ORIGINAL ARTICLE

Factors Predicting Postoperative Esophageal Stricture after Repaired Tracheoesophageal Malformation in Children with Esophageal Atresia

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Background: An esophageal stricture is the most frequent complication after surgical correction for esophageal atresia (EA) patient, resulting in hospitalization or surgical intervention.

Objective: To describe the characteristics of EA with a stricture and assess the factors influencing the postoperative esophageal stricture.

Materials and Methods: All children after surgical correction between 1999 and 2014 were included. All complications at one and five years were recorded and predicting factors for esophageal stricture were analyzed.

Results: Forty-seven patients were recorded. Thirty-one EA patients were divided into two groups as stricture and non-stricture. Stricture had 18 patients and non-stricture had 13 patients. Median follow-up time of EA with esophageal stricture was 10 years (3,690.5 days), and 5.7 years (2082.0 days) for EA without stricture. Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association was found in 38% and 58.1% had anastomotic stricture. The waiting time from birth to surgical repair was significantly longer in the stricture group at 15 versus 3 days (p=0.009). The median esophageal stricture time was about five years (1,829 days). The most common clinical presentation of EA with stricture was dysphagia following with recurrent pneumonia. Respiratory pneumonia was more common in the stricture group (p=0.033).

Conclusion: Primary repairs should not be delayed in EA patients. Anastomotic strictures can be found beyond the fifth year after surgery. A multidisciplinary follow-up plan should be continued for longer than five years to enable the detection of further late stricture formation.

Keywords: Esophageal atresia; Tracheoesophageal fistula; Congenital esophageal atresia; Postoperative esophageal stricture

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Esophageal atresia (EA) is a rare congenital anomaly. It is an anatomical discontinuity of the esophagus with or without tracheoesophageal fistula (TEF)[1]. The etiology is still unknown, although environment and genetics are mentioned[2]. There are five types, which are A to E[2,3]. The most common type, at 75% to 94%, is type C[4-11]. EA prevalence has been stable recently[1-3]. The epidemiology was reported with the prevalence from 1:2,500 to 1:4,500 live births[1,4]. In United States, the incidence is 1.27 to 4.55 per 10,000 live birth[7,8]. Eighty percent of patients with EA are frequently associated with other anomalies[1,2,4,5,9]. Almost 70% are associated with congenital heart disease[1,2,6,7,10,12]. Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association are 9.6% to 23% of EA[1,2,4,5,7,13]. Mortality rate varied at 5% to 9% before the first year of life[5,3,12,14].

The treatment of choice is surgical management[1-7,9,10,14]. Since 1939, the improvement of medical technique increased the survival rate of EA patients to more than 90%[11,12,15]. The common complications are anastomotic stricture, anastomotic leakage, recurrence TEF, gastroesophageal reflux (GER), and recurrence pneumonia[4,5,7,9,10,13,16]. The anastomosis stricture rate is 6% to 50%[5,7,10]. These complications can result in hospitalization or surgical intervention.

The objectives of the present study were to describe the prevalence rate and characteristics of

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EA with esophageal stricture in Maharaj Nakorn Chiang Mai Hospital and to find the factors influencing postoperative esophageal stricture that could improve the outcome of the treatment. In addition, there was an optimal follow-up plan.

Materials and Methods

Definitions

EA was classified using Gross classification[2,3]. VACTERL association was defined when at least three of these anomalies were presented, vertebral, anorectal, cardiac, renal, urinary, or limb[1,2,4,5,7]. The first operation to undergo esophageal reconstruction is categorized as primary repair. For staged repair, there are other operations prior to esophageal reconstruction, which are esophagostomy and fistula ligation. Primary repair is selected as the first options for all patients except type A esophageal atresia or unstable patients. Anastomotic stricture is defined as a narrowing at the level of the anastomosis and associated with significant symptoms such as feeding difficulty, drooling, vomiting, foreign body impaction, aspiration, and poor weight gain[17]. Dysphagia presents with a complaint of difficulty in swallowing or choking[17]. GER is defined as pH monitoring or symptoms including belching, vomiting, or trouble eating[5,16,18,19]. Patients who have clinically suspected stricture are confirmed by contrast study or endoscopy.

