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Does thoracoscopic repair of type C esophageal atresia require emergency treatment?

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Abstract

Background Thoracoscopic repair of esophageal atresia (EA) with tracheoesophageal fistula (TEF) has been performed with increasing frequency. Although many children have underwent surgery within three days after birth, the optimal timing for operation remains undetermined. This study aimed to investigate the appropriate timing for thoracoscopic repair of type C EA and its mid-term clinical outcomes.

Method We retrospectively analyzed 142 patients with EA between April 2009 and April 2023. A total of 109 patients with type C EA who underwent thoracoscopic one-stage repair surgery were included. The patients were divided into two groups based on surgical timing: the early repair group (< 5 days) and the delayed repair group (≥ 5 days). Patients in the two groups were matched using propensity score matching (PSM) to eliminate the imbalance between groups caused by confounding factors such as severe cardiac complications, gestational age, and birth weight.

Result The median age at surgery was 5 days (range: 1–16 days). After matching, 43 patients (out of 59) in the early repair group (group A) and 43 patients (out of 50) in the delayed repair group (group B) were included in the validation cohort. All cases ($n = 86$) successfully completed thoracoscopic one-stage repair surgery. Delayed surgery did not increase the incidence of preoperative and postoperative respiratory tract infections. Intraoperative and postoperative complications were comparable between the two groups. Intraoperative and postoperative complications were comparable between the two groups; however, patients in group B experienced a lower frequency of balloon dilation (1.8 ± 0.8 vs. 3.1 ± 1.1, $P = 0.035$) for anastomotic stricture during follow-up.

Conclusions With improvements in neonatal surveillance, appropriately delayed surgery does not increase the incidence of respiratory infections, allowing surgeons to optimize treatment plans.

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Keywords Esophageal atresia, Tracheoesophageal fistula, Thoracoscopic repair, Anastomotic leakage, Anastomotic stricture

Introduction

Esophageal atresia (EA) is a life-threatening congenital defect in neonates [1], ranking third among gastrointestinal developmental malformations. Surgery is the only option for treating EA. Since 1941, when Haight et al. [2] performed the first one-stage repair of EA and tracheoesophageal fistula (EA/TEF), the overall survival rate for children with EA/TEF has increased significantly [3]. In recent years, with the improvement of surgical techniques and perioperative management, the first thoracoscopic repair for patients with EA/TEF was reported in 2000 [4]. This approach has been widely carried out in multiple centers [4–7], becoming a routine procedure for treating EA. The postoperative survival rate for EA/TEF patients has risen to more than 95%. However, the incidence of anastomotic complications and TEF recurrence still remain high [8, 9]. High rates of postoperative anastomotic leakage and anastomotic stricture are the main factors affecting the long-term quality of life in children with EA/TEF [10, 11].

Nowadays, the optimal timing for surgery in neonates with EA/TEF is still inconclusive [4, 5, 8, 12]. Most researchers believe that children with EA/TEF should undergo surgery between 1 and 3 days after birth [13–16]. However, a few researchers have suggested that the timing of surgery in children with EA/TEF can be appropriately delayed [17–19]. The maximal age for surgery in children with Gross type C EA undergoing one-stage anastomosis repair has been reported to be 26 days, due to delayed diagnosis [7], with good recovery observed postoperatively.

At our center, delayed visit and delayed diagnosis due to referrals in children with EA/TEF, as well as waiting in the hospital with the presence of preoperative respiratory tract infections or severe cardiac conditions can result in the postponement of surgery. Additionally, delays in surgical scheduling due to own set operating days may cause some children with EA/TEF to undergo surgery at an older age. Notably, treatment outcomes for these children are not inferior to those of early surgical intervention. Before conducting this study, we analyzed the clinical data of 73 patients with type C EA who underwent primary thoracoscopic or open esophageal repair between April 2009 and October 2016. We used a ROC curve to evaluate the relationship between the incidence of total postoperative complications and the timing of surgery. The postoperative complications assessed included anastomotic leakage, anastomotic stricture, respiratory infections, recurrent tracheoesophageal fistula, gastroesophageal reflux, tracheomalacia, achalasia of the gastroesophageal junction, esophageal diverticulum, wound healing complications, growth status, and mortality. According to the ROC analysis, the optimal cut-off timing of surgery was 5 days. The postoperative overall complication rate in patients with EA who underwent repair within 5 days of birth was significantly lower than that in those who underwent repair after 5 days (35.5% vs. 59.5%, $P = 0.042$). The corresponding sensitivity was 87.5%, the specificity was 72.9%, the area under the curve was 0.892(95% CI: 0.763–0.934). Therefore, we used 5 days as the cut-off for grouping (data not presented in the text). However, it remains uncertain how delayed surgery affects major postoperative outcomes. Therefore, the purpose of this study is to explore the optimal timing for thoracoscopic repair in type C EA patients based on mid-term outcomes.

