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Review

Overall Survival Following Anastomotic Leakage After Surgery for Carcinoma of the Esophagus and Gastroesophageal Junction: A Systematic Review

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Abstract. *The effect of anastomotic leakage, in patients who underwent surgery for carcinoma of the esophagus and gastroesophageal junction, on overall survival (OS) is a debated and controversial topic. The aim of this systematic review was to clarify the impact of anastomotic leakage on long-term survival of patients with esophageal cancer undergoing esophagectomy. A systematic literature review was carried out from 2000 to 2022. We chose articles reporting data from patients who underwent surgery for carcinoma of the esophagus and gastroesophageal junction. Data regarding 1-, 3- and 5-year OS were analyzed. Twenty studies met the inclusion criteria, yielding a total of 9,279 patients. Analyzing data from selected studies, anastomotic leakage was found to be associated with decreased OS in 5,456 cases while in the remaining 3,823 it had no impact on long term survival ($p<0.05$). However, this result did not emerge from the other studies considered in the systematic review. Anastomotic leakage is a severe postoperative complication, which seems to have an impact on overall survival. However, the topic remains debated and not supported by all case series included in this systematic review.*

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Esophageal cancer is the seventh most common cancer in the world and the sixth in mortality overall (544,000 deaths) in 2020 (1). Approximately 70% of cases occur in men, and there is a 2- to 3-fold difference in incidence and mortality rates between the sexes worldwide (1). Despite improvements in secondary and tertiary prevention, it still remains among the cancers with the highest death rate, with a 5-year survival rate of approximately 20% (2).

Two are the main histological subtypes of esophageal cancer: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) (3). In addition, ESCC accounts for >85% of all esophageal cancer cases and it represents the most frequent histology in Asia and the incidence of EAC (4), especially in Western populations, has increased significantly. The increased incidence of EAC appears to be due to a birth cohort effect (for example, generational changes in prevalence of obesity), and this trend is expected to remain stable in high-income countries until 2030 (5).

Surgery remains the treatment of choice for prolonged survival, the cornerstone of any potential cure and it is integrated in multimodal therapy, especially for advanced disease (6). Esophagectomy is a technically demanding procedure that is still associated with major complications and except in specialized centers, mortality and morbidity

rates approximate 10% and 35%, respectively (7). The most feared complication is esophagogastric anastomotic failure, which is reported in the literature to occur in between 7.2% and 13.6% of patients after esophagectomy (8) with an associated operative mortality between 6% and 50% (9).

Currently, there is no consensus on the effects of anastomotic leakage (AL) on the OS of patients with esophageal cancer undergoing esophagectomy. Some authors reported a reduced OS in patients undergoing complicated esophagectomy with AL (10-14) whereas others did not report a correlation between AL and OS rates (6, 9, 15, 16). In two recent systematic reviews, we highlighted the tendency of AL to influence relapse or survival in distal esophageal and stomach cancer, respectively (17, 18).

The aim of this systematic review is to clarify the impact of AL on postoperative outcomes of patients affected by malignant tumor of the entire esophagus, and not only of the distal tract, as we have already done (17), analyzing in particular the effects of AL on overall survival.

Materials and Methods

Search strategy. A systematic search was conducted using PubMed, Web of Science, Cochrane Library, BMJ Clinical Evidence and UpToDate databases and searching for studies published up until 31 December 2022. We used the following terms, individually or in combination: "Cancer" AND "esophageal" (or "esophagus") AND "esophagogastric junction" AND "anastomotic leakage" (or "fistula" or "dehiscence") AND "overall survival" AND "long-term results". All reference lists from the studies selected following electronic search were analyzed to identify other relevant studies.

Compliance with ethical standards. Procedures performed in the studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study selection. Inclusion criteria were: 1) articles written in English; 2) published between January 2000 and December 2021, with case studies starting from 1985; 3) Open or minimally invasive surgery with curative intent; 4) Cases of ESCC or EAC according to the revised American Joint Committee on Cancer staging system (19); 5) Studies mentioning overall survival.

