

USING SOFA SCORES TO IDENTIFY SEPSIS-3 PATIENTS POST-CARDIOPULMONARY  
BYPASS: A RETROSPECTIVE CHART REVIEW TO ANALYZE PRE- AND PERI- OPERATIVE  
PATIENT PREDICTORS FOR SEPSIS-3 DEVELOPMENT

By

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As members of the Master's Committee, we certify that we have read the thesis prepared by Megan Thorbahn, titled Using SOFA Scores TO Identify SEPSIS-3 Patients Post-Cardiopulmonary Bypass: A Retrospective Chart Review To Analyze Pre- AND Peri- Operative Patient Predictors For Sepsis-3 Development and recommend that it be accepted as fulfilling the dissertation requirement for the Master's Degree.

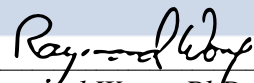
  
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I hereby certify that I have read this thesis prepared under my direction and recommend that it be accepted as fulfilling the Master's requirement.

  
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ARIZONA

TABLE OF CONTENTS

ABSTRACT.....4  
INTRODUCTION.....5  
METHODS.....9  
RESULTS.....11  
DISCUSSION.....19  
CONCLUSION.....23  
REFERENCES.....24

LIST of FIGURES/TABLES

Table 1.....7  
Figure 1.....11  
Table 2.....12  
Table 3.....12  
Table 4.....12  
Table 5.....13  
Table 6.....13-14  
Table 7.....15  
Figure 2.....14  
Table 8.....16  
Table 9.....17  
Figure 3.....18  
Figure 4.....18  
Table 10.....18  
Table 11.....19

## ABSTRACT

Cardiopulmonary Bypass (CPB) allows a cardiothoracic surgeon to operate on a bloodless and still heart, vastly increasing the number of surgical interventions possible to treat various heart diseases. Development of Sepsis-3 after CPB occurs in only a small proportion of the patient population, but this group is characterized by a significantly more complicated post operative course, including a mortality rate above 40%. Sepsis-3 development in this population is due to several reasons, including contact of the blood to the foreign surfaces of the bypass circuit, shear stress from the action of blood being pumped by the circuit, and the general trauma of cardiothoracic surgery. Almost all patients who undergo CPB will experience some level of transient organ dysfunction. However, it is not entirely clear why some patients experience more permanent organ dysfunction and Sepsis-3. The Sequential Organ Failure Assessment (SOFA) score has been used across intensive care units (ICUs) to quickly quantify Sepsis-3 development in patients. Tracking SOFA scores, patients with increase greater than or equal to 2 are diagnosed as Sepsis-3 patients. This retrospective chart review evaluated 102 patients who underwent CPB at Banner University Medical Center - Tucson in 2022, analyzed their pre-operative history, peri-operative values, and post-operative outcomes. SOFA scores were measured at baseline, and then daily post operatively for three days. We found that a higher threshold of increase in SOFA score greater or equal to 4 versus the traditional increase of 2 is required in post CPB patients to accurately discriminate between transient organ dysfunction and actual Sepsis-3 patients. With this new threshold for increase in SOFA score, 13 patients were identified as having Sepsis-3 with suspected or proven infection. Five of them had proven infection with a positive blood, sputum, or urine culture post operatively. The Sepsis-3 group had significantly worse post operative outcomes. This study found that several pre-operative conditions were significantly higher in the Sepsis group; Diabetes, Body Surface Area (BSA), Body Mass Index (BMI), and tobacco use. Of the chemical values typically recorded prior to cardiac surgery, only baseline lactate levels were higher in the Sepsis-3 group when compared to the Non sepsis group. Patients

who develop Sepsis-3 post CPB had longer CPB and Cross-Clamp times. These patients required greater pharmacological and mechanical support post-operatively and had significantly worse morbidities and mortalities. Lactate levels were found to be correlated with a Sepsis-3 development, as well as significantly higher baseline and higher change in lactate levels. Therefore, caution should be used when implementing SOFA scores on CPB patients. Lactate levels could be a biomarker useful for identifying higher risk patients. This can allow physicians to implement prophylactic measures to try and reduce the development of Sepsis-3 post-operatively.

## INTRODUCTION

Cardiopulmonary bypass (CPB) is a process in which a machine takes over the role of the heart and lungs in a patient's body by diverting venous blood away from the heart, oxygenating it, and pumping it back into the aorta. By bypassing the heart and lungs, this allows surgeons to operate on a heart that is not full of blood. In addition, surgeons can place a cross clamp to fully occlude the aorta and deliver a cardioplegic solution solely to heart, which causes it to arrest in diastole. This provides a heart that is still in addition to empty for surgeons to operate on, facilitating complex cardiac procedures such as coronary artery bypass grafts (CABG) and valve replacements. During the early days of CPB, it was observed that a high proportion of patients developed a severe inflammatory response post operatively and were likely to develop infection. This condition was defined as Systemic Inflammatory Response Syndrome (SIRS).(Hirai, 2003; Larmann & Theilmeier, 2004) One of the main causes determined was the contact of the blood with foreign surfaces such as the bypass tubing. This causes an inflammation cascade through activation of the complement system, coagulation cascades, platelets, and immune responses. Other possible causes included general surgical trauma, shear stress from the pump delivering blood to the body, and increased permeability of the endothelial cell layer. This increased permeability can allow for endotoxins from the gut to enter the bloodstream.(Adamik et al., 2000). It also allows for fluid to leave the intervascular space and move into the interstitial space, resulting in edema. This movement of fluid is increased due to dilution of blood volume experienced on cardiopulmonary bypass. Edema can cause

dysfunction of multiple different organ systems. These factors were all found to induce a systemic inflammatory response which can lead to a refractory immunosuppression that might increase susceptibility to infection post operatively.(Träger et al., 2016)

