

**AN AUDIT OF EXTRACORPOREAL MEMBRANE OXYGENATOR OUTCOMES
IN LOW CARDIAC OUTPUT SYNDROME PATIENTS AT CHARLOTTE MAXEKE
JOHANNESBURG ACADEMIC HOSPITAL**

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WITWATERSRAND,
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A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of
Masters of Medicine

March 2024

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DECLARATION

I, Ncamiso Mlotshwa (Student No. 2231643), declare that this research report is my unaided work. It is being submitted for the degree of Masters of Medicine in Cardiothoracic Surgery at the University of Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at any other University. This report is presented in the submissible format for MMed reports by the Faculty of Health Sciences of the University of Witwatersrand.

Signature: 

Date: 30th July 2024

DEDICATION

I dedicate this work to my children, mother, and all who supported me during my undergraduate and postgraduate training.

ABSTRACT

Introduction

ECMO is a mechanical device that supports an inefficient cardiorespiratory system, including the state of LCOS (common after cardiopulmonary bypass), which is refractory to medical treatment. Centers globally have investigated its outcomes. Our center has used ECMO since the mid-1990s, but the associated outcomes must be examined.

Study Aims and Objectives

This study aims to evaluate the 30-day survival results and associated predictive factors of patients with low cardiac output syndrome who utilized ECMO after undergoing open heart surgery.

Methodology

It is a retrospective review of adult patients' records of ECMO within 72 hours following open heart surgery from November 2016 until the end of December 2022. Data collection and analysis were focused on patient demographics, surgical risk scoring, and preoperative and perioperative clinical factors. Continuous data was analyzed using a one-way ANOVA for descriptive analysis. The association of patient characteristics and outcomes was investigated using Fischer's exact test. Statistical analysis was conducted using Stata® 18.0 Edition.

Results:

Of 1131 patients undergoing heart surgery within the period above, 3.36% utilized ECMO, and approximately 16% of the ECMO patients survived to discharge. 30-day mortality occurred in all 32 (84%) patients. Morbidity while on ECMO was evident in 100% of the patients. All surviving patients survived more than 30 days and were discharged from hospital. 100% of the ECMO connection was venoarterial, but 5 (13.5%) patients had peripheral cannulation. All patients with preoperative IABP demised. Normal preoperative urea and creatinine showed double the number of survivors than abnormal urea and creatinine.

Conclusion:

Our ECMO survival following open heart surgery is low (<16%), which is less than other well-established centers. Furthermore, factors for the poor outcomes are multifactorial (presence of preoperative IABP, older age, high surgical risk score, prolonged intraoperative time, coronary artery bypass, postoperative bleeding, sepsis, organ dysfunction, and failure to wean off ECMO).

ACKNOWLEDGEMENTS

I have endless appreciation for the whole team that assisted me in attaining this work.

My supervisor, Dr. Ekene Nweke, was instrumental in providing overall guidance, formulating protocols, and encouraging and supporting. Dr. Itumeleng Taunyane was instrumental in the clinical guidance and formulation of protocols, and Dr. Shungu Mogaladi was helpful with the clinical guidance and formulation of protocols.

My colleague, Dr. Bongane Ngutshane, is responsible for instrumental assistance with data sheet formulation and technical assistance with protocol documents.

An intern, Dr. Mogamat Ismail, for helping with data collection.

The biostatistics office (Dr. Anteneh Yalew and Prof Elenah Libhaber) for assisting with data analysis.

Last, Lynne McNamara for my protocol's scientific write-up of the literature review.

TABLE OF CONTENTS

LIST OF TABLES.....	8
LIST OF ABBREVIATIONS.....	9
INTRODUCTION	10
MATERIALS AND METHODS.....	11
RESULTS	12
DISCUSSION.....	18
CONCLUSION.....	20
LIMITATIONS.....	20
REFERENCES.....	21

LIST OF TABLES

Table 1: Background and clinical characteristics (page 13)

Table 2: Basic Data Outcomes (pages 13 – 14)

Table 3a: Association of outcomes with preoperative covariates/factors (pages 14 – 15)

Table 3b: Association of outcomes with preoperative covariates/factors (pages 15 -16)

Table 4: Association of outcomes with intraoperative covariates/factors (pages 16 -17)

Table 5: Association of outcomes with postoperative covariates/factors (pages 17 - 18)

LIST OF ABBREVIATIONS

BMI – Body mass index

CEO – Chief executive officer

CPB – Cardiopulmonary bypass

ELSO – Extracorporeal life support

ECMO – Extracorporeal membrane oxygenator

HOD – Head of department

HREC – Human Research Ethics Committee

IABP – Intra aortic balloon pump

LCOS – Low cardiac output syndrome

MVR – Mitral valve replacement

NYHA – New York Heart Association

PCS – Post cardiectomy syndrome

V-A ECMO – Veno-arterial ECMO

V-V ECMO – Veno-venous ECMO

WHO – World Health Organization

INTRODUCTION

The evolution of cardiac surgery has been challenging: in the late 1800s to mid-1950s, heart surgeries were performed without a cardiopulmonary bypass (CPB) machine and were associated with high mortality. Open heart surgery required the development of an artificial CPB to improve outcomes (1,2). CPB is suitable for shorter procedures but tolerated less for extended periods. Some patients develop poor heart function in the perioperative period and continue to need mechanical support postoperatively (3). A more diminutive form of mechanical cardiorespiratory support was created, named extracorporeal membrane oxygenator (ECMO).