Methods

Study design

We retrospectively analyzed the clinical data of 142 patients with EA at our center from April 2009 to April 2023. The study included neonates with type C EA who underwent one-stage thoracoscopic repair successfully. The following cases were excluded: patients who underwent thoracotomy, gastrostomy, esophageal replacement, or staged surgery; other types of EA (type A/B/D/E); cases with incomplete medical data; and those lost to follow-up. Ultimately, 109 patients who underwent one-stage thoracoscopic repair and end-to-end esophageal anastomosis were included in the study. Of these, 71 were male and 38 were female. The median gestational age was 37.6 weeks (range: 33.6–40.6 weeks) and the median birth weight was 2.6 kg (range: 1.8–3.1 kg). The average length of the esophageal gap was 1.8 ± 0.3 cm. The median age at surgery was 5 days (IQR: 3–12 days). Informed consent was obtained from the legal guardians of all patients, and the study was approved by the Ethics Committee at the Union Hospital of Tongji Medical College, Huazhong University of Science and Technology (2016-LSZ-S180).

Propensity score matching (PSM)

Since cardiovascular comorbidities, gestational age, and birth weight are known to impact prognosis [20–22], there may be bias in the comparison between the two groups. In observational studies, PSM can be used to minimize confounding bias in non-randomized groupings, thereby achieving an effect similar to that of a randomized design. In this study, 1:1 PSM was employed to minimize the impact of confounding factors such as severe cardiac malformations, gestational age, and birth weight. Logistic regression was used to model the confounding factors. Patients from the two groups with similar propensity scores, as estimated by the logistic model, were matched, with a caliper value of 0.02.(Fig. 1).

Data collection and definitions

Intraoperative events and indicators operation time, conversion to thoracotomy, difficulty in intubation (more than three attempts to replace the tracheal tube during anesthesia induction), hypoxia events (oxygen saturation (SpO2) decrease to less than 90% or drops by more than 10% from baseline), hypothermia events (core body tem-