Exclusion criteria were: 1) Treatment for disease recurrence; 2) Case report; 3) Letter of Editor; 4) Review and metanalysis. In case of articles published by the same author or analyzing the same cohort of patients, the most recent analysis was included in the study.

Data extraction and quality assessment. Two reviewers (AM and MP) independently screened the articles by the title, abstract and keyword, and then selected and analyzed the relevant articles, according to the inclusion criteria. From each article, data regarding first author, year of publication, study design, number of patients with AL after esophagectomy, treatment regimen and OS rates were extrapolated and analyzed. Any disagreement was resolved by discussion with the senior author (PA). PRISMA statement guidelines for conducting and reporting systematic reviews were followed (20).

Study quality was established following the Newcastle-Ottawa scale, the instruments recommended by the Cochrane Collaboration were used in order to minimize bias risk for non-randomized studies included in systematic review (21).

Results

Study selection. A total of 11,718 articles were selected and evaluated from the initial search (Figure 1). Based on the analysis of the title and abstract and, according to the inclusion and exclusion criteria listed in the Materials and Methods section, we excluded 11,692 papers. A total of 25 articles were potentially eligible for the study and, of these, 14 more were excluded for the following reasons: in 11 articles, the OS was calculated by mixing all types of complications, not only the anastomotic leakage; in an article the authors did not report data about overall survival; in an article data analysis focused on perioperative mortality and in another one data about esophagectomies and gastrectomies were mixed. Finally, we analyzed the data of 11 articles extracted from the literature search and data of nine articles retrieved by searching through references, for a final total of 20 articles (9-11, 13, 14, 16, 22-34).

This pool of articles consisted of 15 retrospective reports (11, 16, 22, 23, 25-35) and 5 prospective case series (9, 10, 13, 14, 24). These articles analyzed data from patients who underwent surgery for esophageal cancer from 1987 to 2019, for a total of 9,279 patients.

Characteristics of the patients. The main features of the patients are summarized in Table I. The median age of the population was 63 years. Male patients represented 81% of the total population, with a male to female ratio of 4:1.

Tumor characteristics are shown in Table II. We collected data about tumor location, histology and AJCC stage. The most represented histotype was EAC. Most patients underwent an Ivor-Lewis esophagectomy (Table III). Finally, three articles report data from patients who underwent transhiatal esophagectomy or esophagectomy with the McKeown technique (9, 24, 28).

Anastomotic leakage. AL occurred in 3 to 36% of patients analyzed in the selected articles. In the article by Martin *et al.* (31), 30 cases of AL occurred in 476 patients who underwent esophagectomy for esophageal cancer. The extent of leak was categorized as contained or uncontained based upon appearance on imaging studies; from the univariate analysis that compared the uncontained versus contained leak, the median of survival between the two groups was not statistically significant (p=0.16) (31). Kamarajah *et al.* (16) analyzed data from patients with and without leaks and