ECMO supports an inefficient cardiorespiratory system, such as a state of low cardiac output syndrome. Low cardiac output syndrome (LCOS) is when the cardiac performance fails to meet the body's metabolic demands. LCOS is a frequent problem after cardiopulmonary bypass and is treated with medical treatment, such as the utilization of appropriate intravenous fluids and high amounts of multiple inotropic medications. Failure of medical therapy will then require the implantation and institution of ECMO to augment myocardial recovery. Globally, the utilization of ECMO is growing, including Charlotte Maxeke, Johannesburg Academic Hospital (CMJAH) (4,5,6).

As ECMO is intended to allow the body and its organs to remain functional while the heart recovers, indications for ECMO must be for reversible causes or used as a bridge to a heart transplant (5,6,7,8). Except for a smaller group of patients, possible utilization of ECMO is often unanticipated preoperatively. Intensive care unit (ICU) care of an ECMO patient is labor-intensive and usually associated with complications. The utilization of ECMO must be principled to ensure that the correct patient group benefits from it (6). The selection of patients is guided by the preoperative ability to recover towards the disconnection of ECMO or to another permanent mode of treatment like a heart transplant. Using ECMO is not risk-free, as complications like bleeding, organ dysfunction, reoperation, embolic phenomenon, and systemic inflammatory response syndrome (SIRS) can occur (8,9,10, 12, 13).

For an ECMO user, the survival rate to discharge from hospital statistics following heart surgery ranges between 17% and 52% across different hospitals (15). Significantly,

experience, correct indications for ECMO, early correction of physiological derangements, and prevention of complications contribute to positive outcomes (17).

The CMJAH clinical records of cardiac patients show that ECMO has been used since the mid-1990s, but the associated outcomes still need to be investigated. In South African centers, no postcardiotomy ECMO outcomes have been published (23, 24). Therefore, this study aims to evaluate the outcomes regarding 30-day survival, length of hospital stay, ICU stay, and associated preoperative, intraoperative, and postoperative factors of patients with LCOS and ECMO in CMJAH.

MATERIALS AND METHODS

Study site and population

It was a single-center, retrospective study of patients needing ECMO following open heart surgery. The study period spanned from November 2016 to December 2022. There are no dedicated books for patients utilizing ECMO in our unit. The perfusionist consumable list provided clues as to which patients had ECMO, and subsequent records were analyzed to separate files of patients needing ECMO. The necessary patient files were examined through the hospital's ORBIT system, where all patient files were scanned into PDF electronic records.

Inclusion criteria involved all adult patients (age 14 years and older) using ECMO within 72 hours following open heart surgery. Excluded were all pediatric (age < 14 years) patients needing correction of congenital lesions and requiring ECMO, except adult patients with congenital lesions. Others excluded were all patients utilizing ECMO for reasons other than open heart surgery. Only one 14-year-old was included in the study based on the hospital criteria that a 14-year-old is managed as an adult patient

Data collection

Study data was based on our aim (30-day mortality) and objectives of collecting demographic and clinical information with regards to preoperative state (such as diagnoses, BMI, New York Heart Class, STS Surgical risk score for mortality, EUROScore, the urgency of surgery, kidney function, assistive device, preoperative comorbidities), Intraoperative state (such as duration of cardiopulmonary bypass, ECMO cannulation strategy, duration of procedure,

redo sternotomy, ECMO connection, procedure) and postoperative state (such Lactate levels, ECMO duration, Relook surgery, complications developed, organ dysfunction, antibiotic use, sternum closed/open, successfully weaning ECMO, duration of stay in ICU and Hospital and, subsequent discharge from hospital). The above data was collected using 2023 RedCap® electronic data capture tools hosted at Witwatersrand University. All collected data was converted onto a Microsoft® Excel (office 16) spreadsheet, formulated, and data was transferred to Stata® (Version 18, StataCorp Basic edition) for statistical analysis.

Statistical analysis

Stata®Corp 18.0, Basic Edition was utilized to run the following: The Shapiro-Wilk test was used for normality testing. For descriptive analysis, continuous data (i.e., creatinine, STS mortality, EUROScore, Duration of procedure, CPB time, Cross clamp time, Lactate levels, ECMO duration, ICU stay, and Hospital stay) was calculated using a one-way ANOVA test and represented as a median and interquartile range or mean and standard deviation. Categorical variables (i.e. Demographics, BMI, Comorbidities, NYHA class, Urea, Ugerncy of surgery, type of procedure, redo sternotomy, preoperative IABP, ECMO cannulation strategy, ECMO connection, Rolook surgery, complications organ dysfunction, antibiotic use, sternum status, successful weaning off ECMO, discharged from hospital) were represented as frequencies and percentages Fisher's exact was used for the association of categorical variables to outcomes. A p-value of 0.05 or less was considered significant.

RESULTS

Baseline data

Overall, thirty-eight patients had ECMO implantation during the study period, which equated to 2.85% of the total (1131) cardiac surgeries done in the same period in our center. Initially, 60 (4.5%) patients were registered to have had ECMO, but only 38 (2.85%) patients met the study selection criteria. There were 20 (52.6%) female and 18 (47.4%) male patients. Age ranged from 14-78 years, with the working class (WHO ages between 16 and 64 years) dominating with 30 (78.95%) patients, followed by the post-working class (WHO ages between 65 and 74 years) with 7 (18.4%) patients. African patients were the largest group,

with 22 (57.9 %) patients, and others (White, Indian, and Coloured) totaled 16 (42.1%) patients. Regarding BMI, 16 (42.11%) of the patients had normal BMI, and the other 21 (55%) ranged from overweight to morbidly obese. For timing of surgery, 15 (39.5%) patients were elective surgery cases versus 17 (44.7%) patients needing to be operated urgently. All patients had one or more preoperative comorbidity (comorbidities shown in Table 3a). A summary of the data is in Table 1.

