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Thesis

PEDIATRIC SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE IN A CONGENITAL HEART DEFECT POPULATION

by

ZACHARY ABBATE

B.S., State University of New York Binghamton 2018

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
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DEDICATION

For Faith.
Her help is immeasurable and my love and appreciation for her is limitless.

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This work would not be possible without the help of many whom I wish to thank. I would like to thank Amanda Baier and Izabela Leahy for allowing me the opportunity to be a part of the internship at Boston Children's. I thank Dr. Koichi Yuki, for working with and guiding me through my project. I would also like to thank my lab partner Neha Narayanan for her contributions.

PEDIATRIC SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE IN A CONGENITAL HEART DEFECT POPULATION

ZACHARY ABBATE

ABSTRACT

Background: Researchers recently created a new scoring system for characterizing organ dysfunction in critically ill pediatric patients, named the pSFOA (pediatric sequential organ failure assessment). Support for applying this scoring system in pediatric patients who suffer from cyanotic and acyanotic congenital heart diseases has not been evaluated.

Objectives: To compare the pSOFA scores between pediatric patients with acyanotic and cyanotic congenital heart disease (CHD). Exampine the pSOFA results of CHD patients with pediatric patients who underwent hematopoietic stem cell transplantations.

Methods: A retrospective case-study of pediatric patients with congenital heart disease admitted to the CICU at Boston Children's Hospital in 2018. Patients were included if between 1 and 5 years of age, neonates of less than a month old were excluded. A total of 101 patients were reviewed, 50 with cyanotic CHD and 51 with acyanotic CHD. Patient vital signs were assessed using the pSOFA scoring system, with scores assigned based on indices of respiratory, coagulation, hepatic, cardiovascular, neurologic, and renal system function. Scores were analyzed using two-tailed nonparametric Mann-Whitney tests with an alpha of 0.05. The pSOFA scores of CHD patients were then compared to patients who were admitted to the ICU at Boston Children's Hospital after they received a hematopoietic stem cell transplantation (HSCT). Dunn's multiple comparisons tests were performed for the two CHD groups and the HSCT patients. An alpha value of 0.05 was also used for these tests.

Results: Parameters determined to be statistically significant between the cyanotic and acyanotic CHD patients were, Total High Direct score, Total Average Direct score, Total Low Indirect Score, Total High Indirect score, Neurologic High score, Average Neurologic score, Renal High score, Average Renal score, and Hepatic Low Indirect score. The parameters that were statistically different between the CHD groups and the HSCT group were Age, Maximum Coagulation, Maximum Renal, Maximum Hepatic, and Maximum Total pSOFA scores. Parameters that were significantly different only between cyanotic CHD and HSCT were Maximum Cardiovascular and Maximum

Respiratory. Scores that were significantly different between acyanotic CHD and HSCT were Maximum Neurologic.

Conclusions: There were significant differences in pSOFA scores between children with cyanotic CHD and acyanotic CHD, specifically regarding total direct, total indirect, neurologic, and renal scores. Additional research is required to explain these scores differences and validation of these scores in predicting morbidity and mortality outcomes in these patient populations.

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LIST OF ABBREVIATIONS

ASD	Atrial Septal Defect
CHD	Congenital Heart Disease
CICU	Cardiac Intensive Care Unit
ESICM	European Society of Intensive Care Medicine
FiO_2	Fraction of Inspired Oxygen
HSCT	Hematopoietic Stem Cell Transplantation
ICU	Intensive Care Unit
LA	Left Atrium
LOS	Length of Stay
LV	Left Ventricle
LVH	Left Ventricular Hypertrophy
MAP	Mean Arterial Pressure
PaO_2	Arterial Partial Pressure of Oxygen
pSOFA	Pediatric Sequential Organ Failure Assessment
RA	Right Atrium
RV	Right Ventricle
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral Oxygen Saturation
TA	Tricuspid Atresia

INTRODUCTION

Quantifying the degree of a patient's illness is a relatively new idea in the field of medicine. The first scoring system for quantifying the critical care was created in 1974 by Cullen et al., named the Therapeutic Intervention Scoring System [1]. This system was based on categorizing the therapeutic measures used to treat the patient, rather than evaluating the physiological status of the patient. One of the first systems to account for the physiological state of the patient was the Sepsis Score, produced by Elebute and Stoner in 1983 [3]. While proving to be a fairly accurate predictor of outcomes in patients with sepsis, this scoring system inadequately characterized outcomes in critically ill patients without sepsis [2]. Concurrently, various scoring systems were being developed for such a purpose, each with their own inherent strengths and weaknesses when applied to the clinical setting.

In October of 1994, the European Society of Intensive Care Medicine (ESICM) created the so-called sepsis-related organ failure assessment (SOFA) score, in an effort to appropriately describe the issues of organ failure [4]. While there were previous scoring systems designed to describe multiple organ failure, none of them addressed the issue completely. They assumed organ dysfunction was a binary process, either present or absent, rather than incorporating degrees of organ dysfunction in their scoring models. The original 1994 SOFA score allowed organ failure to be accurately described as a process, and thus, the SOFA score criteria included a scale to allow various ranges of functionality to the organ system [4]. Table 1 contains the original SOFA scoring criteria created in 1994.

Table 1. The Sepsis-Related Organ Failure Assessment Score [4]

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2, mm Hg	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation Platelets x 10^3 / mm^3	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/L)	1.2 – 1.9 (20 – 32)	2.0 – 5.9 (33 – 101)	6.0 – 11.9 (102 – 204)	>12.0 (>204)
Cardiovascular Hypotension	MAP < 70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)[a]	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system Glasgow Coma Score	13 – 14	10 – 12	6 – 9	<6
Renal Creatinine, mg/dL (µmol/L) or urine output	1.2 – 1.9 (110 – 170)	2.0 – 3.4 (171 – 299)	3.5 – 4.9 (300 – 400) or <500 mL/day	>5.0 (>400) or <200 mL/day

Table 1. Original Scoring System established for SOFA scores

In 2016, the definitions for sepsis and septic shock were updated by a team of medical professionals at The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [5]. Prior to that, these definitions were last revised in 2001. During those 15 years, medical research related to sepsis and critical illnesses has vastly increased our knowledge of these disease processes, and as a result, scoring systems should be updated to reflect this improved understanding. As a result of this, the Sequential Organ Failure Assessment (SOFA) score (previously known as the sepsis-related organ failure assessment score) was validated as one, if not the best, method to quantify organ dysfunction as well as predict an increased mortality in patients that have or are suspected of having an infection [5].

Simultaneously the need to establish a scoring system that was applicable for sick pediatric patients was recognized as an area of future research [5]. Children have different physiology compared to adults and therefore a scoring system that reflects these differences is necessary [5]. A scoring system for pediatric patients, aptly named the Pediatric Sequential Organ Failure Assessment (pSOFA) score, was debuted in 2017 in *Adaptation and Validation of a Pediatric Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children* [6]. In this article, researchers developed and validated a new pediatric scoring method that mirrors the adult SOFA, showing that these definitions are valid in critically ill children [6].

Children born with congenital heart diseases (CHD) can often be critically ill. CHD encompass variable developmental anatomical defects to the heart and/or great vessels. CHD can be further classified into cyanotic and acyanotic lesions depending on how the defect affects blood oxygenation. Depending on the defect, the aberrant circulation and its effects on systemic oxygen delivery, pulmonary over circulation and heart failure results in a higher morbidity and mortality rate for these children [7].

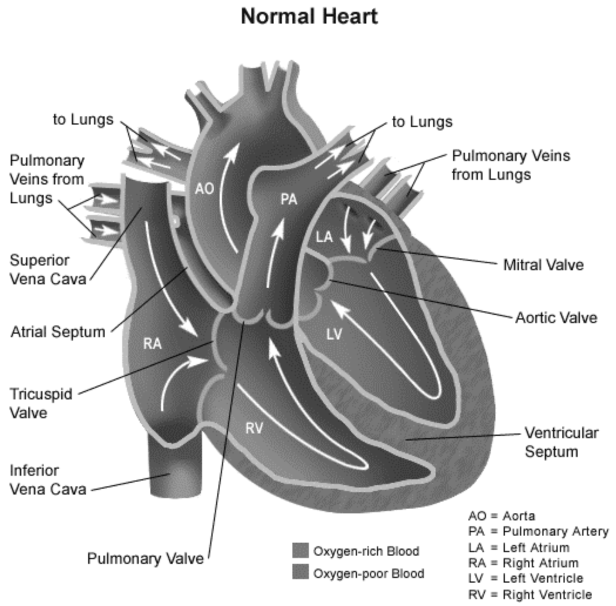

Figure 1. Diagram of a heart with normal anatomy and circulation (Stanford Children's Health; www.stanfordchildrens.org/en/topic/default?id=blood-circulation-in-the-fetus-and-newborn-90-P02362)

In a heart where the anatomy and circulation are normal (figure 1.), deoxygenated blood returns from the systemic venous system via the vena cava veins to the right side of the heart. From the vena cava, the blood enters the right atrium (RA) followed by the right ventricle (RV) through the tricuspid valve. The RV pumps the blood into the pulmonary artery which carries the deoxygenated blood to the lungs to be oxygenated. Once the blood becomes oxygenated in the lungs, it returns to the left side of the heart, specifically the left atrium (LA) via the pulmonary veins. From the LA, the blood travels through the mitral valve into the left ventricle (LV) where it is pumped out the aorta into systemic circulation for oxygen delivery to the body.

However, children (and adults) with CHD have a different circulation because they are born with abnormalities to structures of the heart and/or the great vessels. The various defects can alter the normal flow of blood within the heart resulting in alterations in pulmonary and systemic circulations. How the blood flow specifically changes, and the physiologic result depends on the specific anatomy. Cyanotic CHD is described as a right to left shunt. This occurs when deoxygenated blood (from the systemic venous circulation) mixes with the oxygenated blood in the heart (the left circulation) [7]. This mixing results in decreased systemic oxygenation and cyanosis of various tissues. An example of a cyanotic CHD is tricuspid atresia (TA) [8]. Tricuspid atresia (figure 2.) is when the tricuspid valve that normally allows deoxygenated blood to flow from the right atrium to right ventricle fails to open or is absent. In order to survive, defects within the atrial and ventricular septum must exist to allow adequate mixing and pulmonary blood flow. The amount of pulmonary blood flow is variable, dependent on a patent ductus arteriosus or a ventricular septal defect, but nevertheless decreased which causes cyanosis in these patients [8].

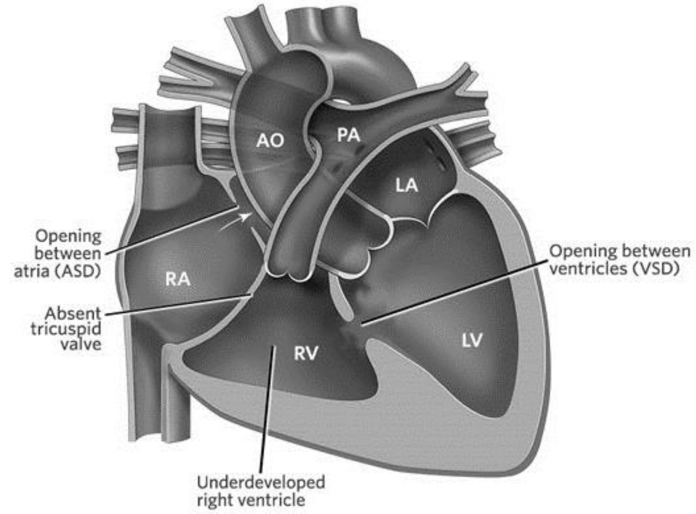

Figure 2. Diagram of heart with tricuspid atresia (Children's Hospital of Philadelphia; www.chop.edu/conditions-diseases/tricuspid-atresia)

Abnormalities in which oxygenated blood mixes with the deoxygenated part of the circulation via a defect is called a left to right shunt. These types of defects are categorized as acyanotic CHD as patients have a normal oxygen saturation. The left to right shunt can result in too much pulmonary blood flow, heart failure and inadequate systemic perfusion [7]. Acyanotic CHD is also associated with obstructive lesions, a narrowing of any of the vessels or the valves between chambers [8]. An example of an acyanotic CHD is an Atrial Septal Defect (ASD) [7]. An atrial septal defect (figure 3.) is when there is a hole in the septum between the right and left atria of the heart. This hole results in oxygenated blood from the left side to circulate to the deoxygenated right side, which can cause right ventricular, right atrial, and/or pulmonary arterial dilatation [7]. An estimated 6/1000 live births have a form of moderate to severe CHD. It is a serious condition with significant morbidity and mortality [9].

