The Inadequate Oxygen Delivery Index and Low Cardiac Output Syndrome Score as predictors of adverse events associated with Low Cardiac Output Syndrome early after cardiac bypass

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Abstract

Objective

To evaluate the effectiveness of two scoring systems, the Inadequate Oxygen Delivery (IDO2) Index, a risk analytics algorithm (Etiometry Inc. MA USA) and the Low Cardiac Output Syndrome Score (LCOSS), in predicting adverse events recognised as indicative of Low Cardiac Output Syndrome (LCOS) within 72 hours of surgery.

Design

A retrospective observational pair-matched study.

Setting

Tertiary pediatric cardiac intensive care unit.

Patients

Children undergoing cardiac bypass for congenital heart defects. Cases experienced an adverse event linked to LCOS in the 72 hours following surgery (extracorporeal membrane oxygenation, renal replacement therapy, cardiopulmonary resuscitation and necrotising enterocolitis), and were matched with a control patient on criteria of procedure, diagnosis and age who experienced no such event.

Interventions

None.

Measurements and Main Results

Of a total 536 bypass operations in the study period, 38 patients experienced one of the defined events. Twenty-eight cases were included in the study after removing patients who suffered an event after 72 hours or who had insufficient data. Clinical and laboratory data were collected to
derive scores for the first 12 hours after surgery. The IDO2 Index was calculated by Etiometry using 
vital signs and laboratory data. A modified LCOSS (mLCOSS) was calculated from clinical and 
therapeutic markers. The mean IDO2 and mLCOSS were compared within each matched pair using 
the Wilcoxon signed-rank test. IDO2 correctly differentiated adverse events in 13/28 matched pairs, 
with no evidence of IDO2 being higher in cases (p=0.71). mLCOSS correctly differentiated adverse 
events in 23/28 matched pairs, with strong evidence of a raised score in LCOS cases (p<0.01).

Conclusions

Although IDO2 is an FDA approved indicator of risk for low mixed venous oxygen saturation, early 
post-operative average values were not linked with medium term adverse events. The indicators 
included in the mLCOSS had a much stronger association with the specified adverse events.
Introduction

LCOS remains a significant post-operative problem and is characterised by poor oxygen delivery to tissues due to myocardial dysfunction (1). Direct measurements of cardiac output following open heart surgery in neonates have previously identified low cardiac output syndrome (LCOS) in 25% of patients (2). LCOS is important since it is associated with complications including organ failure, longer length of stay, increased healthcare resource utilisation and death (3–5). Early identification and treatment of LCOS has great potential to improve outcomes for patients. However, there are no clear established criteria for the clinical definition of LCOS, with recent clinical trials utilising a range of thresholds for its definition (5, 6). Furthermore it has been noted that the diagnosis of LCOS can be subjective and vary between clinicians (7). There has been recent interest in the development of objective methods to identify patients with LCOS for use in cardiac intensive care unit (CICU) settings.

A risk analytics algorithm has been developed by Etiometry (Etiometry Inc., MA, USA) to assess patient specific risk of inadequate oxygen delivery (IDO2) (8). The IDO2 index aims to reflect the likelihood that a patient is experiencing inadequate oxygen delivery, with an increasing value indicating an increasing risk of inadequate oxygen delivery. The continuous IDO2 Index is calculated using multiple physiologic measures and laboratory results collected by Etiometry’s T3 Data Aggregation & Visualization platform. The IDO2 Index has been validated to show an association between a raised IDO2 Index and a mixed venous oxygen saturation (SvO₂) measurement below 40%. In a study of 312 post-cardiopulmonary bypass neonates, IDO2 had an area under the curve of 0.79 (0.76-0.82), showing good prediction of low SvO₂ (8). Further studies have shown an association between a raised IDO2 Index on days 2-4 post surgery and increased length of stay in post-cardiopulmonary bypass neonates (9).