Table 1: Background and clinical characteristics summary

CHARACTERISTICS	LEVEL	n (%)
AGE (Years)	Young class (0-14)	1 (2.63)
	Working class (15-64)	30 (78.95)
	Post working class (65-74)	7 (18.42)
Gender	Male	18 (47.37)
	Female	20 (52.63)
Race	African	22 (57.90)
	Other (White, Indian, and Coloured)	16 (42.10)

ECMO Outcomes

Out of the 38 ECMO users, 15.8% (5 females + 1 Male; $p=0.184$) survived till hospital discharge following the index hospital admission from the 34% of patients that were successfully weaned off ECMO. 97% of the patients had ECMO intraoperatively; the remaining 3% had ECMO placed as an emergency two days after the index surgery. Death in 30 days was observed in 100% of the patients that were demised while in hospital. All six surviving patients were discharged from the hospital and survived beyond 30 days following the index procedure. All the patients developed a form of complication (morbidity on ECMO). A hundred percent of the ECMO connections were venoarterial, but 5 (13.5%) patients had peripheral cannulation. All survivors were centrally cannulated. Table 2 summarises the above results.

Table 2: Demographic data association with outcomes

CHARACTERISTICS	Level	30-DAY SURVIVAL STATUS		p-Value
		Alive	Demised	
Gender	Female	5 (13.1)	15 (39.47)	0.184

	Male	1 (2.63)	17 (44.73)	
Age (in Years)	Young (0-14)	0	1 (2.63)	0.897
	Working class (15-64)	5 (13.1)	25 (65.78)	
	Post working class (>64)	1 (2.63)	6 (15.78)	
Race	African	5 (13.15)	17 (44.73)	0.370
	Other	1 (2.63)	15 (39.47)	

The mean (SD) for standard data and the Median (IQR) for non-normal data were used. The Wilcoxon rank-sum test was used for median equity.

Association of preoperative clinical parameters with 30-day survival

There was no statistical difference in age between the survivors and demised patients, but there were preoperative predictors of poor outcomes. Though the number of patients was small, patients with lower surgical risk scores (STS/EUROSore) tended to have better survival. There was no statistical significance from NYHA classes ($p=1.000$). Survivors from NYHA classes ($p=1.000$) were NYHA II - 3 (7.9%) patients, NYHA III – 2 (5.3%), and 1(2.6%) from NYHA IV. All eight preoperative intra-aortic balloon pump (IABP) patients demised ($p=0.309$). The urgency of the procedure showed better survivors from the elective group (3 (7.8%) patients)) versus the semi-urgent (1(2.6%) patient)) and urgent groups (2 (5.3%) patients)); however, this was not significant statistically ($p=0.871$). Preoperatively, patients with normally functioning kidneys had twice the number of survivors compared to abnormal kidney function marked by urea ($p= 0.660$) and creatinine ($p=0.00005$). Tables 3a & 3b summarize the association between patient factors and outcomes.

Table 3a: Association of outcomes with preoperative covariates/factors

CHARACTERISTICS	Level	30-DAY SURVIVAL STATUS		p-Value
		Alive	Demised	
BMI	Normal	4 (10.52)	12 (31.57)	0.470
	Overweight	2 (5.26)	19 (50.0)	
	Underweight	0 (0)	1 (2.63)	
Preoperative Comorbidities	Previous Heart surgery	1 (2.63)	4 (10.52)	1.000

	Dyslipidemia	0 (0)	5 (13.15)	0.570
	Diabetes Mellitus	0 (0)	9 (23.68)	0.303
	Hypertension	2 (5.26)	16 (42.10)	0.663
	Retroviral disease	1 (2.63)	5 (13.15)	1.000
	Rheumatic heart disease	0 (0)	4 (10.52)	0.360
	Smoking	0 (0)	10 (26.31)	0.168
	Other	4 (10.52)	21 (55.26)	0.961
NYHA Class	I	0 (0)	1 (2.63)	1.000
	II	3 (7.89)	11 (28.94)	
	III	2 (5.26)	12 (31.57)	
	IV	1 (2.63)	8 (21.05)	

The mean (SD) for standard data and the Median (IQR) for non-normal data were used. The Wilcoxon rank-sum test was used for median equity. NYHA – New York Heart Association, BMI – Body Mass Index.

Table 3b: Association of outcomes with preoperative covariates/factors

CHARACTERISTICS	Level	30-DAY SURVIVAL STATUS		p-Value
		Alive	Demised	
Urea (mmol/L)	Normal	4 (10.52)	15 (39.47)	0.660
	Abnormally elevated	2 (5.26)	17 (44.73)	
Creatinine (umol/L)	Creatinine	89.5 (52 – 101)	93 (73.5 – 117)	0.212
Urgency	Elective	3 (7.89)	12 (31.57)	0.871
	Semi urgent	1 (2.63)	4 (10.52)	
	Urgent	2 (5.26)	15 (39.47)	
	Salvage	0 (0)	1 (2.63)	
Surgical risk scoring	STS mortality	1.02 (0.77 – 1.14)	1.59 (0.94 – 3.04)	0.0001
	EUROScore	2.69 (2.42 –	3.12 (1.56 –	0.000

		15.32)	7.57)	
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The mean (SD) for standard data and the Median (IQR) for non-normal data were used. The Wilcoxon rank-sum test was used for median equity. Statistically significant p-values are bolded in bold numbers. ICU stands for intensive care unit, and ECMO stands for extracorporeal membrane oxygenator.