Many advancements have since been made to decrease the inflammatory response caused by CPB. For example, the circuits used for bypass surgery are now coated with hydrophilic and hydrophobic chemicals to try and reduce the activation of the complement system, platelets, and other pathways (Dekker et al., 2020). Additionally, it is common practice for antibiotics to be prescribed prior to initiation of surgery, and in some centers be placed in the liquid used to prime the cardiopulmonary bypass circuit prior to the start of the case as well.(Minton et al., 2017). Steroid administration was implemented as a method to suppress the immune cascade but fell out of favor due to the increased instance of sternal wound infections observed.(Kristeller et al., 2014; Kunihara et al., 2022; Ng et al., 2020).

Despite the preventative measures now implemented, a small proportion of patients continue to develop inflammation and multiple organ dysfunction post-operatively. Although a small proportion of the total CPB patient population, this group represents a significant amount of the total morbidity and mortality rates in the CPB (Howitt et al., 2018). Patients who develop this response post CPB have a significantly more complicated hospital course, including longer stays and higher morbidity and mortality rates.(Hekmat et al., 2010; Howitt et al., 2018; Squicciarro et al., 2019) The following pre-operative variables have been previously associated with increased risk of developing post-operative dysfunction: diabetes, hypertension, and increased age and BMI .(Fowler et al., 2005) However, few studies have looked into the pre-operative laboratory values and perioperative variables such as on pump duration to assess their association with risk of this condition following CPB.

In the literature, SIRS diagnosis is no longer used, as it was found to not fully encompass all of the organ systems involved in this inflammatory pathology (Charkraborty & Burns, 2022; Day & Taylor, 2005). Sepsis-3 diagnosis is the term now used to describe this multi-organ system dysfunction and infection. Sepsis-3 is described as “a life threatening organ dysfunction caused by a dysregulated host

response to infection with particularly profound circulatory cellular, and metabolic circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than Sepsis alone”(Singer et al., 2016). Sepsis-3 can sometimes be a challenge to correctly diagnose in patients, especially when a positive culture proving infection has not been obtained. The Sequential Organ Failure Assessment Score is an effective tool to diagnose patients with Sepsis-3(Liu et al., 2022). The SOFA score has 6 categories each for a major organ system, and each category offers a score of 0-4; 0 meaning no organ dysfunction, 4 indicating severe organ dysfunction. The 6 category scores are summed up to give an overall score that ranges from 0 to 24 and can be seen in Table 1. Meant to be compared over time, a Delta SOFA score change greater than or equal to 2 indicates Sepsis-3 development.(Medlej, n.d.) Some studies have validated the use of SOFA scores in a cardiac surgery ICU, however, others have cautioned the use because the SOFA score does not account for transient organ dysfunction that is typically associated with bypass surgery, opening for the potential to incorrectly diagnose a patient. (Ceriani et al., n.d.; Pätälä et al., 2006; Velho et al., 2022). This results in the possibility of incorrectly diagnosing patients as having Sepsis-3 when in fact they have no significant post-operative complications.

SOFA SCORE	0	1	2	3	4
Respiration PaO <sub>2</sub> /FiO <sub>2</sub>	>400	<400	<300	<200	<100
Coagulation: Platelets	>150	<150	<100	<50	<20
Liver: Bilirubin	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular: Hypotension	None	MAP <70mmhg	Dopamine <5 or dobutamine	Dopamine >5, Epi/Norepi<0.1	Dopamine>15, Epi/Norepi >0.1
CNS: Glascow come score	15	13-14	10-12	6-9	<6
Renal: Creatinine	<1.2	1.2-1.9	2.0-3.4	3.4-4.9	>5.0

CPB has notable effects on all the major organ systems, the severity of which is case dependent. There are three major occurrences on bypass that contribute to transient organ dysfunction. Gaseous Micro-Emboli (GME) are small air bubbles that make it past the numerous filters and bubble traps within

the bypass circuit and get transfused systemically. Although small, these micro emboli can still cause dysfunctions when delivered to organs. Edema resulting from increased permeability in the endothelial cell layer can affect the function of multiple organs. Additionally, transitioning the body from a pulsatile system to a constant flow system can contribute to organ dysfunction. “Pump Lung” is a term used to characterize the effect felt on the respiratory system from CPB. Increased fluid in the interstitial space because of fluid moving out of the intravascular space from osmolarity changes reduces the lungs’ ability to oxygenate the blood. This increases a patients need for respiratory support.(Nteliopoulos et al., 2022)

