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Prevalence, Mortality, and Associated Anomalies in Esophageal Atresia: A Retrospective Study of Finnish Population Data (2004-2017)

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Abstract

Introduction

The aim of the study was to investigate the prevalence of esophageal atresia (EA), frequency of associated anomalies and mortality during 2004–2017 in the Finnish population. We hypothesized the Spitz classification and the presence of other congenital malformations would predict mortality in patients with EA as well as assumed the survival to be high among patients with EA.

Material and Methods

This retrospective, population-based study was based on the registries maintained by THL Finnish Institute for Health and Welfare and Statistics Finland. The cases were identified and classified according to ICD-9 and ICD-10 codes and accompanying written diagnosis. Associated anomalies were classified based on the EUROCAT criteria, and minor anomalies were excluded. All statistical tests were performed as two-sided significance level set at $p<0.05$. Chi-square test or Fisher's exact test were utilized for categorical variables. The change in prevalence rates during the study period was evaluated with linear regression.

Results

In total, 337 cases with EA were identified including 295 (87.5%) live births, 17 (5.0%) stillbirths and 25 (7.4%) terminations of pregnancy. The total prevalence for EA in Finland was 4.17/10 000 births with no significant change during the study period, P=0.35. Neonatal mortality was 5% (n=15) and 1-year survival 91.5%. Mortality was associated to syndromic cases (p=0.002). The Spitz classification predicted the neonatal mortality better than cardiac anomalies alone ($p<0.001$ and p=0.6, respectively). Type C was the most common atresia type (65.9%) followed by type A (14.8%) and B (6.8%). The most common group of associated malformations were heart defects (35.0%) followed by other gastrointestinal tract malformations (15.3%) and limb anomalies (12.2%). Syndromic cases (12.2%) were associated with type A and B atresias (p=0.001). VACTERL association was observed in 16.6% of the cases.

Conclusion

The overall prevalence of EA remains stable and relatively high in Finland. Despite the high prevalence of co-occurring malformations, the overall survival rate is high. Spitz classification predicted neonatal survival well.

Keywords: esophageal atresia, prevalence, mortality, associated anomalies, Spitz classification

Introduction

Esophageal atresia (EA) and/or tracheoesophageal fistula (TEF) is the commonest esophageal anomaly with a reported overall prevalence varying greatly in Europe from 1.27 to 4.55/10 000[1]. Reported prevalence in the United States is approximately 2.3/10 000 with the highest prevalence of 2.5/10 000 births in white non-Hispanic population[2] while the lowest prevalences has been reported in China averaging at 0.57/10 000.[3] However, the majority of the studies on the prevalence of esophageal atresia have only included live births and total prevalence including stillbirths and elective terminations remains unknown. EA is classified into six subtypes according to Gross based on the presence and anatomic location of the fistula. Type C atresia with distal TEF is the most common comprising about 85 % of the cases.[1,4,5] As there usually is no continuation in esophagus, this anomaly requires surgery shortly after birth.

EA results from a failure of separation of the primitive foregut around 4th to 6th gestational weeks and 45–54 % of the cases are estimated to be isolated.[1,2] The etiology of EA remains largely unknown, but genetic signaling pathway malfunction as well as environmental and maternal factors, especially maternal diabetes, have been noted to increase the risk of EA.[6-8]

EA is strongly linked with other congenital anomalies, cardiovascular defects being the most common anomaly group as presented in 23–30% of the cases followed by urinary (16%) and other gastrointestinal tract (15%) defects.[1] VACTERL association, which is defined by the presence of at least three of the following malformations: vertebral defects, anorectal malformation, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities is present in about 10% of the cases.[1,9] Also, chromosomal abnormalities are common, especially Trisomy 18 and 21, with or without CHARGE-syndrome, defined as coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, and ear anomalies/deafness.[10] Nevertheless, commonly EA is sporadic and non-syndromic.[1,6,11]