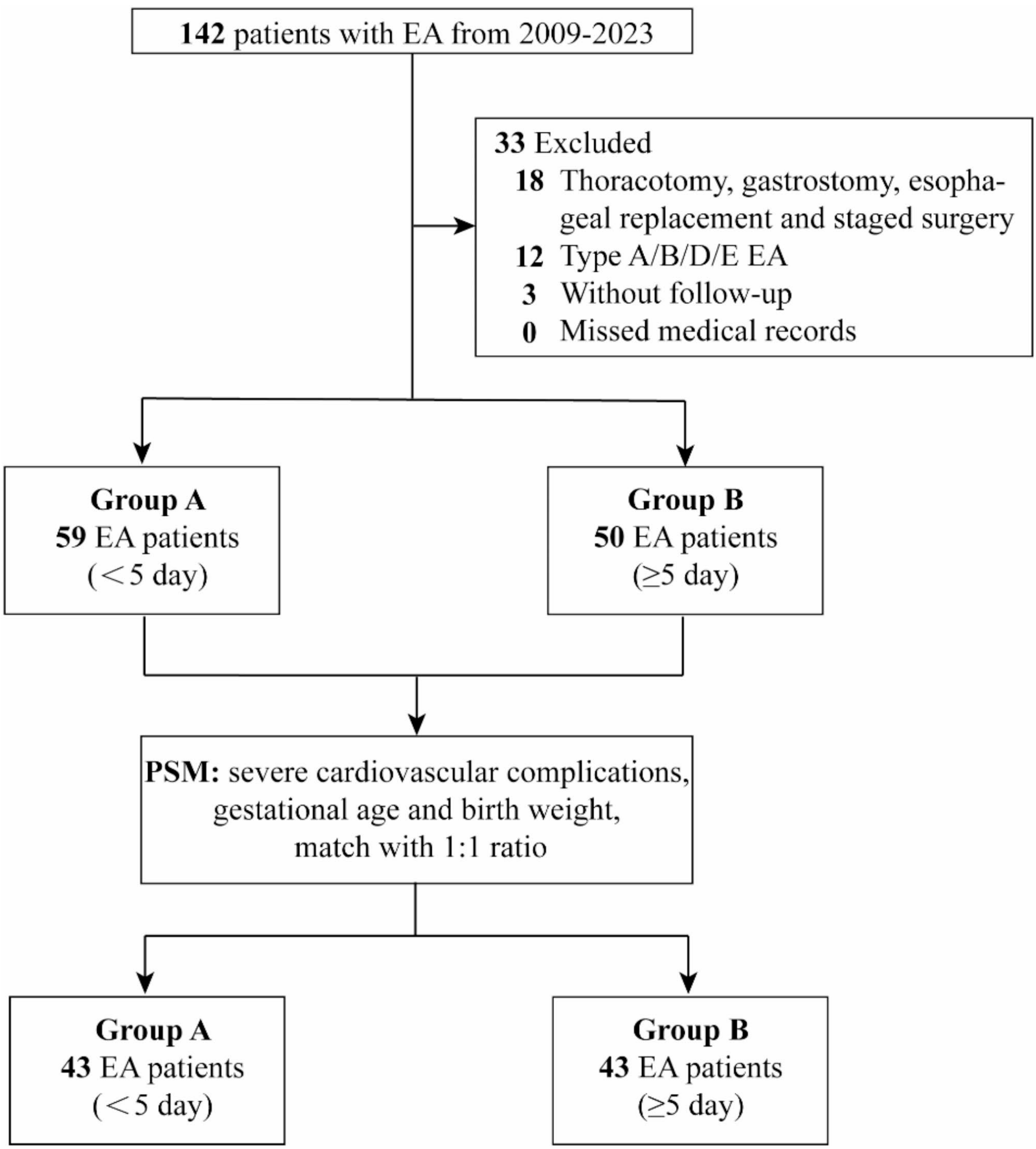

Fig. 1 Flow diagram of patient selection. PSM: Propensity Score Matching

perature falls below 36 °C during the procedure), peak $PaCO_2$, intraoperative use of vasopressors, and intraoperative blood transfusion.

Postoperative conditions and outcomes postoperative mechanical ventilation time, postoperative sedation days, nasogastric tube feeding time, oral feeding time, and postoperative hospital stay, total hospital stay; postoperative outcomes: anastomotic leakage (clinical manifestations combined with gastrointestinal contrast agent leakage), anastomotic stricture (requiring at least one balloon dilatation), recurrent esophageal fistulas, recurrent respiratory tract infection, and mortality (one patient in the early repair group, aged 1 day at the time of surgery, died).

Preoperative management

Preoperatively, to prevent the retention of secretions and subsequent aspiration, a nasogastric tube should be promptly inserted into the proximal esophageal blind pouch and maintained with continuous low-negative-pressure suction. Oral and nasopharyngeal secretions should be cleared every 15–30 min. To reduce the risk of reflux and aspiration, the patient should be positioned laterally with the head and shoulders elevated by 15–30°and the diaphragm lowered to facilitate breathing. The patient should be turned every 2 h and back percussion should be performed to prevent respiratory infections and atelectasis, while promoting the drainage of respiratory secretions. In cases of respiratory distress or cyanosis, oxygen should be delivered via mask at a flow rate of 4 L/min. For premature infants experiencing respiratory distress, tracheal intubation and mechanical ventilation are required. By positioning the endotracheal tube below the tracheal opening of the tracheoesophageal fistula and using mild, low-pressure ventilation, the risk of respiratory gases entering the stomach through the distal fistula is reduced, thereby minimizing the risk of gastric distension and rupture.

Surgical procedure

The patient's position and trocar placement were performed according to the method described by Rothenberg [23]. Once inside the thoracic cavity, the azygos vein was carefully mobilized and ligated. The nasogastric tube was then used to assist in progressively dissecting the proximal esophageal pouch, and the distal esophagus was mobilized along the fibrous band. The esophageal fistula was identified, dissected, and subsequently ligated. Both the proximal and distal ends of the atretic esophagus were incised, and a 5 – 0 absorbable suture was employed to perform an interrupted anastomosis of the posterior esophageal wall. After the anastomosis was completed, the nasogastric tube was advanced into the distal esophagus and passed into the stomach, following which interrupted sutures were applied to the anterior wall of the esophagus. Finally, a chest drain was inserted near the anastomosis site via the lower trocar, and the trocar incisions were closed in layers.

Postoperative management

After surgery, the infant was first sent to the neonatal intensive care unit (NICU). Postoperatively, the infant routinely received intravenous antibiotics for 24 h and was kept under absolute sedation. Discharge criteria included adequate oral feeding without vomiting or coughing, stable respiration, and no signs of pulmonary infection on chest X-ray. Iodine contrast imaging was performed 1 month postoperatively, with follow-up visits every 3 months thereafter.

