

# 2-Year Outcomes After Complete or Staged Procedure for Tetralogy of Fallot in Neonates



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## ABSTRACT

**BACKGROUND** There is ongoing debate about the best strategy to treat patients with tetralogy of Fallot who are symptomatic in the neonatal period.

**OBJECTIVES** The aim of this study was to compare the outcomes of complete versus staged surgery (i.e., initial palliative procedure for possible later complete repair).

**METHODS** A retrospective cohort study was performed using the Pediatric Health Information System database, including patients who underwent complete or staged tetralogy of Fallot repair prior to 30 days of age. The primary outcome was death during 2-year follow-up after the initial procedure. Inverse probability-weighted Cox and logistic regression models were used to examine the association between surgical approach group and mortality while accounting for patient- and hospital-level factors. Causal mediation analyses examined the role of intermediate variables.

**RESULTS** A total of 2,363 patients were included (1,032 complete and 1,331 staged). There were 239 deaths. Complete neonatal repair was associated with a significantly higher risk for mortality during the 2-year follow-up period (hazard ratio: 1.51; 95% confidence interval: 1.05 to 2.06), between 7 and 30 days after the initial procedure (hazard ratio: 2.29; 95% confidence interval: 1.18 to 4.41), and during the initial hospital admission (odds ratio: 1.72; 95% confidence interval: 1.15 to 2.62). Post-operative cardiac complications were more common in the complete repair group and mediated the differences in 30-day and 2-year mortality.

**CONCLUSIONS** Complete surgical repair for neonates with tetralogy of Fallot is associated with a significantly higher risk for early and 2-year mortality compared with the staged approach, after accounting for patient and hospital characteristics. Post-operative cardiac complications mediated these findings. (J Am Coll Cardiol 2019;74:1570-9)  
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**T**etralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, affecting approximately 1,650 children in the United States every year (1,2). This disease is characterized by varying degrees of obstruction to pulmonary blood flow (from pulmonary valve stenosis to atresia). The ventricular septal defect allows shunting of blood

between the right and left ventricles, often resulting in cyanosis. Surgical repair for asymptomatic patients with no or acceptable levels of cyanosis occurs electively in the first year of life.

There is a subset of patients with TOF who are symptomatic in the neonatal period and require immediate intervention. Symptoms include



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unacceptable levels of cyanosis or dependency on the ductus arteriosus to maintain pulmonary blood flow. Less commonly, neonates present with “tetralogy” spells, or life-threatening episodes of increased cyanosis, hyperpnea, and agitation (3). Symptomatic patients require a surgical or catheter-based intervention in the neonatal period to augment pulmonary blood flow and improve oxygenation. There is ongoing debate about the best treatment strategy for symptomatic neonates with TOF (4-7). Theoretical advantages of palliation followed by later repair (i.e., the staged approach) include a less complex initial procedure with shorter neonatal hospital stay, potential reduction in the need for transannular patch upon future complete repair, and promotion of pulmonary artery growth. Potential advantages of early complete repair include earlier resolution of cyanosis, avoidance of a second hospital admission for reoperation, and potentially less distortion of the pulmonary arteries. The currently reported risk for death after either approach is approximately 6% (4,8-10).

To date, most studies comparing neonatal interventions in TOF have been single-center studies or multicenter studies that included other diseases or outcomes (5,6,8,11-14). Although these studies have elucidated some of the risks and benefits of each option, they have not determined which therapeutic approach yields the best outcomes for symptomatic neonates with TOF. Often, the decision is made according to surgeon or center preference (9). We studied the comparative effectiveness of surgical approaches in a multicenter cohort study using administrative data to investigate differences in mortality after neonatal TOF intervention.

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## METHODS

**SOURCE POPULATION AND STUDY SAMPLE.** The Pediatric Health Information System (PHIS) is an administrative database that contains discharge data from inpatient, emergency department, ambulatory surgery, and observation encounters from more than 50 nonprofit, tertiary care pediatric children’s hospitals for major metropolitan areas across the United States, maintained by the Children’s Hospital Association (Lenexa, Kansas). Data are deidentified at the time of submission by participating hospitals and undergo a number of reliability and quality checks before being included in the database. The PHIS contains daily billing data on clinical services, pharmacy, supplies, imaging, laboratory tests, and room-and-board charges, as well as patient demographics, discharge disposition, and up to 42 procedure and

discharge diagnoses reported in the International Classification of Diseases-Ninth Revision-Clinical Modification codes (15-17) (Online Table 1).

