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# INCREASED MORTALITY RATE IN PATIENT WITH FROTHY SPUTUM AFTER TOF TOTAL CORRECTION SURGERY

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**Abstract.** Tetralogy of Fallot (TOF) is the most common congenital heart disease. The most common risk factor for TOF is Down syndrome(DS). There are two management approaches for TOF: medication and operation. Operation/surgical treatment is consisted of palliative shunt and definitive repair. In several case patients with TOF develop collaterals or major aortopulmonary collateral arteries (MAPCAs), which can lung overflow can be initiated after surgery procedure was completed. This causes the CPB time in the repair operation to be long so that the risk of RV/LV dysfunction due to ischemic use of the CPB machine is very high. Frothy sputum is the one of signs of lung injury that related to left and/or right ventricular dysfunction, it may increased mortality in patients TOF repaired. The aim of this study was to identify frothy sputum associated with mortality in patient repaired of TOF. This study is cross-sectional study. We collect data retrospectively through medical record list from 2019 to 2020. In our study, there were 32 patients data included, consisted with more dominant male (n = 22) compare to female (n = 10). It was found that 7 female patients and 9 male patients experienced frothy sputum after TOF repair surgery. There are association not only mortality (p-value 0.033) but also frothy sputum with pulmonary regurgitation (p-value 0.049). Although any result of the study and weakness described previously, the study can be as basis for futher research so that an appropiate guideline can be established to deal frothy sputum in patients TOF repaired.

**Keywords:** frothy sputum; CHD; TOF; down syndrome; MAPCAs; myocardial dysfunction.

## INTRODUCTION

Tetralogy of Fallot is the most common congenital heart disease (CHD) which includes ventricular septal defect (VSD), pulmonary stenosis (PS), right ventricular hyperthropy (RVH) and overriding aorta (Apandi et al., 2020); (Soebroto et al., 2020). The most common risk factor for TOF and other CHD is Down syndrome (DS) condition (Quélin et al., 2009). Although, TOF is categorized in cyanotic CHD not all patients present with "*bluish discoloration*" or sometimes referred to "*pink TOF*". In TOF, cyanosis is caused by limitation blood to the lungs combined with VSD results in oxygen-poor blood supply from rigth to left shunt due to high pressure in right ventricle from pulmonary stenosis. If the pulmonary stenosis is mild with balance shunting direction in the VSD, the clinical presentation usually less cyanotic (Siriapisith et al., 2010). There are two management approaches for TOF: medication and surgical repair. For medical treatment, propanolol 0.5 – 2.0 mg/kg oral is given every 6 hours to prevent hypoxic spell. Surgical treatment is consisted of palliative shunt and definitive repair. Palliative surgical procedure such as Blaloq-Taussiq shunt (BT shunt) is recommended in several case such as TOF and pulmonary atresia, infants with hypoplastic pulmonary annulus, infants with hypoplastic arteries, coronary artery anomalies, infants <3-4 months and hypoxic spells cannot be treated medically and the baby's body weight is <2.5 kg (Park, 2014). Primary repair of tetralogy of Fallot has been performed succesfully in young infants and childrens for the last 45 years, with low surgical mortality (<5%) and excellent long-term result (Park & Salamat, 2020); (Ma et al., 2018); (Makhija et al., 2018). In several case patients with TOF develop collaterals or major aortopulmonary collateral arteries (MAPCAs) in response to decreased pulmonary blood flow and ongoing hypoxemia. This causes the CPB time in the repair operation to be long so that the risk of RV/LV dysfunction due to ischemic use of the CPB machine is very high (Liu et al., 2020).

Frothy sputum is the one of signs of lung injury that related to left and/or right ventricular dysfunction. It may be found in patient post repair of TOF and associated with increased mortality (Ovechkin et al., 2007); (Yang et al., 2021). The aim of this study was to identify frothy sputum associated with increase mortality in patient repaired of TOF.

