Definitions of low cardiac output syndrome after cardiac surgery and their effect on the incidence of intraoperative LCOS: A literature review and cohort study

Anna Schoonen1*, Wilton A. van Klei1,2,3,4, Leo van Wolfswinkel1 and Kim van Loon1

1Department of Anesthesiology, University Medical Center Utrecht, Utrecht, Netherlands.
2Department of Anesthesiology and Pain Management Toronto General Hospital, University Health Network, Toronto, ON, Canada.
3Department of Anesthesiology and Pain Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada.
4Department of Anesthesiology and Pain Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada.

Objectives: Low cardiac output syndrome (LCOS) is a serious complication after cardiac surgery. Despite scientific interest in LCOS, there is no uniform definition used in current research and clinicians cannot properly compare different study findings. We aimed to collect the LCOS definitions used in literature and subsequently applied the definitions obtained to existing data to estimate their effect on the intraoperative LCOS incidences in adults, children and infants.

Design: This is a literature review, followed by a retrospective cohort study.

Setting: This is a single-institutional study from a university hospital in the Netherlands.

Participants: Patients from all ages undergoing cardiac surgery with cardiopulmonary bypass between June 2011 and August 2018.

Interventions: We obtained different definitions of LCOS used in the literature and applied these to data obtained from an anesthesia information management system to estimate intraoperative incidences of LCOS. We compared intraoperative incidences of LCOS in different populations based on age (infants, children and adults).

Measurements and main results: The literature search identified 262 LCOS definitions, that were applied to intraoperative data from 7,366 patients. Using the 10 most frequently published LCOS definitions, the obtained incidence estimates ranged from 0.4 to 82% in infants, from 0.6 to 56% in children and from 1.5 to 91% in adults.

Conclusion: There is an important variety in definitions used to describe LCOS. When applied to data obtained from clinical care, these different definitions resulted in large distribution of intraoperative LCOS incidence rates. We therefore advocate for standardization of the LCOS definition to improve...
Clinical understanding and enable adequate comparison of outcomes and treatment effects both in daily care and in research.

**KEYWORDS**

Low cardiac output syndrome, complication, definitions, incidence, cardiac surgery, LCOS

**Introduction**

Low cardiac output syndrome (LCOS) is a frequently occurring complication after cardiac surgery. LCOS is characterized by an inadequate cardiac pump function resulting in reduced oxygen delivery and tissue hypoxia, in both adults and children (1). Clinicians may refer to LCOS for a symptomatic state that ranges from mild myocardial stunning to severe cardiogenic shock with the need for mechanical ventricular assistance. The reported incidence of LCOS varies from 2 to 27% in the adult population (2–8). In the pediatric population reported incidences are between 17 and 67% (9–11).

Most studies describe the occurrence of LCOS, considering the associated morbidity (renal and pulmonary failure, stroke, myocardial infarction, sepsis, and a prolonged length of stay), mortality (up to 38%) and, therefore, increased healthcare costs (2–4, 6, 8, 12).

In order to properly address the features of LCOS that make it a potentially serious complication and to reduce its occurrence and seriousness, it is of crucial importance to study the syndrome. However, despite the obvious interest in LCOS from a clinical perspective, researchers do not use uniform criteria based on specific thresholds to describe the syndrome (definition) (13, 14). Several therapies have been evaluated for their effect on LCOS and compared in meta-analyses, however LCOS definitions differ among studies varying from the temporary use of a single vasoactive agent to counteract “stunning” to the requirement of mechanical support (15, 16).

The comparison of study findings without the standardization of the LCOS definition including the use of uniform criteria (predefined thresholds) therefore is hampered.

We hypothesized that the variety in operational definitions of LCOS at least partly explains the wide range in reported incidences of LCOS. The primary aim of this study was to evaluate the variety of LCOS definitions described in literature among adult and pediatric cardiac surgery populations and subsequently to examine to what extent these different definitions affect the incidence of intraoperative LCOS.

**Methods**

**Design and conduct of the study**

In this study, we combined a literature review approach with a retrospective cohort study. A study protocol was not published nor registered. The literature review was used to extract LCOS definitions. Subsequently, we applied the definitions found to a retrospective intraoperative cohort, to study the effects of the different definitions on the estimated incidence of LCOS. The cohort included cardiac surgery with cardiopulmonary bypass patients from all ages, i.e., both children and adults.

**Review of the literature**

The following literature search was performed in the PubMed database (17) on August 24th, 2020:

```
(((Low cardiac output syndrome[Title/Abstract]) OR LCOS[Title/Abstract])) AND (((((Surger*) OR Operation*) OR Surgical procedure*) OR operative surgical procedure*) OR operative procedure*)) AND (((Heart) OR cardiac)) OR ((("Heart"[Mesh]) AND "Surgical Procedures, Operative"[Mesh]) OR "Cardiac Surgical Procedures"[Mesh]))).
```