The study population consisted of PHIS patients with TOF who underwent an initial procedure (i.e., complete surgical repair or staged approach) in the neonatal period (first 30 days of life) between January 1, 2004, and March 31, 2015. We used an identification and validation algorithm to identify neonates with TOF in the PHIS, which was previously published (18).

This study used deidentified administrative data and was determined to be exempt from human subject protection by our Institutional Review Board. The prior cohort validation study was approved by our Institutional Review Board (18).

**EXPOSURES, COVARIATES, AND OUTCOMES.** The exposure was the initial surgical treatment: complete or staged. The primary outcome was time from initial procedure to death within a 2-year follow-up period. All deaths were included: after neonatal procedure (in-hospital and after discharge) for both groups, between initial neonatal procedure and completion of TOF repair in the staged group (interstage death), and deaths that occurred subsequent to completion of TOF repair in the staged group.

Patient-level covariates included sex, age, race, insurance type, prematurity, birth weight, genetic syndromes, and extracardiac malformations. Pre-treatment acuity was defined by the use of mechanical ventilation and/or prostaglandin infusion to maintain patency of the ductus arteriosus. Hospital-level covariates included number of hospital beds, number of cardiac surgery cases per year, hospital preference for type of surgery, and length of hospital stay for a commonly performed cardiac surgery (i.e., closure of ventricular septal defect), detailed later. Post-operative complications included need for post-operative circulatory support (extracorporeal membrane oxygenation), delayed sternal closure, pericardial effusion requiring pericardiocentesis, pleural effusion requiring a chest tube, need for cardiopulmonary resuscitation, any shock of the heart, pacemaker insertion, pacing of the heart, and electric cardioversion.

**STATISTICAL ANALYSIS.** The goal of the study was to determine whether the surgical approach (complete or staged) in the neonatal period was related to overall survival. To control for differences in patient- and hospital-level characteristics between the 2 groups, we used a propensity score model to estimate the probability of undergoing complete or staged

## ABBREVIATIONS AND ACRONYMS

<b>BT</b>	=	Blalock-Taussig
<b>CI</b>	=	confidence interval
<b>HR</b>	=	hazard ratio
<b>PA</b>	=	pulmonary artery
<b>PHIS</b>	=	Pediatric Health Information System
<b>RV</b>	=	right ventricle
<b>TOF</b>	=	tetralogy of Fallot

repair on the basis of pre-operative characteristics. Because patients were nested within treatment centers, we used a multilevel propensity score model to account for the interrelatedness of patients at each center (19). We used a mixed-effects logistic regression model with a random intercept for hospital and included patient and hospital-level covariates as fixed effects (19).

Patient-level and hospital-level characteristics were used as predictors of assignment to complete surgery because both types of characteristics influence the choice of surgical approach received (Online Appendix). Length of hospital stay after a commonly performed cardiothoracic procedure was used as a proxy for hospital quality (20). Because hospital preference could affect the individual likelihood of receiving one treatment over the other, we calculated the percentage of patients who underwent complete surgery and assigned each hospital to a quintile (included in the model) associated with that percentage. Hospital-level quintiles for number of beds and number of cardiac patients were included as predictors.

The analysis of surgical approach and mortality was weighted using inverse probability weighting, creating a pseudopopulation in which the measured covariates are not confounded with initial procedure type (21-24). We used stabilized weights, taking individual weights that were the inverse probability of undergoing complete surgery and multiplying them by the marginal probability of surgical approach received in the sample (25) (Online Appendix). To verify that the distribution of each baseline covariate was balanced across the complete and staged groups, we computed standardized differences for continuous and dichotomous variables weighted by the inverse probability of treatment (25-27). We considered a standard difference of <10% to be a negligible imbalance (21).

To estimate the effect of the initial procedure on the hazard of mortality, we used an inverse probability-weighted Cox model with the observation period from the date of initial procedure to death within a 2-year follow-up period (late mortality). Secondary analyses examined the time until death within 30 days (early mortality). Patients who did not die by the end of follow-up were censored at the last date observed in the PHIS within the 2-year follow-up time or at the end of the study period (March 31, 2015) (28).

If the effect of surgery violated the proportional hazards assumption, we included interaction terms for surgical treatment type by time in the Cox regression models, providing hazard ratios (HRs) for surgery during the time intervals in which the proportional hazards assumption was satisfied.

We used robust standard errors to account for within-hospital correlation in outcome and used a bootstrap-based method performed within each hospital to account for additional correlation introduced by the use of inverse probability weights (29).

For the analysis of mortality within the first hospitalization, we used logistic regression instead of a survival model because the length of the first hospitalization varied considerably among patients. To estimate the effect of initial procedure on the odds of mortality within the first hospitalization, we used inverse probability-weighted logistic regression with robust standard errors to account for the within-hospital correlation in outcomes.

