The outcome of surgical repair of tetralogy of Fallot in KwaZulu-Natal, South Africa

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ABSTRACT

Background: Surgical repair of tetralogy of Fallot (TOF) is recommended during infancy. Late patient presentation, coupled with limited surgical and intensive care services in our setting results in late repair, potentially worsening patient outcomes.
Objectives: To analyse the clinical characteristics and outcome of patients undergoing complete TOF repair at Inkosi Albert Luthuli Central Hospital (IALCH).
Method: Hospital records of all TOF patients who had complete surgical repair from January 2005 - December 2017 were analysed following ethical approval (BREC/00000476/2019).
Results: Two hundred and ninety-two patients had surgical repair; most (91%) were operated at ≥12 months of age. Preoperatively, 5 patients had infective endocarditis, 1 presented with a brain abscess and 1 suffered a cardiac arrest from a severe hypercyanotic spell. Early mortality occurred in 15 patients (5.1%). These were associated with age at repair <12 months (p=0.017), wasting (p=0.031), prolonged cardiopulmonary bypass (p=0.004), prolonged aortic cross-clamping (p=0.001) and culture proven post-operative infection (p=0.026). Eighteen (6%) suffered major post-operative morbidities, predominantly central nervous system (CNS) complications. One hundred and eighteen (40.4%) children were lost to follow-up.
Conclusion: Most patients at IALCH had late repair and a significant number were lost to follow-up. Age at repair, nutritional status, duration of bypass and infections significantly influenced early mortality.
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BACKGROUND

Tetralogy of Fallot (TOF) is a congenital cyanotic heart disease characterised by a ventricular septal defect (VSD) with an overriding aorta, right ventricular outflow tract (RVOT) obstruction and right ventricular hypertrophy (RVH). In a systematic review and meta-analysis on birth prevalence of congenital heart disease worldwide, TOF was noted to occur in 34 per 100 000 live births.[1]

Though the timing for elective surgical repair of TOF remains controversial, there is a trend towards repair in infancy.[2-4] Due to delays in diagnosis and the limited cardiac surgical and intensive care services in developing countries, surgical interventions for most patients with TOF are done after the age of 1 year.[5,6] The centre under study, Inkosi Albert Luthuli Central Hospital (IALCH), has limited cardiac surgical and intensive care facilities hence there are long delays for patients awaiting surgery. This is further compounded by late presentation and diagnosis resulting in late repairs. In view of these limitations, this review assessed the average age at which the diagnosis and surgical repair of TOF are done at IALCH.

Delayed repair of TOF may result in complications. A chronic cyanotic state as well as persistent exposure of the right ventricle to high pressures may result in poor outcomes in TOF patients who are repaired late.[5,7,8] Increased risk of arrythmias has been reported in patients with TOF who had late repair.[5,9] The study assessed trends in pre-operative characteristics and their effect on outcome.

Post-surgical repair TOF patients may require reoperation in the early post-operative period due to residual RVOT obstruction or significant ventricular septal defect leak. Intra-operative transesophageal echocardiography (TOE) has been shown to be beneficial in detecting residual lesions allowing their correc-

tion before the patient leaves the operating room.[10,11] This study includes populations operated on before and after the availability of intra-operative TOE at IALCH, allowing comparisons between these 2 groups.

Duration of intubation and length of stay (LoS) in the intensive care unit (ICU) may be used as parameters indicating ICU morbidity.[12] Factors that may influence ICU morbidity include duration of cardiopulmonary bypass (CPB) and aortic cross-clamping (AXC) as well as the age and weight of the patient at repair.[12,13]

The mortality in post primary repair of TOF patients was noted to be 1.3% and 2.5% in analysis of two databases.[2,14] In a data analysis in low and medium income countries (LMICs), the mortality after primary repair was 3.3%.[6] This study assessed factors influencing ICU morbidity and mortality in TOF patients post primary surgical repair at IALCH and the factors contributing to it.

