

1  
2  
3 The Inadequate Oxygen Delivery Index and Low Cardiac Output Syndrome Score as  
4  
5  
6 predictors of adverse events associated with Low Cardiac Output Syndrome early after  
7  
8  
9 cardiac bypass

10 Libby Rogers<sup>1</sup> MMath, Samiran Ray<sup>2,3</sup> MBChir MA, Mae Johnson<sup>4</sup> MBBS, Yael Feinstein<sup>4</sup> MBBS, Troy  
11  
12 Dominguez<sup>4</sup> MD, Mark J Peters<sup>2,3</sup> MBChB PhD, Aparna Hoskote<sup>4</sup> MBBS, Katherine L Brown<sup>4</sup> MPH MD  
13

- 14  
15 1. Clinical Operational Research Unit, University College London, UK  
16  
17 2. Paediatric Intensive Care Unit, Great Ormond Street Hospital NHS Trust, London, UK  
18  
19 3. Respiratory, Critical Care and Anaesthesia Section, UCL GOS Institute of Child Health,  
20  
21 London, UK  
22  
23 4. Cardiac Critical Care Unit, Great Ormond Street Hospital for Children NHS Foundation Trust,  
24  
25 London, UK  
26  
27

28  
29  
30  
31 Corresponding author:

32  
33 Dr Samiran Ray

34  
35 [samiran.ray@gosh.nhs.uk](mailto:samiran.ray@gosh.nhs.uk)

36  
37 Paediatric and Neonatal Intensive Care Unit

38  
39 Great Ormond Street Hospital NHS Trust

40  
41 London WC1N 3JH

42  
43 Tel: 0442074059200 ext 0032

44  
45 Fax: 0442078138206  
46  
47

48  
49 **Conflicts of Interest:** None to declare  
50  
51

52  
53 **Keywords:** cardiac surgery; low cardiac output syndrome; morbidity; pediatric; physiologic  
54  
55 monitoring  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 **Funding:** This work was undertaken at Great Ormond Street Hospital/UCL Institute of Child Health,  
2 which received a proportion of funding from the Department of Health's NIHR Biomedical Research  
3 Centre's funding scheme.  
4  
5

6  
7 **Copyright Disclosure Statement:** Drs. Ray and Peters' institutions received funding from Great  
8 Ormond Street Hospital Children's Charity (GOSHCC). Dr. Peters received funding from Faron  
9 pharmaceuticals (advisory board) and Therakind. Drs. Peters and Brown received support for article  
10 research from GOSHCC. Dr. Brown received other support from GOSHCC PICU infrastructure grant  
11 supporting Libby Rogers. The remaining authors have disclosed that they do not have any potential  
12 conflicts of interest.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3 **Abstract**

4 **Objective**

5  
6 To evaluate the effectiveness of two scoring systems, the Inadequate Oxygen Delivery (IDO2) Index,  
7  
8 a risk analytics algorithm (Etiometry Inc. MA USA) and the Low Cardiac Output Syndrome Score  
9  
10 (LCOSS), in predicting adverse events recognised as indicative of Low Cardiac Output Syndrome  
11  
12 (LCOS) within 72 hours of surgery.

13  
14  
15  
16 *Design*

17  
18  
19 A retrospective observational pair-matched study.

20  
21  
22 *Setting*

23  
24  
25 Tertiary pediatric cardiac intensive care unit.

26  
27  
28 *Patients*

29  
30  
31 Children undergoing cardiac bypass for congenital heart defects. Cases experienced an adverse  
32  
33 event linked to LCOS in the 72 hours following surgery (extracorporeal membrane oxygenation, renal  
34  
35 replacement therapy, cardiopulmonary resuscitation and necrotising enterocolitis), and were  
36  
37 matched with a control patient on criteria of procedure, diagnosis and age who experienced no such  
38  
39 event.  
40  
41

42  
43  
44 *Interventions*

45  
46  
47 None.

48  
49  
50 *Measurements and Main Results*

51  
52  
53 Of a total 536 bypass operations in the study period, 38 patients experienced one of the defined  
54  
55 events. Twenty-eight cases were included in the study after removing patients who suffered an  
56  
57 event after 72 hours or who had insufficient data. Clinical and laboratory data were collected to  
58  
59  
60  
61  
62  
63  
64  
65

1 derive scores for the first 12 hours after surgery. The IDO2 Index was calculated by Etiometry using  
2 vital signs and laboratory data. A modified LCOSS (mLCOSS) was calculated from clinical and  
3  
4 therapeutic markers. The mean IDO2 and mLCOSS were compared within each matched pair using  
5  
6 the Wilcoxon signed-rank test. IDO2 correctly differentiated adverse events in 13/28 matched pairs,  
7  
8 with no evidence of IDO2 being higher in cases ( $p=0.71$ ). mLCOSS correctly differentiated adverse  
9  
10 events in 23/28 matched pairs, with strong evidence of a raised score in LCOS cases ( $p<0.01$ ).  
11  
12