Population and data collection

The present study was a retrospective descriptive study. The present study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, research ID 3991. The data were collected from the electronic medical record in Maharaj Nakorn Chiang Mai Hospital. The inclusion criteria were EA patient that underwent esophageal reconstruction in Maharaj Nakorn Chiang Mai Hospital between 1999 and 2014. The authors excluded the patients who did not received surgery, were operated in other hospitals, or could not be follow up in Maharaj Nakorn Chiang Mai Hospital for at least one year after operation.

All operations were decided and operated by experienced Pediatrics surgeon team. Postoperative medical condition was co-managed by Pediatrics surgeons and Pediatricians.

In the present study collected demographic characteristics of EA patients, perioperative status, postoperative complication, re-operative management, and nutritional status at the first and the fifth-year follow-up evaluated by weight/age or height/age. Those were reported in percentile scale. The postoperative complications were anastomosis stricture, re-fistula, anastomosis leakage, GER, and pneumonia. The operated EA patients were routinely follow-up by Pediatrics surgeons and Pediatricians in Maharaj Nakorn Chiang Mai Hospital.

The total number of patients required was calculated[14]. Ninety-eight patients were included in the present study.

Statistical analysis

All statistical analyses were performed using Stata Statistical Software. Categorical variables were using Fisher's exact test and reported by number and percentage. Continuous variables were using Student's t-test and reported by mean and standard deviation (SD) in normally distributed data or using Mann-Whitney U test and reported by median and interquartile range (IQR) in non-normally distributed data. A p-value of less than 0.05 was considered statistically significant. Kaplan-Meier survival curve was used in the analysis of the median time to stricture of esophagus after tracheoesophageal malformation repaired. Due to the limited number of patients, multivariable analysis was not done.

Results

Forty-seven patients of EA (97.92%) recorded in the medical database underwent surgery. One patient could not tolerate the operation due to cardiac failure. Three patients underwent surgery from other hospitals. Mortality rate was 13.63% (6/44 patients). The death occurred during the first admission. The causes of death were from underlying heart disease (two cases), sepsis of newborn (two cases), respiratory failure (one case), and anastomotic leakage (one case). Thirty-one patients were included in the analyses. Eighteen patients (58.1%) developed esophageal stricture (Figure 1). Median follow-up time of EA with esophageal stricture was 10 years or 3,690.5 days (IQR 2,689.0, 5,077.0), and 5.7 years or 2,082.0 days for EA without stricture (IQR 1,630.0, 3,200.0). Maximum follow-up time was almost 20 years or 7,622 days in EA with stricture group, and about 13 years or 4,981 days in the other group. Twenty-three patients were male and eight patients were female (M:F 2.9:1). Most of the EA were type C with 28 patients (90.32%). The other types were type A for two cases (6.45%) and type D for one case (3.23%). Most of demographic characteristics, except APGAR score at 5-minute, admission source,

Table 1. Demographic characteristics

Characteristics	Total (n=31)	Esophageal stricture (n=18)	Non-esophageal stricture (n=13)	p-value
EA type; n (%)				0.320
A	2 (7)	2 (11)	0 (0)	
C	28 (90)	16 (89)	12 (92)	
D	1 (3)	0 (0)	1 (8)	
Sex: n (%)				0.095
Male	23 (74)	11 (61)	12 (92)	
Female	8 (26)	7 (39)	1 (8)	
Birth weight (g) (28 cases): mean [SD]	2,230.1 [561.8]	2,248.9 [486.2]	2,205.0 [671.7]	0.840
APGAR score; mean [SD]				
At 1 minute (25 cases)	8.7 [1.5]	9.1 [0.9]	8.2 [1.5]	0.076
At 5 minute (25 cases)	9.5 [0.8]	9.9 [0.5]	9.1 [0.9]	0.017
At 10 minute (4 cases)	8.3 [1.3]	9.0 [1.4]	7.5 [0.7]	0.312
Associated anomalies; n (%)				
VACTERL	13 (42)	7 (39)	6 (46)	0.730
Congenital heart disease	11 (35)	5 (28)	6 (46)	0.450
Comorbidities before surgery; n (%)				1.000
Apnea of newborn	1 (3)	1 (6)	0 (0)	
Pneumonia	5 (16)	5 (28)	0 (0)	
Bronchopulmonary dysplasia	3 (10)	2 (11)	1 (8)	
Admission source (30 cases); n (%)				0.034
Birth	22 (73)	16 (89)	6 (50)	
Transfer	8 (27)	2 (11)	6 (50)	
Discharge status; n (%)				1.000
Discharge	29 (94)	17 (94)	12 (92)	
Transfer	2 (6)	1 (6)	1 (8)	
Follow-up time; median (IQR)	3,200 (2,045, 4,435)	3,690.5 (2,689, 5,077)	2,082 (1,630, 3,200)	0.022

