SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM

DEPARTMENT OF CARDIOLOGY

CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT TRERAPY

A THESIS SUBMITTED FOR THE DEGREE OF

DM CARDIOLGY

DR. VISHNU S

JANUARY 2021

DECLARATION

I, Dr. Vishnu.S, hereby declare that the project in this book, titled "**CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT THERAPY**" was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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CERTIFICATE

I hereby certify that the work in this dissertation titled "**CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT THERAPY"** is a certified record of original research work undertaken by Dr. Vishnu.S in the Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology in partial fulfilment of requirement for the purpose of award of D.M. Cardiology degree.

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CERTIFICATE

I hereby certify that the work in this dissertation titled"**CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT THERAPY**" is a certified record of original research work undertaken by Dr. Vishnu. S in the Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology in partial fulfilment of requirement for the purpose of award of D.M. Cardiology degree under my guidance and supervision.

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TITLE

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Dr. Vishnu S

ABBREVIATIONS

AF - Atrial fibrillation

AFL - Atrial flutter

APW - Aorto pulmonary window

ASD - Atrial septal defect

AVCD - Atrio Ventricular Cushion Defect

BSA - Body surface area

CATH - Catheterization

CHB – complete Heart Block

DILV - Double Inlet Left ventricle

DMT – Disease Modifier Therapy

DORV - Double outlet Left Ventricle

EF - Ejection fraction

ES - Eisenmenger Syndrome

ETA – Endothelin receptor Antagonist

Echo - Echocardiography

HF – Heart Failure

Hb - Hemoglobin

IE – infective Endocarditis

JVP - Jugular venous Pulse

LV – Left ventricle

LVED - Left ventricular end diastolic pressure

MAPCA – Major Aorto Pulmonary Collaterals

MPAP - Mean pulmonary artery pressure

MVO2 – mixed venous Oxygen saturation

NT – PRO BNP - N Terminal pro B type natriuretic peptide .

OP ASD- Ostium Primum Atrial septal defect

OS ASD - Ostium Secundum Atrial septal defect

PA - Pulmonary artery

PAH - Pulmonary artery hypertension

PASP - Pulmonary artery systolic pressure

PAW - Pulmonary artery wedge

PCV - Packed red Cell Volume

PDA - Patent Ductus Arteriosus

PDEI – Phosphodiesterase Inhibitor

PE - Pericardial effusion

PR - Pulmonary regurgitation

PVR - Pulmonary vascular resistance

Qp/Qs - Pulmonary blood flow/ systemic blood flow

RV – Right ventricle

RVED - Right ventricular end diastolic pressure

RVID – RV internal diameter

RVSP - Right ventricular systolic pressure

RAm - Mean Right atrial pressure

SD - Standard deviation

SV - Single Ventricle

SV ASD - Sinus Venosus Atrial septal defect

SVR - Systemic Vascular Resistance

SpO2- saturation

TA – Truncus Arteriosus

TAPSE – Tricuspid Annular Plane Systolic Excursion

TAPVC - Total Anomalous Pulmonary Venous Connection

TGA - Transposition of Great arteries

TR - Tricuspid regurgitation

VSD - Ventricular Septal Defect

VT – Ventricular Tachycardia

WHO FC - World Health organization Functional Class

SYNOPSIS

SYNOPSIS

Background of study: Paucity of new studies focused on clinical characteristics of Eisenmenger syndrome. Limited data is available based on shunt type specific clinical characteristics, outcomes of disease targeted treatment and survival pattern from our population.

Aim: To study the clinical profile, survival pattern, mortality predictors and outcome of disease targeted therapy in patients with Eisenmenger syndrome.

Materials & Methods: Single center retrospective case enrollment and cross sectional follow up study. Study period between January2000 to January2020. Consecutive patients with Clinical and Echocardiographic ± Catheterization diagnosis of Eisenmenger syndrome were included in study, those patients not consented for study were excluded. Lost to follow up patients were contacted over phone for clinical visit if alive, and enquired about terminal events if not alive. Clinical outcomes evaluated were RV dysfunction, clinical heart failure on follow up, atrial arrhythmias , embolic episodes, brain abscess, infective endocarditis , all cause & cause specific mortality.

Results: 206 patients were included in study .139 were females, age of presentation varied from 3 months to 65 years (mean 23.4±14.3). Post tricuspid lesions (47.5%) were most common followed by pre tricuspid (34.4%) and complex defects (18%).Atrial septal defect (33.3%),Ventricular septal defect (26.6%), Patent ductus arteriosus (16.5%) were most commonly seen anatomic lesions. Mean resting basal systemic saturation 87.7± 6.3% and during follow up was 85.8± 7.3% (p=0.001).18% of patients was in WHO functional class III/IV which increased to 40% (p=0.001) on follow up. Atrial arrhythmias and RV dysfunction was more common in pre tricuspid lesions (p=0.001). Fifty six (31.5%) patients died during a mean follow-up period of 85.2±75.3 months. Congestive heart failure (59%) and haemoptysis (15%) Sudden cardiac deaths(11%), were the most predominant causes of death. The acturial survival for the entire patient population at 1year,3year, 5 years, 10 years and 20 years was 96%, 89% 85%,77%,69% respectively. Post tricuspid shunt lesion have better survival (log rank p=0.001).No difference in survival observed in pre tricuspid and complex lesions. Unadjusted survival analysis and after propensity score regression adjustment for baseline clinical differences a Disease modifier therapy is associated with better survival (HR;-1.72) .Of all the

variables tested in uni variate analysis resting saturation on follow up ≤ 80%, presence of atrial arrhythmias, use of disease modifier therapy was independently associated with mortality.

Conclusion: Eisenmenger syndrome patients having good short and intermediate term survival, though long term survival is not good. Pre tricuspid shunt lesions having high proportion of arrhythmic events, heart failure and mortality among different shunt types .Post tricuspid shunt having better survival compared to other shunt types. Disease modifier therapy associated with improved survival. Resting systemic saturation ≤ 80% on follow up and presence of atrial arrhythmias, use of disease modifier therapy predicts mortality.

This study adds: Post tricuspid shunt having better survival after diagnosis of eisenmenger physiology compared to other shunt types. Disease modifier therapy associated with improved survival.

INTRODUCTION

INTRODUCTION

In 1897, Victor Eisenmenger (1) described the clinical presentation and autopsy findings of a 32- year-old man known to be cyanosed and short of breath for many years but working actively as a coachman till the onset of heart failure shortly before death. The autopsy findings showed a large ventricular septal defect with some aortic override, enlargement of right ventricle and atheroma of the pulmonary artery. For the next 50 years aortic override was considered an essential part of Eisenmenger syndrome. Bing(2) drew the attention to the fact that pulmonary hypertension and pulmonary vascular obstruction were the determinants of the left to right shunt in ventricular septal defect . Bond (3) corroborated the same idea and noted a variety of congenital cardiac defects that has been reported in association with Eisenmenger complex . In 1958 Paul Wood (4) expanded the anatomical concept of Eisenmenger syndrome to include any large systemic pulmonary communication at aorto-pulmonary, ventricular or atria1 level. He defined the condition as pulmonary hypertension at or near systemic level with reversed or bidirectional shunt between the pulmonary and systemic circulation and pulmonary vascular resistance above 10 Wood units. He added that at times the shunt may be balanced so delicately that there may be no net shunt in either direction. He enlisted no less than 12 anatomical conditions which can result in such a physiology and called the condition Eisenmenger syndrome. Saha et al (5) Large follow up study of 201 patients of Eisenmenger syndrome for a study period of 16years from 1976 to 1992 in our institute and analysed their data to determine their survival pattern, impact of the disease on the life style and complications during long-term follow-up, this study concluded that Eisenmenger syndrome, although implies a hopeless situation, is compatible with a fair intermediate term survival. History of syncope at presentation, elevated right-sided filling pressure at presentation and systemic arterial desaturation (below 85%) indicate poor prognosis.

Paucity of newer studies in the era of disease modifier therapy in Eisenmenger patients regarding clinical profile outcomes of disease targeted treatment, survival pattern and mortality predictors from our population. This study aims to find clinical profile of patients with Eisenmenger syndrome and to assess outcomes of disease targeted therapy and mortality predictors.

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

Eisenmenger syndrome defined as pulmonary hypertension at or near systemic level with reversed or bidirectional shunt between the pulmonary and systemic circulation and pulmonary vascular resistance above 10 Wood Units. Patients were grouped into 3 categories based on shunt types ,pre tricuspid, post tricuspid, and complex defects(6).In the pre tricuspid group, included patients with large, non-restrictive atrial septal defects, anomalous pulmonary venous connections with no significant post tricuspid defect. The post tricuspid group included patients with large, non-restrictive ventricular septal defects, patent ductus arteriosus , aorto pulmonary window with no major pre tricuspid defect. The complex group included patients with complete atrioventricular septal defect truncus arteriosus, Single ventricle physiology with unobstructed pulmonary blood flow, transposition of the great arteries , pulmonary atresia with ventricular septal defect with large aortopulmonary collaterals supplying entirely to both lung and documented high pulmonary vascular resistance on cardiac catheterisation included for the study.

Paul Wood (4) in 1958 , 127 cases of ES were analysed . 53 autopsies from well investigated during life studied. Equal sex incidence noted in this study. PDA with Eisenmenger reaction is well tolerated. Size of the defect and communication duct with size 0.7-1.5 cm , Ventricular septal defect 1.5-3 cm, Atrial septal defect 3-8cm, Average age of natural death was 33 in Aorto pulmonary defects, 33 in VSD, 36 in ASD. Cause of death known in 42, most common cause was hemoptysis 29%, Surgical repair of defect caused 26% of mortality ,Congestive heart failure in 17%,sudden cardiac death (VF) in 14%,Infective endocarditis/ Cerebral abscess/ Cerebral thrombosis/ Pregnancy induced in 5%.

Saha et al(5) studied the long-term survival pattern and predicting variables and complications occurring during follow-up. 201 diagnosed with Eisenmenger syndrome were followed up for 16 years from 1976 to 1992. One hundred nine patients were females 19 (3-65) years. The most common three being VSD (33%) ASD (29.8%) and PDA (14%). 20 patients died in mean follow-up period of 5 years. SCD (30%), CCF (25%) and haemoptysis (15%) were the most common causes of mortality. Only one patient died due to pregnancy related issues. Survival at 5 years, 10 years and 15 years was 86%, 79% and 76%, respectively. Type of shunt not related to survival. In univariate analysis, history of syncope at presentation , elevated mean right atrial pressure (≥8 mmHg) and systemic arterial desaturation < 85% were independent predictor of a poor prognosis.

Daliento et al(7) in 1998 assessed the natural history, risk factors for death and causes of deterioration in ES.188 patients followed for a median period of 31 years. Lesions grouped into simple (128) and complex (60) congenital heart disease. Patients with complex heart disease and Eisenmengerisation had earlier clinical deterioration and short survival. 20% patients had at least one episode of haemoptysis 13% had pulmonary thromboembolism at a mean age of 35years. Fifteen (8%) had a stroke and seven (4%) had cerebral abscess. 61 patients died on follow-up, most common cause was sudden death (29%), followed by heart failure (23%) and haemoptysis (11%). 8 patients had heart and lung transplant and 5 died on follow up. worsening symptoms, age, complex defects, RV dysfunction and non-cardiac surgery affected the prognosis adversely .

Cantor et al(8) in 1999 retrospectivly studied Eisenmenger syndrome to identify clinical characteristics and prognostic determinants.109 adults (mean age 29 years, 43% men) were followed for a median duration of 6 years. 60% had simple cardiac anatomy (13 atrial septal defect, 43 ventricular septal defect,10 patent ductus arteriosus);remainder had complex cardiac anatomy. 33 deaths and 9 transplant during follow-up. Median survival was 53 years. Multivariate Cox regression analysis identified age at diagnosis , SVT ,precordial electrocardiogram voltage , and poor NYHA as independent predictors of mortality.