METHOD

A retrospective, descriptive, and analytical observational study was done at Inkosi Albert Luthuli Central Hospital (IALCH), a quaternary referral hospital for the province of KwaZulu-Natal in South Africa. Computerised medical records of all patients who had complete TOF repair at the hospital from January 2005 - December 2017 were analysed. Included in the study were all patients who had complete TOF repair during the 13-year period. Patients excluded from the study were those with TOF with pulmonary atresia, absent pulmonary valve and those with TOF who did not undergo complete repair.

Pre-operative data collected included demographic data, nutritional status, neurodevelopment, hypercyanotic spells, haemoglobin, haematocrit, and pre-operative morbidity. Nutritional status was assessed using World Health Organisation Child Growth Standards.[15-17] Children were classified using body mass index (BMI) or weight-for-length / height (normal if ≥-2 to +2, overweight or obese if >+2 and wasted or severely wasted if <-2) and length / height-for-age (normal if ≥-2 to +2, tall if >+2 and stunted or severely stunted if <-2). The relevant growth charts were used for children with Down syndrome.[18]

TOF repairs were done electively or as emergencies. Some patients had initial palliative procedures prior to TOF repair. The TOF repair was valve sparing or non-valve sparing in which case a trans-annular patch (TAP) was used. The ventricular septal defect (VSD) was closed through the right atrium (RA) or the right ventricle (RV). The duration of CPB and AXC was recorded. Intra-operative TOE was available during TOF repair for patients who had repair during the last 6 years of the study (2012 - 2017).

Duration of intubation, LoS in ICU, arrhythmias, infections and major morbidities were noted in the post-operative period. Early mortality and re-operation were defined as mortality or re-operation prior to discharge.

Echocardiographic assessment during the initial post-operative follow-up included assessment for severity of pulmonary regurgitation (PR), RVOT gradient and RV function as assessed with the Tricuspid Annular Plane Systolic Excursion (TAPSE). The number of patients lost to follow-up was also noted.

Data was collected and captured on a Microsoft Excel spreadsheet. The data was analysed with various statistical methods with the assistance of a professional statistician from the School of Public Health, Biostatistics Department at the University of KwaZulu-Natal.

Permission to conduct the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00000476/2019).

RESULTS

Two hundred and ninety-two patients had complete TOF repair from January 2005 - December 2017. Figure 1 shows the number of patients operated each year during the 13-year study period.

One hundred and eighty-six (63.7%) were male and 106 (36.3%) were female. Forty-one (14.0%) patients were wasted or severely wasted while nearly one third (n=93, 31.8%) were stunted or severely stunted. Neurodevelopmental delay was noted in 38 (13.0%) patients. Twenty-four (8.2%) patients had underlying syndromes, the most common syndromes being 22q11 deletion and Trisomy 21 present in 12 and 10 patients respectively. These pre-operative clinical characteristics are shown in Table I.

The median age of presentation and TOF repair was 24 and 42.5 months respectively. The median duration between diagnosis and repair was 4.8 months as shown in Table II. The majority of patients (267, 91.4%) were repaired after infancy with only 8.6% (25) undergoing complete TOF repair below the age of 1 year.

