Cardiology in the Young

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Original Article

Cite this article: Loomba RS, Dyamenahalli U, Savorgnan F, Acosta S, Elhoff JJ, Farias JS, Villarreal E, and Flores S (2023) The effect of clinical and haemodynamic variables on post-operative length of stay immediately upon admission after biventricular repair with Yasui operation following an earlier Norwood operation. *Cardiology in the Young* **33**: 2066–2071. doi: 10.1017/S1047951122003948

Received: 13 July 2022
Revised: 19 November 2022
Accepted: 20 November 2022
First published online: 20 December 2022

Keywords:
CHD; Congenital heart surgery; Yasui operation; Post-operative care; Statistics; Bayesian; Statistics; regression analysis

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The effect of clinical and haemodynamic variables on post-operative length of stay immediately upon admission after biventricular repair with Yasui operation following an earlier Norwood operation

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Abstract

Background: There are a variety of approaches to biventricular repair in neonates and infants with adequately sized ventricles and left-sided obstruction in the presence of a ventricular septal defect. Those who undergo this in a staged manner initially undergo a Norwood procedure followed by a ventricular septal defect closure such that the neo-aorta is entirely committed to the left ventricle and placement of a right ventricular to pulmonary artery conduit (Yasui operation). This study aimed to determine clinical and haemodynamic factors upon paediatric cardiac ICU admission immediately after the two-stage Yasui operation that was associated with post-operative length of stay. *Methods:* This was a retrospective review of patients who underwent the Yasui procedure after the initial Norwood operation between 1 January 2011 and 31 December 2020. Patients with complete data on admission were identified and analysed using Bayesian regression analysis. *Results:* A total of 15 patients were included. The median age was 9.0 months and post-operative length of stay was 6days. Bayesian regression analysis demonstrated that age, weight, heart rate, mean arterial blood pressure, central venous pressure, pulse oximetry, cerebral near infrared spectroscopy, renal near infrared spectroscopy, pH, pCO2, ionised calcium, and serum lactate were all associated with post-operative length of stay. *Conclusion:* Discrete clinical and haemodynamic factors upon paediatric cardiac ICU admission after staged Yasui completion are associated with post-operative length of stay. Clinical target ranges can be developed and seem consistent with the notion that greater systemic oxygen delivery is associated with lower post-operative length of stay.

Yasui and colleagues reported two infants with interruption of the aortic arch and severe aortic stenosis in 1987 in whom they performed a surgical repair consisting of arch reconstruction, a Damus–Kaye–Stansel anastomosis, transection of the distal main pulmonary artery, and placement of a right ventricle to pulmonary artery conduit.[1] This kind of repair and similar repairs are now referred to as the Yasui operation. This operation can be done as a single-stage biventricular repair in the neonatal period or staged fashion after the initial repair of the aortic arch and later Damus–Kaye–Stansel anastomosis.[2] Several modifications to this primary Yasui operation have been adapted with variable outcomes.[3–5] The staged approach is often used when left-sided structures are smaller and facilitates the growth of these left-sided structures, allowing for eventual successful biventricular repair.[6,7]

When done in a staged fashion, there is a transition from parallel circulation, wherein the saturation of the pulmonary blood flow and systemic blood flow is equal, to biventricular circulation. Such a transition could lead to post-operative morbidity either because of anatomic or physiologic reasons, therefore resulting in a relatively longer post-operative length of stay compared to other operations for congenital malformations of the heart.

The primary objective of this study was to determine clinical and haemodynamic factors upon admission immediately after the Yasui operation that was associated with post-operative length of stay in patients who had undergone a Norwood operation earlier in life.

Materials and methods

Study design

This was a single-centre retrospective study. Data were collected from the institution's electronic medical record. The study received approval from the institutional review board and is in concordance with the Helsinki declaration.

Patient identification

Patients who underwent a Norwood operation initially and then ultimately had a biventricular repair consisting of closure of an interventricular communication and placement of a right ventricle to pulmonary artery conduit at Advocate Children's Hospital between 1 January 2011 and 31 December 2020 were identified. Those who had a primary Yasui operation were not included.

Variables of interest

Data were collected for the following variables of interest: age at the time of operation (months), weight at the time of operation (kg), heart rate (beats per minute), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), mean arterial blood pressure (mmHg), central venous pressure (mmHg), pulse oximetry (%), cerebral near-infrared spectroscopy (%), renal near-infrared spectroscopy (%), pH (units), partial pressure of carbon dioxide (mmHg), serum lactate (mmol/L), ionised calcium (mmol/L), and haemoglobin (g/dL). The following parameters were calculated: shock index and rate pressure product. Shock index was calculated as heart rate divided by systolic blood pressure. Rate pressure product was calculated as the product of heart rate and systolic blood pressure.

