Variability in the reporting of baseline characteristics, treatment and outcomes in esophageal atresia publications: a systematic review

Authors and affiliations:

Nadine M. Teunissen[1,2] MD, Julia Brendel[3] MD, Simon Eaton[1,4] PhD, Nigel J. Hall[5] PhD, Rebecca M. Thursfield[6] MBChB MD(Res), L.W. Ernest van Heurn[7] MD PhD, Benno M. Ure[3] MD PhD, René M.H. Wijnen[1] MD PhD

[1] Department of Pediatric Surgery and Pediatric Intensive Care Unit, Erasmus University Medical Centre - Sophia Children's Hospital, Rotterdam, The Netherlands

[2] Dutch Institute for Clinical Auditing, Leiden, The Netherlands

[3] Department of Pediatric Surgery, Hannover Medical School, Hannover, Germany

[4] Developmental Biology and Cancer Research and Teaching Programme, UCL Great Ormond Street Institute of Child Health, London, United Kingdom

[5] University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, UK

[6] Department of Paediatric Respiratory Medicine, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool, United Kingdom

[7] Department of Pediatric Surgery, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Amsterdam Reproduction and Development Research Institute and the Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

Corresponding author:

Nadine Teunissen, MD
Department of Pediatric Surgery and Pediatric Intensive Care Unit
Erasmus University Medical Center – Sophia Children's Hospital
Wytemaweg 80, 3015 CN Rotterdam, The Netherlands
Telephone: +31 (0) 6 52 55 26 15
E-mail: n.teunissen@erasmusmc.nl

Contributions

The study was designed by NT, RW, JB and SE. Inclusion and exclusion criteria, assessment strategy, and the utilized Excel-based data extraction framework were developed by all authors. NT developed the search strategy, and NT, JB, and SE were responsible for screening, as well as data extraction and analyses. NT and JB drafted the manuscript which was revised by SE; all authors read, provided feedback, and approved the final manuscript.

Funding

The European Commission funded the EPSA|ERNICA Registry in the 3rd Health Program, HP-PJ-2019.

ABSTRACT

Introduction

As survival rates of infants born with esophageal atresia (EA) have improved considerably, research interests are shifting from viability to morbidity and longer-term outcomes. This review aims to identify all parameters studied in recent EA research and determine variability in their reporting, utilization, and definition.

Materials and methods

Following PRISMA guidelines, we performed a systematic review of literature regarding the main EA care process, published between 2015 and 2021, combining the search term 'esophageal atresia' with 'morbidity', 'mortality', 'survival', 'outcome' or 'complication'. Described outcomes were extracted from included publications, along with study- and baseline characteristics.

Results

From 209 publications that met the inclusion criteria, 731 studied parameters were extracted and categorized into patient characteristics (n=128), treatment- and care process characteristics (n=338), and outcomes (n=265). Ninety-two of these were reported in more than 5% of included publications. Most frequently reported characteristics were sex (85%), EA type (74%), and repair type (60%). Most frequently reported outcomes were anastomotic stricture (72%), anastomotic leakage (68%), and mortality (66%).

Conclusions

This study demonstrates considerable heterogeneity of studied parameters in EA research, emphasizing the need for standardized reporting to compare results of EA research. Additionally, the identified items may help develop an informed, evidence-based consensus on outcome measurement in esophageal atresia research and standardized data collection in registries or clinical audits, thereby enabling benchmarking and comparing care between centers, regions, and countries.

Keywords: esophageal atresia, outcome, characteristics

INTRODUCTION

With approximately one new case in 3000 to 4000 births, esophageal atresia (EA) – with or without tracheoesophageal fistula – is a rare congenital anomaly, which requires surgical repair during the neonatal period.[1] Survival rates of EA patients have improved remarkably over the last decades of the 20th century and have since remained stable, with the probability of survival depending mainly on the presence of additional anomalies or chromosomal or genetic syndrome diagnoses such as VACTERL association.[2,3] Because of the improved survival, the focus of EA research has shifted from mortality to parameters such as long-term outcomes, and quality of life for EA patients, as well as quality of care.