### 13 *Conclusions*

14  
15  
16 Although IDO2 is an FDA approved indicator of risk for low mixed venous oxygen saturation, early  
17  
18 post-operative average values were not linked with medium term adverse events. The indicators  
19  
20 included in the mLCOSS had a much stronger association with the specified adverse events.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## Introduction

1  
2  
3  
4 LCOS remains a significant post-operative problem and is characterised by poor oxygen  
5  
6 delivery to tissues due to myocardial dysfunction (1). Direct measurements of cardiac output  
7  
8 following open heart surgery in neonates have previously identified low cardiac output syndrome  
9  
10 (LCOS) in 25% of patients (2). LCOS is important since it is associated with complications including  
11  
12 organ failure, longer length of stay, increased healthcare resource utilisation and death (3–5). Early  
13  
14 identification and treatment of LCOS has great potential to improve outcomes for patients.  
15  
16 However, there are no clear established criteria for the clinical definition of LCOS, with recent clinical  
17  
18 trials utilising a range of thresholds for its definition (5, 6). Furthermore it has been noted that the  
19  
20 diagnosis of LCOS can be subjective and vary between clinicians (7). There has been recent interest  
21  
22 in the development of objective methods to identify patients with LCOS for use in cardiac intensive  
23  
24 care unit (CICU) settings.  
25  
26  
27  
28  
29

30  
31 A risk analytics algorithm has been developed by Etiometry (Etiometry Inc., MA, USA) to  
32  
33 assess patient specific risk of inadequate oxygen delivery (IDO2) (8). The IDO2 index aims to reflect  
34  
35 the likelihood that a patient is experiencing inadequate oxygen delivery, with an increasing value  
36  
37 indicating an increasing risk of inadequate oxygen delivery. The continuous IDO2 Index is calculated  
38  
39 using multiple physiologic measures and laboratory results collected by Etiometry's T3 Data  
40  
41 Aggregation & Visualization platform. The IDO2 Index has been validated to show an association  
42  
43 between a raised IDO2 Index and a mixed venous oxygen saturation (SvO<sub>2</sub>) measurement below  
44  
45 40%. In a study of 312 post-cardiopulmonary bypass neonates, IDO2 had an area under the curve of  
46  
47 0.79 (0.76-0.82), showing good prediction of low SvO<sub>2</sub> (8). Further studies have shown an association  
48  
49 between a raised IDO2 Index on days 2-4 post surgery and increased length of stay in post-  
50  
51 cardiopulmonary bypass neonates (9).  
52  
53  
54  
55  
56

57  
58 The IDO2 Index has received approval from the US Food and Drug Administration (FDA) for  
59  
60 use in pediatric patients aged 12-and-under in intensive care with weight above 2kg (10), and is in  
61  
62  
63  
64  
65

1 use in several pediatric intensive care units in North America in conjunction with the T3 Data  
2 Aggregation & Visualization platform.  
3

4  
5 The Low Cardiac Output Syndrome Score (LCOSS) (11) uses raised heart rate (HR) (>20%  
6 above post-induction HR in the operating room), low urine output (<1mL/kg/hr), low temperature  
7 (<30°C), raised inotropic requirement (in excess of milrinone 0.5µg/kg/min), increased volume  
8 administration (>30mL/kg/d), decreased near infra-red spectroscopy (NIRS) measurement (Cerebral  
9 and renal NIRS<50% and 75% of arterial saturations respectively) and high arterial lactate  
10 (>2mmol/L) as markers of deterioration. A point is given for each indicator that is present. In the  
11 prospective evaluation of LCOSS carried out by Ulate et al (11), measurements of LCOSS were  
12 recorded at arrival on CICU, and at 8,12, and 24 hours postoperatively and used to calculate a peak  
13 and cumulative LCOSS, and in a single centre study this was found to be strongly linked to a  
14 composite measure of post-operative morbidity.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27

28  
29 In this study, our central hypothesis was:  
30

31  
32 'A higher mean IDO2 index early post operation will be linked to LCOS related post-  
33 operative adverse events whereas a lower mean IDO2 index in the same period will be linked to non-  
34 occurrence of such post-operative events.'  
35  
36  
37  
38  
39

40 A secondary hypothesis was:  
41

42  
43 'Conventional clinical measures of LCOS that make up the LCOSS early post operation are  
44 linked to subsequent post-operative adverse events.'  
45  
46  
47  
48