Data were collected as recorded in the electronic medical record. Data must have been recorded within the first 20 minutes of admission to the cardiac ICU. Data were captured using the Phillips monitoring system (Koninklijke Philips N.V., Best, The Netherlands). All blood pressure values were collected from an arterial line. At our institution, it is a routine practice to place such arterial lines in the femoral artery. Data regarding renal and cerebral near-infrared spectroscopy were collected using the Medtronic Somanetics system (Medtronic, Minneapolis, MN, United States of America). Patients without data for both cerebral and renal near-infrared spectroscopy were not included in this study. As the physiology after the Yasui operation consists of fully septated, biventricular circulation with arterial saturation that should be close to 100%, we elected to use the raw cerebral and renal near-infrared spectroscopy values for statistical analysis versus using the arterial-venous oxygen difference or the oxygen extraction ratio. No correction to cerebral and renal near-infrared spectroscopy values was made to account for arterial or capillary contamination as it was this study's intention to present data as would be visualised by providers in real-time.

Post-operative length of stay was recorded in days.

Statistical Analyses

Bayesian analysis rather than frequentist analysis was primarily used. The specifics of the Bayesian versus frequentist framework is beyond the scope of this paper and can be found elsewhere. In brief, the Bayesian framework treats all variables as being random including the dependent variable while the frequentist framework does not. The Bayesian framework tries to estimate the probability of a variety of outcomes rather than trying to identify a "finite" outcome. Unlike the frequentist framework, the Bayesian framework does not utilise p-values and arbitrary p-value cut-offs to define "significance". The American College of Cardiology and the American Heart Association have both proposed that the Bayesian framework should be used to create clinical practice guidelines.[8]

Initially, univariable analyses were conducted. Bayesian correlation analyses were done to assess the correlation between post-operative length of stay and the other collected variables of interest. Correlation coefficients and Bayes factors were calculated. To summarise how to clinically interpret Bayes factors, a Bayes factor of 1–3 demonstrates weak evidence to reject the null hypothesis and accept there is a significant correlation, 3–10 moderate evidence, and greater than 10 strong evidence.

Next, a Bayesian linear regression was conducted with the post-operative length of stay as the dependent variable. The following variables were entered as independent variables: age, weight, heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, central venous pressure, pulse oximetry, cerebral near-infrared spectroscopy, renal near-infrared spectroscopy, pH, partial pressure of carbon dioxide, lactate, ionised calcium, and haemoglobin. The Jeffreys–Zellner–Siow prior was utilised for this regression as there were no available data for use as a prior. For those less familiary with Bayesian regression, the posterior probability of inclusion of variables in any model presents the probability of the specific variable being included in the top 20 most probable models. The posterior mean is synonymous to the beta-coefficient and represents the change in post-operative length of stay with every 1-unit increase in the variable of interest.

Next, graphs were constructed for each variable that was retained in the most probable model. The variable of interest (i.e. heart rate or mean arterial pressure) was graphed on the x-axis while the post-operative length of stay was plotted on the y-axis. The aim of these graphs was to help determine values that may be clinically relevant with respect to minimising the post-operative length of stay.

In addition to the graphs above to help determine clinically relevant values for each variable of interest, receiver operator curve analyses were conducted as well. As the post-operative length of stay was collected as a continuous variable, this was converted into a dichotomous variable by using the median post-operative length of stay such that patients were divided into two groups: those with a length of stay less than or equal to the median post-operative length of stay and those with a post-operative length of stay greater than the median post-operative length of stay. The outcome of interest entered into the receiver operator curve analyses was then post-operative length of stay greater than the median. The utility of the variables of interest to predict the post-operative length of stay greater than the median was assessed using the area under the curve. Optimal cut-offs for each value were determined by identifying the point furthest from the diagonal line with a slope of 1 originating from the intersection of the x and y axes.

These data along with the aforementioned graphs were then utilised to determine clinically relevant values for the variables of interest found to be significantly associated with post-operative length of stay from the regression analysis.