We excluded articles when the full text was not available, those written in non-English language, those including a non-human study population and duplicate papers. We also excluded articles without a definition of LCOS (for example where LCOS was not a main outcome), systematic reviews, case reports, editorials, author’s opinions and letters to the editor. We did not exclude articles based on publication year. The remaining articles were reviewed, the definitions of LCOS were extracted and categorized. We classified the articles on the following items: study population (adult/pediatric/both/questionnaires completed by pediatric Intensive Care Unit (PICU) professionals), reproducibility and scope. Definitions included “inotropes,” “cardiovascular...
mechanical support,” “acidosis,” “cardiac pump function,” “blood pressure,” “clinical signs of hypoperfusion,” “saturation,” “pulmonary capillary wedge pressure,” “renal replacement therapy,” “hemodynamic instable,” “cardiac arrest,” “death,” and “others.” Definitions were listed as reproducible, when they had cut-off values in their definition and when they did not use vague terms without further explanation, such as “a situation, in which circulation and organ perfusion is barely maintained” (18). Detailed information about selection, data extraction, and scoring is provided in Supplementary material 1. Screening, selection and data extraction was done by author AS and in case of uncertainty discussed with KL.

Retrospective cohort study

We listed the 10 most frequently published LCOS definitions and used these to determine the intraoperative incidence of LCOS according to these definitions. The study data were collected from the University Medical Center Utrecht (UMCU; The Netherlands) and the Wilhelmina Children’s hospital, which is part of the UMCU. The UMCU is a tertiary referral hospital for pediatric and adult cardiac surgery. The study population included patients of all ages who underwent cardiac surgery with cardiopulmonary bypass (CPB) between June 2011 and August 2018. Our center performs the full range (Basic Aristotle score 1.5–15) of congenital cardiac surgery, including neonatal Norwood procedures, with an average Basic Aristotle score of 7.06 (SD 2.97). We did not use postoperative intensive care data as the AIMS and intensive care databases were not connected, nor similarly constructed. The Medical Ethics Review committee reviewed the study protocol and waived the need for patient consent (WAG/rgj/18/022047).

We collected the following variables: age, gender, weight, height, type of surgery, surgical urgency, duration of CPB, vital parameters, laboratory tests, inotropic drugs administration and in-hospital mortality. Patient characteristics, laboratory tests and in-hospital mortality were obtained from the Electronic Medical Record system (HX 5.2, ChipSoft, Amsterdam, The Netherlands). Intraoperative data were obtained from the anesthesia information management system (AIMS) database (Anstat, Carepoint, Ede, The Netherlands). The first postoperative laboratory test results of lactate, arterial pH, arterial oxygen saturation, mixed venous oxygen saturation and central venous oxygen saturation were used. Variables extracted from the AIMS database were stored as median per minute values during the intraoperative period. These variables included intraoperative vital signs, anesthesia ventilator data and data on inotropic use. For the vital parameters and inotropic drugs, we used the mean, timeframes, or limits defined otherwise of all variables stored in the AIMS after the patients were weaned from the CPB. We used the 50th percentile of the national growth charts to estimate the height of children, because the documentation of this variable was unreliable (19). We considered other missing data to occur under the “missing not at random” condition as cardiac vascular monitoring and treatment is initiated based on clinical indication. Therefore, no further missing data assumptions were made.

The primary outcome was the difference in incidence of LCOS. We applied the 10 most frequently reported LCOS definitions to the data obtained to determine the incidences. To calculate LCOS incidences, we used the total population as the denominator (i.e., the patients with and without missing data) to prevent biased estimates due to selective missingness of data. When LCOS definitions were built with “OR” condition statements (e.g., “the use of inotropes OR mechanical support”), patient data were considered missing only if all parts of the statement could not be filled in (e.g., in this case, patient data were only considered missing if there was no data available on the use of inotropes AND no data on mechanical support).

As secondary outcome, we compared incidences between adults (≥18 years), children (≥6 months and <18 years) and infants (<6 months). We chose 6 months as cut-off point between infants and children, because maturation of the human heart is completed at 6 months of age, anatomically (remodeling of pulmonary blood flow and closure of the foramen ovale, ductus venosus and ductus arteriosus), histologically (growth of mitochondria numbers, myofibrils numbers and sarcomere volume and development the sarcoplasmatic reticulum) and physiologically (increasing the coronary oxygen supply and preload due to a decreased heart rate) (20).

Statistical analysis

The statistical analysis was performed with R-studio software, version 1.1.456 (21). Continuous variables are presented as means ± standard deviations (SD) or when skewness or kurtosis was observed, as medians with interquartile ranges (IQR). Categorical variables are presented as proportions.

Results

Literature search

The literature search identified 964 records that were handled as presented in Figure 1. Ultimately, 250 articles were included (Supplementary material 2). In five of these articles multiple definitions were used (5 (15), 5 (9), 2 (22), 3 (23) and 2 (24), respectively), initially resulting in a total of 262 definitions.

Of the 262 included definitions, 177 (68%) focused on adult surgery, 80 (31%) focused on pediatric surgery and 5 (2%) used information gained by questionnaires completed by pediatric ICU professionals as study population. Of the 262 definitions, 175 definitions (67%) were reproducible, i.e., definitions were
Literature search. LCOS, low cardiac output syndrome.

clearly described and used cut-off values, and 87 definitions (33%) were not. Twelve items were repeatedly used within the LCOS definitions, namely: the use of inotropes; mechanical support; metabolic acidosis; cardiac pump function; blood pressure; clinical signs of hypoperfusion; saturation; pulmonary capillary wedge pressure (PCWP); renal replacement therapy; clinical judgement; cardiac arrest and death (Table 1). The definition of LCOS in studies among adults more often included need for mechanical support and cardiac pump function, while definitions used in pediatric studies more often included metabolic acidosis and clinical signs of hypoperfusion (Table 1).