The IDO2 Index has received approval from the US Food and Drug Administration (FDA) for use in pediatric patients aged 12-and-under in intensive care with weight above 2kg (10), and is in
use in several pediatric intensive care units in North America in conjunction with the T3 Data Aggregation & Visualization platform.

The Low Cardiac Output Syndrome Score (LCOSS) (11) uses raised heart rate (HR) (>20% above post-induction HR in the operating room), low urine output (<1mL/kg/hr), low temperature (<30°C), raised inotropic requirement (in excess of milrinone 0.5µg/kg/min), increased volume administration (>30mL/kg/d), decreased near infra-red spectroscopy (NIRS) measurement (Cerebral and renal NIRS<50% and 75% of arterial saturations respectively) and high arterial lactate (>2mmol/L) as markers of deterioration. A point is given for each indicator that is present. In the prospective evaluation of LCOSS carried out by Ulate et al (11), measurements of LCOSS were recorded at arrival on CICU, and at 8,12, and 24 hours postoperatively and used to calculate a peak and cumulative LCOSS, and in a single centre study this was found to be strongly linked to a composite measure of post-operative morbidity.

In this study, our central hypothesis was:

‘A higher mean IDO2 index early post operation will be linked to LCOS related post-operative adverse events whereas a lower mean IDO2 index in the same period will be linked to non-occurrence of such post-operative events.’

A secondary hypothesis was:

‘Conventional clinical measures of LCOS that make up the LCOSS early post operation are linked to subsequent post-operative adverse events.’

To test these hypotheses we evaluated the performance of IDO2 and LCOSS in predicting which patients would go on to suffer defined and prospectively detected post-operative adverse events that are recognised to be related to LCOS in post-operative cardiac patients.
Materials and Methods

The study population included patients undergoing cardiac bypass procedures and cared for in CICU at Great Ormond Street Hospital, London, UK (GOSH). The CICU at GOSH has approximately 800 admissions every year, with postoperative cardiac patients generally representing 66% of this total (12) and has been using the T3 monitoring system since June 2015. The IDO2 Index has not been added to the monitors, so the clinical care of patients has been carried out without any reference to the IDO2 index.

Adverse events were defined as initialisation of Extracorporeal Membrane Oxygenation (ECMO), Renal Replacement Therapy (RRT), Cardio-Pulmonary Resuscitation (CPR) or the diagnosis of Necrotising Enterocolitis (NEC). These events were considered as they commonly occur in the context of LCOS (13–15), and were defined based on consistent criteria from a subset of known complications following congenital heart surgery (16, 17). In our centre we prospectively document the occurrence of all of these events as part of the local quality assurance process and we review all such events on a weekly basis at a multi-disciplinary conference. Our local protocol for initiation of RRT in post-operative patients is to do so if there is oligo-anuria for 4-6 hours despite optimisation of pre load, inotropic support and administration of diuretics. Patients, who had returned to the CICU already receiving ECMO were excluded since in these patients there was no 12 hour period in the unit during which scores could be derived (the adverse event had already happened).

We conducted a retrospective observational matched study of children who underwent surgical repair or palliation of CHDs under bypass at GOSH from 1 June 2015 – 31 May 2016. All patients that experienced one of the specified events in the 72 hours following surgery were considered as cases and included in the study if T3 data were available. A patient was considered as a possible control patient if they did not experience one of the specified events while in the CICU following a cardiac procedure. For each case, the next patient without any of the specified events, matching based on the following variables, was included as a control.
• Risk Adjustment for Congenital Heart Surgery (RACHS) 1 Category (18)
• Ventricular status (Univentricular or Biventricular)
• Age band: less than 1 year, 1 to 5 years, and above 5 years. Matching patients had to be in the same age band and:
  o If age<1 match must be within 3 months in age
  o If 1<age<5 match must be within a year of age
  o If age>5 match must be within 2 years of age

Patient information including age, weight at the time of surgery, diagnosis, and surgical procedure and pre-operative serum creatinine was obtained from the medical record. The RACHS risk category was determined based on the surgical procedure and the ventricular status from the diagnostic information.

