State of Play: Eight Decades of Surgery for Esophageal Atresia

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Eur J Pediatr Surg 2019;29:39–48.

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Abstract

Aim Surgical expertise and advances in technical equipment and perioperative management have led to enormous progress in survival and morbidity of patients with esophageal atresia (EA) in the last decades. We aimed to analyze the available literature on surgical outcome of EA for the past 80 years.

Materials and Methods A PubMed literature search was conducted for the years 1944 to 2017 using the keywords "esophageal/oesophageal atresia," "outcome," "experience," "management," and "follow-up/follow up." Reports on long-gap EA only, non-English articles, case reports, and reviews without original patient data were excluded. We focused on mortality and rates of recurrent fistula, leakage, and stricture.

Results Literature search identified 747 articles, 118 manuscripts met the inclusion criteria. The first open end-to-end anastomosis and fistula ligation was reported in 1941. Thoracoscopic fistula ligation and primary anastomosis was performed first in 2000. Reported mortality rate decreased from 100% before 1941 to 54% in 1950 to 1959, 28% in 1970 to 1979, 16% in 1990 to 1999, and 9% nowadays. Rates of recurrent fistula varied over time between 4 and 9%. Leakage rate remained stable between 11 and 16%. However, stricture rate increased from 25 to 38%.

Conclusion Including a full range of articles reflecting the heterogeneity of EA, mortality rate significantly decreased during the course of 80 years. Along with the decrease in mortality, there is a shift to the importance of major postoperative complications and long-term morbidity regardless of surgical technique.

Keywords
- esophageal atresia
- outcome
- surgical techniques
- mortality rate
- long-term morbidity

Introduction

Advances in surgical expertise, technical equipment as well as anesthetic and neonatal intensive care management, have contributed to decreased mortality and morbidity rates of patient with esophageal atresia (EA) in the last decades.[1–3]

Before gradual implementation of surgical management, the mortality rate of EA patients was 100%. The first survivors with the condition were independently reported by Leven and Ladd in 1939, who managed their cases with a staged approach consisting of initial gastrostomy, subsequent fistula ligation or division with cervical esophagostomy, and finally creation of an antethoracic skin tube conduit from the esophagostomy to the gastrostomy.[4–7] The first successful open end-to-end anastomosis and fistula ligation was reported in 1941 by Haight and Towsley.[8] At a later time, Haight revised his technique from a left extrapleural approach with single-layer anastomosis to two-layer anastomosis and a right extrapleural approach.[4] Many of Haight's initial techniques still guide our current management of neonates born with EA.[4]

received
May 15, 2018
accepted
June 27, 2018
published online
August 15, 2018

DOI https://doi.org/10.1055/s-0038-1668150.
ISSN 0939-7248.

Another milestone in EA surgery was achieved with the introduction of minimal invasive surgery. In 1999, the first successful thoracoscopic repair of a pure EA was performed.[9] One year later, Rothenberg reported the first thoracoscopic fistula ligation and primary anastomosis.[10] Since then, minimal invasive EA repair is deployed in increasing numbers worldwide.[11]

This report aims to elucidate and compare the outcome development of EA throughout the decades since the first end-to-end anastomosis to modern era. Besides mortality rates, we focused on common and severe postoperative complications after EA repair, such as occurrence of recurrent fistula, anastomotic leakage, and stricture.

Materials and Methods

In January 2018, a PubMed literature search was conducted for the years 1944 to 2017 using different combinations of the following keywords: "esophageal/oesophageal atresia," "outcome," "experience," "management," and "follow-up/follow up." Additionally, reference lists of included papers were screened manually for further studies. Duplicates were deleted.

Selection Criteria and Data Extraction

Relevant articles were reviewed by title, abstract, and keywords, and full-text of selected articles were assessed by one of the authors (J.Z.). Only articles in English language were considered. Reports on long-gap EA only, case reports, and reviews without original patient data were excluded. We focused on mortality and rates of recurrent fistula, leakage, and stricture. The data were standardized extracted into an electronic database, containing the characteristics of the study (authors, publication year, time frame of the study, number of patients, age/mean follow-up time, mortality rate, and percentage of patients with recurrent fistula, leakage, and stricture).

Statistical Analysis

Microsoft Excel was used for data analysis. The percentage of patients with recurrent fistula, leakage, and stricture as well as the percentage of patients who died was compared between the different decades.