However, the evaluation and comparison of (quality of) EA care between hospitals, regions or even countries through clinical audits is made difficult by the lack of standardization of measured process indicators and clinical outcomes. The current implementation of an European clinical audit for esophageal atresia care necessitates the generation of an overview of all possible outcomes described in EA research, as well as patient characteristics and treatment- and care process characteristics to - in time - be able to correct for case mix in (quality of) care comparisons.[4]

EA research is equally hindered by a lack of standardization of measured outcomes. As EA is rare, prospective trials with adequate patient numbers are generally even more rare. Best practice and "gold standard" in EA care is mainly based on expert consensus.[5,6] The significant increase in the number of publications on EA over the last decades could potentially contribute to more evidence-based practice,[7] but overarching comparisons of results - such as meta-analyses - are difficult because measured outcomes and their corresponding definitions and manner of reporting widely vary. A core outcome set would enable such comparison of published research, and is under development (OCELOT).[8]

Hence a comprehensive overview of all possible EA outcomes, would be essential in the development of: (i) indicators (process, outcome) for use in audits and registries to allow comparisons between centers, regions, care pathways etc. with appropriate case-mix adjustment; and (ii) a core outcome set for use in EA research.

The primary aim of this explorative systematic review was to create such a comprehensive list of all reported outcomes in recently published peer-reviewed research on the main EA care process, as well as the variability in utilization, definition and reporting thereof. The secondary aim was to identify and define patient characteristics, as well as treatment and care process characteristics that could enable future interpretation of comparison of (quality of) care and outcome results. For the purpose of this paper, the term ‘studied parameters’ refers to all patient characteristics, treatment- and care process characteristics and outcomes. To our knowledge, this is the first effort to create such a detailed summary of studied parameters in EA research.

METHODS

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and guidelines.[9] A broad search strategy for Medline, Embase, and the Cochrane Library was developed in collaboration with an experienced medical librarian of the Erasmus University Medical Center. The search was based on the search term 'esophageal atresia', combined with the following terms: 'morbidity' or 'mortality' or 'survival' or 'outcome' or 'complication'. Complete search strategies are provided in Supplementary File 1. The search was performed in September 2021.

Inclusion and exclusion criteria

The search aimed to find all papers concerning any aspect of the main esophageal atresia care process, including surgical and non-surgical management. Hence, studies only focusing on the outcome of redo surgery were excluded. Subsequently, papers published before 2015 were excluded to warrant contemporaneousness. Lastly, non-English-language publications were excluded, as well as animal research and *in vitro* studies, case series with less than ten patients, editorials, letters, meeting abstracts and reviews, guidelines, and consensus statements.

Selection process

NT and JB independently screened the titles and abstracts of all search results to evaluate eligibility on the grounds of reporting care for and management of patients with esophageal atresia. Subsequently, the full texts of eligible articles were screened on relevance for the review. Any disagreement was discussed and, if necessary, resolved by SE. Reviewing authors were not blinded for the title, authors, or journal name.

Data extraction, analysis, and results

An Excel-based framework facilitated data extraction. Similar studied parameters were categorized and, following agreement between NT and JB, merged into an overarching term. The most frequently reported parameters were noted in the framework. Uncommon parameters, those mentioned in less than 5% of papers, were noted in a separate file. If available, definitions of studied parameters were extracted and noted, as well as utilized standardized ways of assessing the parameters, such as medical scores, scales and questionnaires, if the result thereof was directly reported in the included publication. Estimates of the parameters themselves were not extracted nor interpreted, and the methodological quality of included publications was not assessed.

RESULTS

Included articles

The applied search identified 3577 publications. After removal of duplicates and limiting the results to those articles published after 2015, 818 articles remained, of which 209 met the inclusion criteria (Fig. 1). A summary of study characteristics of all included publications is presented in table 1. An individualized overview of included studies and corresponding study characteristics can be found in Supplementary File 2.