To address unmeasured confounding and quantify how strong unmeasured confounding would have to be to explain away the associations observed, we calculated E values (with 95% confidence intervals [CIs]) for the estimated HRs and odds ratios obtained from the weighted Cox models and weighted generalized estimating equation model (30).

**Causal mediation analysis.** We used causal mediation methods to understand if the effect of surgical approach on mortality was direct (i.e., independent of) or mediated through post-operative cardiac complications (31). Potential mediators were in-hospital cardiac complications within the first 30 days after the initial procedure (and prior to hospital discharge) (listed previously). We used the mediation approach on the basis of counterfactuals in which 2 sets of weights were created (one for the exposure and one for the mediator) and then used these to generate an overall weight, which was applied to the Cox proportional hazards model (or logistic regression model for the initial hospitalization) (31,32). The same set of patient- and hospital-level covariates used in the propensity score model was used to create the 2 sets of weights. We assumed that this set of covariates accounted for the exposure-outcome, mediator-outcome, and exposure-mediator confounding.

**Sensitivity analysis.** We obtained data beyond the end of the study period to determine if additional follow-up time for the patients that were censored with <2 years of follow-up time would substantially change the conclusions. We reviewed the data for any activity within PHIS hospitals from March 31, 2015, to December 31, 2017. Those patients with additional PHIS activity after March 31, 2015, were presumed to be alive at 2-year follow-up. We ran the primary analysis after imputing survival time to 2 years with censoring for patients with an unknown status at 2 years.

**Subgroup analyses.** We conducted 2 additional analyses to examine how the effects of Blalock-Taussig

(BT) shunt in the staged group and right ventricle (RV)-to-pulmonary artery (PA) conduit in the complete group might influence the results. First, we examined the effect of the initial procedure on the hazard of 2-year mortality by comparing the complete group with only the staged group that received BT shunts using an inverse probability-weighted Cox proportional hazards model. Second, we estimated the unadjusted odds of 2-year mortality within the complete group comparing those who received RV-PA conduits with those who did not. We did not conduct a weighted analysis splitting groups by type of treatment within groups (e.g., BT shunt, no BT shunt, RV-PA conduit, no RV-PA conduit) because of difficulty obtaining weighted analyses in 4 groups.

All descriptive statistics (mean ± SD, percentage) as well as modeling results for the combined sample of complete and staged patients were weighted. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina). All statistical tests were 2 sided, and alpha was 0.05.

**RESULTS**

A total of 2,363 patients were included in the study sample. Overall there were 1,318 male patients (55.8%) and 1,518 whites (64.2%), 308 African Americans (13.0%), and 485 Hispanics (20.5%). Genetic syndromes were present in 746 patients (31.6%), and 349 (14.8%) were born prematurely (<37 weeks' gestation). There were 1,032 patients (43.7%) in the complete group and 1,331 patients (56.3%) in the staged group. Prior to weighting, 892 patients (86.4%) in the complete group and in 1,206 patients (90.6%) in the staged group had increased pre-operative acuity (Online Table 2). The unweighted mean ages at first procedure were 11.3 ± 7.8 days (complete) and 9.9 ± 7.4 days (staged). In the weighted sample, the complete and staged groups were well balanced in terms of demographics and clinical patient characteristics, with nonsignificant standard differences (<10%) for all patient characteristics (Table 1).

Patients were treated at 45 different hospitals. Eleven hospitals (24.4%) performed >65% complete repairs, 15 hospitals (33.3%) performed >65% staged repairs, and 19 hospitals (42.2%) had relatively equal proportions of treatment groups. Length of stay for the initial hospitalization was comparable between the 2 groups, with complete surgery patients having a median length of stay of 16 days (interquartile range: 10 to 31 days) and staged patients having a median length of stay of 15 days (interquartile range: 8 to 29 days). In the weighted sample, the complete and staged groups had balanced distributions of