Results

A total of 747 articles were identified through literature search, of which 118 manuscripts met the inclusion criteria (►Fig. 1). Included articles and their reported outcomes are shown in ►Table 1. An overview of the included study types is given in ►Table 2. All except for seven were retrospective studies.[3,12–17] One was a randomized controlled trial as reported by Upadhyaya et al.[18] It is notable that some reports comprise outcome data of several decades, which were matched to the related period.

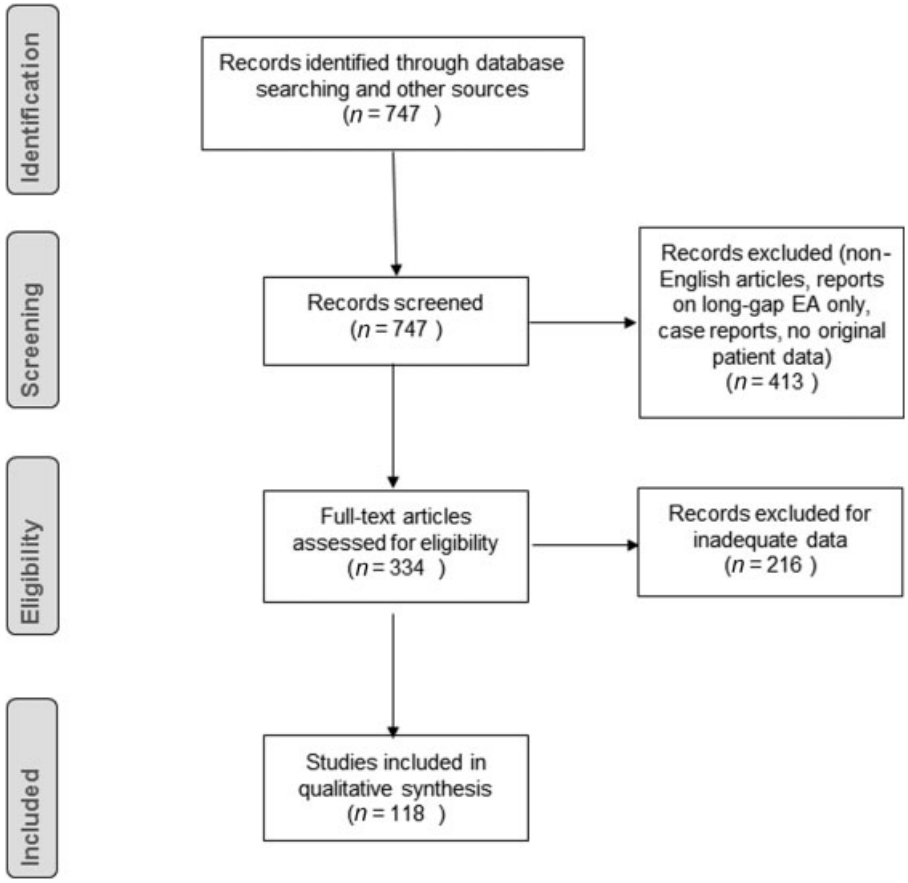

Fig. 1 PRISMA flow chart for data extraction. EA, esophageal atresia; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Included articles and their characteristics for this study (chronological order)