“Pump head” is the term used to describe the effects of these physiological changes felt on the brain. Gaseous Micro emboli (GME) and edema contribute to temporary neurological defects. Patients can be initially slower to respond or more confused after CPB. Researchers have also observed a temporary increase in liver enzymes after CPB, most likely due to the lack of pulsatile flow while on pump. The kidneys are one of the organs most susceptible to CPB damage, mainly to GME and loss of pulsatility. This has been found to cause a decrease in glomerular filtration rate, and a transient increase in creatinine. Hematological imbalances are common due to the interaction of blood with the foreign surface of the tubing, where platelets are inappropriately activated in response to the activated complement system. Heparin Induced Thrombocytopenia can also occur as a reaction to the use of Heparin to keep patients anticoagulated while on CPB, contributing to observed low platelet levels after the procedure. (Gravlee et al., 2015) For most patients, these effects are short lived, and resolved while recovering from bypass. Because the SOFA score gives only a quantitative value to each organ system, the symptoms of CPB could temporarily raise a patients score as the organ systems recover. Therefore, when we compare SOFA scores from pre-operative to post-operative, transient organ dysfunction can elevate the change in SOFA score, resulting in a patient meeting the criteria for Sepsis-3 diagnosis. However due to the fact that most patients recover with no lasting symptoms from this transient dysfunction, this diagnosis is incorrect, and could reduce the SOFA scoring’s selectivity.

This retrospective chart review looked at patients who went cardiopulmonary bypass and analyzed pre- peri- and post-operative variables that might be associated with risk of developing Sepsis -3 post CPB. We sought to assess whether SOFA scoring was an effective diagnostic tool for discerning between transient organ dysfunction and Sepsis-3 development. SOFA scoring was used to diagnose patients and separate them into non-sepsis patients and Sepsis-3 patients with suspected or proven infection. Secondly, we aimed to determine if there was any significant difference in pre-operative values between the two groups. Determining pre-operative values that could indicate a patient might be more susceptible to Sepsis-3 development could help practitioners identify these high-risk patients and implement prophylactic measures to try and reduce the instance of this post-operative outcome.

## METHODS

This retrospective chart review was pitched as an idea for a project in January of 2023. At this time a Research Intake Application was drafted and submitted to Banner Health. Once approved, we were able to submit this project to the IRB for approval. When the IRB approved our project, we then submitted a data request form allowing us to have access to the patient charts. Surgical patients were identified through the Operating Room Schedule. All patient data was manually extracted from Cerner. Data was taken from the following documents: Cardiothoracic Clinic Note, Daily ICU progress note, Discharge Notes, Death Note (if applicable), and cardiology consults. Peri-operative data was also taken from the Perfusion Record. All lab values and cultures were pulled from the Results Review section in Cerner. A full data record for a patient took about 45 minutes in total. A Timeline of data can be observed in Figure 1. 102 patients who underwent cardiopulmonary bypass surgery in 2022 at Banner University Medical Center – Tucson for a cardiac procedure were analyzed. All surgical procedures were included except for Lung Transplants, due to the extensive immunosuppression therapy in this patient population. Patients were of 18-89 years of age, and all genders and races were included. Any subject who was brought in emergently for surgery and subsequently did not have any pre-operative lab values were not

included for this study. Patients who underwent a lung or heart transplant surgery were also not included, due to the immunosuppression therapy required for transplantation. Patients who came into the Operating room on Extra-corporeal Membrane Oxygenator (ECMO) support were also not included, due to their long-term exposure to a bypass device. Pre and post operative laboratory values were recorded from the patient chart. Pre-operative patient history was taken from the patient's cardiothoracic clinic note. Perioperative values were taken from the cardiopulmonary bypass record. Post operative outcomes were pulled from daily progress notes from the patient chart. Length of stay for patients was taken from their discharge summary, or their expiration was noted from their death note. A baseline SOFA score was calculated from their pre-operative values, and was subsequently calculated after surgery, and at 24-, 48-, and 72-hours post operation. SOFA scores were calculated using the chart in Table 1. For each section, the lowest value for that day was utilized. There were some limitations in the patient chart in regard to the SOFA scoring. Urine output could not be reliably obtained, so creatinine values were used for assessing kidney function. Bilirubin values were not consistently recorded in patients who had normal levels, so it was assumed that Bilirubin values were not elevated unless recorded. Arterial blood gases were used for the Pao<sub>2</sub>/Fio<sub>2</sub> ratio when available, and if not available, Fio<sub>2</sub> scores were assumed to be the established value for the amount of nasal cannula flow. Pharmacological pressor support was taken from the daily progress notes. Appendix 1 displays the full range of data recorded in the Redcap sheets utilized for this study.

All data was entered into RedCap analyzed using STATA(Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. StataCorp.). Based on the sample sizes and the inability to assume normality on multiple data points, non-parametric analysis was used for data analysis. The Wilcoxon Rank Sum test was used to analyze if there was significant difference between the mean values for each variable, and the Fisher's exact test was used to determine if there was difference in rate of categorical variables.