49 To test these hypotheses we evaluated the performance of IDO2 and LCOSS in predicting  
50 which patients would go on to suffer defined and prospectively detected post-operative adverse  
51 events that are recognised to be related to LCOS in post-operative cardiac patients.  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## Materials and Methods

1  
2  
3  
4 The study population included patients undergoing cardiac bypass procedures and cared for  
5  
6 in CICU at Great Ormond Street Hospital, London, UK (GOSH). The CICU at GOSH has approximately  
7  
8 800 admissions every year, with postoperative cardiac patients generally representing 66% of this  
9  
10 total (12) and has been using the T3 monitoring system since June 2015. The IDO2 Index has not  
11  
12 been added to the monitors, so the clinical care of patients has been carried out without any  
13  
14 reference to the IDO2 index.  
15  
16  
17

18  
19 Adverse events were defined as initialisation of Extracorporeal Membrane Oxygenation  
20  
21 (ECMO), Renal Replacement Therapy (RRT), Cardio-Pulmonary Resuscitation (CPR) or the diagnosis  
22  
23 of Necrotising Enterocolitis (NEC). These events were considered as they commonly occur in the  
24  
25 context of LCOS (13–15), and were defined based on consistent criteria from a subset of known  
26  
27 complications following congenital heart surgery (16, 17). In our centre we prospectively document  
28  
29 the occurrence of all of these events as part of the local quality assurance process and we review all  
30  
31 such events on a weekly basis at a multi-disciplinary conference. Our local protocol for initiation of  
32  
33 RRT in post-operative patients is to do so if there is oligo-anuria for 4-6 hours despite optimisation of  
34  
35 pre load, inotropic support and administration of diuretics. Patients, who had returned to the CICU  
36  
37 already receiving ECMO were excluded since in these patients there was no 12 hour period in the  
38  
39 unit during which scores could be derived (the adverse event had already happened).  
40  
41  
42  
43  
44

45  
46 We conducted a retrospective observational matched study of children who underwent  
47  
48 surgical repair or palliation of CHDs under bypass at GOSH from 1 June 2015 – 31 May 2016. All  
49  
50 patients that experienced one of the specified events in the 72 hours following surgery were  
51  
52 considered as cases and included in the study if T3 data were available. A patient was considered as  
53  
54 a possible control patient if they did not experience one of the specified events while in the CICU  
55  
56 following a cardiac procedure. For each case, the next patient without any of the specified events,  
57  
58 matching based on the following variables, was included as a control.  
59  
60  
61  
62  
63  
64  
65

- 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:

- If age<1 match must be within 3 months in age
- If 1<age<5 match must be within a year of age
- 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.



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

13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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 Mann-Whitney rank sum test (age, weight). The association between emergency surgery and the presence of an adverse event was tested using odds ratios.

1 The mean of the IDO2 score and the mean of mLCOSS between return to the CICU following  
2 surgery and 12 hours after surgery (or onset of the adverse event, or the equal time after surgery for  
3 control cases, if earlier) were compared for cases and controls using the Wilcoxon signed-rank test  
4 for matched samples.  
5  
6  
7  
8  
9

10 Data were analyzed using Stata software (StataCorp. 2015. Stata Statistical Software:  
11 Release 14. College Station, TX: StataCorp LP). The study was approved by Great Ormond Street  
12 Hospital for Children NHS Foundation Trust as a clinical audit project.  
13  
14  
15  
16  
17  
18  
19

## 20 Results

21  
22  
23

24 Of a total 536 cardiac operations with bypass carried out at GOSH in the study period, 38  
25 patients experienced a subsequent adverse event while in the CICU following surgery. Of these, 1  
26 had an adverse event after 72 hours post-admission to CICU, 3 returned from theatre on ECMO and  
27 6 children had insufficient T3 data – these cases were all excluded from further analysis. This  
28 resulted in 28 cases for analysis, which were matched to 28 control patients. The demographic and  
29 clinical data of the 28 pairs of cases and controls are shown in Table 1. **There were no significant  
30 differences between the two groups, including the number of children having emergency surgery  
31 and pre-operative serum creatinine.**  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 The percentage of high resolution T3 data available for each record is shown in Table 2,  
44 broken down according to each variable.  
45  
46  
47

48 Twenty-four of the 28 cases included in the study had RRT as their primary adverse event, 2  
49 of which went on to also have ECMO initiated shortly afterwards. Three patients underwent CPR,  
50 after which 2 were transferred on to ECMO. One patient was diagnosed with NEC. As all the cases of  
51 ECMO following cardiac surgery were either initialised in the operating theatre, or occurred  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 following another adverse event, no patients had ECMO as their primary adverse event. For the  
2 majority of patients, their primary adverse event occurred within 24 hours of surgery.  
3