The need of inotropes was used in the definition in 71 and 61% of the articles including adult and pediatric cardiac surgery patients, respectively. There were four different ways in which inotropes were used in definitions, namely: (1) the duration of inotrope administration; (2) the specific inotropic drug used (epinephrine, norepinephrine, dopamine, dobutamine and milrinone); (3) the Vasoactive-Inotropic Score (VIS), a formula that quantifies the amount of cardiovascular support (25, 26); and (4) the number of used inotropes (Table 1). In studies involving the adult population, the cut-off value for the duration of inotrope administration in LCOS definitions was shorter (median 2.0 h) than for the studies involving the pediatric population (median 24.0 h). Compared to the pediatric population, in studies including adults, the inotropic drug was more often specified (25 vs. 9%) and VIS and the number of inotropes used were less likely used in the definition (1 vs 16%, and 7 vs 24%, respectively).

Cohort study

Between June 2011 and August 2018, 7,366 patients underwent cardiac surgery with cardiopulmonary bypass. The cohort included 5,934 (80.6%) adults, 690 (9.4%) children and 742 (10.1%) infants (Table 2). In all groups, there were more males than females. In adults, coronary artery bypass grafting (CABG) was the most frequently performed procedure. Repairs for atrial septal defects and ventricle septal defects were performed most frequently in the pediatric and infant group, respectively. Adults and infants had a higher in-hospital mortality rate than children: 3.1, 3.0, and 0.7%, respectively.

Incidences of low cardiac output syndrome

We used the complete cohort (5,934 adults, 690 children, 742 infants) as denominator within the LCOS incidence calculation for the 10 most frequently published definitions. Tables 3, 4 show the number of patients available to count the LCOS cases in the numerator. We were unable to calculate the incidences for all
TABLE 1 Variables used in low cardiac output syndrome definitions.

| Definition                                                                 | Definitions in a study with an adult study population, n (%) | Definitions in a study with a pediatric study population, n (%) | Definitions in a study where PICU workers were interviewed, n (%) |
|----------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| No. of definitions                                                        | 177 (100)                                                    | 80 (100)                                                     | 5 (100)                                                      |
| Reproducible                                                              | 135 (76)                                                     | 39 (49)                                                      | 1 (20)                                                       |
| Duration of the use of inotropes                                          | 126 (71)                                                     | 49 (61)                                                      | 3 (60)                                                       |
| Type of inotropes                                                         | 69 (39)                                                      | 7 (8.8)                                                      | 0 (0.0)                                                      |
| VIS                                                                       | 45 (25)                                                      | 7 (8.8)                                                      | 0 (0.0)                                                      |
| Number of used inotropes                                                  | 2 (1.1)                                                      | 13 (16)                                                     | 0 (0.0)                                                      |
| Mechanical support                                                        | 13 (7.3)                                                     | 19 (24)                                                      | 3 (60)                                                       |
| ECMO                                                                      | 11 (6.2)                                                     | 6 (7.5)                                                      | 0 (0.0)                                                      |
| IABP                                                                      | 80 (45)                                                      | 2 (2.5)                                                      | 0 (0.0)                                                      |
| VAD                                                                       | 5 (2.8)                                                      | 2 (2.5)                                                      | 0 (0.0)                                                      |
| Not specified                                                              | 14 (7.9)                                                     | 8 (10)                                                      | 0 (0.0)                                                      |
| Metabolic acidosis                                                        | 11 (6.2)                                                     | 51 (64)                                                     | 3 (60)                                                       |
| High lactate                                                              | 7 (4.0)                                                      | 38 (48)                                                     | 1 (20)                                                       |
| High base difference                                                      | 0 (0.0)                                                      | 13 (16)                                                     | 0 (0.0)                                                      |
| Low pH                                                                    | 0 (0.0)                                                      | 4 (5.0)                                                      | 0 (0.0)                                                      |
| Low bicarbonate                                                           | 0 (0.0)                                                      | 3 (3.8)                                                      | 0 (0.0)                                                      |
| Cardiac pump function                                                     | 115 (65)                                                     | 16 (20)                                                      | 0 (0.0)                                                      |
| Low CI                                                                    | 114 (64)                                                     | 9 (11)                                                      | 0 (0.0)                                                      |
| Low ejection fraction                                                     | 1 (0.6)                                                      | 6 (7.5)                                                      | 0 (0.0)                                                      |
| Blood pressure                                                            | 115 (65)                                                     | 16 (20)                                                      | 0 (0.0)                                                      |
| Low systolic blood pressure                                               | 58 (33)                                                      | 7 (8.8)                                                      | 0 (0.0)                                                      |
| Low mean arterial pressure                                                | 5 (2.8)                                                      | 4 (5.0)                                                      | 0 (0.0)                                                      |
| Low central venous pressure                                               | 4 (2.3)                                                      | 2 (2.5)                                                      | 0 (0.0)                                                      |
| High systemic vascular resistance                                         | 4 (2.3)                                                      | 2 (2.5)                                                      | 0 (0.0)                                                      |
| Clinical signs of hypoperfusion                                           | 9 (5.6)                                                      | 2 (2.5)                                                      | 0 (0.0)                                                      |
| Oliguria                                                                  | 20 (11)                                                      | 43 (54)                                                     | 2 (40)                                                       |
| Tachycardia                                                               | 4 (2.3)                                                      | 33 (41)                                                     | 3 (60)                                                       |
| Cold extremities                                                          | 16 (9.0)                                                     | 35 (44)                                                     | 2 (40)                                                       |
| Altered mental state                                                      | 10 (5.6)                                                     | 2 (2.5)                                                      | 0 (0.0)                                                      |
| Clammy skin                                                               | 4 (2.3)                                                      | 0 (0.0)                                                      | 0 (0.0)                                                      |
| Others                                                                    | 14 (7.9)                                                     | 3 (3.8)                                                      | 0 (0.0)                                                      |
| Decreased oxygen saturation                                               | 11 (6.2)                                                     | 28 (35)                                                     | 1 (20)                                                       |
| High difference between arterial and venous saturation                    | 3 (1.7)                                                      | 0 (0.0)                                                      | 0 (0.0)                                                      |
| Low arterial oxygen pressure                                              | 5 (5.1)                                                      | 10 (13)                                                     | 0 (0.0)                                                      |
| PCWP                                                                      | 16 (9.0)                                                     | 0 (0.0)                                                      | 0 (0.0)                                                      |
| Renal replacement therapy                                                 | 2 (1.1)                                                      | 1 (1.3)                                                      | 0 (0.0)                                                      |
| Clinical judgement                                                        | 9 (5.1)                                                      | 1 (1.3)                                                      | 0 (0.0)                                                      |
| Cardiac arrest                                                            | 5 (5.1)                                                      | 12 (15)                                                     | 1 (20)                                                       |
| Death                                                                     | 2 (1.1)                                                      | 6 (7.5)                                                      | 0 (0.0)                                                      |
| Other                                                                     | 9 (5.1)                                                      | 9 (11)                                                      | 0 (0.0)                                                      |