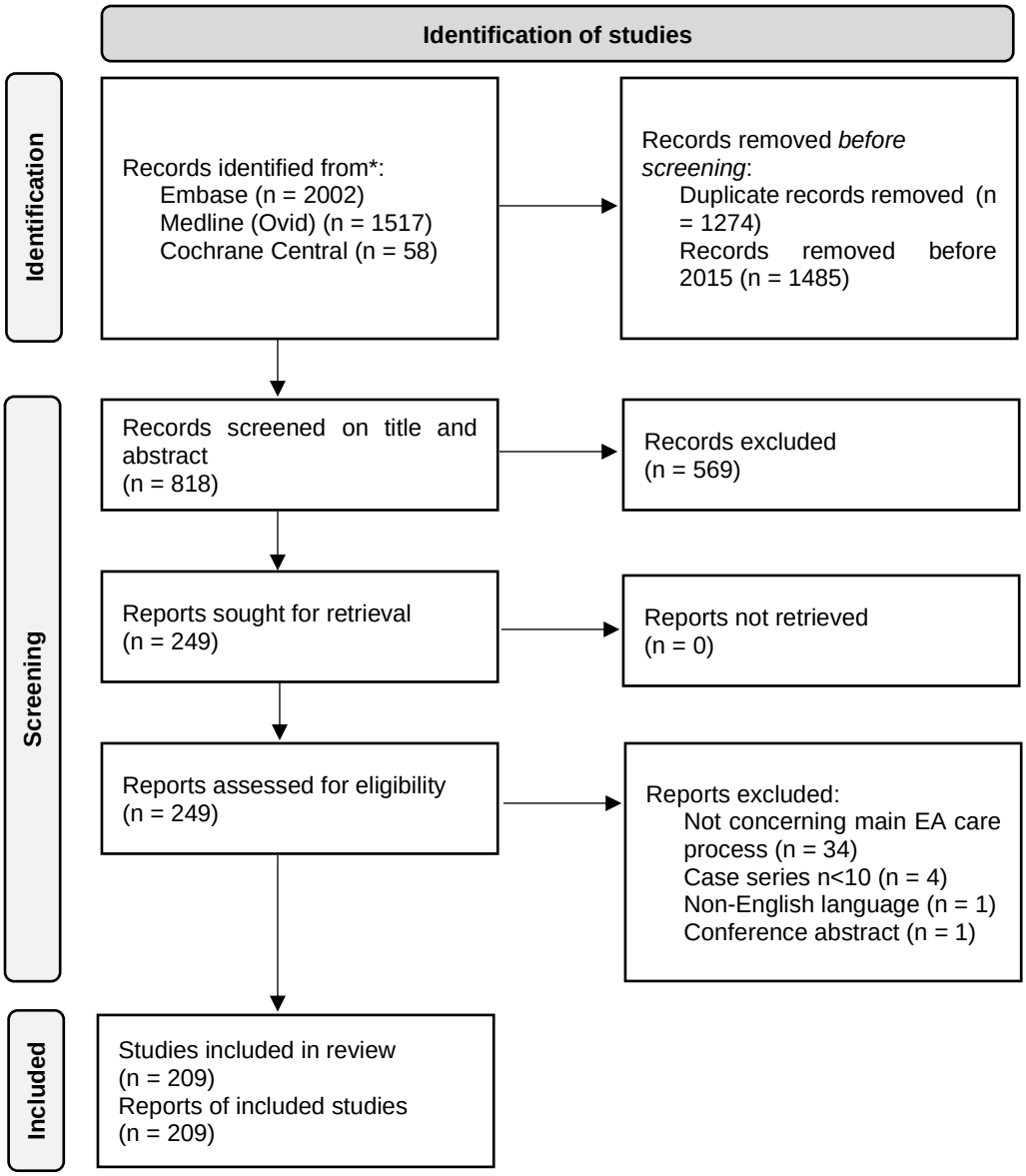

Figure 1: PRISMA Flowchart: systematic review of studied parameters in esophageal atresia research

Table 1: Study characteristics of included publications

		n =	%
Originated in	Africa	8	(4%)
	Asia	49	(23%)
	Europe	87	(42%)
	North-America	44	(21%)
	Oceania	10	(5%)
	South-America	2	(1%)
	Intercontinental	9	(4%)
Study design	Retrospective	148	(71%)
	Prospective	21	(10%)
	Cross-sectional	37	(18%)
	Mixed design	3	(1%)
Type of study	Observational	119	(57%)
	Comparative	90	(43%)
Study design	Cohort	198	(95%)
	Case-control	8	(4%)
	Trial	3	(1%)
Year of publication	2015	19	(9%)
	2016	23	(11%)
	2017	36	(17%)
	2018	27	(13%)
	2019	23	(11%)
	2020	35	(17%)
	2021	46	(22%)
Included type of EA	Only type C*	31	(15%)
	Only type A*	2	(1%)
	Only type E*	4	(2%)
	Long gap†	10	(4%)
	Multiple types*	31	(15%)
	All types*	129	(62%)
	Other‡	2	(1%)

*According to Gross Classification; †Following the definition of the included publication.
‡Inclusion of patients based on other criterion: long gap and complication in primary repair (1), prenatal suspicion of EA (1).