4  
5 Two examples of the IDO2 score over the 12 hours post-surgery for a matched pair are  
6 shown in Figure 1.  
7

8  
9  
10 Of the 28 pairs of matched patients, the 12-hour mean IDO2 score was higher for cases in 13  
11 pairs out of 28 (46.4%). This showed no evidence that cases had higher IDO2 scores ( $p=0.71$ ). The  
12 median difference (case less control) between IDO2 in each pair was -0.1 (IQR -7.4 – 11.8)  
13  
14  
15

16  
17  
18 The IDO2 values for each matched pair are shown in Figure 2.  
19

20  
21 Two examples of the mLCOSS score over the 12 hours post-surgery for a matched pair are  
22 shown in Figure 3.  
23

24  
25  
26 Of the 28 pairs of matched patients, the 12-hour mean mLCOSS was higher for 23 pairs out  
27 of 28 (82.1%). This showed strong evidence that cases had a higher mLCOSS score ( $p<0.01$ ). The  
28 median difference (case less control) between mLCOSS in each pair was 23.1 (IQR 9.2 – 33.7),  
29 representing on average between 1 and 2 additional deterioration marker in cases compared to  
30 controls in each matched pair. The indicators which had the strongest association with LCOEs were  
31 urine output and temperature, as shown in Table 1: Baseline characteristics for cases and controls.  
32  
33 Baseline characteristics are shown for the 28 patients with low cardiac output related adverse  
34 events (defined as need for cardiopulmonary resuscitation (CPR), need for ECMO, need for renal  
35 replacement therapy (RRT), or diagnosis of necrotising enterocolitis(NEC)), and 28 controls matched  
36 by RACHS category, ventricular status and age. Pre-operative serum creatinine was defined as the  
37 last creatinine measurement prior to surgery. Creatinine data were not available for 2 patients (1  
38 case and 1 control). Continuous variables were compared using the Student's t-test for normally  
39 distributed values (creatinine) and Mann-Whitney rank sum test (age, weight). The association  
40 between emergency surgery and adverse events was tested using odds ratios (Odds ratio for an  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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.

1 **Table 2: Data completion for cases and controls.** The table shows the availability of data for the 28  
2 cases and 28 controls from T3 and the electronic patient health record. Data were lost if the monitor  
3 was not connected to the local area network, the case was not admitted on the bedside monitor or  
4 if the electronic health record system was undergoing maintenance.  
5  
6  
7

8 **Table 3.**  
9

## 10 11 12 13 14 15 16 17 **Discussion** 18

19  
20  
21  
22 This study set out to test the performance of two objective scoring systems for identification  
23 of LCOS during the first 12 hours after surgery, based on the ability to pick out patients who  
24 experienced an adverse event linked to LCOS within 72 hours. IDO2 is a newly developed risk  
25 analytics algorithm designed to represent the likelihood that a patient is experiencing inadequate  
26 oxygen delivery. The LCOSS is a clinical and therapeutic based risk score designed to be indicative of  
27 LCOS. We were surprised to find that IDO2 in the first 12 hours following surgery did not have a  
28 significant relationship with subsequent adverse event occurrence whereas mLCOSS had a strong  
29 association with the evolution of such adverse events.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

42 IDO2 has been shown to be successful at predicting an SvO<sub>2</sub> value below 40% (8), however,  
43 evidence of its use beyond this remains sparse. Our findings are consistent with a study that showed  
44 a raised IDO2 in the 24-96 hours after surgery had a significant relationship with increased length of  
45 stay following cardiac surgery, but no significant relationship was found over the first 24 hours (9),  
46 limiting its predictive ability. We note that the IDO2 can be highly variable over a 12 hour period and  
47 this may limit the discriminative ability of the average score. Further research to explore values and  
48 cut offs might shed further light on this.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 The findings on the effectiveness of mLCOSS in predicting adverse events in our study  
2 reinforces the results of the original development and testing of the score by Ulate et al (11).  
3  
4

5 This is the first study to examine the usefulness of IDO2 early after operation in predicting  
6 adverse outcomes linked to LCOS in patients in the immediate post-operative period. This study  
7 could uniquely take place at GOSH, where the T3 bedside monitor system have been in use for over  
8 2 years without the inclusion of the IDO2 index, meaning IDO2 could be tested in an environment  
9 where it had not influenced clinical decisions.  
10  
11  
12  
13  
14  
15  
16