## METHODS

This study is a cross-sectional study in the cardiovascular centre of Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. We collect data retrospectively through medical record list from 2019 to 2020. The inclusion criteria used were all patients who underwent tetralogy of Fallot repair with frothy sputum and diagnostic catheterization prior to surgery. Thirty-two patients who met inclusion criteria were enrolled in the study.

Population characteristic were listed and grouped into before, during and after surgery. Those included in preoperative data were age at the time of surgery,

gender, baseline of saturation, follow up duration, right pulmonary area size (mm), left pulmonary area (mm), McGoon ratio and we also assessed baseline laboratorium such as Hb (gr/dL), hematocrite, leucocyte, platelet, PT, APTT. The McGoon ratio was calculated using the equation of left and right pulmonary arterial diameter summation divided by the aorta diameter at diaphragm level. Right pulmonary area and left pulmonary artery were measured proximal to the first branching point of each artery. Data included in the perioperative group were cardiopulmonary bypass time (minutes), aortic cross-clamp time (minutes), length of stay in ICU, and duration of intubation. After surgery, we assessed frothy sputum with routine suction.

The baseline data were described using mean, median, or proportion as appropriate. We performed bivariate analysis using Chi-square test and univariate analysis to determine the association between each predictor.

## RESULTS AND DISCUSSION

There were 32 patients data included, consisted with more dominant male (n = 22) compare to female (n = 10). It was found that 7 female patients and 9 male patients experienced frothy sputum after TOF repair surgery. All patients were not diagnosed with DS. Two out of three patients diagnosed with "*pink TOF*" had frothy sputum (66.7%), while from sample with "*blue TOF*"/cyanotic TOF, fourteen of 29 patients had frothy sputum (48.3%). Based on the resected part of PS, there were 17 infundibular type, 2 valvular type, with 13 of them is combination of both. Seven out of seventeen infundibular type have frothy sputum (41.2%), similar to 7 out of 13 mixture type (53.8%) while all valvular type have frothy sputum. There were 3 samples with a history of previous BT shunt surgery, one (33.3%) had frothy sputum and 9 samples had MAPCAs findings and 4 (44.4%) had frothy sputum. In some patients undergoing TOF repair surgery procedure without patch, all of them had frothy sputum, patients with TOF repair procedure with transannular patch of 19 patients, 9 of whom had frothy sputum. Patients with TOF repair and MPAP procedures do not have frothy sputum, in TOF repair with the Rastelly procedure, there was no frothy sputum, while for the intervention of the TOF repair monocusp procedure, about 4 (44.4%) had frothy sputum.

**Table 1.** Frothy Sputum results on categorical independent variables

| | Frothy Sputum | | | | | |
|---|---|---|---|---|---|---|
| | **Frothy** | **Non Frothy** | **N** | **OR** | **95%CI** | **p-value** |
| **Gender** | | | | | | |
| Female | 7(70%) | 3(30%) | 10 | 6.030 | 0.834- | 0.075 |
| Male | 9(40.9%) | 13(59.1%) | 22 | | 43.574 | |
| **Down** | | | | | | |