**TABLE 1 Weighted Patient Characteristics by Surgical Treatment Group**

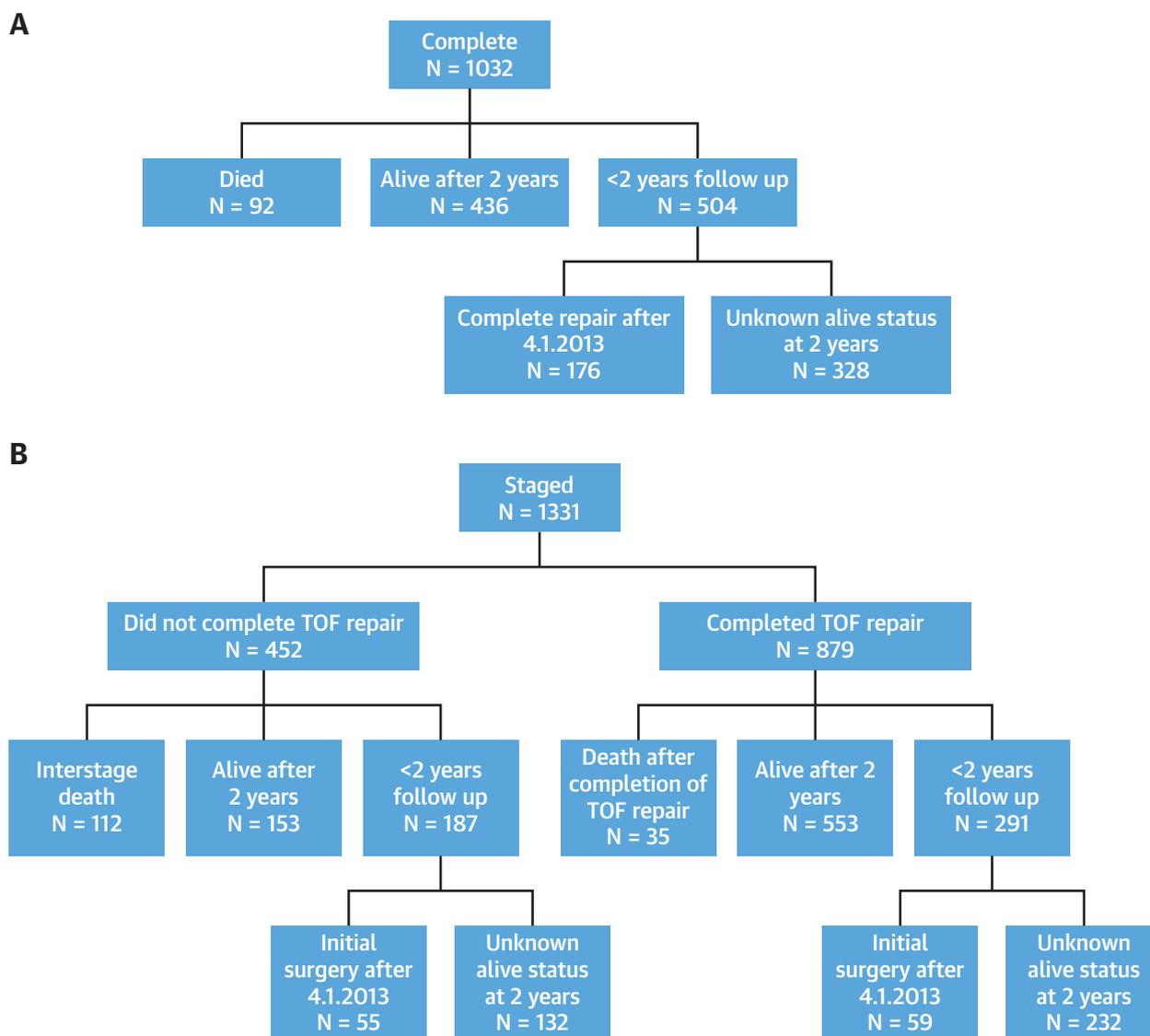
	Complete Neonatal Repair (n = 1,032)	Staged Repair (n = 1,331)	Standard Difference (%)
Male	590 (56.6)	726 (55.0)	3.16
Race			
White or Caucasian	668 (64.0)	854 (64.8)	-1.44
Black or African American	147 (14.1)	174 (13.2)	2.68
Other	227 (21.8)	291 (22.0)	0.56
Insurance payer			
Private	396 (38.0)	527 (39.9)	-4.04
Public	547 (52.5)	656 (49.7)	5.56
Other	99 (9.5)	136 (10.3)	-2.71
Genetic syndrome	340 (32.6)	424 (32.1)	1.11
Extracardiac anomalies	155 (14.9)	190 (14.4)	1.44
Prematurity (<37 weeks)	162 (15.6)	194 (14.7)	2.48
Mean birth weight, kg	2.71 ± 0.92	2.73 ± 0.76	-2.37
High pre-operative acuity	915 (87.8)	1,158 (87.8)	-0.092
Age at first procedure, days			
0-5	343 (32.9)	419 (31.7)	2.54
6-8	201 (19.3)	270 (20.5)	-2.88
9-15	230 (22.1)	301 (22.8)	-1.87
16-30	268 (25.7)	329 (25.0)	1.72

Data are count (%) or mean ± SD, unless otherwise indicated.

hospital-level characteristics except for a slight imbalance in the percentage of patients in each group in the lowest quartile of hospital preference for complete repair (standard difference 10.6%) (Online Table 3).