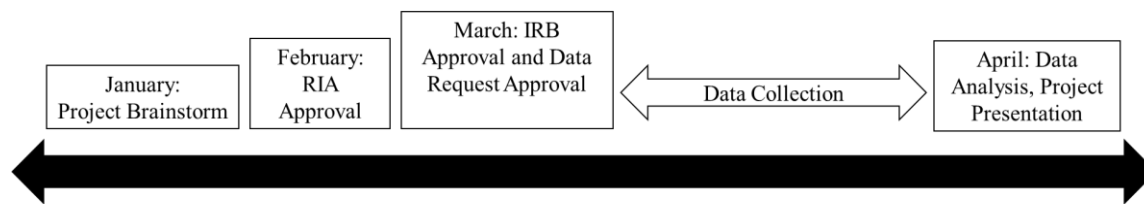


Figure 1. Timeline of Thesis Project, all in 2023. Outlined from Initial Project Brainstorm to Final Project Presentation

## RESULTS

1. Assessing various thresholds of change in SOFA score for diagnosing Sepsis-3 in patients post CPB surgery: Using SOFA Scores  $\geq 2$  to determine Sepsis-3 development in Cardiac Patients provides falsely high rates of sepsis-3 in patients

To analyze the change in SOFA scores in our patient population, a Delta SOFA score was calculated from the baseline value and each time point after CPB, and those with a Delta score greater or equal to two were grouped into Table 2. When using the threshold of a change of greater or equal to 2, a disproportionately large number of patients were indicated as developing Sepsis-3. This was inconsistent with a majority of patients post operative outcomes and discharge notes, where for most patients had no significant complications were listed. Consequently, we determined that in order to increase the specificity of this scoring system, we needed to increase the threshold to a change in SOFA greater than or equal to 4 in Table 3. Additionally, the Delta SOFA between baseline and POD3, to give time for resolution of transient organ dysfunction. Increasing this threshold gave us 89 patients who classified as non-sepsis, and 13 patients who had a delta SOFA greater or equal to 4, and diagnosed with Sepsis-3. We then analyzed blood, sputum, and urine cultures. 5 patients out of the 13 had positive cultures post operatively, therefore classifying them as Sepsis-3 with proven infection. No patients with a delta SOFA less than 4 had confirmed sepsis or infection during the post-operative period, indicating that increasing the threshold did not result in any false negatives. Therefore, increasing the threshold of SOFA score from  $>2$  to  $>4$  reduces the false positive rate for post-operative Sepsis-3 diagnosis, and increases the selectivity of this test.

Table 2. Patients with $\Delta$ SOFA $\geq 2$ from Baseline to Each Post-Operative Score	
$\Delta$	Number of Patients(%)
Baseline-POD0	93 (91%)
Baseline-POD1	72 (71%)
Baseline-POD2	52 (51%)
Baseline-POD3	26 (25%)
Table 3. Patients with $\Delta$ SOFA $\geq 4$ from Baseline to Each Post Operative Score	
$\Delta$	Number of Patients(%)
Baseline-POD0	82 (80%)
Baseline-POD1	54 (52%)
Baseline-POD2	34 (33%)
Baseline-POD3	13 (10%)

## 2. Patient demographics between the two groups

Patient Demographics between the two groups is described in Table 4. There was no significant difference in age between the two groups. The Non-sepsis-3 group has a significantly higher rate of men than our Sepsis-3 group. These two findings were not consistent with the preexisting literature of sepsis-3 development in cardiac surgery patients. The Sepsis-3 with suspected or proven infection patients had significantly higher Body Surface Area and BMI than the non-sepsis group.

Table 4. Patient Demographics compared between $\Delta$ SOFA $< 4$ and $\geq 4$ from Baseline to POD3			
Demographics	$\Delta$ SOFA $< 4$ (N=89) (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection (n=13) SOFA $\geq 4$	P-Value
Age (years)	65.7	67.7	0.34
N of Males (%)	71(79)	7 (54)	0.05
BSA (m <sup>2</sup> )	1.92	2.09	0.05
BMI(units)	26.3	29.8	0.02

We then examined the patients' medical history, social history, and reason for cardiac surgery. Patient's social and medical history is outlined in Table 5. The Sepsis-3 with suspected or proven infection group had a significantly higher proportion of patients with diabetes. All other relevant preexisting health conditions were not significantly different between each group; however, hypertension was trending towards significance with a p-value of 0.08. There was no significant difference in alcohol and drug use between the two groups, but the Sepsis-3 group had a significantly higher number of

patients who were either current or former tobacco users compared to the non-sepsis-3 group. The number of patients who had previously undergone CPB was also not significantly different between the two groups.

Table 5. Patient Social/Medical History compared between patients with $\Delta$ SOFA <4 and $\geq$ 4 from Baseline to POD3			
	$\Delta$ SOFA <4 (N=89) (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection (N=13) SOFA $\geq$ 4	P-Value
Diabetes, N (%)	33 (37%)	3(23%)	0.03
Hypertension, N (%)	68 (76%)	7(54%)	0.08
Pulmonary Hypertension, N (%)	2(0.02%)	0(0%)	0.76
COPD, N (%)	1(0.08%)	1(0.08%)	0.24
Hyperlipidemia, N (%)	49(55%)	6	0.38
Former/Current Smoker, N (%)	48(54%)	12(92%)	0.01
Drug use, N (%)	19(21%)	3(23%)	0.56
Previous Cardiac Surgery, N (%)	6(0.06%)	1(0.08%)	0.63

Cardiac Pathologies were recorded, and sub-grouped by valve pathologies, dysrhythmias, and contractile dysfunctions in Table 6a-c. Pre-operative hematological disorders were also recorded, including strokes, DVTs, and PEs. There was no significant difference observed between the two groups in regard to any of these values. However, the number of patients with no observed valve pathology was significantly smaller in the Sepsis-3 group with a p-value of 0.010. This indicates that more patients who developed sepsis post operatively had at least one valvular pathology when compared to the non-sepsis-3 group.