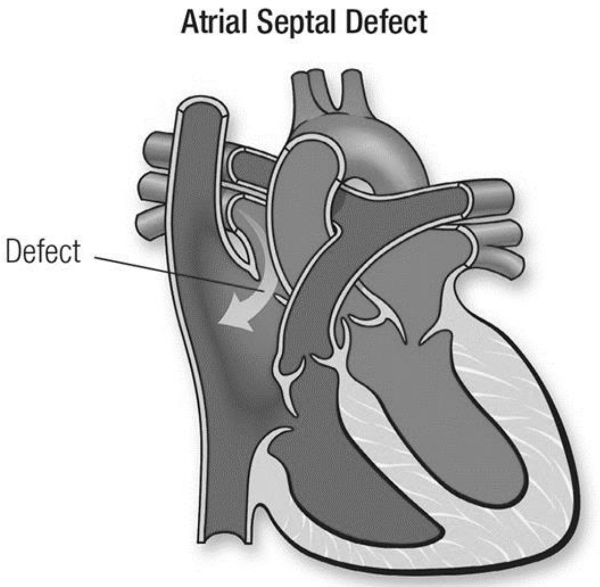

Figure 3. Diagram of a heart with atrial septal defect (American Heart Association; www.heart.org/en/health-topics/congenital-heart-defects/about-congenital-heart-defects/atrial-septal-defect-asd)

This thesis also describes a population of children who have undergone hematopoietic stem cell transplantation (HSCT), therefore, it is pertinent to discuss some background information about this patient population. Hematopoietic stem cell transplantation is a procedure performed for patients who as a result of their diseases, including cancers and autoimmune disorders, have ineffective hematopoietic systems [10]. The procedure involves irradiating the patient and then administering hematopoietic stem cells to "restart" their system. There are various complications associated with this procedure but recently these risks have decreased [10].

Validation of the new pSOFA scoring system, behooves researchers to examine how applicable the system describes different populations of sick children. Children who suffer from CHD may have significantly different pSOFA values compared to children who have no cardiovascular anomalies and children with cyanotic CHD may also exhibit pSOFA differences compared to acyanotic CHD children. It is noteworthy to see how pSOFA values may be similar or differ in various disease populations. One specific population is children who underwent hematopoietic stem cell transplantation. (HSCT).

SPECIFIC AIMS

This study’s objective is to examine the pSOFA scores amongst pediatric patients who have congenital heart diseases (CHD). We also want to look more specifically at differences in pSOFA scores between cyanotic versus acyanotic CHD patients. Additionally, this thesis explores the differences between children with cyanotic and acyanotic CHD and children who underwent hematopoietic stem cell transplants. Comparing pSOFA values between patient populations with different physiological states may be beneficial for researchers and medical teams in understanding patients’ overall health and the pSOFA scoring system’s validation in these unique disease states.

METHODS

Data Collection

A retrospective case study was performed. Patients were selected from a list of patients who had been born with CHD and admitted to the Cardiac Intensive Care Unit (CICU) at Boston Children’s Hospital during the year of 2018. Patients were selected between the ages of 1 year and 5 years of age or, on a special case basis, neonates of less than a month old. Patients from this list were then separated into cyanotic and acyanotic heart conditions by Dr. Koichi Yuki, M.D., an Associate in Cardiac Anesthesia, in the Department of Anesthesia at Boston Children’s Hospital. Patients’ vitals were then reviewed, recorded, and assigned a Pediatric Sequential Organ Failure Assessment (pSOFA) score based on the guidelines created in the study by Matics et al (Table 2.) [6]. Patients vitals were retrieved using PowerChart, an electronic medical records system.

The six different components of the pSOFA score are respiratory, coagulation, hepatic, cardiovascular, neurologic, and renal. The scores ranged from integers 0 to 4, with 0 being normal and healthy vitals for that age group, and 4 indicating severe organ dysfunction/failure. Accounting for the six different systems, an individual’s possible minimum total score is 0 and their possible maximum total score is 24.

Respiratory scores were calculated by the ratio of the partial pressure of oxygen in the arterial blood (PaO_2) over the fraction of inhaled oxygen (FiO_2) for a patient, or the ratio of the oxygen saturation in the blood (SpO_2) over the FiO_2. Both the ratios PaO_2:FiO_2 and SpO_2: were used to calculate the scores, along with whether the patient was on any respiratory support system. PaO_2:FiO_2 ratios were favored over SpO_2:FiO_2 when available due to the increased validity of this information.

Coagulation scores were calculated by recording the patient's platelet count during their stay, measured in platelet count per microliters.

For hepatic scores, two different bilirubin results were available, direct bilirubin and indirect bilirubin. Both were separately recorded to create two different hepatic sub scores, called direct hepatic sub score and indirect hepatic sub score. These sub scores were also separately incorporated into the total scores to create two different total scores; the score which includes the direct hepatic bilirubin sub score is referred to as the direct total score; the one that has indirect hepatic bilirubin sub score is the indirect total score.

Cardiovascular scores were calculated by measuring the patient's mean arterial pressure (MAP) by age group. Cardiovascular sub scores also considered whether the patient was given specific inotropes during their stay in the CICU.

Neurologic scores were calculated based on their Glasgow Coma Scores that were assigned to the patient by the medical team during their admission.

Lastly, the patients' renal scores were calculated from their creatinine level adjusted for normal values by age.

The worst vital signs for that calendar day stay in the CICU were recorded and a score was calculated for each organ system, and then totaled to create a "total score". If a vital was absent from their medical chart on any day, it was assumed that there was no issue for that system and a score of zero was assigned. 50 cyanotic patients and 51 acyanotic patients scores were recorded.

Data from a previous study that involved children with hematopoietic stem cell transplantations (HSCT) was available for us to review, via the study "The Outcomes of Pediatric Hematopoietic Stem Cell Transplantation Recipients Requiring Intensive Care Unit Admission- A Single Center Experience" by Royce Kwon et al. Data included their pSOFA scores upon admission as well as their maximum pSOFA values during their stay in the ICU at Boston Children's Hospital. These 75 children were patients who underwent a HSCT at Boston Children's Hospital and subsequently admitted to the ICU during the same admission [11].

Data Analysis

Scores were analyzed via PRISM software (GraphPad Software, San Diego, CA). Two tailed nonparametric Mann-Whitney tests were performed for the parameters obtained between the cyanotic (n=50) and acyanotic (n=51) patients. Tests compared the median values between the two different groups for each of the sub score and total score parameters. For example, the respiratory sub score was analyzed in 3 different ways. The lowest respiratory sub scores for each of the cyanotic patients compared to the lowest respiratory sub scores for the acyanotic group. This was also done for the highest scores obtained during the patients' stay in the CICU as well as for the patient's average scores during their stay.

The maximum values between the cyanotic and acyanotic patients were than compared to the HSCT children (n=75) from group A of Kwon et al and a Kruskal-Wallis test was performed for age, each of the sub scores of pSOFA, and for the total pSOFA score (when comparing total scores, the maximum indirect pSOFA scores was used for the cyanotic and acyanotic patients). A Dunn's multiple comparisons test was also performed for the two CHD groups and the HSCT group. An alpha value of 0.05 was used to determine significance for the tests.

Table 2. Pediatric Sequential Organ Failure Assessment Score [6]

	Score[a]				
Variables	0	1	2	3	4
Respiratory					
PaO_2:FiO_2[b]	≥ 400	300-399	200-299	100-199 with respiratory support	<100 with respiratory support
SpO_2:FiO_2[c]	≥ 292	264-291	221-264	148-220 with respiratory support	<148 with respiratory support
Coagulation					
Platelet count x 10^3/μL	≥ 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, mm Hg or µg/kg/min[d]					
<1 mo	≥ 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
1-11 mo	≥ 55	<55			
12-23 mo	≥ 60	<60			
24-59 mo	≥ 62	<62			
60-143 mo	≥ 65	<65			
144-216 mo	≥ 6	<6			
>216 mo[e]	≥ 70	<70			
Neurologic					
Glasgow Coma Score[f]	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1 mo	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥ 1.6
1-11 mo	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥ 1.2
12-23 mo	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥ 1.5
24-59 mo	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥ 2.3

60-143 mo	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥ 2.6
144-216 mo	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥ 4.2
>216 mo[e]	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥ 5

[a] The pSOFA was calculated for every 24-hour period. The worst value for every variable in each 24-hour period was used to calculate the sub score for each of the 6 organ systems. If a variable was not recorded in each 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 sub scores (range, 0-24; higher scores indicate a worse outcome).

[b] PaO2 was measured in millimeters of mercury

[c] Only SpO2 measurements of 97% or lower were used in calculations

[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.

RESULTS

Of the 50 cyanotic patients, 31 (62%) were male. There was a 4% mortality rate during the same admission as their stay in the CICU. Median age was 26 months, with a median length of stay of 3.0 days in the CICU. Of the 51 acyanotic patients, 34 (66.67%) were male. Of the acyanotic patients that were reviewed, there was a 0% mortality during the same admission as their stay in the CICU. The median age was 23 months, and the median length of stay was 5.4 days. Age difference was not significant with a p value of 0.9744 (figure 4). There was a significant difference in terms of length of stay between the cyanotic and acyanotic populations of children, with a p value of <0.0001 (figure 5).

The parameters that were found to be significantly different between the cyanotic and acyanotic populations in terms of pSOFA values were Total High Direct score (p value < 0.0001) (figure 7), Total Average Direct score (p value = 0.0133) (figure 10), Total Low Indirect score (p value = 0.0172) (figure 8), Total High Indirect score (p value = 0.0008) (figure 9), Neurologic High score (p value < 0.0001) (figure 22), Average Neurologic score (p value < 0.0001) (figure 23), Renal High score (p value < 0.0001) (figure 25), Average Renal score (p value < 0.0001) (figure 26), and Hepatic Low Indirect score (p value = 0.0006) (figure 30) respectively. All parameters and their p values are recorded on tables 3 and 4.

HSCT group had a mortality of 26.7%. Between cyanotic CHD, acyanotic CHD and HSCT, there was a significant difference in age (figure 34). The Kruskal-Wallis test approximated a p value of 0.0030. The significance was between the entire CHD group and the HSCT group. In evaluating the cardiovascular parameter, there was a significant difference between only the cyanotic group and the HSCT group, but not between the acyanotic and the HSCT, with a mean rank difference of 22.24 (figure 35). For the coagulation parameter, there was a significant difference between each CHD group and the HSCT group with the HSCT group having a much higher mean sub score compared to the CHD groups (figure 36). Analyzing the hepatic score, there was a significant difference between the CHD groups and the HSCT group, with an approximate p value of 0.0174 (figure 40). With the neurologic calculation, there was a significant difference between only the acyanotic CHD group and the HSCT group with a mean rank difference of -51.05 (figure 37). With the renal parameter, there was a significant difference between all groups, with an approximate p value of <0.0001 (figure 38). With the respiratory parameter, there was only a significant difference between the cyanotic CHD group and the HSCT group, with a mean rank difference of 31.72 (figure 34). Finally, there was a significant difference in the total pSOFA values between all the groups, with an approximate p value of < 0.0001 (figure 39).