Two hundred thirty-nine patients died by 2 years, with 92 deaths (12.5%) in the complete group and 147 deaths (10.8%) in the staged group. In the complete group, 436 patients were alive at 2 years; 73 of 92 deaths occurred during the initial hospitalization, and 19 of 92 deaths occurred between initial hospitalization discharge and 2 years. There were 328 patients who had <2 years of follow-up in PHIS and an unknown mortality status at 2 years and 176 patients who were operated on after April 1, 2013, and could not be followed for 2 years (Figure 1).

Of the 1,331 staged patients, 879 survived the initial palliation and later received completion of TOF repair. There were 147 deaths in the staged group: 84 occurred during the initial procedure hospitalization, and 63 were interstage deaths that occurred after discharge from the initial procedure hospitalization. Thirty-five of those 63 deaths occurred after completion of TOF surgery. There were 364 patients in the staged group who had <2 years of follow-up and had an unknown mortality status at 2 years and 114 patients who were operated on after April 1, 2013, and thus could not be followed for 2 years (Figure 1).

**FIGURE 1** Description of the Complete and Staged Groups

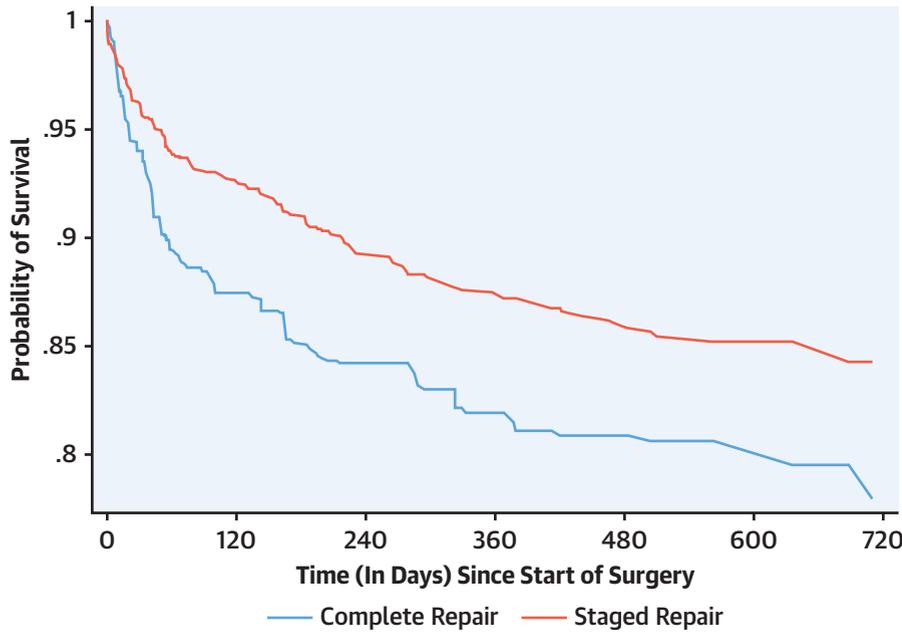
Detailed flowchart demonstrating the breakdown of the cohort by survivors, deaths, and incomplete follow-up for both groups. TOF = tetralogy of Fallot.

**SURVIVAL ANALYSIS.** Patients who underwent complete neonatal repair had a greater risk for mortality within the 2-year follow-up period than those with staged repair (HR: 1.51; 95% CI: 1.05 to 2.06;  $p = 0.024$ ) (Central Illustration, Table 2). For the survival analysis for mortality within the first 30 days, the effect of initial treatment did not satisfy the proportional hazards assumption (i.e., the hazard of complete vs. staged was not constant over time). We separated the estimates into the time intervals in which the proportional hazards assumption was satisfied (0 to 6 days and 7 to 30 days). Using the

weighted Cox proportional hazards model, there was no difference in the risk for mortality between the 2 groups in the first week after the initial procedure (HR: 0.68; 95% CI: 0.17 to 1.48;  $p = 0.49$ ). However, from day 7 until day 30 after the initial procedure, patients in the complete group had a greater risk for mortality than patients in the staged group (HR: 2.29; 95% CI: 1.18 to 4.41;  $p = 0.011$ ) (Figure 2, Table 2).