EA=esophageal atresia; SD=standard deviation; IQR=interquartile range

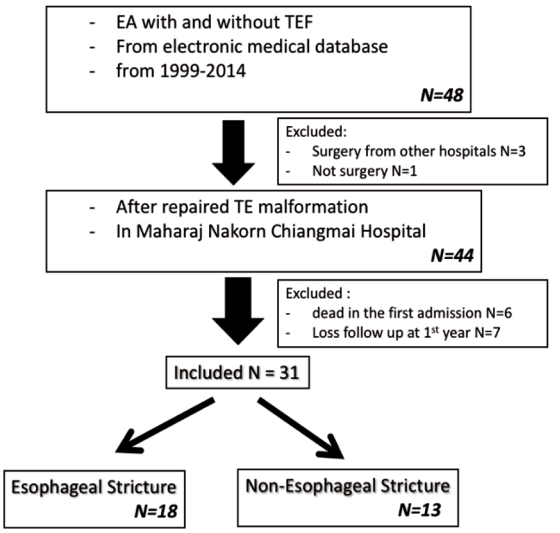

Figure 1. Flow chart of esophageal atresia in the present study.

and follow-up time, were not significantly different between esophageal stricture and non-stricture group, as shown in Table 1.

Ninety percent of EA patients (28 patients) underwent primary repair while three patients underwent staged repair, two underwent esophagostomy, and one underwent fistula ligation. Even though all of non-stricture were performed primary repair, there was no statistically significant difference between groups (p=0.245). Preoperative gastrostomy was done in 13 patients (41%). The stricture group had longer waiting time from birth to primary operation at 15 days versus three days, which was statistically significant (p=0.009). The averaged gap length of both groups was 1.6 cm. Median gap lengths were similar in both stricture (1.5 cm) and non-stricture group (1 cm) (p=0.076). In other words, stricture did not present in only long gap length but found in the averaged gap length. In stricture group, the time to definite repair was 15 days (IQR 6, 20). Surgical technique including suture material type or size, and gap length between end pouches of esophagus were not different between

Table 2. Perioperative status

Parameters	Total (n=31)	Esophageal stricture (n=18)	Non-esophageal stricture (n=13)	p-value
Operation; n (%)				0.245
Primary repair	28 (90)	15 (83)	13 (100)	
Staged repair	3 (10)	3 (17)	0 (0)	
First operations; n (%)				0.050
Esophagostomy	2 (7)	2 (11)	0 (0)	
Esophagoesophagostomy	28 (90)	15 (83)	13 (100)	
Ligate fistula	1 (3)	1 (6)	0 (0)	
Time to definite repair (days) (29 cases): median (IQR)	7 (3.0,16.0)	15 (6.0, 20.0)	3 (1.5, 8.0)	0.009
Gap (cm); median (IQR)	1.5 (1.0, 2.0)	1.5 (1.3, 2.0)	1.0 (0.5, 1.0)	0.076
Operative time (hours); mean [SD]	2.6 [0.9]	2.1 (0.5)	2.9 [1.0]	0.029
Suture material (20 cases); n (%)				0.470
Vicryl	1 (5)	1 (10)	0 (0)	
Maxon	16 (80)	8 (80)	8 (80)	
Dexon	2 (10)	0 (0)	2 (20)	
Monocryl	1 (5)	1 (10)	0 (0)	
Number of suture material (18 cases); n (%)				0.780
4-0	2 (11)	1 (12.5)	1 (10)	
5-0	4 (22)	1 (12.5)	3 (30)	
6-0	12 (67)	6 (75)	6 (60)	
Gastrostomy (18 cases): n (%)				1.000
Preoperative	13 (72)	8 (73)	5 (71)	
Postoperative	5 (28)	3 (27)	2 (29)	