Studies have shown that the period immediately following cardiac surgery is a period of reduced cardiac output (2). Therefore, to provide a consistent analysis period over which the predictive scoring approaches would be assessed, we focussed on the immediate 12 hours following surgery. Further, we considered that the utility of these scores comes from their potential ability to differentiate patients who go on to recover well following surgery compared to those who develop adverse events in the hours immediately following surgery, since this enables their care to be adjusted appropriately. Recognising that the time course over which an adverse event may be triggered can vary and entail a range of precursors, we considered a full 12 hour period.

On return to CICU following surgery the patient’s physiological variables at 5 second intervals were stored on a secure server by the T3 Data Aggregation platform. The calculation of the IDO2 index, based on these physiological variables and blood gas measurements, was carried out by Etiometry for the period of interest for the matched group of patients. The case/control label was not provided to Etiometry. The mean IDO2 score over the 12 hours following surgery was calculated.

Patients that did not have T3 data in the time window of interest were excluded.
The LCOSS score for the equivalent 12 hour period was calculated for each of the study patients based on the clinical and laboratory criteria set out by Ulate et al (11). One difference in the application of the LCOSS score in our study was that data were retrospective, hence the timing of measurements could not be controlled, hence we refer to this as a modified LCOSS (mLCOSS). To allow for data becoming available at different times following surgery, and to ease comparison with IDO2, the mLCOSS was adjusted to a value between 0 and 100 using the variables available at that time, and was updated as new data became available. For example, if only data on heart rate, volume administration and inotropic requirement had become available at a particular time, the score would be calculated using only those 3 variables, and rescaled between 0 and 100. NIRS measurements were excluded as these are not currently available for patients treated in the CICU at GOSH. Similarly to the IDO2 measurements, the mean of mLCOSS over the first 12 hours following surgery for each patient was taken.

Post-induction HR was taken from anaesthetic charts, heart rate while on CICU was taken from the T3 monitoring system and urine output, peripheral temperature, inotropic treatment, volume administration and arterial lactate were taken from the electronic patient records. As low urine output is an indicator for starting RRT, which was one of the adverse events, the analysis of mLCOSS was repeated excluding low urine output as an indicator to ensure that the difference in the score between cases and controls was not just indicating the presence of renal dysfunction.

Data on adverse events, RACHS 1 category and ventricular status are presented as frequencies and proportions. Data on age, weight and event timing are presented as medians and interquartile ranges, pre-operative creatinine as mean and standard deviation. Baseline characteristics are compared using the Student’s t-test (pre-operative creatinine) and the Man-Whitney rank sum test (age, weight). The association between emergency surgery and the presence of an adverse event was tested using odds ratios.
The mean of the IDO2 score and the mean of mLCOSS between return to the CICU following surgery and 12 hours after surgery (or onset of the adverse event, or the equal time after surgery for control cases, if earlier) were compared for cases and controls using the Wilcoxon signed-rank test for matched samples.

Data were analyzed using Stata software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The study was approved by Great Ormond Street Hospital for Children NHS Foundation Trust as a clinical audit project.

Results

Of a total 536 cardiac operations with bypass carried out at GOSH in the study period, 38 patients experienced a subsequent adverse event while in the CICU following surgery. Of these, 1 had an adverse event after 72 hours post-admission to CICU, 3 returned from theatre on ECMO and 6 children had insufficient T3 data – these cases were all excluded from further analysis. This resulted in 28 cases for analysis, which were matched to 28 control patients. The demographic and clinical data of the 28 pairs of cases and controls are shown in Table 1. There were no significant differences between the two groups, including the number of children having emergency surgery and pre-operative serum creatinine.

The percentage of high resolution T3 data available for each record is shown in Table 2, broken down according to each variable.

Twenty-four of the 28 cases included in the study had RRT as their primary adverse event, 2 of which went on to also have ECMO initiated shortly afterwards. Three patients underwent CPR, after which 2 were transferred on to ECMO. One patient was diagnosed with NEC. As all the cases of ECMO following cardiac surgery were either initialised in the operating theatre, or occurred
following another adverse event, no patients had ECMO as their primary adverse event. For the majority of patients, their primary adverse event occurred within 24 hours of surgery.