Data extraction

Full-text analysis of the 209 included manuscripts identified 731 parameters described in at least one of the included publications, which were then categorized into three overarching categories: patient characteristics (n=128), treatment- and care process characteristics (n=338), and outcomes (n=265). As several parameters could arguably be included in more than one category (e.g. length of primary hospital stay; number of surgeries), categorization followed agreement between the first two authors. We further arranged the parameters by topic, such as comorbidities, primary treatment, specific complications and

long-term outcome, to facilitate the comparison of variation in studied parameters within similar subjects. A complete list of all identified, categorized items is attached in Supplementary File 3.

Extracted studied parameters

Of 731 identified studied parameters, 92 parameters were described in more than 5% of included publications. These studied parameters are listed in table 2. Patient characteristics mentioned in more than two-thirds of included publications were sex, gestational age, presence of a cardiac malformation, and birth weight. The type of esophageal atresia according to the Gross classification was mentioned in 74% of papers. The type of surgical repair was stated in 60% of included articles. All other primary (surgical) treatment characteristics were mentioned in fewer than half of included publications.

Anastomotic stricture was the most frequently described complication; i.e., in 72% of included publications, followed by anastomotic leakage (69%). Mortality rate was reported in 66% of included publications. Length of primary hospital stay and duration of follow-up were mentioned in only one-third of articles (37% and 39%, respectively). In general, definitions of studied parameters varied widely between publications, rendering the extraction of unambiguous definitions impossible.

Variability in utilized standardized instruments to measure parameters such as quality of life was equally wide. To illustrate, health-related quality of life was described in 16/209 publications (8%), using twelve different tools or instruments. Other long-term outcomes, such as (motor) development, cognitive functioning, and behavior, were mentioned less often, yet the variability of used assessment tools was comparably large. A list of standardized scales, scores or instruments that were used in included publications to assess these outcomes is displayed in table 3.

Table 2. Identified studied parameters in EA research

		n =	%
Baseline characteristics	Sex	178	(85%)
	Gestational age or prematurity	154	(74%)
	Type of esophageal atresia	154	(74%)
	Cardiac malformation / Congenital heart disease	149	(71%)
	Birth weight	144	(69%)
	Age at surgery	98	(47%)
	Long Gap / Gap length	97	(46%)
	VACTERL*-association	88	(42%)
	Any other congenital malformation	83	(40%)
	Chromosomal / Genetic abnormalities	82	(39%)
	Renal/Genitourinary anomalies	76	(36%)
	Musculoskeletal / Limb anomalies	74	(35%)
	Anorectal malformation	67	(32%)
	Intestinal malformation	57	(27%)