| | Frothy Sputum | | | | | |
|---|---|---|---|---|---|---|
| | **Frothy** | **Non Frothy** | **N** | **OR** | **95%CI** | **p-value** |
| **syndome** | 0 | 0 | 0 | - | - | - |
| Yes | 16(50%) | 16(50%) | 32 | | | |
| No | | | | | | |
| **Diagnosis** | | | | | | |
| TOF (pink Fallot) | 2(66.7%) | 1(33.3%) | 3 | 0.992 | 0.056-17.507 | 0.996 |
| TOF (blue) | 14(48.3%) | 15(51.7%) | 29 | | | |
| **PS type** | | | | | | |
| Infundibular | 7(41.2%) | 10(58.8%) | 17 | 0.556 | 0.217-1.426 | 0.222 |
| Valvular | 2(100%) | 0(0%) | 2 | | | |
| Infundibular, valvular | 7(53.8) | 6(46.2%) | 13 | | | |
| **Confluent** | | | | | | |
| Confluent | 15(51.7%) | 14(48.3%) | 29 | 7.018 | 0.304-162.087 | 0.224 |
| Non confluent | 1(33.3%) | 2(66.7%) | 3 | | | |
| **Previous BT shunt** | | | | | | |
| Yes | 1(33.3%) | 2(66.7%) | 3 | 0.481 | 0.030-7.619 | 0.604 |
| No | 15(51.7) | 14(48.3%) | 29 | | | |
| **MAPCAs** | | | | | | |
| Yes | 4(44.4%) | 5(55.6%) | 9 | 0.835 | 0.147-4.735 | 0.839 |
| No | 12(52.2%) | 11(47.8%) | 23 | | | |
| **Intervention** | | | | | | |
| TOF repair w/o patch | 2(100%) | 0(0%) | 2 | | | |
| TOF repair with TAP | 9(47.4%) | 10(52.6%) | 19 | 1.588 | 0.798-3.162 | 0.188 |
| TOF repair with MPAP | 0(0%) | 1(100%) | 1 | | | |
| TOF repair + Rastelly | 1(100%) | 0(0%) | 1 | | | |
| TOF repair monocusp | 4(44.4%) | 5(55.6%) | 9 | | | |

Table 1. A table of frothy sputum results on categorical independent variables. From the table of sex for frothy sputum, p-value is 0.075. In the "*pink*" and "*blue*" TOF categories for frothy sputum, a p-value of 0.996 was obtained. In the PS type category for frothy sputum, a p-value of 0.222 was obtained. For the confluent and non-

confluent categories of frothy sputum, the p-value was 0.604. In the category of history of BT shunt and not for frothy sputum, the p-value was 0.604. In the MAPCAs category and not for frothy sputum, the p-value was 0.839. Intervention category for frothy sputum, p-value 0.188. Based on the p-value, it can be concluded that there is no significant variable on frothy sputum, meaning that there is no categorical independent variable that does not affect frothy sputum. Based on the OR value, patients with female gender gave an effect of 6,030 times and patients with pink fallot confluency had an effect of 7,018 times on frothy sputum.

**Table 2.** Frothy Sputum results on numeric independent variables

| | **Frothy Sputum** | | | | |
|---|---|---|---|---|---|
| | **Mean** | **ST Deviation** | **OR** | **95%CI** | **p-value** |
| Age (years) | 4.03 | 5.270 | 1.546 | 0.772-3.097 | 0.219 |
| Saturation (%) | 80.97 | 8.567 | 1.048 | 0.893-1.229 | 0.568 |
| PG (mmHg) | 88.78 | 17.573 | 1.043 | 0.935-1.162 | 0.452 |
| RPA size (mm) | 490.578 | 223.021 | 0.346 | 0.070-1.696 | 0.191 |
| LPA size (mm) | 32.831 | 136.223 | 3.095 | 0.702-13.641 | 0.135 |
| PV annulus | 6.56 | 2.884 | 0.835 | 0.455-1.534 | 0.562 |
| Mc Goon ratio | 2.072 | 0.442 | 26.577 | 0.117-6021.190 | 0.236 |
| CPB time (minutes) | 107.687 | 34.106 | 1.083 | 0.970-1.210 | 0.156 |
| Cross clamp time (minutes) | 39.937 | 20.463 | 0.834 | 0.658-1.057 | 0.134 |
| Hb (g/dl) | 16.668 | 3.516 | 0.634 | 0.169-2.375 | 0.499 |
| Hematocrite | 50.721 | 10.155 | 0.962 | 0.585-1.580 | 0.877 |
| Leukocytes | 8956.83 | 4161.89 | 1.000 | 0.999-1.000 | 0.161 |
| Platelet ($x10^9$) | 272.46 | 98.46 | 1.002 | 0.982-1.021 | 0.877 |
| PT | 11.81 | 1.66 | 0.752 | 0.193-2.924 | 0.680 |
| APTT | 37.99 | 6.93 | 1.161 | 0.808-1.668 | 0.419 |