Oya et al (9) in 2002 investigated the long-term prognosis and factors predictive of the prognosis in ES. 106 (37 men, mean age 35years) .53 atrial septal defect, 23 VSD, 14 PDA, and 16 patients had complex defects. 42 patients died during a mean follow-up period of 7 years. The mean survival time was 5years. Survival rate was 98% at 1 year, 76% at 5 years, and 57% at 10 years. NYHA functional classification, syncope, right atrial pressure, total pulmonary resistance, arterial oxygen partial pressure, and serum creatinine level correlated with mortality. Multivariate analysis showed elevated right atrial pressure and reduced systemic blood flow were independently associated with increased mortality

Guo chen et al in 2013 studied clinical features and hemodynamic parameters of adult patients with ES. 224 ES with atrial septal defect (n = 67), ventricular septal defect (n = 104) and PDA (n = 53). 157 patients were female with a mean age of (29± 9.9) years. mean 6MW distance (371 ± 75) m. The majority of patients were in WHO-FC ii (70%) and iii (28%). Mean right atrial pressure was (8.9 ± 5) mm, mean pulmonary arterial pressure (77 ± 19) mm Hg, cardiac index (3 ± 1.3)l/min and pulmonary vascular resistance (1621 ± 888) dyn.s.cm-5. Concluded that

deterioration in Eisenmenger syndrome is non-parallel to mean pulmonary arterial pressure and pulmonary vascular resistance.

Dimopoulos et al (10) in 2009 studied role of advanced therapy in Eisenmenger syndrome in improving pulmonary hemodynamics, functional class, and the 6-minute walk distance also examined the potential effect of advanced therapy on survival in this population. 229 patients (35% male) were included. Most common lesion was complex category, and 53% in NYHA class iii at baseline. Mean resting SpO2 was 84%.29% patients were on advanced therapy .During a median follow-up of 4.0 years, 52 patients died, only 2 of them were on advanced therapy. Patients on advanced therapy showed significantly lower risk of death, both unadjusted and after propensity score regression adjustment (P=0.01) and propensity score matching concluded that advanced therapy for pulmonary arterial hypertension in a contemporary cohort of adults with ES was associated with a lower risk of mortality. Survival benefits together with improved hemodynamic parameters and WHO functional class.

Kempny et al (11)in 2016 investigated survival and predictors of death in a large, contemporary cohort of 1098 Eisenmenger syndrome (median age 34.4 years; 65% female;31.9% trisomy 21). The most common shunt was post tricuspid defect (58%), followed by complex (28.7%) and pre tricuspid lesion (12.7%). Median follow-up of 3 years (IQR, 1.4–5.9).278 patients died and 6 underwent transplant. On multivariable Cox regression analysis, only age , pretricuspid shunt, oxygen saturation at rest, presence of sinus rhythm , and presence of pericardial effusion remained significant predictors of death.

Gerhard-Paul Diller (12)looked at B-type natriuretic peptide concentrations in ES and predictive value and DMT response in a follow-up period of 3 years. 20 including 7 trisomy patients died on follow up. Higher B-type natriuretic peptide concentrations were predictive of all cause mortality on univariate analysis in patients with or without Trisomy 21. On multivariable Cox proportional hazard analysis, B-type natriuretic peptide predicted survival independently of renal function, Down syndrome, or 6 min walk test distance .Increases in BNP level found to predict mortality. Treatment with disease targeting therapies associated with a significant reduction in B-type natriuretic peptide levels. Disease targeting therapies may help to reduce B-type natriuretic peptide level , Treatment naïve patients have abnormal B-type natriuretic peptide level.

Montani et al(13) in his article on treatment algorithm of severe pulmonary hypertension highlighted the importance of vasoreactivity testing during right heart catheterization to screen potential long-term responders to calcium channel blocker. In the absence of acute vasodilator response or absence of long-term response to calcium channel blockade, specific PAH therapies targeting endothelial dysfunction are indicated. The choice of the drugs and route of administration depends on the clinical severity based on NYHA functional class. Intravenous epoprostenol is recommended as a first line therapy for all the most severe patients in NYHA functional class IV. All approved drugs may be proposed as first-line therapy for patients in NYHA functional class III. ERS/ESC guidelines(6) proposed oral specific PAH therapy (ERA/ PDE5I) as first-line treatment.

Van De Bruaene et al(14) in a study evaluated whether deterioration in exercise capacity and resting oxygen saturation are related with adverse outcome in ES patients. 77 (mean age (SD) 36.2(14) years, 30% males) patients prospectively followed up. Clinical deterioration was defined as decrease in exercise capacity or SatO2-rest. Outcome defined as the hospitalization need due to CCF, transplantation, or all-cause mortality & prognosis by deterioration in exercise capacity and SatO2-rest. During a follow-up period of 4 years, 27 (35%) events happened; univariate predictor of events were deterioration in NYHA class, 6 minute walk distance and SpO2-rest . Multivariate cox regression analysis indicated that clinical deterioration was independently associated with adverse events.

Mukhopadhyay et al (15), in a trial, compared the efficacy of tadalafil with placebo in Eisenmenger Syndrome. Endpoint primarily used was change in 6-minute walk test distance. Secondarily were the effect of the drug on SpO2, PVR, SVR, effective pulmonary blood flow , and World Health Organization functional class. 28 ES patients included all patients were in WHO class II and III. 40mg of tadalafil or placebo for 6 weeks and later interchanged to the other drug after 2 weeks. Assessment of WHO class, exercise capacity, and various hemodynamic parameters by cardiac catheterization demonstrated at baseline, 6 weeks and at end. Noted significant increase in 6 MW distance following drug intake versus baseline .Compared with placebo, tadalafil showed significant decrease in PVR and significant increase in EPBF, SpO2 % and WHO functional class with no significant change in SVR. Concluded that the drug was tolerated and significantly improved exercise capacity, functional class, SpO 2, and hemodynamic parameters.

Zhen-Ning Zhang et al (16)investigated with the sildenafil and effects on clinical and haemodynamic parameters in 84 patients with Eisenmenger syndrome . WHO functional class ii and iv patients. Sildenafil 20 mg three times daily orally administered. 6-min walk distance test, resting systemic arterial blood oxygen saturation, haemodynamic parameters, safety and tolerability. The overall treatment effects at 12 months from baseline were 56 m increase in 6MW distance, and 2.4% increase in resting SaO2. Improvements were also seen in mean pulmonary arterial pressure and pulmonary vascular resistance index. Concluded that oneyear of oral sildenafil treatment was well tolerated and appeared to improve exercise capacity, systemic arterial oxygen saturation and haemodynamic parameters.

Diller et al(17) in 2016(German Regisatry) assessed the contemporary outcome of the use of disease targeting therapies.153 ES were included (mean(SD) age 34(13) years, 46% females). 57.5% were treated with mono therapy (76% Bosentan, 20% Sildenafil) 17% were on dual therapy.24% of patients received digoxin, 10%ACEI/ARB, and 17% beta blockers. 17% of patients were treated with oral anticoagulants, while 23% of patients received Aspirin. The survival rate at 1, 5, and 10 years of follow-up was only 92%, 75%, and 56% in all patients, and in treatment naive patients 86%, 60%, and 34% respectively. Use of disease modifier therapy associated with an improved survival .Treatment naive ES had high mortality up to 60–70% at 10 years. Treatment with disease modifiers associated with improved survival.

Hascoet et al(18) , in 2017 analysed pulmonary arterial hypertension-specific drug therapy and mortality benefit in Eisenmenger syndrome (from French registry). 340 patients with ES: syndromic association 35.3%; pre tricuspid defect 22%. 81% patients received disease modifier. Monotherapy in 46%, dual therapy in 40.9%, triple therapy in 9.1%. Median treatment duration was 5.4 years. Death, lung or heart-lung transplant in 27.9% patients. Occurrence of events was 16.7% and 46.4% at 40 and 60 year. Occurrence of events was lower in patients on one or two advanced medications with the differences in the post-tricuspid defect versus patient with-out disease modifiers. By multivariable Cox analysis, with time since PAH diagnosis as time span, WHO FC III/IV, lower SpO2 and pre tricuspid defect were associated with a higher risk for an event, and one or two disease modifier therapy with low risk for an adverse oucome.

ESC 2020 adult congenital heart disease recommendation for treatment of Eisenmenger syndrome(19).In Eisenmenger patients with reduced exercise capacity (6-minute walk distance

<450 m), a treatment strategy with initial endothelin receptor antagonist monotherapy should be considered followed by combination therapy if patients fail to improve (Class IIa).

AIM OF THE STUDY

&

HYPOTHESIS

AIM

To study the clinical profile of patients with Eisenmenger syndrome. To find the clinical & survival patterns in different shunt types. To assess outcomes of disease targeted therapy and mortality predictors.

HYPOTHESIS

Patients with Eisenmenger syndrome clinical profile and survival pattern among different shunt types are comparable and these patients have improved survival on currently recommended disease targeted medications.

MATERIALS & METHODS

MATERIALS & METHODS

This study is a Single center retrospective case enrollment and cross sectional follow up. Study period between January 2000 to January 2020 . Consecutive patients with Clinical and Echocardiographic, with or without cardiac catheterization diagnosis of Eisenmenger syndrome were included in study.

INCLUSION CRITERIA

Consecutive patients with Clinical and Echocardiographic, with or without cardiac catheterization diagnosis of Eisenmenger syndrome were included in study.

EXCLUSION CRITERIA

Those patients not consented for study excluded. In VSD with pulmonary atresia with MAPCA dependent pulmonary circulation excluded patients with stenosis at origin of MAPCAs, non-uniform supply to lung segments, tortuous MAPCAs, patients with MAPCA dependent pulmonary circulation that cannot entered during catheterization.