Statistical analysis

All analyses were carried out using SPSS Statistics 26.0 (IBM, Armonk, NY) and R 4.3.3 (The R Foundation, Vienna, Austria). Continuous data were expressed as mean ± standard deviation or median (range or interquartile range, IQR), and comparisons were made using the Student's *t*-test or Mann-Whitney *U* test. Categorical data were presented as frequency (n) and percentage (%), and comparisons were performed using the Pearson chi-square test or Fisher's exact test. All tests were bilateral, and $P < 0.05$ was considered statistically significant.

Result

Elimination of confounding factors between groups

The distribution of individual propensity scores between the two groups before and after matching is shown in the Fig. 2. After matching, 43 patients (out of 59) in group A and 43 patients (out of 50) in group B were included. The scatter plot of the propensity score distribution (Fig. 3) suggests that the matching is excellent. The median age at surgery was 3 days (range: 1–5 days) in group A, and 7 days (range: 5–16 days, including 5 days) in group B. All surgeries were performed by the same surgical team, which included one experienced surgeon and 1–2 skilled assistants.

Comparison of baseline data in the validation cohort

The clinical baseline characteristics of patients in the validation cohort before and after PSM are presented in Table 1. There was no significant statistical difference in the baseline data between the two groups after PSM matching. The congenital malformation after matching between the two groups was as follows: 31 cases (72.1%) in group A were associated with various congenital malformations, and 32 cases (74.4%) in group B. There was no significant difference in congenital malformation between the two groups. Furthermore, there was no significant difference in preoperative respiratory