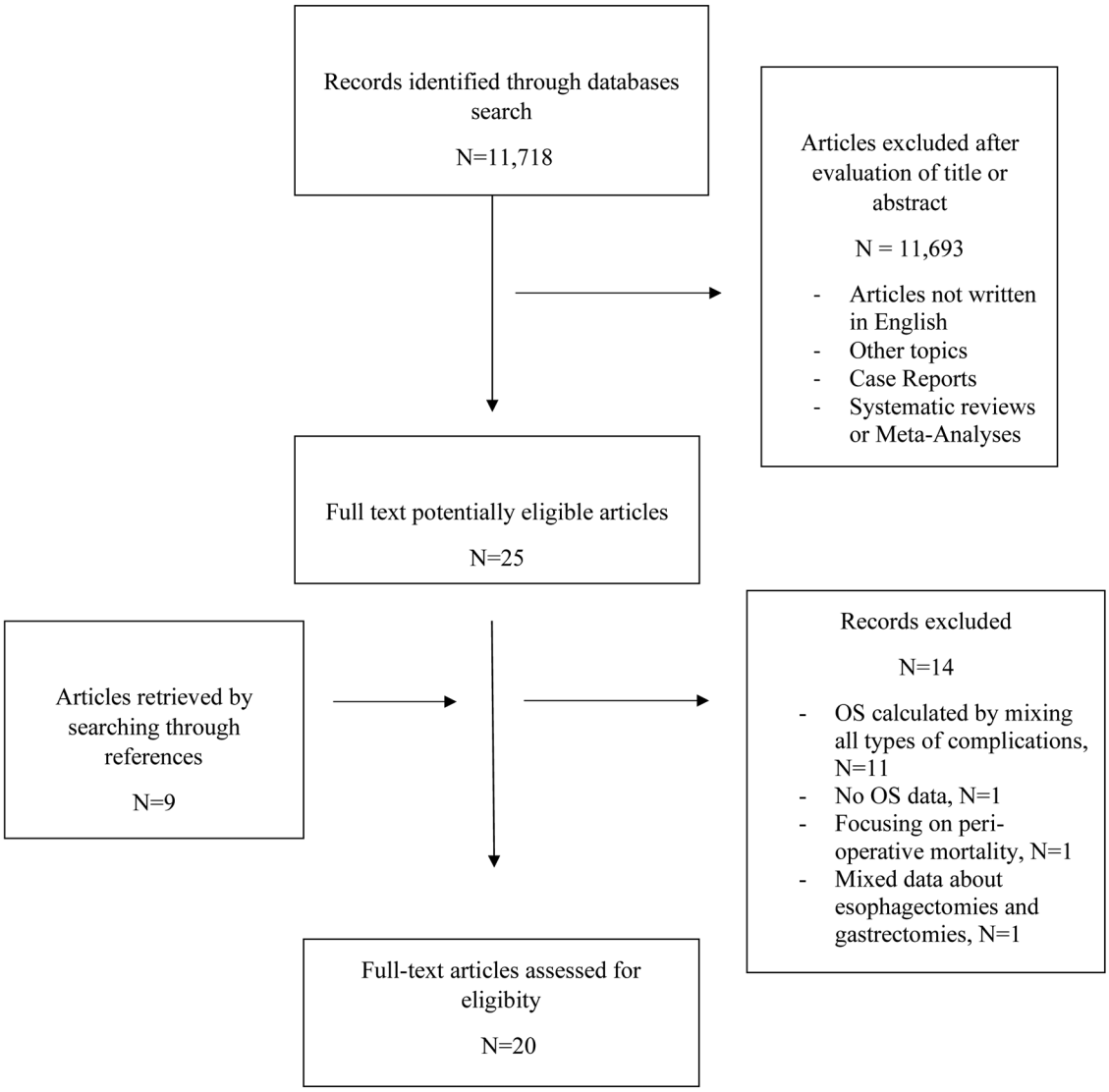

Figure 1. *Literature search strategy.*

found that there was no significant difference in OS between the two groups of patients (p=0.058). Fransen *et al*. collected data from 1,225 patients who underwent minimally invasive esophagectomy; 226 patients developed a postoperative AL (13). The Kaplan–Meier survival analysis showed that patients with an anastomotic leak had a statistically significant poorer OS with a 5 year OS of 44.0% *vs*. 57.2% for patients who didn't develop AL (p=0.005) (13). Fransen *et al*. had previously analyzed survival in patients undergoing esophageal surgery who experienced AL, in an article published in 2021 (36). Also in this work, which analyzed data from 13 high-volume centers, they found a statistically significant difference (p=0.043) in the OS of patients who developed an AL (36). In the article by Tverskov (28), patients who experienced an AL after esophagectomy were divided in three different groups according to the type of AL: Type 1 (leak treated medically or with dietary modification), Type 2 (leak requiring intervention but not surgical therapy) and Type 3 (leak requiring surgical intervention). They found that only patients with Type 3 AL had shorter OS compared to patients with non-severe leak (Type 1-2) and no leak (p=0.011) (28).

