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Validation of utilizing the pediatric Sequential Organ Failure Assessment scoring system in patients with congenital heart disease

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VALIDATION OF UTILIZING THE PEDIATRIC SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORING SYSTEM IN PATIENTS WITH CONGENITAL HEART DISEASE

by

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ABSTRACT

The Sequential Organ Failure Assessment has been used to track a patient's status for over two decades. It essentially provides a numeric value to quantify the severity of organ dysfunction, most commonly used in sepsis (1). This assessment system was primarily developed for adult patients. However, this threshold cannot be applied in pediatric patients as organ function matures over time. A team of researchers published a paper in 2017 describing the SOFA scale adjusted for pediatric populations (Pediatric Sequential Organ Failure Assessment; pSOFA). Furthermore, they conducted a retrospective study to validate the use of their pSOFA scoring system in pediatric patients admitted to the general Intensive Care Unit. This demonstrated a good correlation with the study for adult patients (2). Patients with congenital heart disease (CHD) often have abnormal circulatory patterns, which can significantly affect cardiovascular and respiratory systems at baseline. This thesis project aims to explore the utilization of pSOFA in assessing the severity of illness in critically ill pediatric patients with congenital heart disease (CHD). Retrospective data collection was carried out in a population of patients with CHD during their stay in the Cardiac ICU (CICU) at Boston Children's Hospital. Two pSOFA scores, separated based

on using indirect vs. direct bilirubin values, were assigned each day spent in the CICU for 101 patients. Of these 101 patients, 50 had a diagnosis of cyanotic CHD while 51 patients had acyanotic CHD. pSOFA scores were compared between cyanotic and acyanotic patients with CHD as well as with a cohort of patients without CHD. This was an exploratory study which provides a deeper understanding for future analysis in order to validate the utilization of pSOFA in a population of patients with CHD.

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LIST OF ABBREVIATIONS

BU ..... Boston University

CHD.....Congenital Heart Disease

HSCT.....Hematopoietic Stem Cell Therapy

pSOFA..... Pediatric Sequential Organ Failure Assessment

SOFA..... Sequential Organ Failure Assessment

INTRODUCTION

Subsection 1: Summary/Aims

The Sequential Organ Failure Assessment (SOFA) score was originally developed in the 1990s to describe the severity and risk of organ dysfunction. It is frequently used for quantification in critically ill patients with sepsis based on the Sepsis-3 definition (1). SOFA is comprised of six sub-scores for six organ systems which will be explained in more detail in the following section. The SOFA was developed primarily for adult patients; however, since pediatric patients undergo organ development and maturation, it is critical to use different criteria from the SOFA. In 2017, a group of investigators published the SOFA scoring system in which the cardiovascular and renal system scores were adjusted for pediatric patients. The respiratory system score was expanded to account for cases in which only noninvasive measurements were available (1).

This adjusted Pediatric SOFA scoring system will be called the pSOFA. This scoring system was validated by the investigators using data from Intensive Care Unit (ICU) patients in their institution, which demonstrated a good correlation with the original SOFA, particularly in the context of in-hospital mortality. Following this report, Dr. Koichi Yuki's group tested the pSOFA in patients who were admitted to the ICU after receiving hematopoietic stem cell therapy (HSCT). In line with the previous study, higher pSOFA scores correlated well with higher mortality.

This thesis aims to examine the pSOFA scoring system in patients with congenital heart disease (CHD) who were admitted to the Cardiac Intensive Care Unit (CICU). Patients with CHD were further classified into acyanotic CHD and cyanotic CHD. We hypothesized pSOFA scores for patients with cyanotic CHD to be significantly higher than those of patients with acyanotic CHD secondary to presumed higher respiratory scores (23-27). Further background information and details regarding methods are discussed in the following section.

Subsection 2: SOFA & pSOFA

The SOFA scoring system is often used to track the severity and progression of organ dysfunction due to severe sepsis (10). The SOFA score is subdivided into 6 subscores. These include respiratory, coagulation, hepatic, cardiovascular, neurologic, and renal subscores (1). The respiratory score uses PaO_2/FiO_2 (mmHg) or SpO_2/FiO_2 values. PaO_2/FiO_2 is the ratio of partial pressure of arterial oxygen to the percentage of inspired oxygen, while SpO2/FiO2 is the ratio of blood oxygen saturation level to the percentage of inspired oxygen (30). The coagulation subscore uses platelet count values (x $10^3/mm^3$), the hepatic subscore uses total bilirubin values (mg/dL), the cardiovascular subscore uses mean arterial pressure (MAP) in mmHg, the neurologic subscore uses the Glasgow coma score, and the renal subscore is measured by creatinine levels (mg/dL) or urine output (mL/day). The original SOFA system is illustrated Table 1 (1).

SOFA Score	0	1	2	3	4
Respiration					
PaO_2/FiO_2 (mmHg)	>400	≤400	<300	<200 With respiratory support	<100 With respiratory support
Coagulation					
Platelets x $10^3/mm^3$	>150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (µmol/l)	<1.2 <20	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (< 204)
Cardiovascular					
Hypotension	No hypotension	MAP <70	Dopamine ≤ 5 or dobutamine (any dose)[a]	Dopamine > 5 or epinephrine ≤ 0.1or norepinephrine ≤0.1	Dopamine >15 or Epinephrine > 0.1 or norepinephrine >0.1
CNS					
Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (µmol/l) or urine output (mL/day)	<1.2 (<110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (> 440) or <200 mL/day

MAP, mean arterial pressure; CNS, central nervous system

[a] Adrenergic agents administered for at least 1 h (doses given in µg/kg/min)

Table 1. Sequential Organ Failure Assessment Score. Primarily developed for adult patients and was used as a basis to develop the modified pediatric version (1).

This SOFA scoring system was developed for adults and does not have age-adjusted value cut-offs which would be more appropriate for children (13). A study conducted in 2001 adjusted the cardiovascular subscore and made a modified SOFA (m/SOFA) scoring system for pediatric patients after cardiac surgery (5). They found that with the m/SOFA system, an initial score of greater than 5 predicted higher postoperative mortality as well as an increased need for intensive care (5). This study however did not have age adjusted measures for the renal subscore (2). This was a concern due to findings that suggested that

there could be increased severity of kidney dysfunction in children admitted to the ICU (15-17). Therefore, the renal subscore in the pSOFA table was adjusted for age as well. Similarly, there have been no modifications of the respiratory subscore either (2). The pSOFA modification in regard to the respiratory subscore includes the option of using SpO_2/FiO_2 when PaO_2/FiO_2 is unavailable. This is due to the lower frequency of having an arterial line or obtaining an arterial sample in pediatric patients (18-20). Given these three modifications in the respiratory, cardiovascular, and renal subscores, the modified pediatric version of SOFA (pSOFA) is presented in **Table 2** (2). The coagulation and neurologic subscores remained from the original SOFA. The hepatic score is calculated with total bilirubin in this chart; however, this thesis also aimed to explore the differences in utilizing indirect and direct bilirubin values. Therefore, two hepatic scores and furthermore two total scores (utilizing indirect and direct bilirubin values) were assigned to each patient in this study. This is further explained in the methods section.

	Score[a]				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory					
PaO_2/FiO_2[b] or SpO_2/FiO_2[c]	≥400 ≥292	300-399 264-291	200-299 221-264	100-199 with respiratory support 148-220 with respiratory support	<100 with respiratory support <148 with respiratory support
Coagulation					
Platelet count, $x10^3/\mu L$	≥150	100-149	50-99	20-49	<20
Hepatic					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular					

MAP by age group or vasoactive infusion, mmHg or μg/kg/min[d]					
<1mo	≥46	<46	Dopamine hydrochloride ≤5 or dobutamine hydrochloride (any)	Dopamine hydrochloride <5 or epinephrine ≤0.1 or norepinephrine bitartrate ≤0.1	Dopamine hydrochloride <15 or epinephrine <0.1 or norepinephrine bitartrate >0.1
1-11mo	≥55	<55			
12-23mo	≥60	<60			
24-59mo	≥62	<62			
60-143mo	≥65	<65			
144-216mo	≥67	<67			
>216mo[e]	≥70	<70			
Neurologic					
Glasgow Coma Score[f]	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1mo	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥1.6
1-11mo	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥1.2
12-23mo	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥1.5
24-59mo	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥2.3
60-143mo	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥2.6
144-216mo	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥4.2
>216mo[e]	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5

Abbreviations: FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; pSOFA, pediatric Sequential Organ Failure Assessment; SpO_2, peripheral oxygen saturation.
SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.104; creatinine to micromoles per liter, multiply by 88.4; and platelet count to $x10^9$/L, multiply by 1.
[a]The pSOFA score was calculated for every 24-hour period. The worst value for every variable in each 24-hour period was used to calculate the subscore for each of the 6 organ systems. If a variable was not recorded in a given 24-hour period, it was assumed to be normal and a score of 0 was used. Daily pSOFA score was the sum of the 6 subscores (range, 0-24 points; higher scores indicated a worse outcome).
[b]PaO_2 was measured in millimeters of mercury.
[c]Only SpO_2 measurements of 97% or lower were used in the calculation.
[d]MAP(measured in millimeters of mercury) was used for scores 0 and 1; vasoactive infusion (measured in micrograms per kilogram per minute), for scores 2 to 4. Maximum continuous vasoactive infusion was administered for at least 1 hour.
[e]Cutoffs for patients older than 18 years (216 months) were identical to the original SOFA score.
[f]Glasgow Coma Scale was calculated using the pediatric scale.

Table 2. Pediatric Sequential Organ Failure Assessment. Modified version with measurements and cutoffs adjusted to pediatric patients (2).

Subsection 3: pSOFA with HSCT Recipients

A previous study in this lab evaluated the utilization of the pSOFA scoring system in 2018 with a population of patients who were admitted to the ICU after receiving Hematopoietic Stem Cell Therapy (HSCT) with the attempt to delineate the risk factors associated with mortality. Data collection from this study was used as a non-CHD patient population. This was compared to the CHD patient populations (cyanotic and acyanotic) in order to explore the possibility of pSOFA utilization in two different disease populations. This subsection aims to provide further information regarding this past study as well as information about the data collected from the non-CHD patient population used in this thesis.

HSCT is used to treat many hematological diseases such as lymphoma, leukemia, and immune-deficiency illnesses in the pediatric population with a survival rate of ≥ 80% (21). However, many patients do suffer from complications after receiving HSCT. Some of them are admitted to the ICU, and those admitted to the ICU are associated with high mortality. Therefore, further studies can be done to understand the risk factors that could lead to ICU admission following HSCT as well as the risk factors associated with mortality.

In order to address this, this study was conducted using a retrospective review of the electronic medical records of pediatric patients admitted to the ICU following HSCT at Boston Children's Hospital between January 2010 and June 2018. Data was used from 104 patients and was divided into three groups. Group A (n_a=75) is a population of pediatric patients admitted to the ICU after their first

HSCT. Group B (n_b = 15) is a population of pediatric patients discharged home following HSCT but re-admitted to the ICU due to post-transplant complications. Group C (n_c = 14) who had failed HSCT(s) and were admitted to the ICU after an additional HSCT. pSOFA subscores were assigned to the each of the six organ systems, and a pSOFA score was assigned to each day the patient stayed in the ICU in order to assess for organ injury. The mortality rate was calculated and the pSOFA scores were used to determine risk factors associated with mortality using univariable and multivariable statistical analysis. Overall, this study found that higher neurologic and cardiovascular subscores were associated with a higher incidence of mortality. These results are illustrated in the table below.

Group A	Survivor (n=55)	Non-survivor (n=20)	P value	Odds Ratio (95% C.I.)
Age (years)	3.75 [1.00, 9.17]	12.25 [2.48, 16.27]	0.029*	1.09 [1.01-1.17]
Gender	Male 34 (61.8%)	Male 9 (45.0%)	0.196	0.51 [0.18-1.42]
Admission pSOFA	7.00 [5.00, 9.00]	8.50 [6.00,11.25]	0.232	1.08 [0.95-1.23]
Average pSOFA	6.00 [5.19, 7.85]	12.70 [10.14, 15.67]	< 0.001*	2.23 [1.49-3.33]
Maximum pSOFA	9.00 [7.00, 13.00]	18.00 [15.75, 19.25]	< 0.001*	1.67 [1.32-2.11]
Duration of ICU Stay	11.00 [5.00, 32.00]	33.50 [11.00, 51.50]	0.446	1.01 [0.99-1.02]
Group B	Survivor (n=11)	Non-survivor (n=4)	P value	Odds Ratio (95% C.I.)