Table 6a. Valve Pathologies compared between patients with $\Delta$ SOFA <4 and $\geq$ 4 from Baseline to POD3			
	$\Delta$ SOFA<4 (N=89) (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection (N=13)	P-Value
Aortic Stenosis, N (%)	10 (11%)	4(31%)	0.07
Aortic Regurgitation/Insufficiency, N (%)	10(11%)	3(23%)	0.21
Mitral Stenosis, N (%)	1(0.01%)	0(0%)	0.87

Mitral Regurgitation/Insufficiency, N (%)	18(20%)	5(38%)	0.13
Tricuspid Regurgitation, N (%)	6(0.07%)	0(0%)	0.43
Pulmonary Stenosis, N (%)	0(0%)	0(0%)	n/a
Endocarditis, N (%)	4(0.04%)	2(15%)	0.17
None, N (%)	55(62%)	3(23%)	0.01

Table 6b. Cardiac Pathologies compared between patients with  $\Delta$ SOFA<4 and  $\geq$ 4 from Baseline to POD3

	$\Delta$ SOFA<4 (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection	P-Value
Coronary Artery Disease, N (%)	61(69%)	7(54%)	0.23
Right Ventricular Hypertension, N (%)	0(0%)	0(0%)	n/a
Atrial Dysrhythmias, N (%)	10(11%)	2(15%)	0.47
Ventricular Dysrhythmias, N (%)	5(0.06%)	0(0%)	0.50
NSTEMI/STEMI, N (%)	21(24%)	2(15%)	0.40
None, N (%)	18(20%)	5(38%)	0.13

Table 6c. Blood Pathologies compared between patients with  $\Delta$ SOFA<4 and  $\geq$ 4 from Baseline to POD3

	$\Delta$ SOFA<4 (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection	P-Value
Stroke, N (%)	2(0.02%)	0(0%)	0.76
DVT, N (%)	2(0.02%)	0(0%)	0.76
PE, N (%)	0(0%)	0(0%)	n/a
Sickle Cell, N (%)	0(0%)	0(0%)	n/a
Cold Agglutinins, N (%)	0(0%)	0(0%)	n/a

- Sepsis-3 patients with suspected/proven infection had increases morbidity and mortality.

As a means to validate our data collection, post operative outcomes were compared between the two groups, namely length of stay in the ICU, hospital, and intubation times in Table 7. The Sepsis-3 with Suspected or Proven infection Group had significantly longer lengths of stay in the ICU, the hospital, and remained intubated significantly longer. When looking at box plots of these variables, the Sepsis-3 with Suspected or Proven Infection group displayed no significant outliers, displaying that there was no one patient skewing these values. Conversely, there were significant

outliers in the non-sepsis group, which caused a rightward skew in the data, and indicated that there was likely an even greater difference between the two groups.

We then analyzed post-operative morbidity and mortality rates in each group in Table 8. The Sepsis-3 with Suspected or Proven Infection group had a significantly higher proportion of patients requiring intervention, including transfusions and continuous renal replacement therapy, kidney failure (CRRT). We also found that the rate of mechanical support required post operatively was trending towards significance. Incidence of stroke was significantly higher in the Sepsis-3 with suspected or proven infection group compared to the non-sepsis group. Mortality was also higher in our Sepsis-3 with Suspected or Proven infection group. Only one subject in the Non-Sepsis-3 group died, and the cause of death was listed as stroke, compared to 4 patients who died in the Sepsis-3 with Suspected or Proven Infection.

Outcomes	$\Delta$ SOFA<4 (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection	P-Value
Total Time Intubated (hrs)	10.4	87.6	<0.01
LOS ICU (days)	3.19	6.69	<0.01
LOS Hospital (days)	6.52	9.61	<0.01

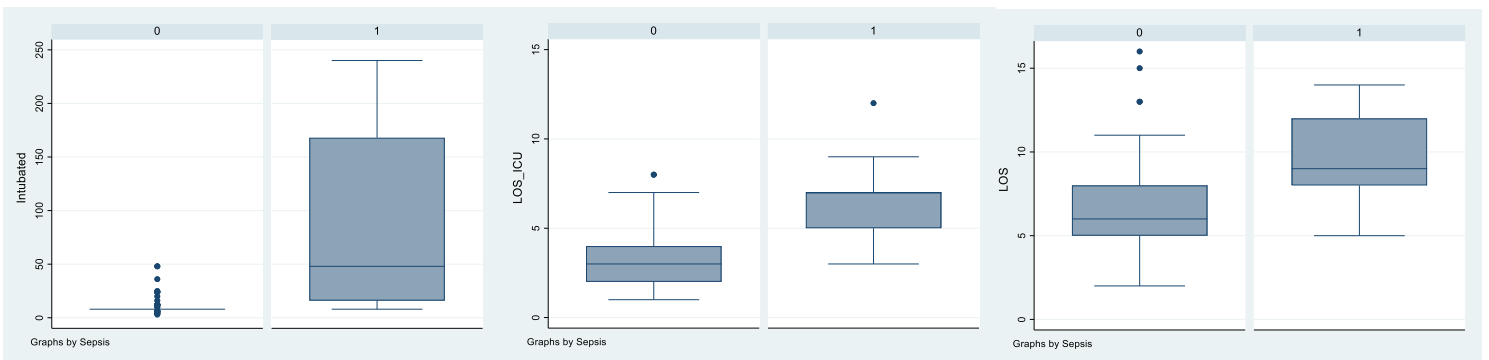


Figure 1. Box Plots Comparing (Left to Right) Total time Intubated, Total Length of Stay in ICU, Total Length of stay in Hospital between Non-Sepsis-3 and Sepsis-3 patients with suspected/proven infection.