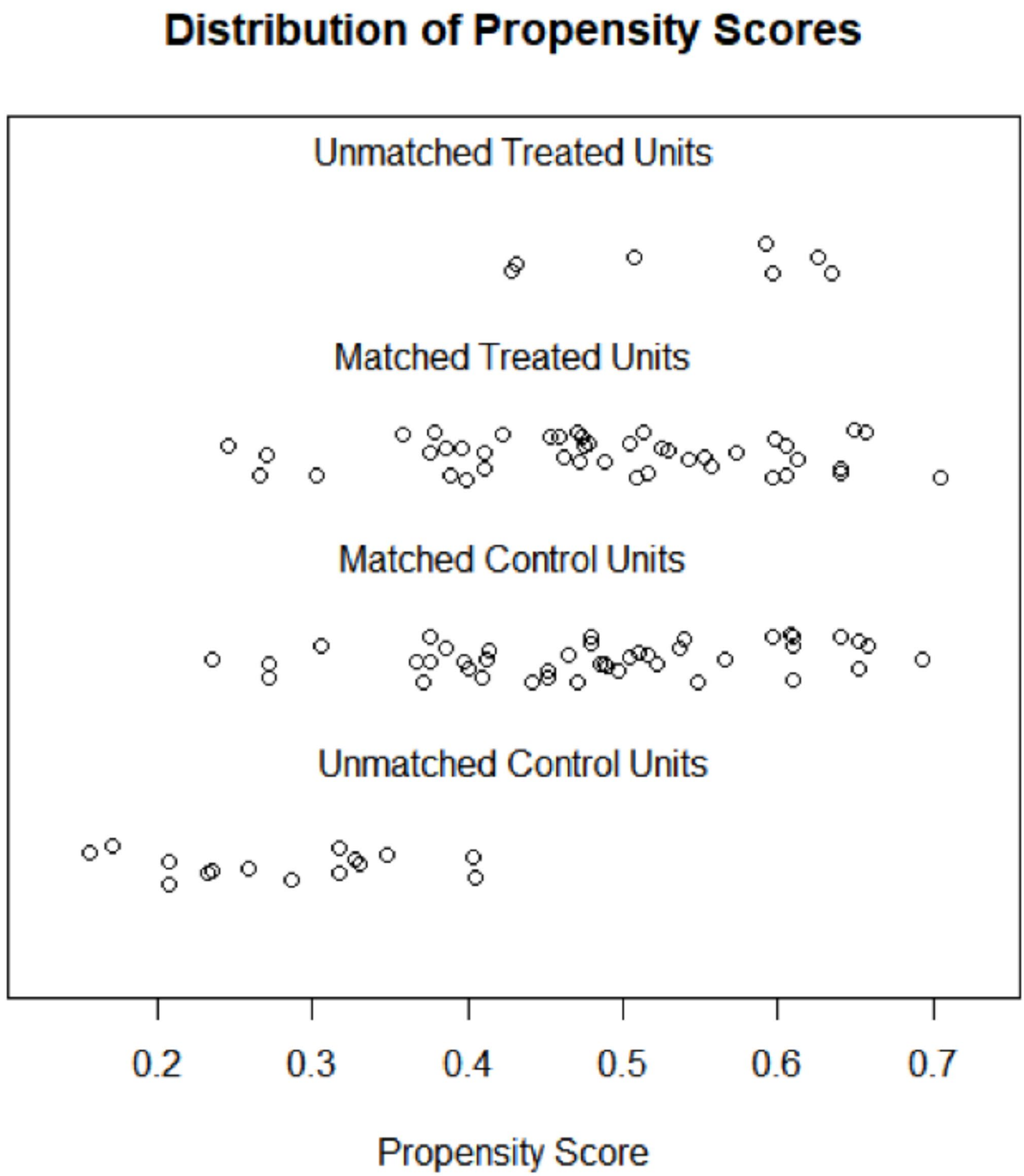

Fig. 2 After matching, the two groups of propensity score distribution scatter plot. Treated Units: Group B; Control Units: Group A

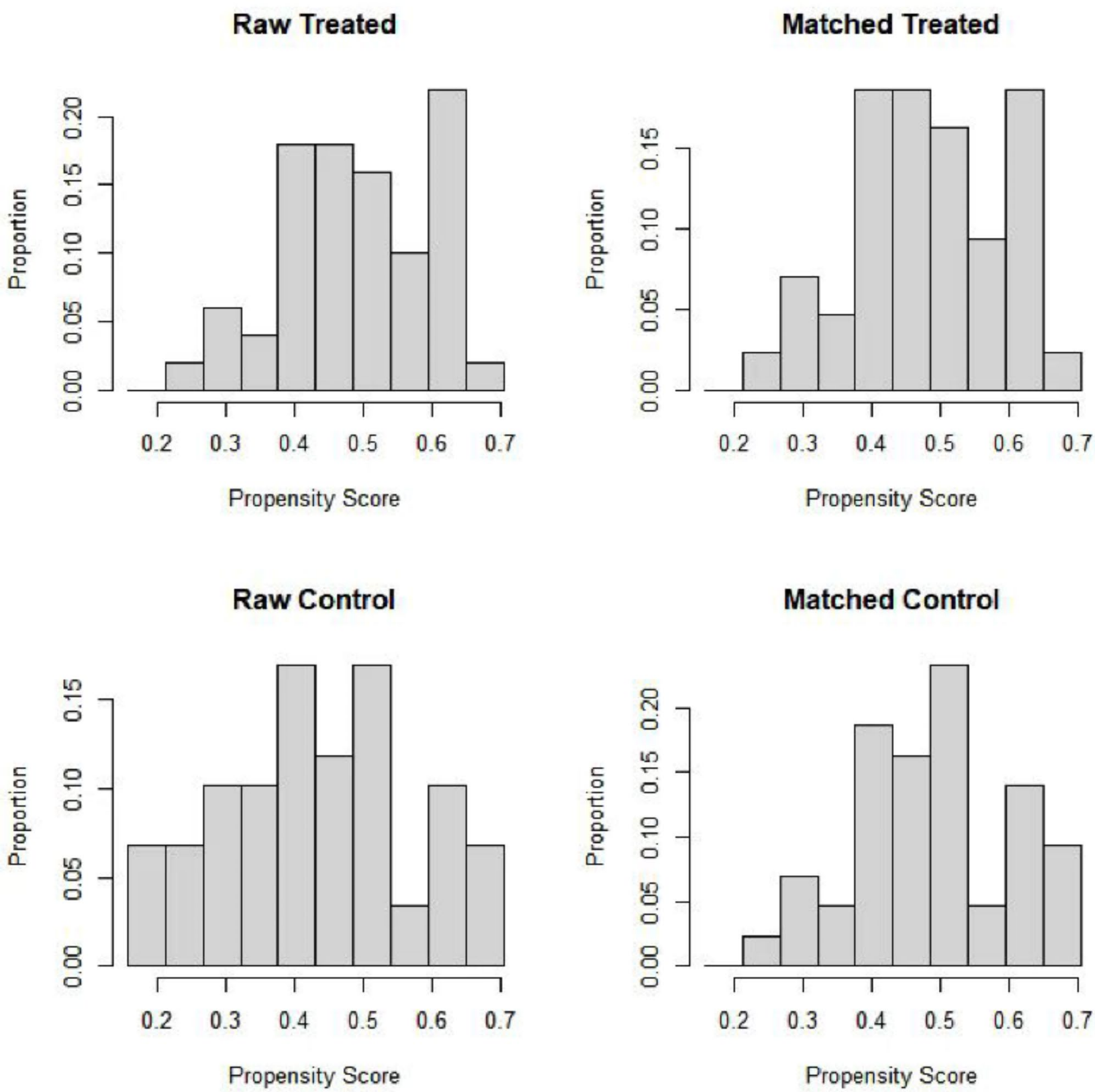

Fig. 3 Two groups of individual propensity score distribution histogram before and after matching. Treated Units: Group B; Control Units: Group A

tract infections and ventilator-assisted ventilation rates between the two groups.