SD=standard deviation; IQR=interquartile range

Table 3. Postoperative status

Parameters	Total (n=31) median (IQR)	Esophageal stricture (n=18) median (IQR)	Non-esophageal stricture (n=13) median (IQR)	p-value
Total length of stay (days) (27 cases)	46.0 (28.0, 105.0)	57.0 (33.0, 105.0)	39.5 (26.5, 84.0)	0.330
Postoperative mechanical ventilation (days) (23 cases)	3.0 (2.0, 8.0)	3.0 (1.0, 3.0)	4 (2.5, 10.5)	0.160
Postoperative TPN (days) (21 cases)	18.0 (14.0, 30.0)	28.0 (16.0, 48.0)	16.0 (13.5, 24.5)	0.170
Postoperative day to start feeding (days) (23 cases)	10.0 (7.0, 21.0)	10.0 (7.0, 17.0)	9.5 (7.0,21.5)	0.950

TPN=total parenteral requirement; IQR=interquartile range

the groups as shown in Table 2. In postoperative period (Table 3), the length of stay (LOS) and total parenteral requirement (TPN) in stricture group were longer than non-stricture group, but there were no statistically significant difference, with LOS at 57.0 (33.0, 105.0) days versus 39.5 (26.5, 84.0) days and TPN at 28.0 (16.0, 48.0) days versus 16.0 (13.5, 24.5) days, respectively. The patients required mechanical ventilation for three days in the stricture group and four days in the non-stricture group ($p>0.05$).

During the first admission, postoperative complications occurred. Two patients (6.4%) had anastomotic stricture, one patient (3.2%) had anastomotic leakage, one patient (3.2%) had re-fistula, seven patients (22.5%) had pneumonia, and four patients (12.9%) had GER (Figure 2A). At the first-year follow-up, the authors found the number of stricture cases raised up to nine patients (29.0%). In addition, the number of cases were increased in most of the complications except leakage of anastomosis (Figure 2B). At the fifth-year follow-up, there were six patients (19%) who were diagnosed with esophageal stricture. The others, including pneumonia, GER, and anastomotic leakage, declined as shown in Figure 2C. For overall anastomotic leakage, and GER, there were no statistically significant difference in both stricture and non-stricture group. The postoperative complications were compared at each period as shown in Figure 3.

The median esophageal stricture time was five

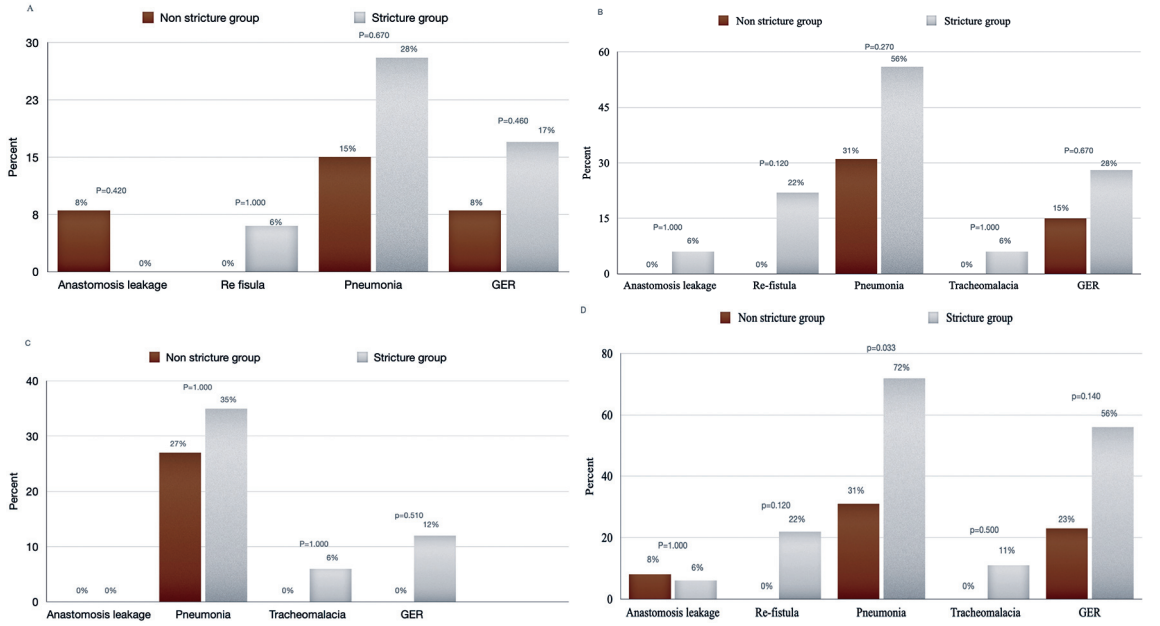

Figure 2. The postoperative complications: (A) In the first admission, (B) At the first year follow up, (C) At the fifth year follow up, (D) Overall.