Table 3. CHD Patient Statistics *denotes statistical significance

	Cyanotic (n=50)	Acyanotic (n=51)	P value
Mortality, % (no.)	4% (2)	0% (0)	n/a
Male, % (no.)	62% (31)	66.67 (34)	n/a
Age, median (IQR), mo	26 (16.25 - 37.75)	23 (17.5 - 45.5)	0.9734
Length of Stay, median (IQR), days	3 (2.1 - 4.63)	5.4 (5.1 - 5.8)	**<0.0001***

Table 4. CHD pSOFA values *denotes statistical significance

Parameter Statistic, median (IQR)	Cyanotic (n=50)	Acyanotic (n=51)	P value
Lowest Total Direct Score	2 (1-3)	3 (1-4)	0.1120
Highest Total Direct Score	9 (7-11)	6 (5-7)	**<0.0001***
Average Total Direct Score	5.25 (4.4-7)	4.43 (3.32-5.5)	**0.0133***
Lowest Total Indirect Score	2 (1-3)	3 (1-5)	**0.0172***
Highest Total Indirect Score	9.5 (7-11.75)	7 (5-8.5)	**0.0008***
Average Total Indirect Score	5.3125 (4.41-7)	5 (3.59-6.16)	0.2054
Lowest Respiratory Score	0 (0-2)	1 (0-2)	0.5537
Highest Respiratory Score	4 (3-4)	3 (3-4)	0.1420
Average Respiratory Score	2.25 (1.33-3.13)	2 (1.33-2.75)	0.8272
Lowest Coagulation Score	0 (0-0)	0 (0-0)	0.3002
Highest Coagulation Score	1 (0-2)	0 (0-1)	0.3678
Average Coagulation Score	0.354 (0-1)	0 (0-0.77)	0.1901
Lowest Cardiovascular	1 (0-1)	1 (0-1)	>0.9999

Score			
Highest Cardiovascular Score	3 (1-3)	2 (1-3)	0.2328
Average Cardiovascular Score	1.333 (1-1.75)	1.29 (1-1.585)	0.1842
Lowest Neurologic Score	0 (0-0)	0 (0-0)	0.1120
Highest Neurologic Score	4 (2-4)	0 (0-0)	**<0.0001***
Average Neurologic Score	1.333 (0.77-1.95)	0 (0-0)	**<0.0001***
Lowest Renal Score	0 (0-0)	0 (0-0)	0.0597
Highest Renal Score	0 (0-0)	0 (0-1)	**<0.0001***
Average Renal Score	0 (0-0)	0 (0-0.62)	**<0.0001***
Lowest Hepatic Direct Score	0 (0-0)	0 (0-0)	0.4950
Highest Hepatic Direct Score	0 (0-0)	0 (0-0)	0.2999
Average Hepatic Direct Score	0 (0-0)	0 (0-0)	0.1472
Lowest Hepatic Indirect Score	0 (0-0)	0 (0-1)	**0.0006***
Highest Hepatic Indirect Score	0 (0-1)	0 (0-2)	0.4496
Average Hepatic Indirect	0 (0-0.32225)	0 (0-1.855)	0.3376

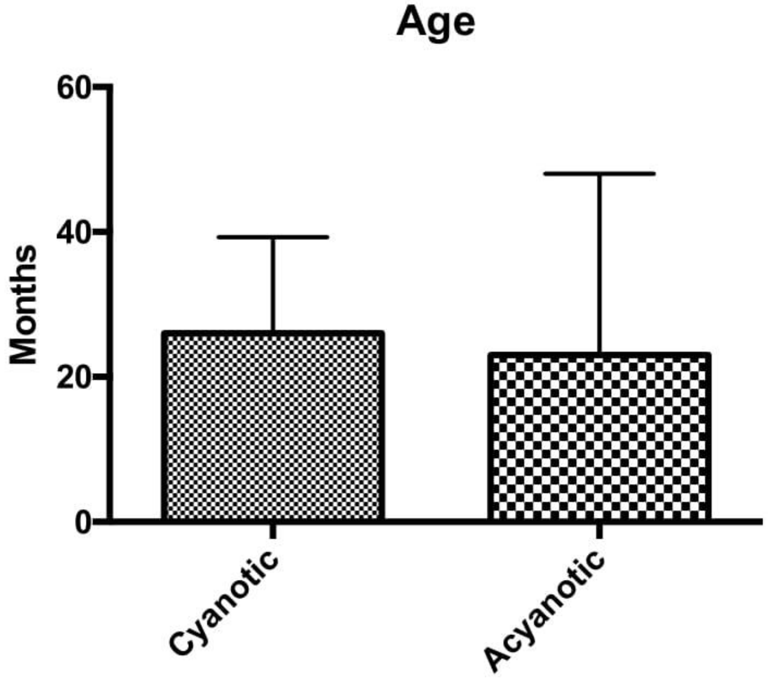

Figure 4. Median age (months) of cyanotic and acyanotic CHD patients with IQR

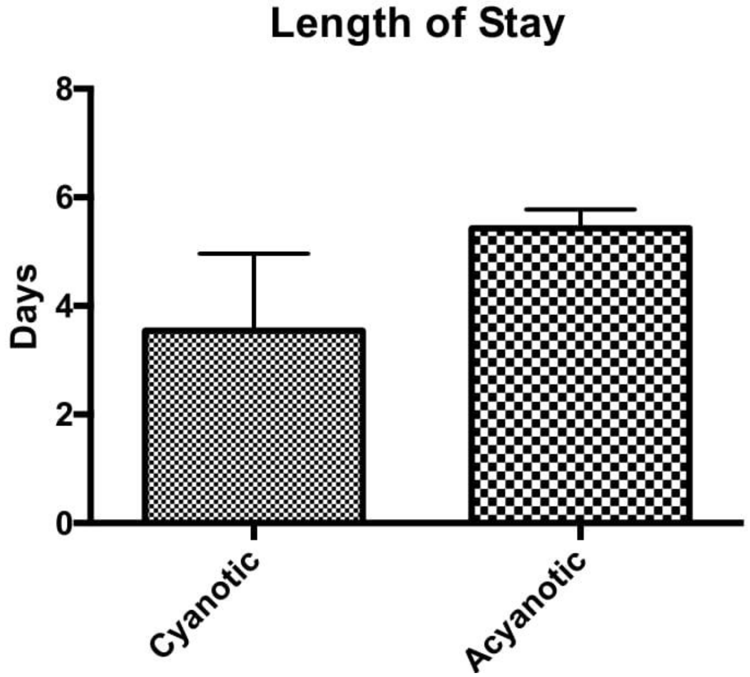

Figure 5. Median length of stay (days) of cyanotic and acyanotic CHD patients with IQR

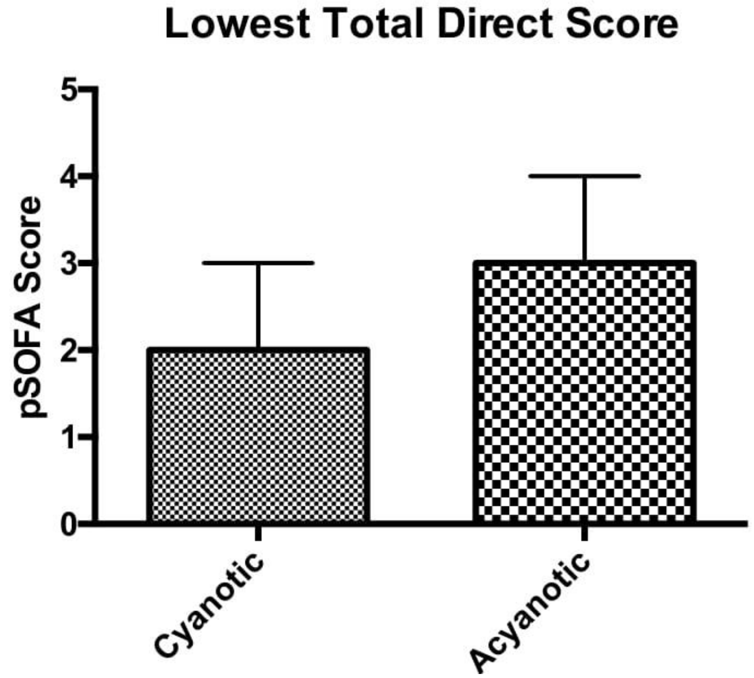

Figure 6. Median of the lowest total direct pSOFA scores of the cyanotic and acyanotic CHD patients (incorporates the direct hepatic sub score) with IQR

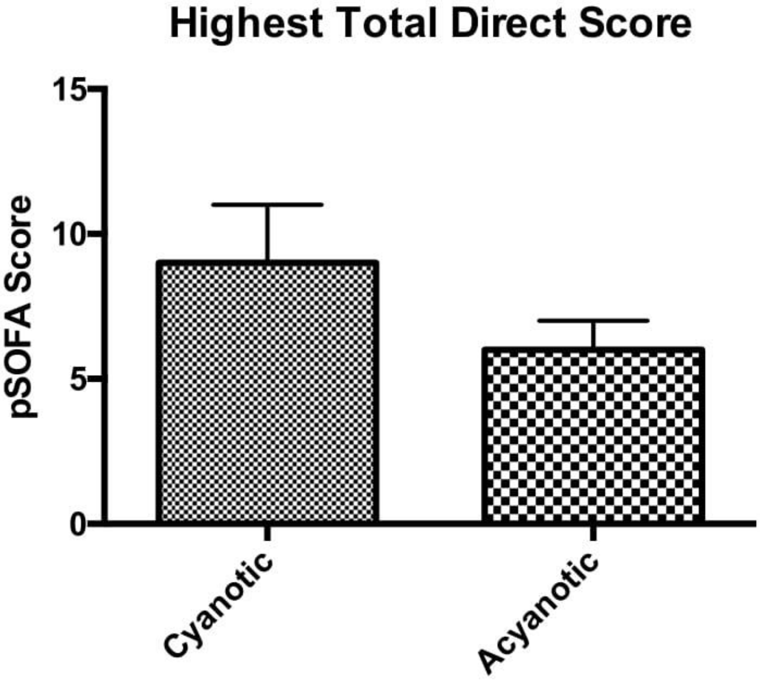

Figure 7. Median of the highest total direct pSOFA scores of the cyanotic and acyanotic CHD patients (incorporates the direct hepatic sub score) with IQR

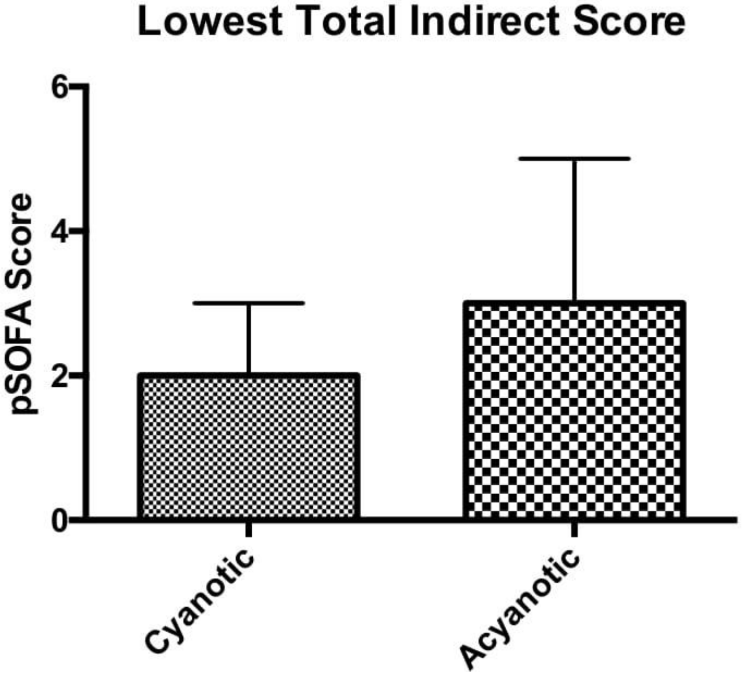

Figure 8. Median of the lowest total indirect pSOFA score of cyanotic and acyanotic CHD patients (incorporates the indirect hepatic sub score) with IQR

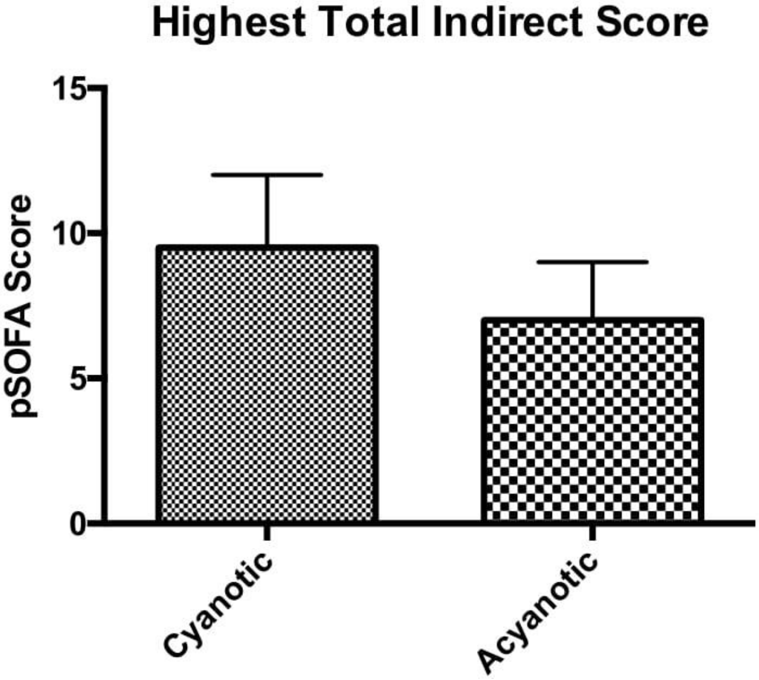

Figure 9. Median of the highest total indirect pSOFA score of cyanotic and acyanotic CHD patients (incorporates the indirect hepatic sub score) with IQR

