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A Cross-Sectional Nationwide Survey On Esophageal Atresia And Tracheoesophageal Fistula

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ABSTRACT

BACKGROUND - Our study aims at disclosing epidemiology and most relevant clinical features of Esophageal Atresia (EA) pointing to a model of multicentre collaboration.
METHODS - A detailed questionnaire was sent to all Italian Units of paediatric surgery in order to collect data of patients born with EA between January and December 2012. The results were crosschecked by matching date and place of birth of the patients with those of diagnosis-related group provided by the Italian Ministry of Health (MOH).
RESULTS - A total of 146 questionnaires were returned plus a further 32 patients reported in the MOH database. Basing on a total of 178 patients with EA born in Italy in 2012, the incidence of EA was calculated in 3.33 per 10000 live births. Antenatal diagnosis was suspected in 29.5% patients. 55.5% showed associated anomalies. The most common type of EA was Gross type C (89%). Postoperative complications occurred in 37% of Type C EA and 100% of Type A EA. A 9.5% mortality rate was reported.
CONCLUSIONS - This is the first Italian cross-sectional nationwide survey on EA. We can now develop shared guidelines and provide more reliable prognostic expectations for our patients.

KEYWORDS

Introduction

Esophageal atresia (EA) is a rare disease and represents the most frequent congenital anomaly of the esophagus. The aetiology is still unknown but environmental and/or genetic factors have been suggested [1-3]. The epidemiology of EA has been shown to vary in reported series with prevalence raging from 1:2500 to 1:4500 live births [1-2, 4-11]. The most frequently encountered variant (75-90% of cases) is EA with distal TEF, type C according to Gross classification [1, 7, 10, 11-13]. Over 50% of EA patients have associated anomalies involving organs and systems [2, 5, 7-8, 11,12,14]. Advances in surgical techniques and in intensive neonatal care improved survival over the past decades, with a rate now approaching 90% also in infants with severe associated anomalies and 100% in those without [2, 7-8, 12, 15-18]. The absence of a international data collection system makes providing a reliable EA epidemiology very difficult, which is of outmost importance in order to identify risk factors, provide better prognostic expectations and educate families. At present, most of reports on EA are based on few single institution retrospective or population-based studies, focused on descriptive epidemiology and survival rates. Inspired by other national and international cohort studies [1,5,7,11], our study addressed the epidemiology and most relevant clinical features of EA in Italy, focusing on a model of multicentre collaboration similar to the previously reported by Sfeir and co-workers in France, and Burge and colleagues in the United Kingdom [5,11]. This study aims at providing reliable epidemiological data for physicians dealing with this rare congenital disease in Italy as well as abroad. Furthermore, we will provide detailed information regarding clinical fetaures, short term outcome and survival that will turn extremely useful to a reliable prenatal and/or postnatal counseling. Finally, the results of our study will hopefully help in implementing nationally shared guidelines to improve the overall outcome of our patients.

Materials and methods

The Italian Society of Pediatric Surgery (ISPS) Directorate implemented this prospective observational cross-sectional study project during the 42nd national Congress that was held in Padua in September 2011. Resorting to the national Ministry of Health (MOH) database cross-matched with the ISPS database we could identify and enrol a total of 52 Units of Pediatric Surgery dealing with newborn surgery in Italy. A questionnaire was sent to each responsible pysician who was asked to send back the completed questionnaire immediately after patients' discharge from the Hospital (the list of responsible physician in each Unit is available in Appendix 1). The questionnaire was implemented by a committee of paediatric surgeons (experts from the ISPS

directorate) and addressed various issues (63 to 69 items based on type of EA) including demography (5 items), family history (3 items), pregnancy (7 items), perinatal period (4 items), associated anomalies (9 items), clinical features and perioperative management (12 items), surgical details according to type of EA (10 to 16 items), postoperative information (4 items), morbidity and early mortality (within 30 days of life) (9 items) (Appendix 2).

2.2 Definitions

EA was classified according to Gross classification [19] and risk groups were defined according to Spitz classification [20]. Surgical details, complications and short term outcome were addressed separately for type A/B and type C/D EA given the similarity of those EA types. Similarly, type 5 EA, not requiring esophageal anastomosis, underwent specific considerations. VACTERL association was defined when at least 3 of the following congenital anomalies were also present: vertebral, ano-rectal, cardiac, renal, urinary, and limb abnormalities.

2.3 Inclusion/exclusion criteria

The questionnaire was sent in November 2011 to all Italian Units of paediatric surgery. Patient's inclusion criteria were: 1) neonatal confirmed diagnosis of EA/TEF; 2) date of birth between the 1st of January and the 31st of December 2012. Exclusion criteria were: 1) stillborn with EA/TEF, and 2) voluntary pregnancy termination due to EA/TEF suspicion. Collecting questionnaires deadline was set on the 30th of June 2013 to allow the inclusion of late responders. The questionnaire included all data collected by the surgeon in charge of the patient at first discharge from the hospital, excluding those concerning esophageal strictures that were collected throughout the entire study period up to the deadline for submission. Duplicates were identified and removed. In case of missing or implausible data, the first author to clarify the issue and complete the entries contacted the reporting centre.

2.4 Cross check and data exhaustivity

The cross-check of the correspondence was provided for all records by the Units of Pediatric Surgery participating to the survey by matching date and place of birth of the patients with those of diagnosis-related group (DRG 750.3) officially provided by the Italian Ministry of Health (MOH). In case of mismatch, the attending physician was contacted to check for correct address and date and place of birth in order to revise the incorrect entries.