Age (years)	7.33 [2.25, 9.75]	14.58 [13.46, 15.27]	0.113	1.24 [0.95, 1.62]
Gender	Male 5 (45.5%)	Male 0 (0%)	n/a	n/a
Admission pSOFA	5.00 [2.50, 7.00]	7.25 [5.00, 9.25]	0.541	1.08 [0.84, 1.39]
Average pSOFA	3.75 [2.89, 5.83]	8.60 [7.85, 9.12]	0.074	1.78 [0.95, 3.35]
Maximum pSOFA	5.00 [4.00, 11.0]	11.00 [10.00, 12.75]	0.222	1.17 [0.91, 1.50]
Duration of ICU Stay	4.00 [1.00, 5.00]	4.00 [4.00, 31.50]	0.307	1.04 [0.97, 1.11]
Group C	Survivor (n=55)	Non-survivor (n=20)	P value	Odds Ratio (95% C.I.)
Age (years)	6.42 [2.58, 13.42]	5.50 [2.42, 8.92]	0.428	0.92 [0.74, 1.33]
Gender	Male 7 (77.8%)	Male 4 (80.0%)	0.923	1.14 [0.08, 16.95]
Admission pSOFA	6.00 [4.00, 7.00]	6.00 [5.00, 9.00]	0.816	0.96 [0.68, 1.35]
Average pSOFA	6.21 [5.33, 7.75]	12.31 [8.69, 14.83]	0.111	1.29 [0.99, 1.68]
Maximum pSOFA	10.00 [6.00, 11.00]	18.00 [18.00, 19.00]	0.064	1.29 [0.99, 1.68]
Duration of ICU Stay	9.00 [7.00, 11.00]	29.00 [21.00, 63.00]	0.167	1.03 [0.99, 1.07]

Table 3. Characteristics of patients who received HSCT and admitted to ICU. Profiles of survivors and non-survivors in Groups A, B, and C. Age, admission pSOFA, average pSOFA, maximum pSOFA and duration of ICU stay were shown as median [25th percentile, 75th percentile]. *denotes statistical significant. C.I denotes confidence interval; n/a denotes not available.

	No. of Survivors	No. of Non-survivors	Mortality
Group A (n=75)	55	20	26.7%
Group B (n=15)	11	4	26.7%
Group C (n=14)	9	5	35.7%

Table 4. Incidence of Mortality of patients who received HSCT and admitted to ICU.

Group A				
Type of Organ Injury	**Survivor (n=55)**	**Non-survivor (n=20)**	**P values**	**Odds ratio (95% C.I.)**
Neurological Injury	0.00 [0.00, 1.00] (0.64)	4.00 [3.00, 4.00] (3.00)	< 0.001*	2.92 [1.86-4.58]
Cardiovascular Injury	0.00 [0.00, 1.00] (0.18)	1.50 [0.00, 3.00] (1.60)	< 0.001*	2.96 [1.66-5.26]
Respiratory Injury	0.00 [0.00, 0.00] (0.65)	1.50 [0.25, 2.75] (1.55)	0.010*	1.74 [1.14-2.65]
Hepatic Injury	0.00 [0.00, 0.00] (0.31)	2.00 [0.00, 2.00] (1.20)	0.003*	2.34 [1.34-4.11]
Renal Injury	0.00 [0.00, 1.00] (0.32)	1.00 [0.00, 2.00] (1.00)	0.019*	1.86 [1.11-3.12]
Hematologic Injury	0.00 [0.00, 0.00] (0.09)	0.00 [-1.00, 1.00] (0.05)	0.847	0.94 [0.50-1.77]
Group C				
Type of Organ Injury	**Survivor (n=9)**	**Non-survivor (n=5)**	**P values**	**Odds ratio (95% C.I.)**
Neurological Injury	0.00 [0.00, 1.00] (0.44)	3.00 [2.50, 4.00] (3.20)	n/a	n/a

Cardiovascular Injury	0.00 [0.00, 2.00] (0.78)	3.00 [1.00, 3.50] (2.40)	0.100	1.98 [0.88-4.48]
Respiratory Injury	0.00 [0.00, 2.00] (0.89)	3.00 [2.00, 4.00] (3.00)	0.065	5.46 [0.90-33.18]
Hepatic Injury	0.00 [0.00, 1.50] (0.78)	1.00 [0.00, 2.00] (1.00)	0.738	1.17 [0.47-2.88]
Renal Injury	0.00 [0.00, 0.50] (0.78)	1.00 [0.00, 2.00] (1.00)	0.235	2.63 [0.53-12.92]
Hematologic Injury	1.00 [0.00, 1.00] (1.00)	0.00 [-0.50, 1.50] (0.40)	0.416	0.64 [0.21=1.89]

Table 5. Correlation between type of organ injury and mortality. Correlation between progression of organ injury and mortality was examined using multivariable and univariable analysis for Group A and C (only multivariable analysis is presented here). d(subscore) defined as [maximum pSOFA – admission pSOFA] was used for this purpose and shown as median [25th percentile, 75th percentile] (mean). *denotes statistical significance. C.I., confidence interval.

For the purpose of this thesis, scores from Group A were used as non-CHD comparison. This was due to the fact that Group A was more homogenous from disease progression than Groups B and C. Further background information about the cohort of patients with congenital heart disease is discussed in the following subsection.

Subsection 4: Congenital Heart Disease

This thesis examines a population of pediatric patients diagnosed with congenital heart disease admitted to the CICU, focusing on acyanotic CHD. Congenital heart disease encompasses various structural malformations of the heart present at birth. A structural abnormality can present in the heart walls, valves or, nearby arteries or veins which could disrupt normal blood flow.

Depending on how normal blood flow is disrupted, CHD can be categorized into acyanotic and cyanotic CHD (22). In acyanotic CHD, biventricular circulation exists; however, a left to right shunt increases pulmonary blood flow, decreasing the efficiency of the system. In cyanotic CHD, a right to left shunt decreases overall O_2 levels (22).

$$\frac{Qp}{Qs} = \frac{[SaO_2 - SvO_2]}{[SpvO_2 - SpaO_2]}$$

Fig 1. Pulmonary Systemic Blood Flow Ratio. Qp (L/min) = pulmonary blood flow. Qs (L/min) = systemic blood flow. SaO_2 = O_2 saturation of aorta. SvO_2 = O_2 saturation of SVC. $SpaO_2$ = O_2 saturation of pulmonary artery. $SpvO_2$ = O_2 saturation of pulmonary vein.

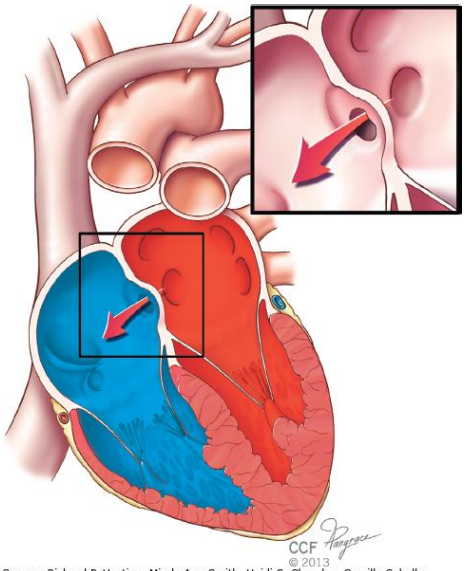

Fig 2. Diagram of Acyanotic Congenital Heart Disease. (23)

METHODS

Subsection 1: Retrospective Research Review

Patients with congenital heart disease were extracted and filtered for acyanotic CHD. pSOFA scores were assigned for each of the six organ systems which were summed to obtain a pSOFA total score. A total score was calculated for each day a patient stayed in the ICU. Data from electronic medical records of 51 patients diagnosed with acyanotic congenital heart disease were extracted and organized. Each patient's medical records number, age (months), sex, and length of stay (days) in the ICU were recorded. Values and assigned subscores were recorded throughout their ICU stay.

According to the pSOFA scoring table, values corresponding to each subscore category were recorded every day of ICU stay. In order to calculate the respiratory subscore, PaO_2 values and FiO_2 values were recorded for each day. Only the highest ratio for the day was recorded as that would be the highest pSOFA subscore. If PaO_2 was not available, SpO_2 was used instead and the highest SpO_2/FiO_2 ratio for the day was recorded. SpO_2 was not recorded for every day, it was only recorded if PaO_2 was not available. In order to differentiate PaO_2 and SpO_2 during data collection, cells were highlighted green when SpO_2 had to be utilized as illustrated in **Table 6**. Utilizing SpO2 was differentiated using highlighting during data collection in order to explore potential differences between using the two values in further analysis. Potential differences in respiratory subscores and total scores between PaO_2 and SpO_2 not be discussed

in this thesis but, was noted as a potential limiting factor for future studies. The remaining subscores are explained in the table below.

pSOFA Subscore	**Recorded value utilized to assigned pSOFA subscore**
Respiratory	Explained in text.
Coagulation	Lowest platelet count/day
Hepatic (indirect score)	Highest indirect value/day
Hepatic (direct score)	Highest direct value/day
Cardiovascular	Lowest MAP/day & administered medications according to pSOFA
Neurologic	Lowest Glasgow coma score/day
Renal	Highest creatinine value/day

Table 6. Values Recorded for pSOFA Score Assignment.

Each patient received two hepatic subscores and therefore, two total scores in order to account for utilizing indirect versus direct bilirubin values. This was done in order to account for any hemolytic events that may increase the hepatic (indirect) subscore which can be potentially determined using indirect bilirubin values. Templates used to record and organize patient data taken from Power Chart is presented in **Table 7** and **Table 8** below.

MRN			
Date	Day 1	Day 2	Day 3
Time			
PaO_2			
FiO_2			
Ratio			
pSOFA Score			

Table 7. Respiratory Subscore Data Collection. Date, time, PaO_2, and FiO_2 values are recorded in this table. PaO_2/FiO_2 ratios were calculated and the highest ratio was recorded. pSOFA score was then assigned. A green highlighted ratio cells indicates the use of SpO_2/FiO_2 for the respiratory subscore.

MRN	**Date**	Highest Hepatic Value (direct bilirubin)	Hepatic Score	pSOFA Score (direct bilirubin)	Highest Hepatic Value (indirect bilirubin)	Hepatic Score	pSOFA Score (indirect bilirubin)

Table 8. Subscores & Total Score Data Collection.

Subsection 2: Statistical Analysis

Statistical analysis was carried out using Prism software (GraphPad Software, San Diego, CA) and Excel (correlation, regression). Patient demographics such as mortality, age, sex, and length of stay are expressed with percentage and number. For each patient, the lowest, highest, and average score from their whole ICU stay was used to perform analysis. These 3 scores (low, high, average) were recorded for each subscore and total scores. This culminates in 21 subscores for each patient (3*7 subscores due to utilizing indirect and direct bilirubin values for two hepatic subscores) and 6 total scores

for each patient (3*2 total scores due to utilizing indirect and direct bilirubin values). **Table 10** illustrates this breakdown. Subscores and total scores are expressed as median and interquartile range. Mann Whitney (non-paramentric) tests were carried out to determine significant differences between acyanotic and cyanotic CHD pSOFA scores. Results are shown with median, interquartile ranges, and whether p-values are greater than or less than 0.05 or with a confidence interval of 95%. $p < 0.05$ was considered to be significant.

The Kruskal-Wallis test was used in Prism software to do a three-way comparison of both CHD populations with HSCT patients within parameters including the Highest or Maximum Cardiovascular, Coagulation, Hepatic Indirect, Neurologic, Renal, Respiratory, and Total Indirect Scores. Their means were compared and significance is indicated with alpha values used. The specific p-values of each comparison are not given. Graphs of the three-way analysis are displayed with median and interquartile ranges.