17 In addition to LCOSS, a variety of risk scores designed to reflect the risk of adverse events  
18 following pediatric cardiac surgery have been published (19–21), with different levels of emphasis  
19 put on using high resolution physiological data as opposed to lower frequency variables and risk  
20 factors. As more high frequency data becomes available for analysis, it would seem advantageous to  
21 make use of it. However, the findings of this study may indicate that variation in physiology amongst  
22 patients post-surgery may contain more noise than signal, and therefore risk scores based on lower  
23 frequency values may be more informative.  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34

35 LCOSS uses readily available clinical indicators to signal potential future deterioration,  
36 whereas IDO2 uses vital signs and laboratory data to produce a black box risk score. The findings of  
37 this paper indicate that IDO2 may not add to the clinical recognition of LCOS and events associated  
38 with it.  
39  
40  
41  
42  
43  
44

45 This study has a number of limitations. There is no consensus definition of LCOS and to  
46 measure cardiac output in order to detect true cases of LCOS requires a different and prospective  
47 study design. Although the adverse events used in this study have a strong association with LCOS,  
48 they also have a range of other contributory factors. Patients who developed LCOS following cardiac  
49 surgery may not have experienced any of the events considered, possibly due to early clinical  
50 intervention. Over 80% of the adverse events included in the study were RRT. The initialisation of  
51 RRT is a clinical decision. This is a single centre study and the findings will be influenced by local  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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.

22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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.

37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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.

## 50 Conclusion

52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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.

1 More research into the development and effectiveness of such algorithms is needed before  
2 they can be usefully incorporated into clinical use as an early indicator of significant deterioration.  
3  
4  
5  
6  
7

8 **Acknowledgements**  
9

10 We thank Etiometry for calculating the IDO2 index.  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65



## References

1. Wessel DL: Managing low cardiac output syndrome after congenital heart surgery. *Crit Care Med* 2001; 29:S220-230
2. Wernovsky G, Wypij D, Jonas RA, et al.: Postoperative Course and Hemodynamic Profile After the Arterial Switch Operation in Neonates and Infants: A Comparison of Low-Flow Cardiopulmonary Bypass and Circulatory Arrest. *Circulation* 1995; 92:2226–2235
3. Ma M, Gauvreau K, Allan CK, et al.: Causes of death after congenital heart surgery. *Ann Thorac Surg* 2007; 83:1438–1445
4. Parr GV, Blackstone EH, Kirklin JW: Cardiac performance and mortality early after intracardiac surgery in infants and young children. *Circulation* 1975; 51:867–874
5. Hoffman TM, Wernovsky G, Atz AM, et al.: Efficacy and Safety of Milrinone in Preventing Low Cardiac Output Syndrome in Infants and Children After Corrective Surgery for Congenital Heart Disease. *Circulation* 2003; 107:996–1002
6. James C, Millar J, Horton S, et al.: Nitric oxide administration during paediatric cardiopulmonary bypass: a randomised controlled trial. *Intensive Care Med* 2016; 42:1744–1752
7. Tibby SM, Hatherill M, Marsh MJ, et al.: Clinicians' abilities to estimate cardiac index in ventilated children and infants. *Arch Dis Child* 1997; 77:516–518
8. Baronov D, McManus M, Butler E, et al.: Next generation patient monitor powered by in-silico physiology. *Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf* 2015; 2015:4447–4453
9. Salvin J, Almodovar MC, Baronov D, et al.: Inadequate Oxygen Delivery Index (iDO<sub>2</sub>) as a Predictor of CICU Length of Stay. In: 12th Annual Meeting of the Pediatric Cardiac Intensive Care Society. 2016.

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](https://www.accessdata.fda.gov/cdrh_docs/pdf16/K163065.pdf)
11. Ulate KP, Yanay O, Jeffries H, et al.: An Elevated Low Cardiac Output Syndrome Score Is Associated With Morbidity in Infants After Congenital Heart Surgery. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc* 2017; 18:26–33
12. PICANet 2016 Annual Report - Tables & Figures [Internet]. [cited 2016 Nov 24] Available from:  
[http://www.picanet.org.uk/Audit/Annual-Reporting/PICANet\\_Annual\\_Report\\_Tables\\_and\\_Figures\\_2016.pdf](http://www.picanet.org.uk/Audit/Annual-Reporting/PICANet_Annual_Report_Tables_and_Figures_2016.pdf)
13. McElhinney DB, Hedrick HL, Bush DM, et al.: Necrotizing Enterocolitis in Neonates With Congenital Heart Disease: Risk Factors and Outcomes. *Pediatrics* 2000; 106:1080–1087
14. Brown KL, Ridout DA, Goldman AP, et al.: Risk factors for long intensive care unit stay after cardiopulmonary bypass in children. *Crit Care Med* 2003; 31:28–33
15. Chiravuri SD, Riegger LQ, Christensen R, et al.: Factors associated with acute kidney injury or failure in children undergoing cardiopulmonary bypass: a case-controlled study. *Pediatr Anesth* 2011; 21:880–886
16. Brown KL, Pagel C, Brimmell R, et al.: Definition of important early morbidities related to paediatric cardiac surgery. *Cardiol Young* 2017; 27:747–756
17. Mavroudis C, Mavroudis CD, Jacobs JP, et al.: Procedure-based complications to guide informed consent: analysis of society of thoracic surgeons-congenital heart surgery database. *Ann Thorac Surg* 2014; 97:1838-1849; discussion 1849-1851