Association of Intraoperative parameters with 30-day survival

Indications for ECMO showed better survival in patients with right heart failure. The type of procedure showed better survival ($p = 0.010$) for valvular and other cardiovascular procedures than coronary surgery patients, where 100% mortality was seen. The duration of the procedure was insignificant ($p=0.976$), but cardiopulmonary bypass (CPB) time ($p=0.010$) and cross-clamp time ($p=0.049$) were significantly associated with survival.

Table 4: Association of outcomes with intraoperative covariates/factors

CHARACTERISTICS	Level	30-DAY SURVIVAL STATUS		p-Value
		Alive	Demised	
Type of procedure	Congenital	1 (2.63)	0 (0)	0.010
	Valvular	2 (5.26)	16 (42.10)	
	Coronary	0 (0)	12 (31.57)	
	Other	3 (7.89)	4 (10.52)	
Duration of procedure	Duration of procedure	410 (370 – 590)	511 (372.5 – 630)	0.976
CPB time	CPB time	290 (238-351)	269.5 (220 – 371.5)	0.010
Cross Clamp time	Cross clamp	168 (121 – 289)	176 (111.5 – 209)	0.049
Redo Sternotomy	Redo Sternotomy	1 (2.63)	5 (13.15)	1.000
Preop IABP	Preop IAPB	0 (0)	8 (21.05)	0.309
ECMO Mode of Cannulation	Central venous + central artery	5 (13.15)	28 (73.68)	1.000
	Opposite femoral artery / Vein	1 (2.63)	4 (10.52)	
Type of ECMO Connection	Veno arterial	6 (15.78)	32 (84.2)	
Type of ECMO	Central	6 (15.78)	28 (73.68)	1.000
	Peripheral	0 (0)	4 (10.52)	

The mean (SD) for standard data and the Median (IQR) for non-normal data were used. The Wilcoxon rank-sum test was used for median equity. Statistically significant p-values are bolded in bold numbers. IABP – Intra-aortic balloon pump, CPB – Cardiopulmonary bypass, ECMO – Extracorporeal membrane oxygenator.

The association of postoperative parameters with 30-day survival

There was no significant association of postoperative clinical state (relook, ECMO days, complications, sepsis, open sternum, use of antibiotics, and ICU stay) with outcomes (Table 5)—furthermore, all patients who had more than one complication while on ECMO did not survive. Of the total who had relooks (32), 6 (18.7%) survived, and 26 (81.2%) died (p=0.562). Sepsis developed in 2.63% of the alive and 39.47% of the demised (p=0.370) patient groups. Organ dysfunction, with acute kidney injury developing in most patients, was in 65.8% (p=0.047) of the total patients.

Table 5: Association of outcomes with postoperative covariates/factors

CHARACTERISTICS	Level	30-DAY SURVIVAL STATUS		p-Value
		Alive	Demised	
1 st Hour on ECMO	MAP (mmHg)	60 (52 – 70)	65 (52 – 77.5)	0.392
	Pulse rate (bpm)	85.5 (62 – 103)	87 (64 – 100.5)	0.825
	Lactate (mmol/L)	4.7 (1.8 – 7.3)	7.6 (5 – 12.6)	0.056
	pH	7.34 (7.28 – 7.35)	7.31 (7.20 – 7.4)	0.0000
On ECMO	Duration (Days)	3 (1-5)	5 (2.5 – 8)	0.011
	Relooked	6 (15.78)	26 (68.42)	0.562
	Complications	4 (10.52)	27 (71.05)	0.302
	Organ dysfunction	2 (5.26)	25 (65.75)	0.047
	Developed sepsis	1 (2.63)	15 (39.47)	0.370
Antibiotic use	None	0 (0)	1 (2.63)	0.203
	Prophylactic	5 (13.16)	11 (28.95)	
	Empiric	1 (2.63)	11 (28.95)	

	Directed	0 (0)	9 (23.68)	
Sternum status	Closed	0 (0)	4 (10.52)	1.000
	Open	6 (0)	28 (0)	
Outcomes	Successfully weaned ECMO	6 (15.78)	7 (18.42)	0.001
	Total ICU stay	7.5 (5 – 10)	7 (4 – 14.5)	0.0001
	Total Hospital stay	22 (20 – 43)	14.5 (8 – 19)	0.001
	Discharged from Hospital	6 (15.79)	0 (0)	0.000

The mean (SD) for standard data and the Median (IQR) for non-normal data were used. The Wilcoxon rank-sum test was used for median equity. Statistically significant p-values are bolded in bold numbers. ICU—intensive care unit, ECMO—extracorporeal membrane oxygenator, MAP—mean arterial pressure.

DISCUSSION

The establishment of cardiopulmonary support devices, like CPB machines and ECMOs, and their uses are well documented (1). The heart is subject to functioning poorly after cardiac surgery, and some patients go into a state of severe LCOS (2). So, for those whose hearts cannot maintain acceptable systemic pressures, a mechanical support device is critical until the heart recovers (3). As reported by literature that inotropic support plays a vital role before consideration of a mechanical device (3), our patients were no less different. So, ECMO was used after doing all possible maneuvers to avoid mechanical support. This study identified the outcomes of patients on ECMO.