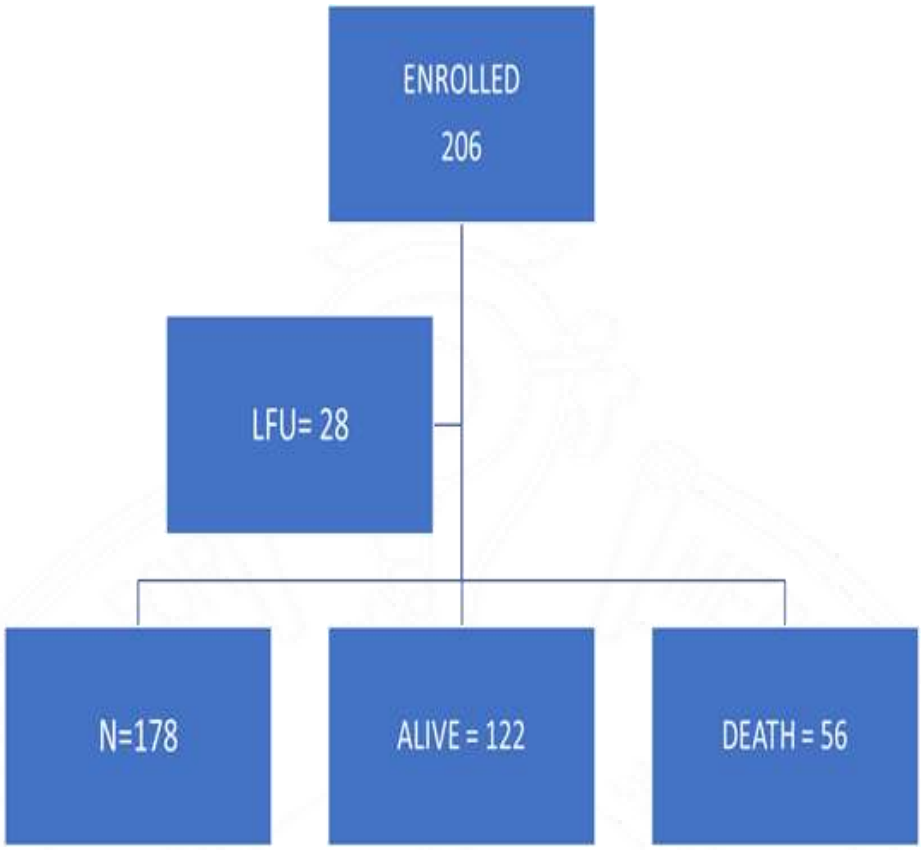
METHODOLOGY

Consecutive patients with clinical and echocardiographic, with or without cardiac catheterization diagnosis of Eisenmenger syndrome were included in study. Shunt lesions classified as pre tricuspid , post tricuspid and Complex defects(6). In complex group Ventricular septal defect with pulmonary atresia and major aorto-pulmonary collaterals (VSD PA MAPCA) were included only when MAPCA originating from aorta supplying entire lung without tortuosity or stenosis at MAPCA origin and cardiac catheterization demonstrated high PVR. Baseline data of old patients were collected from Medical records and follow up data were collected during in hospital visit. Patients were seen during OPD visit or IP admission. Lost to follow up patients were contacted over phone for clinical visit if alive, and enquired about terminal events if not alive. Clinical parameters evaluated includes demographic data , symptoms, cyanosis , clubbing, JVP elevation, cardiomegaly, presence of clinical tricuspid regurgitation , WHO functional class at diagnosis and follow up, Resting oxygen saturation at diagnosis and follow up performed via pulse oximetry or saturation in arterial blood gas analysis , 6-MWT(20) was performed indoors, along a long, flat, straight, enclosed corridor with a hard surface. The walking course was 30 m in length. A starting line, which marks the beginning and end of each lap, marked on the floor using brightly coloured tape. Procedure explained to patient and time was monitored with stop watch. Patients unwilling to do 6MWT and severe functional

limitation (class IV) was excluded. Reported as the distance covered in six minutes in meters. Echocardiographic data including ejection fraction, RV systolic pressure, TAPSE, presence of pericardial effusion ,CATH data including pre and post oxygen mixed venous saturation, Aortic saturation, mean right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, Fick's principle was used for shunt calculation pulmonary vascular resistance (PVR) estimation . If re-catheterization done on sildenafil repeated shunt fraction & PVR also taken. Pulmonary hypertension specific medications (phosphodiesterase-5 inhibitor, Endothelin receptor antagonist) use and compliance also checked. On follow up clinical outcomes evaluated were RV dysfunction, clinical heart failure (according to AHA 2018 criteria(21) for diagnosis of chronic HF in congenital heart disease patients on stage C and D were taken as chronic HF)on follow up, Arrhythmias (documented atrial arrhythmias on ECG or Holter study) , embolic episodes, brain abscess, infective endocarditis , All cause & cause specific mortality.

ANALYSIS

Statistical analysis was done with SPSS v.25.0, Categorical data were displayed as proportions continuous data as mean± standard deviation. Pearson's Chi-square test was used for comparison of discrete variables continuous variable means compared using independent sample t- test and one way ANOVA. The relation between parameters and all-cause mortality assessed with uni- and multivariable time-dependent Cox proportional hazards regression analysis. Survival analysis was done using the Kaplan-Meier method, with inter-group comparison by the log-rank test. ROC analysis was also done for generating cut off values .Propensity matched analysis was done for assessing role disease modifier therapy in survival of Eisenmenger patients. Baseline variables used for propensity matched analysis was age, sex, presence of post tricuspid shunt, Trisomy 21 resting saturation at diagnosis $\leq 85\%$, atrial arrhythmia at diagnosis, clinical heart failure at diagnosis. Match tolerance kept at 0.3, 43 matched pairs(86 patients out of 176 on follow up) taken for Kaplan-Meire survival analysis.



Flow chart showing number of patients enrolled in the study and follow up (LFU, lost to follow up, numbers indicates number of patients)

RESULTS

RESULTS

A total of 206 patients with Eisenmenger syndrome were identified (136 females, 66%). Hemodynamic data confirming systemic pulmonary artery pressure was available for 156 patients, and the remaining 50 patients were judged to have Eisenmenger physiology from clinical assessment and echocardiography. Age of presentation varied from 3 months to 65 years, with mean (SD) age of diagnosis for all patients were 23.4(14.3) years, pre tricuspid shunt 34.16(12.32) years, post tricuspid shunt 20.32(12.1) years and complex defects 10.7(7.6) years. Anatomic lesions based on shunt type were pre tricuspid shunt 71 (34.4%), post tricuspid shunt 98 (47.6%) and complex defect 37 (18%). The most common shunt lesion was atrial septal defect 68 (33%) followed by ventricular septal defect 55(26.6%) and patent ductus arteriosus 34(16.5%), (Figure1 shows percentage of different anatomic lesions).

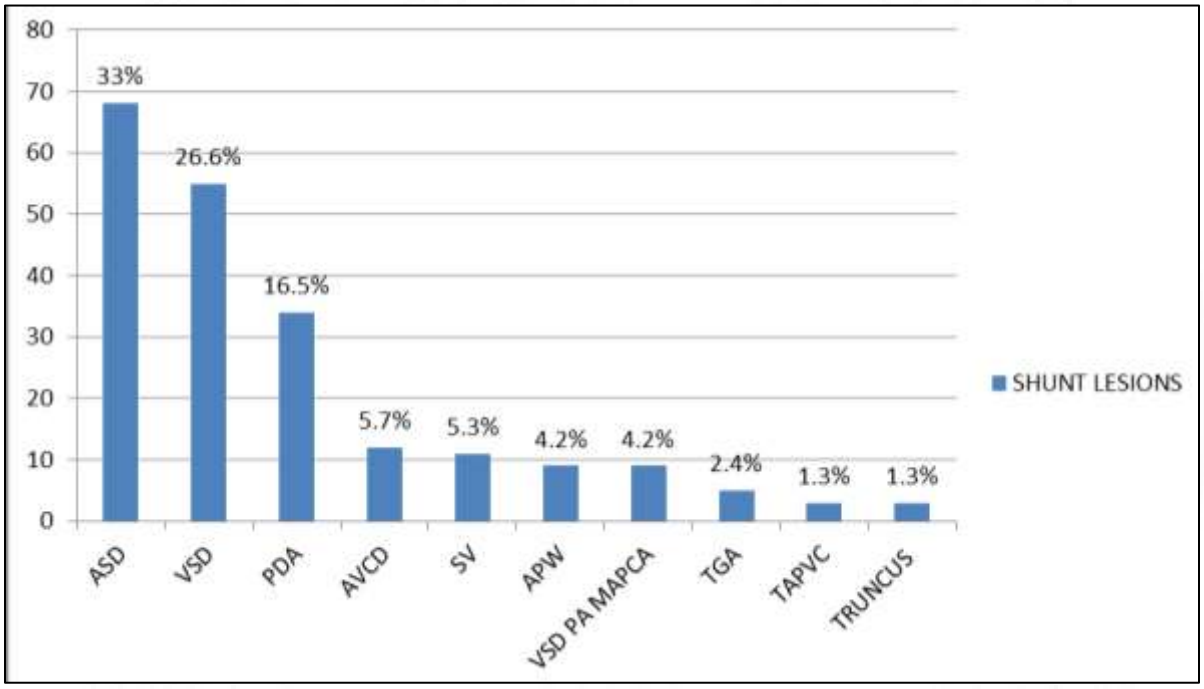


Figure1. Percentage of anatomic lesions in the decreasing order of frequency.Y-axis shows number of patients in each group [ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; AVCD, atrio ventricular septal defect; SV, single ventricle; APW, aorto-pulmonary window; VSD PA MAPCA, ventricular septal defect pulmonary atresia with major aorto-pulmonary collaterals dependent pulmonary circulation with documented elevated pulmonary vascular resistance; d TGA, d-transposition of great arteries; TAPVC, total anomalous pulmonary venous connection; and Truncus Arteriosus].

Effort intolerance, palpitation, hemoptysis, pedal edema and syncope were the common presenting symptoms. Cyanosis present in 64%, clubbing in 62%, Cardiomegaly in 40%, Jugular venous pressure elevation in 23%, Grade II &III right ventricular heave in 64% and tricuspid regurgitation in 21% (Table 1).

Table.1 Frequency & percentages of symptoms and signs in patients with Eisenmenger syndrome.

Effort intolerance	174 (84%)
Palpitation	48 (23%)
Hemoptysis	45 (22%)
Pedaledema	34(17%)
Syncope	23 (12%)
Hyper viscosity symptoms	20(10%)
Angina	20(10%)
Asymptomatic	15 (8%)
Cyanosis	136 (63%)
Clubbing	130 (62%)
Elevated JVP	45(23%)
Cardiomegaly	82(40%)
Grade II & III RV heave	130(64%)

Mean (SD) resting oxygen saturation at the time of diagnosis for all patients was 87.7(6.3) %, pre tricuspid shunt 88.1(5.12) %, post tricuspid shunt 89.6(5.1)% and complex defects 81.7(8.3)%; with lowest resting baseline oxygen saturation noted in the complex group(p=0.001). 171 (83%) patients were in WHO functional class I & II and 35 (17%) in WHO functional class III & IV at the time of diagnosis. Mean (SD) PR interval in electrocardiography was 157.7 (32.5) ms and mean (SD) QRS duration was 102.1(20.8)ms ; atrial arrhythmia was present in10 (5%) patients at the time of diagnosis. In echocardiography mean (SD) Right Ventricular Systolic Pressure (RVSP) was 88.3 (18.3) mmHg, mean(SD) Left Ventricular Ejection Fraction 64.7 (8.1)%,TAPSE 17.9 (2.3)mm and RVID 30.1(19.2)mm. Pericardial

effusion was present in 24 (12%),RV dysfunction in 26 (13 %) and LV systolic dysfunction in 5 (2%) patients at the time of diagnosis.

Cardiac catheterization data was available for 156 patients. Most of the patients underwent cardiac catheterization under local anesthesia except for age less than 12 years in which cardiac catheterization done under general anesthesia .Degree of arterial desaturation was similar in all patient groups except in complex defects with mean resting aortic saturation 81.37±10.7% (p=0.001). Mean right atrial pressure in normal range in all the three major groups with highest mean value in the pre tricuspid shunt 7.2(2.8)mmHg (p=0.45) while mean left heart filling pressure was higher in the post tricuspid shunt 12(2.9)mmHg) (p=0.05). The mean (SD) pulmonary artery mean pressure in all patient group was 72.8(14.2) mmHg with pre tricuspid shunt being the lowest 63.56(12.3) mmHg (p=0.001). Mean (SD) aortic pressure was 85.6(13.4) mmHg. Mean pulmonary vascular resistance was 21.3(10.8) Wood units, with lowest mean PVR in the pre tricuspid shunt 16.9 (7.07) Wood Unit (p=0.001). Lowest shunt fraction was in the post tricuspid shunt 0.9± 0.4 (p=0.047). For demonstrating reversibility 100% oxygen inhalation was used in 92% of patients and inhaled nitric oxide in 14(8%); use of these agents in pulmonary artery did not bring about any significant change in shunt in either direction or in vascular resistance (Table 4).Clinical cyanosis predicted pulmonary vascular resistance ≥10 Wood Units with 95% sensitivity and 87% specificity. 7 patients who had re catheterization after a mean duration of 3.5 months of phosphodiesterase-5 inhibitor therapy showed mean (SD) pulmonary vascular resistance of 15.1(5.3) Wood Units and mean(SD)shunt fraction of 0.9(0.3). As compared with baseline pulmonary vascular resistance, phosphodiesterase-5 inhibitor therapy group showed median decline in the pulmonary vascular resistance of 5.4 Wood Unit. No patient become operable after sildenafil therapy who had PVR more than 10 WU on basal study. Significance was not checked in view of low numbers in post phosphodiesterase-5 inhibitor therapy group. Previous studies also showed similar hemodynamic findings(16).