Reported prenatal ultrasound detection rates vary from 22 to 78% depending on the atresia type and gestational age at the time of ultrasound.[12,13] However, in most cases, EA is diagnosed after birth. Reported overall survival rates are high, reaching 91–98% in high income countries.[14] Spitz classification (birth weight <1500 g and/or major cardiac anomaly) is commonly used to give a

prognostic estimation.[12,14,15] Over the years, survival also in long-gap EA have risen to 93% due to development in both operative and intensive care management.[16]

The aim of this population-based study is to investigate the current prevalence of EA, frequency and distribution of associated anomalies, mortality rates as well as possible changes in these variables during 2004-2017 in the total Finnish population. We hypothesized that survival of EA in Finland to be high, and the Spitz classification and the presence of other congenital malformations, cardiac and VACTERL-association, would predict mortality.

Materials and Methods

This study is based on the following national, population-based registries maintained by the Finnish Institute for Health and Welfare: The Finnish Register of Congenital Malformations (FRM), the Register of Induced Abortions, the Medical Birth Register and Cause of Death Register maintained by Statistics Finland. These registers contain data on all live and stillbirths and terminations of pregnancy due to fetal anomalies (TOPFA).

The data collection is done using “Notification of Malformation” forms received from the maternity and pediatric hospitals. The FRM also identifies cases with malformation code from other registers. Before the data are entered to the register, the list of diagnosis is acquired and ratified with the registries above and additional information (patient records, radiographs, specialist consultation, etc.) is requested if necessary. Medical geneticist double-checks all recorded information and confirms the final diagnoses.[17] All national register studies remain under strict control by The Finnish Social and Health Data Permit Authority (Findata). Data is stored and analyzed in a secure operating environment (Kapseli®) provided by Findata.

As every single entry to our national database is confirmed by a clinical geneticist, there is always a delay of at least 2-3 years before the data is accessible. Hence the data we have, is the most recent available as we applied for study permits in 2020 and received the data for analysis in 2023.

The diagnoses are coded according to the World Health Organization's International Classification of Diseases and Health Related Problems (ICD) revisions nine and ten (ICD-9, Atlanta modification, ICD-10). The cases were identified and classified with ICD-10 codes Q 39.0, Q39.10, Q39.11, Q39.2, Q39.3 and ICD-9 codes 750300, 750310, 750320, 750340. Also, the diagnoses were ascertained from the accompanying written diagnosis text in the FRM.

All cases with diagnosed EA between January 1st 2004 and December 31st 2017 were included in the study and were classified based on Gross classification by two authors (SA, AR).[5] Patients without EA were excluded. Associated anomalies and syndromes were classified according to EUROCAT and minor anomalies were excluded.[18,19] If there were discrepancy between ICD codes and written diagnosis, cases were classified as undefined. Risk classification according to Spitz et al. was used for neonatal mortality.[15] Neonatal mortality was defined as death during first 28 days of life and infant mortality as death during the first year of life. The cases were categorized as isolated when no other major congenital malformations were observed, as cases with multiple congenital anomalies (MCA) in the presence of other major anomalies, or syndromic (SDR).

All statistical tests were performed as two-sided significance level set at $p<0.05$. Chi-square test or Fisher's exact test were utilized for categorical variables. The change in prevalence rates during the study period was evaluated with linear regression. According to EUROCAT, birth, live birth, and total prevalence rates are given per 10 000[20] and 95% confidence interval (CI) was calculated for total prevalence of atresia types. SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, North Carolina, United States) was used for analyses.

The approval of the institutional review board at the Turku University Hospital was obtained before conducting this study. Also, Findata gave permission to utilize national register data in this study (THL/6258/14.02.00/2020).

Results

In total, 337 cases with EA were identified in the registers including 295 (87.5%) live births, 17 (5.0%) stillbirths and 25 (7.4%) terminations of pregnancy for fetal anomaly (TOPFA). The total prevalence

for EA was 4.17/10 000 with no significant change during the study period, P=0.35 (Figure 1). Live birth prevalence was 3.73/10 000 and birth prevalence 3.86/10 000. Mean gestational age at birth was 37.4 weeks (standard deviation [SD] 3.5) and mean weight at birth 2641g (SD 843g, range 450 – 4850g). Male-female ratio was 1.3:1 (male 57.7%). Mean maternal age at birth was 31.1 years (SD 6.1, range 17 – 50 years).