Author and year	Study period	Study type	No. of patients	Anastomotic leak	Recurrent fistula	Stricture rate	Mortality
Donoso and Lilja 2017[53]	1994–2013	Retrospective	129	Yes	No	Yes	Yes
Tröbs et al 2017[54]	2006–2013	Retrospective	24	N/R	N/R	N/R	Yes
Long et al 2017[15]	2008–2009	Prospective	21	Yes	No	Yes	N/R
Acher et al 2016[17]	Not specified	Prospective	445	Yes	N/R	Yes	N/R
Bakal et al 2016[55]	1996–2011	Retrospective	51	Yes	N/R	Yes	Yes
Bradshaw et al 2016[56]	2004–2013	Retrospective	58	Yes	N/R	Yes	Yes
Dingemann et al 2016[25]	2007–2012	Retrospective	75	Yes	Yes	Yes	No
Donoso et al 2016[57]	1994–2013	Retrospective	129	Yes	Yes	Yes	Yes
Hannon et al 2016[27]	1993–2015	Retrospective	9	N/R	Yes	N/R	Yes
Hartley et al 2016[58]	1996–2014	Retrospective	120	Yes	N/R	N/R	Yes
Malakounides et al 2016[35]	2001–2011	Retrospective	200	N/R	N/R	N/R	Yes
Okata et al 2016[59]	2000–2015	Retrospective	28	Yes	No	Yes	N/R
Tong et al 2016[60]	2008–2014	Retrospective	35	Yes	N/R	N/R	N/R
Okuyama et al 2015[21]	Not specified	Retrospective	58	Yes	Yes	Yes	Yes
Pini Prato et al 2015[14]	2011–2013	Prospective	146	Yes	Yes	Yes	Yes
Uygun et al 2015[61]	2009–2013	Retrospective	6	Yes	N/R	Yes	Yes
Allin et al 2014[12]	2008–2009	Prospective	151	Yes	Yes	Yes	Yes
Dunkley et al 2014[52]	1990–2007	Retrospective	66	Yes	Yes	Yes	Yes
Fallon et al 2014[62]	2002–2012	Retrospective	91	Yes	Yes	Yes	Yes
Lee et al 2014[63]	2008–2013	Retrospective	23	Yes	Yes	Yes	N/R
Schneider et al 2014[13]	2008–2009	Prospective	307	Yes	Yes	Yes	Yes
Sulkowski et al 2014[48]	1999–2012	Retrospective	3479	N/R	Yes	N/R	Yes
Wang et al 2014[1]	2000–2009	Retrospective	4168	N/R	N/R	N/R	Yes
Yamato et al 2014[29]	2001–2012	Retrospective	26	Yes	Yes	Yes	No
Burge et al 2013[16]	2008–2009	Prospective	151	Yes	N/R	N/R	Yes
Dingemann et al 2013[26]	2001–2011	Retrospective	44	Yes	Yes	No	No
Koivusalo et al 2013[37]	1991–2001	Retrospective	130	Yes	Yes	Yes	Yes
Niramis et al 2013[64]	2003–2010	Retrospective	132	Yes	Yes	Yes	Yes
Rothenberg 2013[24]	2000–2012	Retrospective	61	Yes	No	Yes	No
Sfeir et al 2013[3]	2008–2009	Prospective	307	N/R	Yes	Yes	Yes
Sfeir et al 2013[65]	2008–2009	Retrospective	307	N/R	N/R	N/R	Yes
Huang et al 2012[46]	2007–2012	Retrospective	33	Yes	Yes	Yes	Yes
Jawaid et al 2012[66]	1999–2009	Retrospective	119	Yes	Yes	Yes	Yes
Oddsberg et al 2012[47]	1964–2007	Retrospective	1126	N/R	N/R	N/R	Yes
Rothenberg 2012[30]	N/R	Retrospective	49	Yes	No	Yes	No
Spoel et al 2012[50]	2005–2009	Retrospective	37	N/R	N/R	Yes	N/R
Burford et al 2011[67]	1993–2008	Retrospective	72	Yes	Yes	Yes	N/R
Sistonen et al 2011[68]	1947–1985	Retrospective	101	Yes	Yes	Yes	Yes
Szavay et al 2011[22]	2002–2010	Retrospective	68	Yes	N/R	N/R	No
Zhao et al 2011[69]	2000–2009	Retrospective	85	Yes	N/R	Yes	N/R
Jong et al 2010[70]	2000–2006	Retrospective	59	Yes	Yes	Yes	Yes
Lacher et al 2010[36]	1988–2009	Retrospective	111	Yes	Yes	Yes	Yes
Serhal et al 2010[71]	2000–2005	Retrospective	62	Yes	N/R	N/R	N/R

(*Continued*)

Table 1 (*Continued*)

