27.5	786	20.9	1.372	1.165	1.617	<0.001
ASA score	I	561	17.0	40	8.8	601	16.0	0.517	0.381	0.702	<0.001
	II	2054	62.2	281	61.8	2335	62.2	0.993	0.919	1.072	0.855
	III	673	20.4	131	28.8	804	21.4	1.413	1.204	1.657	<0.001
	IV	7	0.2	3	0.7	10	0.3	3.110	0.807	11.989	0.099
	Unknown	7	0.2	0	0	7	0.2	–	–	–	–
Histology	Adenocarcinoma	2462	74.6	338	74.3	2800	74.5	0.996	0.941	1.055	0.900
	Squamous cell carcinoma	739	22.4	103	22.6	842	22.4	1.011	0.844	1.213	0.902
	Other	76	2.3	12	2.6	88	2.3	1.146	0.628	2.090	0.657
	Unavailable	5	0.2	0	0	5	0.1	–	–	–	–
	Unknown	20	0.6	2	0.4	22	0.6	0.726	0.170	3.096	0.665
Site of tumour	Cervical	2	0.1	0	0	2	0.1	–	–	–	–
	Proximal third	49	1.5	7	1.5	56	1.5	1.037	0.472	2.275	0.928
	Middle third	529	16.0	73	16.0	602	16.0	1.001	0.800	1.253	0.990
	Distal third	2159	65.4	307	67.5	2466	65.6	1.032	0.964	1.105	0.368
	Esophagogastric junction	550	16.7	67	14.7	617	16.4	0.884	0.700	1.117	0.302
	Unknown	13	0.4	1	0.2	14	0.4	0.558	0.073	4.260	0.574
Neo-adjuvant therapy	Chemotherapy	150	4.5	11	2.4	161	4.3	0.532	0.291	0.974	0.041
	Chemoradiotherapy	2924	88.6	403	88.6	3327	88.6	1.000	0.966	1.036	0.990
	Radiotherapy	3	0.1	2	0.4	5	0.1	4.838	0.810	28.890	0.084
	No neo-adjuvant therapy	217	6.6	37	8.1	254	6.8	1.237	0.885	1.729	0.212
	Unknown	8	0.2	2	0.4	10	0.3	1.814	0.386	8.521	0.450
Surgical approach	Open surgery	593	18.0	65	14.3	658	17.5	0.795	0.628	1.008	0.058
	Laparoscopy	126	3.8	21	4.6	147	3.9	1.210	0.770	1.900	0.409
	Thoracoscopy	95	2.9	13	2.9	108	2.9	0.993	0.561	1.759	0.981
	Thoracoscopy and laparoscopy	2488	75.3	356	78.2	2844	75.7	1.038	0.986	1.094	0.157
	Unknown	0	0	0	0	0	0	1.000	0.907	1.103	1.000
Location of astomosis	Cervical	1504	45.5	199	43.7	1703	45.3	0.960	0.860	1.073	0.472
	Thoracic	1798	54.5	256	56.3	2054	54.7	1.033	0.947	1.127	0.460
	Unknown	0	0	0	0	0	0	1.000	0.907	1.103	1.000

BMI Body-mass index. *ASA score* ASA physical status classification system. *IQR* Inter-quartile range. *RR* Relative risk ratio. *L* Lower boundary of 95% confidence interval. *U* Upper boundary of 95% confidence interval. [1] *p*-value obtained with Mann-Whitney *U* test.

Table 2
Comparison of postoperative outcomes between younger and older patients.