Continuous variables were described as median and range while dichotomous variables were described as absolute count and relative frequency. The Bayesian correlations and regression were performed using JASP Version 0.16 (Amsterdam, The Netherlands). p-Values are not part of the Bayesian framework and thus do not

https://doi.org/10.1017/S1047951122003948 Published online by Cambridge University Press

Table 1. Patient values at admission

Variable	Median (minimum to maximum)
Age (months)	9.0 (5.0 to 55.2)
Weight (kg)	8.5 (6.1 to 10.5)
Heart rate (bpm)	164 (119 to 180)
Systolic blood pressure (mmHg)	96 (76 to 133)
Diastolic blood pressure (mmHg)	50 (40 to 60)
Mean Arterial blood pressure (mmHg)	65 (52 to 77)
Central venous pressure (mmHg)	10 (3 to 22)
Pulse oximetry (%)	99 (90 to 100)
Cerebral near infrared spectroscopy (%)	63 (24 to 93)
Renal near infrared spectroscopy (%)	68 (30 to 83)
pH	7.38 (7.28 to 7.45)
Partial pressure of carbon dioxide (mmHg)	42 (38 to 56)
Ionised calcium (mmol/L)	1.4 (1.1 to 1.7)
Serum lactate (mmol/L)	2.5 (1.6 to 3.9)
Post-operative length of stay (days)	6 (3 to 39)

Data are presented as median (range).

Table 2. Univariate correlation analyses between admission values and post-operative length of stay

	Correlation coefficient with post-operative length of stay	Bayes factors (BF10)
Age at operation (months)	−0.17	0.37
Weight at operation (kg)	−0.37	0.76
Heart rate (bpm)	0.08	0.33
Systolic blood pressure (mmHg)	−0.27	0.49
Diastolic blood pressure (mmHg)	0.14	0.35
Mean arterial blood pressure (mmHg)	−0.11	0.34
Central venous pressure	0.01	0.31
Pulse oximetry	−0.60	4.37
Cerebral near infrared spectroscopy	−0.23	0.44
Renal near infrared spectroscopy	−0.59	2.68
pH	−0.45	1.24
Partial pressure of carbon dioxide	0.39	0.84
Ionised calcium	0.23	0.44
Haemoglobin	−0.07	0.32
Serum lactate	−0.04	0.32

Bayes factor clinical interpretation: 1–3 (weak evidence for correlation), 3–10 (moderate evidence for correlation), and >10 (strong evidence for correlation).

appear except for in the frequentist regression results. Bayes factors are reported with results for Bayesian analyses. The receiver operator curves were done using SPSS version 23.0.

Results

Cohort characteristics

A total of 15 patients were included in the final analyses. The median post-operative length of stay was 6 days. A 12 mm aortic homograft was used for the RV-PA conduit. One patient required extracorporeal membrane oxygenation post-operatively. No patient experienced a cardiac arrest or inpatient mortality.

Median values

The median values of all admission values are listed in Table 1.

Univariable correlation analyses

Only three of the variables had a correlation to the post-operative length of stay with a Bayes factor of over one: pulse oximetry (correlation coefficient −0.60, Bayes factor 10 4.37), renal near-infrared spectroscopy (correlation coefficient −0.59, Bayes factor 10 2.68), and pH (correlation coefficient, Bayes factor 10 1.24) (Table 2).

Bayesian regression analysis

The three most probable models for the post-operative length of stay are outlined in Table 3. The most likely model had a posterior probability of 0.142, meaning that this model had a probability of 14.2% to represent to be the model that fits these data. This model included the following independent variables: age, weight, heart rate, mean arterial blood pressure, central venous pressure, pulse oximetry, renal near-infrared spectroscopy, pH, pCO2, ionised calcium, and lactate. The Bayes factor model for this model was 1.99 meaning that the odds of this model increased 1.99 times after the data were considered. The Bayes factor 10 for this model was 1.00. The R-squared value for this model was 0.721, indicating that the next most probable model was the null model which had a posterior probability of 0.140 and a Bayes factor 10 of 0.99. The third most likely model had a probability of 0.03 and included only pulse oximetry.

With respect to the independent variables entered the regression, the probability of each independent variable of being included in one of the resulting models is outlined in Table 4. The independent variables with the highest posterior probability of being included in a model were: pulse oximetry (0.51), renal near-infrared spectroscopy (0.50), and pH (0.46). The remaining independent variables had probabilities that ranged from 0.41 to 0.43.

Using the most likely model, the following independent variables were associated with an increase in post-operative length of stay: greater age at operation, greater weight at operation, higher mean arterial blood pressure, higher central venous pressure, higher cerebral near-infrared spectroscopy, higher partial pressure of carbon dioxide, higher ionised calcium, and higher serum lactate. The following independent variables were associated with a decrease in post-operative length of stay: higher heart rate, higher pulse oximetry, higher renal near-infrared spectroscopy, and higher pH.