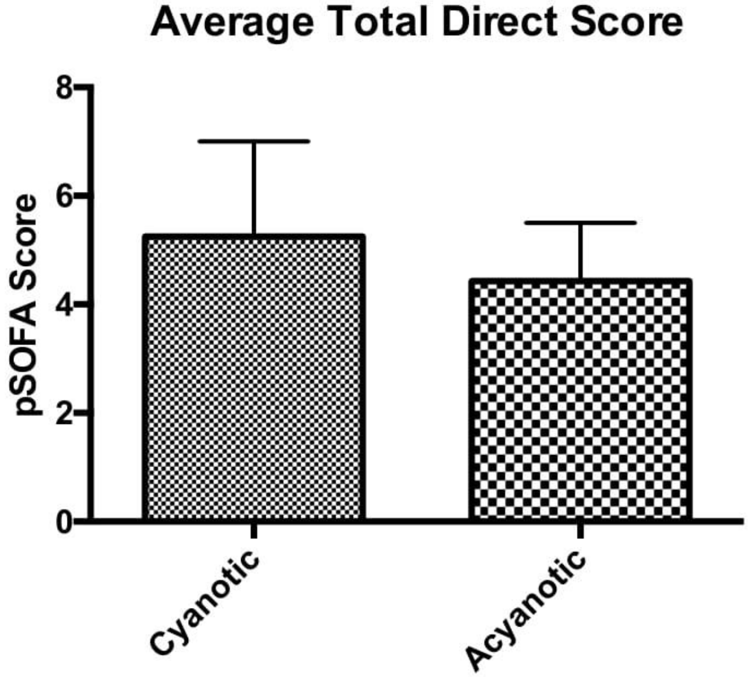

Figure 10. Median of the average total direct pSOFA score of the cyanotic and acyanotic CHD patients (incorporates the direct hepatic sub score) with IQR

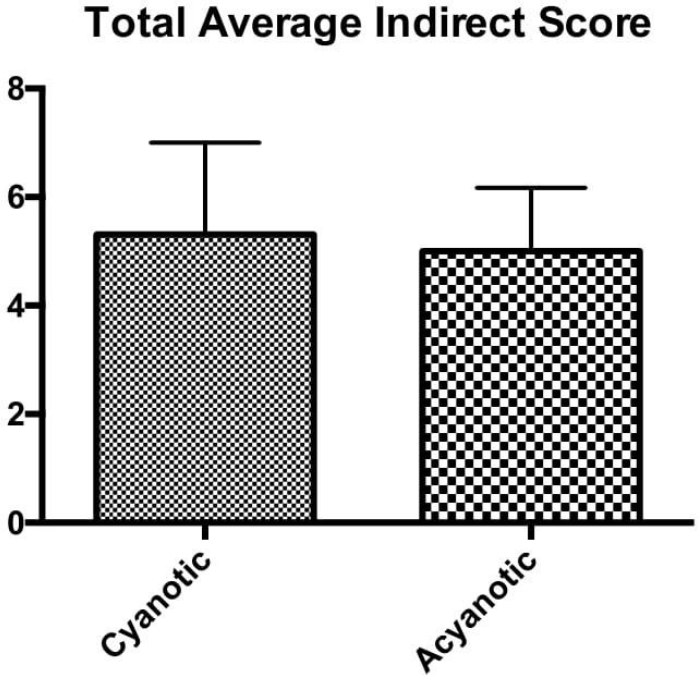

Figure 11. Median of the average total indirect pSOFA score of the cyanotic and acyanotic CHD patients (incorporates the indirect hepatic sub score) with IQR

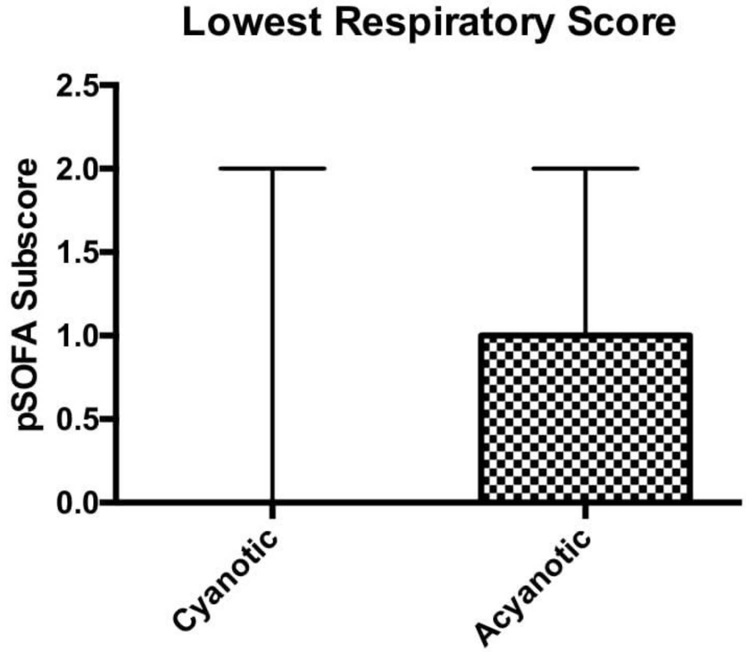

Figure 12. Median of the lowest respiratory pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

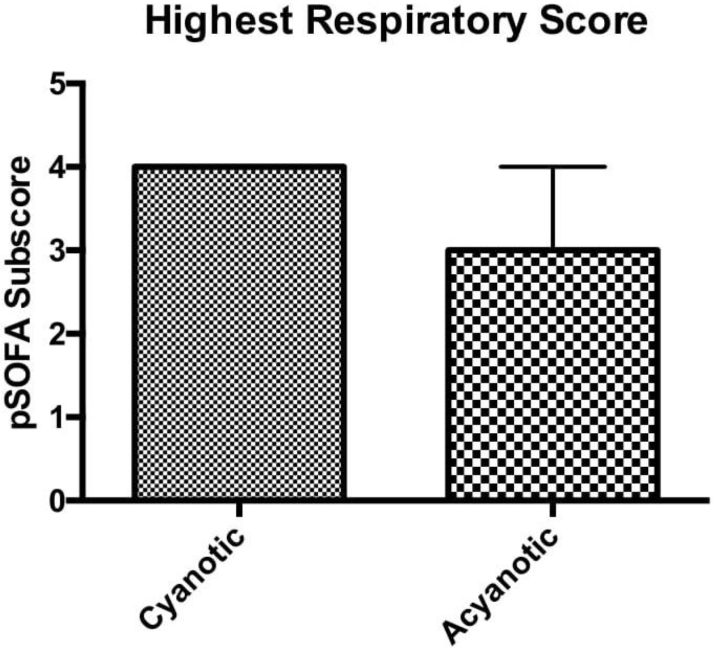

Figure 13. Median of the highest respiratory pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

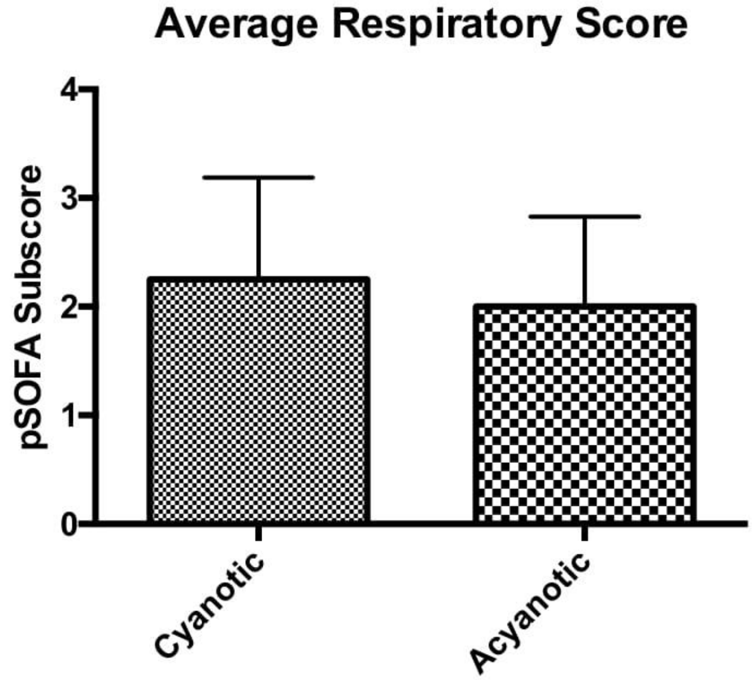

Figure 14. Median of the average respiratory pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

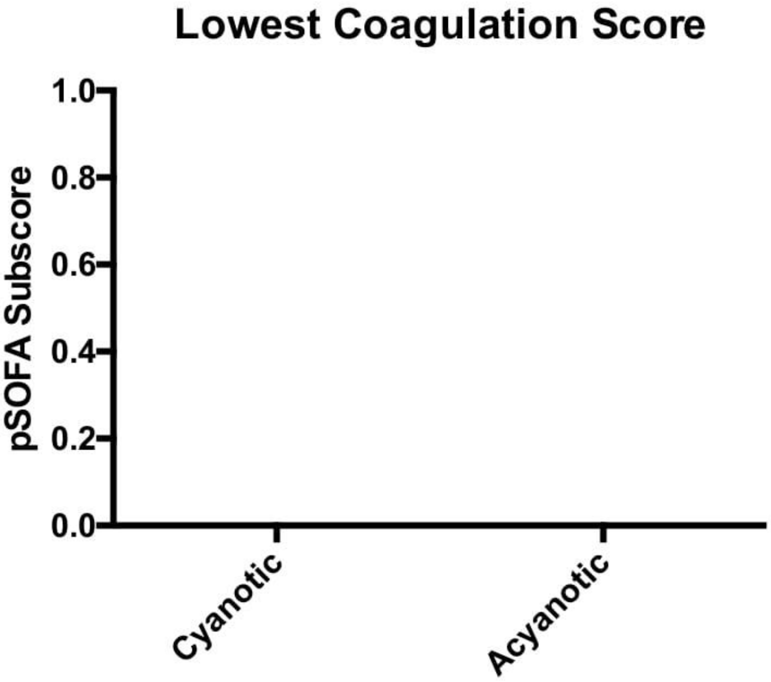

Figure 15. Median of the lowest coagulation pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

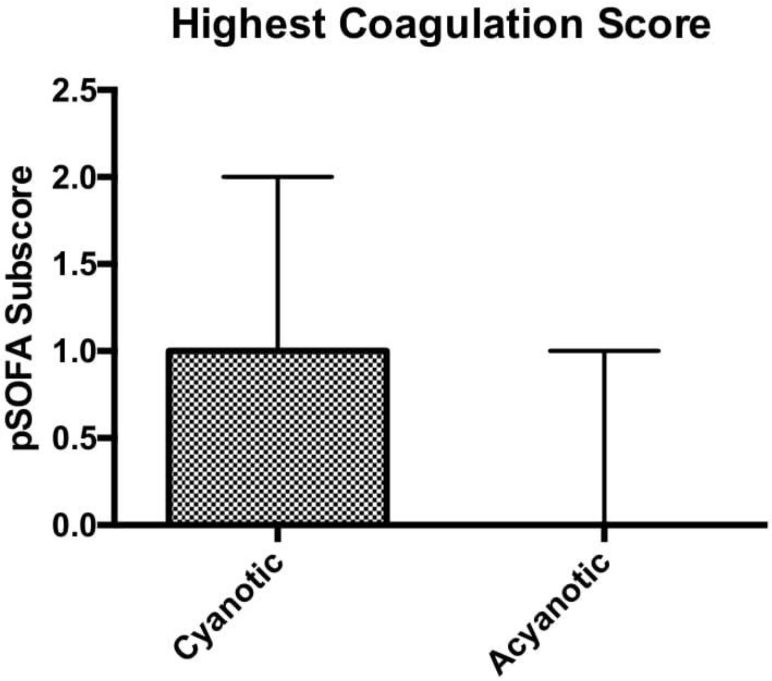

Figure 16. Median of the highest coagulation pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