Table 2 Catheterization data (values at the time of diagnosis) includes oximetry & pressure

	Baseline	Post 100% oxygen
Mean mixed venous oxygen saturation, %	65.5± 7.3	73.9±8.4
Mean Aortic oxygen saturation, %	88.3± 7.1	96.7±5.7
Mean RA mean, mmHg	6.9± 2.8	7±2.7
Mean RVED, mmHg	9.3±3.1	
Mean PA mean pressure ,mmHg	72.8± 14.2	74.2± 22.6
Mean PCWP, mmHg	10.2 ± 4.2	
Mean Qp/Qs	0.9± 0.4	1.3± 0.7
Mean PVR	21.3± 10.8	15.4± 8.8
Re cath PVR	15.1±5.3	9.1±4.2
Re cath Qp/Qs	0.9±0.3	1.4±0.9

Patients were followed up for a median duration of 6 years (1.5-11.5 years). Follow up data included mean(SD) resting saturation of 85.8(7.3)% as compared to 87.7(6.3)% at diagnosis(p=0.001).Significant desaturation on follow up was noted in all patient groups. Number of patients with WHO functional class I & II was 171 (83%) at the time of diagnosis which decreased to 108 (60%) on follow up. Number of patients with WHO functional class III and IV was 35 (17%) at the time of diagnosis increased to 70 (40%) on follow up (p=0.001). There is significant change in functional class noted among all patient group (Table.3). Mean (SD) 6 MWT distance in meters was 310.3(75.6), with significant difference in the post tricuspid lesions 349(52.6) m as compared with pre tricuspid shunt 251.4(10.7)m and complex defects 252.7(85.9)m (p=0.001). Baseline values of six minute walk test were not available for comparison. NT-Pro BNP values were available in 76 patients. Median NT-Pro BNP level was 645 (84.5-2325) pg/mL. Mean hemoglobin level at diagnosis was 16.1± 2.64 (9.7-25) mg/dL and at follow up was 18.1± 2.7 mg/dL (p=0.001) and Mean Packed Red Cell Volume at diagnosis was 49.6 ± 8.4% (31-78) and at follow up was 54.6 ± 9.7(p=0.001) increase in haemoglobin level could indicate increased erythropoiesis in response to progressive worsening of hypoxia.

Table 3 Comparison of saturation and WHO functional class at baseline and follow up			
	Baseline	Follow up	P value
Resting systemic saturation, %	87.7± 6.3	85.8± 7.3	0.001***
WHO Functional Class I&II	171(83%)	108(60%)	0.001**
WHO Functional Class III&IV	35 (17%)	70 (40%)	
** Pearson's Chi square, *** one way ANOVA			

136 (76%) of total patients received disease modifier therapy (Table 4)(figure 2). 28.6 % received dual therapy (Phosphodiesterase-5 Inhibitor and Endothelin Receptor Antagonist) , 48% oral iron therapy ,46% digoxin, 47% diuretics , 5% ACEI/ARB, 5% beta blocker , 10% anti platelets and 17% anticoagulation therapy (given for arrhythmias and pulmonary thrombosis).9% Antiarrhythmic therapy .Home oxygen therapy was given for 4(2%) patients . Phlebotomy needed in 80(45%) patients. In pre tricuspid shunts 75% patients received disease modifier therapy among that 32.7% patients received dual therapy. In post tricuspid shunts 87.5% patients received disease modifiers out of which 30.6 % patients received dual therapy. In complex defects 45% received disease modifiers with17 % of patients in dual therapy. Significantly lower proportion of patients were not in disease modifier therapy in the complex group (p=0.003) (figure .2).

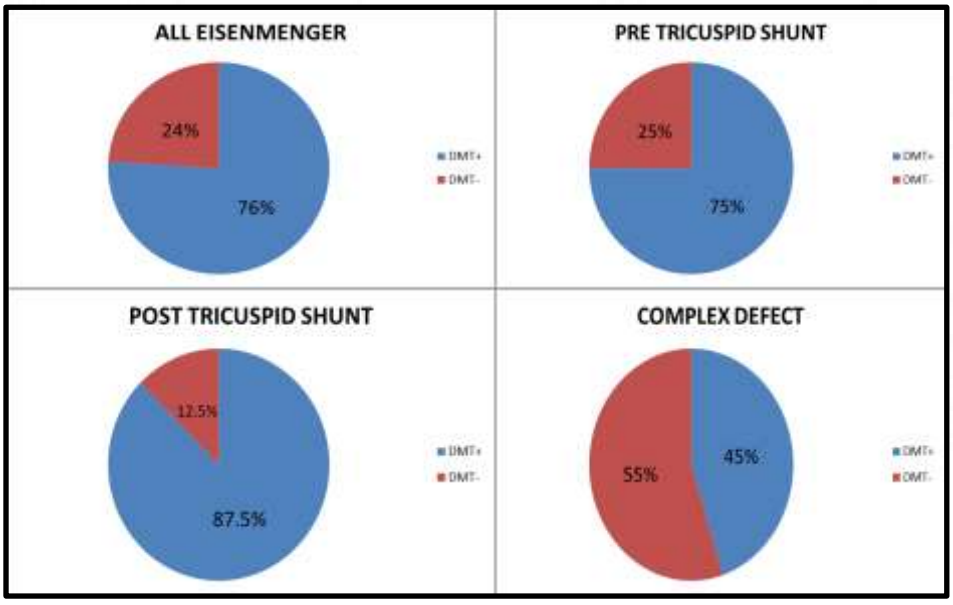


Figure 2. showing distribution of disease modifier therapy in all patients and across shunt types.

Complications observed during follow up (Table 4) were RV dysfunction in 66 (32%); predominantly in the pre tricuspid shunt (p=0.001). 59% of patients in pre tricuspid group & 41% of patients in complex group developed RV dysfunction (p=0.001).LV systolic dysfunction was present in 19 (10%)(p=0.12), Atrial arrhythmia at the time of diagnosis in 5% and on follow up 14% (p=0.001) showed significant atrial arrhythmia burden on follow up. Atrial fibrillation seen in 11 patients, Atrial flutter in 9 patients, 3 patients developed complete heart block and 1 patient had ventricular tachycardia (figure 4). 30% of patients in pre tricuspid group developed atrial arrhythmia on follow up(p=0.001). Mean age of onset of atrial arrhythmia in pre tricuspid group was 43.56± 8.9 years.

Pulmonary thrombosis occurred in 8(5%), Stroke/ Peripheral arterial embolism in 8(5%), brain abscess in 13 (7%) of total patients .17% patient in complex defect developed brain abscess (p=0.21),infective endocarditis seen in 4 (2%) seen only in post tricuspid group, 69 (39%) of total patient were in congestive heart failure on follow up 60% of patients in pre tricuspid and 55% of patients in complex group were in clinical heart failure on follow up while only 18% of post tricuspid patients were in clinical heart failure (p=0.001).

56 (31.5%)patients died during follow up (Table 4), 44.8 % of patients in complex group and 44.2 % of patients in pre tricuspid shunt had mortality while 18% of patients in post tricuspid lesion had mortality (p=0.001). Mean (SD) age at death in all patient group was 33.4(15.1) years ,42(12.4) years in pre tricuspid shunt , 32.5(12.4) in post tricuspid shunt, 17.4(8.2) years in the complex group(p=0.001).Causes of death (figure 3)was predominantly heart failure in 59%, hemoptysis 16%, pneumonia and other infections in 14%, and sudden cardiac death in 11%.

Table 4. Different clinical parameters in all Eisenmenger patients and based on shunt type.

	All ES patients	Pre tricuspid	Post tricuspid	Complex defects	P value
N,% of total	206(100%)	71(34%)	98(48%)	37(18%)	
Females , N & % with in defect	136(66%)	51(72%)	63(64%)	22(59%)	
Mean age at diagnosis, years	23.4±14.3	34.16±12.3	20.32±12.1	10.7±7.6	0.001***
Mean follow up duration, months	85.2±75.3	66.07± 62.5	100.4± 70.3	80.5± 86.21	
Mean resting saturation,% Baseline	87.7± 6.3	88.08± 5.12	89.6± 5.1	81.7±8.3	0.001***
Mean resting saturation%,Followup	85.8± 7.3	85.96± 6.4	87.6± 7.2	79.1±7.1	
WHO functional class III/IV Baseline , N & % with in defect	37 (18%)	19 (31%)	10 (11%)	8 (27.5%)	0.016**
WHO functional class III/IV Follow up, N & % with in defect	70 (40%)	38 (62%)	19(21.5%)	13(45%)	
Trisomy 21, N & % with in defect	11(5%)	1 (1.4%)	3(3%)	7 (19%)	0.002**
RV dysfunction	66(38%)	36 (59%)	18(20%)	12(41%)	0.001**
Atrial arrhythmia	25(14%)	18(29.5%)	3(3.4%)	4(14%)	0.001**
Mean age of onset atrial arrhythmia,years	38.6 ± 12.9	43.56± 8.9	36± 12.2	18.2±5.6	0.001***
Pericardial effusion	24(13%)	13(21%)	9(10.2%)	2(7%)	0.17**

6 MWT, meters	310.3±75.6	251.4±10.7	349±52.6	252.7±85.9	0.001***
Mean Aortic oxygen saturation, %	88.3± 7.1	89.5±5.3	89.73±5.5	81.37±10.7	0.001***
Mean PA mean pressure ,mmHg	72.8± 14.2	63.56±12.37	79.27±14.1	73.3±10.55	0.001***
Mean PCWP, mmHg	10.2 ± 4.2	9.5±4.9	12±2.9	9.4 ±3.3	0.05***
Mean Qp/Qs	0.9± 0.4	1.06± 0.32	0.9±0.4	1.01±0.5	0.049***
Mean PVR	21.3± 10.8	16.9±7.07	24.8±12.2	20.9±9.9	0.001***
Mono/Dual DMT	136 (76%)	46(75%)	77(87.5%)	13(45%)	0.003**
Dual drug therapy	52 (27%)	20 (32.7%)	27(30.6%)	5(17%)	0.217**
Phlebotomy	77(45%)	29 (49%)	31(36%)	17 (58%)	0.067**
Pulmonary thrombosis	8 (5%)	3(5%)	4(4.5%)	1(3.4%)	0.16**
Stroke / peripheral arterial embolism	8 (5%)	4(6.5%)	3(3.4%)	1(3.4%)	0.71**
Brain abscess	13(7%)	3(5%)	5(6%)	5(17.2%)	0.21**
Infective endocarditis	4(2%)	0	4(4.5%)	0	0.112**
HF on follow up	69(39%)	37(60%)	16(18%)	16(55%)	0.000**
All cause mortality	56(31.5%)	27(44.2%)	16(18%)	13(44.8%)	0.001**
Mean age of death, year	33.5± 15.1	42± 12.4	32.5±12.4	17.4±8.2	0.001***
Lost to follow up	28 (13.5%)	10 (14%)	10(10.2%)	8 (21.6)	
*t-test,** Pearson's chi square,*** one way ANOVA					