Comparison of intraoperative data in the validation cohort

Thoracoscopic one-stage repair and esophageal end-to-end anastomosis were performed without conversion to thoracotomy in all instances ($n=86$). Regarding the operation time, difficulty with intubation, hypoxia and hypothermia events, peak PaCO2 levels, intraoperative use of vasopressors, and intraoperative blood transfusion, there were no statistically significant differences between the two groups. (Table 2)

Comparison of postoperative outcomes in the validation cohort

Patients in group B needed mechanical ventilator support an average of one extra day than those in group A, but there was no statistically significant difference [1.0(1.0, 3.0) vs. 2.0(1.0, 3.0) days; $P=0.417$]. The timing of the onset of nasogastric feeding, the complete oral feeding, the postoperative and total hospital stay, and

Table 1 Demographic data of the patients before and after PSM

Variable	Before PSM			After PSM		
	Group A ($n=59$)	Group B ($n=50$)	*P*	Group A ($n=43$)	Group B ($n=43$)	*P*
Sex (male)	37(62.7)	32(64.0)		26(60.5)	22(51.2)	
Gestational age (weeks)	37. 8 ± 1.4	37.2 ± 1.4	0.031*	37.3 ± 1.3	37.3 ± 1.4	0.856
Birth weight (kg)	2.7 ± 0.2	2.6 ± 0.2	0.018*	2.6 ± 0.2	2.6 ± 0.2	0.995
Weight at surgery (kg)	2.6 ± 0.1	2.7 ± 0.1	0.336	2.7 ± 0.1	2.7 ± 0.1	0.643
Vogt type (IIIa: IIIb)	12:47	11:39	0.832	9:34	8:35	0.787
Esophageal gap length [a] (cm)	1.8 ± 0.3	1.7 ± 0.2	0.305	1.8 ± 0.3	1.7 ± 0.2	0.090
Albumin [b] (g/L)	34.6 ± 1.5	35.2 ± 1.9	0.066	34.8 ± 1.6	35.1 ± 1.9	0.359
Associated anomalies						
Cardiovascular (n, %)	34(57.6)	28(56.0)	0.864	24(55.8)	26(60.5)	0.827
VACTERL (n, %)	4(6.8)	3(6.0)	1.000	4(9.3)	3(7.0)	1.000
Spina (n, %)	3(5.1)	3(6.0)	1.000	2(4.7)	2(4.7)	1.000
Gastrointestinal (n, %)	7(11.9)	6(12.0)	0.983	5(11.6)	6(14.0)	0.747
Kidney (n, %)	0	1(2.0)	1.000	0	1(2.3)	1.000
Anal rectum (n, %)	3(5.1)	3(6.0)	1.000	2(4.7)	2(4.7)	1.000
Limb (n, %)	2(3.4)	1(2.0)	1.000	2(4.7)	1(2.3)	1.000
Preoperative respiratory tract infections (n, %)	15(25.4)	16(32.0)	0.448	13(30.2)	14(32.6)	0.816
Preoperative mechanical ventilation (n, %)	6(10.2)	6(12.0)	0.761	5(11.6)	6(14.0)	0.747

* $p < 0.05$ was considered statistically significant. [a] The length of the silk thread segments were measured externally, and these segments were then used to measure the esophageal gap intrathoracically. [b] Serum albumin levels measured in the laboratory on the day before surgery

Table 2 Intraoperative and postoperative data of the patients after PSM

Variable	Group A ($n=43$)	Group B ($n=43$)	*P*
Operative time (minutes)	165.3 ± 9.0	162.1 ± 9.2	0.109
Difficulty in intubation [a] (n, %)	8(18.6)	5(11.6)	0.366
Hypoxia [b] (n, %)	22(51.2)	20(46.5)	0.666
Hypothermia [c] (n, %)	9(20.9)	5(11.6)	0.243
Peak PaCO2 (mm Hg)	59.3 ± 6.4	60.4 ± 8.0	0.476
Use of vasopressors (n, %)	4(9.3)	5(11.6)	1.000
blood transfused (n, %)	4(9.3)	7(16.3)	0.333