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	$\Delta$ SOFA<4 (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection $\Delta$ SOFA $\geq$ 4	P-Values
Transfusion Required Post-Op (pRBCs) , N (%)	29 (33%)	10(77%)	<0.01
Stroke, N (%)	1(0.01%)	2(15%)	0.04
DVT/PE, N (%)	0(0%)	0(0%)	n/a
CCRT Required, N (%)	2(0.02%)	4(31%)	<0.01
Mechanical Support Required, N (%)	4 (1 IABP, 1 Impella, 3 VA ECMO) (0.04%)	4 (1 IABP, 1 Impella, 3 VA ECMO) (31%)	0.06
Death, N (%)	1(0.01%)	4(31%)	<0.01

4. Patients with a SOFA score  $\geq$  4 on POD3 experienced longer bypass and cross clamp times, and well as increased intervention during surgery.

Peri-operative values were recorded from the Perfusion Record and listed in Table 9. The Sepsis-3 with Suspected or Proven Infection group were on bypass for significantly longer times and experienced significantly longer cross clamp periods. Longer cross clamp time requires more cardioplegia more proper myocardial infection, so it follows that this group also received significantly more cardioplegia during the operation. All patients in this study received Del Nido as the cardioplegic solution. We hypothesized that the Sepsis-3 group might be cooled to lower temperatures during surgery that could play a factor in later low platelet counts, but there was no significant difference in coldest core temperature experienced on pump. We hypothesize with a large patient population that the Sepsis group will experience significantly colder core temperatures.

We recorded the highest lactate level observed while on bypass, and this was significantly higher in our Sepsis-3 group, and this was also in hyperlactemia range. We also recorded the total amount of phenylephrine delivered while on bypass. As the perfusionist takes on the primary role of pressure control, this variable could provide insight into a patient developing vasoplegia while on pump that could translate to increased pressure requirements in the ICU. This value was not significantly different between the two groups, but again we observed some skewedness from high outliers in the non-sepsis group. This can also be seen when we compared the non-sepsis group to just the Sepsis with Proven infection, where the proven infection group required significantly more phenylephrine. While the strength

of this test is reduced due to the small number of subjects in the Sepsis-3 with Proven Infection, the p-value for this test was 0.001. A significantly higher proportion of patients in the sepsis-3 group required pRBCs during bypass surgery. There was no significance in the number of patients who needed mechanical support to terminate CPB.

Table 9. Peri-Operative Data compared between patients with a $\Delta$ SOFA from Baseline to POD3 of $<4$ and $\geq 4$			
	$\Delta$ SOFA $<4$ (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection $\Delta$ SOFA $\geq 4$	P-Value
Total CPB Time (min)	123.4	192.9	$<0.01$
Total XC Time (min)	94.6	130.8	0.02
Total Cardioplegia Delivered (ml)	1504.7	2245.3	$<0.01$
Coldest Core Temp (Celsius)	34.29	34.0	0.12
Highest Lactate (mmol/L)	1.65	3.66	$<0.01$
Total Phenylephrine used on pump (mg)	4.88	7.38	0.13
N of patients requiring pRBC transfusion on pump, N (%)	7(0.08%)	9(69%)	$<0.01$
N of patients requiring mechanical support, N (%)	6(0.07%)	3(23%)	0.08

Figure 3. Box Plot of Highest Lactate on pump between  $\Delta$ SOFA $<4$  and  $\Delta$ SOFA $\geq 4$  from baseline to POD3

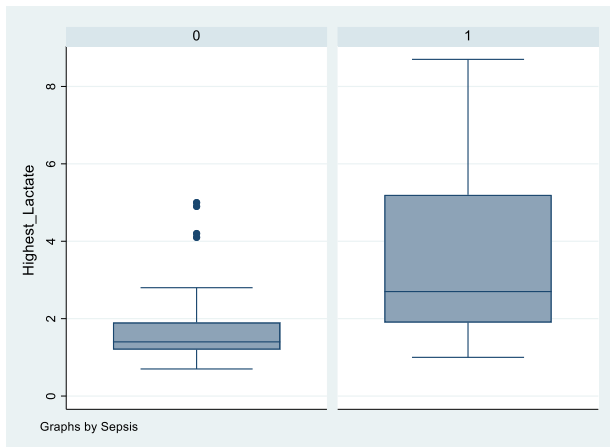
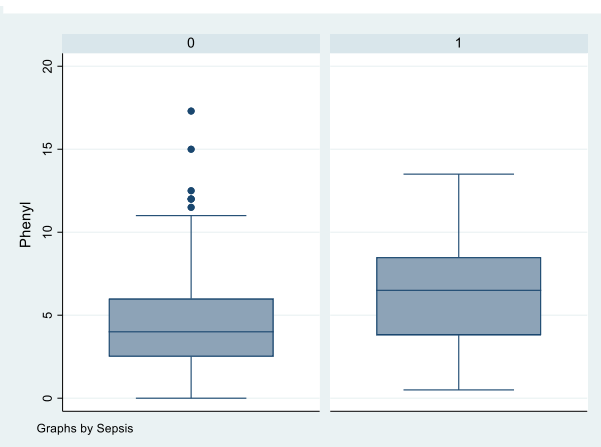