Though our sample size (38 patients) was small, there was a low survival rate of ECMO patients following cardiac surgery in our unit. The results showed only one survivor from the post-working group, which was in keeping with other studies that determined that being an elderly patient does not have a favorable outcome, especially for elderly female patients (16). Results from this study also showed that most survivors were African females below the age of 45 years. The survival of patients was associated with a lesser rate of bleeding than that of demised patients, where almost all patients had significant postoperative bleeding and relooks. Another critical parameter of survival was slightly preserved left heart function. A heart with only the right side failing improved better than the hearts with mainly the left or both sides failing. The patients with right heart failure showed better survival compared to any other group.

Correct patient selection should help improve ECMO outcomes (4,5). It is unclear how the patients were selected in this center. Internationally, the choice of patients is guided by a specific ECMO team (4,5). From the data, there were 4 (10.5%) patients who were demised during surgery after the institution of ECMO, and bleeding was the main problem causing hypovolemic shock and subsequent death. From the documents, only one patient had CPR preoperatively, and another patient had CPR postoperatively, and ECMO was used to salvage the situation; none of those patients survived. This group of patients may not be appropriate for ECMO. Thus, an ECMO team would have helped decide before using ECMO. Complications like sepsis proved detrimental to weaning off ECMO. For most right heart failure patients, ECMO was a precious treatment method for the recovery of the patients.

Our study showed that preoperative indicators of survival were not statistically significant, but all patients with poor preoperative state and placed on ECMO did not survive. A high-risk score (NYHA, STS, EUROScore) preoperatively was associated with poor outcomes when ECMO was used. Preoperative planning for ECMO was considered for the patients undergoing salvage cardiac procedures but did not make any difference regarding survival. Intraoperatively, a prolonged surgical time was a factor in bad outcomes. Other intraoperative factors like myocardial protection are poorly documented, so it is unclear whether they contributed to our poor ECMO outcomes.

Bleeding, AKI, and sepsis are well-recognized complications of CPB and ECMO (20). Our patients had similar complications postoperatively. Three significant complications, bleeding, acute kidney injury, sepsis, and cardiac failure, were noted in most patients who were not weaned off CPB—almost all patients who had significant bleeding as a complication were demised. Bleeding was inevitably associated with massive blood and blood product transfusion. Blood transfusion is a risk for SIRS and blood-borne infections (25, 26). The patient group from this study showed that preserved renal function postoperatively was associated with the ability to wean ECMO and subsequent survival to discharge. The duration of ECMO played a role in the development of sepsis as the chest remained open, and the patients were subjected to relooks, which increased the risk for sepsis. Thus, none of the patients were weaned off ECMO after developing sepsis while on ECMO. Sepsis was suspected clinically and, in some patients, confirmed through biochemical markers. In this study, limb ischemia while on ECMO was not a good predictor of bad/good outcomes as two of the patients had lower limb ischemia, but only one patient survived to discharge after a subsequent bilateral above-knee amputation. Furthermore, the mode of cannulation was

overwhelmingly central except for four patients who had peripheral cannulation (two patients had lower limb ischemia). The mode of cannulation is highly dependent on the clinical indication for ECMO. Generally, veno-venous cannulation gives better outcomes when compared to veno-arterial cannulation, which is usually the patient with a much more severe clinical condition (21, 22).

The poor outcomes of ECMO are multifactorial from our limited number of patients. Most patients had correct indications for ECMO, and the few dying on the theatre table probably did not meet the criterion for ECMO. As described in the literature review, most centers have a special ECMO team/committee; the lack of usage of a special ECMO committee in our center probably led to undeserving patients for ECMO and thus increased the number of bad outcomes.

CONCLUSION

This study showed poor 30-day survival (<16%) outcomes of patients on ECMO. Additionally, patients who were successfully weaned off ECMO indicated that surviving ECMO post-cardiac surgery at CMJAH is possible. Older age, particularly over 45 years, high surgical risk, presence of preoperative IABP, and poor renal dysfunction were the preoperative factors associated with poor outcomes. The identifiable intraoperative factors associated with poor outcomes are the long duration of the procedure, bleeding, and bypass time. There are identifiable postoperative factors associated with poor ECMO outcomes, i.e. relook surgery, organ dysfunction and sepsis. As one of the few institutions utilizing ECMO in South Africa, a multi-faceted approach regarding selection criteria and ICU management to maximize the survival of ECMO should help improve our survival.

LIMITATIONS

A major limitation was the small number of patients that we had. It affected the study's statistical significance and prevented advanced assessment of associations like linear regression.

During data collection, identifying ECMO patients was a challenge as there is no capturing system of patients using ECMO, the perfusionist consumable list gave clues as to which patients used ECMO. Accessing the data was a challenge as it may only be collected from the hospital area where records are kept electronically.