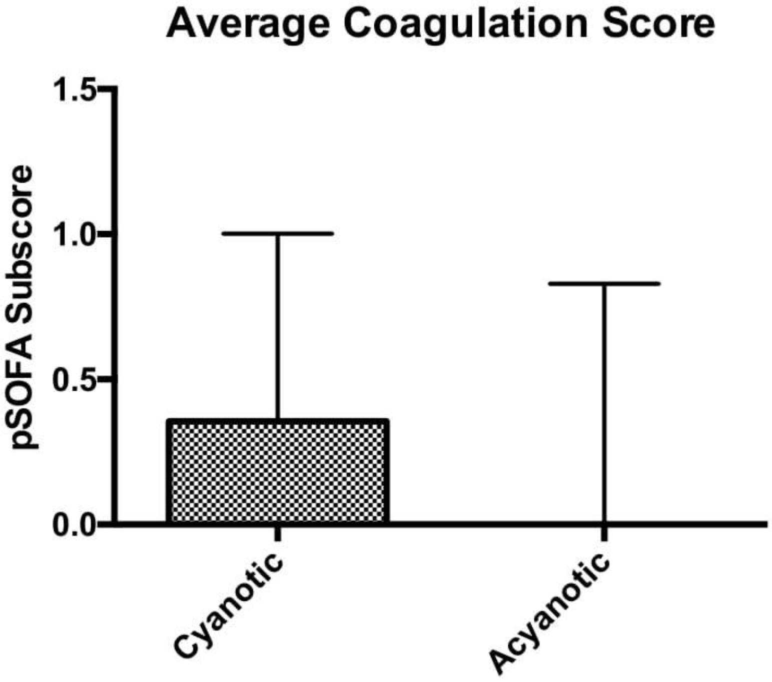

Figure 17. Median of the average coagulation pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

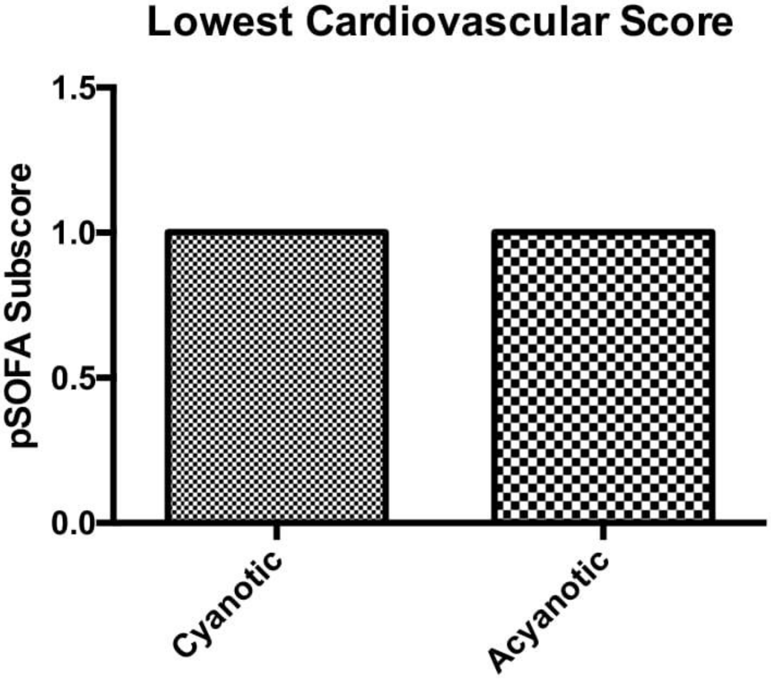

Figure 18. Median of the lowest cardiovascular pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

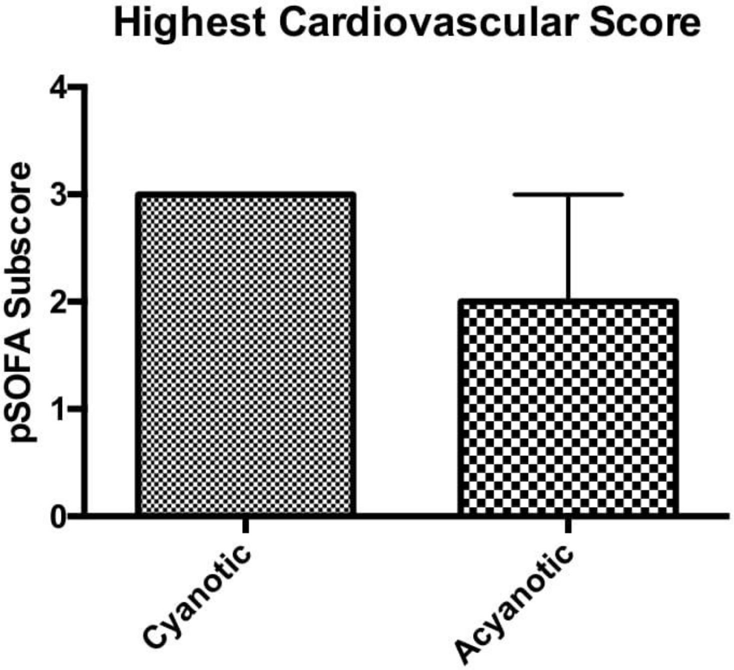

Figure 19. Median of the highest cardiovascular pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

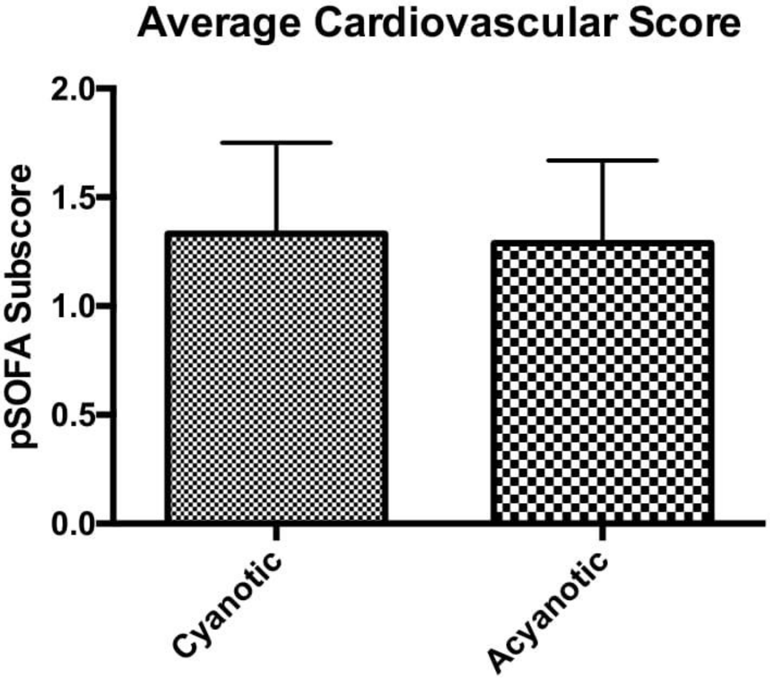

Figure 20. Median of the average cardiovascular pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

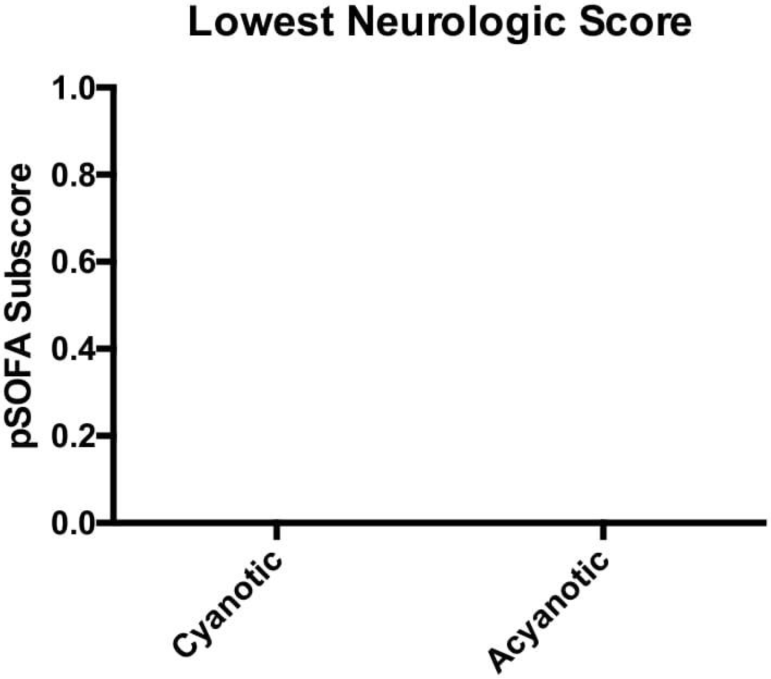

Figure 21. Median of the lowest neurologic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

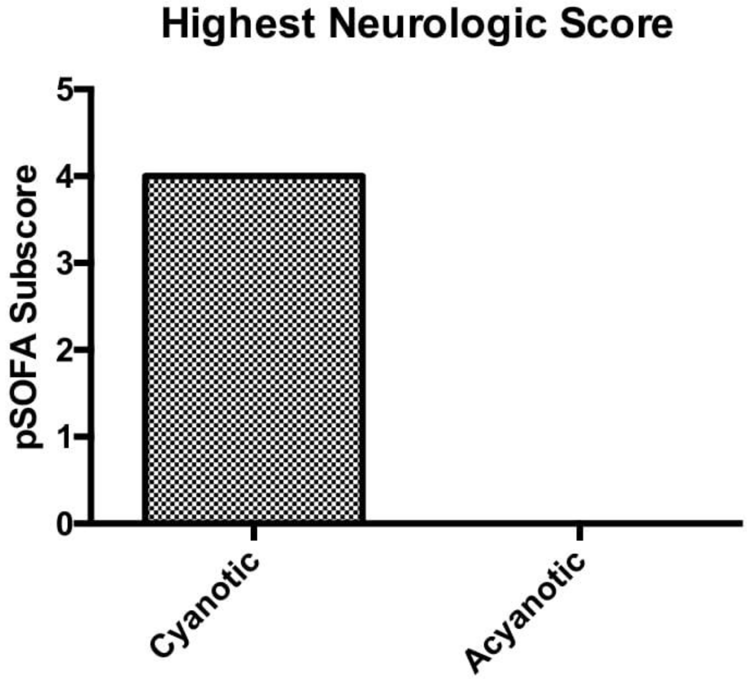

Figure 22. Median of the highest neurologic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

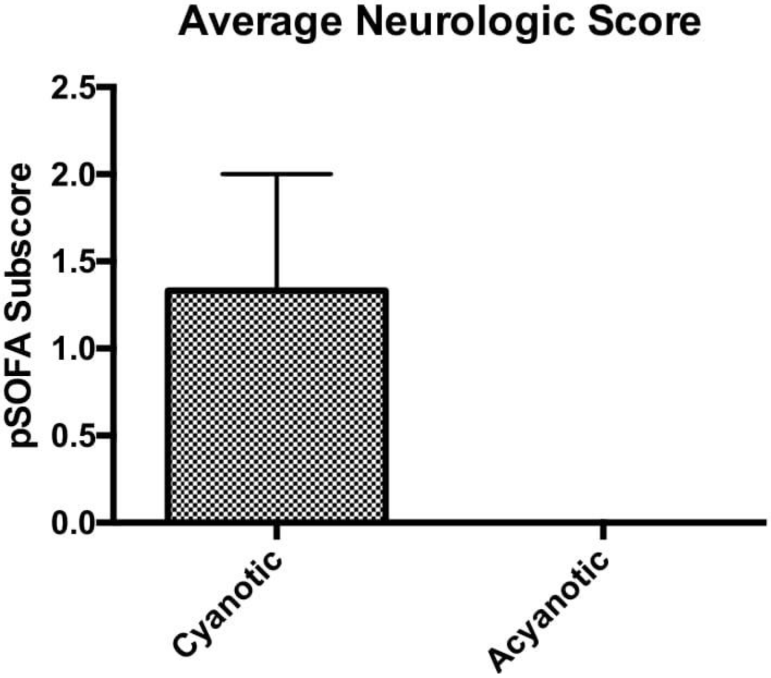

Figure 21. Median of the average neurologic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