Figure 4. Box Plot of Phenyl Use on Pump between  $\Delta$ SOFA $<4$  and  $\Delta$ SOFA $\geq 4$  from baseline to POD3



## 5. Pre-operative Lab Values

Pre-operative lab values commonly taken prior to CPB were recorded for each patient and are displayed in Table 10. There was no significant difference in all values except for baseline lactate levels. The Non sepsis group displayed significantly lower baseline lactate levels when compared to the Sepsis-3 with Suspected or Proven Infection group.

Table 10. Pre-Operative Lab Values compared between patients with a $\Delta$ SOFA<4 and a $\Delta$ SOFA $\geq$ 4 from Baseline to POD3			
Lab Value	$\Delta$ SOFA<4 (Non-Sepsis-3)	Sepsis-3 with Sepsis/Proven Infection ( $\Delta$ SOFA $\geq$ 4)	P-Value
Creatinine ( $\mu$ mol/L)	1.14	1.49	0.84
BUN (mg/dL)	19.43	21.46	0.71
Bilirubin ( $\mu$ mol/L)	0.65	0.65	0.67
WBC ( $\times 10^9$ /L)	7.81	7.93	0.63
Platelets ( $\times 10^3$ / $\mu$ L)	216.4	208.45	0.64
Lactate (mmol/L)	1.03	1.51	0.01

#### 6. Post-Operative Lab Values

For each patient, the highest recorded WBC count, highest recorded body temperature, and highest creatinine were documented in Table 11. None of these values were significantly different between the two groups. This could be due to the fact that these values were recorded at any time post-operatively. Therefore, the highest WBC for a non-sepsis-3 patient could have been recorded directly after surgery, and then all subsequent values could have been reduced back to normal. From these values we calculated the change in WBC count from pre-operative lab values to highest recorded post operatively. This value was also not significantly different. The change in lactate was calculated by finding the difference between the pre-operative value and the highest value recorded on pump. The change in lactate was found to be significantly higher in our Sepsis-3 with Suspected or Proven Infection group. So not only did the Sepsis-3 group display higher baseline lactate, and a higher point of lactate on pump, they also experienced a stronger increase of lactate while on CPB. These findings display the effect transient organ dysfunction has on the body, and how it can be difficult to discern between the Sepsis-3 and CPB aftereffects.

Table 11. Post-Operative Lab Values compared between patients with a $\Delta$ SOFA<4 and a $\Delta$ SOFA $\geq$ 4 from Baseline to POD3			
Lab Values	$\Delta$ SOFA<4 (Non-Sepsis-3)	Sepsis-3 with Suspected/Proven Infection ( $\Delta$ SOFA $\geq$ 4)	P-Value
Highest WBC ( $\times 10^9/L$ )	15.37	15.26	0.59
Change in WBC	7.55	7.32	0.80
Highest Body Temp (Celsius)	37.6	37.6	0.93
Highest Creatinine( $\mu\text{mol/L}$ )	1.38	2.1	0.21
Change in Lactate	0.62	2.15	0.01

DISCUSSION

There were several pre-operative conditions that we found to be associated with a greater chance of Sepsis-3 development post-operatively: Body Surface Area/Body Mass Index, Tobacco use, and Diabetes. Increased BSA and BMI levels have long been linked to comorbidities and poor patient outcomes. Effect of the use of Tobacco is established in the literature, where the dysregulation of the immune systems caused by diabetes contributes to an increased likelihood of infection and Sepsis-3. Tobacco use was higher in the Sepsis-3 with Suspected or Proven infection group. Tobacco use is associated with an increase in respiratory infection, as well as systemic inflammation from oxidative stress. (Zhang et al., 2022) These factors can contribute to an increased chance of sepsis-3 development postoperatively due to the contribution they make toward a patient’s susceptibility towards organ dysfunction.

This study found that using the SOFA score diagnosis of greater than or equal to two results in a falsely high proportion of Sepsis-3 diagnosis in CPB patients. We found that the transient organ dysfunction associated with CPB gave these patients high SOFA scores, but they did not display any Sepsis-3 symptoms and had a normal recovery progression. Factors commonly associated with CPB post operative course, including mechanical ventilation and pressor requirements contribute to the elevated SOFA scores in this population Both these factors would be gradually weaned until a patient was

tolerating room air and on no pressors, as patients recovered from their transient organ dysfunction.

Increasing the threshold for Sepsis-3 diagnosis proved to be much more effective at patient separation. We were able to effectively separate patients who developed Sepsis-3. This was validated by the fact that all patients who had a positive post-operative culture were included in our Sepsis-3 group, and no patients with a SOFA change below 4 had a positive culture post-operatively.

The patients identified as developing Sepsis-3 with suspected or proven infection displayed outcomes consistent with the literature of similar studies. They had longer stays in the ICU, the hospital, and remained intubated for longer amounts of time. They experienced higher rates of mortality, incidence of stroke. They required a greater number of interventions including CRRT and blood transfusions, These findings highlight that although a small proportion of CPB patients develop Sepsis-3 post operatively, they represent a significant challenge to the hospital in terms of recovery. Therefore, minimizing this patient population is very important.