	Age at time of study (survey, follow-up, intervention)	56	(27%)
	Weight at operation	41	(20%)
	Pulmonary / respiratory anomalies or conditions	36	(17%)
	Neurologic / Central nervous system anomalies	31	(15%)
	Fistula: yes/no	28	(13%)
	Previous esophageal surgery	27	(13%)
	Referred from other hospital	25	(12%)
	"Other" comorbidity (unspecified)	23	(11%)
	CHARGE† syndrome	23	(11%)
	Age at presentation / admission / diagnosis	22	(11%)
	Race/Ethnicity	18	(9%)
	Otolaryngeal anomalies / Auditory / Hearing issues	13	(6%)
	Laryngeal cleft / Laryngo-tracheo-oesophageal cleft	12	(6%)
	Spitz classification	12	(6%)
	Intra-uterine growth retardation/ Small-for-gestational age	11	(5%)
	Twin / Multiple birth	11	(5%)
Treatment- and care process characteristics	Type of repair (primary, secondary, interposition)	125	(60%)
	Age at surgery	98	(47%)
	Duration of follow-up	82	(39%)
	Gastrostomy at any point in time	81	(39%)
	Thoracotomy or thoracoscopy	79	(38%)
	Length of primary hospital stay	78	(37%)
	Number of dilatations	74	(35%)
	Duration of ventilation/intubation	64	(31%)
	Use of anti-acid medication (at any point in time)	61	(29%)
	Operation time	37	(18%)
	Aortopexy: yes or no	33	(16%)
	Cervical esophagostomy until surgery / at any point in time	33	(16%)
	Conversion thoracoscopy to thoracotomy	29	(14%)
	Time to start oral feeding (postoperatively)	29	(14%)
	Tracheostomy	27	(13%)
	Tension-free anastomosis / Concern regarding tension	27	(13%)
	Time on (neonatal) intensive care (days)	27	(13%)
	Prenatal diagnosis	26	(12%)
	Intra-operative chest tube	23	(11%)
	Bronchoscopy (intraoperative)	22	(11%)
	Transanastomotic tube	21	(10%)
	Polyhydramnios on antenatal ultrasound	19	(9%)
	Elongation procedure	19	(9%)
	Need for preoperative intubation/ventilation	19	(9%)
	Time to start tube feeding	14	(7%)
	Contrast study postoperative	13	(6%)
	Lung function (spirometry) in follow-up	13	(6%)
	Time between diagnosis and surgery	13	(6%)

	Time to full oral feeding	13	(6%)
	Thoracotomy: left or right approach	12	(6%)
	Use of inhalation medication	12	(6%)
	Echocardiography	11	(5%)
	Number of surgeries that patient underwent	11	(5%)
Outcome	Anastomotic stricture/stenosis	150	(72%)
	Anastomotic leakage	143	(69%)
	Mortality	137	(66%)
	Dilatations: yes or no	128	(61%)
	Gastroesophageal reflux	110	(53%)
	Anti-reflux surgery: yes or no	88	(42%)
	Recurrent fistula	84	(40%)
	Redo surgery (esophageal)	79	(38%)
	Tracheomalacia	63	(30%)
	Growth / Weight / Failure to thrive	61	(29%)
	Oral feeding issues	61	(29%)
	Respiratory complications / symptoms / chronic disease	59	(28%)
	Pneumonia	57	(27%)
	Dysphagia / Swallowing difficulties	52	(25%)
	Sepsis	43	(21%)
	Recurrent respiratory infections	38	(18%)
	Pneumothorax	36	(17%)
	Aortopexy: yes or no	33	(16%)
	Vocal cord complications / Voice changing	28	(13%)
	Gastro-intestinal symptoms	23	(11%)
	Blood loss during primary surgery	22	(11%)
	Wound complications	20	(10%)
	Chylothorax	19	(9%)
	Chest wall deformity	19	(9%)
	Quality of Life	16	(8%)
	Readmission	16	(8%)
	Graft necrosis / Graft failure / Graft loss	15	(7%)
	Complications: yes or no	14	(7%)
	Motor-/Neurodevelopment	13	(6%)
	Complications (intra-operative)	11	(5%)
	Esophageal perforation after dilatation	11	(5%)

*VACTERL: Vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies and limb abnormalities. †CHARGE: Coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities and ear abnormalities.

Table 3. Identified tools/instruments utilized and reported in one or more included publications

		n =	**%**
Behavior	(Modified) Vineland Social Maturity Scale	2	(<1%)
	Behavior Assessment System for Children (BASC II)	1	(<1%)