RESULTS

Subsection 1: Comparison of Acyanotic and Cyanotic Patients

Table 9 summarizes some demographic data as well as ICU length of stay and mortality rate of patients with CHD and compares cyanotic versus acyanotic patients. **Table 10** presents statistical analysis including median, interquartile range, and p-values of pSOFA scores assigned to patients with cyanotic and acyanotic CHD. “Low” scores indicate the lowest or minimum total score and subscore for each patient. “High” indicates the highest or maximum total score and subscores for each patient. “Average” indicates the average pSOFA score for each patient. “Direct” indicates the usage of direct bilirubin values from Power Chart. “Indirect” indicates the usage of indirect bilirubin values from Power Chart. These two CHD populations were compared to determine any potential differences in pSOFA scores.

We speculated the patients with acyanotic CHD would have lower respiratory and cardiovscuar subscores leading to higher total pSOFA scores. However, these subscores and total scores were not significantly different from patients with cyanotic CHD. Results display that there were significant differences between the two groups for Highest Total Direct Score (<0.0001), Average Total Direct Score (0.013), Lowest Total Indirect Score (0.0172), Highest Total Indirect Score (0.0008), Average Total Indirect Score (0.0035), Highest Neurologic Score (<0.0001), Average Neurologic Score (<0.0001),

Highest Renal Score (<0.0001), Average Renal Score (<0.0001), and Lowest Hepatic Indirect Score (0.0006).

	Acyanotic (n=51)	Cyanotic (n=50)	p-value
Male (%, no.)	66.67%, 34	62%, 31	n/a
Age in mo. (median, IQR(Q3-Q1))	23, 28 (45.5-17.5)	26, 21.5 (37.75-16.25)	0.9744
Length of ICU Stay in Days (median, IQR(Q3-Q1))	5.4, 0.7 (5.8-5.1)	3, 2.525 (4.625-2.1)	<0.0001*
Mortality (%, no.)	0%, 0	4%, 2	n/a

Table 9. Statistics of Patients with Congenital Heart Disease. Comparison of age, sex, length of ICU stay and mortality rate in patients with CHD. *Indicates statistical significance, α = 0.05

Parameters		Acyanotic (n-51)		Cyanotic (n=50)		p-value
		Median	IQR (Q3-Q1)	Median	IQR (Q3-Q1)	
Total Direct Score	Lowest	3	3 (4-1)	2	2 (3-1)	0.1120
	Highest	6	2 (7-5)	9	4 (11-7)	<0.0001*
	Average	4.43	2.185 (5.5-3.135)	5.25	2.6025 (7-4.3975)	0.013*

Total Indirect Score	Lowest	3	4 (5-1)	2	2 (3-1)	0.0172*
	Highest	7	3.5 (8.5-5)	9.5	4.75 (11.75-7)	0.0008*
	Average	7	2.57 (6.155-3.585)	5.3125	2.58575 (7-4.41425)	0.0035*

Respiratory Score	Lowest	1	2 (2-0)	0	2 (2-0)	0.5537
	Highest	3	1 (4-3)	4	1 (4-3)	0.1420
	Average	2	1.42 (2.75-1.33)	2.25	1.79225 (3.12525-1.333)	0.8272

Coagulation Score	Lowest	0	0 (0-0)	0	0 (0-0)	0.3002
	Highest	0	1 (1-0)	1	2 (2-0)	0.3678
	Average	0	0.77 (0.77-0)	0.354	1 (1-0)	0.1901

Cardiovascular Score	Lowest	1	1 (1-0)	1	1 (1-0)	>0.9999
	Highest	2	2 (3-1)	3	2 (3-1)	0.2328
	Average	1.29	0.585 (1.585-1)	1.333	0.75 (1.75-1)	0.1842

Neurologic Score	Lowest	0	0 (0-0)	0	0 (0-0)	0.1120
	Highest	0	0 (0-0)	4	2 (4-2)	<0.0001*
	Average	0	0 (0-0)	1.333	1.18 (1.95-0.77)	<0.0001*
Renal Score	Lowest	0	0 (0-0)	0	0 (0-0)	0.0597
	Highest	0	1 (1-0)	0	0 (0-0)	<0.0001*
	Average	0	0.62 (0.62-0)	0	0 (0-0)	<0.0001*
Hepatic Direct Score	Lowest	0	0 (0-0)	0	0 (0-0)	0.4950
	Highest	0	0 (0-0)	0	0 (0-0)	0.2999
	Average	0	0 (0-0)	0	0 (0-0)	0.1472
Hepatic Indirect Score	Lowest	0	1 (1-0)	0	0 (0-0)	0.0006*
	Highest	0	2 (2-0)	0	1 (1-0)	0.4496
	Average	0	1.855 (1.855-0)	0	0.32225 (0.32225-0)	0.3376

Table 10. pSOFA Scoring of Patients with Acyanotic & Cyanotic Congenital Heart Disease. Summary of all parameter data for both patient populations with congenital heart disease. *Indicates statistical significance, α = 0.05

Subsection 2: Aycanotic CHD Correlation Studies

Table 11 presents acyanotic congenital heart disease patients' scores for Lowest Total Indirect Score, Highest Renal Score, Average Renal Score, and Lowest Hepatic Indirect Score. Correlation studies performed between Renal and Total Scores as well Hepatic and Total scores did not show any strong correlations. Lowest Total Indirect Score is not correlated with Highest Renal Score ($r^2 = 0.443$), Lowest Total Indirect Score is not correlated with Average Renal Score ($r^2 = 0.542$), and Lowest Total Indirect Score is not correlated with Lowest Hepatic Indirect Score ($r^2 = 0.294$).

Patient	Lowest Total Indirect Score	Highest Renal Score	Average Renal Score	Lowest Hepatic Indirect Score
1	2	0	0	0
2	2	1	0.33	0
3	1	0	0	0
4	4	0	0	0
5	2	0	0	0
6	5	1	0.33	0
7	1	1	0.17	0
8	3	3	2.33	0
9	2	1	0.33	0
10	4	1	0.5	0
11	3	0	0	2
12	6	1	0.67	3

13	0	0	0	0
14	3	2	0.83	0
15	3	2	1.22	2
16	1	0	0	0
17	3	0	0	2
18	0	1	0.17	0
19	0	0	0	0
20	1	0	0	0
21	1	0	0	0
22	0	1	0.17	0
23	1	1	0.17	0
24	3	3	2.5	0
25	7	2	2	2
26	6	1	0.83	3
27	1	0	0	0
28	4	0	0	0
29	9	3	2.43	2
30	1	0	0	0
31	4	1	0.43	0
32	1	0	0	11
33	5	0	0	0
34	4	0	0	0
35	2	0	0	0
36	4	0	0	0
37	3	0	0	0
38	6	1	0.83	0
39	9	2	1.29	3
40	8	2	2	4
41	2	1	0.57	0
42	3	0	0	0
43	3	0	0	0
44	8	0	0	2
45	0	0	0	0
46	6	2	1.29	2
47	2	0	0	0
48	5	0	0	0
49	5	0	0	0

50	5	2	1.43	2
51	2	0	0	0

Table 11. Parameters for Correlation Studies – Patients with Acyanotic Congenital Heart Disease. Summary of all data used to conduct correlation analysis. Scores significantly higher than scores of patients with cyanotic CHD were chosen for correlation studies.

Subsection 3: Comparison of Patients with Congenital Heart Disease (Acyanotic & Cyanotic) and Patients who underwent HSCT (non-CHD):

Table 12 summarizes statistical analysis performed between both congenital heart disease populations and HSCT patients who were admitted to the ICU after one treatment. The Kruskal-Wallis test done in Prism software did not have an output of specific p-values but, determined significance and indicated the alpha used. All parameters are compared using the highest or maximum scores.

Parameters	**Acyanotic CHD & Cyanotic CHD**	**Acyanotic CHD & HSCT**	**Cyanotic CHD & HSCT**
Total (Indirect)	Significant, $p<0.0001$	Significant, $p<0.0001$	Significant, $p<0.0001$
Respiratory	Not significant	Not significant	Significant, $p<0.05$
Coagulation	Not significant	Significant, $p<0.05$	Significant, $p<0.05$
Cardiovascular	Not significant	Not significant	Significant, $p<0.05$

Neurologic	Significant, $p<0.05$	Significant, $p<0.05$	Not significant
Renal	Significant, $p<0.0001$	Significant, $p<0.0001$	Significant, $p<0.0001$
Hepatic	Significant, $p<0.05$	Significant, $p<0.05$	Significant, $p<0.05$

Table 12. Comparison of pSOFA Scores in Patients with Congenital Heart Disease & Patients who Underwent HSCT. Summary of significant and nonsignificant differences between all three populations across the parameters listed.

DISCUSSION

Subsection 1: Comparison of Patients with Acyanotic and Cyanotic CHD

This discussion will focus on the differences in pSOFA scores between the two patient populations with CHD. We hypothesized that we would observe higher scores associated with in-hospital mortality in patients with cyanotic CHD. Patients with acyanotic CHD did not have any mortality while patients with cyanotic CHD only had 2 cases of in-hospital mortality.

This was an exploratory study and discussion of significant and nonsignificant differences have led to understanding further measures to be taken when conducting future studies. Overall, the pSOFA scoring system did present significant differences between the two CHD patient populations in assessing the risk of organ failure since there were total higher scores in the cyanotic CHD population compared to the acyanotic CHD population. The hypothesis in expecting higher respiratory subscores in patients with cyanotic CHD was not met, which may be due to the inconsistent use of PaO_2 and SpO_2 values. Details regarding each of the subscores are provided in the follow tables. Further analysis should be conducted with stricter filtering of patients based on the data available in PowerChart according to the following parameters:

- PaO_2 values: Using SpO_2 values when PaO_2 was not available may have introduced a confounding variable. Future studies should select for patient data when one value is consistently available, preferably PaO_2. Another option is selecting for patient data when both values are consistently

available. This would provide for score comparisons between utilizing PaO_2 versus SpO_2.

- Type of malformation: Future studies should separate patients based on the type of heart malformation. This would provide for further comparison rather than overall comparisons between acyanotic and cyanotic CHD.
- Total bilirubin level calculation and scoring: This study broke down hepatic subscores into one subscore using indirect bilirubin and one subscore using direct bilirubin. Future studies should also calculate total bilirubin and assign one hepatic and one total score. It would be interesting to explore potential differences in scores between the CHD cohorts when total bilirubin values are used.
- Glasgow coma scores: Glasgow coma scores were not available for all patients. Future studies should select for patients who have Glasgow coma scores available.
- Underlying renal conditions: Future studies should separate patients who have underlying renal conditions in order to understand potential differences seen in the renal subscores.
- Surgery history: Future studies should record surgery history for each selected patient as this information may be needed to understand higher scores seen in patients with acyanotic CHD.
- Length of stay: In this study, the length of stay in the CICU of patients with acyanotic CHD was significantly higher than that of patients with cyanotic

CHD. This could be used to explain some of the higher pSOFA subscores in the acyanotic CHD population. They could have had underlying complications that required a longer CICU stay, which could have affected the scores as well.

	Significant Difference	Non-significant Difference
Total Direct	Highest Average	Lowest
Total Indirect	Lowest*(M) Highest Average	
Respiratory		Lowest Highest Average
Coagulation		Lowest Highest Average
Cardiovascular		Lowest Highest Average
Neurologic	Highest Average	Lowest
Renal	Highest*(Q3) Average*(Q3)	Lowest
Hepatic Direct		Lowest Highest Average
Hepatic Indirect	Lowest*(Q3)	Average Highest

Table 13. Significant and Non-significant Scores Between Patients with Acyanotic and Cyanotic CHD. *(M) denotes patients with acyanotic CHD have a higher median than patients with cyanotic CHD. *(Q3) denotes patients with acyanotic CHD have a higher 75th percentile than patients with cyanotic CHD.

Absence of * denotes patients with cyanotic CHD have higher scores than patients with acyanotic CHD.

Patients with cyanotic CHD had significantly higher Highest & Average Total Direct Scores, Highest & Average Total Indirect Scores, as well as Highest & Average Neurologic Scores. These were expected to be higher in patients with cyanotic CHD because they have overall lower O_2 levels. Patients with acyanotic CHD had significantly higher Lowest Total Indirect Score, Lowest Hepatic Indirect Score, and Highest & Average Renal Scores. This was not expected and could be explained due to potential hemolytic events or surgical histories of some patients in this cohort. Some patients could have had underlying renal issues which could have caused the renal scores to be higher. Future studies should record this information for each patient to gain a better understanding of these scores.