		<75		≥75		RR	L	U	*p*
		N	%	N	%				
Total		3302	100	455	100				
Primary outcome	Severe complications	1140	34.5	184	40.4	1.026	0.991	1.062	0.144
Secondary outcomes	Overall complications	2032	61.5	309	67.9	1.031	1.003	1.060	0.032
	Leak	668	20.2	92	20.2	0.995	0.963	1.029	0.778
	Pulmonary complication	1113	33.7	177	38.9	1.023	0.988	1.059	0.201
	Infection	106	3.2	14	3.1	1.004	0.980	1.029	0.735
	Recurrent laryngeal nerve injury	150	4.5	27	5.9	1.019	0.990	1.048	0.195
	Chyle leakage	310	9.4	49	10.8	1.010	0.983	1.039	0.467
	Postoperative haemorrhage	26	0.8	6	1.3	1.002	0.988	1.015	0.799
	Permanent injury	29	0.9	5	1.1	1.004	0.985	1.025	0.667
	Reintervention	870	26.3	133	29.2	1.008	0.973	1.044	0.670
	Radiologic intervention	376	11.4	51	11.2	0.992	0.964	1.020	0.566
	Endoscopic intervention	384	11.6	66	14.5	1.018	0.987	1.049	0.251
	Surgical intervention	458	13.9	63	13.8	0.989	0.960	1.020	0.483
	Hospital length of stay [1]	12	11	14	13				<0.001
		0	200	5	148				
	30-day mortality	67	2.0	15	3.3	1.009	0.993	1.026	0.262
	90-day mortality	88	2.7	20	4.4	1.010	0.992	1.029	0.270
	In-hospital mortality	102	3.1	19	4.2	1.006	0.988	1.024	0.537

RR Relative risk ratio. *L* Lower boundary of 95% confidence interval. *U* Upper boundary of 95% confidence interval. [1] First row in consecutive order: median, IQR, median, IQR; second row in consecutive order: lower and upper boundary from patients <75 years, and from ≥75 years.

Table 3
Comparison of postoperative outcomes between younger and older patients that underwent TMIE.

		<75		≥75		RR	L	U	*p*
		N	%	N	%				
Total		2,488	100	356	100				
Primary outcome	Severe complications	891	35.8	150	42.1	1.034	0.995	1.075	0.092
Secondary outcomes	Overall complications	1,517	61.0	237	66.6	1.031	0.998	1.064	0.063
	Leak	523	21.0	76	21.3	1.004	0.967	1.043	0.832
	Pulmonary complication	804	32.3	135	37.9	1.029	0.989	1.070	0.153
	Infection	69	2.8	9	2.5	1.002	0.976	1.027	0.905
	Recurrent laryngeal nerve injury	118	4.7	19	5.3	1.009	0.978	1.041	0.568
	Chyle leakage	246	9.9	29	8.1	0.983	0.955	1.012	0.246
	Postoperative haemorrhage	15	0.6	3	0.8	1.000	0.987	1.013	0.972
	Permanent injury	27	1.1	3	0.8	0.997	0.978	1.016	0.746
	Reintervention	680	27.3	108	30.3	1.015	0.975	1.056	0.464
	Radiologic intervention	284	11.4	38	10.7	0.989	0.958	1.021	0.514
	Endoscopic intervention	321	12.9	58	16.3	1.026	0.990	1.064	0.155
	Surgical intervention	352	14.1	48	13.5	0.987	0.954	1.021	0.444
	Hospital length of stay [1]	11	9	14	14				<0.001
		0	200	5	148				
	30-day mortality	48	1.9	11	3.1	1.009	0.991	1.027	0.332
	90-day mortality	63	2.5	14	3.9	1.010	0.989	1.030	0.360
	In-hospital mortality	70	2.8	14	3.9	1.007	0.987	1.028	0.505

RR Relative risk ratio. *L* Lower boundary of 95% confidence interval. *U* Upper boundary of 95% confidence interval. [1] First row in consecutive order: median, IQR, median, IQR; second row in consecutive order: lower and upper boundary from patients <75 years, and from ≥75 years.

Table 4
Comparison of postoperative outcomes between younger and older patients that had a severely complicated postoperative course.