Two examples of the IDO2 score over the 12 hours post-surgery for a matched pair are shown in Figure 1.

Of the 28 pairs of matched patients, the 12-hour mean IDO2 score was higher for cases in 13 pairs out of 28 (46.4%). This showed no evidence that cases had higher IDO2 scores (p=0.71). The median difference (case less control) between IDO2 in each pair was -0.1 (IQR -7.4 – 11.8)

The IDO2 values for each matched pair are shown in Figure 2.

Two examples of the mLCOSS score over the 12 hours post-surgery for a matched pair are shown in Figure 3.

Of the 28 pairs of matched patients, the 12-hour mean mLCOSS was higher for 23 pairs out of 28 (82.1%). This showed strong evidence that cases had a higher mLCOSS score (p<0.01). The median difference (case less control) between mLCOSS in each pair was 23.1 (IQR 9.2 – 33.7), representing an average between 1 and 2 additional deterioration marker in cases compared to controls in each matched pair. The indicators which had the strongest association with LCOEs were urine output and temperature, as shown in Table 1: Baseline characteristics for cases and controls.

Baseline characteristics are shown for the 28 patients with low cardiac output related adverse events (defined as need for cardiopulmonary resuscitation (CPR), need for ECMO, need for renal replacement therapy (RRT), or diagnosis of necrotising enterocolitis(NEC)), and 28 controls matched by RACHS category, ventricular status and age. Pre-operative serum creatinine was defined as the last creatinine measurement prior to surgery. Creatinine data were not available for 2 patients (1 case and 1 control). Continuous variables were compared using the Student's t-test for normally distributed values (creatinine) and Mann-Whitney rank sum test (age, weight). The association between emergency surgery and adverse events was tested using odds ratios (Odds ratio for an
adverse event following emergency surgery 1.53, 95% CI 0.42-5.57). Note two patients with RRT and two patients with CPR as the primary event went on to have ECMO shortly afterwards.

**Table 2: Data completion for cases and controls.** The table shows the availability of data for the 28 cases and 28 controls from T3 and the electronic patient health record. Data were lost if the monitor was not connected to the local area network, the case was not admitted on the bedside monitor or if the electronic health record system was undergoing maintenance.

**Table 3.**

The mLCOSS values for each matched pair are shown in Figure 4.

When excluding the marker for low urine output, mLCOSS remained higher for cases in 22 pairs out of 28 (78.6%), still exhibiting a strong positive association (p<0.01).

The median difference in IDO2 and mLCOSS and the median difference in the percentage of time that each of the mLCOSS indicators were present is summarised in Table 1: Baseline characteristics for cases and controls. Baseline characteristics are shown for the 28 patients with low cardiac output related adverse events (defined as need for cardiopulmonary resuscitation (CPR), need for ECMO, need for renal replacement therapy (RRT), or diagnosis of necrotising enterocolitis (NEC)), and 28 controls matched by RACHS category, ventricular status and age. Pre-operative serum creatinine was defined as the last creatinine measurement prior to surgery. Creatinine data were not available for 2 patients (1 case and 1 control). Continuous variables were compared using the Student’s t-test for normally distributed values (creatinine) and Mann-Whitney rank sum test (age, weight). The association between emergency surgery and adverse events was tested using odds ratios (Odds ratio for an adverse event following emergency surgery 1.53, 95% CI 0.42-5.57). Note two patients with RRT and two patients with CPR as the primary event went on to have ECMO shortly afterwards.
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Table 3.

Discussion

This study set out to test the performance of two objective scoring systems for identification of LCOS during the first 12 hours after surgery, based on the ability to pick out patients who experienced an adverse event linked to LCOS within 72 hours. IDO2 is a newly developed risk analytics algorithm designed to represent the likelihood that a patient is experiencing inadequate oxygen delivery. The LCOS is a clinical and therapeutic based risk score designed to be indicative of LCOS. We were surprised to find that IDO2 in the first 12 hours following surgery did not have a significant relationship with subsequent adverse event occurrence whereas mLCOSS had a strong association with the evolution of such adverse events.