2.5 Data recording and statistical analysis

The formal approval of the review board of the ISPS directorate was obtained in late 2011. All collected informations were recorded in a digital database according to the Italian Personal Data Protection Act and data analysed by 2 physicians (one blinded [MC] and the other involved [APP] in the implementation of the questionnaire. Data were compared with official annual report regarding national demography and birth rate, as published by ISTAT (Italian National Institute of Statistics, on the web site http://www.istat.it or http://dati.istat.it/?lang=en) to perform statistics and epidemiological studies.

Given the possible regional variation of the incidence of this rare disease, we considered five major socio-economic Italian regions for a more reliable statistical analysis, according to the Nomenclature of territorial units of statistics (*NUTS*1) definition, as provided by Eurostat 2006 [21], namely 1) north-west, 2) north east, 3) centre, 4) south and 5) islands (Appendix 2).

Descriptive statistics were reported as percentages. A 95% confidence interval (CI) was provided when appropriate. Median and range was used for ages, weight, time and size measurements, given the wide variability in our series. Differences in the frequencies of each categorical variable were evaluated by the Chi-square test. Comparison of continuous data was performed using the 2-tailed unpaired t-test. In case of scant data or non-normal distribution, non-parametric tests (Man-Whitney) were used. A *p* value lower than 0.05 was considered statistically significant. Bonferroni's correction was applied in case of multiple testing (> 5 measures for each variable). Analyses were performed using Stata for Windows statistical package (release 9.0, Stata Corporation, College Station, TX).

Results

3.1 Demographics

All eligible Pediatric Surgery Units (52 Units, Appendix 1) participated to the study by returning completed questionnaires directly to the ISPS Directorate. A total of 146 cases of EA were reported (M=90, F=56, M:F; ratio 1.60:1). The cross-check analysis with the Italian MOH identified 178 neonates discharged with a DRG code 750.3 in 2012 (M=108, F=70, M:F ratio 1,54:1). All records provided by the Units of Pediatric Surgery showed correspondence with those provided by the MOH. As a consequence we report reliable data on 82% of Italian EA born in 2012. The attending physician could not be identified in the remaining missing 32 patients (18%). During the study period the ISTAT registry reported 534365 live births. The incidence of EA was subsequently calculated as 3.33 per 10000 live births (95%CI, 2.88-3.89). Comparing incidence in NUTS1 regions, we did not remark significant differences though Islands regions showed the lowest EA

incidence (for details, direct contact with corresponding Author - Appendix 1). Eighteen out of 52 participating Units (35%) reported no EA admitted in 2012, 34 (65%) reported at least 1 patient, 26 (50%) reported up to 5 whereas 8 (15%) reported more than 5. The median number of patients treated by each Unit was 2 (range 1 to 13).

3.2 Familial History

Familiarity for congenital abnormalities was described in 16 cases (11.1%) being one (0.7%) represented by EA (cousin of the proband). Apart from EA, familial issues were represented congenital heart diseases in 5, chromosomopathies in 2, thyroid malfunction in 2 and miscellanea in the remaining 6 patients.

3.3 Pregnancy and delivery

Antenatal ultrasound was performed in 145 patients (99%). EA was suspected in 43 cases (29.6%). Median gestational age at prenatal diagnosis was 28 weeks (20 to 35 weeks). Polyhydramnios was the most frequent finding described in 80 (55%). Absent/small stomach and/or presence of a dilated proximal pouch were reported in 36 patients (84%). Antenatal diagnosis of EA without evidence of polyhydramnios was suspected in 6 cases (14%). Evaluation of the correct prenatal diagnosis in neonatal EA different types showed that a prenatal diagnosis was significantly more frequent in type A and B compared to type C and D EA (8/10 = 80% vs 34/131 = 26%) ($p = 0.0010$). Sampling for karyotype analysis (amniocentesis or chorionic villous sampling) was performed in 37/146 cases (25.3%) and in 18/43 (42%) of those with a suspected antenatal diagnosis ($p = 0.0547$). Chromosomal anomalies were confirmed in 3 patients (2 Edwards and 1 Down Syndrome) at this stage (8% of total tested). Mode of delivery was vaginal in 60 cases out of 139 patients with available data (43%). When an antenatal diagnosis of EA was suspected, vaginal delivery was reported in 18 cases (42%) with no statistically significant differences in those with and without antenatal diagnosis of EA ($p=0.8972$).

3.4 Perinatal period and postnatal diagnosis

Gestational age at birth was available in only 86 of 146 patients (59%). Thirty of these (35%) were born preterm, 10 of whom before the 32nd week of gestation (12%). Birth weight was reported in 144 patients (98%). Median weight at birth was 2580 g (825-4000 g); it was lower than 1500 g in 16 (11%), and lower than 1000 g in 4 (3%). Median maternal age was 32 years (19-43 years) and median gestational age was 37 weeks (24-41 weeks). APGAR score at 1 minute was reported in 133 over 146 overall cases (91%). APGAR at 1 minute scored below 6 in 30 patients (22.6%) and above

in the remaining 103. Timing of post-natal diagnosis of EA was available from 141 patients (96%) 43 of whom with a prenatal diagnosis. When focusing on the 103 patients without prenatal diagnosis 34 received the diagnosis in the delivery room (33%), 58 during the first 24 hours of life (56%) and 10 afterwards (10%).

3.5 Associated Anomalies

Eighty-one out of 146 patients (55%, 95%CI, 47%-63%) showed associated anomalies, ranging between 47% and 65% in various NUTS1 regions without significant differences. Cardiovascular malformations were the most frequent associated anomalies, reported in 26.7% of cases. Survival was significantly lower in patients with cardiovascular malformations when compared to those without (90% vs 98%) ($p = 0.0438$). Similarly, the survival of patients with major associated anomaly (regardless of type) was significantly lower (92% vs 100%) ($p = 0.0336$). Details regarding various co-morbidities are reported in Table 1. VACTERL association was reported in 30 patients (20.5%, 95%CI, 14.8-27.8) and CHARGE in 1 (0.7%, 95%CI, 0.1-3.7). Chromosomal abnormalities were identified in 5% of the patients (95%CI, 2.8-10.4), namely Down syndrome in 5, Edwards syndrome in 2 and Di George Syndrome in 1. One further patient presented with clear dysmorphic features but a recognizable syndrome could not be determined, yet.