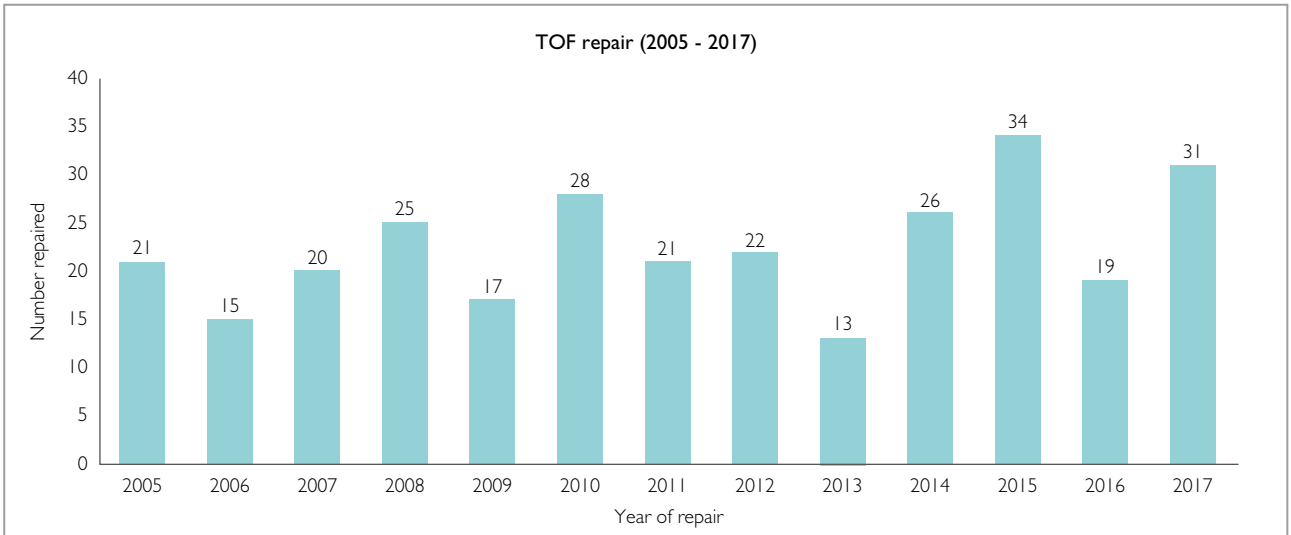

FIGURE 1: Tetralogy of Fallot repair at Inkosi Albert Luthuli Central Hospital from January 2005 - December 2017.

TABLE I: Pre-operative clinical characteristics.

Clinical characteristics	Findings	Number	Percentage
Sex	Male	186	63.7
	Female	106	36.3
Race	African	274	93.8
	Indian	13	4.5
	White	1	0.3
	Mixed race (Coloured)	4	1.4
Nutrition	Normal	230	78.8
	Overweight / Obese	9	3.1
	Wasted / Severely wasted	41	14
	Unknown	12	4.1
Development	Normal	234	80.1
	Delayed	38	13
	Unknown	20	6.8
Syndrome*	Syndromic	24	8.2
	Non-syndromic	253	86.6
	Unknown	15	5.1

**S22q11 deletion: 12, Trisomy 21: 10, Goldenhar syndrome: 1, Fetal Alcohol Spectrum Disorders: 1.*

The mean haemoglobin and haematocrit were 16.3g/dl (range 8.9-30, SD ±3.36) and 49.1% (range 28-80, SD ±9,83) respectively.

The commonest pre-operative morbidity encountered was hypercyanotic spells which occurred in 132 patients (45.2%) with 1 patient complicating with cardiac arrest during a hypercyanotic spell. Figure 2 shows the number of hypercyanotic spells in infancy and older children. Infective endocarditis occurred in 5 (1.7%) patients while brain abscess was noted in 1 patient.

Table III shows the peri-operative management and complications. Initial palliation in the form of a systemic to pulmonary artery shunt was required in 22 patients (7.7%). Twelve (4.1%) patients had emergency TOF repair while 280 (95.9%) had elective repairs. Most patients (n=275, 94.2%) had the VSD closed through a RA approach as opposed to a RV approach. Pulmonary valve sparing surgery was done in 173 (59.2%) patients. Intra-operative TOE was carried out in 118 (40.4%) patients during the last 6 years of the study period. The mean

TABLE II: Age at presentation, age at repair of TOF and time difference between diagnosis and TOF repair.

	n=292	Median	IQR*		Minimum	Maximum
Age at presentation (months)		24	6	58.5	0.04	205
Age at repair (months)		42.5	21	69.5	1.6	210
Diagnosis to repair (months)		4.85	1	16	0.03	103

IQR: Interquartile range.*

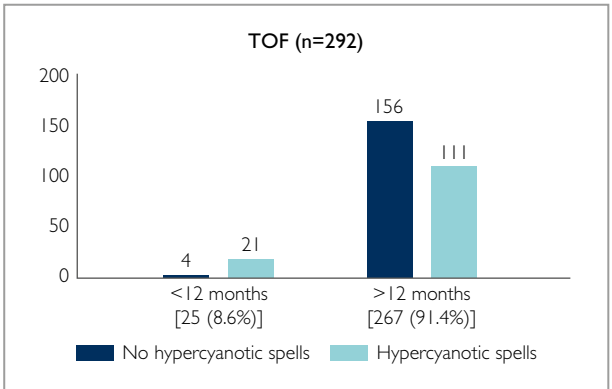

FIGURE 2: Tetralogy of Fallot.