The patients classified as Sepsis-3 with Suspected/Proven Infection displayed longer pump runs and cross clamp times. This indicates that longer times on pump increases the chance for organ dysfunction, due to GME, ischemia, edema, and inflammatory responses from the blood's contact with foreign surfaces. A higher proportion of patients who developed Sepsis-3 post-operatively required Red Blood Cell Transfusion while on pump.

One of the main aims of this study was to find any pre-operative lab values that were significantly abnormal in the sepsis group, which could provide clinicals with an indication that a specific patient might be more susceptible to sepsis development post CPB. The novel finding of this retrospective study came from the lactate levels. Of all variables assessed, only lactate levels were significantly higher in the Sepsis group when compared to the non-sepsis group, at 1.5 mmol/L. Peak Lactic Acid levels while on pump were significantly higher in the Sepsis-3 patient group.

Lactic acid is produced by anaerobic metabolism and is developed and cleared at normal physiological rates. Blood lactate levels have been indicated as a measure of organ function, including respiratory, cardiac, and liver function. Increased lactic acid in the blood could be due to an increase of anaerobic metabolism, which would occur when the tissues of the body are not receiving enough oxygen for aerobic metabolism.(Foucher & Tubben RE, 2023) Lactate levels have long been used as a diagnostic marker for severity of diseases and disease progression. While mainly a marker for inadequate oxygen delivery, lactate levels can be severe as an indication of multiple other organ system dysfunction. For example, the liver is the major mechanism for clearance of lactate, and rising lactate levels could indicate liver dysfunction.(Andersen et al., 2013) However, when looking at the pre-operative bilirubin levels, we observed no difference in baseline values between our two groups, indicating that liver dysfunction is not the cause for this increase in baseline lactate. There is some research to suggest that Diabetic patients can also have elevated lactate levels due to ketoacidosis. (Andersen et al., 2013). Considering we observed a higher incidence of diabetics in our Sepsis group, this could be one possible explanation for why the baseline lactate levels were higher for this group. A stronger argument could be made for the correlation between lactate levels and myocardial dysfunction.

Reducing the function of the heart decreases the perfusion of the tissues in the body, resulting in an increase of anaerobic metabolism and blood lactate levels. Additionally, the heart itself starts to produce lactate when it is not being adequately perfused due to coronary artery disease. Interestingly, while the lactate level was elevated when compared to the non-sepsis group, the average was still underneath diagnosis threshold for hyperlactemia (2 mmol/L). Therefore, these patients are not flagged as having decreased tissue perfusion or occurrence of lactic acidosis, but we still found that this population developed severe organ dysfunction post-operatively compared to patients with lower baseline levels. Therefore, elevation in baseline lactate levels could serve as a predictor for increased susceptibility to organ dysfunction and even Sepsis-3 development postoperatively, as it is indicative of mild organ ischemia/dysfunction that could be easily exaggerated with cardiopulmonary bypass.

Additionally, the sepsis group experienced significantly higher peak lactate levels on pump as well as greater increases of lactate levels. The environment of cardiopulmonary bypass could cause increasing blood lactate levels due to the disturbance from normal tissue perfusion (Foucher & Tubben RE, 2023; Minton et al., 2017). Increasing lactate levels on pump are used to indicate inadequate oxygen delivery as well as acidosis Lactic Acid elevation on pump has also been contributed to Septic shock (CITE). Longer pump run times are associated with greater increases of Lactate levels. This finding was observed in our patient population. Previous studies have found that an elevated lactate level perioperatively can predict post operative complications and mortality. (ANISS) This study corroborates this finding and displays a correlation between increasing lactate levels perioperatively and post-operative sepsis-3 development.

A close monitoring of baseline lactate levels could help isolate patients susceptible to Sepsis-3 development post-operatively. Our findings show that even mild elevation of lactate not normally flagged as abnormal (above 1.5 mmol/L) could indicate a patient having a higher risk of Sepsis-3 development postoperatively.

The main limitation of this study is the small patient population. With a larger patient population, the strength of statistical analysis will increase. Increasing the group of patients with proven infection will help improve our statistical analysis. Additionally, the study can isolate groups based on social history and type of surgical intervention. Being able to isolate specific variables of interest by controlling for other variables will increase the strength of our results.

## CONCLUSIONS

The goal of this chart review was to find any pre-operative lab values that could indicate a patient as more likely to develop Sepsis-3 Post-operatively, and determine the efficacy of the SOFA score to discern between Sepsis-3 and transient organ dysfunction from CPB. It was found that SOFA scoring was

not entirely effective at discerning between these two groups. Therefore, we conclude that the SOFA scoring tool should be altered when used on cardiopulmonary bypass patients due to transient organ dysfunction. We found that baseline blood lactate levels above 1.5mmol/l and a change in lactate levels above 2.0 mmol/L can both be indicative of later Sepsis-3 development. Therefore, Lactate levels might be a useful biomarker for predicting which patients might be more susceptible to Sepsis-3 after CPB. Using this biomarker could help physicians target certain patients at a higher risk for post-operative complications, and implement prophylactic measures.

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