Proposed clinical cut-offs

The regression analysis demonstrates general trends of independent variables with a post-operative length of stay that does not necessarily mean that these are definitive. Some of these relationships were not necessarily linear but were in fact U-shaped or inverted U-shaped. To better identify more precise clinical ranges,

Table 3. Three models with the highest posterior probability for the post-operative length of stay

Posterior probability	Variables in model	Bayes factor for model (BF_M)	Bayes factor (BF_{10})
0.142	Age, weight, heart rate, mean arterial blood pressure, central venous pressure, pulse oximetry, renal near infrared spectroscopy, cerebral near infrared spectroscopy, pH, pCO2, ionised calcium, lactate	1.99	1.00
0.140	Null model	1.98	0.99
0.03	Pulse oximetry		0.39

pCO2, partial pressure of carbon dioxide.

Table 4. Probability of inclusion and posterior mean (coefficient) for the variables included in the best-fitting model.

Variable	Posterior probability of inclusion in any model	Posterior mean (coefficient)
Age at operation	0.41	0.02
Weight at operation	0.43	1.21
Heart rate	0.42	−0.08
Mean arterial blood pressure	0.43	0.36
Central venous pressure	0.42	0.31
Pulse oximetry	0.51	−0.64
Cerebral near infrared spectroscopy	0.44	0.12
Renal near infrared spectroscopy	0.50	−0.21
pH	0.46	−15.49
Partial pressure of carbon dioxide	0.43	0.18
Ionised calcium	0.42	3.33
Serum lactate	0.43	4.71

area under the curve analyses were done to help define optimal cut-off points. The area under the curve for each independent variable included in the most probable model is outlined in Table 5. The independent variables with the highest area under the curve were: pH (0.63), renal near-infrared spectroscopy (0.63), and serum lactate (0.59).

Combining the optimal cut-off points from the receiver operator curve analyses and the graphs of the independent variables plotted against the post-operative length of stay, clinical "target" ranges were developed. These are outlined in Table 5.

Discussion

This study demonstrates that post-operative length of stay can be predicted by clinical and haemodynamic variables at the time of ICU admission immediately after a staged Yasui procedure.

The results of this study demonstrate that age and weight at the time of the operation are associated with post-operative length of stay. Older and heavier are not necessarily better. An age of 8–12months and a corresponding weight of 8–9 kg seem to be associated with a lower post-operative length of stay.

Table 5. Area under the curve and clinical targets for variables included in the regression

Variable	Area under the curve	Target from receiver operator curve analysis and graphical analysis
Age	0.44	8 to 12 months
Weight	0.57	8 to 9 kg
Heart rate	0.58	150 to 160 bpm
Mean arterial blood pressure	0.38	55 to 65 mmHg
Central venous pressure	0.44	Less than 9 mmHg
Pulse oximetry	0.44	Greater than 95%
Cerebral near infrared spectroscopy	0.55	60 to 85%
Renal near infrared spectroscopy	0.63	Greater than 65
pH	0.63	7.32 to 7.43
Partial pressure of carbon dioxide	0.37	42 to 50
Serum lactate	0.59	Less than 3.2
Ionised calcium	0.34	1.3 to 1.5

Clinical targets were developed from receiver operator curve analyses and from qualitative analysis of graphs plotting the various endpoints of interest against post-operative length of stay.

There are several changes in cardiovascular and respiratory physiology that occur from the neonatal period. In regard to respiratory physiology, younger infants often have less control over their respiration and may have periodic breathing. Younger infants also have smaller more compliant airways, higher metabolic oxygen demand, smaller functional residual capacity, lesser chest wall compliance, and less efficient respiratory muscles. This makes younger infants more likely to develop post-operative apnoea, ventilatory impairment, increased airway resistance and subsequent increased work of breathing, rapid desaturation, and airway obstruction.[9] With respect to cardiovascular physiology, younger infants are more vulnerable to transitional circulation, have decreased myocardial compliance, have decreased function cardiac reserve, and have high endogenous circulating catecholamine. This makes younger infants more likely to develop decreased peripheral tissue oxygen delivery, cardiac dysfunction, and unresponsiveness to exogenous catecholamines.[9] These respiratory and cardiovascular physiologic considerations may translate into benefit of waiting into later infancy for more technically involved cardiac operations such as the Yasui repair. Longer cardiopulmonary bypass times are tolerated better at greater age and weight for these reasons as well as changes in the infant immunologic and inflammatory system.[10]