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65
18. Jenkins KJ, Gauvreau K, Newburger JW, et al.: Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg* 2002; 123:110–118
  19. Rusin CG, Acosta SI, Shekerdemian LS, et al.: Prediction of imminent, severe deterioration of children with parallel circulations using real-time processing of physiologic data. *J Thorac Cardiovasc Surg* 2016; 152:171–177
  20. Jeffries HE, Soto-Campos G, Katch A, et al.: Pediatric Index of Cardiac Surgical Intensive Care Mortality Risk Score for Pediatric Cardiac Critical Care. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc* 2015; 16:846–852
  21. Gaies MG, Gurney JG, Yen AH, et al.: Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc* 2010; 11:234–238

## 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.

**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: 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

Patient factor	Cases (%)	Controls (%)	<u>p-value</u>
Primary Adverse Event			
No event (control)	-	28 (100.0)	
CPR	3 (10.7)	-	
NEC	1 (3.6)	-	
RRT	24 (85.7)	-	
ECMO	0 (0)	-	
RACHS Category			
RACHS I	0 (0)	0 (0)	
RACHS II	8 (28.6)	8 (28.6)	
RACHS III	12 (42.9)	12 (42.9)	
RACHS IV	6 (21.4)	6 (21.4)	
RACHS V	0 (0)	0 (0)	
RACHS VI	2 (7.1)	2 (7.1)	
<u>Emergency surgery</u>	<u>7 (25.0%)</u>	<u>5 (17.9%)</u>	<u>0.52</u>
UVH/BVH			
BVH	26 (92.9)	26 (92.9)	
UVH	2 (7.1)	2 (7.1)	
Age (months)– median (IQR)	3.4 (0.6-8.4)	2.1 (0.4-6.8)	<u>0.94</u>
Weight (kg) – median (IQR)	4.4 (3.5 – 8.1)	4.0 (3.2 - 7.0)	<u>0.88</u>
<u>Pre-operative serum creatinine (umol/L) – mean (sd)</u>	<u>32.0 (10.6)</u>	<u>34.2 (14.8)</u>	<u>0.59</u>
First adverse event time (hours) – median (IQR)	21.3 (16.3-27.6)	-	

**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.

Note two patients with RRT and two patients with CPR as the primary event went on to have ECMO shortly afterwards.

<b>Data Completion</b>	<b>Cases</b>	<b>Controls</b>
Median proportion of time with IDO2 calculated (IQR)	93.5% (75.1% - 95.3%)	95.0% (91.6% - 96.1%)
Patients with urine output recorded	28 (100%)	28 (100%)
Patients with temperature recorded	27 (96.4%)	24 (85.7%)
Patients with arterial lactate recorded	28 (100%)	28 (100%)
Patients with heart rate recorded	27 (96.4%)	26 (92.9%)
Patients with fluid intake recorded	28 (100%)	26 (92.9%)
Patients with inotropic support recorded	28 (100%)	28 (100%)