		<75		≥75		RR	L	U	*p*
		N	%	N	%				
Total		1140	100	184	100	1.000	1.000	1.000	0.922
	Leak	542	47.5	77	41.8	0.965	0.913	1.020	0.209
	Pulmonary complication	647	56.8	109	59.2	1.001	0.953	1.052	0.970
	Infection	53	4.6	7	3.8	0.993	0.950	1.039	0.775
	Recurrent laryngeal nerve injury	71	6.2	16	8.7	1.032	0.980	1.046	0.254
	Chyle leakage	173	15.2	25	13.6	0.989	0.944	1.037	0.647
	Postoperative haemorrhage	26	2.3	6	3.3	0.997	0.961	1.070	0.063
	Permanent injury	28	2.5	5	2.7	1.008	0.944	1.028	0.261
	Reintervention	870	76.3	133	72.3	0.976	0.936	1.017	0.241
	Radiologic intervention	376	33.0	51	27.7	0.961	0.908	1.018	0.175
	Endoscopic intervention	384	33.7	66	35.9	1.018	0.961	1.078	0.551
	Surgical intervention	458	40.2	63	34.2	0.953	0.901	1.009	0.097
	ICU readmission or prolonged stay	265	23.2	43	23.4	1.001	0.963	1.041	0.947
	ICU length of stay	4	10	5	12				0.067
		0	183	0	125				
	Hospital length of stay [1]	23	28	26	31				0.005
		0	200	7	148				
	30-day mortality	67	5.9	15	8.2	1.019	0.980	1.059	0.341
	90-day mortality	88	7.7	20	10.9	1.017	0.975	1.061	0.423
	In-hospital mortality	102	8.9	19	10.3	1.006	0.964	1.050	0.778

RR Relative risk ratio. *L* Lower boundary of 95% confidence interval. *U* Upper boundary of 95% confidence interval. [1] of which[2] First row in consecutive order: median, IQR, median, IQR, p value in the last column; second row in consecutive order: lower and upper boundary from patients <75 years, and from ≥75 years.

status etc.) cannot be ruled out in a retrospective study [4]. Third, while all patients were deemed to have resectable esophageal cancer, and therefore different TNM stages were grouped together, more extensive resections could have been performed on patients with higher TNM stages, potentially affecting the risk of postoperative morbidity and mortality. Sensitivity analysis, however, did show that TNM stage was not an independent risk factor of severe complications.

Like our study, several recent studies have shown that age is not associated with increased rates of severe complications [6,32–34]. In contrast, one study by Tapias et al. [35] and one by Li et al. [36] did show that an age of 70 years or older was associated with increased rates of severe complications. However, these studies did not classify severe complications according to Clavien-Dindo but used a composite outcome that included a wide variety of postoperative complications, which might have led to an overestimation of major complications. In addition, one population-based study by Schlottmann et al. showed that increased age was associated with increased complication rates, however, complications were not further classified according to severity, which may have also led to an overestimation of severe complications [37].

Interestingly, in multivariable analysis, we found that TMIE, as opposed to OE, was an independent risk factor for severe complications, which contrasts large trials comparing MIE with OE [8,9,38]. In addition, the MIRO trial showed fewer Clavien-Dindo ≥ II complications after MIE [10]. Several other studies comparing MIE with OE in older patients, showed fewer overall complications but more pulmonary complications after MIE [36,39,40]. In our view, the significant risk of severe complications after TMIE as found in this study may (partially) be due to a learning curve, since the study data stems from a transition period in which TMIE was introduced in the Netherlands [41].

Length of stay was significantly longer in older patients compared with younger patients in all analyses. Older patients in this study had higher CCI and ASA scores preoperatively, which are factors known to be associated with prolonged hospital stays [42]. In addition, since older patients have more limited physiological reserves, they need more time to recover from complicated postoperative courses, which is reflected in similar rates of complications but increased length of stay in our subgroup analysis [43]. In addition, since older patients tend to be discharged to institutional care facilities more often after surgery, while space may not always be readily available, waiting lists may have contributed to prolonging length of hospital stays for older patients in this study [44–46]. Unfortunately, data on discharge location were not available.

Increased risk of postoperative mortality in sensitivity analysis using three age groups with increased age could be explained by differences in baseline characteristics, since more patients <60 had ASA = 1 and CCI = 0 compared with patients 60–75 years. However that does not explain why age ≥75 years was not an independent risk factor for postoperative mortality. Furthermore, the overall mortality rate in this cohort is low, and the exact cause of mortality is not given by the DUCA. Therefore, it remains difficult to draw conclusions based on the current data.