TOF: Tetralogy of Fallot.

TABLE III: Peri-operative management and complications.

		Number (%)
Management	Initial palliation	22 (7.7)
	Emergency	12 (4.1)
	RA approach	275 (94.2)
	Valve sparing surgery	173 (59.2)
	TOE	118 (40.4)
Complications	Arrhythmias	34 (11.6)
	Proven infections	51 (17.5)
	Early mortality	15 (5.1)
	Early re-operation	11 (3.8)

RA: right atrium, TOE: trans-oesophageal echocardiography.

CPB was 119.5 minutes (range 49 - 294) while mean AXC duration was 83.9 minutes, range (23 - 208). Post-operative arrhythmias were noted in 34 (11.6%) patients. Proven infections in the post-operative period occurred in 51 (17.5%) patients. Other major post-operative morbidities included central nervous system complications in 9 patients, upper airway obstruction in 4 patients, combination of upper airway obstruction with a central nervous system complication in 1 patient, complete heart block in 2 patients requiring permanent pacemakers and chylothorax in 2 patients. Eleven (3.8%) patients required reoperation prior to hospital discharge. Early mortality was 5.1%.[15]

The median duration of intubation and LoS in the ICU post-operatively was 1 and 3 days respectively with a range of 1 to 37 days.

Trans-thoracic echocardiographic (TTE) findings on the first post-operative follow-up are noted in Table IV. Severe PR

TABLE IV: First post-operative follow-up trans-thoracic echocardiography.

Follow-up TTE	Severity	Number (%)
Pulmonary regurgitation	<Severe	105 (36.0)
	Severe	127 (43.5)
	Unknown	60 (20.5)
RVOT gradient	<Severe (≤40mmHg)	145 (49.7)
	Severe (>40mmHg)	100 (34.2)
	Unknown	47 (16.1)
TAPSE (2012 - 2017)	Normal to low (≥-3 SD)	51 (35.2)
	Very low (<-3 SD)	72 (49.7)
	Unknown	22 (15.1)

RVOT: Right ventricular outflow tract, SD: Standard deviation, TAPSE: Trans-annular plane systolic excursion, TTE: Transthoracic echocardiography.

was noted in 127 (43.5%) patients while significant residual RVOT gradient was noted in 100 (34.2%). Seventy-two (49.7%) patients had very low right ventricular systolic function as indicated by very low TAPSE. Eighteen (6.2%) patients were lost to follow-up on their first post-operative follow-up visit. Assessment of TAPSE at the study centre started in 2012 prior to which it was not assessed.

Early mortality was found in 15 (5.1%) patients and was significantly associated with age at repair <12 months (p=0.017, 95% CI [1.3 - 15.1]), wasting (p=0.031, 95% CI [1.1 - 11.2]), prolonged CPB (p=0.004), prolonged AXC time (p=0.001) and proven infection (p=0.026, 95% CI [1.2 - 10.0]).

Early re-operation was required in 11 (3.8%) patients. There was no significant association with early repair (p=0.9, 95% CI [0.02 - 8.13]), availability of TOE (p=0.4, 95% CI [0.53 - 5.93]), or surgical technique (p=0.75, 95% CI [0.24 - 2.75] for valve sparing or non-valve sparing surgery (p=0.097, 95% CI [0.05 - 1.28] and for RA or RV approach. The most common indications for re-operation were patch dehiscence due to infective endocarditis in 3 patients, and residual lesions in 2 patients.

Post-operative arrhythmias occurred in 34 (11.6%) patients, 26 (8.9%) of whom had junctional ectopic tachycardia (JET), 2 with complete heart block requiring permanent pacemaker insertion, 2 with transient complete heart block, 2 with ventricular arrhythmias and 2 with tachycardias which were not otherwise specified. There was a statistically significant association between arrhythmias and repair <12 months of age (p=0.051, 95% CI [0.14 - 1.01]).