PICU, pediatric intensive care unit; VIS, vasoactive-inotropic score; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; VAD, ventricle assistant device; CI, cardiac index; PCWP, pulmonary capillary wedge pressure.
TABLE 2 Patient demographics and baseline characteristics.

|                          | Adults (N = 5,934) | Children (N = 690) | Infants (N = 742) |
|--------------------------|--------------------|--------------------|-------------------|
| Male sex, n (%)          | 4,136 (70)         | 368 (53)           | 432 (58)          |
| Age, median (IQR)        | 66 (56–73) years   | 3.0 (1.8–9.0) years | 2.0 (0.0–4.0) months |
| Body surface area, median (IQR) | 1.96 (1.8–2.1) | 0.8 (0.5–1.1) | 0.3 (0.2–0.3) |
| Urgency of surgery, n (%) |                    |                    |                   |
| Elective                 | 5,383 (91)         | 677 (98)           | 710 (96)          |
| Emergency                | 551 (9.3)          | 13 (1.9)           | 32 (4.3)          |
| Reoperation, n (%)       | 255 (4.3)          | 90 (13)            | 121 (16)          |
| Type of surgery, n (%)   |                    |                    |                   |
| CABG                     | 2,462 (41.5)       | ASD surgery 135 (19.6) | Combined congenital surgery 160 (21.6) |
| MV surgery 304 (5.1)     | VSD surgery 87 (12.6) | VSD surgery 118 (15.9) |
| Thoracic aortic surgery 201 (3.4) | Repair of anomalous pulmonary venous connection 71 (10.3) | Arterial switch operation 62 (8.4) |
| CABG and AV surgery 475 (8.0) | Combined congenital surgery 82 (11.9) | Tetralogy of Fallot 91 (12.3) |
| Duration of operation (min), median (IQR) | 282 (239–351) | 247 (197–310) | 282 (230–337) |
| Length of CPB (min), median (IQR) | 107 (78–158) | 68 (48–114) | 113 (72–147) |
| Need of MCS, n (%)       | 316 (53.3)         | 4 (0.6)            | 3 (0.4)           |
| 30-day mortality, n (%)  | 182 (3.1)          | 5 (0.7)            | 22 (3.0)          |

*Reoperation was defined as any patient, who had more than one cardiac surgery in our institution between June 2011 and August 2018.

**In this table we only show the five most frequently performed procedures.

IQR, interquartile range; CABG, coronary artery bypass grafting; AV, aortic valve; MV, mitral valve; ASD, atrial septum defect; VSD, ventricle septum defect; PV, pulmonary valve; min, minutes; CPB, cardiopulmonary bypass; MCS, mechanical circulatory support.

We found 171 different definitions and using the 10 most frequently reported ones resulted in an estimated incidence of intraoperative LCOS ranging from 1.5%—91% and 0.6%—56% in adults and in children, respectively. To the best of our knowledge, this is the first article to focus on the description and use of different LCOS definitions.