IDO2 has been shown to be successful at predicting an SvO2 value below 40% (8), however, evidence of its use beyond this remains sparse. Our findings are consistent with a study that showed a raised IDO2 in the 24-96 hours after surgery had a significant relationship with increased length of stay following cardiac surgery, but no significant relationship was found over the first 24 hours (9), limiting its predictive ability. We note that the IDO2 can be highly variable over a 12 hour period and this may limit the discriminative ability of the average score. Further research to explore values and cut offs might shed further light on this.
The findings on the effectiveness of mLCOSS in predicting adverse events in our study reinforces the results of the original development and testing of the score by Ulate et al (11).

This is the first study to examine the usefulness of IDO2 early after operation in predicting adverse outcomes linked to LCOS in patients in the immediate post-operative period. This study could uniquely take place at GOSH, where the T3 bedside monitor system have been in use for over 2 years without the inclusion of the IDO2 index, meaning IDO2 could be tested in an environment where it had not influenced clinical decisions.

In addition to LCOSS, a variety of risk scores designed to reflect the risk of adverse events following pediatric cardiac surgery have been published (19–21), with different levels of emphasis put on using high resolution physiological data as opposed to lower frequency variables and risk factors. As more high frequency data becomes available for analysis, it would seem advantageous to make use of it. However, the findings of this study may indicate that variation in physiology amongst patients post-surgery may contain more noise than signal, and therefore risk scores based on lower frequency values may be more informative.

LCOSS uses readily available clinical indicators to signal potential future deterioration, whereas IDO2 uses vital signs and laboratory data to produce a black box risk score. The findings of this paper indicate that IDO2 may not add to the clinical recognition of LCOS and events associated with it.

This study has a number of limitations. There is no consensus definition of LCOS and to measure cardiac output in order to detect true cases of LCOS requires a different and prospective study design. Although the adverse events used in this study have a strong association with LCOS, they also have a range of other contributory factors. Patients who developed LCOS following cardiac surgery may not have experienced any of the events considered, possibly due to early clinical intervention. Over 80% of the adverse events included in the study were RRT. The initialisation of RRT is a clinical decision. This is a single centre study and the findings will be influenced by local
practice patterns: although as outlined in methods a protocol for deployment is used in our unit, the threshold and timing for initialisation is open to some subjectivity. We compared the pre-operative renal function of cases and controls finding that there was no significant difference between the pre-operative serum creatinine between case and controls (t-test p=0.59). This leads us to believe that LCOS was at least a strong contributor to these patients requiring RRT. We note that due to complexities in diagnosis of acute kidney injury immediately after open heart surgery the National Congenital Heart Diseases Audit in the UK and the Society of Thoracic Surgery and Congenital Heart Surgeons Database in the USA rely on use of RRT as the main definition of renal failure in this context.

This study only considered the first 12 hours following surgery and further research entailing different time criteria might add information. We note that a previous study showed that the discriminative ability of IDO2 increases beyond 24 hours following surgery (9). However, as most of the adverse events in our dataset occurred within the first 24 hours of surgery, and since motivation for our study related to prediction of adverse events, looking beyond this would have been of limited use.

The number of cases considered is small. However, this cohort represents all patients at GOSH who suffered one of the specified adverse events following bypass surgery for the year from June 2015 to May 2016, so is an appropriate test of the clinical utility of IDO2 in a realistic setting. To achieve a significant result, IDO2 would have had to be higher in the case than the control in at least 19 of the matched pairs, an additional 6 pairs.

Conclusion

Although IDO2 has been validated to be predictive for short term changes in physiologic variables, care should be taken if using it as an indicator of medium term deterioration. The indicators included in the LCOSS had a much stronger association with events indicative of LCOS.
More research into the development and effectiveness of such algorithms is needed before they can be usefully incorporated into clinical use as an early indicator of significant deterioration.