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R49 Mr N Mlotshwa

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220618**

NAME:
(Principal Investigator)

Mr N Mlotshwa

DEPARTMENT:

School of Clinical Medicine
Department of Surgery
Division of Cardiothoracic Surgery
Medical School
University

PROJECT TITLE:

*An audit of extracorporeal membrane oxygenator outcomes
in low cardiac output syndrome patients at Charlotte
Maxeke Johannesburg Academic Hospital*

DATE CONSIDERED:

2022/06/24

DECISION:

Approved unconditionally

CONDITIONS:

NOTE:

If contact information regarding student study participants is required,
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SUPERVISOR:

Messrs S Mogale, N Ekene and I Taunyane

APPROVED BY:

Dr CB Penny
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL:

2022/11/23

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in June and therefore reports and re-certification will be due in the month of June each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

DEPARTMENT OF CARDIOTHORACIC SURGERY,

WITWATERSRAND UNIVERSITY COMPLEX

AN AUDIT OF ECMO OUTCOMES IN LOW CARDIAC OUTPUT
SYNDROME AT CHARLOTTE MAXEKE JOHANNESBURG
ACADEMIC HOSPITAL

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1. TABLE OF CONTENTS

EXECUTIVE SUMMARY	28
LITERATURE REVIEW	3
RESEARCH QUESTION	32
HYPOTHESIS	33
AIM.....	33
STUDY OBJECTIVE.....	33
METHODOLOGY	33
STUDY SITE	33
INCLUSION AND EXCLUSION CRITERIA	34
STUDY DESIGN	34
SAMPLE SIZE	34
MATERIALS.....	34
DATA COLLECTION	34
DATA ANALYSIS.....	35
ETHICAL CONSIDERATIONS.....	35
LIMITATIONS:	36
TIMELINE:	36
Abbreviations.....	14
REFERENCES	37

2. EXECUTIVE SUMMARY

An extracorporeal membrane oxygenator (ECMO) is a technological and mechanical device that supports an inefficient cardiorespiratory system, such as a state of low cardiac output syndrome. Globally, there are centres well acquainted with ECMO, including Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Johannesburg. Low cardiac output syndrome (LCOS) is a state where cardiac performance fails to meet the metabolic demands of the body. LCOS is a frequent problem after cardiopulmonary bypass and is treated with medical treatment but refractory to maximal medical treatment in very few patients where ECMO is then implanted to augment myocardial recovery. Although CMJAH has been using ECMO since the mid-1990s, the associated outcomes have not yet been investigated. This study aims to evaluate the results of patients with low cardiac output syndrome and ECMO

and associated predictive factors. The study will involve all CMJAH patients with acquired cardiac conditions requiring ECMO in the perioperative period between 2008 and 2020. Following ethical approval, a retrospective analysis of patient records will be conducted. Statistical analysis will be carried out using the Statistica software.

3. LITERATURE REVIEW

Wiesse (2011) states that heart surgery is a relatively young specialty (1). Due to the high mortality associated with heart surgery before the cardiopulmonary bypass (CPB) era, few surgeons attempted heart surgery. Many heart-related procedures between 1890 and 1953 were extracardiac. Valvular heart diseases that were surgically treated before the introduction of CPB were done without inducing cardiac arrest. Only after the introduction of CPB in 1954 was open-heart surgery done on more patients at the Mayo Clinic, and the rest of the world followed. Inoperable heart failure remains a problem for some patients, and they require heart transplantation, which was a historic milestone when first done in 1967 by Dr Christiaan Barnard in Cape Town. As more patients were waiting for heart transplants, the need for mechanical support increased; and mechanical support devices other than CPB were developed to assist the heart for more extended periods (1).

According to Lomivorotov and colleagues (2017), low cardiac output syndrome (LCOS) is a common sequela of CPB and myocardial ischaemia. Patients with LCOS post-surgery are usually supported with inotropes for adequate organ perfusion. However, some patients are treated with mechanical support until the heart regains function (2).

Monaco and colleagues (2020) state that, after cardiac surgery, adequate mechanical effort of the heart and lung is essential to separate the CPB machine used for the procedure successfully. Many patients require pharmacological support for separating from the CPB machine, but some require mechanical support such as CPB, ECMO, or an intra-aortic balloon pump (IABP). The need for ECMO is seldom anticipated preoperatively. Preoperative planning of ECMO is considered when there are very high scores (STS, EUROSCORE, and others) used to predict perioperative morbidity and mortality in cardiac surgery patients. Before considering mechanical support, all causes for a poorly functioning heart need to be excluded and treated. ECMO may then be considered, provided the heart will recover, or the patient is a candidate for a heart transplantation procedure (3).

Makdisi and colleagues (2015) and Bartlett (2014) mention that ECMO is a medically recognised advancement worldwide, reserved only for patients with the highest mortality

from the conventional treatment. A recognised body (extracorporeal life support - ELSO) to control and guide the successful development of ECMO was formed in the 1980s (4,5).

A cardiopulmonary bypass (CPB) machine is used for safe routine heart surgery. Only when the main procedure is completed is the heart restarted and allowed to resume its function. Very few patients end up requiring an ECMO, a smaller CPB machine that supports the heart and lungs while allowing the heart to resume its function slowly is usually sufficient (6). ECMO is a device that replaces the function of the heart and lungs. Once the organ function has improved, the mechanical support can be disconnected (7,8).

Preoperative ECMO indications are usually the cardiogenic shock from a severe acute coronary syndrome, mitral valve regurgitation, and pericardial tamponade (9). ECMO utilisation allows recovery of the heart and lungs or provides a bridge to a long-term solution such as a heart transplant; ECMO should not be considered for patients, not in this group (9). ECMO indication includes failure to wean off CPB, LCOS which may develop in the perioperative period, respiratory failure causing hypoxia, in paediatric patients with congenital heart defects requiring mechanical support until corrective surgery is done and extracorporeal CPR (10). V-V ECMO patients with pulmonary dysfunction have better outcomes than patients on V-A ECMO as only one system needs support (10,11). The mode of cannulation appropriate for cardiogenic shock is VA ECMO (12). Survival outcomes are similar between centrally implanted VA ECMO and peripheral VA ECMO cannulation; however, the risk of bleeding and blood transfusion is much lower in peripheral ECMO (13).