	Behavior Rating Inventory of Executive Function Preschool	1	(<1%)
	Child Behavior Checklist	1	(<1%)
Birth	Score for Neonatal Acute Physiology with Perinatal Extension (SNAPPE-II)	1	(<1%)
Cognition	Wechsler Intelligence Scale for Children (WISC)	3	(1%)
	Wechsler Preschool & Primary Scale of Intelligence (WPPSI)	2	(<1%)
	Ankara Developmental Screening Inventory	1	(<1%)
	Children's Memory Scale	1	(<1%)
	Developmental Neuropsychological Assessment (NEPSY)	1	(<1%)
	Revised Amsterdam Intelligence Test (RAKIT)	1	(<1%)
	Test of Everyday Attention for Children	1	(<1%)
	Wide Range Achievement Test (WRAT)	1	(<1%)
Coping, transition and commitment to care	Coping Strategy Checklist	1	(<1%)
	Fragebogen zur Messung der Patientenzufriedenheit (ZUF-8)	1	(<1%)
	Patient Activation Measure (PAM)	1	(<1%)
Development	Bayley Scales of Infant and Toddler Development (BSID)	4	(2%)
	Movement Assessment Battery for Children (M-ABC)	3	(1%)
	Ages and Stages Questionnaire	1	(<1%)
	Developmental Assessment Scale for Indian Infants	1	(<1%)
	Gross Motor Function Classification System (GMFCS)	1	(<1%)
	Kinderturntest plus / Deutscher Motorik Test	1	(<1%)
	Trivandrum Development Screening Chart (TDSC)	1	(<1%)
Feeding	Functional Oral Intake Score (FOIS)	3	(1%)
	Montreal Children's Hospital Feeding Scale (MCH-FS)	2	(<1%)
	International Dysphagia Diet Standardization Initiative (IDDSI)	1	(<1%)
	Karaduman Chewing Performance Scale (KCPS)	1	(<1%)
	Penetration and aspiration scale	1	(<1%)
	Turkish Feeding / Swallowing Impact Survey	1	(<1%)
(Mental) health status and symptomatology	German Health Survey for Children and Adolescents (KIGGS)	2	(<1%)
	Gastrointestinal Symptom Rating Scale (GSRS)	1	(<1%)
	Strength and Difficulties Questionnaire – 20 (SDQ-20)	1	(<1%)
	Risk Adjustment for Congenital Heart Surgery Score (Rachs)	1	(<1%)
Quality of life	Pediatric Quality of Life Inventory (PedsQL)	8	(4%)

	Gastrointestinal Quality of Life Index (GIQLI)	4	(2%)
	Self-developed questionnaire	2	(<1%)
	World Health Organization Quality of Life Questionnaire (WHOQOL-BREF)	2	(<1%)
	Child Health Questionnaire (CHF87-BREF)	1	(<1%)
	DISABKIDS Chronic Generic Measure - 47	1	(<1%)
	KIDSCREEN-27	1	(<1%)
	Short Form Survey (SF-36)	1	(<1%)
	TNO AZL Children's Quality of Life (TACQOL)	1	(<1%)
	TNO AZL Adult's Quality of Life (TAAQOL)	1	(<1%)
	WHO-5 / WHO-5 parental	1	(<1%)
Trauma and stress	Impact of Events Scale (IES-13)	1	(<1%)
	Parental stress scale	1	(<1%)

Multiple instruments or tools may have been used in one publication.

DISCUSSION

To the best of our knowledge, this is the first systematic review that summarizes all parameters studied in recent clinical research on esophageal atresia. More than 730 different patient characteristics, treatment characteristics and outcomes were identified in 209 included publications, demonstrating substantial variation in research interest and reporting. However, most of the parameters were mentioned solely in a handful of papers. Of 265 identified outcomes, only 5 (2%) were mentioned in more than 50% of included publications. The proportions of patient characteristics (5/128, 4%) and treatment- and care process characteristics (1/338, <1%) that were studied and reported in more than 50% of included publications, proves to be similarly small. Additionally, studied parameters were defined and assessed inconsistently across included publications, thereby impeding comparison and benchmarking of parameters, even if they were more frequently studied.

In addition to generating an extensive list of all studied parameters, our study reveals several noteworthy observations. First, as expected, most studies were retrospective cohort studies, which emphasizes the need for more prospective studies (audits, registries, research studies, randomized trials) to establish best practice. Second, the studied parameters mainly refer to primary surgical repair of esophageal atresia and its complications. Although some studies addressed long-term outcomes such as follow-up and transition programs or long-term complications,[10–16] the complete list of parameters suggests that the esophageal atresia research of recent years generally had a short-term focus. By contrast, a recent overview of publication trends and global collaborations on esophageal atresia research found particular interest in the long-term outcome, surgical techniques, and epidemiology when assessing key points of the ten most-cited EA publications since 1945.[7] Thus, there is a mismatch between the short-term focus of the large majority of EA research versus the long-term outcomes that professionals and advocacy groups deem most important. Obviously, the reporting of short-term outcomes is easier than the reporting