Acknowledgements

We thank Etiometry for calculating the IDO2 index.
References


10. U.S. Food and Drug Administration: T3 Software (Version 3.0) approval letter - K163065

[Internet]. 2017; [cited 2017 Nov 10] Available from:
https://www.accessdata.fda.gov/cdrh_docs/pdf16/K163065.pdf


http://www.picanet.org.uk/Audit/Annual-
Reporting/PICANet_Annual_Report_Tables_and_Figures_2016.pdf


Figure Legends

Figure 1: Examples of the IDO2 value over 12 hours following surgery for two matched pairs. The example on the left demonstrates high IDO2 values in the patient with a subsequent adverse event (red) compared to the matched control patient (blue). The example on the right however shows a pair where the IDO2 value was higher in the control patient compared to the patient with a subsequent adverse event.

Figure 2: The mean IDO2 values for each case and control in a matched pair. Each dot represents a case-control pair. The green dots represent pairs where the mean IDO2 over the first 12 hours was higher in the patient with the subsequent adverse event; the red dots represents pairs where the mean IDO2 was higher in the matched control patients. The dashed line marks where the values are equal for the case and control.

Figure 3: Examples of the mLCOSS value over 12 hours following surgery for two matched pairs. The example on the left demonstrates low mLCOSS values in the patient with a subsequent adverse event (red) compared to the matched control patient (blue). The example on the right shows a pair where the mLCOSS value was lower in the control patient compared to the patient with a subsequent adverse event.

Figure 4: The mean mLCOSS values for each case and control in a matched pair. Each dot represents a case-control pair. The green dots represent pairs where the mLCOSS over the first 12 hours was higher in the patient with the subsequent adverse event; the red dots represents pairs where the mLCOSS was higher in the matched control patients. The dashed line marks where the values are equal for the case and control. There are more green dots than red, compared to figure 2, indicating the superior predictive ability of mLCOSS over IDO2 for a pre-defined adverse event.

Tables

Table 1: Baseline characteristics for cases and controls. Baseline characteristics are shown for the 28 patients with low cardiac output related adverse events (defined as need for cardiopulmonary resuscitation (CPR), need for ECMO, need for renal replacement therapy (RRT), or diagnosis of necrotising enterocolitis (NEC)), and 28 controls matched by RACHS category, ventricular status and age. Pre-operative serum creatinine was defined as the last creatinine measurement prior to surgery. Creatinine data were not available for 2 patients (1 case and 1 control). Continuous variables were compared using the Student’s t-test for normally distributed values (creatinine) and Mann-Whitney rank sum test (age, weight). The association between emergency surgery and adverse events was tested using odds ratios (Odds ratio for an adverse event following emergency surgery 1.53, 95% CI 0.42-5.57). Note two patients with RRT and two patients with CPR as the primary event went on to have ECMO shortly afterwards.
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Table 3: Median difference between deterioration indicators in the 12 hours following surgery. The median difference between the cases and controls for IDO2 and mLCOSS are shown. In addition, the percentages of time when each of the individual components of the scoring systems indicate deterioration are listed.
<table>
<thead>
<tr>
<th>Patient factor</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Adverse Event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No event (control)</td>
<td>-</td>
<td>28 (100.0)</td>
<td></td>
</tr>
<tr>
<td>CPR</td>
<td>3 (10.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>1 (3.6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>RRT</td>
<td>24 (85.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>0 (0)</td>
<td>-</td>
<td></td>
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<tr>
<td><strong>RACHS Category</strong></td>
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<tr>
<td>RACHS I</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>RACHS II</td>
<td>8 (28.6)</td>
<td>8 (28.6)</td>
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<tr>
<td>RACHS III</td>
<td>12 (42.9)</td>
<td>12 (42.9)</td>
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<tr>
<td>RACHS IV</td>
<td>6 (21.4)</td>
<td>6 (21.4)</td>
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<tr>
<td>RACHS V</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>RACHS VI</td>
<td>2 (7.1)</td>
<td>2 (7.1)</td>
<td></td>
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<tr>
<td><strong>Emergency surgery</strong></td>
<td>7 (25.0%)</td>
<td>5 (17.9%)</td>
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<tr>
<td><strong>UVH/BVH</strong></td>
<td></td>
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</tr>
<tr>
<td>BVH</td>
<td>26 (92.9)</td>
<td>26 (92.9)</td>
<td></td>
</tr>
<tr>
<td>UVH</td>
<td>2 (7.1)</td>
<td>2 (7.1)</td>
<td></td>
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<tr>
<td><strong>Age (months) – median (IQR)</strong></td>
<td>3.4 (0.6-8.4)</td>
<td>2.1 (0.4-6.8)</td>
<td>0.94</td>
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<tr>
<td><strong>Weight (kg) – median (IQR)</strong></td>
<td>4.4 (3.5 – 8.1)</td>
<td>4.0 (3.2 - 7.0)</td>
<td>0.88</td>
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<tr>
<td><strong>Pre-operative serum creatinine (umol/L) – mean (sd)</strong></td>
<td>32.0 (10.6)</td>
<td>34.2 (14.8)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>First adverse event time (hours) – median (IQR)</strong></td>
<td>21.3 (16.3-27.6)</td>
<td>-</td>
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</tbody>
</table>