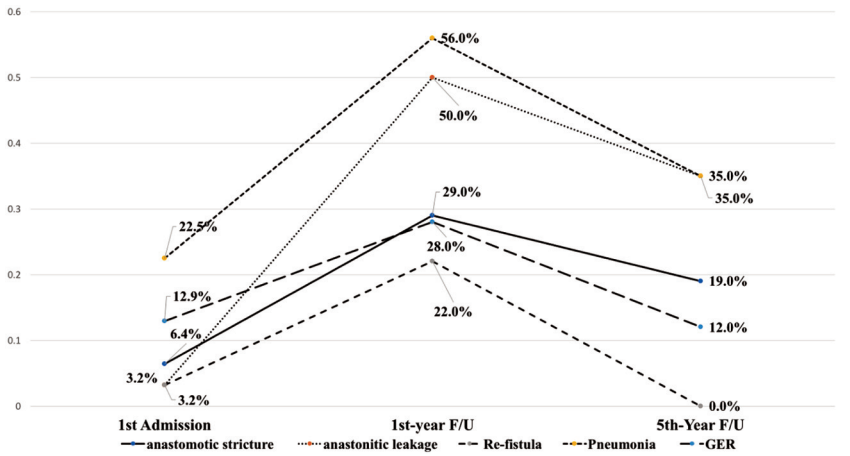

Figure 3. Compared postoperative complication at period of time.

years or 1,829 days (95% CI 474 to 2,138) (Figure 4). All EA with esophageal stricture underwent esophageal dilatation. The minimum size was 4 Fr, and the maximum size was 36 Fr. The median frequency of dilatation was three times (IQR 2, 5).

GER occurred in thirteen EA patients (41.9%) of the patients. Most of GER were resolved by medication. Only three patients (23.0%) underwent fundoplication, which two were EA with stricture. Not only nutritional status was not statistically significant different, but also lower than average of Thai children in both stricture and non-stricture

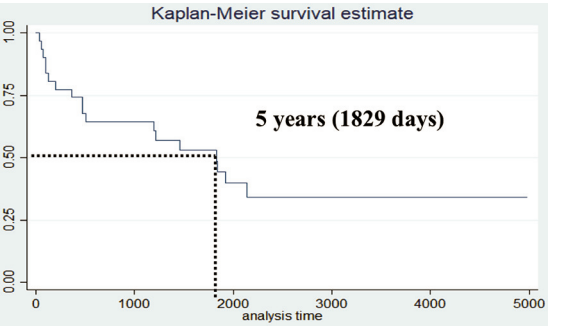

Figure 4. The time to esophageal stricture (days).