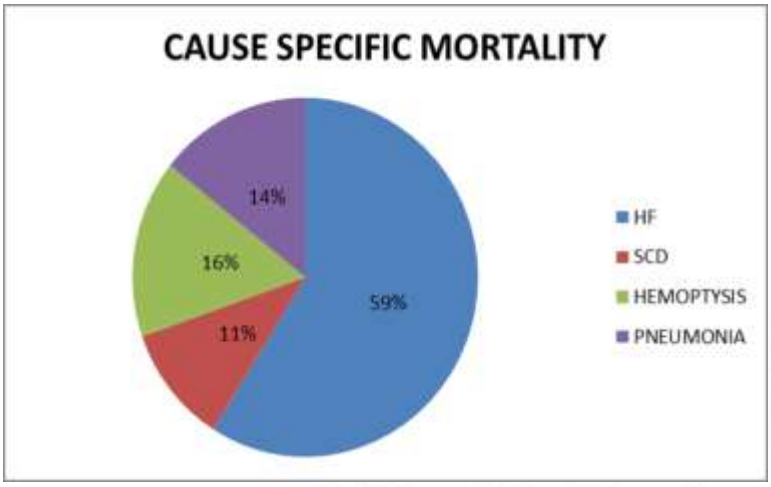


Figure 3.Cause specific mortality showing percentage of total deaths (HF- Heart failure, SCD-Sudden cardiac death)

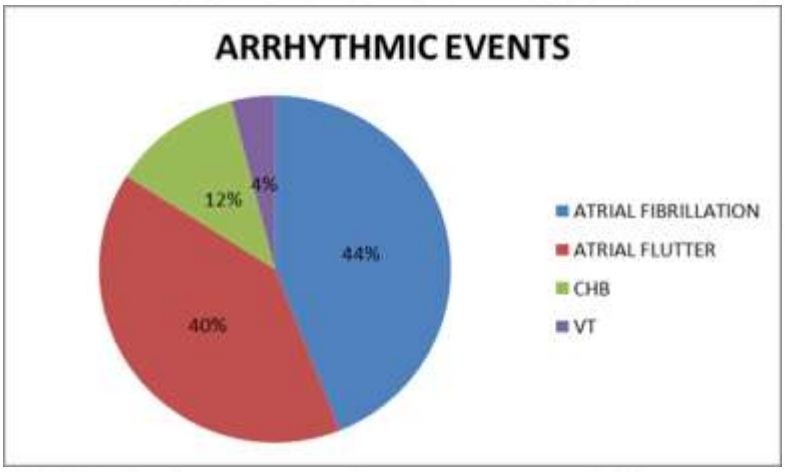


Figure 4. Arrhythmic events in the all Eisenmenger patients with percentage of individual arrhythmias.(CHB –complete heart block, VT- ventricular tachycardia)

The proportion of patients whose functional class deterioration on follow up was lower in the group that received any disease modifier therapy(Table 5) .Monotherapy (PDE,5I or ETA alone) or dual therapy (PDE,5I & ETA) were less likely to have WHO functional class deterioration on follow up (30/43 patients deteriorated from I/II to III/IV who were not on DMT compared to 43/135 deteriorated from I/II to III/IV who were on DMT; p=0.001)(figure 5), mean saturation difference on follow up were not significant (1.62% in patients received DMT as compared to 2.11% in treatment naïve; p=0.612) as compared to treatment naïve .Disease modifier therapy is associated with significant mortality reduction 27/43(62.7%) treatment naïve patients vs 29/135(21.4%) patients on disease modifier therapy (p=0.001). More treatment naïve patients died on follow up.

Table 5. Disease modifier therapy comparison pre and post treatment				
Disease modifier therapy (mono/dual)		mean difference	p value	CI
WHO FC on follow up I&II TO III&IV	30/43 (DMT-)			0.18-2.13
WHO FC on follow up I&II TO III&IV	43/135 (DMT+)		0.001**	
Resting SPO2 on follow up,%	87.35 ± 6.2	DMT+=1.62 DMT-=2.11	0.612**	-1.4 - 2.38
Mortality	29/135DMT+ 27/43 DMT-		0.001**	

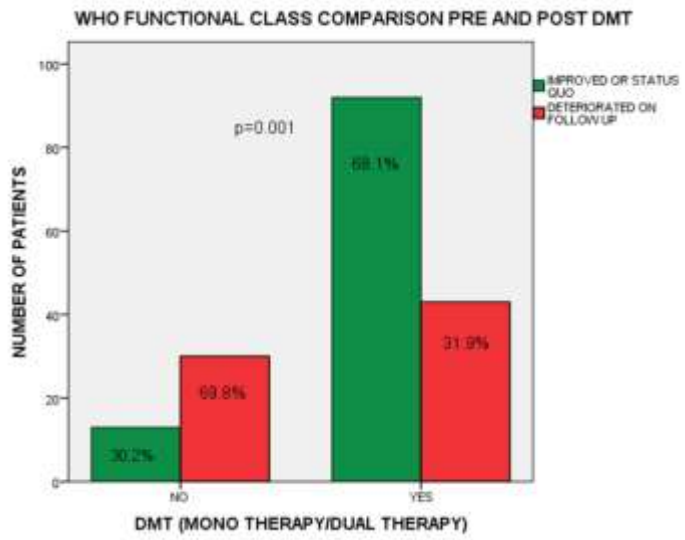


Figure 5 .Comparison of WHO functional class pre and post disease modifier therapy (DMT)

The proportion of patients whose functional class deterioration on follow up was lower in the group that received dual disease modifier therapy as compared to monotherapy (12/51 deteriorated from I/II to III/IV on dual therapy compared to 60/84 deteriorated from I/II to III/IV who were on mono therapy ; p=0.003)(figure 6), mean saturation difference on follow up between groups were 1.35% in patients received dual therapy as compared to 1.89 in patients received mono therapy (p=0.552). Comparing mono and dual disease modifier therapy 3 out of

51 patients on dual therapy compared to 26/84 patients on mono therapy (p=0.001) died during variable follow up period. Dual therapy compared with mono therapy shows significant less number of mortality but mean follow up duration for dual therapy was significantly less compared with mono therapy hence require more follow up duration of dual therapy to make a conclusion on mortality benefit .

Table 6. Dual therapy comparison pre and post treatment

Dual Therapy(PDEI + ETA therapy)		mean diff	p value	CI
WHO FC on follow I&II TO III&IV	60/84 (dual -)		0.003**	
WHO FC on follow I&II TO III&IV	12/51 (dual +)			
Resting SPO2 on follow up,%	88.4± 3.7	1.89 (dual -) 1.35 (dual+)	0.552*	-1.2- -2.3
Mortality	26/84 (dual -) 3/51 (dual+)			0.001**

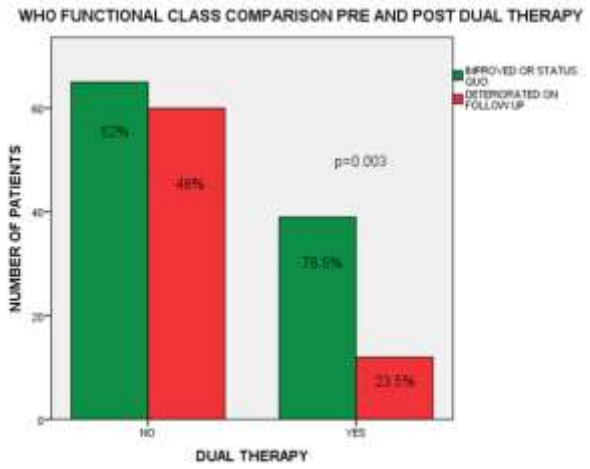


Figure 6 .Comparison of WHO functional class pre and post dual disease modifier therapy

Survival Analysis

For the entire patient population the actuarial survival by Kaplan meier analysis showed at the end of 1 year, 3 years, 5years and 10 years and 20 years was 96%, 89%, 85%, 77%, and 69%respectively (Fig.7).

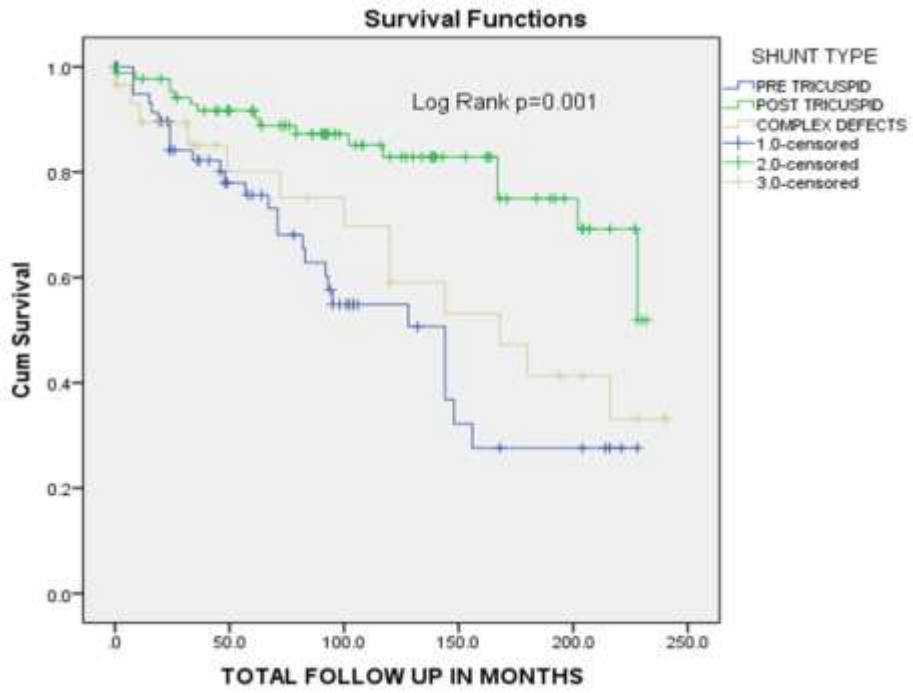


Figure7. Survival curve of Eisenmenger patients based on shunt type .

For the patients with pre tricuspid level shunts the actuarial survival(table7) at the end of 1 year, 3 years, 5 years and 10 years and 20 years were 95%, 84%, 79%, 65% and 55% respectively. For patients with post tricuspid level shunt the values were 98%, 92%, 89%, 87% and 82% respectively. For patients with complex lesions, the values were, 91%, 86%, 79%, 68% and 53% respectively. Log rank test showed significant difference in survival in post tricuspid compared to pre tricuspid (log rank p=0.001) and complex lesions ((log rank p=0.018) .There is no significant difference in survival between pre tricuspid and complex lesions (log rank p=0.371).

Table 7. Survival pattern of all Eisenmenger syndrome, across shunt types and Trisomy21					
	1 year	3 year	5 year	10 year	20 year
ALL EISENMENGER SYNDROME	96%	89%	85%	77%	69%
PRE TRICUSPID	95%	84%	79%	65%	55%
POST TRICUSPID	98%	92%	89%	87%	82%
COMPLEX DEFECTS	91%	86%	79%	68%	53%
TRISOMY 21+	90%	82%	73%	46%	36%

For patients with Trisomy 21 survival was,90%, 82%, 73%, 46% and 36% respectively. Log rank test showed significant difference in survival in Eisenmenger syndrome patients with and without trisomy 21 (log rank p=0.001) (figure 8) .

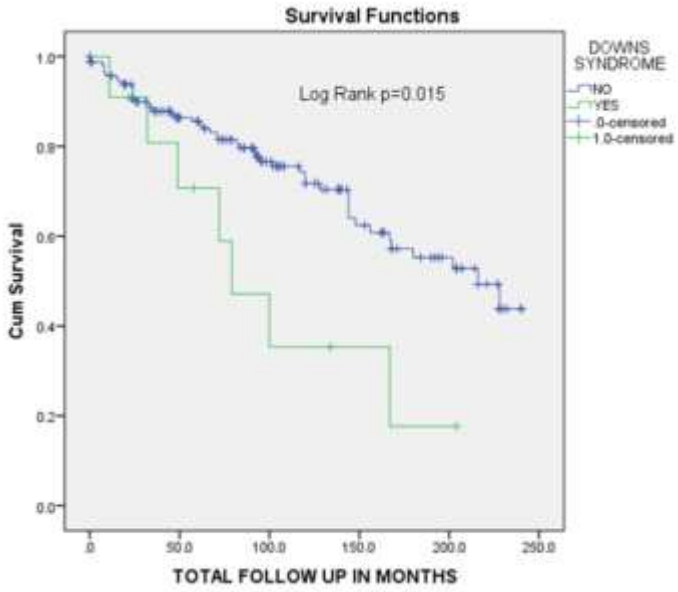


Figure 8. Survival curve of Eisenmenger patients with and with out Trisomy 21.