Table 2. Is a table of frothy sputum results on numerical independent variables. The table shows that age for frothy sputum obtained p-value 0.219. The saturation of frothy sputum shows a p-value of 0.568. For pressure gradient (PG) obtained p-value of 0.452, RPA size (p-value 0.191), and LPA size (p-value 0.135). PV annulus to obtained p-value 0.562. For CPB time and cross clamp time, respectively, p-values are 0.156 and 0.134. Likewise, the results of laboratory examinations obtained p-value> 0.05. In table 2 it can be seen that the p-value of all variables is not below the value of 0.05, so there are no significant variables. Based on the OR value of the patient, the higher the

MC goon ratio, the greater the effect of 26,577 on frothy sputum.

**Table 3.** Mortality results on categorical independent variables

| | Mortality | | | | | |
|---|---|---|---|---|---|---|
| | **Frothy** | **Non Frothy** | **N** | **OR** | **95%CI** | **p-value** |
| **Gender** | | | | | | |
| Female | 7(70%) | 3(30%) | 10 | 1.608 | 0.223-11.584 | 0.637 |
| Male | 4(18.2%) | 18(81.8%) | 22 | | | |
| **Down syndome** | 0 | 0 | 0 | - | - | - |
| Yes | 7(21.9%) | 25(78.1%) | 32 | | | |
| No | | | | | | |
| **Diagnosis** | | | | | | |
| TOF (pink Fallot) | 0(0%) | 3(100%) | 3 | 0.000 | 0.000 | 0.999 |
| TOF (blue) | 7(24.1%) | 22(75.9%) | 29 | | | |
| **PS type** | | | | | | |
| Infundibular | 2(11.8%) | 15(88.2%) | 17 | 0.500 | 0.170-1.468 | 0.207 |
| Valvular | 1(50%) | 1(50%) | 2 | | | |
| Infundibular, valvular | 4(30.8) | 9(69.2%) | 13 | | | |
| **Confluent** | | | | | | |
| Confluent | 6(20.7%) | 23(79.3%) | 29 | 0.988 | 0.060-16.397 | 0.993 |
| Non confluent | 1(33.3%) | 2(66.7%) | 3 | | | |
| **Previous BT shunt** | | | | | | |
| Yes | 0(0%) | 3(100%) | 3 | 0.000 | 0.000 | 0.999 |
| No | 15(51.7) | 14(48.3%) | 29 | | | |
| **MAPCAs** | | | | | | |
| Yes | 1(11.1%) | 8(88.9%) | 9 | 0.356 | 0.029-4.336 | 0.418 |
| No | 12(52.2%) | 11(47.8%) | 23 | | | |
| **Intervention** | | | | | | |
| TOF repair w/o patch | 0(0%) | 2(100%) | 2 | | | |
| TOF repair with TAP | 4(21.1%) | 15(78.9%) | 19 | 1.069 | 0.532-2.147 | 0.852 |
| TOF repair with MPAP | 0(0%) | 1(100%) | 1 | | | |
| TOF repair + Rastelly | 0(0%) | 1(100%) | 1 | | | |

| | | | |
|---|---|---|---|
| TOF repair monocusp | 3(33.3%) | 6(66.7%) | 9 |

Table 3 is a table of mortality results for categorical independent variables. In the gender category for mortality, a p-value of 0.637 was obtained. For pink TOF and blue TOF, the p-value is 0.999. In PS type category, p-value is 0.207, confluent category p-value is 0.993. For BT shunt obtained p-value 0.999. In the MAPCAs category, the p-value is 0.418. Likewise intervention, p-value >0.05. In Table 3. It can be seen that the p-value of each variable is above 0.05 so that there are no significant variables. The OR value of the variable that has a major influence only reaches one-fold, namely on the gender and intervention variables.