* $p < 0.05$ was considered statistically significant. [a] Difficulty in intubation: more than three attempts to replace the tracheal tube during anesthesia induction; [b] Hypoxia: oxygen saturation (SpO2) decreases to less than 90% or drops by more than 10% from baseline; [c] Hypothermia: core body temperature falls below 36 °C during the procedure

the postoperative sedation did not differ significantly between the two groups. The median follow-up time was 24 months (range: 12–36 months). Patients in group B experienced a lower incidence of anastomotic leakage (7.0 vs. 14.0%, $P = 0.481$) and anastomotic stricture (11.6 vs. 20.9%, $P = 0.243$) than those in group A, but there was no statistical difference. Anastomotic stricture can be resolved with repeated balloon dilatation, and no problems were noted following dilatation during the follow-up. The number of balloon dilations required in group B was significantly lower than that in group A (1.8 ± 0.8 vs. 3.1 ± 1.1, $P = 0.035$). However, there was no significant difference between the two groups in terms of recurrent esophageal fistulas or recurrent respiratory tract infections. (Table 3)

Table 3 Postoperative outcomes of the patients before and after PSM

Variable	Group A ($n=43$)	Group B ($n=43$)	*P*
Time to postoperative mechanical ventilation (days)	1.0(1.0, 3.0)	2.0(1.0, 3.0)	0.417
Time to postoperative sedation (days)	2.0(1.0, 3.0)	2.0 (1.0, 6.0)	0.291
Time to feeding via nasogastric tube (days)	4.0(2.0, 5.0)	3.0(2.0, 5.0)	0.193
Time to oral feeding (days)	12.0(11.0, 15.0)	13.0(11.0, 15.0)	0.142
Postoperative hospital stay (days)	19.3 ± 1.5	18.7 ± 1.6	0.069
Total hospital stay (days)	21.3 ± 1.6	22.1 ± 2.0	0.065
Anastomotic leakage (n, %)	6(14.0)	3(7.0)	0.481
Anastomotic stricture (n, %)	9(20.9)	5(11.6)	0.243
Number of balloon dilations	3.1 ± 1.1	1.8 ± 0.8	0.035*
Recurrent esophageal fistulas (n, %)	4(9.3)	4(9.3)	1.000
Recurrent respiratory tract infection (n, %)	17(39.5)	9(20.9)	0.060
mortality (n, %)	1 (2.3)	0	1.000

* $p < 0.05$ was considered statistically significant

Discussion

In this study, PSM was used to eliminate differences in severe cardiac malformations, gestational age, and birth weight between the two groups, thereby reducing the influence of confounding factors from baseline data. This ensures that the observed differences in complications after EA/TEF repair were attributed to the timing of surgery. The results showed that delayed surgery did not increase the incidence of preoperative and postoperative respiratory tract infections. Moreover, the incidence of anastomotic complications was similar between the two groups, but the delayed repair group experienced a lower frequency of balloon dilation for anastomotic stricture. To our knowledge, this is the first clinical study to investigate the optimal timing for surgery in a cohort of demographically matched neonates with EA/TEF.

With increasing age at the time of surgery, respiratory tract infection becomes the most common preoperative complication in neonates with EA. Older neonates are more likely to experience repeated aspiration of secretions from the blind pouches, which increases the burden of airway clearance and elevates the risk of preoperative pneumonia. However, previous studies have indicated that delayed surgery does not significantly increase the risk of preoperative respiratory tract infections in children with severe cardiac disease or low birth weight [18, 19]. This suggests that delayed surgery for EA is feasible; therefore, we applied this concept to children who experience delayed presentation or referral, or who have concomitant respiratory tract infections. Consistent with our findings, the incidence of respiratory tract infections and ventilator-assisted ventilation did not significantly increase in the delayed repair group. Furthermore, delayed surgery allows for a more thorough evaluation of the condition of children with EA/TEF, provides adequate time for preoperative preparation, improves the children's preoperative physiological state, and enhances overall surgical safety.

There are many complications following thoracoscopic repair for EA/TEF. Anastomotic leakage and stricture are the most prevalent surgical complications in children with EA/TEF, and they have a significant effect on esophageal function and long-term quality of life in children [24, 25]. In this study, we focused on detecting these complications. According to the literature, the incidence of anastomotic leakage ranges from 7.6 to 27% in open surgery and 10.2–21% in thoracoscopic surgery [26–28]. The high incidence can be attributed to the esophagus structure, which lacks a serosa layer, and the predominance of striated muscle in the upper esophagus, resulting in poor tensile strength and healing ability [29–32]. Neonates have a high body water content (75–80%) [33], making their tissues fragile and prone to tearing at the suture site, which is detrimental to anastomotic healing [29]. Delayed surgery can appropriately reduce neonatal moisture content by approximately 4–5% over a week [33], which may enhance the neonate's tolerance to injuries from dissection and sutures, thereby improving their overall healing ability [34]. Additionally, appropriately delayed surgery allows neonates to pass the post-natal adaptation period, promotes further system development, and ensures stable nutrition, all of which increase their surgical tolerance. Furthermore, delayed surgery allows surgeons to do a comprehensive assessment and increases the patient's weight by 100–200 g over six days [35, 36], thereby providing surgeons with more confidence in surgery. Literature showed that surgeons' confidence was necessarily correlated with their technical performance [37]. Recent systematic reviews further emphasize the importance of technical skills, highlighting that superior performance positively affected patient outcomes [38].