3.6 Clinical features

3.6.1 Overall

The most common type of EA was Gross type C (130 patients, 89% of total cases, 95%CI, 83-93). Type A EA was reported in 7 patients (5%, 95%CI, 2.3-9.6), type E in 5 (3%, 95%CI, 1.5-7.8), type B in 3 (2%, 95%CI, 0.7-5.9) and type D in 1 (0.7%, 95%CI, 0.1-3.8).

One-hundred forty-four (98.6%) patients underwent preoperative cardiological ultrasound. A right aortic arch was reported in 3 patients (2%, 95%CI, 0.7-5.9).

Eighty-seven patients (59%) had a naso-esophageal Replogle placed in the upper pouch before surgery (median calibre 8 Ch, ranging from 5 to 12 Ch). Preoperative respiratory distress requiring mechanical ventilation was experienced in 36 out of 135 patients (26.7%, 95%CI, 19.9-34.7) and led to death in 1. This complication occurred in 23 patients with Replogle tube and in 8 without (5

patients who experienced respiratory distress missed this datum), showing no differences between groups (*p = 0.2063*). Upper esophageal pouch or gastric perforation occurred in 3 cases.

According to the Spitz classification risk, 108 patients (74%, 95%CI, 66.3-80.4) were graded in Group 1, 35 patients (24.7%, 95%CI, 18.4-32.2) in Group 2 and 2 patients (1.4%, 95%CI, 0.4-4.8) in Group 3. One missed sufficient data to define the risk group. Six of the 146 reported patients died before one month of life. The highest early mortality was observed in group 3 (1 patient, 50% mortality, 95%CI, 9.4-90.5). Five patients in Group 2 and no patients in Group 1 died showing 14.3% (95%CI, 6-29) and 0% (95%CI, 0-3.4%) mortality rate respectively.

According to APGAR score at 1 minute, 6 patients out of 30 who scored 6 or below (20%) died within one months of life and none of the patients who scored above did (*p = 0.0001*).

3.6.2 Type E EA (5 patients)

All 5 patients with type E EA experienced neonatal feeding-related respiratory distress. The diagnosis was performed at a median age of 4 days (range 2 to 5). The following investigations were required for the diagnosis: upper GI contrast study in 4, CT scan in 1, combined laryngotracheoscopy and esophagoscopy in 4. The fistula was located in the cervical esophagus in 4 patients, at the thoracic outlet (mid thoracic esophagus) in one. Surgical approach was cervical in all patients.

3.7 Surgical details, complications and outcome

One-hundred-forty-four patients (98.6%) underwent surgery. One patient died before surgery because of respiratory failure and one did not undergo surgery because of bioethical considerations (the baby suffered from Edwards syndrome with polyvalvular disease and Dandy-Walker variant).

3.7.1 Type C and D EA (130 patients)

Preoperative laryngo-tracheoscopy was performed in 61 patients (47%) being the fistula cannulated in 19 (31%). Ten patients (8%), required an urgent fistula ligation. The approach was thoracoscopic in 4 patients (3%) and thoracotomic in 127 (97%). One patient required conversion to open surgery due to technical issues. Surgical details are reported in Table 2.

Postoperatively, 109 patients had a postoperative contrast study of the esophagus performed at median postoperative day 7 (4 to 24) and oral feeding started at median postoperative day 8 (1 to 42). Postoperative complications were observed in 47 patients (37% out of 127 patients with available data, 95%CI, 29.1-45.6). Infections were observed in 8 patients (6.2%, 95%CI, 3.2-11.9), anastomotic leak in 12 (9.4%, 95%CI, 5.4-15.7), and stricture (defined as symptomatic esophageal narrowing requiring dilatation) in 27 (21.2%, 95%CI, 15-29.1). Leakage and stricture occurred after a median postoperative time of 72 hours (6 h to 240 h) and 40 days (6 d to 150 d), respectively. Reoperations were required in 4 patients (3.1%, 95%CI, 1.2-7.8). When correlating the incidence of anastomotic complications, namely leakage and stricture to possible risk factors such as tension of the anastomosis, wide dissection of the upper pouch, interposition of synthetic or biological patches (fibrin glue, pericardial flap, mediastinic connective tissue, etc), absence of trans-anastomotic naso-gastric tube or para-anastomotic drain, and lack of prolonged mechanical ventilation, no statistically significant difference was identified.

3.7.2 Type A and B EA (long gap EA, 10 patients)

All patients but one underwent gastrostomy at birth. No standardized protocol for either pre or intra-operative gap assessment has been routinely used. Nonetheless, mostly flexible endoscope and Hegar dilators were adopted to identify and measure the inferior esophageal pouch. Only one patient underwent contrast study for gap assessment. Gap assessment showed a long gap (i.e. > 3 vertebral bodies) in 8 out of 10 cases.

Primary anastomosis was attempted at birth in 1 neonate, whereas it was delayed at a median age of 63 days (range 28 to 100) in 4. All the five patients who a had primary esophageal anastomosis experienced complications: upper pouch recurrent fistula in 1, anastomotic leak in 1 (primary anastomosis), and anastomotic stricture requiring dilatation in 4. Cervical esophagostomy was performed in 3 patients showing a gap > 6 vertebral bodies. None of these patients underwent esophageal replacement, yet. The two remaining patients are still waiting for a possible delayed anastomosis with a replogle tube under continuous suction.