Impact of anastomotic leakage on survival. Analysis of the data from selected studies did not provide clear evidence about the association between AL and overall survival (Table IV). In nine studies, which analyzed the data of a total of 5456 patients, a statistically significant difference was found

Table I. *Characteristics of the included studies.*

Author, year (Ref)	Study type	Country	Study period	n. pts	Median age, years	Sex, M/F	AL, n (%)	NOS score
Martin 2005 (31)	RCS	USA	1987-2004	476	60.4	414/62	30 (6.3)	6
Junemann-Ramirez 2005 (32)	RCS	UK	1992-1999	276	66.1	188/88	14 (5.1)	5
Kondra 2008 (35)	RCS	Canada	2001-2006	168	64.0	143/25	34 (20.2)	5
Escofet 2010 (9)	PCS	UK	1998-2008	240	61.0	188/52	20 (8.3)	6
Rutegaard 2012 (14)	PCS	Sweden	2001-2005	567	/	460/107	46 (8.1)	4
Hii 2013 (10)	PCS	Australia	1998-2011	316	/	264/52	36 (11.1)	6
Lindner 2014 (27)	RCS	Germany	2005-2010	134	63.0	111/23	18 (13.4)	5
Markar 2015 (11)	RCS	France	2000-2010	2,439	60.6	2,000/439	208 (11.2)	6
Booka 2015 (33)	RCS	Japan	1997-2012	402	62.0	256/28	55 (19.4)	6
Van Daele 2016 (34)	RCS	Belgium	2005-2014	412	62.0	318/94	12 (3)	5
Saeki 2017 (22)	RCS	Japan	1990-2013	580	63.8	504/76	133 (22)	6
Kataoka 2017 (23)	RCS	Japan	/	314	61.0	282/32	45 (14)	5
Hayami 2018 (24)	PCS	Japan	1988-2015	70	64.6	65/5	9 (12.9)	5
Rasmussen 2018 (25)	RCS	Denmark	2010-2015	133	65.0	85/48	10 (11)	5
Aoyama 2020 (26)	RCS	Japan	2008-2018	122	68.0	106/16	44 (36)	6
Sugimura 2020 (30)	RCS	Japan	1997-2017	73	61.5	63/10	14 (19)	6
Kamarajah 2020 (16)	RCS	England	1997-2016	1,063	65.0	811/252	87 (8)	4
Kitadani 2021 (29)	RCS	Japan	2001-2019	61	68.0	59/2	9 (14)	5
Tverskov 2021 (28)	RCS	Israel	2010-2017	208	67.0	133/75	32 (15)	5
Fransen 2022 (36)	PCS	Multiple	2010-2016	1,225	65.0	756/469	226 (18)	6

n. pts: Number of patients; M: male; F: female; AL: anastomotic leakage; N: number; NOS: Newcastle-Ottawa Scale.

in terms of OS between patients who suffered from AL and those who did not suffer (10, 11, 13, 22, 25, 26, 29, 34, 35). Instead, in the remaining 11 studies, analyzing a smaller number of patients (3,823), AL did not seem to be related to a reduction in OS (9, 14, 16, 23, 24, 27, 28, 30-33). Lindner *et al*. found that neither overall complications nor pulmonary complications or anastomotic insufficiency significantly affected survival in esophageal cancer patients (27).

We believe that these differences may be due to different definitions of AL, based on clinical and/or radiological criteria.

The mechanism by which AL might affect survival remains uncertain. It is believed that an AL could represent a route of diffusion of tumor cells in the mediastinum, leading to a worsening of the patient's prognosis. However, this assumption is not validated in routine clinical practice (37).