**Table 4.** Mortality result on numeric independent variables

| | **Mortality** | | | | |
|---|---|---|---|---|---|
| | **Mean** | **ST Deviation** | **OR** | **95%CI** | **p-value** |
| Age(years) | 4.03 | 5.270 | 1650.76 | 0.000- | 0.997 |
| Saturation(%) | 80.97 | 8.567 | 194.11 | 0.000- | 0.995 |
| PG(mmHg) | 88.78 | 17.573 | 0.010 | 0.000- | 0.996 |
| RPA size(mm) | 490.578 | 223.021 | 0.000 | 0.000- | 0.996 |
| LPA size(mm) | 32.831 | 136.223 | 75277038.02 | 0.000- | 0.996 |
| PV annulus | 6.56 | 2.884 | 0.000 | 0.000- | 0.995 |
| Mc Goon ratio | 2.072 | 0.442 | 6.61E+24 | 0.000- | 0.998 |
| CPB time(minutes) | 107.687 | 34.106 | 0.119 | 0.000- | 0.996 |
| Cross clamp time(minutes) | 39.937 | 20.463 | 111.81 | 0.000- | 0.994 |
| Hb(g/dl) | 16.668 | 3.516 | 4.483 | 0.000- | 1.000 |
| Hematocrite | 50.721 | 10.155 | 1.491 | 0.000- | 1.000 |
| Leukocytes | 8956.83 | 4161.89 | 0.998 | 0.037-27.196 | 0.999 |
| Platelet($x10^9$) | 272.46 | 98.46 | 0.894 | 0.000-1.967E+27 | 0.997 |
| PT | 11.81 | 1.66 | 306076.49 | 0.000- | 0.998 |
| APTT | 37.99 | 6.93 | 47.046 | 0.000- | 0.997 |

It is a table of mortality results for the numerical independent variables. Based on the p-value, it can be concluded that there are no variables that affect mortality, because the p-value of each variable is above 0.05. based on the OR value, age, saturation, LPA size, and PT variables have a big influence.

**Table 5.** Effect of pulmonary valve on frothy sputum

| | Frothy Sputum | | | | | |
|---|---|---|---|---|---|---|
| | **Frothy** | **Non Frothy** | **N** | **OR** | **95%CI** | **p-value** |
| **Pulmonary valve** | | | | | | |
| Pulmonary regurtitation | 7(77.8%) | 2(22.2%) | 9 | 45.549 | 1.274-1628.222 | 0.049 |
| Pulmonary stenosis | 9(39.1%) | 14(60.9%) | 23 | | | |

Based on Table 5, the p-value obtained is 0.049 which means that between pulmonary valve(PV) and frothy sputum is significant or PV has an effect on frothy sputum. The resulting OR value shows that PV has an effect of 45,549 times on frothy sputum.

**Table 6.** Effect of Frothy Sputum on Mortality

| | Mortality | | | | | |
|---|---|---|---|---|---|---|
| | **Yes** | **No** | **N** | **OR** | **95%CI** | **p-value** |
| **Frothy sputum** | | | | | | |
| Frothy | 6(37.5%) | 10(62.5%) | 16 | 9.000 | 0.936-86.522 | 0.033 |
| Non Frothy | 1(40.9%) | 15(59.1%) | 16 | | | |

Based on Table 6, the p-value obtained is 0.033 which means that between frothy sputum and significant mortality or frothy sputum has an influence on mortality. The resulting OR value indicates that frothy sputum has a 9-fold effect on mortality.