Subsection 2: Aycanotic CHD Correlation Studies

No correlations were found between the variables observed. This could mean there was no link between the scores that were higher than those of the cyanotic population. More data would need to be collected to understand the reasoning behind higher acyanotic CHD scores as discussed in the previous subsection.

Subsection 3: Comparison of Patients with Congenital Heart Disease (Acyanotic & Cyanotic) and HSCT Recipients

Patients who underwent HSCT had significantly higher hepatic, renal, respiratory, and total scores as seen in **Graphs 32 - 38**. This could be due to the fact that patients who underwent HSCT had a higher incidence of mortality however; further information and a larger sample size is needed to understand this result.

These comparisons between patients with CHD and patients without CHD provide a step into understanding whether pSOFA can be used across different pediatric disease populations. Further data collection and analysis are needed to gain a better understanding of whether pSOFA can be utilized across different pediatric disease populations.

Conclusion:

The results and discussion based on comparisons between acyanotic and cyanotic CHD could be mean that pSOFA is a promising scoring assessment that can be used to assess risk of organ dysfunction within one type of pediatric disease population. Further data collection and analysis, accounting for stricter parameters found from this study, is needed to begin validating pSOFA for this utilization in CHD populations.

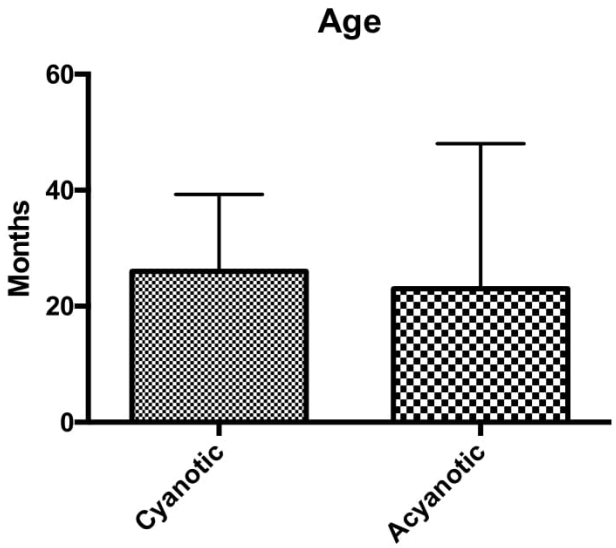

Figure 3. Age of Acyanotic (median = 23, Q3 = 45.5) and Cyanotic (median = 26, Q3 = 37.75) patient populations. There is no significant difference ($p = 0.9744$, $\alpha = 0.05$).

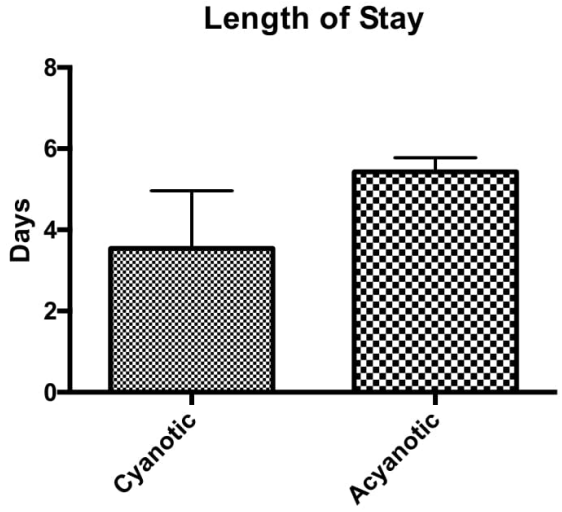

Figure 4. Length of ICU stay of Acyanotic (median = 5.4, Q3 = 5.8) and Cyanotic (median = 3, Q3 = 4.625) patient populations. There is a significant difference ($p < 0.0001$, $\alpha = 0.05$).

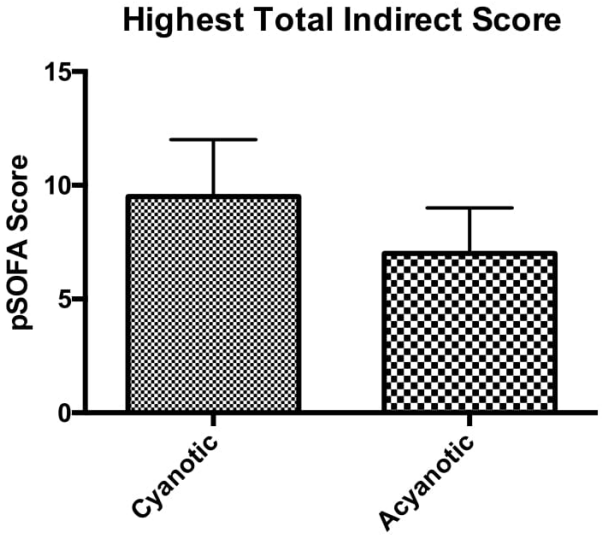

Figure 5. Highest Total Indirect Scores of Acyanotic (median = 7, Q3 = 8.5) and Cyanotic (median = 9.5, Q3 = 11.75) patient populations. There is a significant difference ($p = 0.0008$, $\alpha = 0.05$).

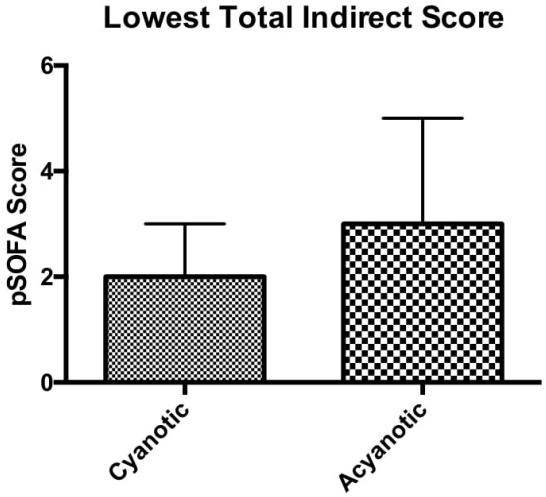

Figure 6. Lowest Total Indirect Scores of Acyanotic (median = 3, Q3 = 5) and Cyanotic (median = 2, Q3 = 3) patient populations. There is no significant difference ($p = 0.0172$, $\alpha = 0.05$).

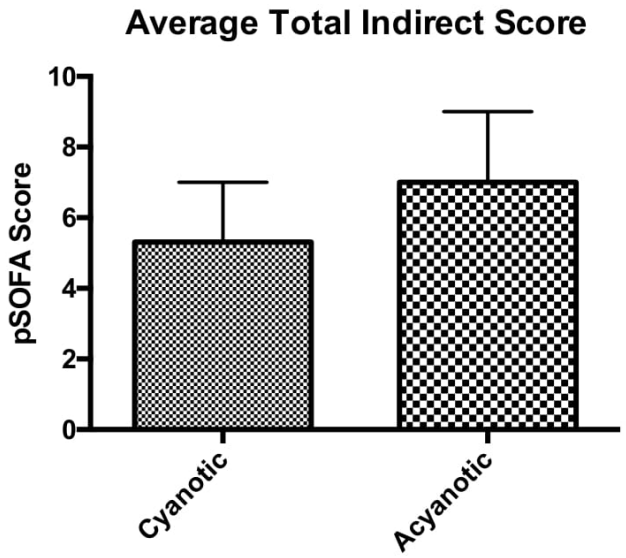

Figure 7. Average Total Indirect Scores of Acyanotic (median = 7, Q3 = 6.155) and Cyanotic (median = 5.3, Q3 = 7) patient populations. There is a significant difference ($p = 0.0035$, $\alpha = 0.05$).

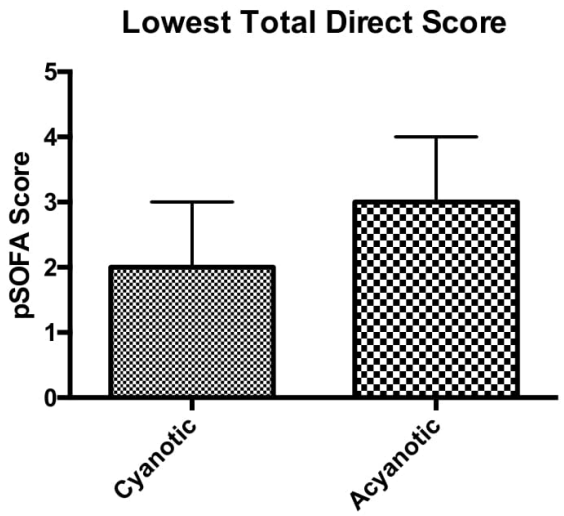

Figure 8. Lowest Total Direct Scores of Acyanotic (median = 3, Q3 = 4) and Cyanotic (median = 2, Q3 = 3) patient populations. There is no significant difference ($p = 0.1120$, $\alpha = 0.05$).

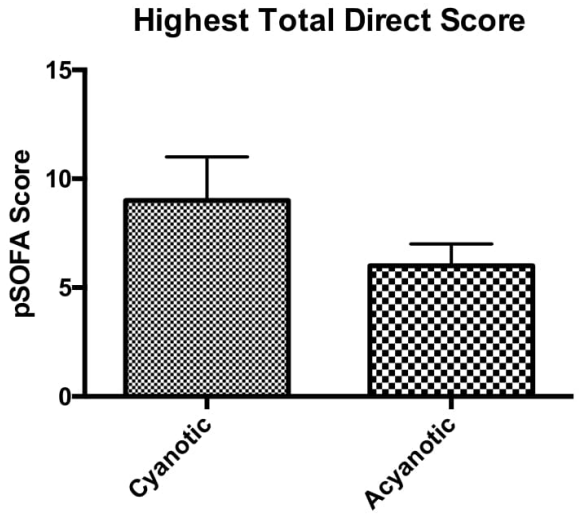

Figure 9. Highest Total Direct Scores of Acyanotic (median = 6, Q3 = 7) and Cyanotic (median = 9, Q3 = 11) patient populations. There is a significant difference ($p < 0.0001$, $\alpha = 0.05$).

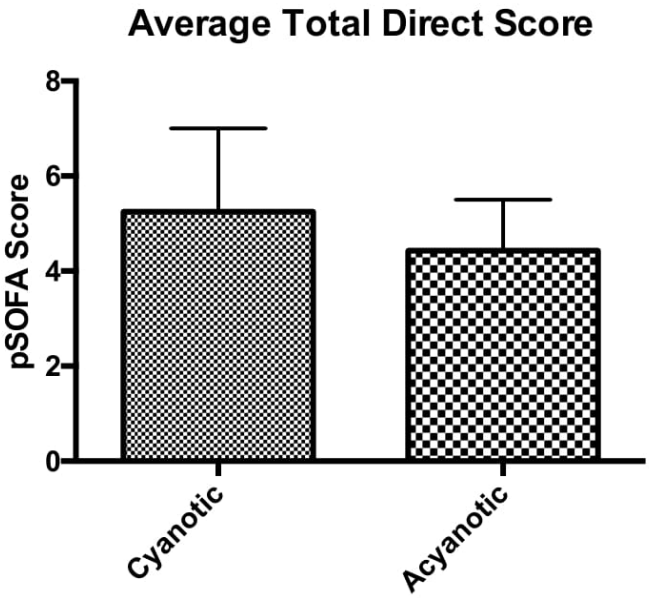

Figure 10. Average Total Direct Scores of Acyanotic (median = 4.43, Q3 = 5.5) and Cyanotic (median = 5.25, Q3 = 7) patient populations. There is a significant difference ($p = 0.013$, $\alpha = 0.05$).

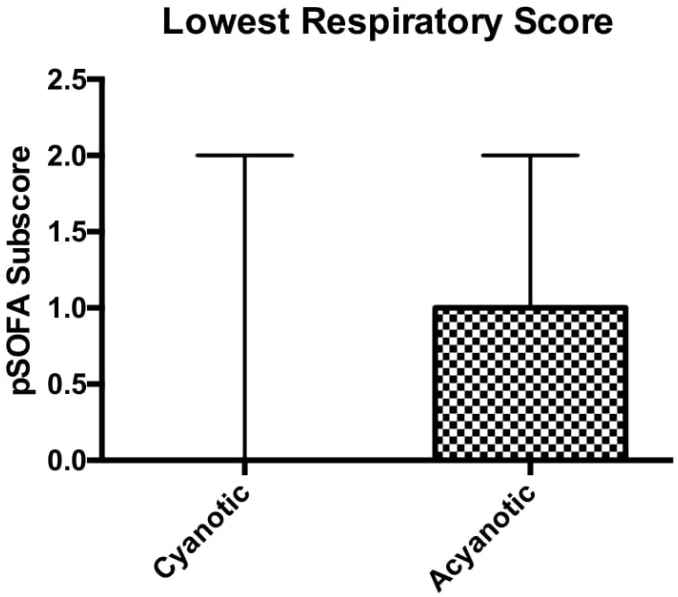

Figure 11. Lowest Respiratory Scores of Acyanotic (median = 1, Q3 = 2) and Cyanotic (median = 0, Q3 = 2) patient populations. There is no significant difference ($p = 0.5537$, $\alpha = 0.05$).