Author and year	Study period	Study type	No. of patients	Anastomotic leak	Recurrent fistula	Stricture rate	Mortality
MacKinlay 2009[72]	N/R	Retrospective	36	Yes	Yes	Yes	Yes
Patkowsk et al 2009[73]	2005–2008	Retrospective	23	Yes	No	Yes	Yes
Petrosyan et al 2009[2]	1987–2009	Retrospective	25	Yes	No	Yes	Yes
Tandon et al 2009[74]	2007–2008	Retrospective	98	Yes	N/R	N/R	Yes
Lilja et al. 2008[38]	1986–2005	Retrospective	147	Yes	Yes	Yes	Yes
Lugo et al 2008[23]	2000–2006	Retrospective	33	Yes	N/R	Yes	No
Sri Paran et al 2007[75]	1977–2004	Retrospective	26	N/R	N/R	Yes	Yes
Upadhyaya et al 2007[18]	2004–2006	RCT	50	Yes	N/R	Yes	Yes
van der Zee and Bax 2007[76]	2000–2006	Retrospective	51	Yes	Yes	Yes	Yes
Al-Salem et al 2006[33]	1989–2004	Retrospective	94	Yes	Yes	Yes	Yes
Sugito et al 2006[34]	1975–2003	Retrospective	24	Yes	Yes	Yes	Yes
Uchida et al 2006[77]	1979–2003	Retrospective	42	Yes	Yes	Yes	Yes
Yang et al 2006[31]	1994–2003	Retrospective	15	Yes	No	Yes	Yes
Al-Malki et al 2005[78]	1990–2000	Retrospective	101	N/R	N/R	N/R	Yes
Holcomb et al 2005[39]	N/R	Retrospective	104	Yes	Yes	Yes	N/R
Calisti et al 2004[79]	1999–2002	Retrospective	75	Yes	Yes	Yes	Yes
Deurloo et al 2004[80]	1982–2002	Retrospective	197	Yes	Yes	N/R	Yes
Orford et al 2004[81]	1970–2000	Retrospective	152	Yes	N/R	Yes	Yes
Tonz et al 2004[82]	1973–1999	Retrospective	104	Yes	Yes	Yes	Yes
Touloukian, Seashore[83]	1968–2003	Retrospective	143	Yes	Yes	Yes	Yes
Konkin et al 2003[84]	1984–2000	Retrospective	144	Yes	Yes	Yes	Yes
Little et al 2003[43]	1972–1990	Retrospective	69	Yes	N/R	Yes	N/R
van der Zee and Bax 2003[85]	2002	Retrospective	13	Yes	N/R	Yes	N/R
Deurloo et al 2002[86]	1947–2000	Retrospective	371	Yes	Yes	Yes	Yes
Sharma et al 2000[32]	1972–1996	Retrospective	585	Yes	Yes	Yes	Yes
Sparey et al 2000[87]	1985–1997	Retrospective	120	N/R	N/R	Yes	Yes
Nawaz et al 1998[88]	1981–1996	Retrospective	41	Yes	No	Yes	Yes
Somppi et al 1998[89]	1963–1993	Retrospective	60	N/R	N/R	N/R	Yes
Okada et al 1997	1957–1995	Retrospective	159	Yes	Yes	Yes	Yes
Tsai et al 1997[90]	1957–1995	Retrospective	81	Yes	N/R	Yes	Yes
Engum et al 1995[91]	1971–1993	Retrospective	227	N/R	Yes	Yes	Yes
Rokitansky et al 1994[92]	1960–1991	Retrospective	309	N/R	N/R	N/R	Yes
Spitz et al 1994[28]	1980–1992	Retrospective	372	N/R	N/R	N/R	Yes
Alexander et al 1993[93]	1966–1986	Retrospective	25	Yes	Yes	Yes	Yes
Rokitansky et al 1993[45]	1975–1991	Retrospective	223	Yes	Yes	Yes	Yes
Touloukian 1992[94]	1968–1990	Retrospective	68	Yes	Yes	Yes	Yes
Poenaru et al 1991[95]	1962–1988	Retrospective	131	Yes	Yes	Yes	Yes
McKinnon and Kosloske 1990[96]	1976–1989	Retrospective	64	Yes	Yes	Yes	Yes
Adebo 1990[97]	1977–1987	Retrospective	11	Yes	N/R	Yes	Yes
Chittmittrapap et al 1990[98]	1980–1987	Retrospective	199	Yes	Yes	Yes	N/R

Table 1 (*Continued*)