3.7.3 Type E EA (no atresia, 5 patients)

Surgery was performed with a cervical incision. Fistula was cannulated in 4 patients. Tissue interposition was adopted in 3. No patients died. None experienced postoperative complications, such as vocal cord paralysis, leakage or fistula recurrence. Feeding was mainly re-established in the post-operative day 6.

3.8 Missing data and unreported patients

Data regarding 32 missing patients (reported by the national registry) were only recorded in the database provided by the MOH that was anonymous and did not allow to track down the patients and/or the attending physician. Only a few demographic data were available for these patients. Those data are summarised below.

Of these 32 missing patients, 11 died within 1 month of life. Deaths occurred after at median age of 2 days (1 to 15). Six patients died before 48 hours of life. Median birth weight of patients who died was 1430 gr (580 gr to 2570 gr). Male to female ratio of patients who died was 0.57:1 (4 males and 7 females). Regional belonging of these patients was randomly distributed.

3.9 Overall mortality

Summing reported and unreported cases, a total of 17 out of 178 patients with EA died before one month of life for an early mortality rate that can be calculated into 10% (95%CI, 6.5-15.4). Birth weight of patients who experienced early death was lower than 1500 g in 5 out of 12 patients with available data (42%). Overall male to female ratio was 0.7:1 (7 males and 10 females). When comparing gender of patients who died we observed that females have a higher risk, though the difference cannot be considered as statistically significant (mortality in males 6.5%, mortality in females 14.5%, $p = 0.1147$). Cause of death was respiratory distress in 3 patients, heart failure in 3 and unknown in 11 (national registry).

Discussion

This is the first Italian cross-sectional nationwide survey on EA performed so far. Based on the results of our study, the incidence of EA in Italy in 2012 was calculated in 3,33 per 10000 live births. This incidence (1:3000) is coherent with what previously reported in the literature, that set between 1:2500 and 1:4500 live births the incidence of EA [12,13], but nearly two-folds higher than

what recently reported in Europe by Burge (UK), Sfeir (France), Nassar and Pedersen (international cohorts). These Authors reported a prevalence of EA between 1.7 and 2.44 per 10000 (1:5800 – 1:4100) [1,5,7,11]. The lower incidence of EA observed in Islands NUTS1 regions (nealry 1:4200) suggested a protective role of the insular environment in our Country (for details, direct contact with corresponding Author - Appendix 1). This epidemiological issue along with the extremely low prevalence of familial cases in our cohort (< 1%) disclaim the genetic aetiology of the disease, which seems to be more environmental-derived than inherited. Larger series and longer follow ups are required to better address this issue.

Basically all patients in this survey underwent prenatal ultrasound investigations throughout pregnancy. Polyhydramnios was the most relevant but unspecific prenatal finding, reported in over half of pregnancies. However, antenatal diagnosis of EA was suspected in less than 30% of cases. In accordance with the literature [5,7,11], our results confirmed the higher sensitivity of prenatal diagnosis in case of EA without distal TEF (type A and B EA).

In accordance with previous reports [3,5-7,10], also in our series the prevalence of chromosomal abnormalities was relatively low (5%). Nonetheless, prenatal karyotype analysis was performed more frequently in patients with a suspected antenatal diagnosis of EA (42% vs 25%). Regardless of the antenatal diagnosis, this survey reported also a c-section rate of 57%, which is nearly four-folds higher than the 15% recommended by WHO [22,23]. Thus a more accurate study on risk-benefit of invasive prenatal diagnostic procedure as well as c-section delivery has to be considered in these cases.

Data regarding EA subtypes are in line with previous reports: less than 5% of the patients with EA do not have a TEF; more than 50% have associated malformations; congenital heart defects are the most commonly encountered abnormalities in patients with EA and have an incidence that is significantly higher than observed in the general population [24]. On the other hand, VACTERL association was observed with a higher prevalence in our series when compared with data from EUROCAT working study group (*20% vs 9.6%*, respectively) while CHARGE syndrome and chromosomal abnormalities showed a similar prevalence [7].

As previously underlined by Burge and co-workers [11], preoperative echocardiography remains a diagnostic key-point in clinical practice to guide operative approach; this was performed in 83% of cases in their series and its wide use was confirmed by a recent survey from EUPSA group (81%) [25]. This investigation was basically performed in all patients from our survey and a right aortic arch was detected in 2% of cases, being this prevalence in the lower range of other reports that

ranged between 2% and 5% These Authors as well as the recent EUPSA questionnaire suggested to adopt a left thoracotomy in case of preoperatively assessed right-sided aortic arch and descending aorta. However, no more than 56% of surgeons would change their right thoracotomy when the anomaly is an intraoperative unexpected finding [25-27]. The combination of the reported safety of a routine right thoracotomy and the low prevalence of right aortic arch, as confirmed by our survey, could support this approach but warrants careful consideration when known preoperatively.

The lower than expected use of Replogle tubes to decompress the upper esophageal pouch in our survey (59% of cases vs over 95% in previous reports) can be hardly explained by assessing the whole data provided by the study. We speculate that urgent/emergent surgery can imply only intermittent suction, without the need for permanent suction tube positioning. This clinical attitude proved not to interfere with the incidence of preoperative complications (in particular respiratory failure) that was consistent with previously reported data [5,11] and not influenced by the presence of a cotinuous suction.

Most of surgeons resorted to thoracotomy with extrapleural approach and azygos vein division to repair EA, as first described by Haight himself [28]. Of note, only a minority of the patients (3%) underwent thoracoscopic repair, in agreement with EUPSA survey that underlined that the preponderance of thoracotomy over thoracoscopy was evident (94% vs 6%). Also the incidence of postoperative complications turned out to be in accordance with previous reports [2,12,15,26,27]. Furthermore, none of the potential risk factors significantly correlated with the incidence of short-term complications.