This population-based study shows that age and CCI score were not independent risk factors for severe complications, in contrast to previously published literature [2]. However, increased ASA score *was* an independent risk factor. While on the surface this may sound contradictory, it is important to realize that the ASA score is used to present a patient's overall preoperative health, while the CCI score is used to predict a patient's 10-year overall mortality rate using a selection of predefined comorbidities. Therefore, we believe that age and overall comorbidity, combined with other patient-related factors, such as frailty and fitness, should be integrated in determining a patient's fitness for esophagectomy with curative intent for esophageal cancer. Future studies should elucidate the role of age and comorbidity regarding frailty, fitness, and patient outcome.

5. Conclusions

Age and Charlson Comorbidity Index are not adequate predictors of postoperative morbidity and mortality after esophagectomy with curative intent for esophageal cancer.

Author statement

Nikolaj Baranov, Linda Claassen, Frans van Workum, Camiel Rosman: Conceptualization, Methodology; Nikolaj Baranov, Linda Claassen: Formal Analysis, Writing – Original Draft/Review & Editing; Frans van Workum, Camiel Rosman: Writing – Review & Editing.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgements

None.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2022.101789.

References

[1] P.C. Enzinger, R.J. Mayer, Esophageal cancer, N. Engl. J. Med. 349 (23) (2003) 2241–2252.
[2] L. Backemar, P. Lagergren, T. Djarv, A. Johar, A. Wikman, J. Lagergren, Comorbidities and risk of complications after surgery for esophageal cancer: a nationwide cohort study in Sweden, World J. Surg. 39 (9) (2015) 2282–2288.
[3] J.P. Dolan, T. Kaur, B.S. Diggs, R.A. Luna, P.H. Schipper, B.H. Tieu, et al., Impact of comorbidity on outcomes and overall survival after open and minimally invasive esophagectomy for locally advanced esophageal cancer, Surg. Endosc. 27 (11) (2013) 4094–4103.
[4] M.A. Makary, D.L. Segev, P.J. Pronovost, D. Syin, K. Bandeen-Roche, P. Patel, et al., Frailty as a predictor of surgical outcomes in older patients, J. Am. Coll. Surg. 210 (6) (2010) 901–908.
[5] S.R. Markar, A. Karthikesalingam, S. Thrumurthy, A. Ho, G. Muallem, D.E. Low, Systematic review and pooled analysis assessing the association between elderly age and outcome following surgical resection of esophageal malignancy, Dis. Esophagus 26 (3) (2013) 250–262.
[6] N.S. Baranov, F. van Workum, J. van der Maas, E. Kouwenhoven, M. van Det, F.J. H. van den Wildenberg, et al., The influence of age on complications and overall survival after Ivor Lewis totally minimally invasive esophagectomy, J. Gastrointest. Surg. 23 (7) (2019) 1293–1300.
[7] J.C. Hol, J. Heisterkamp, I.S. Martijnse, R.A. Matthijsen, B.S. Langenhoff, Morbidity and mortality in elderly patients after minimally invasive esophagectomy, Ann Esophagus 2 (3) (2019).
[8] S.S.A.Y. Biere, M.I. van Berge Henegouwen, K.W. Maas, L. Bonavina, C. Rosman, J. R. Garcia, et al., Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial, Lancet 379 (9829) (2012) 1887–1892.
[9] C. Mariette, S.R. Markar, T.S. Dabakuyo-Yonli, B. Meunier, D. Pezet, D. Collet, et al., Hybrid minimally invasive esophagectomy for esophageal cancer, N. Engl. J. Med. 380 (2) (2019) 152–162.
[10] S. Sihag, A.S. Kosinski, H.A. Gaissert, C.D. Wright, P.H. Schipper, Minimally invasive versus open esophagectomy for esophageal cancer: a comparison of early surgical outcomes from the society of thoracic surgeons national database, Ann. Thorac. Surg. 101 (4) (2016) 1281–1289.