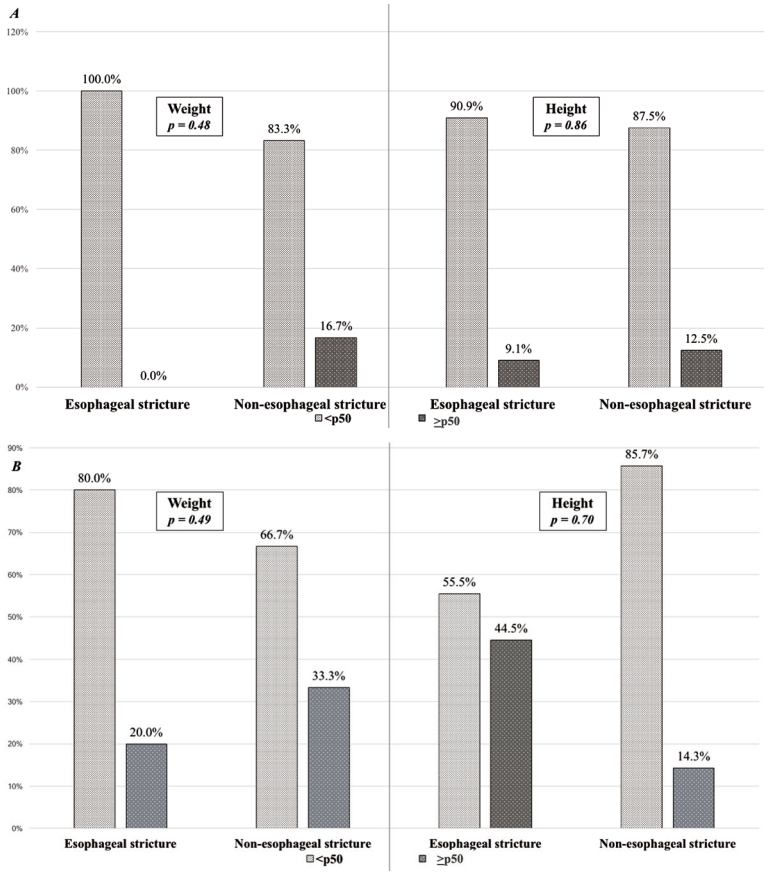

Figure 5. The nutritional status: (A) At the first-year follow-up, (B) At the fifth-year follow-up.

groups (Figure 5). The most common clinical presentation of EA with stricture was dysphagia in 61%, along with recurrence pneumonia as the second most. At the first year follow up, the presentations of stricture group were dysphagia (61%), recurrence pneumonia (50%), reflux (22%), dyspnea (11%), and cough (6%). Subsequently, there were dysphagia (29%), recurrence pneumonia (29%), cough (12%), and reflux (6%) at the fifth-year follow-up.

Discussion

EA is a rare disease, and the epidemiology of EA has been stable for decades[1-3]. The present study showed similar demographic characteristics with the previous studies. The most common type is type C at 90.32% and congenital heart disease was the most frequent associated anomaly at 35%. From the previous reports, 75% to 94% of EA patient were type C[4-7,9-11], and 26.7% to 35% had congenital heart anomaly[1,2,6,7,10,12]. The prevalence of VACTERL was higher than the previous data if comparing with EUROCAT study at 38% versus 9.6%[1,4]. The differences might happen from race, socioeconomic, and multi-factorials. Other demographic characteristics were similar to the other reports. Although, APGAR score at 5-minute and admission source were statistically significant differences between groups, there were no clinical differences. The stricture rate (58.1%) is comparable to other reports. The incidence of anastomotic stricture after EA repair has been reported at 32% to 59% in recent studies, but studies report up to 80% according to the variety of definitions. Routine postoperative contrast study commonly shows narrowing of the anastomosis, but it is not clinically relevant to stricture, which might be from healing process[17]. The authors have investigated the patients' clinically suspected stricture and did not routinely do a post op contrast study. Stricture might occur one month later and are commonly diagnosed within the first year after repair. Median follow-up time of EA with esophageal stricture in the present study was 10 years, which could demonstrate the long-term anastomotic stricture after repair. Because these

might be more carefully and continuously follow-up in every postoperative complication treatment, follow-up time was longer than in non-stricture group.

The authors could not demonstrate the difference in gap length, type of operation, suture material, and surgical feeding tube. In contrast to the previous studies, gap length greater than 3 cm was a predictive morbidity because of the presence of the long gap between the two ends of the esophagus increased the risk of anastomotic stricture[6]. In the present study, the average gap lengths were similar in both stricture at 1.5 cm and non-stricture group at 1 cm and was less than 3 cm in average. In other words, stricture was not presented in only long gap length but also found in averaged gap length. Although EA repaired within 24 hours was correlated with morbidity rate[12], delay anastomosis of more than 61.5 hours also increased the rate of stricture formation[12]. In the present study, the authors found that longer time to definite repair associated with stricture. The cause of prolonged time to definite repair in the present study was from the consequence of delayed time to be admitted and delay diagnosis from other hospitals that might cause aspiration pneumonia, which also affected the time to repair. As a result, delayed anastomosis should be avoided due to increase rate of stricture. Early diagnosis and aspiration prevention strategies were important to reduce morbidity. Regardless, postoperative outcomes including LOS and TPN days were inferior to the previous series[3], and there were no statistically significant differences between the groups. The patients required postoperative mechanical ventilation for three days in stricture group and four days in non-stricture group. The ventilator duration depended on multiple factors, such as underlying lung condition, preoperative mechanical ventilation, and infection, which did not result from only stricture status.