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<table>
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<th>Data Completion</th>
<th>Cases</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Median proportion of time with IDO2 calculated (IQR)</td>
<td>93.5% (75.1% - 95.3%)</td>
<td>95.0% (91.6% - 96.1%)</td>
</tr>
<tr>
<td>Patients with urine output recorded</td>
<td>28 (100%)</td>
<td>28 (100%)</td>
</tr>
<tr>
<td>Patients with temperature recorded</td>
<td>27 (96.4%)</td>
<td>24 (85.7%)</td>
</tr>
<tr>
<td>Patients with arterial lactate recorded</td>
<td>28 (100%)</td>
<td>28 (100%)</td>
</tr>
<tr>
<td>Patients with heart rate recorded</td>
<td>27 (96.4%)</td>
<td>26 (92.9%)</td>
</tr>
<tr>
<td>Patients with fluid intake recorded</td>
<td>28 (100%)</td>
<td>26 (92.9%)</td>
</tr>
<tr>
<td>Patients with inotropic support recorded</td>
<td>28 (100%)</td>
<td>28 (100%)</td>
</tr>
</tbody>
</table>
Table 3: Median difference between deterioration indicators in the 12 hours following surgery.

The median difference between the cases and controls for IDO2 and mLCOSS are shown. In addition, the percentages of time when each of the individual components of the scoring systems indicate deterioration are listed.

<table>
<thead>
<tr>
<th>Deterioration indicator in 12 hours post-surgery</th>
<th>Median difference (Case – Control) (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDO2</td>
<td>-0.1 (-7.4 – 11.8)</td>
</tr>
<tr>
<td>mLCOSS</td>
<td>23.1 (9.2 – 33.7)</td>
</tr>
<tr>
<td>Percentage of time with HR indicator</td>
<td>1.9% (-1.2% - 54.6%)</td>
</tr>
<tr>
<td>Percentage of time with urine output indicator</td>
<td>16.3% (0.0% - 51.3%)</td>
</tr>
<tr>
<td>Percentage of time with temperature indicator</td>
<td>14.4% (0.0% - 72.8%)</td>
</tr>
<tr>
<td>Percentage of time with inotrope indicator</td>
<td>3.1% (-4.4% - 43.9%)</td>
</tr>
<tr>
<td>Percentage of time with volume administration indicator</td>
<td>11.8% (-8.2% - 51.2%)</td>
</tr>
<tr>
<td>Percentage of time with arterial lactate indicator</td>
<td>0.0% (-9.2% - 39.0%)</td>
</tr>
</tbody>
</table>