Type C was the most common atresia type (222/66%) followed by type A (50/15%) and type B (23/7%). Syndromic cases were mainly associated to atresia types A and B (p=0.001) while distribution of MCA was more even (Table 2). There were 10 (3.0%) cases where atresia type could not be defined due to not accurate enough ICD-9, ICD-10 diagnose codes or written diagnosis. Termination of pregnancy was rare in isolated cases (n=1, 0.7%), but more common in MCA (n=15, 9.6%), and syndromic cases (n=9, 22.0%) (Table 3).

Among VACTERL-cases (n=56, 16.6%), type C was the commonest, (36/64.3%) followed by types A (10/17.9%), B and E (2/5.4%), D (2/3.6%), and F (1/1.2%). For two cases we could not set the type due to not specific enough coding. There were 4 syndromic cases, 2 in type A (syndrome nos and Trisomy 18), 1 in type C (Trisomy 18) and 1 in non-diagnosed type (Trisomy 18). Among all SDR cases, VACTERL was presented in 7.3 % (4/41).

There were 140 (41.5%) isolated cases, 156 (46.6%) with other major congenital anomalies (MCA), and 41 (12.2%) syndromic (SDR) cases. VACTERL-association was present in 56 (16.6%). Heart defects were observed in 118 (35%) of the cases, followed by other digestive system 53/15.8%, limb 41/12.2%, urinary tract 37/11 % and spinal 32/9.5% anomalies (Table 1).

Neonatal mortality was 5.1% (N=15) accounting for the majority of deaths, and infant mortality rate was 8.5% (N=25). The Spitz classification[15] predicted neonatal mortality well with only 2.7% mortality in Spitz group 1 vs 25.0% mortality in group 3 (p<0.001) (Table 4). Subgroup analysis regarding mortality among live birth SDR cases (N=30) showed 5 deaths during neonatal period and 2 more during infancy. Both neonatal and infant mortalities were associated with syndromic cases of EA, p=0.002 for both. There was no association between VACTERL and neonatal (1/43) or infant mortality (2/43), p=0.4 and 0.3, respectively.

As heart defects were present in 35% of this population thus being the most common additional anomaly group, we also analyzed mortality associated to heart defects alone. During neonatal period four mortalities out of 15 (26.7%) were associated with heart defect(s) and during infancy 9/16 (36.0%). These findings were not statistically significant, (p= 0.60 and 0.73, respectively). Also, VACTERL associations relation to mortality was analyzed and no statistical significance during neonatal (1 case, 6.7%, p=0.037) or infancy periods (2 cases, 8%, p=0.33) was observed.

Discussion

EA is associated with a broad view of anomalies which are present in more than half of all cases. Despite comorbidities, overall survival exceeds 90% due to development of management yet the situation still sets a challenge to the medical team. Although cardiac anomalies were the most common anomaly group, these anomalies alone were not significantly associated with mortality while the Spitz classification predicted mortality well.

The overall prevalence of EA has remained stable over the past decades. Latest international prevalence rates of EA according to 1987–2006 EUROCAT study was 2.43/10 000 with greatly varying regional prevalence rates from 0.57 to 4.55 per 10,000 births.[1,3] In the current study, we observed a total prevalence of 4.17/10 000 and live birth prevalence of 3.73/10 000 births. Compared to previous study of Kyyrönen et al., the Finnish prevalence has remained stable as the reported prevalence in 1970s was 4.1/10.000.[4] Interestingly, a recent French national register study from 2023 found the live birth prevalence to be only 1.8/10 000.[21] The great variation of prevalences between specific regions is partly explained by the cultural and religious aspects related to of TOPFA.[3] Also, there are national differences how and where malformations are reported.[22,23] It is speculated that genetics, ethnicity and certain maternal risk factors might also play a role and some signaling pathway alterations are known to cause VACTERL-like outcomes in mice.[2,6,8] These factors do deserve more investigations.