Seventy-three (7.1%) of the complete group and 84 (6.3%) of the staged group died prior to discharge. The weighted logistic regression model revealed that patients in the complete group had a greater risk for

**CENTRAL ILLUSTRATION Neonatal Tetralogy of Fallot: Weighted Survival Curves for the First 2 Years After Initial Procedure**



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Weighted survival curves of patients who underwent complete or staged tetralogy of Fallot (TOF) repair prior to 30 days of age. The observation period is from the date of the initial TOF procedure to death within a 2-year follow-up period. Complete neonatal repair was associated with a significantly higher risk for mortality during the 2-year follow-up period (hazard ratio: 1.51; 95% confidence interval: 1.05 to 2.06).

death during the initial hospitalization than patients in the staged group (odds ratio: 1.72; 95% CI: 1.15 to 2.62;  $p = 0.028$ ) (Online Table 4).

It is possible that unmeasured confounding could explain these findings. However, E-value calculations indicated that only the presence of very strong unmeasured confounders associated with both treatment type and mortality with effect estimates of 2.4 to 4.0 each (lower limits of the CIs of 1.28 and 1.66, respectively) could explain the association of operative approach and survival (Table 2).

**CAUSAL MEDIATION ANALYSIS.** At least 1 in-hospital cardiac complication was observed in 249 patients (36.1%) in the complete group within 30 days of the initial procedure, compared with 156 (15.4%) in the staged group. Having at least 1 in-hospital cardiac complication was found to be a mediator of the relationship between initial surgery type and both early (7- to 30-day) and late (2-year) mortality, so we deconstructed the total effect of complete surgery into its indirect effect through having at least 1 cardiac complication and its direct effect through other

undefined pathways. Complete surgery (vs. staged repair) was associated with an increased risk for mortality through the pathway of having at least 1 cardiac complication for 7- to 30-day, 2-year, and in-hospital mortality (Table 3, Online Table 5). The percentage of the total effect of surgical approach on the risk for death that was mediated through cardiac complications was 87% (7 to 30 days), 80% (2 years), and 78.5% (in-hospital) (Table 3). We could not identify a specific cardiac complication that mediated these observed relationships. Having a noncardiac complication or the number of noncardiac complications did not mediate of the treatment-mortality relationship (data not shown).

**SENSITIVITY ANALYSIS.** We obtained additional data beyond the study period and imputed follow-up time for those with <2 years of follow-up. The HRs for complete versus staged were 1.33 (95% CI: 1.05 to 1.68;  $p = 0.019$ ; weighted effect with standard errors) and 1.33 (95% CI: 0.92 to 1.82;  $p = 0.13$ ; weighted effect with robust standard errors and bootstrapped 95% CI), which were similar in magnitude to our main result.

**TABLE 2** Effect of Surgical Treatment Group on Mortality After Initial Procedure

	HR or OR (95% CI)	p Value	E Value	Lower Limit E Value*
<b>Mortality within 2 years from initial procedure</b>				
HR for complete (vs. staged) repair	1.51 (1.05-2.06)	0.024	2.39	1.28
<b>Mortality within 30 days from initial procedure</b>				
HR for complete (vs. staged) repair within first 6 days	0.68 (0.17-1.48)	0.49	NA	NA
HR for complete (vs. staged) repair between 7 and 30 days	2.29 (1.18-4.41)	0.011	4.02	1.66
<b>Mortality during first hospitalization</b>				
OR for complete (vs. staged) repair	1.72 (1.15-2.62)	0.028	2.83	1.57

HR for risk for death is based on weighted Cox proportional hazards model, OR for odds of death is based on a weighted logistic regression model, 95% CI is bootstrapped, and E value is computed for a sensitivity analysis for unmeasured confounding. \*The lower confidence bound of the E value is listed for ease of interpretation of the E value.

CI = confidence interval; HR = hazard ratio; NA = not applicable; OR = odds ratio.

**SUBGROUP ANALYSES.** We conducted a further analysis limiting the staged group to patients who underwent BT shunting and examined the relationship between surgical group and 2-year mortality. There were 1,016 of 1,331 patients (76.3%) in the staged group who underwent BT shunting. The effect estimate was similar in magnitude to that of the main analysis, but there was no statistically significant difference in risk for mortality between complete repair and those palliated with BT shunts (HR for complete repair: 1.40; 95% CI: 0.94 to 2.09;  $p = 0.097$ ). Similarly, within the complete group, there was no difference in the unadjusted odds of 2-year mortality comparing those who received and those who did not receive RV-PA conduits (odds ratio for the complete group: 1.35; 95% CI: 0.86 to 2.13;  $p = 0.20$ ).