Discussion

The aim of our work was to analyze the impact of AL on OS after esophageal cancer surgery, considering the neoplasms of the entire esophagus and not only of the distal tract. The relationship between AL and long-term results after surgery for esophageal cancer is still controversial. Similar analyses of data from patients undergoing gastric surgery for cancer concluded that AL is associated with worse long-term DFS and OS (18, 38) and suggested a closer follow up to promptly identify recurrence patients (39). In 2019, we investigated the possible correlation between recurrence and AL after surgery for carcinoma of the distal esophagus and gastroesophageal junction by analyzing data from 7 case series (17). In this study instead we investigated if there is a direct correlation between AL and OS, not necessarily related to an increased risk of recurrence following AL. We identified 20 case series that correlated AL and overall survival, thus being able to evaluate a higher number of patients than in the previous systematic review, including not only patients affected by carcinoma of the distal esophagus and gastroesophageal junction but also of the remaining tracts of the esophagus (17). Esophageal cancer surgery is technically complex, and it is still associated with a high rate of complications, often major.

AL represents one of the most dramatic complications after esophagectomy, with an incidence that varies widely and ranges from 0 to 35% (40), and clearly the most feared by surgeons. The main reason for this wide variation is the failure to use a single definition of esophageal AL.

For Markar *et al*. AL means a symptomatic disruption of the intrathoracic anastomosis classified as grade III or IV according to the Clavien–Dindo classification (11). Other studies referred to the classification of Clavien–Dindo without giving a definition of AL (37), whereas others gave a definition adapted from that of the Surgical Infection Study Group (26, 41).

In 2015, through an international consensus, Low *et al*. formulated a definition of AL, identifying three degrees of severity and the different types of treatment for each one,

Table II. *Tumor characteristics*.

Author, year (Ref)	Tumor location					Histology		AJCC stage				
	1/3 prox	1/3 middle	1/3 distal	GE junction	Cardia	EAC	ESCC	0	I	II	III	IV
Martin 2005 (31)	42	434	399	60	73	59	157	144	42			
Junemann-Ramirez 2005 (32)	/	/	/	/	/	/	/	5	7	70	185	9
Kondra 2008 (35)	/	14	69	85	/	135	33	2	38	74	52	2
Escofet 2010 (9)	3	25	167	45	0	190	45	2	25	80	115	7
Rutegaard 2012 (14)	/	/	/	/	/	422	135	110	166	230	58	
Hii 2013 (10)	1	22	224	69	0	265	50	41	83	73	114	5
Lindner 2014 (27)	/	/	/	/	/	89	45	/	/	/	/	/
Markar 2015 (11)	281	828	1,330	/	/	1,260	1,105	/	/	/	/	/
Booka 2015 (33)	/	/	/	/	/	19	255	/	/	/	/	/
Van Daele 2016 (34)	/	/	/	/	/	225	107	/	/	/	/	/
Saeki 2017 (22)	102	292	148	/	/	/	580	/	/	/	/	/
Kataoka 2017 (23)	27	155	132	/	/	/	313	/	/	156	158	/
Hayami 2017 (24)	28	29	13	/	/	/	70	2	21	15	31	1
Rasmussen 2018 (25)	/	/	/	/	/	/	133	/	/	/	/	/
Aoyama 2020 (26)	36	86	/	/	/	/	/	/	/	/	/	/
Sugimura 2020 (30)	21	39	13	/	/	73	/	/	24	6	28	15
Kamarajah 2020 (16)	/	/	/	/	/	837	207	49	243	234	450	87
Kitadani 2021 (29)	/	/	/	/	/	/	/	2	16	13	24	6
Tverskov 2021 (28)	47	76	85	143	57	143	57	7	31	29	140	1
Fransen 2022 (36)	17	140	799	266	/	972	253	/	/	/	/	/

GE: Gastroesophageal; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; AJCC: American Joint Committee on Cancer.

from dietary modification to surgical intervention (42). However, our research has identified only one study that used this classification (16). We also found a lack of consensus on the use of post-operative radiological exams that could detect AL. Some authors did not routinely use post-operative barium swallow, while others always performed it on the fifth post-operative day. The short-term negative impact of the AL is evident; Ramirez *et al*. reported that a 30-day mortality for patients with anastomotic leak was 37.5 % compared to 4.2% for patients without leak ($p<0.05$) (32). Many studies have shown that high-volume centers are more able to deliver high-quality outcomes (9, 13-15). However, the impact of AL on long-term oncological outcomes is still unclear. Furthermore, the mechanism by which an esophageal anastomotic leak would lead to an increase in local recurrences is still uncertain.