Low cardiac output syndrome, caused by an inadequate cardiac pump function, is a serious complication after cardiac surgery with high morbidity and mortality (2–4, 6, 8, 12). Far-reaching scientific interest in different kinds of interventions and their effect on LCOS have resulted in numerous publications on the subject. Many studies used the incidence of LCOS as a primary outcome. Although the criteria used to define LCOS were reported in most articles, these were frequently not reproducible (34%) and most articles did not explain why specific criteria were chosen. This resulted in the use of pluriform criteria to define the syndrome. In our study, we found a striking total of 171 different variations to define LCOS. Furthermore, we noticed that definitions used also greatly differed between the adult and pediatric populations. Our study demonstrated that the definition of LCOS is a very important explanatory determinant for the reported incidence of LCOS.

Currently, there is no uniform definition of LCOS, despite the presumed importance that clinicians use the same language...
and the generalizability of future scientific evaluations of new therapies. Therefore, we question whether LCOS should be used to describe an inadequate cardiac pump function after surgery without taking the necessary step toward uniformity. A uniform definition ensures that there will be fewer reasoning errors, misunderstandings, unnecessary controversies or problems in comparing scientific results. We argue that a good definition should be reproducible, generally valid among different populations and measurements should be as less invasive as possible (minimizing the risk of side effects). Abstract concepts, vague terminology and measurements without cut-off values result in unreproducible definitions with an immediate effect on the incidence rate of a certain outcome like LCOS. From our literature review, 34% of the definitions were not reproducible, due to lack of cut-off values or vague terminology. None reproducible criteria hamper generalizability of findings and re-evaluation of study results. Furthermore, definitions should preferably not rely on invasive monitoring technology that is only used in high risk populations, especially if there are good alternatives without those consequences. For example, the pulmonary capillary wedge pressure was frequently used in the definitions of LCOS (10% of the articles with an adult cardiac population). A Pulmonary Artery Catheter gives an inherent risk of mechanical, thrombotic, and infectious complications (93, 94) and is therefore only used in complex cardiac cases. These practical issues bias the incidence of LCOS as a significant part of the study population never adheres to the criteria because PCWP or CI were not routinely measured. Also, PCWP and CI were not measured in children because of technical impossibilities and the unavailability of validated monitoring equipment for pediatric use.

Another interesting finding of this study is the apparent difference between definitions used in adults and children. These differences elicit the question whether we are describing two different disease entities with maybe also a different biochemical origin. For LCOS in adults, studies used the items “mechanical support” and “cardiac pump function” more often, whereas in children, studies frequently used the items “metabolic acidosis” and “clinical signs of hypoperfusion.” Although it needs no explanation that pediatric patients differ from adult cardiac surgery patients, in both settings a valid definition for post-bypass inadequate cardiac pump function or LCOS is valuable and may contribute to the generalizability of scientific work.

Our study certainly has some limitations. First, our literature review was executed in PubMed and other databases were not searched for, and we thus might have missed relevant
TABLE 4 Top 10 most published definitions of Low Cardiac Output Syndrome (LCOS) and corresponding incidence rates in an intraoperative cohort with adults, children and infants.

Top 10 LCOS definitions (see Table 3 for definitions)

| Adults (N = 5,934) | Children (N = 690) | Infants (N = 742) |
|--------------------|--------------------|-------------------|
| No. of patients without missing data | Incidence LCOS in % | No. of patients without missing data | Incidence LCOS in % | No. of patients without missing data | Incidence LCOS in % |
| 1  | 400 | 1.5 | 0 | – | 0 | – |
| 2* | 5,667 | 8.3 | 516 | 23.8 | 534 | 30.1 |
| 3* | 5,667 | 31.5 | 516 | 27.4 | 534 | 32.3 |
| 4  | 2,049 | 12.3 | 688 | 5.1 | 739 | 16.3 |
| 5** | – | – | – | – | – | – |
| 6* | 3,365 | 13.7 | 542 | 6.4 | 571 | 14.4 |
| 7  | 0 | – | 0 | – | 0 | – |
| 8  | 414 | 1.8 | 0 | – | 0 | – |
| 9  | 5,934 | 91.0 | 690 | 55.7 | 742 | 82.2 |
| 10 | 5,934 | 4.5 | 690 | 0.6 | 742 | 0.4 |

* For systolic hypotension and tachycardia we used for children and infants the p-values (91, 92). The p5 for systolic hypotension and p90 for tachycardia.

** Intensive care follow-up data was not available (e.g., maximum duration of inotropic support). Hence, we could not determine the incidence of LCOS using this definition.

LCOS, low cardiac output syndrome.

publications, and we did not publish nor register the study protocol. Second, this is retrospective review of a single-center experience and so this implicates that we could not track down the reasons behind inotropic use, mechanical support and others. We also had to assume the association between the therapeutic interventions and vital parameters measured which might limit generalizability. Third, we did not have any information about observations like cold extremities or altered state of mind, as we used intraoperative data and these were uncommonly observed and documented in the AIMS. As a result, we expressed the clinical signs of hypoperfusion solely with tachycardia and oliguria. Fourth, we had missing data for some of the items in the LCOS definitions that were time dependent. We only used intra-operative data, collected from our AIMS and no postoperative follow-up data, while the peak incidence of LCOS is expected 6–12 h after cardiac surgery. For that reason also, we were unable to calculate the incidence of LCOS in one of the 10 most frequently published definitions, that used inotropic support for 24 h after cardiac surgery as criterion. These limitations may cause under- and/or overestimations of the incidence of LCOS. However, because our primary outcome was the difference in incidence of LCOS using different definitions, we still report these numbers to show the effect different definitions have on the incidence. Finally, most definitions are also applicable during postoperative admission. We did not collect data about decreased cardiac indices or decreased systolic blood pressures at the ICU, which may be considered as a major limitation of our study. However, this study should not be used as a reference for LCOS occurrence after cardiac surgery, because we mainly aimed to illustrate the effect of the absence of a uniform LCOS definition in daily practice. Our study results could additionally serve to compare different age groups.