Noteworthy, the results of this study underlined another key-point of EA management. In fact, we could notice a lack of standardization regarding type A EA management: method and timing of gap assessment, definition of "long" gap and pre/intra operative measurement of the gap, despite some Authors recently addressed this issue in details [29]. A limitation could be the small amount of patients born with this anomaly (less than 5% in most series, only 7 in this survey) and the challenging features that prompt paediatric surgeons to resort to the most heterogeneous approaches. Moreover the survey did not investigate the failure of a primary anastomosis in type C with the subsequent risk of acquired "long gap" EA. A multicentre study should be implemented to address this specific issue, gain standardization and finally improve the overall outcome of our patients. Despite the above mentioned limitations we can summarize that: 1) flexible endoscope and Hegar dilators are the preferred methods for lower pouch identification and measurement, 2) 3 vertebral bodies seem to be the gap to consider a primary immediate anastomosis and 3) a delayed anastomosis can be performed 6-8 weeks after gastrostomy fashioning. Furthermore, it comes clear

that surgery for long gap EA is somehow frustrating as 100% of the patients will experience postoperative complications (either leakage or stricture) compared to less than 40% in case of type C EA.

Overall early mortality in our series turned out to be nearly two-folds higher than what reported by Sfeir and Burge (10% vs 4.8%) [5] but consistent with the data provided by the EUROCAT working group that set in roughly 13% the early mortality for live births with EA [7]. Of note, mortality rate of patients in this study was in accordance with other previously reported national cohorts [11]. The vast majority of patients in our survey who died before 48 hours of life (6 out of 7 patients) were not reported. We could speculate that a preponderance of missing data belong to patients who died before being acknowledged to the surgical staff. Subsequently, early death can be severely underestimated in such a survey. On the ground of these considerations we should set in around 90% the expectation for long term survival of EA patients.

Although the involvement of all Pediatric Surgery Units represents per se an important result, the lack of most of data regarding nearly 20% of EA patients is still a burden that should be addressed. Nonetheless a key-point of this study is the prospective collection of the data that allowed addressing epidemiological, anamnestic, clinical and technical aspects of such a rare disease.

Our data confirmed the survival rate in various risk groups as reported by Spitz in 1994 [20] Nonetheless, this risk stratification for mortality developed in the mid 90's by Spitz and co-workers seems somehow limited [26,30]. In fact, although Spitz's criteria proved to be effective in predicting the outcome in literature reviews as it is in this survey, we could observe that only a minority of patients with EA felt in the highest risk group. We could also speculate that prenatal diagnosis and termination of pregnancy might influence this aspect of the disease in present days. The improvements in clinical practice, intensive care and overall survival of preterm and small for gestational age babies in the last three decades further limited the application of Spitz's criteria. We thus suggest moving to a combination of neonatal features in order to better predict the survival of patients born with EA. Low APGAR score, female gender and associated congenital heart diseases proved to be more represented in patients with poor outcome and to significantly correlate with survival. A combination of those factors could be used to implement a new scoring system in order to improve the prognostic accuracy of present risk groups. A deeper statistical analysis on a larger series of patients is required to confirm this aspect and possibly apply new up-to-date risk factors to our EA patients.

Conclusions

This study provide useful data for surgeons dealing with EA. We can now counsel EA families to the best and provide more reliable prognostic expectations to our patients. This survey will hopefully lead to the implementation of shared national guidelines for diagnosis, treatment and follow-up. We provided a further evidence of the utility of national registries and nationwide surveys that provide unique epidemiological and clinical data helping physician to deliver the best care possible for rare diseases. We now aim at redefining National Heath policies on EA.

Acknowledgments

Competing Interests

The Authors declare that they have no competing interests.

Authors' Contribution

APP conceived the study, participated in the enrolment and drafted the manuscript. **MC** participated in the enrolment and performed part of statistical analysis. **PB** helped to draft the manuscript, participated in the enrolment and revised the final version. **PG** participated in the design of the study, helped to draft the manuscript and participated in the enrolment, **MB**, **EL**, **GP**, **CM**, **BN**, and **AT** participated in the enrolment. **VJ** revised the final version of the manuscript. **GM** helped to draft the manuscript and participated in the enrolment. The whole Authors from the **SICP (ISPS) EA consortium** participated in the design of the study and in the enrolment.

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LEGENDS TO TABLES

Table 1 – Associated anomalies at birth. Eighty-one patients had at least one major associated anomaly. Some of the patients experienced more associations either involving different system or within the same system (i.e. atrial and ventricular septal defects, renal agenesis and undescended testis,). The most frequently encountered abnormalities involved cardiovascular system. We excluded trivial congenital heart anomalies such as patent ductus arteriosum or interatrial defect type ostium secundum, regardless of their cardiovascular effect. Other cardiovascular malformations included: scimitar syndrome, poly-valvular disease, atrioventricular channel and aortic coarctation. Two out of 61 patients who had a preoperative laryngo-tracheoscopy done, 3.3% had associated laryngo-tracheal anomalies. The remaining patient with tracheal anomaly did not undergo preoperative laryngo-tracheoscopy.

Table 2 – Surgical details for EA/TEF repair. Not all the items were addressed correctly and reliably by the responders. Therefore, most of the surgical details have been assessed in less than the overall 130 patients with EA/TEF type C who underwent surgical repair in the neonatal period.

LEGENDS TO APPENDICES

Appendix 1 – List of Authors belonging to various Pediatric Surgery Unit in Italy (by NUTS1 region and City listed in alphabetical order), according to SICP EA consortium. Details regarding these results can be provided directly by contacting the Author at the corresponding addresses.