Author and year	Study period	Study type	No. of patients	Anastomotic leak	Recurrent fistula	Stricture rate	Mortality
Randolph et al 1988[99]	1966–1988	Retrospective	118	Yes	N/R	Yes	Yes
Pohlsen et al 1988[100]	1980–1986	Retrospective	70	Yes	N/R	N/R	Yes
Sillen et al 1988[101]	1967–1984	Retrospective	110	Yes	N/R	Yes	Yes
Biller et al 1987[102]	1950–1960	Retrospective	12	No	N/R	Yes	N/R
Connolly and Guiney 1987[103]	1974–1983	Retrospective	139	Yes	Yes	Yes	Yes
Spitz et al 1987[104]	1980–1985	Retrospective	148	Yes	Yes	Yes	Yes
Manning et al 1986[4]	1935–1985	Retrospective	426	Yes	Yes	Yes	Yes
Bishop et al 1985[105]	1951–1983	Retrospective	240	Yes	Yes	Yes	Yes
Louhimo and Lindahl 1983[106]	1947–1978	Retrospective	500	Yes	Yes	Yes	Yes
O'Neill et al 1982[107]	1971–1980	Retrospective	53	Yes	N/R	Yes	Yes
Lindahl et al 1982[108]	1949–1955	Retrospective	54	Yes	Yes	N/R	Yes
Touloukian 1981[109]	1968–1979	Retrospective	38	Yes	Yes	Yes	Yes
Atwell et al 1980[110]	1967–1976	Retrospective	6	N/R	N/R	Yes	Yes
Strodel et al 1979[42]	N/R	Retrospective	365	Yes	Yes	Yes	Yes
Hrabovsky and Boles 1978[111]	1961–1973	Retrospective	135	Yes	N/R	Yes	Yes
Fasting and Winther 1978[112]	1952–1976	Retrospective	86	Yes	N/R	Yes	Yes
Pietsch et al 1978[113]	1962–1977	Retrospective	52	Yes	Yes	Yes	Yes
Exarhos et al1977[114]	N/R	Retrospective	16	N/R	N/R	Yes	Yes
Orringer et al 1977[115]	N/R	Retrospective	22	N/R	N/R	Yes	N/R
Ein and Themann 1973[49]	2,5 years	Retrospective	38	Yes	Yes	Yes	Yes
Laks et al 1972[116]	1945–1955	Retrospective	45	N/R	N/R	Yes	N/R
Battersby et al 1971[117]	1940–1969	Retrospective	210	N/R	N/R	N/R	Yes
Ferguson et al 1970[118]	1954–1969	Retrospective	69	N/R	N/R	N/R	Yes
Holden and Wooler 1970[119]	1939–1967	Retrospective	116	Yes	N/R	Yes	Yes
Krishinger et al 1969[120]	1944–1968	Retrospective	30	Yes	Yes	Yes	Yes
Romsdahl et al 1966[121]	1949–1965	Retrospective	34	N/R	Yes	Yes	Yes
Wayson et al 1965[41]	1940–1965	Retrospective	89	Yes	Yes	Yes	Yes
Waterston et al 1962[122]	1946–1959	Retrospective	218	N/R	N/R	N/R	Yes
Hays 1962[123]	1950–1960	Retrospective	110	N/R	N/R	N/R	Yes
Rehbein and Yanagiswa 1958[124]	1951–1958	Retrospective	84	Yes	Yes	Yes	Yes
Parish and Cummings 1958[5]	N/R	Retrospective	17	N/R	N/R	Yes	Yes
Ashe and Seibold 1949[125]	N/R	Retrospective	8	Yes	N/R	Yes	Yes
Ladd and Swenson 19947[126]	1940–1946	Retrospective	75	N/R	N/R	N/R	Yes
Daniel 1944[127]	1941–1944	Retrospective	7	N/R	N/R	N/R	Yes
Haight 1944[128]	1935–1944	Retrospective	28	N/R	N/R	N/R	Yes

Abbreviations: N/R, mortality or morbidity not reported; No, no mortality or morbidity occurred during the study period; RCT, randomized controlled trial; Yes, rate for mortality or morbidity is mentioned in the paper.
Note: For reasons of clarity, this table gives only a brief overview of the recorded data of included papers. The extended table with staggered outcome regarding the different decades can be requested from the authors.

Table 2 Overview of included study types (multiple selections possible)

Study type	Number of studies
Randomized controlled trials	1
Prospective studies	7
Retrospective studies	110
Multicenter studies	10
Single-center studies	100
Comparative Studies	7

A total of 102 (86%) of the included studies reported on mortality. Reported mortality rate after EA repair decreased markedly over time. It dropped from 100% in the presurgical era to 81% in the 1940s and to 54% in the 1950s. Further reduction followed in the next decades with 36% in 1960 to 1969, 28% in 1970 to 1979, and 16% in 1980 to 1989 and 1990 to 1999. In the postmillennial era, mortality rate after EA repair decreased further to 12% in 2000 to 2009, and in the current decade, it is 9% (►**Fig. 2**).