Using ECMO requires extensive knowledge in a highly specialised intensive care unit as ECMO can be associated with complications such as wound or blood infections, excessive bleeding and organ failure (6).

A review of 15 articles within our study period showed a 17- 40% survival rate at ten years from 24.8-52% on discharge from the hospital. The 225 articles pooled for this review found that surviving patients are less likely to die from ECMO-related complications once discharged from the hospital. In a similar study of 1764 patients done retrospectively between 2002 and 2006, only 51 patients needed ECMO post-operatively, the indication being postoperative cardiogenic shock (15). These authors found that preoperative risk factors for increased mortality were poor left heart function, low systemic blood pressure, and acidosis. Intraoperative risk of mortality was a lactate level of 8mmol/l or more; reduced platelets and albumin levels were risk factors for decreased survival. Postoperative complications

associated with higher ECMO mortality were acute renal failure, bleeding, and lung infection. Males did not do well compared to females. A body mass index (BMI) of 25 or more, a New York Heart Association (NYHA) score of II or more, preoperative hypotension, diabetes mellitus, and a high euroSCORE were associated with a higher risk of initiating ECMO. Overall, in-hospital mortality from the 51 patients on ECMO was 67%, which is very high (15).

A review by Pappalardo and Montisci (2016) shows the increased mortality rate associated with organ dysfunction that usually does not improve with ECMO following post-cardiotomy cardiogenic shock (PCCS) (16). The authors carefully observed the mortality rate that increases because of renal impairment. By looking at the urine output in the first 24 - 48 hours, they could predict higher mortality when a patient was oliguric and fluid overloaded. It seems moderate to low flow allows the heart to recover quicker, but it does not deliver enough flow to the other organs.

A ten-year review from 2003 to 2013 focusing on patients older than 69 years found that failure to wean off cardiopulmonary bypass after a heart operation was a common indication for ECMO (17). An intra-aortic balloon pump (IABP) was used on some of the patients and, only when there was no success, did they add ECMO. Almost all the patients had central ECMO with chests staying open for the duration. All ECMO cannulas were primed with packed units of blood to reach a haemoglobin level (Hb) of 10g/l and above. A specific ECMO flow strategy was used to maintain mixed venous saturation of more than 60%. There was only a need to initiate heparin infusion after 12 hours of initiation of ECMO, and it was controlled by 140-170s of ACT or Activated PTT of 50-the 60s. Improvement of heart and lung function was used to wean off ECMO, and higher anticoagulation was used during the weaning time. Results were abysmal, indicated by the high percentage (>75%) of deaths. Most patients died from cardiac causes and fewer from sepsis and multiorgan failure. When comparing the older group to a younger population, younger patients survived ECMO, and the cause of death was less likely to be heart failure. The authors concluded that ECMO might be more suitable for the younger population as they are less likely to die from cardiac causes after recovery following the use of ECMO (17).

Whitman (2017) compared the success of ECMO in respiratory indications to PCS patients needing ECMO (18). He found increased use of ECMO for PCS, but good results were lacking. ECMO for PCS had more than 60% mortality compared to 60% survival for respiratory indications. Many problems were associated with ECMO, but almost all patients had bleeding requiring massive transfusions per patient. Multiorgan failure, especially acute kidney injury (AKI) requiring renal replacement, occurred in more than 60% of PCS patients. Other issues such as the very high cost of running ECMO per patient show that funds directed towards the area of need are wasted. As this seems to be an ethical dilemma, other ethical issues were raised, like emotional stress to the patient's family and dignified death.

ECMO application in cardiac failure: Biancardi and colleagues (2018) summarised the fundamentals of ECMO and came up with some information regarding ECMO and cardiac surgery (19). One of the cohort studies reviewed where ECMO was used following cardiac surgery showed improved patient outcomes compared to when ECMO was not used. According to the authors , the first use of VA-ECMO for PCS showed about a 25% survival. Experience in using ECMO improved the outcomes by more than 35%, but the increased cost and hospital stay were not good results. With such high mortality, many centres struggle to identify apparent risk factors associated with the poor survival rate in PCS ECMO patients.

A retrospective study involving more than 750 patients from 19 European centres for eight years was done from 2010 to 2018 (20). The rate of survival was examined and found to be about 35%. Most of the patients had one or more complications that extended their hospital stay. Debilitating complications such as cerebrovascular incidents, septicaemia, renal injury and bleeding were the most common ones identified. All complications were associated with increased expenses for the hospital stay. Of interest from the same review was the higher survival rate where patients on VA-ECMO could receive a ventricular assistive device or heart transplant. Many risk factors that increased mortality significantly were identified, including older age, high lactate levels, female gender, and previous heart surgery.

4. RESEARCH QUESTION

What are the outcomes of ECMO for perioperative LCOS at CMJAH?

5. HYPOTHESIS

Survival outcomes of ECMO for LCOS are poor at CMJAH.

6. AIM

This study aims to evaluate the outcomes of patients with LCOS and ECMO and associated predictive factors.