of long-term outcomes, for sequelae such as motor/neurodevelopment, chest wall deformities, chronic respiratory diseases, and lung function impairment often occur later in childhood or adolescence – and thus require longer follow-up. The third remarkable trend is that only eighteen studies described quality of life outcomes through patient-reported outcome measures (PROMs), and the applied instrument varied across the studies.[10,12–14,17–27] The most used PROM was the generic, child-specific PEDS-QoL, which, however, was mentioned in only 8/209 papers (4%). This scarce use of PROMs is surprising, as there is a general movement to patient-centered care and PROM research across the medical world. This scarce use could possibly be attributed to the lack of a disease-specific PROM during the study period. Meanwhile, an EA-specific PROM for children has been developed in Sweden and Germany and is currently being validated in other countries.[28] Additionally, an EA-specific PROM for adults is being developed and validated in a Dutch nationwide study.[29] Lastly, although the large variety of studied parameters reflects attention for comorbidity and quality of care, mortality remains one of the most reported ones in recently published research.

Our study has some limitations. First, to warrant contemporaneity of results, reports published before 2015 were excluded. It is possible that extension of the time period to include earlier years would have yielded further outcomes that were not included in our review; it would also have potentially allowed an analysis of trends over time. However, on balance it was felt that the 466 different patient- and treatment characteristics and 265 outcomes from 209 publications were representative of current practice. Additionally, non-English publications were excluded, which may have led to underestimation of the variation in studied parameters, considering that geographical differences and local practices could influence the selection thereof.

The extensive list of studied parameters resulting from this systematic review, will serve as the foundation of projects aimed at standardizing EA data collection. Clinical audits or registry-based research will benefit from standardization of data regarding patient characteristics and characteristics of treatment and care processes, enabling further interpretation and correction of measured variation in outcome. Additionally, these datasets must enable comparison or benchmarking between medical centers, thus be able to capture between-hospital variation and reflect (good) care. This review was undertaken as the first stage of defining a “Core Indicator Set” for data collection within the EPSA/ERNICA EA registry, which has the aim of improving EA care across Europe.

Although also aiming to improve patient care, the intention is somewhat different from that of a Core Outcome Set, which is “*an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care*.” The focus of a core outcome set is on trials and therefore the outcomes by which different treatments can be compared. As an example of the distinction between core indicator sets and core outcomes sets, we can take examples

from our literature review. The number of patients having intra-operative bronchoscopy may be an interesting and useful process indicator to look at variation across European centers (and may be represented in a core indicator set) but it is unlikely to become part of a Core Outcome Set. Anastomotic leak, on the other hand, might be selected for both a Core Indicator Set and a Core Outcome set, as it is relevant to both the variation between centers (e.g. leak rate in center X vs. others) and might also be useful to compare different treatments (e.g. thoracotomy vs. thoracoscopy). The application of core outcome sets has become increasingly important to achieve consistency of outcome reporting, with consideration of patients' perception of the importance of outcomes.[30] Defining a core outcome set for EA is already underway (OCELOT).[8] Core outcome sets often suffice to interpret differences between study arms in RCTs, in which baseline-characteristics are balanced, and treatment pathways protocolized.

To ensure recognition and implementation of both core data sets by everybody involved in esophageal atresia care and research, it is of utmost importance to involve all stakeholder groups (health care providers, patients, and researchers) in both endeavors.

CONCLUSION

This review found substantial variability in reported patient characteristics, treatment- and care process characteristics, and outcomes in research regarding the main care process for patients with esophageal atresia. The resulting list of studied parameters could aid in the development of a standardized core outcome set, as well as a core indicator set. Standardized measurement and reporting is necessary to invoke less reporting bias, more interpretable results, and the possibility of more cross-study or cross-healthcare comparisons, which could significantly improve future outcome measurement and reporting in esophageal atresia care, as well as esophageal atresia research. The development and validation of both the standardized core indicator set and core outcome set has started in 2021 with involvement of European expert health care providers as well as patient representatives.

ACKNOWLEDGEMENTS

This article is supported by ERNICA. The authors would like to thank the European Pediatric Surgical Audit group for scientific input. Additionally, the authors wish to thank **Sabrina T.G. Meertens-Gunput**. from the Erasmus MC Medical Library for developing and updating the search strategies. And thanks to **Ko Hagoort** for editing the manuscript. SE acknowledges support from the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital.

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