With respect to the haemodynamic parameters upon admission, the most ideal haemodynamic profile seems to be consistent with greater systemic oxygen delivery. Systemic oxygen delivery is the product of oxygen content and cardiac output. With respect to oxygen content, while haemoglobin did not seem to be associated with post-operative length of stay in this study, saturation was. With respect to cardiac output, higher renal near-infrared

https://doi.org/10.1017/S1047951122003948 Published online by Cambridge University Press

spectroscopy was found to be associated with a lower post-operative length of stay. Using the Fick equation in which cardiac output is equal to the quotient of oxygen consumption and the arteriovenous oxygen content difference, the higher the systemic venous saturation (renal near-infrared spectroscopy being utilised as a surrogate here) the greater the cardiac output.[11] Other findings in other physiologies have demonstrated higher near-infrared spectroscopy values and mixed venous saturations being associated with decreased morbidity and mortality.[12–14] While the overall regression demonstrated higher cerebral near-infrared spectroscopy was associated with longer post-operative length of stay, this was only at values greater than 85%. This likely is a result of the relationship between partial pressure of carbon dioxide and cerebral near-infrared spectroscopy. As carbon dioxide causes cerebral vasodilation and increases cerebral blood flow, there is a subsequent increase in the cerebral near-infrared spectroscopy.[15,16] Similar directionality of the association between partial pressure of carbon dioxide and cerebral near-infrared spectroscopy with a post-operative length of stay supports this. Similar posterior means in the regression supports this notion as well. Serum lactate, although it can be modulated by several factors other than cardiac output and systemic oxygen delivery, did tend to be lower in those with a lower post-operative length of stay. All these findings seem to be consistent with greater systemic oxygen delivery being the underlying mediator of the post-operative length of stay. Other studies have demonstrated association of higher serum lactate with adverse events after paediatric cardiac surgery.[17–24]

Greater heart rate was also found to be associated with decreased post-operative length of stay. Higher heart rates with atrioventricular synchrony do increase stroke volume and subsequently cardiac output and systemic oxygen delivery. With respect to mean arterial blood pressure, there was a U-shaped curve with a post-operative length of stay being lowest in the middle. Mean arterial blood pressure is related to cardiac output in that mean arterial blood pressure is the product of cardiac output and systemic vascular resistance. Augmentation of mean arterial blood pressure can be accomplished by simply increasing systemic vascular resistance. This does not help with systemic oxygen delivery and may actually decrease it by increasing myocardial work and myocardial oxygen consumption.[25] The higher mean arterial blood pressures associated with greater post-operative length of stay may represent a point at which resulting systemic vascular resistance was high. This is not to equate systemic vascular resistance and mean arterial blood pressure but to highlight that there is a correlation.

This study focused on characteristics at the time of initial cardiac ICU admission by design. This was to see if this was a useful metric. Certainly, that clinical state may be different shortly after. The study elected to use only data from this time point to quantify the associations at this time. The resulting model was robust and had a high R- squared value even despite the fact that only a single time point was used. Thus, demonstrating that the immediate admission time point is still a valuable set of data with respect to admission outcomes. This seems to be telling in and of itself. The design of this study and the use of this specific time point are not to dismiss the utility of the data at other time points or the value of longitudinal data but rather to truly investigate the associations at this specific time point.

This study is additive to the literature but is not without its limitations. First, this is a single-centre study and underlying practice patterns may limit the generalisability of results. As this study looks at haemodynamic and clinical variables that are a result of interventions and not the interventions themselves this may be less of an issue. Maintaining the resulting target clinical values by use of various vasoactive or fluids may result in the same findings. Additionally, the aim of this study is to primarily highlight the directionality of change and not necessarily identify the precise magnitude of change. The study does have a low number of patients. This is unfortunately a limitation of all single-centre studies regarding the Yasui, as it is a relatively less frequently employed operation as the anatomic substrate requiring its use is seen relatively less frequently. Additionally, the use of Bayesian versus frequentist statistical tools helps overcome this. While a greater sample size does decrease the variability in the posterior distribution in the Bayesian framework and improves the probability estimates, the overall probability estimates are unlikely to change significantly for the most probable models and the most probably independent variables. This is one of the many strengths and benefits of the Bayesian framework.

Conclusion

A number of clinical and haemodynamic factors upon ICU admission immediately after staged Yasui completion are associated with post-operative length of stay. Clinical target ranges can be developed and seem to be consistent with the notion that greater systemic oxygen delivery is associated with lower post-operative length of stay.

Financial support. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest. None.

Ethical standards. The study received approval from the institutional review board and is in compliance with the Helsinki declaration of 1975 and its subsequent revisions.

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