Appendix 2 – Questionnaire sent to all Pediatric Surgery Unit in Italy.

Appendix 1 – List of Authors belonging to various Pediatric Surgery Unit in Italy (by NUTS1 region and City listed in alphabetical order), according to SICP EA consortium. Details regarding these results can be provided directly by contacting the Author at the corresponding addresses.

Institution	City	Name of Author in SICP EA consortium	NUTS 1 Region
ASN SS: Antonio e Biagio e Cesare Arrigo	Alessandria	Vaccarella F	North-West
Ospedali Riuniti	Bergamo	De Pascale S	North-West
Spedali Civili	Brescia	Alberti D	North-West
Istituto Giannina Gaslini	Genova	Pini Prato A	North-West
Ospedale San Leopoldo Mandic	Merate	Bernardi M	North-West
ICP Ospedale dei Bambini Vittore Buzzi	Milano	Riccipetitoni G	North-West
Ospedale Maggiore Policlinico Mangiagalli	Milano	Leva E	North-West
Ospedale Niguarda Cà Granda	Milano	Falchetti D	North-West
Azienda Ospedaliera Ospedale San Carlo Borromeo	Milano	Caccia F	North-West
Ospedale Maggiore della Carità	Novara	Rossi F	North-West
Policlinico San Matteo	Pavia	Pelizzo G	North-West
Ospedale Infantile Regina Margherita	Torino	Schleef J	North-West
Ospedale Sant'Orsola Malpighi	Bologna	Lima M	North-East
Ospedale di Bolzano	Bolzano	Andriolo P	North-East
Arcispedale Sant'Anna	Ferrara	Franchella A	North-East
Ospedale Policlinico	Modena	Cacciari A	North-East
Azienda Ospedaliero-Universitaria di Padova	Padova	Gamba PG	North-East
Azienda Ospedaliero-Universitaria di Parma	Parma	Caravaggi F	North-East
Ospedale Infermi	Rimini	Federici S	North-East
Ospedale Santa Chiara	Trento	Andermarcher M	North-East
Ospedale Regionale di Treviso	Treviso	Perrino G	North-East
Ospedale Infantile Burlo Garofolo	Trieste	Codrich D	North-East
Policlinico Borgo Roma	Verona	Camoglio FS	North-East
Ospedale San Bortolo di Vicenza	Vicenza	Chiarenza FS	North-East
Ospedale Salesi	Ancona	Martino A	Center
Ospedale Pediatrico Meyer	Firenze	Noccioli B	Center
Ospedale Santa Maria della misericordia	Perugia	Appignani A	Center
Policlinico Gemelli	Roma	Manzoni C	Center
Ospedale Pediatrico Bambin Gesù	Roma	Bagolan P	Center
Ospedale San Camillo Forlanini	Roma	Briganti V	Center
Ospedale Policlinico Sant'Andrea	Roma	Caterino S	Center
Policlinico Umberto I	Roma	Cozzi D	Center
Ospedale Policlinico Santa Maria alle Scotte di Siena	Siena	Messina M	Center
Ospedale Giovanni XXIII	Bari	Paradies G	South
Ospedale Policlinico	Bari	Rizzo A	South
Ospedale Francesco Ferrari	Casarano	Liotta L	South
Azienda Ospedaliera Pugliese-Ciaccio	Catanzaro	Salerno D	South

Azienda Ospedaliera di Cosenza	Cosenza	Aceti MGR	South
Azienda Ospedaliera Universitaria – Ospedali Riuniti	Foggia	Bartoli F	South
Azienda Ospedaliera – Ospedali Riuniti	Foggia	Nobili M	South
Azienda Ospedaliero Universitaria G. Martino	Messina	Romeo C	South
AORN Santobono Pausilipon	Napoli	Tramontano A	South
Policlinico Universitario Federico II	Napoli	Esposito C	South
Ospedale Spirito Santo	Pescara	Lelli Chiesa PL	South
Azienda ospedaliera universitaria S. Giovanni di Dio e Ruggi d'Aragona	Salerno	Clemente E	South
Ospedale SS. Trinità	Cagliari	Mascia L	Islands
Ospedale Garibaldi	Catania	Cacciaguerra S	Islands
Ospedale Vittorio Emanuele	Catania	Di Benedetto V	Islands
Presidio Ospedaliero C.T.O.	Iglesias	Licciardi S	Islands
Azienda Ospedaliero-Universitaria Policlinico P. Giaccone	Palermo	De Grazia E	Islands
Azienda Ospedaliero-Universitaria	Sassari	Ubertazzi M	Islands
Ospedale Sant'Antonio Abate	Trapani	Piazza G	Islands

SURVEY ON ESOPHAGEAL ATRESIA

On behalf of the Italian Society of Pediatric Surgery (SICP / ISPS)

The President: Professor Vincenzo Jasonni

A) DEMOGRAPHIC DATA

1. Initials

    a. Surname   _____

    b. Name   _____

2. Date of Birth __/__/_____

3. Place of birth _____ province (__)

4. Gender   M / F

5. Race (i.e. caucasic) _____

B) HISTORY

B.1) Familial history

6. Congenital anomalies YES / NO
7. Details regarding congenital anomalies (OA/TEF familiarity included)
    a. _____
    b. _____
    c. _____
    d. _____
    e. _____
    f. others:
8. Parents consanguinity   YES / NO