We suggest that consensus should be reached about a reproducible and practical LCOS definition within and between the international scientific societies. Prospective research that evaluates this universal LCOS definition would help to understand the features and occurrence of the syndrome in adults, children and infants. Furthermore, studies (95) in which LCOS is precursor for poor outcome, would enable the use of LCOS as a useful surrogate endpoint.

Conclusion

This study collected different definitions of LCOS and evaluated how they influenced estimations of the intraoperative incidence of LCOS in adults, children and infants. From the 171 different kind of definitions found, we used the 10 most frequently published and applied these to a large sized cohort including patients from all ages. We calculated LCOS incidence estimates ranging form 0.4 to 91%. We would like to advocate for standardization of the LCOS definition to improve clinical understanding and enable adequate comparison of outcomes and treatment effects both in daily care and in research.
Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AS and KvL contributed to conception and design of the study, performed the statistical analysis and wrote the first draft of the manuscript. LvW contributed to the thorough review and rewriting of the manuscript draft. All authors contributed to manuscript revision, read and approved the submitted version.

Funding

WK is supported by the R. Fraser Elliott Chair in Cardiac Anesthesia (Toronto, ON, Canada).

References

1. Lomivorotov VV, Efremov SM, Kirov MY, Fominsky EV, Karasakov AM. Low-cardiac-output syndrome after cardiac surgery. J Cardiothorac Vasc Anesth. (2017) 31:291–308. doi: 10.1053/j.ctva.2016.05.029
2. Maganti M, Badiwala M, Sheikh A, Scully H, Feindel C, David TE, et al. Predictors of low cardiac output syndrome after isolated mitral valve surgery. J Thorac Cardiovasc Surg. (2010) 140:790–6. doi: 10.1016/j.jtcs.2009.11.022
3. Algarni KD, Maganti M, Yau TM. Predictors of low cardiac output syndrome after isolated coronary artery bypass surgery: trends over 20 years. Ann Thorac Surg. (2011) 92:1678–84. doi: 10.1016/j.athoracsur.2011.06.017
4. Rao V, Ivanov J, Weisel RD, Ikonomidou SJ, Christakos GT, David TE. Predictors of low cardiac output syndrome after coronary artery bypass. J Thorac Cardiovasc Surg. (1996) 112:38–51. doi: 10.1016/S0022-5223(96)70176-9
5. Osawa EA, Rhodes A, Landoni G, Galas FRBG, Fukushima JT, Park CHL, et al. Effect of perioperative goal-directed hemodynamic resuscitation therapy on outcomes following cardiac surgery: a randomized controlled trial and systematic review. Crit Care Med. (2016) 44:724–33.
6. Hogae CW, Sundt T, Barzilai B, Schuchman KB, Davila-Román VG. Cardiac and neurologic complications identify risks for mortality for both men and women undergoing coronary artery bypass graft surgery. Anesthesiology. (2001) 95:1074–8. doi: 10.1097/00000542-200111000-00008
7. Algarni KD, Weisel RD, Caldarone CA, Maganti M, Tsang K, Yau TM. Microplegia during coronary artery bypass grafting was associated with less low cardiac output syndrome: a propensity-matched comparison. Ann Thorac Surg. (2013) 95:1532–8. doi: 10.1016/j.athoracsur.2012.09.056
8. Maganti MD, Rao V, Borger MA, Ivanov J, David TE. Predictors of low cardiac output syndrome after isolated aortic valve surgery. Circulation. (2005) 112(9 Suppl) I448–52. doi: 10.1161/CIRCULATIONAHA.104.526087
9. Flores S, Cooper DS, Opoka AM, Iliopoulos I, Pflueckebaum S, Alder MN, et al. Characterization of the glucocorticoid receptor in children undergoing cardiac surgery. Pediatr Crit Care Med. (2018) 19:705–12. doi: 10.1097/PCC.0000000000001572
10. Cavigelli-Brunner A, Hug MI, Dave H, Baeninger O, Rueck C, Bettex D, et al. Prevention of low cardiac output syndrome after pediatric cardiac surgery: a double-blind randomized clinical pilot study comparing dobutamine and milrinone. Pediatr Crit Care Med. (2018) 19:619–25. doi: 10.1097/PCC.0000000000001553
11. Buero PW, Romolo H, Sastrosamoro S, Rachmat J, Sadakin M, Santoso A, et al. Role of terminal warm blood cardioplegia in complex congenital heart surgery. Asian Cardiovasc Thorac Ann. (2018) 26:196–202. doi: 10.1177/0218492318793910
12. Michalopoulos A, Trellep G, Pavlides G, Kriaras J, Dafini U, Gerosalou S. Determinants of duration of ICU stay after coronary artery bypass graft surgery. Br J Anaesth. (1996) 77:208–12. doi: 10.1093/bja/77.2.208
13. Hummel J, Rücker G, Stiller B. Prophylactic levosimendan for the prevention of low cardiac output syndrome and mortality in paediatric patients undergoing surgery for congenital heart disease. Cochrane Database Syst Rev. (2017) 8:CD011312. doi: 10.1002/14651858.CD011312.pub3
14. Burkhardt REU, Rücker G, Stiller B. Prophylactic milrinone for the prevention of low cardiac output syndrome and mortality in children undergoing surgery for congenital heart disease. Cochrane Database Syst Rev. (2015) 2015:CD009515. doi: 10.1002/14651858.CD009515.pub2
15. Iliopoulos I, Alder MN, Cooper DS, Villareal EG, Loomba R, Sahay RD, et al. Pre-operative neutrophil-lymphocyte ratio predicts low cardiac output in children after cardiac surgery. Cardiol Young. (2020) 30:521–5. doi: 10.1017/S1047951120000487
16. Manso PH, Carmona F, Dal-Pizzol F, Petronilho F, Cardoso F, Castro M, et al. Oxidative stress markers are not associated with outcomes after pediatric heart surgery. Paediatr Anaesth. (2013) 23:188–94. doi: 10.1111/pan.12040
17. US National Library of Medicine National Institutes of Health. PubMed - NCBI gov.
18. Ok YJ, Lim JY, Jung SH. Critical illness-related corticosteroid insufficiency in patients with low cardiac output syndrome after cardiac surgery. Korean J Thorac Cardiovasc Surg. (2018) 51:109–13. doi: 10.5090/KJTCVS.2018.51.2.109
19. Talma H, Schönhäck Y, Bakker B, Hirasing RA, van Buuren S. Groothoed: Nederlandse Jongens 6-4 Jaar; Nederlandse Meisjes 6-4 Jaar. Nederlandse Jongens 21 Jaar; Nederlandse Meisjes 21 Jaar. Leiden: TNOKwaltijd van Leven (2011). p. 42–64.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.926957/full#supplementary-material
59. Miecz A, Fiorani B, Danesi TH, Melina G, Sinatra R. Prophylactic intra-aortic balloon pump in high-risk patients undergoing coronary artery bypass grafting: a meta-analysis. *Interact Cardiovasc Thorac Surg.* (2009) 9:291–4. doi: 10.1053/j.ijcts.2008.11.1605