[11] B.A. Yerokun, Z. Sun, C.J. Yang, B.C. Gulack, P.J. Speicher, M.A. Adam, et al., Minimally invasive versus open esophagectomy for esophageal cancer: a population-based analysis, Ann. Thorac. Surg. 102 (2) (2016) 416–423.
[12] M.F.J. Seesing, S.S. Gisbertz, L. Goense, R. van Hillegersberg, H.M. Kroon, S. M. Lagarde, et al., A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in The Netherlands, Ann. Surg. 266 (5) (2017) 839–846.
[13] H. Takeuchi, H. Miyata, S. Ozawa, H. Udagawa, H. Osugi, H. Matsubara, et al., Comparison of short-term outcomes between open and minimally invasive esophagectomy for esophageal cancer using a nationwide database in Japan, Ann. Surg Oncol. 24 (7) (2017) 1821–1827.
[14] T. Sakamoto, M. Fujiogi, H. Matsui, K. Fushimi, H. Yasunaga, Comparing Perioperative Mortality and Morbidity of Minimally Invasive Esophagectomy versus Open Esophagectomy for Esophageal Cancer: A Nationwide Retrospective Analysis, Ann Surg, 2019.
[15] N. Yoshida, H. Yamamoto, H. Baba, H. Miyata, M. Watanabe, Y. Toh, et al., Can minimally invasive esophagectomy replace open esophagectomy for esophageal cancer? Latest analysis of 24,233 esophagectomies from the Japanese national clinical database, Ann. Surg. 272 (1) (2020) 118–124.
[16] C.D. Wright, J.C. Kucharczuk, S.M. O'Brien, J.D. Grab, M.S. Allen, Society of thoracic surgeons general thoracic surgery D. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a society of thoracic surgeons general thoracic surgery database risk adjustment model, J. Thorac. Cardiovasc. Surg. 137 (3) (2009) 587–595, discussion 96.
[17] D.P. Raymond, C.W. Seder, C.D. Wright, M.J. Magee, A.S. Kosinski, S.D. Cassivi, et al., Predictors of major morbidity or mortality after resection for esophageal cancer: a society of thoracic surgeons general thoracic surgery database risk adjustment model, Ann. Thorac. Surg. 102 (1) (2016) 207–214.
[18] The Society of Thoracic Surgeons (STS). General thoracic surgery database | STS [2021 april 17]. Available from:: https://www.sts.org/registries-research-center/sts-national-database/general-thoracic-surgery-database.
[19] P. van Hagen, M.C. Hulshof, J.J. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P. Wijnhoven, et al., Preoperative chemoradiotherapy for esophageal or junctional cancer, N. Engl. J. Med. 366 (22) (2012) 2074–2084.
[20] L.A. Busweiler, B.P. Wijnhoven, M.I. van Berge Henegouwen, D. Henneman, N. C. van Grieken, M.W. Wouters, et al., Early outcomes from the Dutch upper gastrointestinal cancer Audit, Br. J. Surg. 103 (13) (2016) 1855–1863.
[21] S.B. Edge, C.C. Compton, The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM, Ann. Surg Oncol. 17 (6) (2010) 1471–1474.
[22] D. Dindo, N. Demartines, P.A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey, Ann. Surg. 240 (2) (2004) 205–213.
[23] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (5) (1987) 373–383.
[24] R Core Team. R, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2020.
[25] M.J. Knol, S. Le Cessie, A. Algra, J.P. Vandenbroucke, R.H.H. Groenwold, Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression, Can. Med. Assoc. J. 184 (8) (2012) 895–899.
[26] A. Zeileis, T. Hothorn, Diagnostic checking in regression relationships, R. News 2 (3) (2002) 7–10.
[27] A. Zeileis, S. Köll, N. Graham, Various versatile variances: an object-oriented implementation of clustered covariances in R, J. Stat. Software 95 (1) (2020).
[28] A. Zeileis, Object-oriented computation of sandwich estimators, J. Stat. Software 16 (9) (2006).