B.2) Pregnancy

9. Gestational age at birth (___/40)
10. Prenatal ultrasound
    a. Polihydramnios   YES / NO
    b. Prenatal diagnosis of OA/TEF   YES / NO
    c. Timing of prenatal diagnosis (___/40)

   d. Signs suggestive forOA/TEF

       i. _____Polihydramnios   ☐

       ii. _____Small gastric bubbl   ☐

       iii. _____Absent gastric bubble   ☐

       iv. _____Superior oesophageal puch   ☐

       v. other

11. Amniocentesis ☐

12. Choronic villus sampling ☐

13. If items 11 or 12 are thicked, indicate karyotype results _____

14. Mode of delivery

   a. Vaginal

   b. Caesarian section

15. Parents' age at birth (mother's and father's age, respectively) _____ and _____

B.3) Personal Hystory

16. Weight at birth [grams] _____

17. Apgar 1' [0-10] ___

18. Apgar 5' [0-10] ___

19. Timing of diagnosis (whether without prenatal diagnosis)

   a. Delivery room   ☐

   b. Within 24 hours   ☐

   c. After more than 24 hours ☐

20. Associated anomalies

   a. Cardiovascular (details)   _____

   b. Anorectal (details)   _____

   c. Genitourinary (details)   _____

   d. Gastrointestinal (details) _____

   e. Vertebral e/o skeletal (details) _____

   f. Lungs (details)   _____

   g. Others (details)   _____

   h. Associations

       i. VACTERL (details) _____

       ii. CHARGE (details) _____

      iii. SCHISIS (details)   _____

      iv. Others   _____

i. Chromosomopathies

      i. Trisomy 21   ☐

      ii. Trisomy 18   ☐

      iii. Deletion 13q   ☐

      iv. 22q syndrome   ☐

      v. Others (details)   _____

C) CLINICAL FEATURES

21. Type of Atresia (according to Gross classification)

    a. Tipo I – wihtout fistula

        i. long gap (> 3 vertebral bodies)   ☐

        ii. short gap (< 3 vertebral bodies)   ☐

    b. Tipo II – proximal fistula   ☐

    c. Tipo III – distal fistula   ☐

    d. Tipo IV – either proximal and distal fistula   ☐

    e. Tipo V – "H" type fistula (without atresia)   ☐

    f. Tipo VI – congenital stenosi   ☐

    g. Others – (i.e. cleft):_____   ☐

22. Preoperative period

    a. Heart ultrasound scan   ☐

        i. right aortic arch   ☐

        ii. patent ductus arteriosum   ☐

      iii. Pulmonary hypertension ☐

  b. Replogle in upper pouch ☐

  c. Replodge size [Fr/Ch] ___

  d. Central line ☐

  e. Type and size of central line [Fr.] _____

  f. Preoperative complications

      i. Respiratory distress ☐

      ii. Gastric rupture/laceration ☐

      iii. Other (details) _____

  g. Risk group classification (according to Spitz classification)

      i. Group I – birth weight > 1500 g, no congenital heart disease (CHD) ☐

      ii. Group II – birth weight < 1500 g <u>or, alternatively</u> , CHD ☐

      iii. Group III – birth weight < 1500 g <u>with associated</u> CHD ☐

      <<CHD *includes: **cyanogen congenital heart malformation** requiring palliative/corrective surgery or **non-cyanogen congenital heart malformation** requiring either medical or surgical treatment to deal with heart decompensation >>*

D) SURGICAL TREATMENT

D.1) Type 2, 3 and 4 OA/TEF

23. Antibiotic treatment /prohylaxis (Type and lenght of treatment)

24. Laryngotracheoscopy ☐

25. Fistula incannulation preoperatively ☐

26. Urgent fistula ligation ☐

27. Surgical treament

  a. Conventional ("open thoracotomy")

      i. Patient positioning:_____

      ii. Type of incision (thoracic ☐ axillary ☐)

      iii. Muscle sparing ☐

     iv.   Approach (transpleuric ☐ extrapleuric ☐)

     v.   Azygos vein ligation   ☐

     vi.   Lower oesophageal pouch mobilization   ☐

     vii.   Upper oesophageal puoch mobilization   (minimal ☐ extensive ☐)