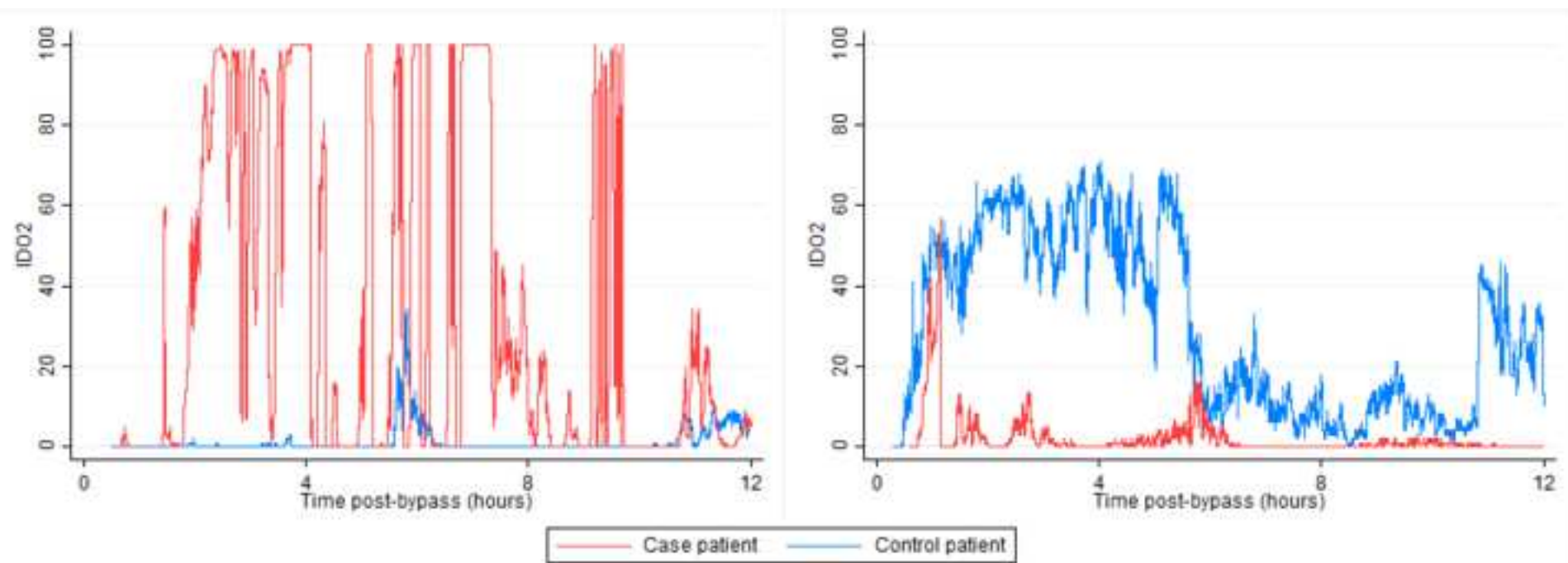
**Table 2: Data completion for cases and controls.** The table shows the availability of data for the 28 cases and 28 controls from T3 and the electronic patient health record. Data were lost if the monitor was not connected to the local area network, the case was not admitted on the bedside monitor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