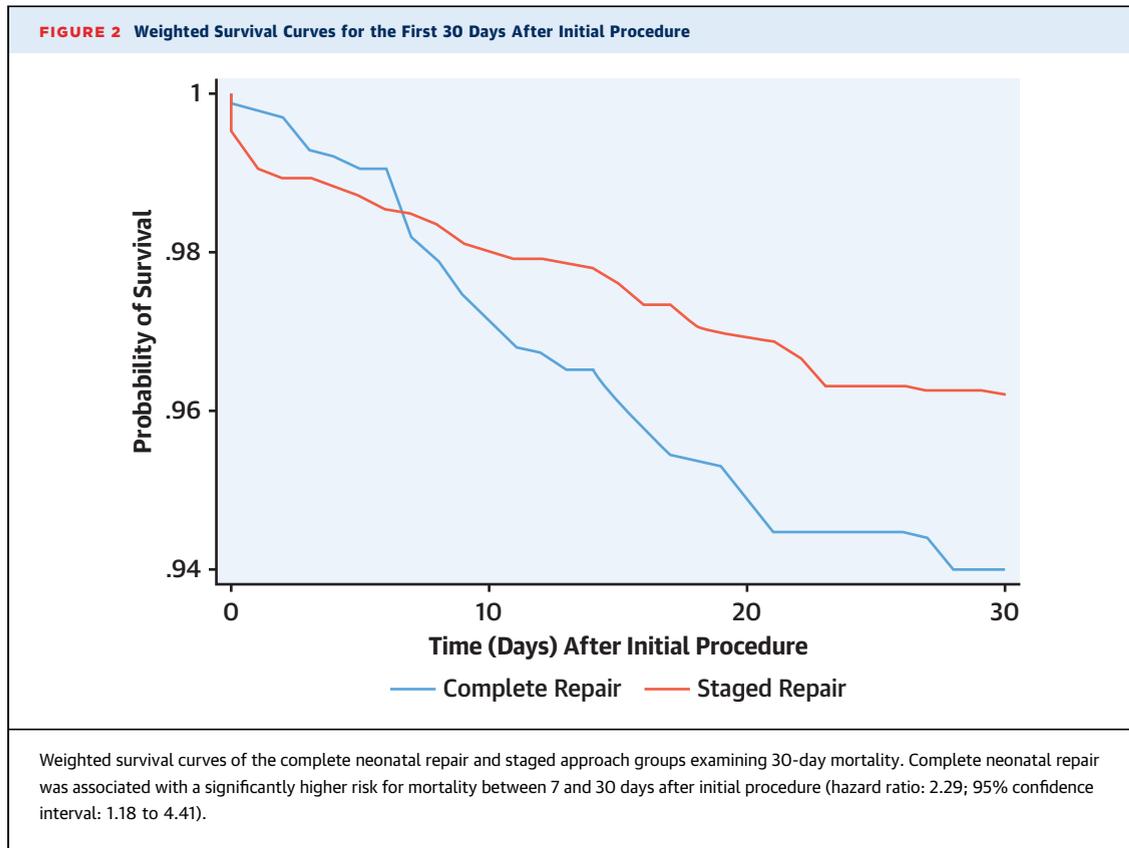
## DISCUSSION

We found that complete neonatal repair for TOF was associated with a higher risk for early and late mortality compared with staged repair in a comparative effectiveness study (**Central Illustration**). We accounted for patient, hospital, and systematic factors in our analysis, which might have influenced the approach taken for each patient, including a hospital preference for one surgical strategy over the other (21,33,34). To our knowledge, this is the first large multicenter study of outcomes after neonatal intervention for TOF with long-term mortality data and extensive consideration of confounders. Other studies have not focused on the outcomes of complete and staged approaches, symptomatic neonates, or center preference and clustering within hospitals (4,6,9,10,35).

Patients with TOF undergoing complete neonatal repair had increased risk for death compared with those in the staged repair group at both early and later time points (7 to 30 days and 2 years after the initial procedure, respectively). This increased risk was mediated in large part by more post-operative cardiac complications that occurred in the first week after complete repair with short- and long-term adverse effects (12,36-40). Although we did not identify a single complication associated with higher risk for mortality, we postulated that this finding reiterates the complex nature of complete TOF repair in newborns and supports the need to identify ideal candidates for complete neonatal repair. Complete neonatal repair could be associated with more complications and higher mortality through an accentuated inflammatory response following cardiopulmonary bypass or the inability of the neonatal right ventricle to maintain or recover function in the perioperative period (41). Procedures that occur in the critical transitional neonatal period potentially have a higher mortality, a well-known phenomenon in general pediatric congenital surgery, likely reflecting greater vulnerability of all organ systems in addition to the complexity of procedures performed (42,43). An intervention to prevent complications after neonatal complete repair could theoretically improve the associated outcomes.