The distribution of EA types in this study (Table 2) differs slightly from previous ones. In other studies, frequencies were reported mainly on types A, C and E atresias as type A 4 to 7%, type C 86 %, type E 4 to 7 %.[11,14,16,24-28] In the current study type A was observed in 15%, type B 7% and C 66%. The

biggest divergence was in type C. This discrepancy could be explained by the inclusion of all live and stillbirths as well as terminated cases.

Termination of pregnancy for fetal anomalies in isolated EA is extremely rare, but in the presence of MCA or SDR, likelihood to TOPFA rises to 9.6% and 22.0%, respectively. The mean termination rate in EUROCAT study was 7.8% [1] and lower rates as 3% have been reported in large series by Bell et al. and Nassar et al.[23,29] The abortion rate of 7.4% in this current study is well in line with the EUROCAT data. In our country, termination of pregnancy for fetal anomalies has been legalized in the 1950s, and TOPFA was legal until 24+0 weeks during the study period. In Finland, generally the number of induced abortions is decreasing, currently averaging at 6.9/1000 women in childbearing age.[30]

EA is associated with a broad spectrum of different congenital anomalies. The high incidence of 58.5% of cases with at least one co-occurring anomaly was observed and most of the anomalies are within VACTERL spectrum. The most important single anomaly group especially for survival prediction is cardiac anomalies, even though cardiac anomalies alone were not associated with mortality. The observed prevalence of 35% in this study is slightly higher than in the past studies show (18–30%) and the trend seems to be increasing.[1,4,25,31] We postulate that this change is likely due to advances and availability in ultrasound imaging techniques.

VACTREL association was present in 16.6% of cases and sets in range as compared to other studies. Pedersen et al.[1], van Lennep et al.[28], and Spitz[32] showed the low incidence of 10%, while Lilja et al.[25] and Brosens et al.[33] found it to be as high as 20%. Interestingly, Sistonen et al. in their long-term follow-up study found that primarily VACTERL association was diagnosed only in 5% of the EA patients. Among those who agreed to participate in the follow-up study, the prevalence rose up to 23 %.[34] This rise in diagnosed patients could be due to developed facilities over study period, but also risen knowledge as well as changed cultural mindset and possible socioeconomical benefits in case of diagnosis.

The Spitz classification[15] has been criticized for not being accurate enough as neonatal intensive care and surgical techniques have gone through a major development during last decades and as putting too much significance for birth weight alone. Also, the matter of criticism has been the fact that does not take other malformations, especially renal, into account.[35-37] Nevertheless, in the recent study

of Yamoto et al., birth weight and cardiac anomalies were still seen as major factors when predicting the survival of EA/TEF patients. They postulated the cut of weight for 50% survival to be 1.9 kg with cardiac anomaly and 1.0 kg without, whereas in Spitz classification the weight of 1.5 kg has been used.[15,38] Regardless, Spitz classification appeared to predict the survival well in the current study ($p < 0.001$). Moreover, we observed no statically significant association between mortality and heart defects alone. Similarly, VACTERL-association did not impact mortality in EA patients during neonatal or infant period in our study.

A multicenter study by Bell et al.[29] containing data from EU, Asia and North and South America observed 89.4% neonatal and 84.5% infant survival rates, middle-income countries having the lowest survival. Survival from the 1980's has risen from 80.3% to 92.6%. In the US, Donovan et al. [39] found in hospital mortality to be 7.8% and can be understood as neonatal mortality, length of stay being 37.2 days. Postoperative mortality was found to be 17.7 % in the study of Cömert et al.[40] and 10.4 % in the study of Schmedding et al. [41]

In the high-income countries, the overall survival has remained high from the late 80's. We observed a 94.9% neonatal and 91.5% one-year survival rates, and these numbers contain all pre and postoperative deaths without any exclusions. The main reason for the high survival, especially in long-gap EA, is the development of the surgical reconstruction techniques and the developed pediatric intensive care pre and postoperatively. Before the 1960's, the overall survival was less than 50%.[16]

Strengths and limitations

The strength of this retrospective register study is a total population coverage of and high quality of validated data.[42,43] Also, the registries contain data on both live and stillbirths as well as TOPFA, which is seldom available. This makes it possible to analyze the total prevalence for EA. The limitations include a relatively limited number of cases and relying only on the retrospective register data. Due to that, there were 10 (3.0%) cases of esophageal atresias which we could not define the type of atresia because of the not accurate enough ICD-9 and ICD-10 diagnosis coding. Likewise, it

was not possible to demerge the pre and postoperative mortality due to register-based data features.