Unadjusted Kaplan Meier analysis (figure 9) showed disease modifier therapy received patients associated with better survival as compared with patients who did not receive DMT. 5 year,10 year survival was 91% and 85% respectively in DMT received patients as compared to 66 and 52% respectively in treatment naïve patients.

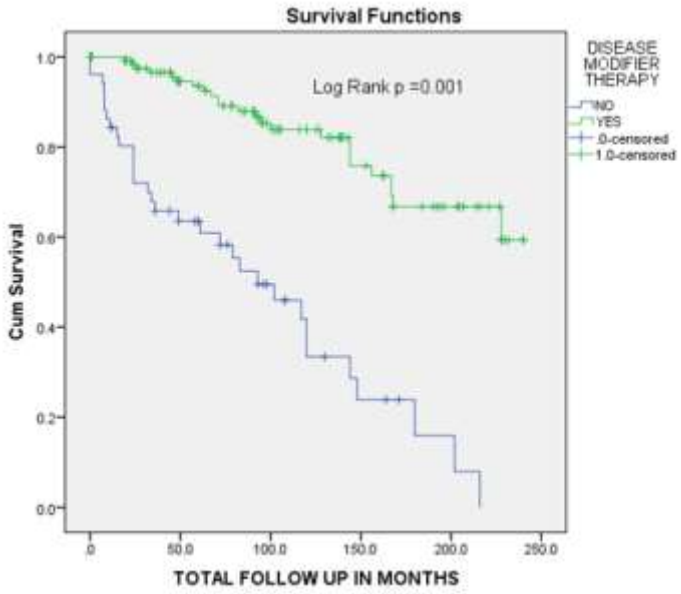


Figure 9. Unadjusted survival analysis of Eisenmenger patients with and with out Disease modifier therapy.

Propensity score regression adjustment for baseline clinical differences showed survival benefit of disease modifier therapy (figure). Survival at 5 years 10 years and 15 years in treatment group was 84%, 69%, 64% where as 66%, 44%, 31% in treatment naïve group.

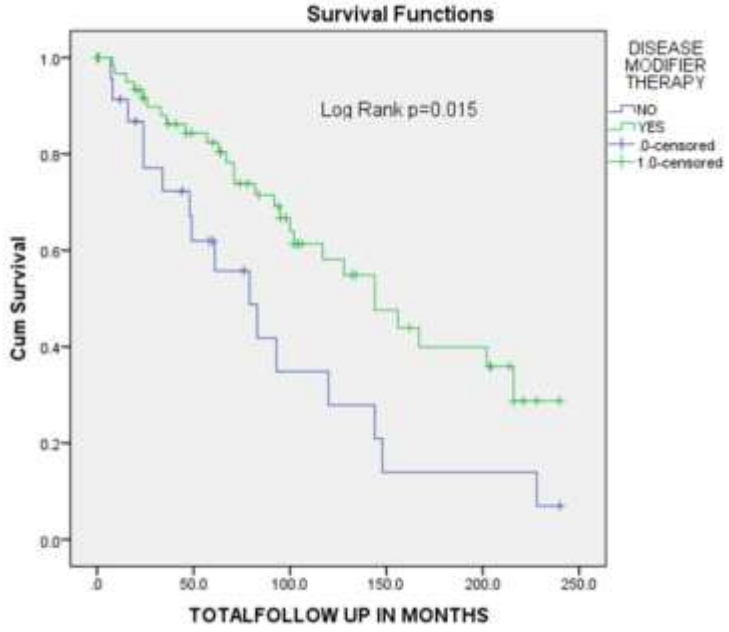


Figure 9. Kaplan meier survival curve post propensity score regression adjustment for baseline clinical differences in Eisenmenger patients with and with out Disease modifier therapy.

A Cox univariate logistic regression was performed in the total population 13 clinical variables selected as predictors for mortality included, Pre tricuspid shunt (p=0.001), Systemic saturation ≤85% (p= 0.001),Mean mixed venous oxygen saturation ≤62 % (p=0.001),Mean aortic saturation, %, ≤ 85% (p=0.001) these baseline clinical parameters showed correlation with mortality.

Atrial arrhythmias(p=0.001),RV dysfunction (p= 0.001),WHO functional class III/IV up(p=0.000),Clinical heart failure (p=0.001),Embolic episodes(p= 0.01),Pericardial effusion (p=0.001),Use of disease modifier therapy,(p= 0.001,HR = -1.72),Mean Systemic saturation ≤ 80% (p=0.001),TAPSE ≤16 mm (p=0.001) these follow up variables found correlating with mortality.

In cox multivariate logistic regression showed predictors for mortality as, Mean Systemic saturation ≤ 80% (95% sensitive and 65% specific for mortality), presence of atrial arrhythmias, Use of disease modifier therapy .

Table 8. Uni- variate Cox Regression Analysis		
Pre tricuspid shunt	0.001**	
Systemic saturation ≤85% at diagnosis	0.001**	
Atrial arrhythmias	0.001**	
RV dysfunction	0.001**	
WHO FC III/IV on follow up	0.000**	
Clinical HF on follow up	0.000**	
Embolic episodes	0.01**	
Pericardial effusion	0.001**	
PAH specific medication (PDE-5 I/ETA)	0.001**	
Uni- variate Cox Regression Analysis	**CI**	**P value**
Mean resting saturation on follow up ≤ 80%	-12.1- -7.2	0.001*
TAPSE ≤ 16mm	-3.2- -1.77	0.001*
Mean mixed venous oxygen saturation,% ≤62%	-8.1- -2.9	0.001*
Mean aortic saturation, ≤ 85% at diagnosis	-7.1- -2.3	0.001*
Mean PA mean pressure ≥ 70 mmHg	-11.8- -6.1	0.030*

Multivariate cox regression analysis	P value	CI	
Resting systemic saturation ≤ 80 % on follow up	0.001	0.68-0.93	**R square - 0.632**
Atrial arrhythmia	0.001	1.01-2.39	
Use of PAH specific medication (HR: -1.72)	0.001	0.23- 0.38	

DISCUSSION

DISCUSSION

In our study that included 206 Eisenmenger syndrome patients, showed female preponderance of 66% comparable to other studies(Table. 9).Mean(SD) age at diagnosis was 23.4(14.3) years which was lower compared to western studies where mean age at diagnosis was 34.5 years (10,11,17). This observation may be due to high prevalence of post tricuspid lesion and complex lesion in our cohort in which mean age of diagnosis was less. Predominant shunt type was post tricuspid shunt. Most common anatomic lesion was atrial septal defect; this observation was different compared with other studies where VSD was most commonly seen except in Dimopaulos et al(10) in which complex lesions were predominant. High prevalence of ASD in our study may reflect referral bias to an adult congenital heart disease unit. Effort intolerance was the most predominant symptom; (84%) with high occurrence in pre tricuspid lesions (91%) compared to post tricuspid shunts (83%) and complex defects (84%). Hemoptysis seen in all three groups with higher frequency in the complex group along with hyperviscosity symptoms. Hemoptysis can be due to extensive systemic-to-pulmonary collateralisation that has developed as a compensatory mechanism to provide pulmonary blood flow(22) and higher degree of hypoxemia contributing to hyperviscosity symptoms. Syncope was common in post tricuspid group, palpitations were more common in pre tricuspid group. Saha et al(5) showed almost equal prevalence of dyspnoea and effort intolerance in all three major subgroups. In our study Cyanosis was in 64% , clubbing in 62%, Cardiomegaly in 40%, Jugular venous pressure elevation in 23%, Grade II&III right ventricular heave in 63%, tricuspid regurgitation in 21% . In Saha et al(5) study Cyanosis in 67%, Clubbing in 61.2%, JVP elevation in 17.4%, right ventricular heave in 78%, and tricuspid regurgitation in 15%. Difference in prevalence of tricuspid regurgitation due to predominant anatomic lesion was atrial septal defect in current study. Total Trisomy 21 patients was 5% in current study which was significantly lower as compared to western studies in which prevalence was 30-35%(11-13). Significant increase in haemoglobin level noted during follow up could indicate increased erythropoiesis in response to progressive worsening of hypoxia. Median follow up duration was 6years (1.5-11.5 years). Follow up duration comparable to western studies.

Current study shows that all Eisenmenger patients shows significant decline in resting systemic saturation and deterioration in functional class on long term follow up. The proportion of patients whose functional class deterioration on follow up was lower in the group that

received any disease modifier therapy. Monotherapy or dual therapy were less likely to have WHO functional class deterioration on follow up .The randomized, placebo-controlled trial BREATHE-5 demonstrated a moderate improvement in functional capacity with Bosentan compared with placebo in patients with ES and functional class III or IV(23). Post tricuspid lesion had greater walk distance compared to pre tricuspid and complex defects. Significant number of patients developed RV dysfunction in the pre tricuspid lesion though pulmonary vascular resistance was low in invasive hemodynamic study in this group compared to post tricuspid and complex lesions attributable to the development of pressure overload to a volume overloaded RV in pre tricuspid lesions (24). High atrial arrhythmia burden also noted in pre tricuspid lesions attributable to right atrial dilation and scarring(25) . Mean age of onset of atrial arrhythmia was also higher in pre tricuspid lesions. Pre tricuspid shunt lesions having high proportion of arrhythmic events, clinical heart failure on follow up and mortality as compared to other shunt types. Disease modifier therapy received in 76% of total patients , Dual therapy received by 28.6% these numbers comparatively low with western studies where 36.9%-57.5%(11,17,18) . Beta blockers and angiotensin converting enzyme inhibitors were received by 4%-5% of patients ;low number likely to reflect the lack of evidence for a beneficial effect of these therapies in this cohort as well as the apprehension that these drugs may induce systemic vasodilation with a subsequent increase in right-to-left shunt(25) and hypotensive effect of these medications preclude use of optimal dose of disease modifiers(17). Lower proportion of patients in complex group received disease modifier therapy this may reflect the lack of evidence for benefit of disease modifier treatment in complex congenital heart disease and concern regarding safety of these medication in children (6) .