Studies have shown that postoperative anastomotic leakage is a high-risk factor for anastomotic stricture [39–42]. In this study, the incidence of anastomotic leakage in the delayed repair group was not higher than that in the early repair group, which may explain the similar incidence of anastomotic stricture in both groups. A direct consequence of anastomotic leakage is anastomotic infection, which induces reactive hyperplasia of granulation tissue at the anastomotic site, promotes the formation and recurrence of stricture, and leads to resistance to expansion therapy [43]. Continuous endoscopic balloon dilatation is widely considered to be an effective therapy for anastomotic stricture [44]. Although the rate of anastomotic stricture following EA/TEF repair is high, it can be generally be managed with balloon dilatation, avoiding the need for additional surgery. Moreover, the delayed repair group achieved resolution of anastomotic stricture with fewer dilations, which may be attributed to the protective effect of delayed surgery on the anastomosis, resulting in less severe stricture This approach can reduce the child's discomfort and simplify postoperative management.

According to Rothenberg et al.'s studies, the incidence of postoperative anastomotic leakage in children with Gross type C EA was 7.6%, which might be attributed to the surgical team's superior technical skills [27]. It is difficult for the majority of surgeons to reach this level. However, the incidence of anastomotic leakage fell to 7.0% following delayed surgery in this study. As a result, appropriate delayed surgery can compensate for the limitations of the surgeon's surgical skill, leading to satisfactory surgical outcomes.

In China, tertiary-grade A hospitals have implemented a medical team leader responsibility system, where the medical team leader is allocated special outpatient hours or designated operating days, et al. A doctor typically focuses on performing surgeries on specific days of the week. On these designated operating day(s), the doctor arranges the surgery schedule in advance and performs multiple operations consecutively in the operating room. This system helps optimize the use of surgical resources and ensures the smooth flow of procedures. Each doctor generally has their own set operating days, such as every Tuesday and Friday, during which multiple surgeries can be scheduled and performed within the same day.

For patients with EA, there is no definitive standard for determining whether repair should be performed earlier or later. While traditional perspectives generally advocate for surgery within 1 to 3 days of birth, this is not mandatory. The timing of surgery should be individualized, taking into account factors such as the patient's age at presentation, overall clinical condition, comorbidities, and the availability of an operating room. Furthermore, during the waiting period, careful attention must be given to airway management to ensure that the patient's airway remains patent and to minimize the risk of potential complications.

The limitations of this study include a single center, a retrospective design, and a limited sample size. Although propensity score matching removes a small number of unmatched samples, there are still differences in the results between matched and unmatched groups within the same cohort. Given the perioperative management challenges and variations in surgical techniques across different centers, a multi-center study is necessary. To further investigate the optimal surgical timing and cut-off point, a prospective clinical study with a larger sample size, longer follow-up, and multi-center involvement are needed.

Conclusions

In conclusion, in patients with type C EA, delayed repair is safe and feasible, with postoperative outcomes not inferior to those of early repair. Scheduling thoracoscopic repair at or after 5 days does not increase the rates of preoperative respiratory infections in a well-equipped NICU compared to performing the repair within 5 days. These results can be used to guide the allocation of operating room resources, such as postponing emergency repairs to scheduled operating days.

Abbreviations

EA	Esophageal atresia
TEF	Tracheoesophageal fistula
PSM	Propensity score matching
NICU	Neonatal intensive care unit

Author contributions

Chen Wang, Guoqing Cao, Kang Li, Shuai Li, and Shao-tao Tang contributed to the study conception, project administration, supervision, validation, and visualization. Chen Wang, Guoqing Cao, Kang Li, Yang Zhang, Mengxin Zhang, Xi Zhang, and Shuiqing Chi contributed to data collection, formal analysis, investigation, and software; Chen Wang, Guoqing Cao, Kang Li, Shuai Li, and Shao-tao Tang contributed to writing-original draft and writing-review and editing. All authors contributed in final approval of the version to be submitted.

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None.

Data availability

The datasets used and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee at the Union Hospital of Tongji Medical College, Huazhong University of Science and Technology (approval No.2016-LSZ-S180), and the procedures followed were in accordance with the Helsinki Declaration. Informed consents were obtained from all patient guardian.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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