Reported rates of recurrent fistula varied over time between 4 and 9%, and leakage rate varied between 11 and 16% (►**Fig. 2**). The number of studies reporting on recurrent fistula and leakage rate were 67 (56%) and 89 (75%), respectively, in this study.

Ninety-one (77%) out of 118 included papers reported on stricture rate. Stricture rate showed a substantial increase in the last decade. Between 1940 and 2009, the reported rate varied between 25 and 31%, whereas the average stricture rate was 38% in 2010 to 2017 (►**Fig. 2**).

Discussion

"To anastomose the ends of an infant's esophagus, the surgeon must be as delicate and precise as a skilled watchmaker. No other operation offers a greater opportunity for pure technical artistry."[19] This statement made by Dr. Willis J. Potts in the 1950s has lost none of its relevance.[19] In addition to surgery and refinement of surgical technique, newly developed drugs and equipment and continuous optimization of treatment strategies has led to constantly improved survival rates of neonates born with EA over time. Before the era of surgical correction, the diagnosis of EA was a death sentence, but overall mortality reached a single-digit rate in the last decade. There is an ongoing discussion for surgical best practice: open or thoracoscopic technique.[20] Several authors postulated that both approaches have a comparable perioperative outcome,[21–23] while others rate minimal invasive repair superior.[24] Careful patient selection and the case load per center may influence surgical outcome after EA correction.[25,26] Additionally, there seems to be a considerable variability in technical aspects of the operation as well as the postoperative management of patients with EA.[11,21] Examples are intrapleural versus extrapleural approaches, choice of suturing and surgical sewing material, and application of chest drains or transanastomotic tubes.[11] Furthermore, use and duration of paralysis, mechanical ventilation, antibiotic treatment, as well as antacid therapy vary widely among different centers worldwide.[11]

Even high-risk groups (very-low-birth-weight infants/extremely premature babies) present currently with acceptable survival rates. Hannon et al demonstrated 50% survival in EA patients with a birth weight below 1 kg.[27] However, in

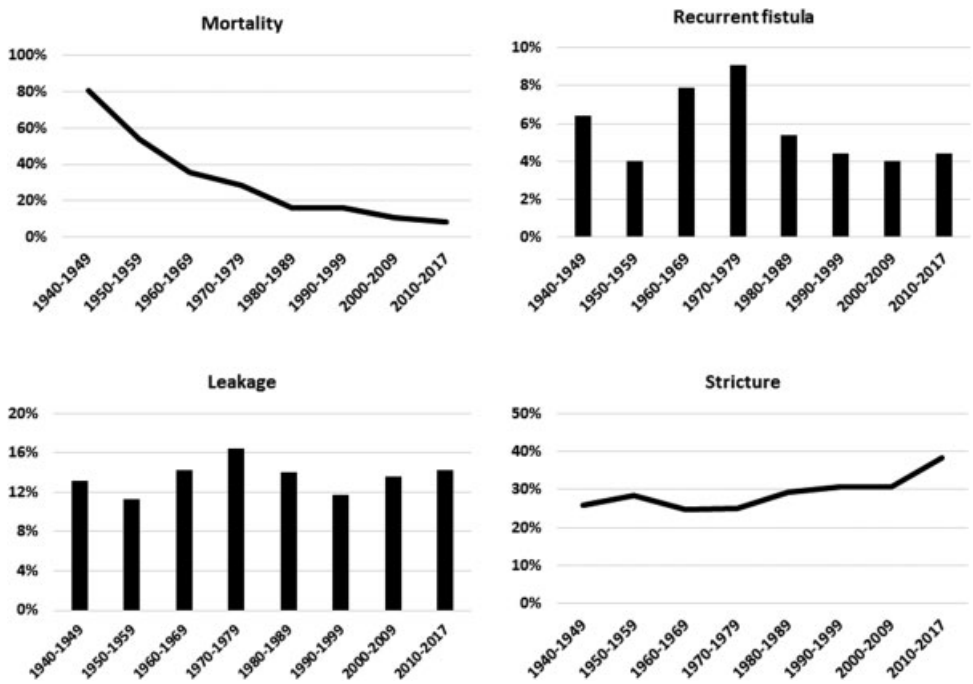

Fig. 2 Reported mortality rate decreased from 100% before 1941 to 54% in 1950 to 1959, 28% in 1970 to 1979, 16% in 1990 to 1999, and 9% nowadays. Rates of recurrent fistula varied over time between 4 and 9% and leakage rate varied between 11 and 16%. However, stricture rate increased from 25 to 38%.