Survival and Predictors of death

Compared with the general population, life expectancy in contemporary patients with Eisenmenger physiology is reduced by 20 years and the mortality risk is increased 3.8-fold (25). Despite this, short-term mortality is relatively low (12.5% at 5 years). Survival prospects in Eisenmenger patients are better than previously appreciated and are far superior to those observed in patients with primary pulmonary hypertension(26).In our study survival at 1 year, 3 years, 5years and 10 years and 20 years was 96%, 89%, 85%, 77%, and 69%respectively indicating good intermediate survival in Eisenmenger patients this result is similar with Saha study (5). Survival prospects were significantly poorer in patients with pre tricuspid lesion and

complex defects where 20 year survival post diagnosis is nearly 50% when compared with those with post tricuspid lesions with 70% survival at 20 years. Patients with trisomy 21 only 50% of patients survived after 10 years indicates poor intermediate term survival in this cohort. Unadjusted survival analysis showed that patients on disease modifier therapy compared to treatment naïve patient was associated with better survival. Propensity score regression adjustment for baseline clinical differences showed survival benefit of disease modifier therapy. Survival at 5 years 10 years and 15 years in treatment group was 84%, 69%, 64% where as 66%, 44%,31% in treatment naïve group. In a single-centre study including 229 patients, the group taking disease modifier therapy had a significantly lower mortality rate by unadjusted analysis, and after propensity score regression adjustment for baseline clinical differences (10).In 153 patients with ES included in the German CHD registry, survival rates in treatment-naive patients were 86%, 60% and34% after 1, 5 and 10 years, and were lower than in patients taking disease modifier therapy (17). In a multicentre, retrospective, inter-national cohort including 1098 patients with ES, disease modifier therapy was associated with a better outcome in the univariate analysis, but the association was lost in the multivariable model(11).Most common cause of death was heart failure in our study followed by hemoptysis and sudden cardiac death. In Paul wood series most common cause was hemoptysis (29%),surgical repair in (26%), heart failure in (17%) and sudden cardiac death(14%). In Saha et al(5) sudden cardiac death which accounted for nearly one-third (30%),followed by heart failure(25%) ,Diller et al(25) study most common cause of death was sudden death (55%) followed by heart failure(45%).In Hascoet et al (18)most common cause of death was heart failure (25.4%) followed by infection(17.6%) and SCD10.5%. studies done in disease modifier therapy era prevalence of heart failure detection and mortality due to heart failure showed increasing prevalence (27).In Multivariate cox regression analysis showed resting saturation ≤ 80%, presence of atrial arrhythmia, and disease modifier therapy associated with mortality. Saha et al (5) showed that syncope ,mean RAP>8 mmHg spo2 <85% are the predictors of mortality .Oxygen saturation was a predictor of outcome in ES in our study as in previous studies (5,11,25).Low oxygen saturation reflects the extent of right-to-left shunting, and low cardiac output and advanced stage of pulmonary vascular disease. History of atrial arrhythmia predicted mortality in previous studies(8) but antiarrhythmic therapy did not show any mortality reduction in the study (25) similar findings also noted in our study.

Table 9. Comparison of data; current study with important existing studies .

	Present study (n=206)	Saha et al (n=201) 1996	Kempny et al (n=1026)	Diller et al (n=153)	Dimopoulos et al (n= 229)	Hascoet et al N=340
Female	66%	54.2%	65.1%	45.8%	56%	69.4%
Mean age at diagnosis , years	23.4±14.3	19.23 ± 12.62	34.4 (25.0–45.3)	34.0+13.3	34.5 ± 12.6	26.5 [11.9—39.7]
Median follow up	6 years(1.8-11.5)	4.5 years	3.1 years (1.–5.9)	5years(1.5-9.3)	4.0 years	
shunt lesion Pre/post/complex	Post tri 47.6% ASD (33%) 34.4/47.6/18	VSD (33.3%)	Post tricuspid 58.6/28.8/12	VSD (66%)	Complex anatomy 56.5%	Post tricuspid 75% VSD 30%
Trisomy 21+	11 (5%)		31.9%	32.7%		35%
SpO2%	87.7±6.3	85.4%	85 (80–90)	81.2+8.9	84.3%.	85 [81—90]
WHO FC I/II	60%		51%	40%	49%	55-60%
WHO FC III/IV	40%	70%	49%	60%	51%	40-45%
Hemoptysis	22%	17%				13%
syncope	12%	7.5%				
Mean 6 MWT	310		360	380	348	
Atrial arrhythmias	14% (AF)		6% (AF)			16%
No therapy	24%					19%
Single therapy	47.4%					46.7%
Dual Therapy	28.6%		36.9%	57.5%	30%	40.9%
HF	39%	18%		31%		23%
mortality	31.5%	10%	27%	30%	23% (2/52)	
Mean age of death ,years	33.4± 15.1	25.2± 11.67				41.8 years [30.9—49.0

cause of mortality	HF(59%), Hemoptysis (16%), (SCD 11%)	SCD(30%), HF (25%)				HF(25.4%),infection(17.6%)SCD10 .5%
Mortality predictor	Spo2 <80%, atrial arrhythmia, DMT	syncope ,mRAP>8 mmHg spo2 <85%	Low spo2, Age, PrT, SR, PE	Low spo2, use of DMT	Patients on advanced therapy showed significantly lower risk of death	WHO FC III/IV, lower SpO2 and pre tricuspid defect and one or two disease modifier therapy
Survival	Good intermediate & pre tricuspid poor long term survival.	Good intermediate & No difference PrT vs PoT	5 year Survival lowest in pre tricuspid shunts	Better survival with mono/dual therapy x Tx naïve	Survival benefits of AT over Tx naïve group	one or two disease modifier therapy with low risk for mortality.
Tx –Treatment, PrT –pre tricuspid shunt, PoT-post tricuspid shunt, AT- Advanced therapy, SCD- sudden cardiac death,HF- heart failure .						

STUDY LIMITATION

STUDY LIMITATION

1. Retrospective, nonrandomized, single-center study representative of a tertiary adult congenital heart disease referral unit specialized in management of PAH patients.
2. Our study population was heterogeneous in terms of both defect location and calendar years of diagnosis and management.
3. Catheterization data available only at baseline so hemodynamic effects of disease modifier therapy could not assessed.
4. No distinction between specific types and dosages of DMT was made in this study.
5. Further studies are needed to validate our results and to explore the impact of disease modifier therapy on survival in Eisenmenger patients.
6. Cause specific mortality data may not be accurate as telephonic enquiry was used.

CONCLUSION

CONCLUSION

1. Eisenmenger Syndrome patients having good short and intermediate term survival, though long term survival is not good.
2. Pre tricuspid shunt lesions having significantly high arrhythmic events, heart failure and mortality among different shunt types.
3. Survival patterns of pre tricuspid shunt and complex defects are similar. Post tricuspid shunt having better survival as compared to other shunt types.
4. Disease targeted therapy associated with improved functional class and better survival compared to treatment naïve patients.
5. Resting systemic saturation ≤ 80% and presence of atrial arrhythmias, use of disease modifier therapy predicts mortality**.**

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BIBLIOGRAPHY

1. Kammerschieidewand EVD angeborenens D der, 1897; des HZKMS, L-28. 32: No Title.
2. Bing RJ VLGFP studies in, Of congenital heart disease ~ results obtained in five cases, Eisenmenger's complex. John Hopkins Hosp Bull 1947;, 323-347. 80: No Title.
3. Cases BVJE complex. R of two, 1951; and review of cases with autopsy study. AHJ, 424-435; No Title.
4. Wood P. The Eisenmenger Syndrome or Pulmonary Hypertension with Reversed Central Shunt. Br Med J. 1958;2(5099):755.
5. Saha A, Balakrishnan KG, Jaiswal PK, Venkitachalam CG, Tharakan J, Titus T, et al. Prognosis for patients with Eisenmenger syndrome of various aetiology. Int J Cardiol. 1994;45(3):199–207.
6. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J [Internet]. 2015;46(4):903–75. Available from: http://dx.doi.org/10.1183/13993003.01032-2015
7. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, et al. Eisenmenger syndrome. Factors relating to deterioration and death. Eur Heart J. 1998;19(12):1845–55.
8. Cantor WJ, Harrison DA, Moussadji JS, Connelly MS, Webb GD, Liu P, et al. Determinants of survival and length of survival in adults with Eisenmenger syndrome. Am J Cardiol. 1999;84(6):677–81.
9. Oya H, Nagaya N, Uematsu M, Satoh T, Sakamaki F, Kyotani S, et al. Poor prognosis and related factors in adults with Eisenmenger syndrome. Am Heart J. 2002;143(4):739–44.
10. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, et al. Improved survival among patients with eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation. 2010;121(1):20–5.
11. Kempny A, Hjortshøj CS, Gu H, Li W, Opotowsky AR, Landzberg MJ, et al. Predictors of Death in Contemporary Adult Patients with Eisenmenger Syndrome: A Multicenter Study.

Circulation. 2017;135(15):1432–40.

12. Diller GP, Alonso-Gonzalez R, Kempny A, Dimopoulos K, Inuzuka R, Giannakoulas G, et al. B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: Predictive value and response to disease targeting therapy. Heart. 2012;98(9):736–42.
13. Montani D, Chaumais MC, Guignabert C, Günther S, Girerd B, Jaïs X, et al. Targeted therapies in pulmonary arterial hypertension. Pharmacol Ther [Internet]. 2014;141(2):172–91. Available from: http://dx.doi.org/10.1016/j.pharmthera.2013.10.002
14. Van De Bruaene A, De Meester P, Voigt JU, Delcroix M, Pasquet A, De Backer J, et al. Worsening in oxygen saturation and exercise capacity predict adverse outcome in patients with Eisenmenger syndrome. Int J Cardiol [Internet]. 2013;168(2):1386–92. Available from: http://dx.doi.org/10.1016/j.ijcard.2012.12.021
15. Mukhopadhyay S, Nathani S, Yusuf J, Shrimal D, Tyagi S. Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger Syndrome-A randomized, placebo-controlled, double-blind crossover study. Congenit Heart Dis. 2011;6(5):424–31.
16. Zhang ZN, Jiang X, Zhang R, Li XL, Wu BX, Zhao QH, et al. Oral sildenafil treatment for Eisenmenger syndrome: A prospective, open-label, multicentre study. Heart. 2011;97(22):1876–81.
17. Diller GP, Körten MA, Bauer UMM, Miera O, Tutarel O, Kaemmerer H, et al. Current therapy and outcome of Eisenmenger syndrome: Data of the German National Register for congenital heart defects. Eur Heart J. 2016;37(18):1449–55.
18. Hascoet S, Fournier E, Jaïs X, Le Gloan L, Dauphin C, Houeijeh A, et al. Outcome of adults with Eisenmenger syndrome treated with drugs specific to pulmonary arterial hypertension: A French multicentre study. Arch Cardiovasc Dis [Internet]. 2017;110(5):303–16. Available from: http://dx.doi.org/10.1016/j.acvd.2017.01.006
19. Baumgartner H, De Backer J, Babu-Narayan S V, Budts W, Chessa M, Diller G-P, et al. 2020 ESC Guidelines for the management of adult congenital heart disease: The Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC). Eur Heart J [Internet]. 2020 Aug 29; Available from: https://doi.org/10.1093/eurheartj/ehaa554
20. Issues S, Test MW, Equipment R, Preparation P. American Thoracic Society ATS

Statement : Guidelines for the Six-Minute Walk Test. 2002;166:111–7.

21. Hsu DT. Chronic heart failure in congenital heart disease. Pediatric Heart Failure. 2005. 567–588 p.
22. Haroutunian LM, Neill CA. Pulmonary complications of congenital heart disease: hemoptysis. Am Heart J. 1972 Oct;84(4):540–59.
23. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A, et al. Bosentan therapy in patients with Eisenmenger syndrome: A multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114(1):48–54.
24. Mebus S, Schulze-Neick I, Oechslin E, Niwa K, T. Trindade P, Eicken A, et al. The Adult Patient with Eisenmenger Syndrome: A Medical Update after Dana Point Part II: Medical Treatment - Study Results. Curr Cardiol Rev. 2010;6(4):356–62.
25. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A, et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: A combined retrospective and case-control study. Eur Heart J. 2006;27(14):1737–42.
26. Hopkins WE, Ochoa LL, Richardson GW TEC of the hemodynamics and survival of adults with severe primary pulmonary hypertension or E syndrome. JHLT 1996 JP 1):100-5. P 8820089. No Title.
27. Opotowsky AR, Landzberg MJ, Beghetti M. The exceptional and far-flung manifestations of heart failure in eisenmenger syndrome. Heart Fail Clin. 2014;10(1):91–104.

APPENDIX

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1370/APRIL-2019

12.04.2019

Dr. Vishnu S
Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Vishnu,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT THERAPY (IEC/1370)" on 12th April, 2019.