Early repair was associated with higher mortality (p=0.017, 95% CI 1.3 - 15.1), prolonged intubation (p=0.001), prolonged ICU stay (p=0.003), severe PR (p=0.02 95% CI [1.52 - 92.24]) and higher RVOT gradient (p=0.04, 95% CI [1.0 - 9.4]) on first follow-up. These associations may be due to the patients being more unstable pre-operatively.

A higher post-operative RVOT gradient was associated with a RA approach and early repair, p=0.04 (95% CI [1.1 - 21.9] for RA approach, 95% CI [1.0, 9.4] for early repair). Severe post-operative PR showed a statistically significant association with non-valve sparing surgery (p<0.001, 95% CI [8.9, 37]) and early repair (p=0.02, 95% CI [1.5 - 2.2]). Poor RV function, based on assessment of TAPSE, was associated with non-valve sparing surgery (p=0.03, 95% CI [1.1 - 7.1]) but no significant association with a RA or RV approach, as well as age at repair. Post-operative data may be negatively affected by patients lost to follow-up and missing data. One hundred and eighteen (40.4%) patients were lost to follow-up.

DISCUSSION

Of the 292 patients included in the study, there was a male predominance of 64% which is in keeping with other studies.[4,19,20] The majority of the patients in this study were black African (93.8%), reflecting the demographics of the patients seen at the hospital under study. The majority of our syndromic patients had 22q11 deletion and trisomy 21 which is similar to a retrospective study by Michielon, et al. though their overall number of syndromic patients (27.8%) was higher than in our study (8.2%).[21]

Elective surgical repair of TOF is recommended during infancy though there is still controversy around the optimal timing of repair, especially in the neonatal period.[3-6,19] TOF repair in infancy reduces the risk of morbidities such as hypercyanotic spells and the associated end-organ damage, right ventricular hypertrophy, cardiac fibrosis and dysfunction, late onset post-operative arrhythmias, as well as negative psychosocial effects on the patient and family.[4,5,7,12] Unfortunately, in our setting and in other LMIC, surgical repair is often delayed resulting in some negative outcomes as shown in our study. The median age of repair in our study was 42.5 months which is higher than the recommended age of repair in infancy. In our study, 91.4% were repaired after the age of 12 months. This resulted from several factors including late presentation with the median age of presentation being 24 months. A South African study on repair of TOF also showed delayed repairs with a median age of repair of 39.5 months, while in another study characterising repair of TOF in developing countries, 54% of the patients were repaired after the age of 1 year.[6,20] Limited antenatal diagnostic services and low early neonatal clinical detection contributes to the late presentation and diagnosis. Cardiac, surgical and intensive care services are limited in LMIC, resulting in long surgical waiting lists, further delaying surgery. Reluctance to giving consent for surgery in some of the patients' families also contributed to further delays in surgery in a few of our patients. Due to delayed surgery, some patients in our study presented with pre-operative morbidities, the most common of which were hypercyanotic spells which occurred in 132 (45.2%) patients, 5 (1.7%) patients had infective endocarditis and 1 had a brain abscess with hemiparesis prior to TOF repair. All 6 of them were more than 12 months old. Earlier TOF repair may have prevented these co-morbidities.

Some studies in developed countries reported early mortality of less than 2% in patients post TOF repair.[2,12,22] Sandoval N, et al. reported an early mortality rate of 3.6% in a study assessing TOF repair in LMIC.[6] However, Benbrik, et al. showed no statistically significant difference in mortality between the patients repaired early and those repaired late in their retrospective study.[5] Early mortality in our study was 5.1% which is higher than the aforementioned studies. There was a statistically significant association between early mortality and pre-operative wasting in our study, in keeping with other studies where poor pre-operative nutritional status in patients with congenital heart disease was noted to be associated with poor post-operative outcome.[6,23,24] Lim CYS, et al. showed higher mortality in patients with low weight for age and a longer duration of intubation and hospital stay in patients with low height for age while Marwali EM, et al. showed longer duration of intubation and LoS in ICU in patients with low weight for age.[23,24] These 2 studies included patients with various congenital heart diseases including TOF. In a study characterising repair of TOF in developing countries, malnutrition was also associated with higher mortality.[6] While our study and the others mentioned above used various parameters to define malnutrition, they all show the negative impacts of pre-operative malnutrition on post-operative outcome in congenital heart diseases.