In conclusion, the prevalence and the survival of EA in our country are one of the highest and have remained stable during the study period. Type C was the commonest type, yet type A was presented in greater percentage than in previous studies. Almost 60% of the EA cases have other concomitant anomalies or syndromes. Most syndromic comorbidities were associated to EA types A and B. Syndromic EA was associated with increased mortality. As mentioned before, the Spitz classification has been judged not to be accurate enough for predicting the mortality of a newborn with EA. This study verifies Spitz classification's position as an important tool for predicting the survival of a newborn with EA. Overall survival is high and isolated esophageal atresia seldom results in termination of pregnancy.

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Figures and tables

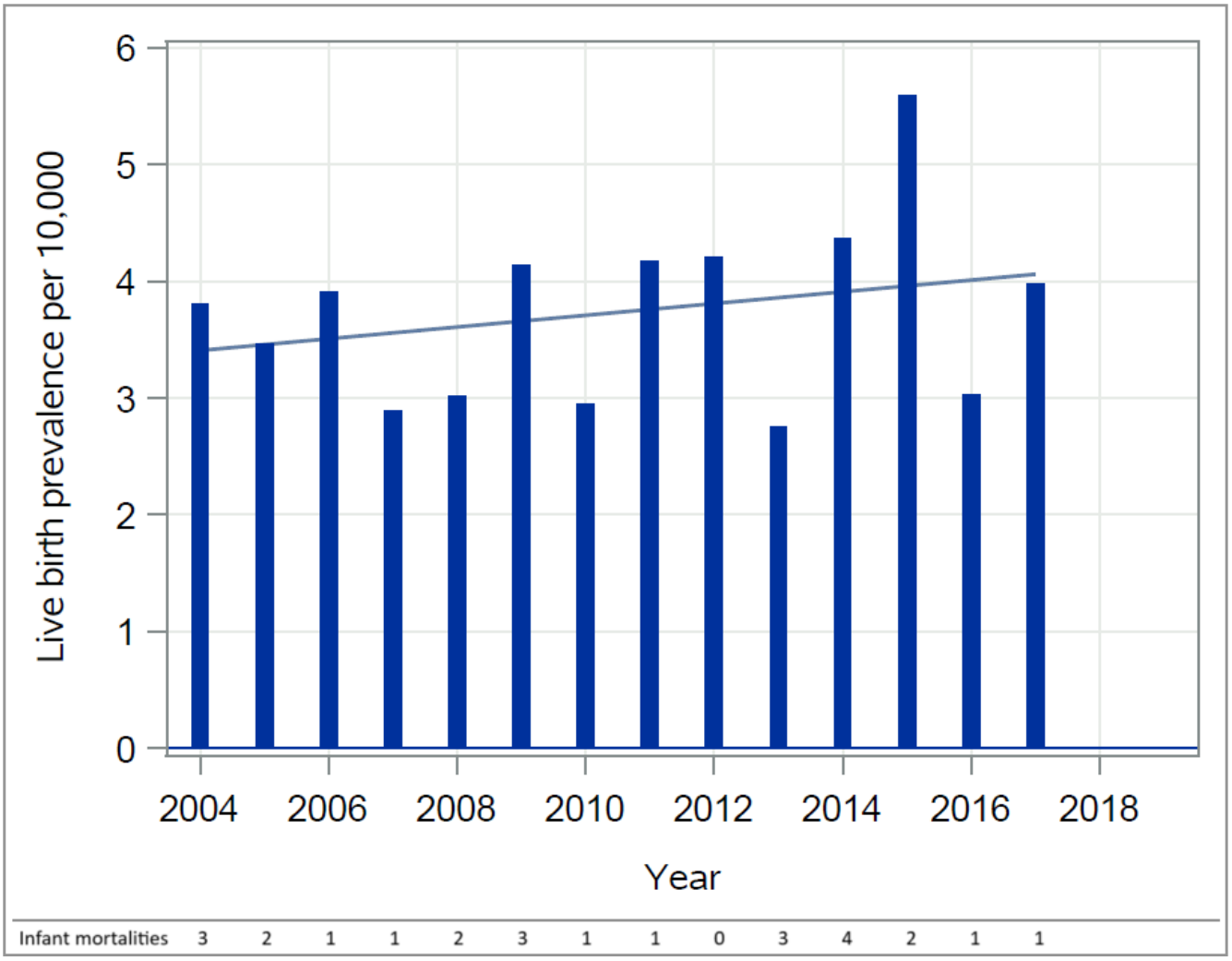

Figure 1: Live birth prevalence of esophageal atresia in Finland 2004-2017 with no significant change over time (p=0.35) accompanied with total number of infant mortalities per year.

Nervous system % (n)	Heart % (n)	Cleft % (n)	Eye % (n)	Ear, face, and neck % (n)	GI % (n)	Respiratory % (n)	Urinary % (n)	Genital % (n)	AWD % (n)	Limb % (n)	Spine % (n)	Chromosomal % (n)	VACTERL % (n)	Other anomalies / syndromes % (n)
8.31 (28)	35.01 (118)	4.15 (14)	1.48 (5)	1.78 (6)	15.83 (53)	5.34 (18)	10.98 (37)	5.34 (18)	0	12.17 (41)	9.50 (32)	9.50 (31)	16.6 (56)	2.08 (7)