The following documents were reviewed:

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 15.03.2019 with checklist*
2. *Forwarding Letter from the HOD*
3. *TAC Approval Letter*
4. *IEC Application Form*
5. *Project Proposal*
6. *Proforma*
7. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
8. *CV of Principal Investigator and Co- Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 12th April, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
5.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
8.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
9.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
10.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
11.	Dr. Anand Kumar A	MD, DM	Male	Clinician	No
12.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

PROFORMA
&
EXCEL CHART

CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT THERAPY

Registered on: **Follow up Date:**

Age	Sex	Place
Age at Diagnosis	Date of Diagnosis	Date of Birth
Ht	Wt	BSA

SPO2	AT DIAGNOSIS	**FOLLOW UP**
UPPER LIMB		
LOWER LIMB		

NYHA	AT DIAGNOSIS	FOLLOW UP

6 MWT	AT DIAGNOSIS	FOLLOW UP

NT PRO BNP	AT DIAGNOSIS	FOLLOW UP

PH	PO2	PCO2	HCO3 -	SAO2 -

	AT DIAGNOSIS	FOLLOW UP
HB		
PCV		
PLATELETCOUNT		

S.FE	FERRITIN	TIBC	S.FE

CLINICAL EVALUATION

EFFORT INTOLERANCE PALPITATION EDEMA SYNCOPE HEMOPTYSIS SQ

	UNIFORM	DIFFERENTIAL
CYANOSIS		
CLUBBING		

BLOOD PRESSURE SYSTOLIC DIASTOLIC JVP - PROMINENT A WAVE

ELEVATED

MEAN PRESSURE RV

HEAVE

CARDIOMEGALY

S2	SINGLE	CLOSE SPLIT	WFS	NORMAL

PULMONARY EJECTION

CLICK PULMONARY

REGURGITATION MURMUR

TRICUSPID RERURGITATION MURMUR

	dose	duration
Diuretics		
Antiplatelets		
Anticoagulants		
ACE Inhibitors		
Digoxin		
Betablockers		
Iron therapy		
Home oxygen		

PH specific therapy	DOSE	FREQUENCY	DATE OF INITIATION DURATION
BOSENTAN			
Sildenafil (dose)			
Ambrisentan			

Epoprostenol			
SURGICAL INTERVENTION			

CXR

- CTR
- SITUS
- ARCH

ECG

- Rhythm Conduction abnormality:
- Looping
- QRS Axis:
- Ventricular hypertrophy

ECHO

- **PRE TRICUSPID / POST TRICUSPID**
- Complete Diagnosis :
- RVSP
- TAPSE
- RV FAC
- TV s'
- Tei Index
- Pulmonary Acceleration Time.
- Ratio of RA to LA area.
- Pericardial effusion
- CMRI
- CARDIAC CT
- **Mortality**
- Date
- Frequency & Dates of previous hospitalizations –

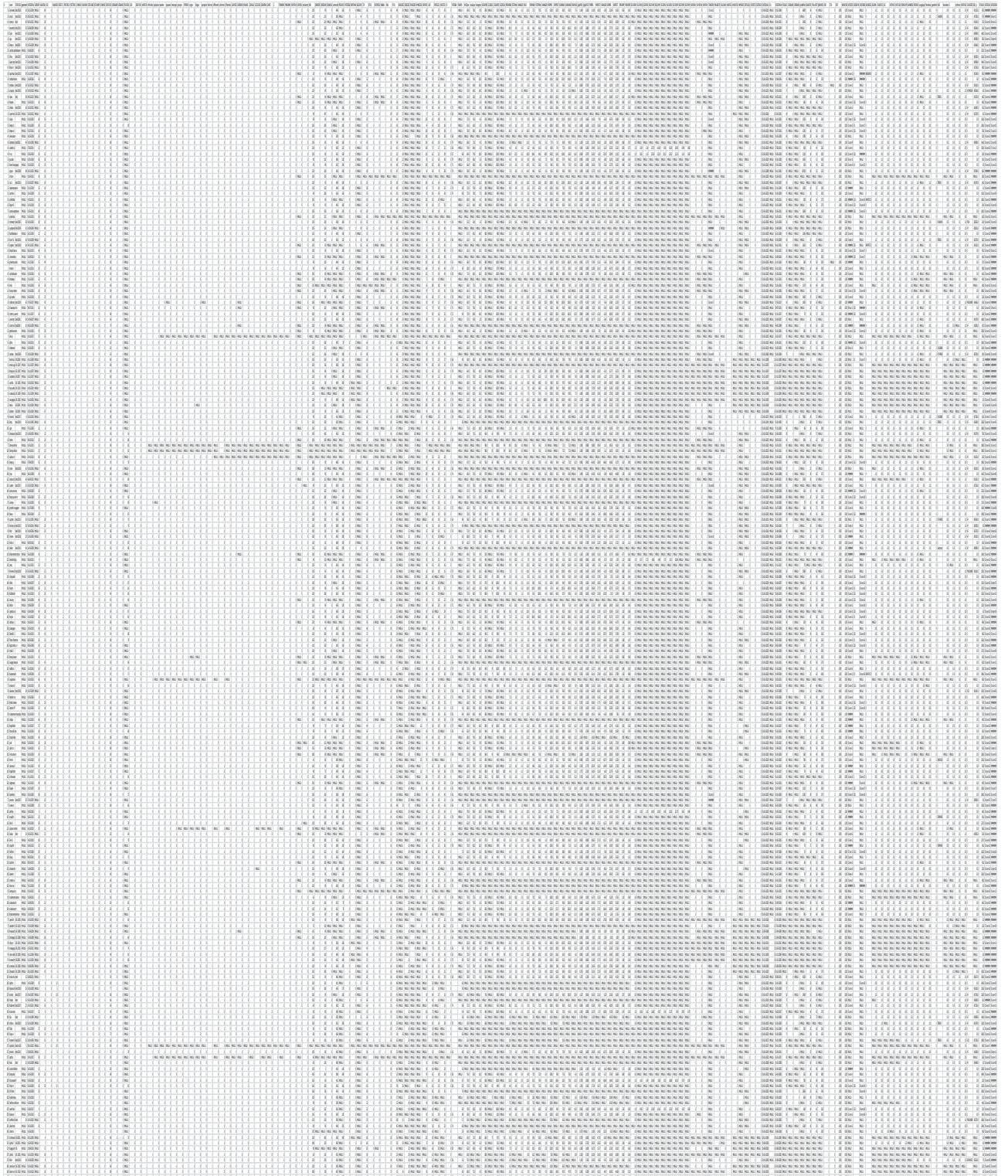
□

□ CAUSE - Sudden Cardiac Death / Thromboembolic / Heart failure / Sepsis

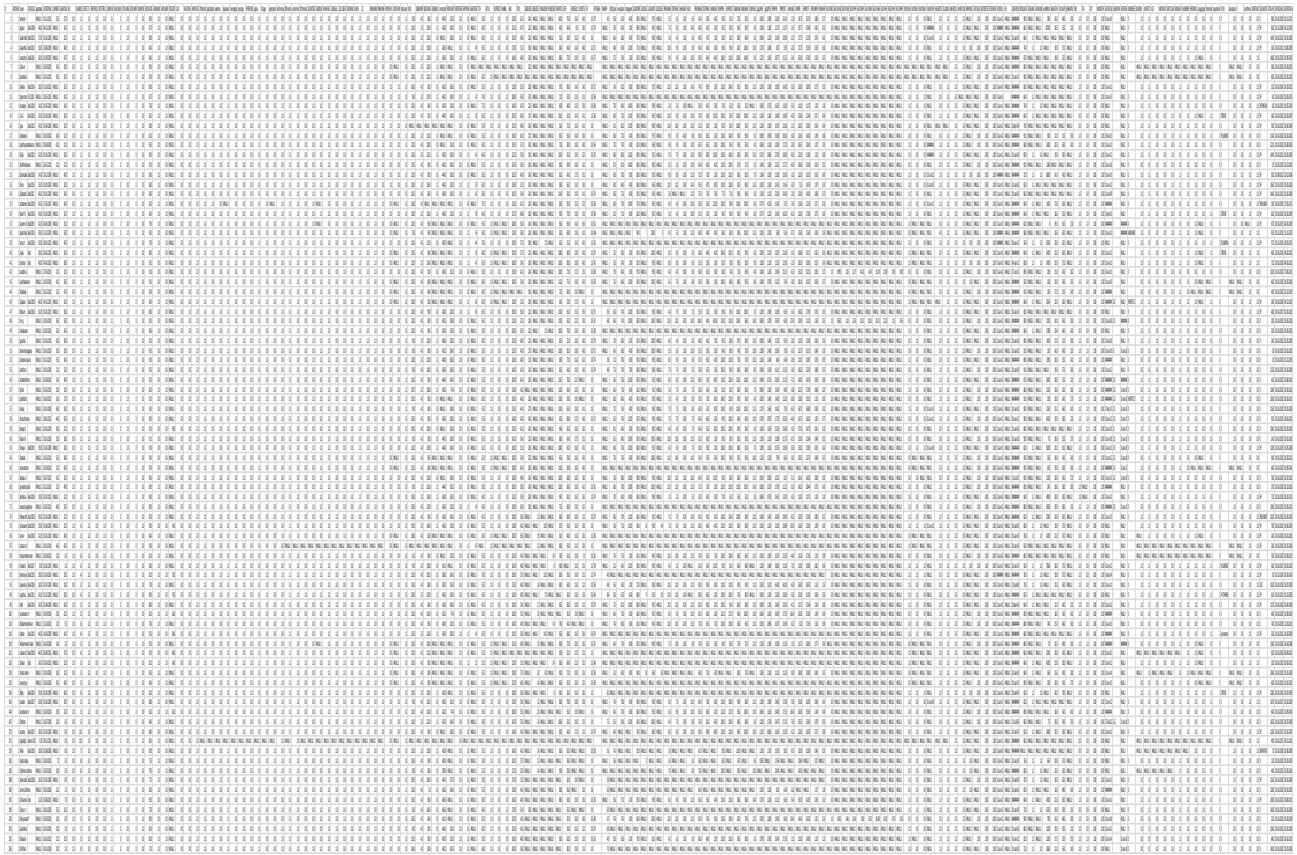
□

□ / Pregnancy related / Hemoptysis / others (specify)

Catheterization data	PRE	POST 100% O2
Ascending aortic saturation		
PA saturation		
SVC saturation		
IVC saturation		
mRAP		
mPAP		
mPCWP		
mAORTIC PRESSURE		
Qp		
Qs		
QP/QS		
PVR		
SVR		
PVR/SVR		



Matched patients excel chart



CONSENT

STUDY CONSENT FORM

TITLE OF THE STUDY: CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT THERAPY

*Study number: ~**200***

Participant's name: Date of Birth / Age (in years):

I_____ _____,

son/daughter of _____ (Please tick boxes).

[ ] Declare that I have read the above information provided to me regarding the study: "**CLINICAL PROFILE OF PATIENTS WITH EISENMENGER SYNDROME AND OUTCOME WITH CURRENT THERAPY** " and have clarified any doubts that I had.

[ ] I also understand that my participation/ participation of my child in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting mine/my child's usual treatment or my legal rights.

[ ] I understand that the study staff and institutional ethics committee members may not need my permission to look at my health records/ records of my child even if I withdraw from the trial. I agree to this access.

[ ] I understand that my/ my childs identity may not be revealed in any information released to third parties or published.

[ ] I voluntarily agree to take part in this study.

[ ] I received a copy of this signed consent form.

Name:

Signature:

Date:

Name of witness:

Relation to participant:

Date:

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

PLAGIARISM REPORT

Plagiarism checked by Plagiarism Checker software was 93% unique content 7% plagiarised content