Prolonged CPB and prolonged AXC time were also significantly associated with early mortality in our study. A study by Hashemzadeh K, et al. also showed an association between prolonged CPB and AXC time and mortality.[25]

Proven infection occurred in 17.5% of our patients and this was associated with early mortality as well. In a study by Sandoval N,

et al. assessing TOF repair in developing countries, 5.9% had major infection with an increased risk of mortality.[6] A study by Sen AC, et al. looking at almost 15 000 patients who had cardiac surgeries in various developing countries also showed a significant association between infection and in-hospital mortality.[26] Improved enforcement of infection control measures may help to reduce in-hospital mortality following TOF repair.

The higher mortality found in patients operated under 12 months is a concern and requires further study. This does not imply that patients should be operated on later, but rather suggests to us that patients with more severe disease, who become symptomatic earlier, are not reaching surgical correction. Possible reasons for this include mortality without diagnosis or timeous referral or mortality before corrective surgery is performed.

A study assessing for optimal age for TOF repair noted reoperation in 3%, some of which were due to residual lesions.[3] Unlike in this comparison study, most of the indications for re-operation in our study were secondary to infective endocarditis induced patch dehiscence. Infection has been noted in our study to contribute towards early re-operation and early mortality hence enforcement of infection prevention measures may help improve outcome. There was however no significant association between re-operation and early repair, availability of intra-operative TOE, or surgical technique used.

Post-operative arrhythmias occurred in 11.6%, predominantly junction ectopic tachycardia (JET), which was found in 8.9% of patients. Other studies showed JET to occur in between 7 and 7.9%, similar to our findings.[3,25,27] However, a study which assessed JET in post-TOF repair in children less than 2 years old showed a higher JET incidence of 29.8% with a significant association between JET and younger age.[28]

While patient with some types of surgically corrected congenital cardiac lesions can be discharged from follow-up, TOF is among those that require life-long follow-up due to late complications such as pulmonary regurgitation requiring possible pulmonary valve replacement in adulthood. Unfortunately, 40.5% of our patients were lost to follow-up. A study by Mackie AS, et al. assessing patients with congenital heart disease lost to follow-up to cardiologist services revealed that 28% were lost to cardiology follow-up on the 6th birthday and the number increased as the years progressed.[29] Failure of follow-up may be associated with poorer outcome such as irreversible right ventricular dysfunction, arrhythmias and increased risk of mortality due to lack of an opportunity for timely assessment and intervention.[30,31] Factors contributing to failure to follow-up in our setting includes lack of understanding of the importance of follow-up, poverty resulting in limited funds for follow-up, religious or traditional beliefs, as well as change of caregivers in some patients with no handover of the patient's follow-up plan to the new guardian. The frequent change of phone numbers as well as the unavailability of phones to some of our patients makes follow-up of these patients challenging.

STRENGTH AND LIMITATIONS

The strength of the current study is that it was done over a long period and included a significant number of patients. The study was however limited by the fact that it was retrospective with missing data due to patients lost to follow up or unrecorded information in the patient's file. This could limit some of the conclusions that can be drawn from the study.

CONCLUSION

Most of our patients with TOF were repaired late and a significant number presented with pre-operative morbidities, the commonest of which was hypercyanotic spells. Pre-operative malnutrition and post-operative infection contribute significantly towards early mortality. A significant fraction of our patients are lost to follow-up.

These findings suggest that there is potential for improved outcomes on a number of levels. These include timeous diagnosis, earlier surgery, improvement in peri-operative and post-operative care, prevention of nosocomial infections and improved follow-up. At an institutional level, such improvement can only be achieved by a continuously evaluating outcomes and implementing changes where possible. Additionally, however, development and strengthening of the child health infrastructure within the province as a whole is necessary for sustained progress.

Conflict of interest: none declared.

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