Two hypotheses have been mainly formulated and in both cases the authors took inspiration from other types of cancers, such as colorectal and breast (43). The first theory states that the leakage of viable esophageal cancer cells provides a nidus for locoregional tumor recurrence (44-46). The second focuses on the proinflammatory response triggered by the enteric content entered into the mediastinum and characterized by the release of proinflammatory cytokines such as IL-32 and TNF-α whose expression is increased in patients with esophageal cancer (47, 48). Another explanation for the increased local recurrence and decreased survival after AL is the inadequate negative oncologic resection margin (23); for this reason, many authors have stressed the concept that better surgical and oncological outcomes could be achieved in high-volume centers where surgeons have greater experience in esophageal surgery (9, 14, 16, 23).

Literature still fails to shed light on this topic, and even this systematic review shows conflicting results. In 2016, Saeki *et al*. showed that the 5-year OS (long rank, $p<0.0001$) of patients with AL was significantly poorer than those without leaks, particularly for pStage 0, I and II (22). However, in 2017, Kataoka *et al*. found that the OS of patients complicated by leaks was nearly identical to that of uncomplicated patients (23).

Two additional eastern studies published in 2020 confirmed the conflicting results (26, 30). Sugimura *et al*. (30) collected data from 73 patients who underwent esophagectomy over a 20-year period and concluded that OS of patients with postoperative complications was markedly poorer than those without complications (HR=2.06; $p=0.017$); analyzing the impact of each individual complication they found no significant differences in the OS of patients with or without AL (HR=1.37; $p=0.377$) (30). Kamarajah *et al*. (16) analyzed data from patients with and without leaks and classified patients with AL associated with

Table III. *Treatment*.

Author, year (Ref)	n. pts	Neoadjuvant		Surgery			Location of anastomosis			R0
		CT	CT+RT	Ivor-Lewis	McKeown	Transhiatal	Cervical	Thoracic	Abdominal	
Martin 2005 (31)	476	93	200	/	/	/	/	476	/	/
Junemann-Ramirez 2005 (32)	276	/	/	276	/	/	/	276	/	276
Kondra2008 (35)	168	40	43	/	/	/	/	/	/	/
Escofet 2010 (9)	240	104	49	147	/	93	93	147	/	240
Rutegaard 2012 (14)	567	31	/	/	/	/	/	/	485	
Hii 2013 (10)	316	/	/	/	/	/	/	/	/	272
Lindner 2014 (27)	134	/	78	134	/	/	/	/	/	124
Markar 2015 (11)	2,439	1,129	698	/	/	/	589	1,850	/	/
Booka 2015 (33)	402	68	24	/	/	/	214	56	/	259
Van Daele 2016 (34)	412	/	189	412	/	/	/	412	/	396
Saeki 2017 (22)	580	43	247	/	/	/	/	/	/	/
Kataoka 2017 (23)	314	/	/	/	/	/	/	/	/	/
Hayami 2017 (24)	70	/	70	67	1	2	3	67	/	51
Rasmussen 2018 (25)	133	/	114	/	/	/	4	129	/	/
Aoyama 2020 (26)	122	51	/	/	/	/	/	/	/	122
Sugimura 2020 (30)	73	/	73	73	/	/	/	73	/	63
Kamarajah 2020 (16)	1,063	563	/	1,063	/	/	/	1,063	/	1,042
Kitadani 2021 (29)	61	11	3	/	/	/	/	/	/	/
Tverskov 2021 (28)	208	162	/	/	163	45	208	/	/	194
Fransen 2022 (36)	1,225	96	996	969	/	256	740	480	/	1,225

n. pts: Number of patients; CT: chemotherapy; RT: radiotherapy.

Table IV. *Relationship between overall survival and anastomotic leakage*.