Mortality rate was relatively high at 8.5%, and mostly occurred during the first admission, followed by one year of life. The major cause of the death was associated with severe cardiac anomaly. From a national wide analysis in the United Stated in 2014, the mortality rate was 9% and the cause of death was associated with severity of preoperative comorbidities[12].

Morbidity in follow-up period was reported to be high. Frequently, nutritional status, gastrointestinal issues, and respiratory problems were reported. GER occurred in 41.9% of EA patients. As previously reported, there were GER at 15% to 75%[5,16,18,19]. GER had no significant relationship between non-stricture and stricture group at 23% versus 56% (p=0.14). In contrast to other studies, anastomotic stricture was also related to the presence of GER[14]. From a nationwide analysis in 2014, frequency of esophageal dilatation increased the risk of esophageal stricture[12]. Twenty-three percent of GER underwent fundoplication, which is similar from previous reports at 10% to 26%[5,16,19]. Respiratory pneumonia developed in 70% of stricture group, which overall was statistically significant different from the non-stricture group. The authors could not conclude that pneumonia increased the risk of stricture, on the other hand pneumonia was a consequence of stricture. Accordingly, when EA patients were diagnosed with pneumonia, anastomotic stricture might be one of the causes of pneumonia, which should be ruled out first.

In the present study, median esophageal stricture time was five years or 1,829 days (95% CI 474 to 2,138), which differed from previous series at 70.5 days (IQR 40.5 to 161.5)[4]. According to the authors knowledges, no previous series reported about stricture complication found in childhood. Prior data recommended to closely observe clinical symptoms for stricture in first two years after repair[17]. Noteworthy, the present study, data showed anastomosis stricture could be lately formed in the sixth year of life. Hence, clinical follow-up should be extended beyond the fifth year. EA with esophageal stricture should undergo esophageal dilatation. The minimum size was 4 Fr, and the maximum size was 36 Fr. The median frequency of dilatation was three times (IQR 2, 5). There are multiple factors influencing stricture formation. Some factors are uncontrollable such as intra-operative technique, surgeons factor, and patients factors. The authors could not demonstrate the difference between gap length, size, and type of suture materials or others preoperative factors to improve stricture formation. Early diagnosis is the key to improve morbidity and mortality of esophageal atresia patients.

As mentioned in dysphagia and recurrent pneumonia, EA with these presentations should be checked for esophageal stricture. It affects the nutritional status, which shows as lower than average of Thai children in both stricture and non-stricture groups. Further investigations and prompt treatments should be considered in these post esophageal repair patients. Furthermore, nutritional status should be emphasized when follow up these patients.

The limitation of this retrospective study is the use of a single center. Therefore, the results are limited in generalizability. For future studies,

a larger sample size should be required to analyze the effects on the stricture formation. However, the present study reported the general characteristics of EA with esophageal stricture, and postoperative outcomes in Maharaj Nakorn Chiang Mai Hospital. Result from these data is also useful for clinical practice. EA is not just a neonatal surgical problem, but a lifelong problem that is encountered in children and adolescents. To improve the outcome and the quality of life in EA patients, follow up guidelines and multidisciplinary team should be formulated for the care of these patients.

Conclusion

Anastomotic stricture is the most common complication after the repair of the esophagus. Primary repair should not be delayed in esophageal atresia patients because long waiting time increases the risk of stricture. Early diagnosis is important to reduce morbidity. Dysphagia is the most common presentation of esophageal stricture, and recurrent pneumonia is the second most common presentation. Anastomotic stricture could be found beyond the fifth year after surgery. Multidisciplinary follow-up plan should be continued over five years to detect late stricture.

What is already known on this topic?

Anastomotic stricture is associated with long waiting time to repair. No differentiation was identified according to surgical technique and gap length.

What this study adds?

Anastomotic stricture is the most common complication after repairing the esophagus. It can occur beyond the fifth year after surgery. Prior data recommended to closely observe clinical symptoms for stricture in the first two years. However, long follow-up plan should be continued over five years to detect late stricture formation. Nutritional and growth should be monitored when following up with the patients.

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Conflicts of interest

The authors declare no conflict of interest.

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