7. STUDY OBJECTIVE

1. To determine outcomes of patients with LCOS and ECMO in terms of 30-day Mortality, in-hospital mortality, morbidities developed whilst on ECMO (circuit-related local complications such as limb ischaemia or compartment syndrome, and systemic complications such as bleeding, pneumonia, myocardial infarction, systemic sepsis, ARDS and, bleeding), discharge from hospital, cardiac function status neurological status outcomes, and modes of cannulation.
2. To determine preoperative factors such as NYHA class, the urgency of the procedure, and other mechanical support devices used, associated with the above outcomes.
3. To determine postoperative factors such as duration of ECMO, antibiotic usage, vital organs functional status and sternal closure/open state associated with the above outcomes.

Methodology

7.1. Study site

The study will be done at the Charlotte Maxeke Johannesburg Academic Hospital. All available records of cardiothoracic patients operated on from 2008 until 2020 will be scrutinised, and the total number of patients needing ECMO during that period separated to be fully assessed.

7.2. Inclusion and exclusion criteria

Inclusion criteria: All adult and paediatric patients with acquired cardiac conditions who needed ECMO following open-heart surgery from 2008 until 2020 will be included in the study.

Exclusion criteria: Patients who had ECMO without heart surgery. Patients with congenital cardiac malformations.

7.3. Study design

Files of cardiothoracic department patients needing ECMO will be analysed for a retrospective descriptive study.

7.4. Sample size

Approximately 60 patients who had ECMO between 2008 and 2020 are expected to partake in the study.

All available statistics of cardiothoracic patients operated on from 2008 to 2020 will be scrutinised. The total number of patients needing ECMO during that period will be separated to be fully assessed according to the information on the datasheet attached.

7.5. Materials

Consent will be obtained from the Head of Department and the hospital CEO to examine old departmental records.

File review will begin once approval for the study has been obtained from the Ethics committee of the University of the Witwatersrand.

A data collection sheet will be drawn up. All available records from patient files, cardiac theatre and the ICU registry will be reviewed for all the information on the data collection sheet.

Before writing up the final report, the study supervisors will review all collected information (Dr SM Mogaladi, Dr IC Taunyane, Dr Ekene E Nweke, and a statistician).

7.6. Data collection

A datasheet will be attached as part of the protocol. The sheet will include each patient's age, gender, diagnosis, comorbid conditions, indication(s) for surgery,

procedure done, preoperative status in terms of NYHA classification, indication(s) for ECMO, ejection fraction and duration of ECMO. Blood tests will include daily urea, creatinine, CRP, WCC, haemoglobin and lactate. The amount of blood transfused and lost (bled) will be noted. Successful or unsuccessful weaning off ECMO, complications on ECMO, mode of ECMO cannulation, presence of sepsis and status at discharge will all be noted. Preoperative IABP and AIBP insertion before ECMO implantation will be taken into consideration.

The success rate will be measured by the total number of patients surviving ECMO - surviving ECMO includes patients that were successfully disconnected from ECMO and remained alive without ECMO for at least 1-2 hours after ECMO removal. The failure rate will be measured by the number of patients dying on ECMO. The possible cause of death of patients dying after ECMO removal will be analysed. From the two statements above: there will be two main groups, which are the survivors and those who demised on ECMO. The group that demised after ECMO extraction will be a subgroup of the group surviving ECMO.

Other treatment modalities that benefit outcomes or are associated with complications, especially for patients on ECMO.

Quality of record-keeping (note-making, methods of record-keeping, and retrievability) will also be recorded.

7.7. Data analysis

Data will be collected and entered onto a standardised spreadsheet using the latest version of Microsoft Excel. Statistical analysis will be carried out using the Statistica software. Continuous data will be calculated using one-way anova test and represented as median and interquartile range. Categorical variables will be calculated using chi-square test and represented as frequencies and percentages. A p-value of 0.05 will be considered significant.

8. ETHICAL CONSIDERATIONS

Ethical approval for the study will be obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg. Permission to perform the study will be requested from the CEO of CMJAH, and the study will be registered on the NHRD. All information will be handled with care to ensure confidentiality is maintained and returned to the hospital record-keeping. File review will be done in a way that respects the rules of the hospital regarding the storing of files. The identity of patients will only be

available to the medical team involved with the study. A coding system will be used to release the collected data so that the files can be traced if necessary. That coding will only be understood by the clinical team involved. No identity of a patient will be shown in any of the publications. The outcome of this study will be used to modify the way ECMO is used in the department for better and more valuable outcomes. The manuscript will be available on request for any educational purposes.

9. LIMITATIONS:

An old filing system might make it difficult to get information on all the patients, and poor documentation might lead to missing data for a concise conclusion. The number of congenital heart conditions needing ECMO might decrease our sample size.

10. TIMELINE:

	Nov 2021	Nov 2021	Mar 2022	Mar 2022	Apr 2022	Apr 2022	May 2022	May 2022	May 2022	June 2022	June 2022	June 2022
Literature Review												
Preparing Protocol												
Protocol assessment												
HOD consent CEO Consent Ethics application HRECH												
Collecting data												
Data analysis												
Writing up-thesis												
Writing up-paper												

Abbreviations

LCOS -Low cardiac output syndrome, CPB -Cardiopulmonary bypass, IABP -Intra aortic balloon pump, STS -Society of thoracic surgeons, EUROSCORE -European System for Cardiac operative risk evaluation, ELSO, Veno arterial extracorporeal membrane oxygenator, VV ECMO-Veno venous extracorporeal membrane oxygenator, NYHA -New York heart association, PCCS -Post cardiectomy cardiogenic shock , ACT -Activated clotting time, PTT -Partial thromboplastin time, AKI -Acute kidney injury, PCS -Post cardiectomy syndrome, ICU -Intensive care unit

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