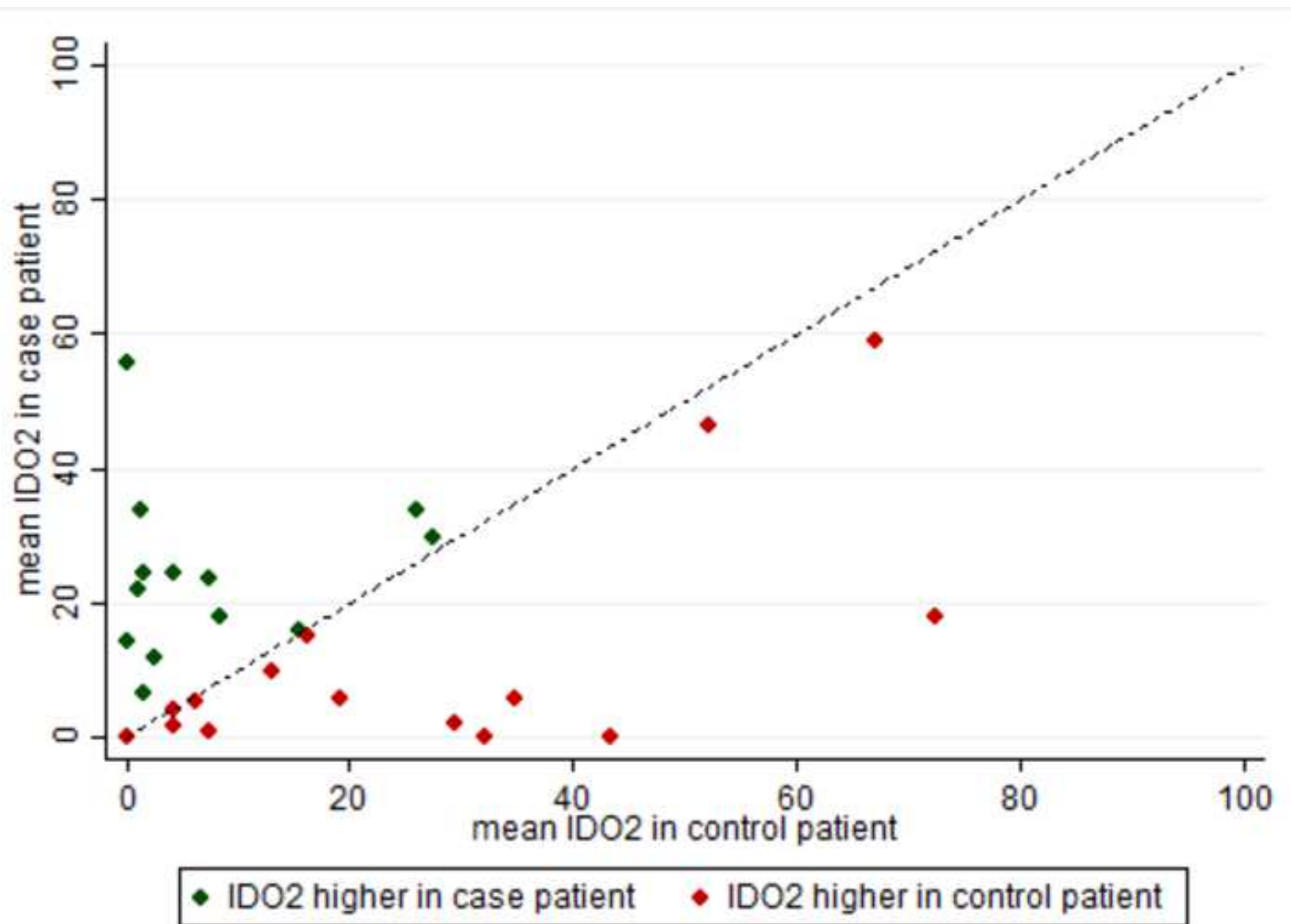


<b>Deterioration indicator in 12 hours post-surgery</b>	<b>Median difference (Case – Control) (IQR)</b>
IDO2	-0.1 (-7.4 – 11.8)
mLCOSS	23.1 (9.2 – 33.7)
Percentage of time with HR indicator	1.9% (-1.2% - 54.6%)
Percentage of time with urine output indicator	16.3% (0.0% - 51.3%)
Percentage of time with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

**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.





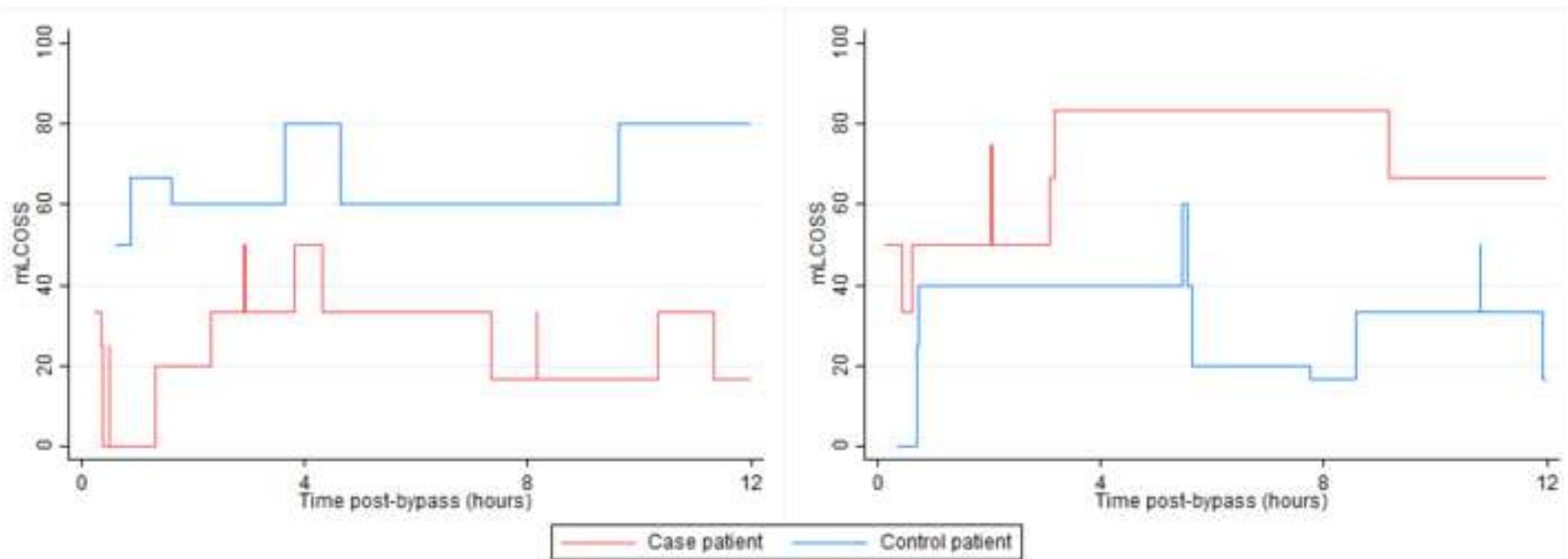


Figure 4