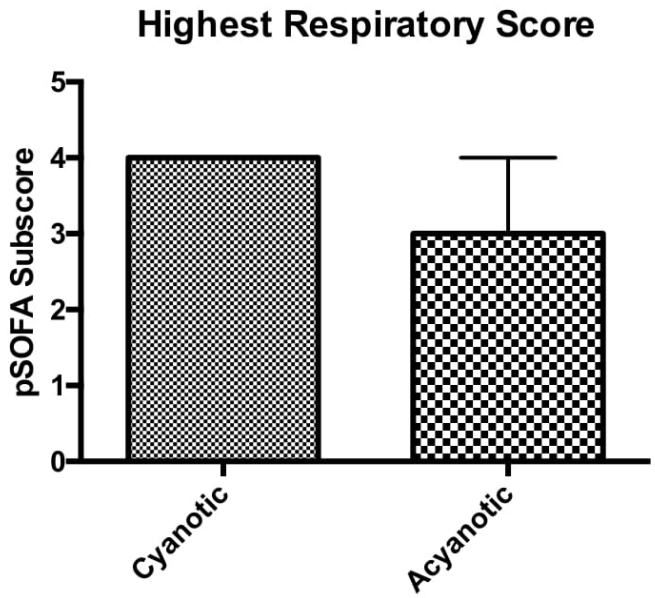

Figure 12. Highest Respiratory Scores of Acyanotic (median = 3, Q3 = 4) and Cyanotic (median = 4, Q3 = 4) patient populations. There is no significant difference ($p = 0.1420$, $\alpha = 0.05$).

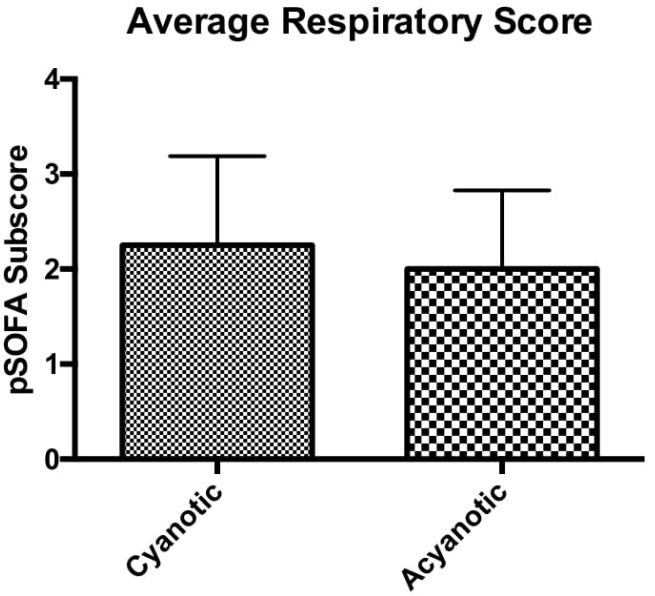

Figure 13. Average Respiratory Scores of Acyanotic (median = 2, Q3 = 2.75) and Cyanotic (median = 2.25, Q3 = 3.13) patient populations. There is no significant difference ($p = 0.8272$, $\alpha = 0.05$).

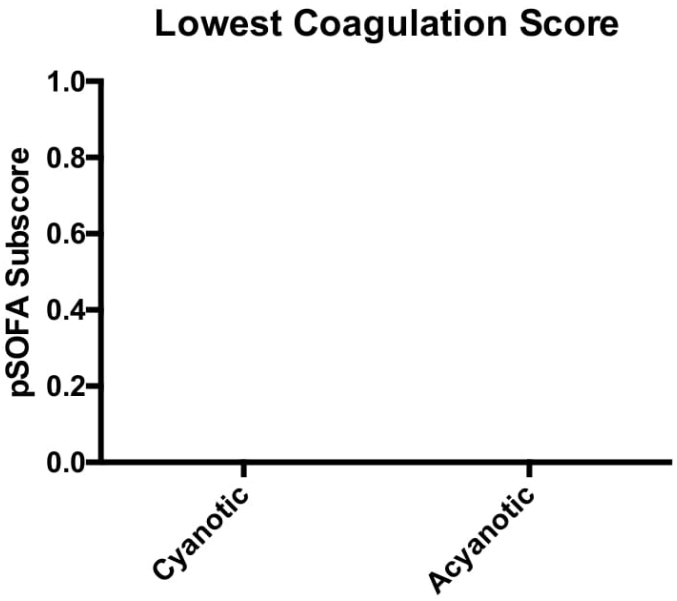

Figure 14. Lowest Coagulation Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 0, Q3 = 0) patient populations. There is no significant difference ($p = 0.3002$, $\alpha = 0.05$).

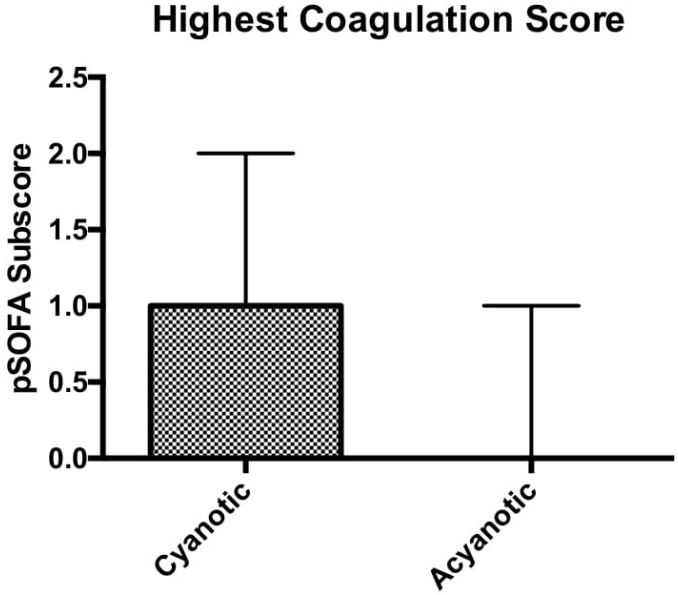

Figure 15. Highest Coagulation Scores of Acyanotic (median = 0, Q3 = 1) and Cyanotic (median = 1, Q3 = 2) patient populations. There is no significant difference ($p = 0.1420$, $\alpha = 0.05$).

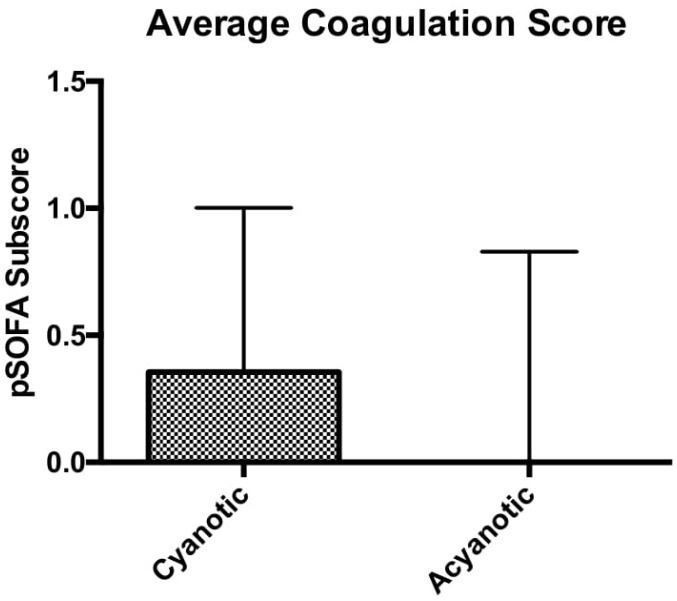

Figure 16. Average Coagulation Scores of Acyanotic (median = 0, Q3 = 0.77) and Cyanotic (median = 0.354, Q3 = 1) patient populations. There is no significant difference ($p = 0.1901$, $\alpha = 0.05$).

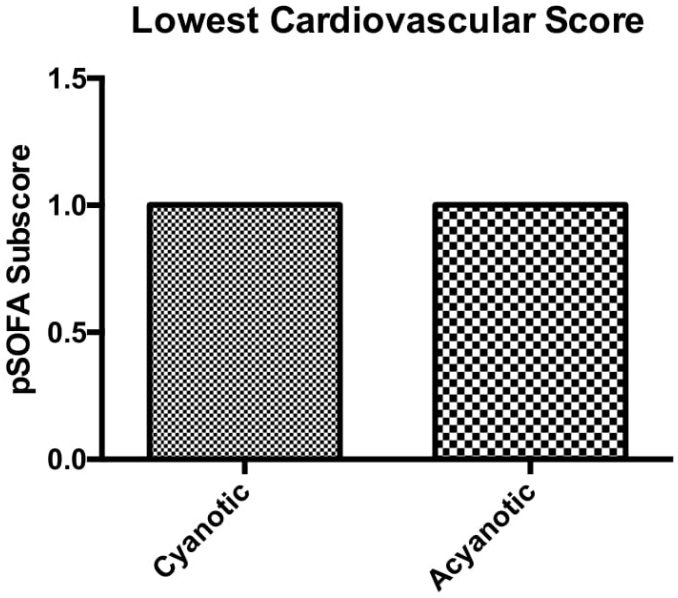

Figure 17. Lowest Cardiovascular Scores of Acyanotic (median = 1, Q3 = 1) and Cyanotic (median = 1, Q3 = 1) patient populations. There is no significant difference ($p > 0.9999$, $\alpha = 0.05$).

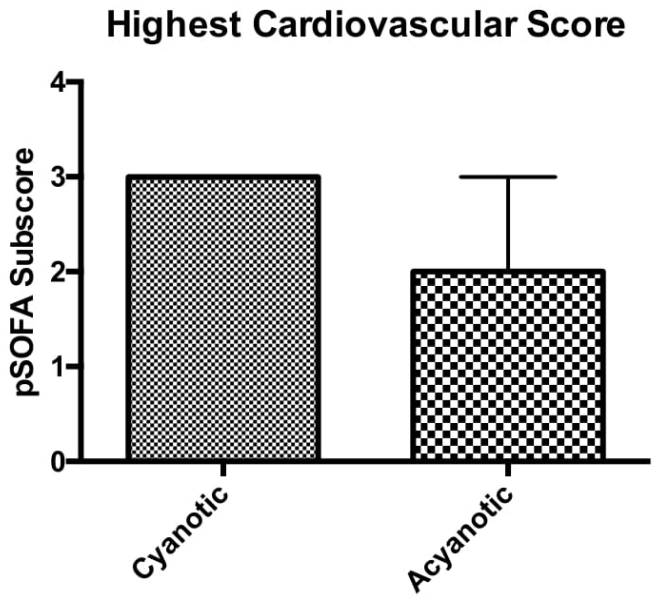

Figure 18. Highest Cardiovascular Scores of Acyanotic (median = 2, Q3 = 3) and Cyanotic (median = 3, Q3 = 3) patient populations. There is no significant difference ($p = 0.2328$, $\alpha = 0.05$).