Table 1: Incidence of individual concurrent anomalies in 337 esophageal atresia cases organized by affected organ system. GI=gastrointestinal, AWD=abdominal wall defects, VACTERL=vertebral, anal, cardiac, trachea-esophageal, renal, limb. Major congenital anomalies were classified, and minor anomalies were excluded according to Eurocat guidelines.

Atresia type	Isolated cases % (n)	MCA % (n)	Syndromic % (n)	Total prevalence per 10 000	95% confidence interval (CI)
Type A, n=50 (15%)	34.0 (17)	36.0 (18)	30 (15)	0.62	0.46 – 0.81
Type B, n=23 (7%)	34.8 (8)	47.8 (11)	17.4 (4)	0.28	0.18 – 0.43
Type C, n=222 (66%)	44.1 (98)	47.3 (105)	9.0 (20)	2.74	2.39 – 3.13
Type D, n=4 (1%)	50.0 (2)	50.0 (2)	0	0.04	0.013 – 0.13
Type E, n=19 (6 %)	47.4 (9)	57.9 (11)	0	0.23	0.14 – 0.37
Type F, n=9 (3%)	44.4 (4)	44.4 (4)	11.1 (1)	0.11	0.05 – 0.21

Table 2: Distribution of co-morbidities in different atresia types according to Gross classification and total prevalences per 10 000 births with 95% CI.

	Isolated % (n)	MCA % (n)	SDR % (n)
Live birth, n=295 (87.5%)	45.1 (133)	44.7 (132)	10.2 (30)
Stillbirth, n=17 (5.0%)	35.3 (6)	52.9 (9)	11.8 (2)
TOPFA, n= 25 (7.4%)	4.0 (1)	60.0 (15)	36.0 (9)
All, n=337 (100%)	41.5 (140)	46,6 (156)	12.2 (41)

Table 3: Distribution of live births, stillbirths, and termination for fetal anomaly (TOPFA) in isolated EA, cases with multiple congenital anomalies (MCA), and syndromic (SDR) cases.

	No. of patients	Neonatal mortality n (%)
Spitz 1: Birth weight ≥ 1500 g, no major congenital heart defect	185	5 (2.7%)
Spitz 2: Birth weight <1500 g or major congenital heart defect	94	6 (6.4%)
Spitz 3: Birth weight <1500 g and major congenital heart defect	16	4 (25.0%)
All live births	295	15 (5.1%)

Table 4: The Spitz classification predicted neonatal mortality well (p<0.001).