[29] S. van Buuren, Flexible Imputation of Missing Data, second ed., Chapman and Hall/CRC, 2018, p. 444.
[30] J.L. Schafer, J.W. Graham, Missing data: our view of the state of the art, Psychol. Methods 7 (2) (2002) 147–177.
[31] S. van Buuren, K. Groothuis-Oudshoorn, Mice: multivariate imputation by chained equations in R, J. Stat. Software 45 (3) (2011).
[32] F. Klevebro, S. Garritano, C.M. Scandavini, A. Shetye, A. Coppola, S. Kamiya, et al., Surgical outcomes of oesophagectomy or gastrectomy due to cancer for patients 75 years of age: a single-centre cohort study, ANZ J. Surg. 89 (3) (2019) 228–233.
[33] H. Zhao, G. Liu, S. Wei, H. Liu, Short- and long-term outcomes of minimally invasive esophagectomy in elderly patients with esophageal squamous cell carcinoma, J BUON 22 (6) (2017) 1540–1546.
[34] M. Kanda, M. Koike, C. Tanaka, D. Kobayashi, M. Hayashi, S. Yamada, et al., Feasibility of subtotal esophagectomy with systematic lymphadenectomy in selected elderly patients with esophageal cancer; a propensity score matching analysis, BMC Surg. 19 (1) (2019) 143.
[35] L.F. Tapias, A. Muniappan, C.D. Wright, H.A. Gaissert, J.C. Wain, C.R. Morse, et al., Short and long-term outcomes after esophagectomy for cancer in elderly patients, Ann. Thorac. Surg. 95 (5) (2013) 1741–1748.
[36] C. Li, H. Wu, G. Xu, R. Xiong, M. Xu, M. Xie, Analysis of short- and long-term outcomes after esophagectomy in elderly cancer patients, Chin. J. Clin. Oncol. 45 (10) (2018) 508–512.
[37] F. Schlottmann, P.D. Strassle, A. Nayyar, F.A.M. Herbella, B.A. Cairns, M.G. Patti, Postoperative outcomes of esophagectomy for cancer in elderly patients, J. Surg. Res. 229 (2018) 9–14.
[38] P.C. van der Sluis, S. van der Horst, A.M. May, C. Schippers, L.A.A. Brosens, H.C. A. Joore, et al., Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial, Ann. Surg. 269 (4) (2019) 621–630.
[39] J. Li, Y. Shen, L. Tan, M. Feng, H. Wang, Y. Xi, et al., Is minimally invasive esophagectomy beneficial to elderly patients with esophageal cancer? Surg. Endosc. 29 (4) (2015) 925–930.
[40] H.B. Wang, Q. Guo, Y.H. Li, Z.Q. Sun, T.T. Li, W.X. Zhang, et al., Effects of minimally invasive esophagectomy and open esophagectomy on circulating tumor cell level in elderly patients with esophageal cancer, World J. Surg. 40 (7) (2016) 1655–1662.
[41] F. van Workum, M. Stenstra, G.H.K. Berkelmans, A.E. Slaman, M.I. van Berge Henegouwen, S.S. Gisbertz, et al., Learning curve and associated morbidity of minimally invasive esophagectomy: a retrospective multicenter study, Ann. Surg. 269 (1) (2019) 88–94.
[42] T.C. Collins, J. Daley, W.H. Henderson, S.F. Khuri, Risk factors for prolonged length of stay after major elective surgery, Ann. Surg. 230 (2) (1999) 251–259.
[43] M. Tahiri, T. Sikder, G. Maimon, D. Teasdale, F. Hamadani, N. Sourial, et al., The impact of postoperative complications on the recovery of elderly surgical patients, Surg. Endosc. 30 (5) (2016) 1762–1770.
[44] A. McCann, J. Sorensen, D. Nally, D. Kavanagh, D.A. McNamara, Discharge outcomes among elderly patients undergoing emergency abdominal surgery: registry study of discharge data from Irish public hospitals, BMC Geriatr. 20 (1) (2020) 72.
[45] C.J. Balentine, A.D. Naik, D.H. Berger, H. Chen, D.A. Anaya, G.D. Kennedy, Postacute care after major abdominal surgery in elderly patients: intersection of age, functional status, and postoperative complications, JAMA Surg 151 (8) (2016) 759–766.
[46] V.J. Legner, N.N. Massarweh, R.G. Symons, W.C. McCormick, D.R. Flum, The significance of discharge to skilled care after abdominopelvic surgery in older adults, Ann. Surg. 249 (2) (2009) 250–255.