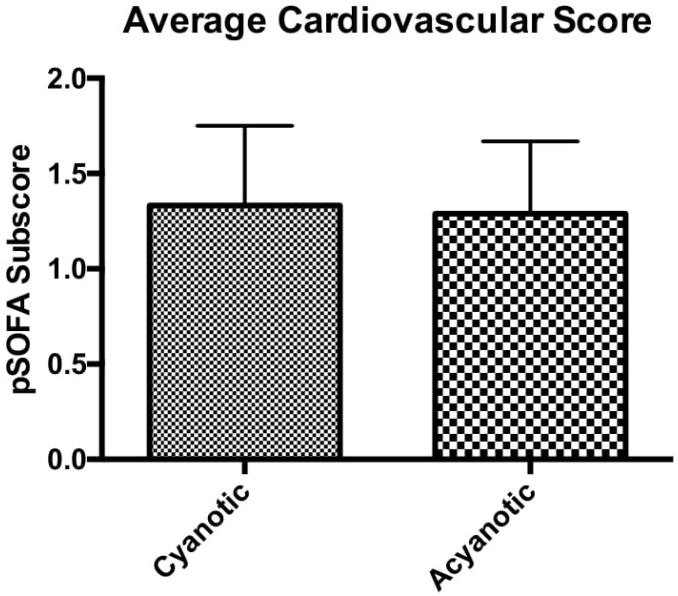

Figure 19. Average Cardiovascular Scores of Acyanotic (median = 1.29, Q3 = 1.585) and Cyanotic (median = 1.33, Q3 = 1.75) patient populations. There is no significant difference ($p = 0.1842$, $\alpha = 0.05$).

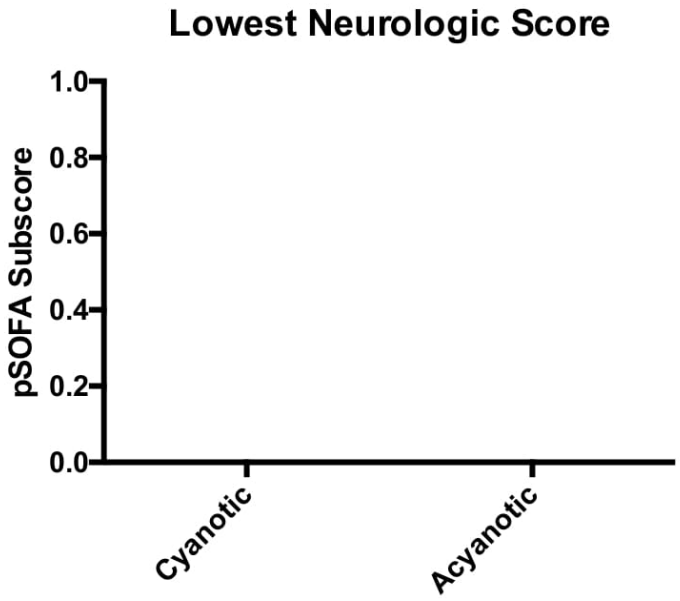

Figure 20. Lowest Neurologic Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 0, Q3 = 0) patient populations. There is no significant difference ($p = 0.1120$, $\alpha = 0.05$).

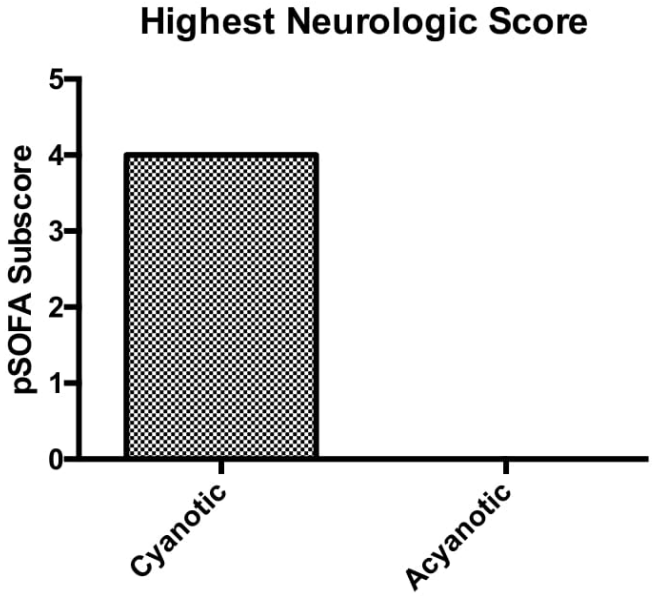

Figure 21. Highest Neurologic Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 4, Q3 = 4) patient populations. There is a significant difference ($p < 0.0001$, $\alpha = 0.05$).

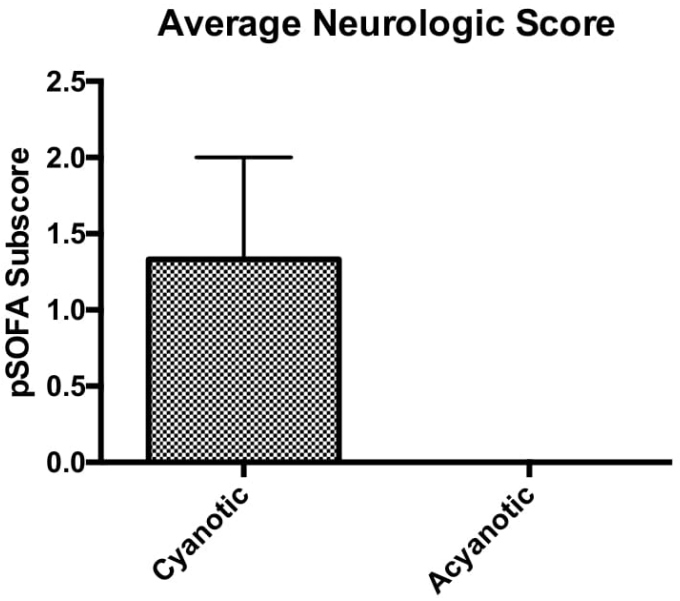

Figure 22. Average Neurologic Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 1.33, Q3 = 1.95) patient populations. There is a significant difference ($p < 0.0001$, $\alpha = 0.05$).

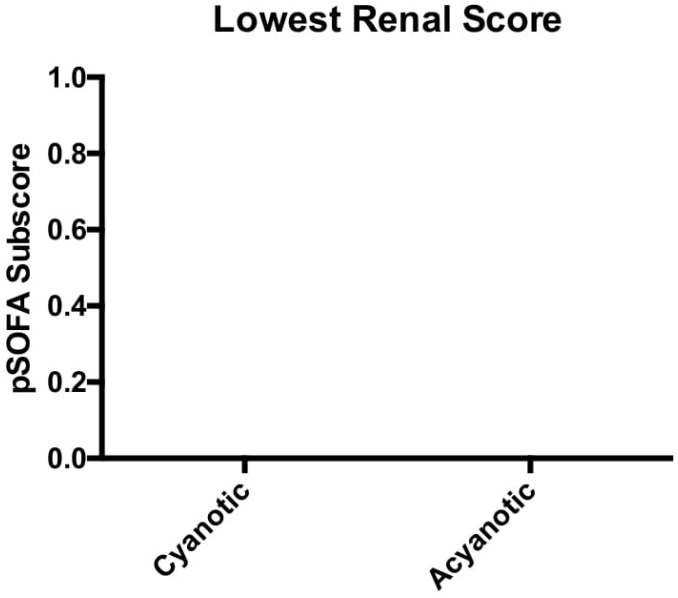

Figure 23. Lowest Renal Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 0, Q3 = 0) patient populations. There is no significant difference ($p = 0597$, $\alpha = 0.05$).

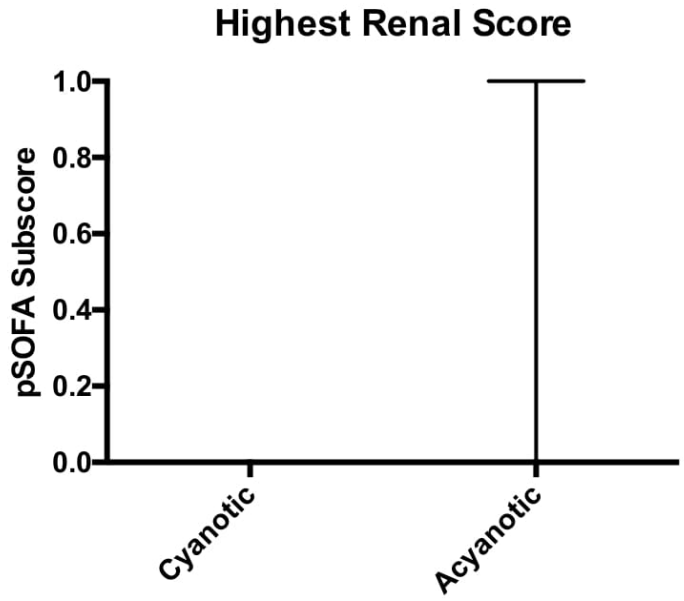

Figure 24. Highest Renal Scores of Acyanotic (median = 0, Q3 = 1) and Cyanotic (median = 0, Q3 = 0) patient populations. There is a significant difference ($p < 0.0001$, $\alpha = 0.05$).

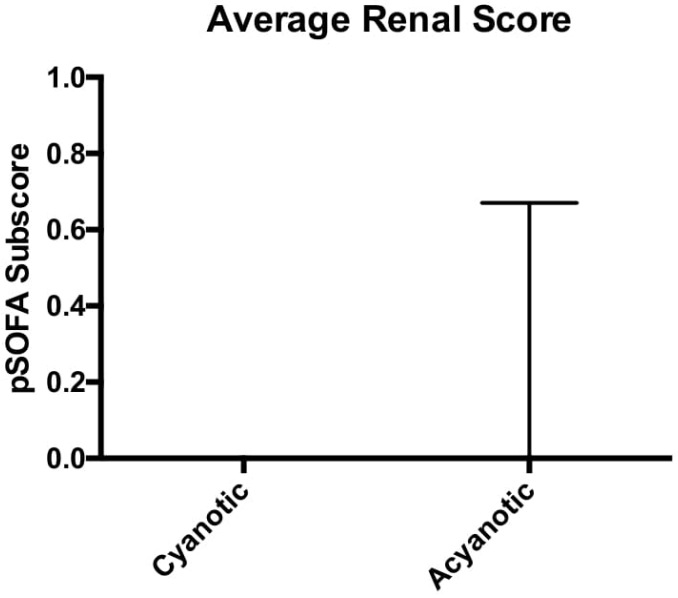

Figure 25. Average Renal Scores of Acyanotic (median = 0, Q3 = 0.62) and Cyanotic (median = 0, Q3 = 0) patient populations. There is a significant difference ($p < 0.0001$, $\alpha = 0.05$).

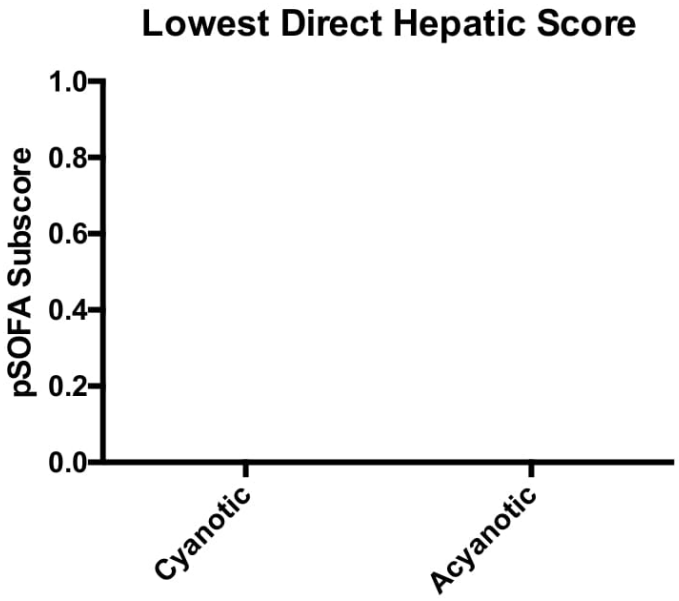

Figure 26. Lowest Direct Hepatic Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 0, Q3 = 0) patient populations. There is no significant difference ($p = 0.4950$, $\alpha = 0.05$).