Contrary to our findings, another multicenter study using PHIS data reported a similar proportion of deaths for complete repair and staged repair and in TOF (10). However, the analysis was not adjusted for confounders. As such, there was a higher proportion of patients with genetic syndromes and coronary artery anomalies in the staged group, which may have biased the study's results toward the null. Furthermore, only patients with surgical procedure codes for BT shunt and TOF repair were included, as opposed to all palliative approaches, and the study did not examine long-term mortality.

A recent meta-analysis compared patients undergoing complete neonatal repair to patients who underwent later repairs preceded by palliation (44). Although the groups were not exactly comparable with those in our study, it is worth highlighting the fact that neonatal complete repair was associated with greater mortality compared with patients who underwent repair at a later age (44). A multicenter study reported increased mortality in patients with TOF undergoing either complete or staged repair prior to 3 months of age, and although the study did not compare outcomes by approach, it demonstrated significant institutional variability in the choice of initial approach, emphasizing the importance of



multicenter studies such as ours that are generalizable (45). These findings, along with ours, suggest that neonatal repair for TOF may be associated with adverse outcome. Although there are fewer reports on outcomes after initial palliation as the approach of choice for symptomatic neonates with TOF, centers that favor a staged approach report low mortality and complication rates (38,46-48). When limiting the comparison to patients who received BT shunts in the staged group, there was no statistically significant difference in the risk for mortality, even though the

magnitude of the effect estimate was similar to that from our main analysis, and the lower bound of the CI barely crossed 1. It is possible that with a smaller sample size, we were underpowered for this analysis.

**STUDY LIMITATIONS.** First, there is the risk for misclassification of surgical approach. We conducted a priori cohort validation to reduce this bias. If present, misclassification would unlikely be differential in terms of the outcome, meaning that any bias would be toward the null (attenuating the results), so that

**TABLE 3** Mediation Analysis

	Total Effect	p Value	Indirect Effect	p Value	Proportion Mediated by Cardiovascular Complications (%)
Mortality within 2 yrs					
Hazard ratio	1.51 (1.05-2.06)	0.024	1.21 (1.00-1.46)	0.047	80.0
Mortality between 7 and 30 days					
Hazard ratio	2.29 (1.18-4.41)	0.011	1.99 (1.34-2.95)	0.0007	87.0
Mortality during first hospitalization					
Odds ratio	1.72 (1.15-2.62)	0.028	1.35 (1.25-1.46)	<0.0001	78.5

The mediator is at least 1 in-hospital cardiac complication within the first 30 days after the initial procedure (and prior to hospital discharge). The hazard ratios, odds ratios, and 95% confidence intervals represent the effect of complete repair (vs. staged repair).

the association between operative approach and outcome may be even stronger than shown.

Second, if sicker patients were more likely to undergo complete repair, this would result in confounding by severity of illness. If higher risk patients were operated on at centers with a preference for complete repairs (or that had worse outcomes), this would result in confounding by center. This is unlikely because: 1) if anything, surgeons generally use a staged repair in sicker patients; and 2) our weighted analysis accounted for pre-operative acuity, patient factors such as lower weight, prematurity, and genetic syndromes that could have influenced the decision surrounding surgical approach, and center factors and apparent center preference for one approach over the other. In addition, an unmeasured confounder would have to have a very strong relationship with the outcome to explain our findings. It is possible but unlikely that such a strong determination of surgery and outcome was not included in our analysis. Although this study focused on the hospitals in the PHIS, the generalizability of these results to centers that perform surgical procedures for TOF is an important strength. We were reassured by the sensitivity analysis, which demonstrated an effect estimate similar to that from our main analysis, despite a nonsignificant p value in the sensitivity analysis using robust errors. An additional limitation was our inability to determine the pulmonary valve anatomy in PHIS in order to take this into account in our analysis.

Finally, this was an observational study, which limits causal inferences. A randomized clinical trial of

surgical approach to TOF may be warranted to confirm these findings before changing clinical practice.

## CONCLUSIONS

Complete neonatal repair for TOF is associated with greater early and late adjusted risk for mortality compared with mortality after staged repair and beyond completion of repair. This risk was mediated by post-operative complications.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

For neonates with TOF, complete surgical repair is associated with a higher risk for mortality than a staged approach, mainly because of post-operative cardiac complications.

### TRANSLATIONAL OUTLOOK:

Randomized trials are needed to compare the short- and long-term outcomes of various strategies to correct TOF in symptomatic neonates.

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**KEY WORDS** cardiac surgery, causal mediation analysis, comparative effectiveness, congenital heart disease, inverse probability weighting, Pediatric Health Information System

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**APPENDIX** For supplemental tables, please see the online version of this paper.