60. Rao V, Ivanov J, Weisel RD, Cohen G, Borger MA, Mickle DAG. Lactate release during reperfusion predicts low cardiac output syndrome after coronary bypass surgery. *Ann Thorac Surg.* (2001) 71:1925–30. doi: 10.1016/S0003-4975(01)02634-0

61. Lio A, Bovio E, Nicolì F, Saitto G, Scafuri A, Bassano C, et al. Influence of body mass index on outcomes of patients undergoing surgery for acute aortic dissection: a propensity-matched analysis. *Tex Heart Inst J.* (2019) 46:7–13. doi: 10.14503/THI-17.2636

62. Garcia-Fuster R, Estevé V, Gil O, Cánovas S, Martínez-Leon J. Mitral valve replacement in rheumatic patients: effects of chordal preservation. *Ann Thorac Surg.* (2008) 86:472–81. doi: 10.1016/j.athoracsur.2008.02.043

63. Hogue CW, Palin CA, Kalilasm R, Lawton J, Nassif A, Dávila-Román VG, et al. C-reactive protein levels and atrial fibrillation after cardiac surgery in women. *Ann Thorac Surg.* (2016) 23:919–23. doi: 10.1093/icvts/ivw251

64. García-Fuster R, Estevé V, Gil O, Cánovas S, Martínez-Leon J. Mitral valve replacement in rheumatic patients: effects of chordal preservation. *Ann Thorac Surg.* (2008) 86:472–81. doi: 10.1016/j.athoracsur.2008.02.043

65. Hogue CW, de Wet CJ, Schechtman KB, Dávila-Román VG. The importance of prior stroke for the adjusted risk of neurologic injury after cardiac surgery for women and men. *Anesthesia* (2003) 98:823–9. doi: 10.1111/j.1399-6576.2003.tb01360.x

66. Hogue CW, Murphy SF, Schechtman KB, Dávila-Román VG. Risk factors for early or delayed stroke after cardiac surgery. *Circulation.* (1999) 100:642–7. doi: 10.1161/01.CIR.100.6.642

67. Nordness MJ, Westrick AC, Chen H, Clay MA. Identification of Low cardiac output syndrome at the bedside: a pediatric cardiac intensive care unit survey. *Crit Care Nurs Clin North Am.* (2019) 31:199–7. doi: 10.1016/j.ccrn.2019.07.001

68. Favia I, Rizza A, Garito C, Haiberger R, di Chiara L, Romagnoli S, et al. Cardiac index assessment by the pressure recording analytical method in infants after paediatric cardiac surgery: a pilot retrospective study. *Interact Cardiovasc Thorac Surg.* (2016) 23:919–23. doi: 10.1093/icvts/ivw251