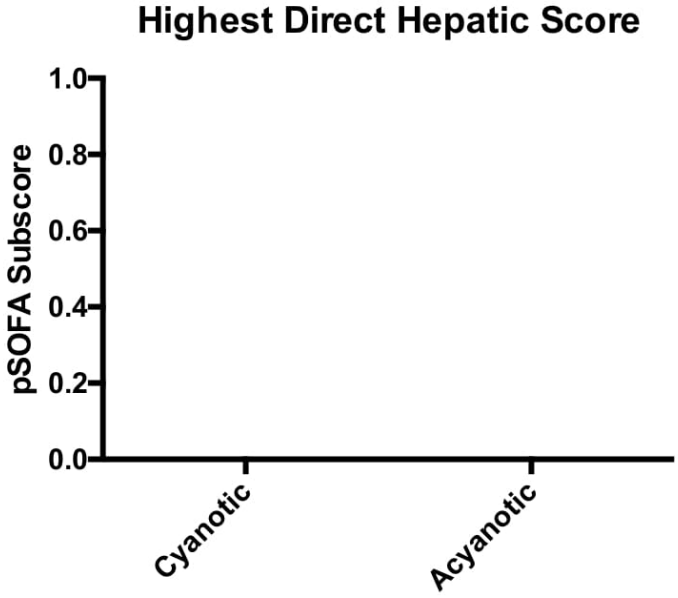

Figure 27. Highest Direct Hepatic Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 0, Q3 = 0) patient populations. There is no significant difference ($p = 0.2999$, $\alpha = 0.05$).

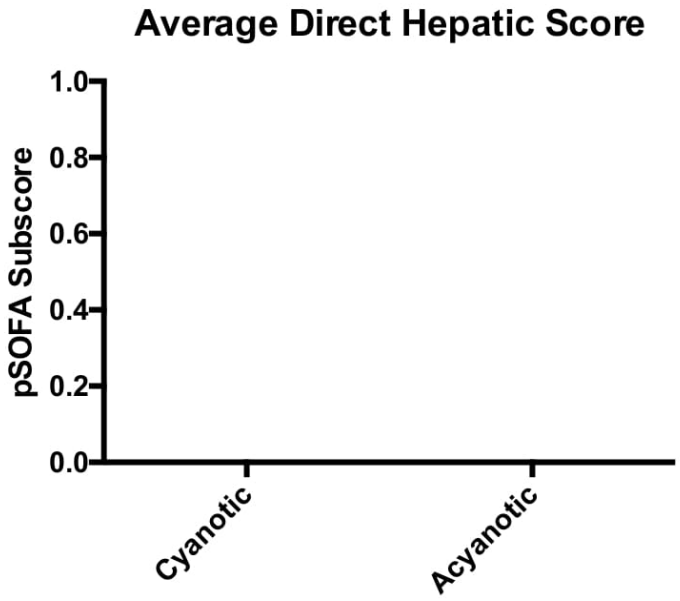

Figure 28. Average Direct Hepatic Scores of Acyanotic (median = 0, Q3 = 0) and Cyanotic (median = 0, Q3 = 0) patient populations. There is no significant difference ($p = 0.1472$, $\alpha = 0.05$).

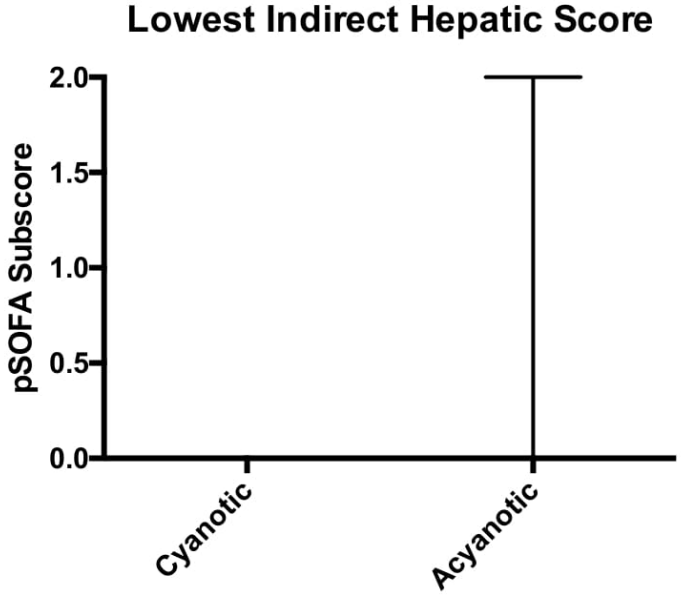

Figure 29. Lowest Indirect Hepatic Scores of Acyanotic (median = 0, Q3 = 1) and Cyanotic (median = 0, Q3 = 0) patient populations. There is a significant difference ($p = 0.0006$, $\alpha = 0.05$).

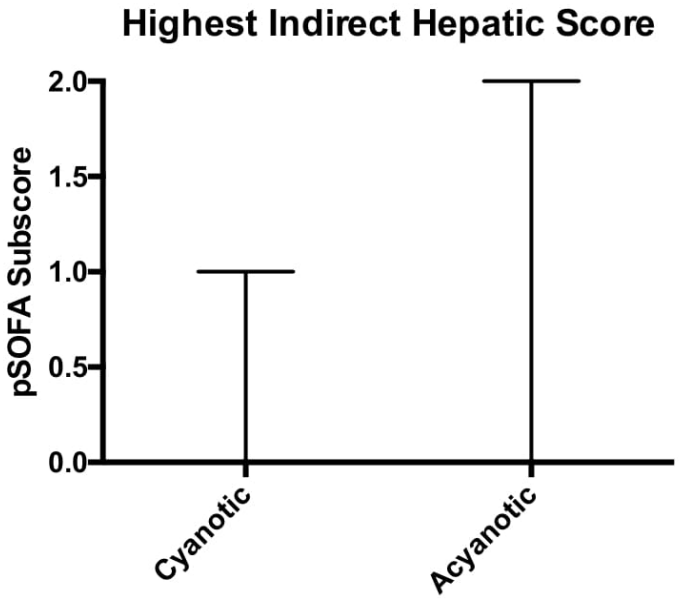

Figure 30. Highest Indirect Hepatic Scores of Acyanotic (median = 0, Q3 = 2) and Cyanotic (median = 0, Q3 = 1) patient populations. There is no significant difference ($p = 0.4496$, $\alpha = 0.05$).

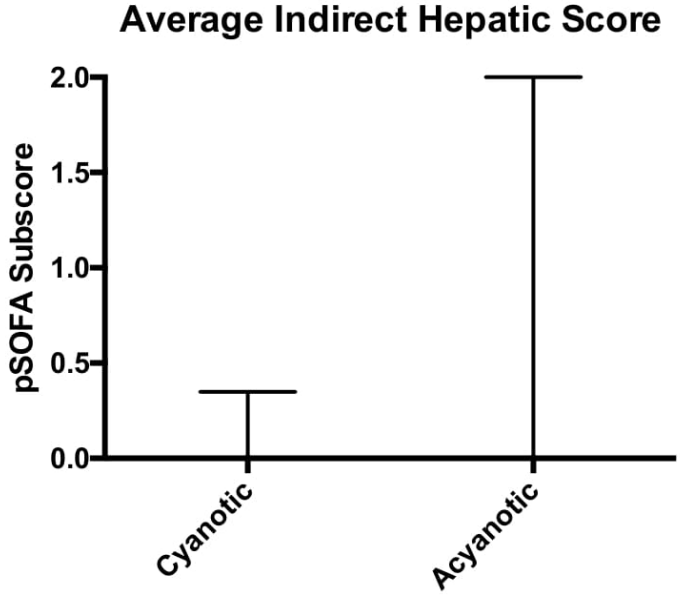

Figure 31. Average Indirect Hepatic Scores of Acyanotic (median = 0, Q3 = 1.855) and Cyanotic (median = 0, Q3 = 0.323) patient populations. There is no significant difference ($p = 0.3376$, $\alpha = 0.05$).

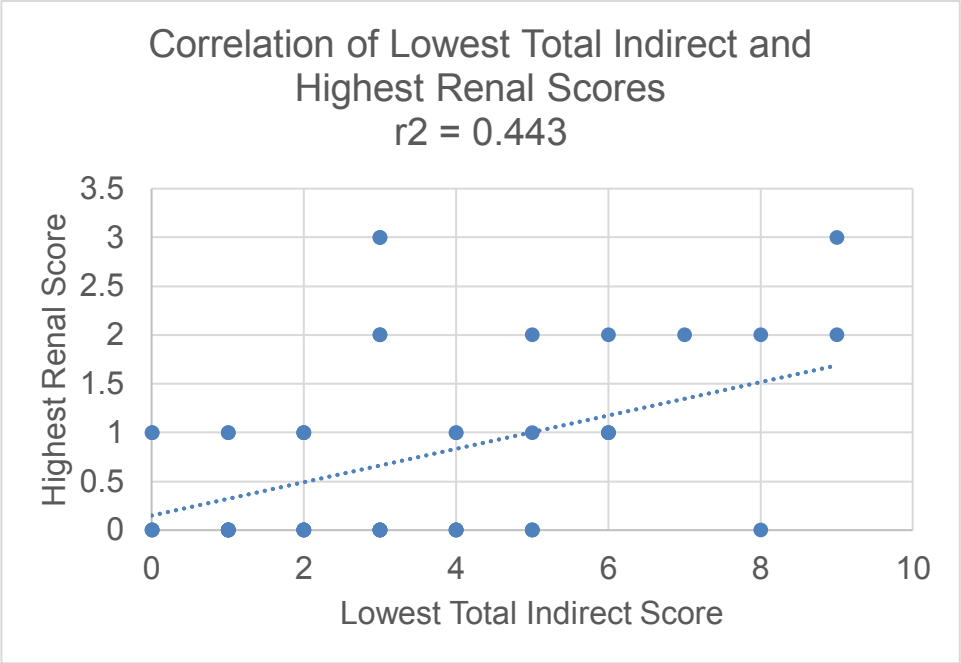

Figure 32. There is no correlation between Highest Renal and Lowest Total Indirect Scores, $r^2 = 0.443$.

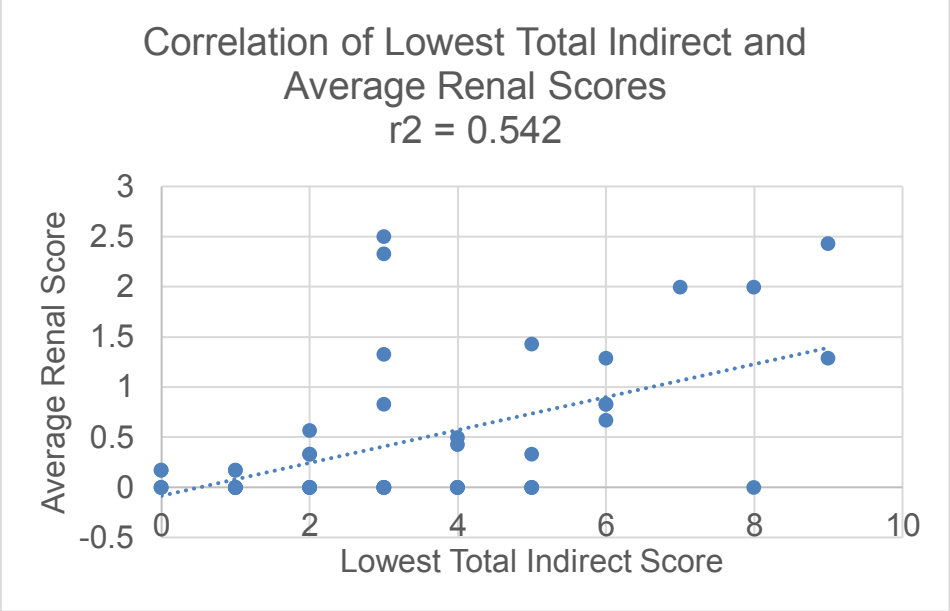

Figure 33. There is no correlation between Average Renal and Lowest Total Indirect Scores, $r^2 = 0.542$.