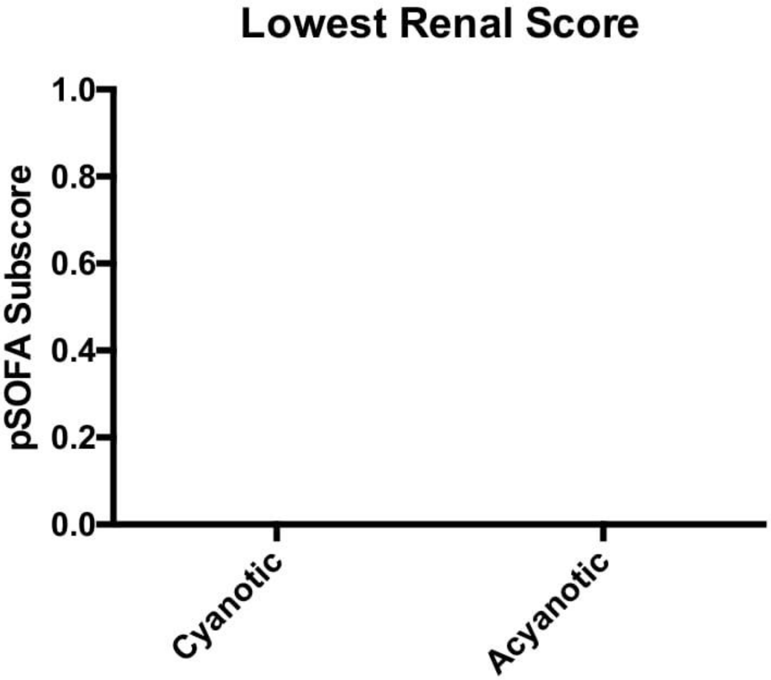

Figure 24. Median of the lowest renal pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

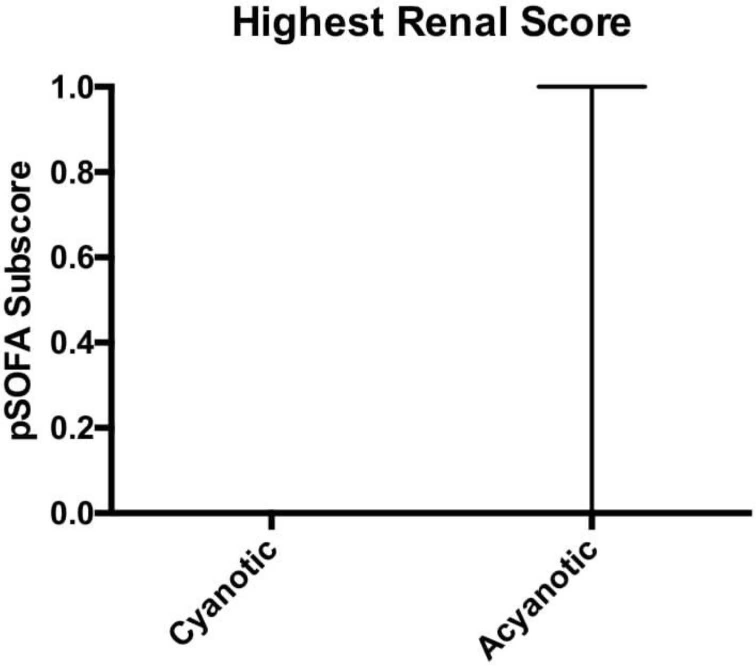

Figure 25. Median of the highest renal pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

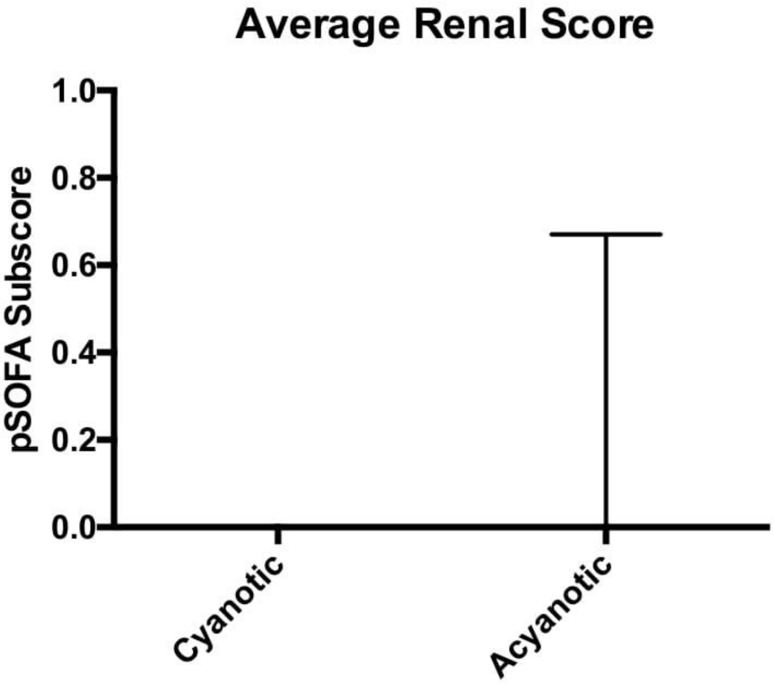

Figure 26. Median of the average renal pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

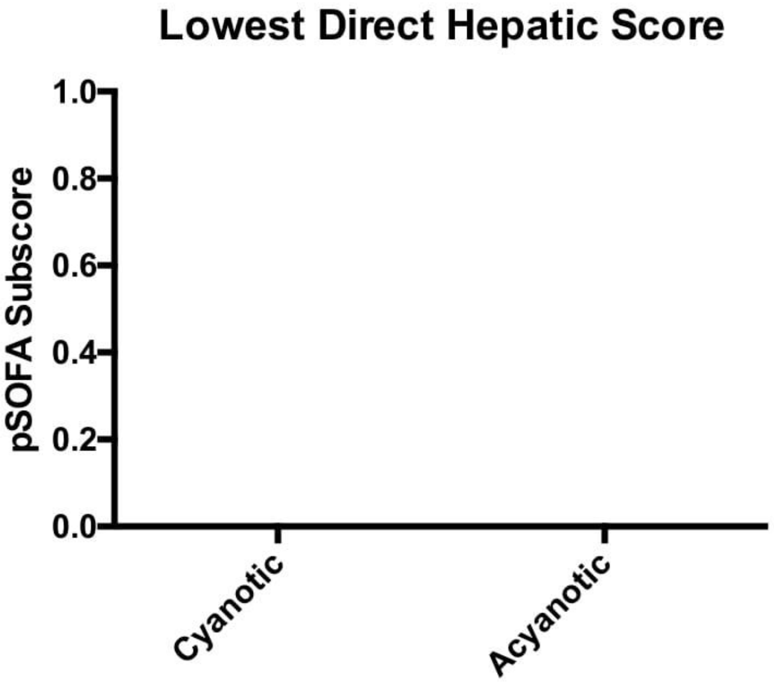

Figure 27. Median of the lowest direct hepatic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

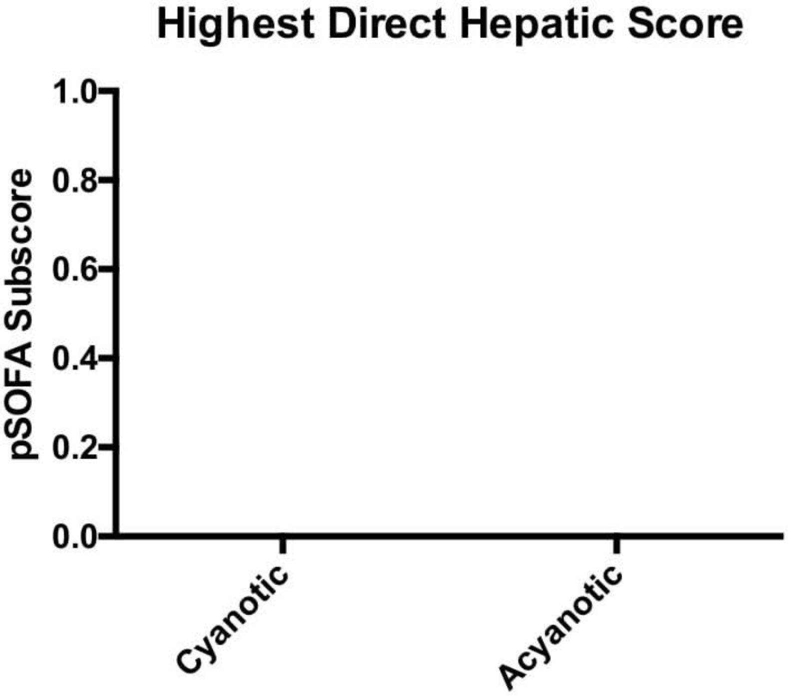

Figure 28. Median of the highest direct hepatic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

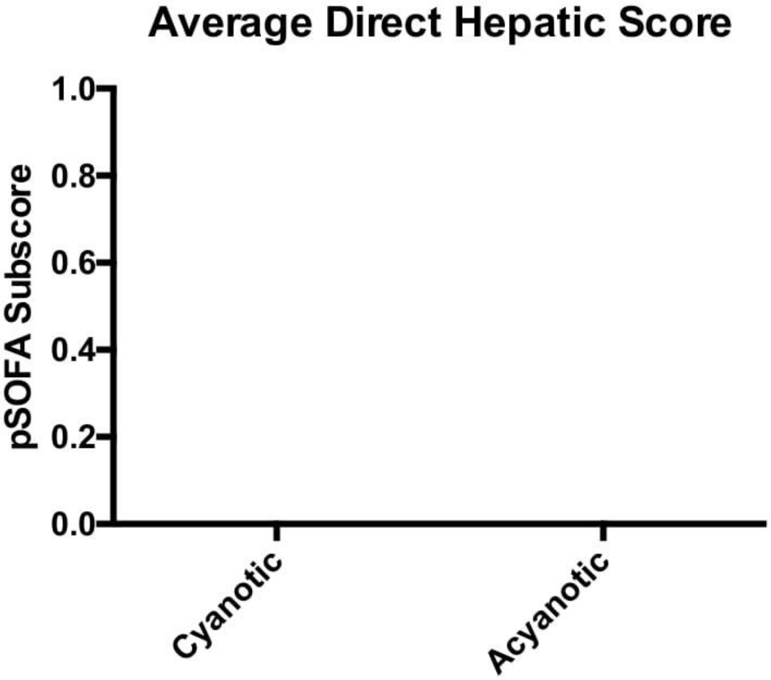

Figure 29. Median of the average direct hepatic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

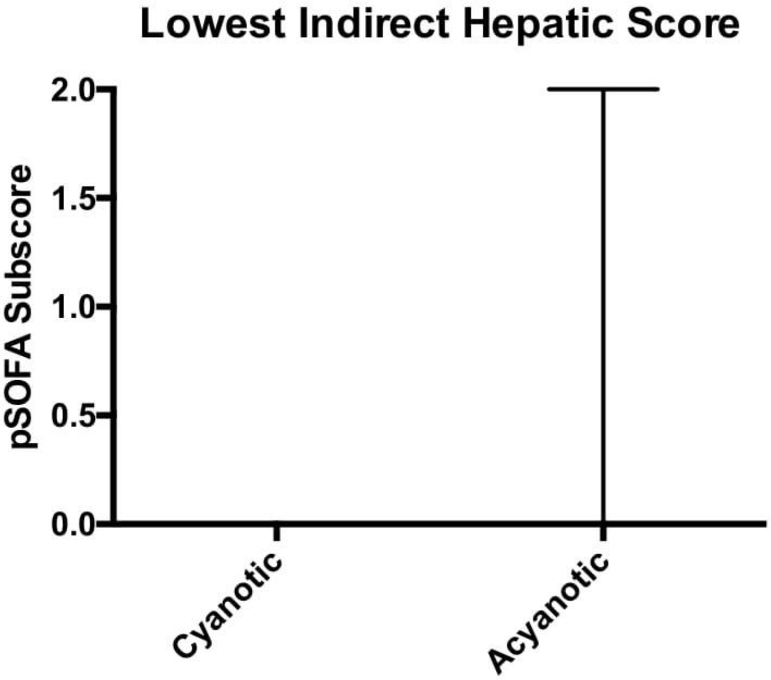

Figure 30. Median of the lowest indirect hepatic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