**Table 7.** ICU stay and LOHS on Mortality

| | Mortality | | | | | |
|---|---|---|---|---|---|---|
| | **Yes** | **No** | **N** | **OR** | **95%CI** | **p-value** |
| **Frothy sputum** | | | | | | |
| Frothy | 6(37.5%) | 10(62.5%) | 16 | 9.000 | 0.936-86.522 | 0.033 |
| Non Frothy | 1(40.9%) | 15(59.1%) | 16 | | | |

Based on Table 7, the characteristics of ICU stay and LOHS are significant on mortality, this can be seen in the p-value which is less than 0.05, which means that ICU stay and LOS stay have an effect on mortality. The resulting OR value shows that ICU stay has an effect of 2.236E+17 times on mortality and LOHS day has an

effect of 244,317 times on mortality.

This study aims to find the association of reverse complication after TOF repair with frothy sputum. However, not all studies investigate the association of the effect frothy sputum to mortality.

Frothy sputum is the one of the signs of lung injury that related to left ventricular (LV) dysfunction or myocardial dysfunction. It may be found in patient post repair of TOF and increase significantly mortality TOF repair was first described in 1955 by Lillehei et all (Maddali et al., 2011). Timing of this operation varies from instution to instution, but early age surgery is generally preferred. Total repair of the defect is carried out under cardiopulmonary bypass, circulatory arrest, and hypothermia. The procedure includes stiches and/or patchs closure of the VSD, preferably through transatrial and transpulmonary artery approach, widening of the right ventricular outflow tract (RVOT) by division or resection of the infundibular tissue, and pulmonary valvotomy, avoiding placement of the fabric patch whenever possible. However, if the pulmonary annulus and main PA are hypoplastic, transannular patch is unavoidable. For patient with uncomplicated TOF, the mortality rate is 2% to 3% during the first 2 years. During the last decades, it has been well recognized that patients with repaired TOF are at risk for exercise intolerance, right heart failure, life-threatening ventricular arrhytmia, and sudden death. Numerous studies have shown a close relationship between the degree of PR and RV dimensions and RV ejection fraction. Varying degrees of pulmonary regurgitation and/or pulmonary stenosis remain in the majority of patients after right ventricular outflow tract (RVOT) reconstruction, and severe PS and free PR are both ends of the spectrum in residual hemodynamic impairment (Yoo & Park, 2013). In addition left ventricular (LV) function deteriorates with progressive RV dysfunction through interventricular interaction, that called "*reversed Berheim effect*". The reverse Bernheim effect occurs when there is right ventricular pressure and volume overload that results in the interventricular septum bulging toward the LV causing LV diastolic impairment[14]. In situations where a part of the RV is akinetic, due to scarring post myocardial infarction or after replacement with a noncontractile material (synthetic patch), the septum is able to maintain circulatory stability as long as the RV is not dilated. In acute RV pressure- or volume-overload states, dilatation of the RV increases intrapericardial pressure and shifts the interventricular septum to the left, altering LV geometry. As a consequence, distensibility of LV decreases, leading to a decreased LV preload, increased LV end-diastolic pressure, and consequently a low cardiac output state. This can cause symptoms of LV failure or dysfunction (Magoon et al., 2020); (Kanter et al., 2010); (Saran et al., 2019). Its similar in our study terdapat asosiasi pulmonary regurgitation terhadap frothy sputum (p-value 0.049).

Although the TOF repair procedure has a mortality rate of <5% and the results of the procedure are satisfactory6. The postoperative morbidity and mortality rate is quite high17. About 75% are due to RV

and/or LV dysfunction18. This study supports our finding that frothy sputum has a significant relationship with mortality (p-value 0.033).

There are certain limitation to this study. The sample of this study is the comparison of the number of genders in the sample is not evenly distributed, not all patients have documented LV/RV function evaluation, but PS/PR is well documented, so other factors cannot be ruled out.

## CONCLUSIONS

Our finding showed frothy sputum was associated with pulmonary regurgitation and mortality. However, the unmeasured factors with confounding and effect modifying potentials affecting frothy sputum cannot excluded. Based on our study frothy sputum not only associated with mortality but also morbidity. Although any result of the study and weakness described previously, the study can be as basis for futher research so that an appropiate guideline can be established to deal frothy sputum in patients TOF repaired.

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7

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