Author, year (Ref)	FU duration (mo)	OS								*p*-Value
		AL				NL				
		1 year (%)	3 years (%)	5 years (%)	Median (mo)	1 year (%)	3 years (%)	5 years (%)	Median (mo)	
Martin 2005 (31)	134.8	68	30	32	16.6	78	40	25	28.9	0.17
Junemann-Ramirez 2005 (32)	48	/	/	/	17.1	/	/	/	18	0.687
Kondra 2008 (35)	/	20	0	0	/	82	58	45	/	0.010
Escofet 2010 (9)	60	80	40	30	22	82	45	38	31	0.314
Rutegaard 2012 (14)	60	58	34	17	22	63	34	22	24.4	0.40
Hii 2013 (10)	51	/	/	/	22	/	/	/	52	0.016
Lindner 2014 (27)	/	/	/	/	33.7	/	/	/	42.8	/
Markar 2015 (11)	54	71	37	18	35.8	81	45	25	54.8	0.002
Booka 2015 (33)	60	62	50	45	/	72	55	50	/	0.415
Van Daele 2016 (34)	27	35	22	0	3	47	30	12	41	<0.001
Saeki 2017 (22)	31	/	/	45	/	/	/	68.3	/	<0.0001
Kataoka 2017 (23)	/	/	57.1	/	/	/	66.3	/	/	0.88
Hayami 2017 (24)	30.2	65	30	0	/	68	38	26.1	/	0.286
Rasmussen 2018 (25)	39	/	/	/	/	/	/	/	/	0.016
Aoyama 2020 (26)	72.5	70	42	40.2	35.8	85	65	53.2	54.8	0.002
Sugimura 2020 (30)	22	72	30	22	/	75	50	40	/	0.377
Kamarajah 2020 (16)	/	70	52	48	41	80	69	60	77	0.058
Kitadani 2021 (29)	28.1	78	40	35	21	81	65	60	44	0.011
Tverskov 2021 (28)	41	31	45	38	/	83	60	45	/	0.081
Fransen 2022 (36)	/	76	56.7	44.0	/	84.1	66.3	57.2	/	0.005

n. pts: Number of patients; FU: follow up; AL: anastomotic leakage; OS: overall survival; NL: non-anastomotic leakage.

grade III-IV complications [according to the Clavien–Dindo grading system (49)] as severe esophageal AL (SEAL) and those with less severe complications [Clavien–Dindo grade I/II (49)] as non-severe leaks (NSLs). The authors found that there was no significant difference in OS between the three groups of patients (p=0.8): patients experiencing SEAL had a median survival of 61 months, compared with 55 months for patients with NSL and 41 months for patients with no AL (16).

Aoyama *et al*. (26) showed different results: the median OS after surgery was 35.8 months in the AL group and 54.8 months in the non-AL group (p=0.022). AL was a significant prognostic factor for OS in the uni- and multi-variate analyses. However they failed to provide a clear explanation of this impact on survival; they only hypothesized a reduced host immunity against the residual tumor and concluded that the detailed mechanism is still unclear (26).

In many studies the impact of the AL on long term outcomes has been compared with other complications, particularly infectious, and these comparisons also led to conflicting results. Kataoka *et al*. reported that the OS of patients with pneumonia was shorter than that of patients without pneumonia, on the contrary the OS of patients with AL was nearly identical to that for patients without leakage (23). However, the opposite was demonstrated in an international multicenter cohort study involving 13 high-volume centers, with a total of 915 minimally invasive esophagectomies. Pulmonary complications were not associated with OS (p=0.897), whereas the occurrence of AL, especially CD grade ≥ III, was associated with a statistically significant poorer survival (p=0.025) (36).

In conclusion, AL is a severe postoperative complication that increases the fragility of patients, lengthening their post-operative hospitalization. In the light of our systematic review, it would also appear to be an independent prognostic factor, having a statistically significant impact on OS in the univariate analysis of many studies included in the review. Other authors do not confirm this result, but we believe that a considerable heterogeneity among the samples analyzed may have influenced the correlation between AL and OS.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

PA approved the final version to be published, MP and AM conceived, designed and wrote the study, FDA provided data, MC, MG and GM collected data, SV and LA analysed data, GB and NP critically revised the article.

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