     viii.   Tracheal fistula suture (stitch type and size) _____

     ix.   Oesophageal anastomosis (stitch type and size) _____

     x.   Tissue interposition:_____

     xi.   Number of stitches for oesophageal anastomosis_____

     xii.   Tension anastomosis   yes ☐ no ☐

     xiii.   Transanastomotic stent   ☐

     xiv.   Para-anastomotic drain   ☐

     xv.   Wound closure (interrupted, running, subcuticular, glue) _____

   b. *Thoracoscopic*

     i.   Patient positioning _____

     ii.   Scope size   _____

     iii.   Angle of the scope   _____

     iv.   Nmber of ports   _____

     v.   Trocars positioning _____

     vi.   Azygos vein ligation   yes ☐   no ☐

     vii.   Lower oesophageal pouch mobilization   si   ☐   no ☐

     viii.   Lower oesophageal pouch mobilization   minimo☐ estensivo☐

     ix.   Tracheal fistula suture (stitch type and size) _____

     x.   Oesophageal anastomosis (stitch type and size) _____

     xi.   Tissue interposition: _____

     xii.   Number of stitches for oesophageal anastomosis _____

     xiii.   Tension anastomosis   yes ☐   no ☐

     xiv.   Transanastomotic stent   ☐

     xv.   Para-anastomotic drain   ☐

     xvi.   Wound closure (interrupted, running, subcuticular, glue) _____

D.2) Surgical details for type 1 OA

28. Neonatal laryngotracheoscopy   ☐

29. Gastrostomy   ☐

30. Methodology for gap assessment (X-rays with contrast medium, endoscopy, Hegar, etc):

_____

_____

_____

31. Gap (vertebral bodies) _____

32. Timing and approach:

    a. Anastomosis within the first month of life   ☐

    b. Delayed anastomosis ☐(details) _____

    c. Esophagostomy for further oesophageal substitution surgery ☐

        i. Gastric trasposition   ☐

        ii. Gastric tubulization   ☐

        iii. Esophagocoloplasty   ☐

            1. Retrosternal   ☐

            2. Medastinic   ☐

        iv. Jejunal interposition   ☐

    d. Delayed anastomosis according to Foker technique   ☐

    e. Other (details) _____

D.3) Surgical treatment of Type 5 TEF

33. Diagnosis

    a. Age at diagnosis (days)_____

    b. Previous surgical treatment ☐

       (details):_____

       _____

       _____

    c. Upper GI barium meal   ☐

    d. Chest CT   ☐

    e. Combined endoscopy (laryngotracheoscopiy + esophagoscopy)   ☐

      f. Symptoms_____

              _____

              _____

      g. Fistula site (upper ☐ intermediate ☐ lower ☐) _____

34. Management

      a. Fistula incannulation   ☐

      b. Incision

             i. cervical   ☐

            ii. Right thoracotomy ☐

           iii. Left thoracotomy   ☐

      c. Tissue interposition   ☐

E) POSTOPERATIVE

35. Paralysis: yes ☐ no ☐ (hours: _____)

36. Transanastomotic tube duration (days) _____

37. X-ray with contrast: yes ☐ no ☐ (timing [days]) _____

38. Timing for oral feeding (hours): _____

39. Need for replacement of chest tube yes ☐ no ☐ (timing [hours]) ___ (reason)

    _____

40. Early complications (within discharge)

    a. Death ☐ (indicate whether preoperative or postoperative and provide details)

    b. Infection yes ☐ no ☐

    c. Bleeding yes ☐ no ☐

    d. Anastomotic leak yes ☐ no ☐ (timing in hours) _____

    e. Anastomotic stricture yes ☐ no ☐ (timing in days) _____

    f. Recurrent fistuls yes ☐ no ☐ (details, timinig and symptoms)

       _____

    g. Acuired tracheobronchial fistula yes ☐ no ☐ (details, timing and symptoms)

       _____

Name or physician filling the quesitonnaire _____

Pediatric Surgery Unit _____

Phone number _____

e-mail _____

Date of questionnaire __/__/_____

Attachment 2 – Collecting data questionnaire developed by experts from SICP directorate.

Table 1 – Associated anomalies at birth. Eighty-one patients had at least one major associated anomaly. Some of the patients experienced more associations either involving different system or within the same system (i.e. atrial and ventricular septal defects, renal agenesis and undescended testis,). The most frequently encountered abnormalities involved cardiovascular system. We excluded trivial congenital heart anomalies such as patent ductus arteriosum or interatrial defect type ostium secundum, regardless of their cardiovascular effect. Other cardiovascular malformations included: scimitar syndrome, poly-valvular disease, atrioventricular channel and aortic coarctation. Two out of 61 patients who had a preoperative laryngo-tracheoscopy done, 3.3% had associated laryngo-tracheal anomalies. The remaining patient with tracheal anomaly did not undergo preoperative laryngo-tracheoscopy.

District	N	Within system (%)	Overall PATIENTS (% - 95%CI)
Cardiovascular			**39 (26.7% - 95%CI,20-34.4%)**
Ventricular septal defect	22	56%	15 %
Tetralogy of Fallot	7	18 %	5 %
Atrial septal defect	6	15 %	6 %
Other	7	38 %	10%
Skeletal			**30 (20.6% - 95%CI,14.8-27.8%)**
Vetrebral anomalies	12	36 %	8 %
Costal anomalies	2	6 %	1 %
Limbs anomalies	16	48 %	11%
Other	3	9 %	2 %
Ano-rectal			**21 (14.4% - 95%CI,9.6-21%)**
Anorectal malformation	18	86 %	12 %
Cloaca	3	14 %	2%
Genito-urinary			**18 (12.3% - 95%CI,7.9-18.6%)**
Kidney agenesis	4	22 %	3
Kydney displasia/Hypoplasia	2	11 %	1 %
Kydney anatomical anomalies	4	22 %	3 %
Hydroureteronephrosis	4	22 %	3 %
Uterine agenesia	1	5 %	1 %
Undescended testis	3	17 %	2%
Hypospadia	3	17 %	2%
Gastrointestinal			**7 (4.8% - 95%CI,2.3-9.6%)**
Malrotation	2	28%	1 %
Duodenal atresia	4	57%	3 %
Omphalocele	1	14%	1 %
Pulmonary			**5 (3,4% - 95%CI,1.4-7.8%)**
Pulmonary hypoplasia	3	60%	2%
Other	2	40%	1%
Others			
Facial and nervous system	12	44 %	8 %
Endocrine system	3	11 %	2%
Larynx and trachea	3	11 %	2%
Single umbilical artery	9	33 %	6 %

Table 2 – Surgical details for EA/TEF repair. Not all the items were addressed correctly and reliably by the responders. Therefore, most of the surgical details have been assessed in less than the overall 130 patients with EA/TEF type C who underwent surgical repair in the neonatal period.

Surgical details for type 3 EA/TEF	N (total)	%
Muscle sparing thoracotomy	92 (131?)	72
Axillary Approach	27 (131?)	20
Extra-pleuric approach	105 (123)	85
Azygos vein division	100 (130)	76
Extensive upper pouch mobilization	74 (129)	57
Lower pouch mobilization	97 (130)	74
Median stitches for anastomosis [median (range)]	8 (5 - 12)	
Anastomosis under tension	34 (123)	28
Perianastomotic drain	115 (126)	91
Transanastomotic tube	112 (127)	88
Timing for transanastomotic tube removal [days] [median (range)]	8 (2 – 42)	
Interposition of patch or prosthetic material between oesophagus and trachea	9 (78)	11