their study, all infants below 800 g body weight had poor outcome.[27] In contrast, there is 95% expected survival in babies of more than 1500 g body weight, depending on their comorbidites.[27,28]

Although several authors published a survival rate of 100% in their center,[22–24,26,29,30] the overall mortality found in this study was between 9 and 11% in the last two decades. This is due to the fact that we also included studies with very-low-birth-weight infants and articles from third world countries in this report.[27,31–34] However, it has been suggested that birth weight is nowadays not an important factor as it was previously, although major cardiac anomalies are still of poor prognostic aspect.[35]

In our report, leakage rate remained stable over time between 11 and 16%, suggesting that surgical variations do not have any substantial influence on this complication. Likewise, neither open nor thoracoscopic technique seems to markedly affect the rate of recurrent fistula.[36–42] Although, there are minor variations between 4 and 9% over time course, there was no further improvement since introduction of the minimal invasive technique. It remains elusive, why we observed a drop to 4% rate of recurrent fistula in the 1950s compared with high rates up to 9% in the following two decades.

Surprisingly, we found that stricture rate after EA repair increased in the last decade. A recent survey admonishes that retrospective studies of EA may underestimate long-term esophageal complications, such as strictures.[17] It is debatable, whether pediatric surgeons have become more aware of this complication during follow-up appointments over time and may therefore indicate endoscopic diagnostic including balloon dilatation or bougienage more generously. On the other hand, there is no uniform definition for "stricture" and indication of therapeutic interventions, which might explain the observed stricture rate variation between 4 and almost 90%. Additionally, thoracoscopic technique and its associated learning curve might also affect anastomotic narrowing. Correspondingly, Rothenberg described stricture rates of almost 50% in their initial minimal invasive series, decreasing later to 20%.[24] Furthermore, babies less than 1500 g of body weight have been found to have an increased risk of stricturing with primary EA repair.[2] In several long-term analyses, dysphagia and swallow difficulties have been shown to be common problems.[36,43,44] However, they seem to occur mainly in the first years of life and become clinically less relevant thereafter as most children learn coping mechanisms over the years.[43,44] Nonetheless, the continuously high complication rates demonstrate that close interdisciplinary long-term follow-up is more important than ever. It is crucial to detect and treat the complications accordingly, and patients born with EA must be assisted for transition to adult care by their pediatric surgeon.

Remarkably, only one randomized control trial[18] and seven prospective studies[3,12–17] could be included in this study. A limited number of multicenter studies[1,3,12,13,21,39,45–48] reported on their experiences, whereas the majority presented single center data. Likewise, also comparative studies were rare.[22,23,29,49–52] Therefore, the current level of evidence in EA treatment is very low, and reference networks such as The European Reference Network on Rare inherited and congenital anomalies (ERNICA), which aims to assure quality treatment with high levels of evidence for EA in the future, are urgently needed.

The authors are aware of study limitations. A key point is the heterogeneity of included EA cases. No distinction was made between different types of EA (gap length, existence of a tracheoesophageal fistula). As we aimed to show the worldwide overall outcome of morbidity and mortality over time course, the articles were not extracted for surgical technique (open vs. minimal invasive, anastomotic technique, and primary vs. staged repair), birth weight/age, associated anomalies, time of follow-up, or country of origin (industrial states vs. third world countries). There is also a potential bias in study selection for the current manuscript. Amount of accessibility of papers from the early decades was restricted. Furthermore, there is a considerable variety of therapeutic regimen and treatment strategies among the different centers involved in EA treatment as well as the possibility of selection bias in the included studies themselves.

Conclusion

This article reflects the heterogeneity of EA, its patients, and its repair modalities during the course of 80 years. The worldwide mortality rate decreased from 100% in the presurgical era to a single-digit range in the last decade. Along with the decrease in mortality, there is a shift to the importance of major postoperative complications and long-term morbidity regardless of surgical technique. Therefore, close and regular follow-up of EA patients must be mandatory to assure health and normal development not only during childhood, but also for transition into adult care. Further studies, particularly prospective or randomized controlled trials, or at least consensus conferences, are needed to achieve higher levels of evidence and quality improvement for current therapeutic strategies for EA treatment.

Conflict of interest

None.

Acknowledgement

Paolo De Coppi wishes to acknowledge support from the National Institute for Health Research.

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