69. Pagowska-Klimek I, Swierko AS, Michalki M, Moll M, Szaló-Podzięzyńska A, Sokolowska A, et al. Activation of the lectin pathway of complement by cardiopulmonary bypass contributes to the development of systemic inflammatory response syndrome after paediatric cardiac surgery. *Clin Exp Immunol.* (2016) 184:257–63. doi: 10.1111/cei.12763

70. Pagowska-Klimek I, Swierko AS, Michalki M, Moll M, Szaló-Podzięzyńska A, Sokolowska A, et al. Manose-binding lectin (MBL) insufﬁciency protects against the development of systemic inﬂammatory response after pediatric cardiac surgery. *Immunology* (2016) 122:175–81. doi: 10.1111/imj.2015.9.010

71. Bailey JM, Hoffman TM, Wessel DL, Nelson DP, Atz AM, Chang AC, et al. A population pharmacokinetic analysis of milrinone in pediatric patients after cardiac surgery. *J Pharmacokinet Pharmacodyn.* (2004) 31:43–59. doi: 10.1023/B:JOPA.0000029488.45177.48

72. Hoffmann TM, Wernovsky G, Atz AM, Bailey JM, Alkbury A, Kocos FJ; Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics. *Am Heart J.* (2012) 164:225–7. doi: 10.1016/j.ahj.2012.01.005

73. Michalopoulos A, Stavridis G, Gruelovolas S. Severe sepsis in cardiac surgical patients. *Eur J Cardiothorac Surg.* (2008) 33:355–60. doi: 10.1016/j.ejcts.2007.10.053

74. Burgos LM, Gil Ramírez A, Seoane I, Espinoza J, Formento JE, Costabel JP, et al. Is the Obesity paradox in cardiac surgery really a myth? Effect of body mass index on early and late clinical outcomes. *J Cardiothorac Vasc Anesth.* (2016) 39:492–4. doi: 10.1053/j.jvca.2015.12.034

75. Boher H, Schmidt H, Motsch J, Gust R, Bach A, Martin E. Reoperative coronary artery bypass grafting versus non-deep hypothermic beating heart strategy: Hyperthermic circulatory arrest versus non-deep hypothermic beating heart strategy. *Eur J Cardiothorac Surg.* (2014) 45:678–84. doi: 10.1093/ejcts/ezu053

76. Kim BJ, Kim YS, Kim HJ, Ju MH, Kim JB, Jung SH, et al. Concomitant mitral valve surgery in patients with moderate ischemic mitral regurgitation undergoing coronary artery bypass grafting. *Thorac Dis.* (2018) 10:3632–42. doi: 10.21037/thoracdis.2018.05.148

77. Mourad F, Cleve N, Nowak J, Wendt D, Sander A, Demircioglu E, et al. Long-term single-center outcomes of patients with chronic renal dialysis undergoing cardiac surgery. *Ann Thorac Surg.* (2020) 109:1442–8. doi: 10.1016/j.athoracsur.2019.08.042

78. Lee WY, Yoo JS, Kim JB, Jung SH, Choi SJO, Chung CH, et al. Outcomes of open surgical repair of descending thoracic aortic disease. *Korean J Thorac Cardiovasc Surg.* (2014) 47:255–61. doi: 10.5090/kjcts.2014.47.3.255

79. Yoo JS, Kim JB, Jung SH, Choi SJO, Chung CH, Lee JW. Surgical repair of descending thoracic and thoracoabdominal aortic aneurysms involving the distal arch: open proximal anastomosis under deep hypothermia versus arch clamping technique. *J Thorac Cardiovasc Surg.* (2014) 148:2101–7. doi: 10.1016/j.jtcvs.2014.06.068

80. Yoo JS, Kim JB, Joo Y, Lee WY, Jung SH, Choi SJO, et al. Deep hypothermic circulatory arrest versus non-deep hypothermic beating heart strategy in descending thoracic or thoracoabdominal aortic surgery. * Eur J Cardiothorac Surg.* (2014) 46:678–84. doi: 10.1093/ejcts/ezu053

81. Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Macnicone I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age. A systematic review of observational studies. *Lancet.* (2011) 377:1011–8. doi: 10.1016/S0140-6736(10)62226-X

82. Rostner B, Cook N, Portmann R, Daniels S, Falkner B. Determination of blood pressure percentiles in normal-weight children. Some methodological issues. *Am J Epidemiol.* (1989) 130:657–66. doi: 10.1093/aje/kw3438

83. Chiang Y, Hosseinian L, Rhee A, Itagaki S, Cavallaro P, Chikwe J. Questionable benefit of the pulmonary artery catheter after cardiac surgery in high-risk patients. *J Cardiothorac Vasc Anesth.* (2015) 29:69–75. doi: 10.1053/j.jvca.2014.07.016

84. Ularte KP, Yanay O, Jeffries H, Baden H, di Gennaro JL, Zimmerman J. An elevated low cardiac output syndrome score is associated with morbidity in infants after congenital heart surgery. *Pediatr Crit Care Med.* (2017) 18:26–33. doi: 10.1097/PCC.0000000000001979