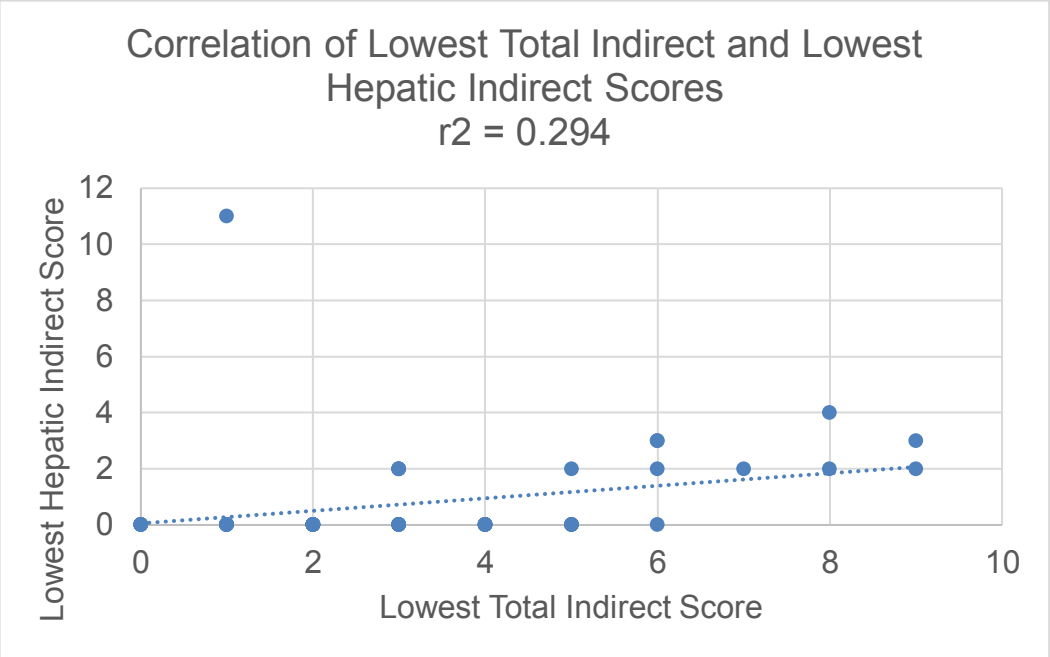

Figure 34. There is no correlation between Lowest Hepatic Indirect and Lowest Total Indirect Scores, r^2 = 0.294.

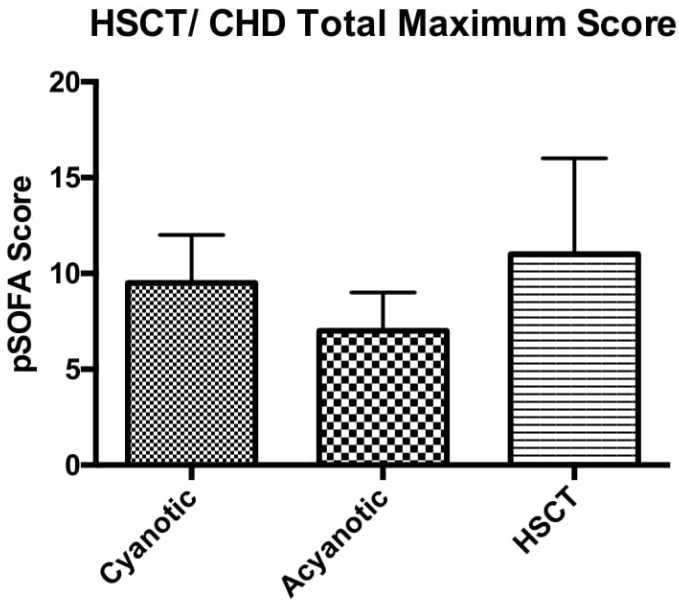

Figure 35. There is a significant difference between HSCT & Cyanotic CHD patients ($p<0.0001$). There is a significant difference between HSCT & Acyanotic CHD patients ($p<0.0001$).

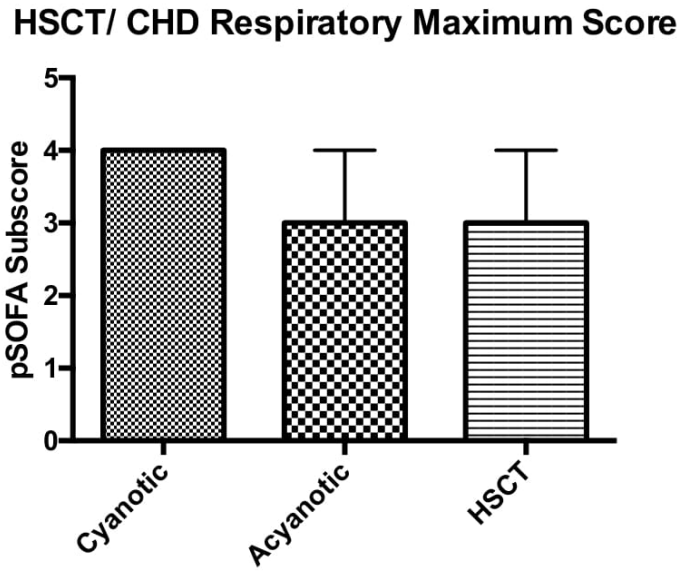

Figure 36. There is a significant difference between HSCT & Cyanotic CHD patients ($p<0.05$). There is no significant difference between HSCT & Acyanotic CHD patients.

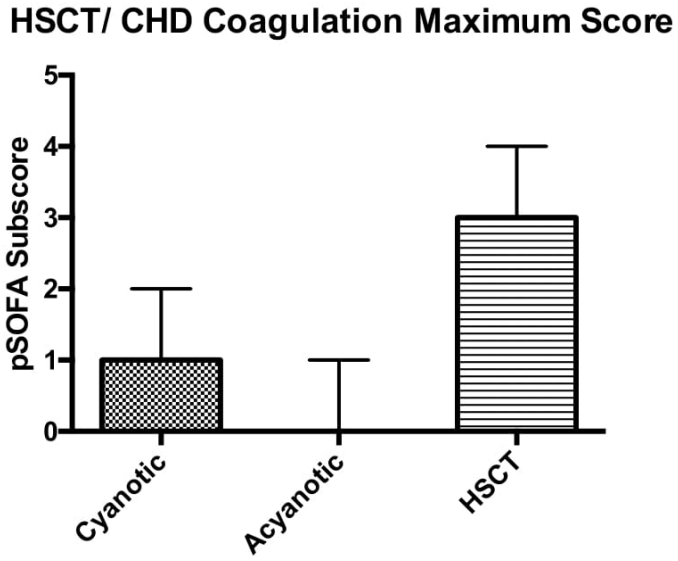

Figure 37. There is a significant difference between HSCT & Cyanotic CHD patients ($p<0.05$). There is a significant difference between HSCT & Acyanotic CHD patients ($p<0.05$).

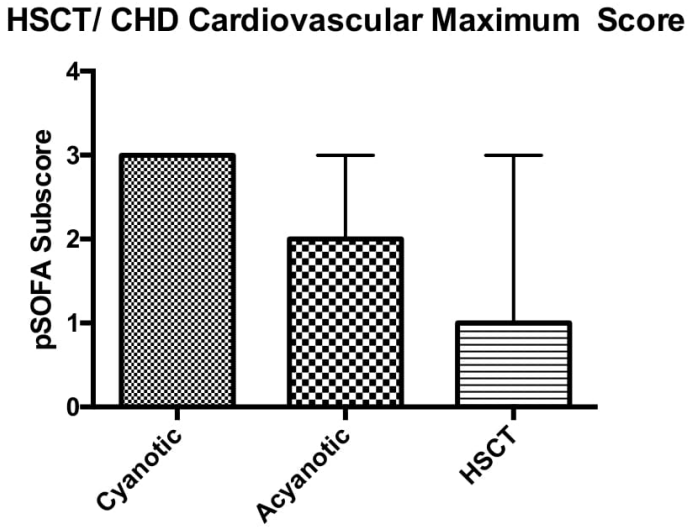

Figure 38. There is a significant difference between HSCT & Cyanotic CHD patients ($p<0.05$). There is no significant difference between HSCT & Acyanotic CHD patients.

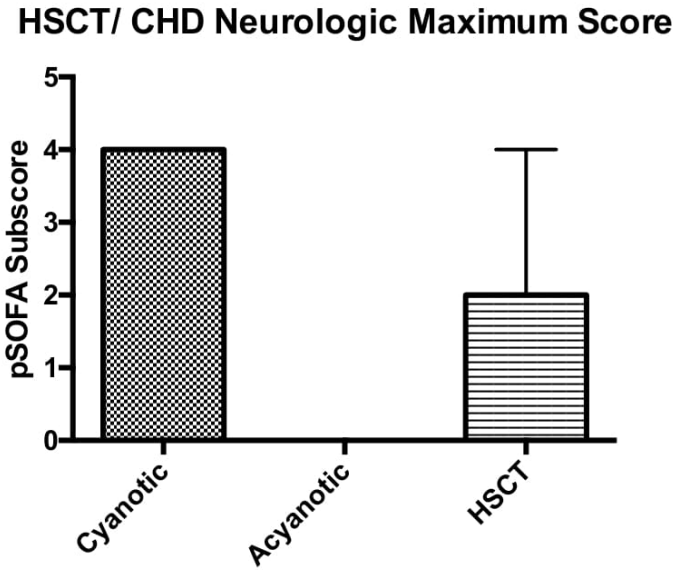

Figure 39. There is no significant difference between HSCT & Cyanotic CHD patients. There is a significant difference between HSCT & Acyanotic CHD patients ($p<0.05$).

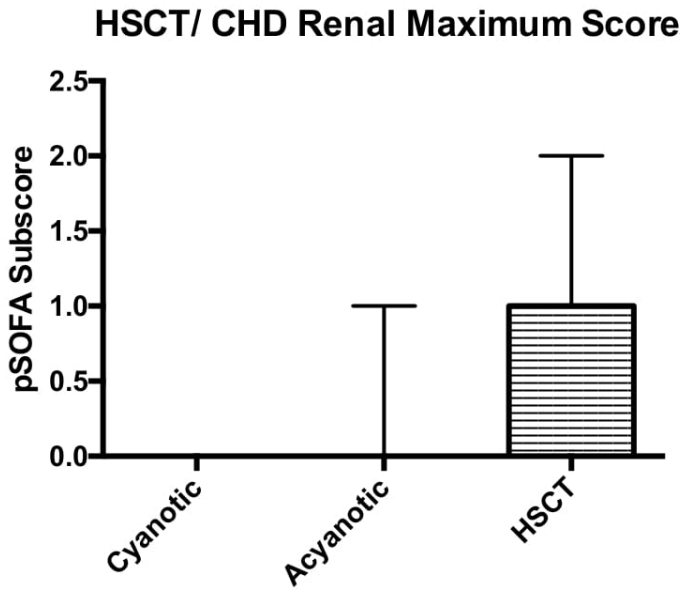

Figure 40. There is a significant difference between HSCT & Cyanotic CHD patients ($p<0.0001$). There is a significant difference between HSCT & Acyanotic CHD patients ($p<0.0001$).

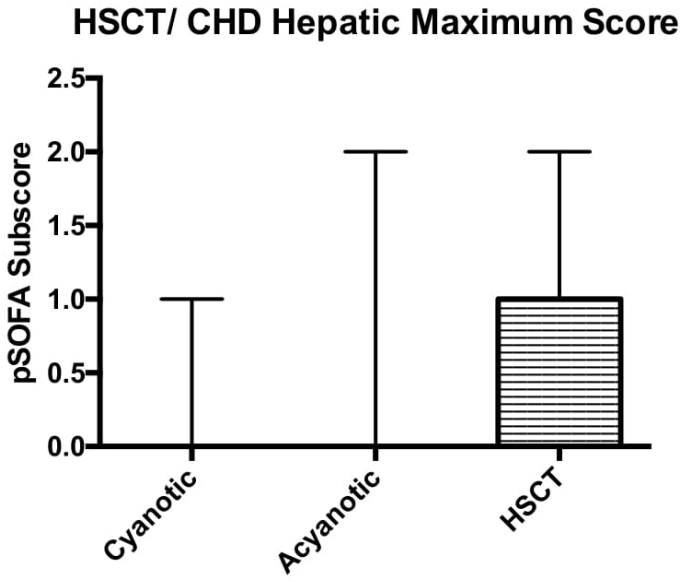

Figure 41. There is a significant difference between HSCT & Cyanotic CHD patients ($p<0.05$). There is a significant difference between HSCT & Acyanotic CHD patients ($p<0.05$).

LIST OF JOURNAL ABBREVIATIONS

Ann Transl Med	Annals of Translational Medicine
Childs Nerv Syst	Child's Nervous System
Crit Care Med	Critical Care Medicine
Curr Cardiol Rev	Current Cardiology Reviews
Intensive Care Med	Intensive Care Medicine
JAMA	JAMA: The Journal of the American Medical Association
J Cardiothorac Vasc Anesth	Journal of Cardiothoracic Vascular Anesthesiology
Yale J Biol Med	Yale Journal of Biology and Medicine

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