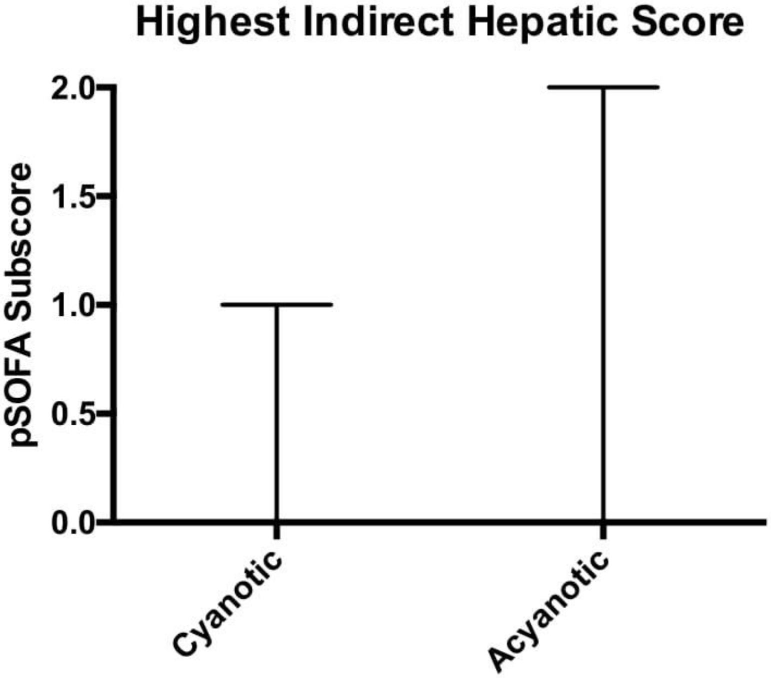

Figure 31. Median of the highest indirect hepatic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

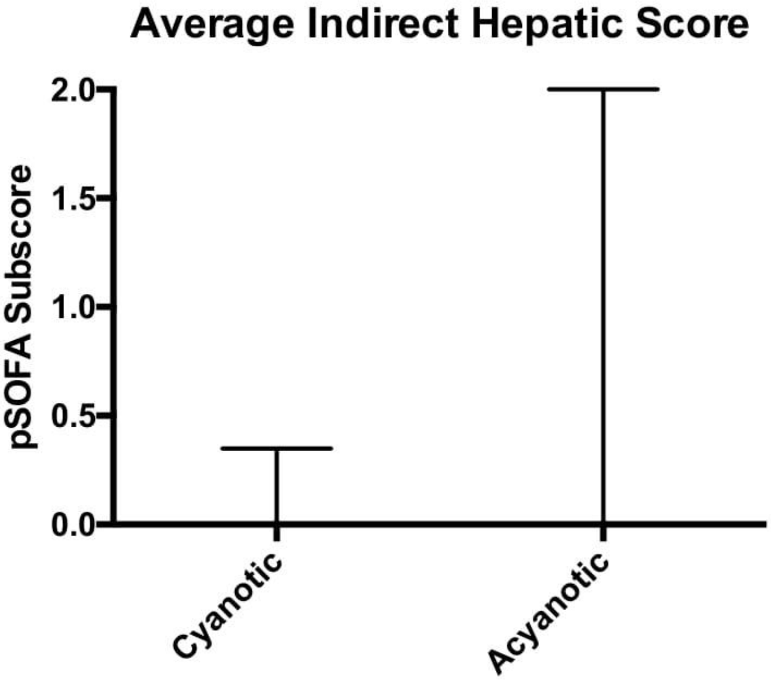

Figure 32. Median of the average indirect hepatic pSOFA sub score of the cyanotic and acyanotic CHD patients with IQR

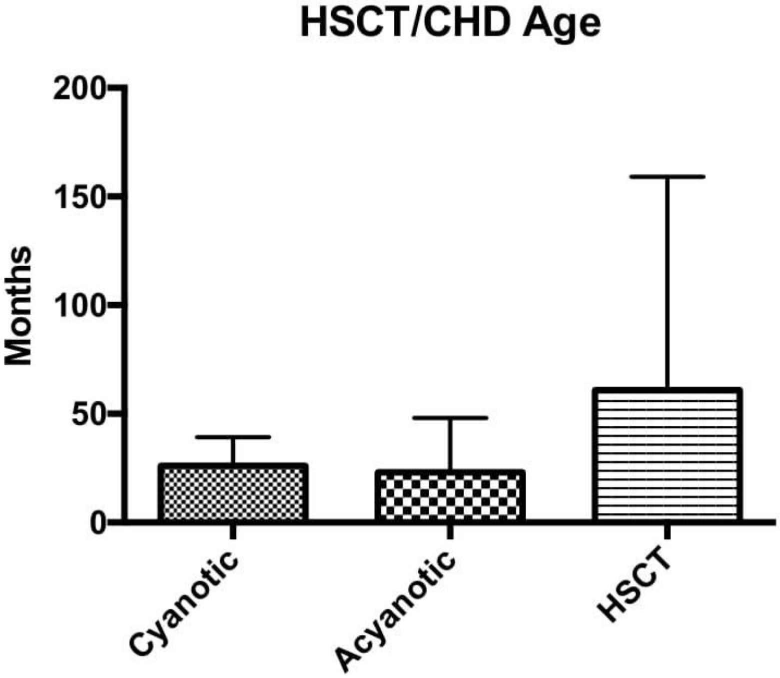

Figure 33. Mean age (months) of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR

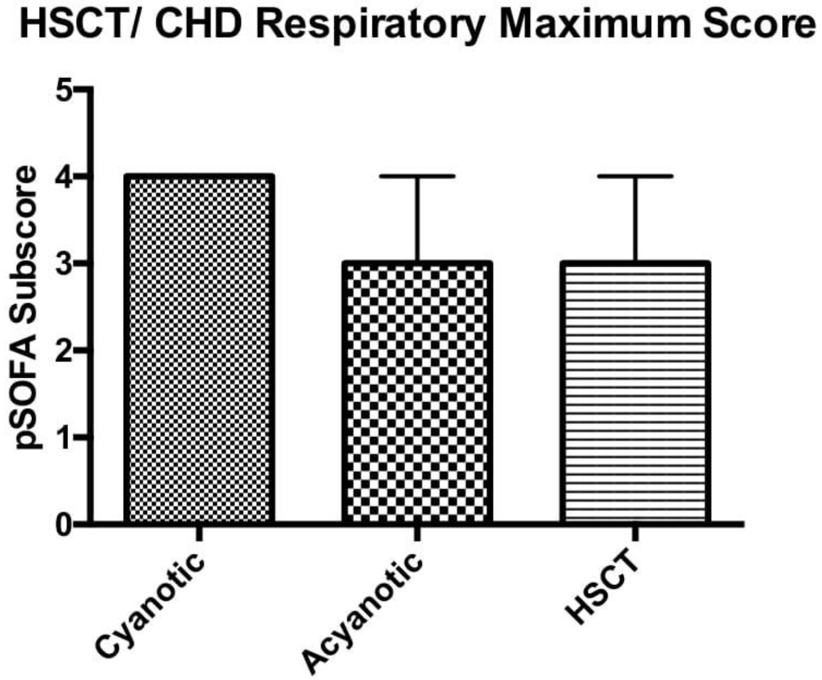

Figure 34. Mean of the maximum respiratory pSOFA sub score of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR

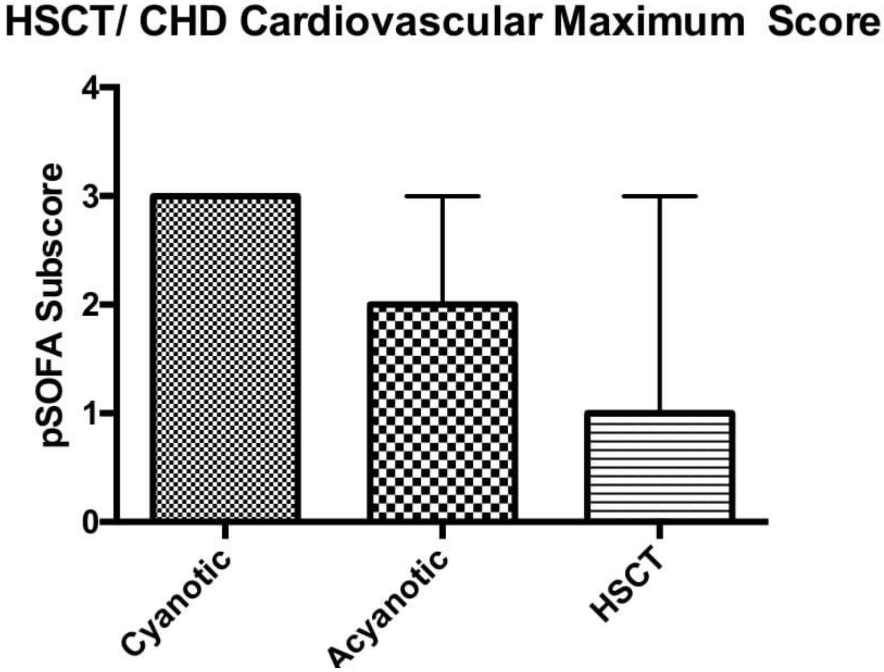

Figure 22. Mean of the maximum cardiovascular pSOFA sub score of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR

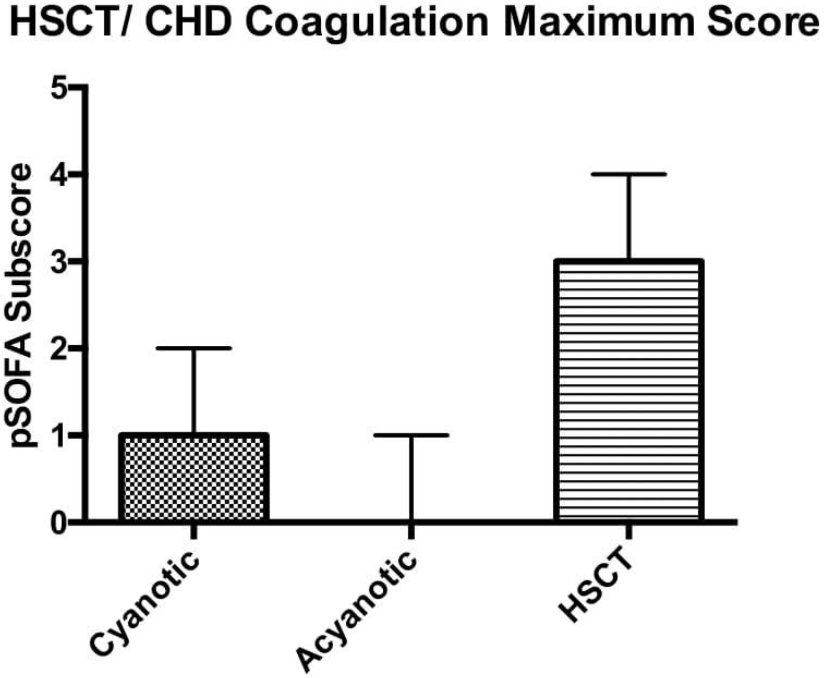

Figure 36. Mean of the maximum coagulation pSOFA sub score of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR

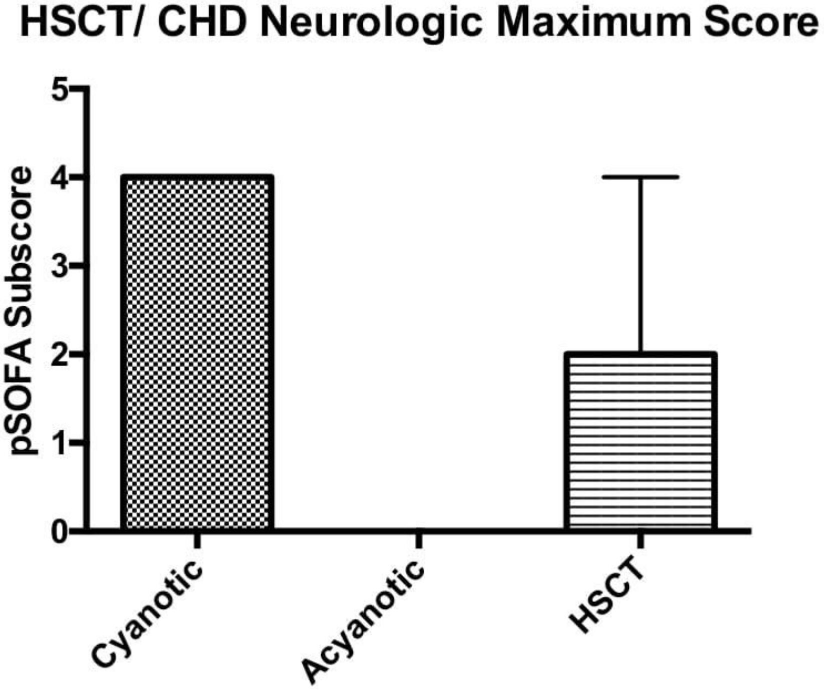

Figure 37. Mean of the maximum neurologic pSOFA sub score of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR

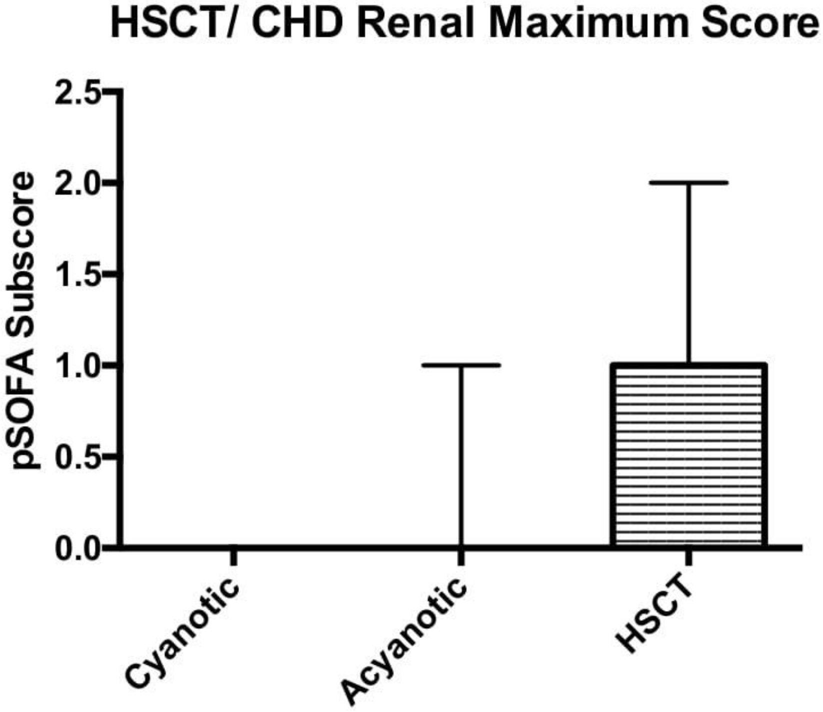

Figure 38. Mean of the maximum renal pSOFA sub score of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR

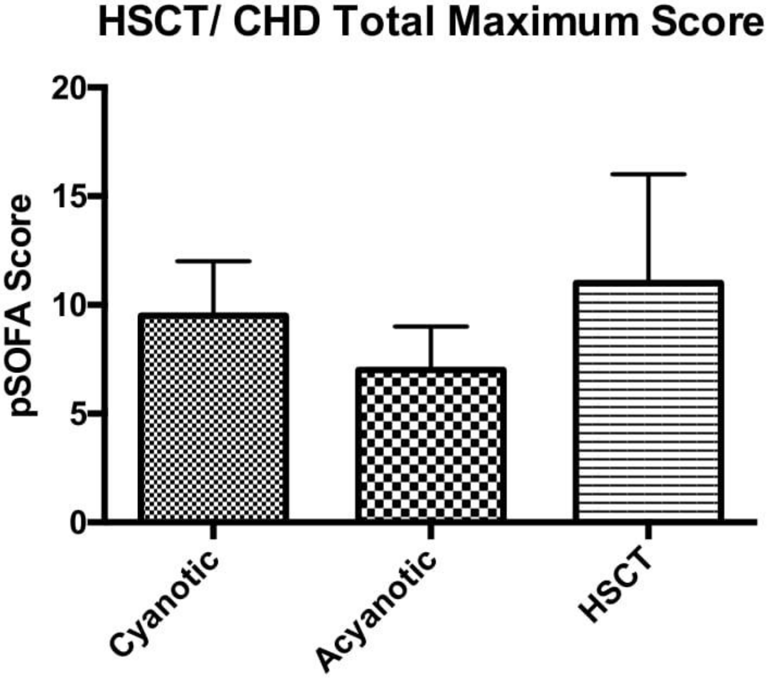

Figure 39. Mean of the maximum total pSOFA score of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR (note: CHD total values are using the indirect total pSOFA score)

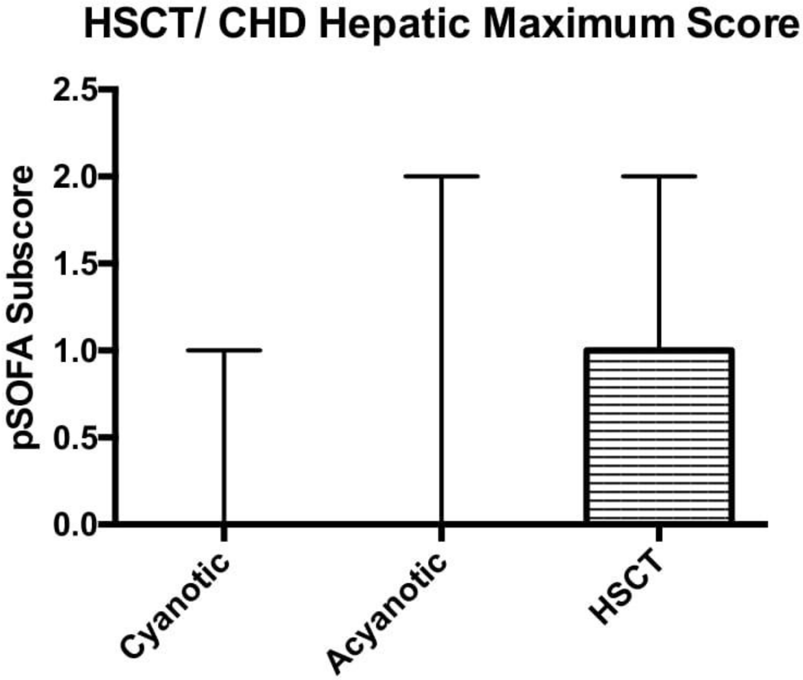

Figure 40. Mean of the maximum hepatic pSOFA sub score of the cyanotic and acyanotic CHD patients and the HSCT patients with IQR (note: CHD hepatic values are using the indirect hepatic sub score)

DISCUSSION

Analysis of total pSOFA scores, demonstrated that children with cyanotic CHD had higher maximum pSOFA scores, when using both direct and indirect bilirubin measurements, indicating more severe organ disfunction. On average, the Total Direct Score was significantly higher for cyanotic children than for acyanotic children (figure 10). However, acyanotic children had a higher minimum total pSOFA score using the indirect bilirubin measurement (figure 8). This could mean that perhaps it is more appropriate to use direct bilirubin measurements for cyanotic children and indirect bilirubin measurements for acyanotic children in terms of what measurement has the most meaning for that type of CHD.

Cyanotic patients scored higher and had more severe sub scores for neurologic issues compared with acyanotic patients (figures 22 and 23). This likely reflects a state of chronic hypoxia from right to left shunting in cyanotic CHD. Additionally, during periods of increased oxygen demand or stress, the additional oxygen requirement is not fulfilled resulting in further neurological oxygen deprivation which is reflected in a low Glasgow coma score. Low Glasgow coma scores will give a high neurologic pSOFA sub score. It is expected that children with cyanotic CHD would demonstrate the highest neurologic scores. The difference is quite remarkable though, with most acyanotic children rarely showing any neurologic symptoms. The acyanotic children on average had little to no neurologic issues with a median sub score of 0, while the cyanotic children on average during their stay in the CICU had a median sub score of 1.33. This should be further explored with future research on how physiologic stress for children with cyanotic CHD can be associated with neurologic problems and deadly consequences.

Cyanotic and acyanotic children had the same median of 0 for their highest renal scores as well as their average renal score during their stay in the CICU (figures 25 and 26); however, the acyanotic children did have a higher range with the average renal score and an even higher range scores when it came to the highest renal score. This caused their score differences to become significantly distinct from one another. Increased renal issues could be caused by a relative lack of systemic perfusion in acyanotic CHD children due to their left to right shunts. The shunting of blood from the systemic circulation back to the pulmonary system in a left to right shunt, decreases organ perfusion and possibly results in a lower glomerular filtration rate. This can result in then cause higher creatinine concentrations in these patients. Future research could delineate if acyanotic children are at a higher risk of renal issues compared with cyanotic children and the pathophysiology behind this kidney dysfunction.

For the lowest hepatic indirect sub score, both cyanotic and acyanotic children had median values of zero; however, acyanotic children had a significantly higher range of values for the lowest hepatic indirect sub score (figure 30).

The difference between the cyanotic and acyanotic CHD groups and the HSCT group in terms of pSOFA values is noteworthy. Some differences, such as in the coagulation and hepatic parameters, likely reflect differences between congenital heart disease and the complications associated with HSCT. Cyanotic and acyanotic patient pSOFA values were more like each other than when compared to HSCT patient pSOFA values. The significantly higher coagulation sub score seen in HSCT patients is not unexpected, considering that the procedure itself involves irradiating and then replacing the hematopoietic stem cells (figure 36). It is reasonable to assume that this procedure hinders the body’s ability to produce coagulation factors such as platelets, for which we measure the coagulation sub score.

The hepatic parameter was notable. The HSCT group having a significantly higher maximum score for this parameter compared to both the cyanotic and the acyanotic groups. Perhaps due to the processes that are involved in the HSCT procedure, there is higher metabolic stress on and injury to the liver. This higher score possibly indicates that patients undergoing HSCT may have to take extra precautions when it comes to protecting their liver from further harm. The cyanotic group, which tends to have lower systemic oxygen concentrations, did not experience similar liver dysfunction as the HSCT patients. Therefore, there must be a factor unique to the HSCT procedure itself or that patient physiology that predisposes them to a degree of liver dysfunction that is not seen to the same extent in cyanotic CHD patients despite lower oxygen organ delivery. These cyanotic CHD patients in the CICU had access to respiratory support if necessary, to support systemic oxygen delivery and scored significantly higher on the respiratory sub score than the HSCT patients.

There were some parameters such as neurologic, cardiovascular, and respiratory in which there was only one CHD group that was significantly different from the HSCT group. In review of neurologic function, acyanotic patients had a very low maximum neurologic score while HSCT had a higher maximum score. HSCT patient’st neurological status was more similar to cyanotic CHD children (figure 37). For cardiovascular, only the cyanotic CHD group's maximum was significantly higher than the HSCT group (figure 35).

The total score results were expected. The higher mortality 26.7 % (n=75) of HSCT patients compared to 4% of cyanotic (n=50) and 0% of acyanotic (n=51), it follows that HSCT patients would have a higher maximum total pSOFA score compared to CHD patients (figure 39). The similarities and differences between both cyanotic and acyanotic CHD, and patients who underwent HSCT, may provide clinicians clues on how to improve patient care and provide earlier interventions when calculating a high pSOFA score during an admission.

There are limitations to this research. There was a significant difference in the length of stay between the cyanotic CHD children and the acyanotic CHD children. Patients were chosen from a pool based on their age. Due to the large number of acyanotic patients on the list, many of those chosen happened to have very similar lengths of stay. There was a significant difference between the length of stays, and thus the patient selection could have been better controlled. Despite this limitation, because of the method of selection given the patient population available supports the findings of this paper. There was also a significant difference in the ages between the CHD patients (both cyanotic and acyanotic) and the HSCT patients. This could have played a role in the significant difference between some of the pSOFA scores and sub scores as children of different ages have varying organ development and physiology.

The occurrence and potential impact of a surgical intervention during a patient's admission was not evaluated. Common issues with CHD surgery such as blood loss, blood product transfusion, anti-coagulation drugs, cardiopulmonary bypass, length of surgery, cardiac ischemic times and postoperative sedation could have had an impact on organ function. Limited time did not allow for this large of a scope. There are also many limitations due to the pSOFA system itself. While it has been validated as a useful scoring system in ill children, it may not be the best possible assessment of the physiological status [6].

Overall, there are some distinct differences between children with cyanotic CHD and children with acyanotic CHD in terms of their pSOFA scores and sub scores. This study revealed some new research avenues that could be explored in the future. Understanding the pathophysiology behind these pSOFA score differences between cyanotic and acyanotic CHD pediatric patients and how these differences can guide treatment decisions for these patients would be beneficial. It is also possible that this information could be used to help refine the pSOFA (and SOFA) scoring system as it continues to evolve to meet pediatric patients' needs.

LIST OF JOURNAL ABBREVIATIONS

Arch Surg	Archives of Surgery
BJS	British Journal of Surgery
Crit Care Med	Critical Care Medicine
JACC	Journal of the American College of Cardiology
JAMA	The Journal of the American Medical Association
Radiol Clin North Am	Radiologic Clinics of North America
Transl Perioper Pain Med	Translational Perioperative and Pain Medicine

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