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ORIGINAL RESEARCH

Accuracy and precision of minimally-invasive cardiac output monitoring in children: a systematic review and meta-analysis

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Abstract Several minimally-invasive technologies are available for cardiac output (CO) measurement in children, but the accuracy and precision of these devices have not yet been evaluated in a systematic review and meta-analysis. We conducted a comprehensive search of the medical literature in PubMed, Cochrane Library of Clinical Trials, Scopus, and Web of Science from its inception to June 2014 assessing the accuracy and precision of all minimally-invasive CO monitoring systems used in children when compared with CO monitoring reference methods. Pooled mean bias, standard deviation, and mean percentage error of included studies were calculated using a random-effects model. The inter-study heterogeneity was also assessed using an I^2 statistic. A total of 20 studies (624 patients) were included. The overall random-effects pooled bias, and mean percentage error were 0.13 ± 0.44 l min^{-1} and 29.1 %, respectively. Significant inter-study heterogeneity was detected ($P < 0.0001$, $I^2 = 98.3$ %). In the sub-analysis regarding the device, electrical cardiometry showed the smallest bias (-0.03 l min^{-1}) and lowest percentage error (23.6 %). Significant residual heterogeneity remained after conducting sensitivity and subgroup analyses based on the various study characteristics. By meta-regression analysis, we found no independent effects of study characteristics on weighted mean difference between reference and tested methods. Although the pooled bias was small, the mean pooled percentage error was in the gray zone of clinical applicability. In the sub-group analysis, electrical cardiometry was the device that provided the most accurate measurement. However, a high heterogeneity between studies was found, likely due to a wide range of study characteristics.

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Keywords Cardiac output · Children · Hemodynamic monitoring · Meta-analysis · Accuracy

1 Introduction

1.1 Rationale

The goal of perioperative hemodynamic management, including cardiac output (CO) optimization, is to ensure adequate oxygen delivery to a patient's tissues. Optimizing this delivery has been proposed as a means for improving perioperative outcomes [1, 2]. Moreover, intraoperatively measuring CO can be useful to quickly detect any hemodynamic perturbations and thus help clinicians to make the most appropriate decisions related to a wide range of interventions such as drug administration and fluid resuscitation. Recently, minimally-invasive cardiac monitoring techniques have been developed in order to measure these valuable parameters with less risk than the pulmonary arterial catheter, although it is still considered the gold standard [3]. While these different minimally invasive CO measurement techniques have been broadly studied in adults, such systematic investigations have been much less common in children, resulting in a gap of clinical application between the two populations. That being said, these minimally-invasive technological approaches have still been examined by various groups using existing references methods such as the pulmonary artery catheter (PAC), Fick principle, and echocardiography [4–6]. Unfortunately, these studies have only examined small cohorts of patients, which has led to a lack of definitive validation, something that is greatly needed for a more widespread acceptance of this technology in children.

1.2 Objective

We conducted a systematic review and meta-analysis of studies comparing minimally-invasive CO monitoring methods with generally accepted reference methods in the pediatric population. The principal outcomes were the accuracy (mean bias) and precision (standard deviation [SD] of the bias) of CO measured by minimally-invasive monitoring compared to that measured by the reference methods. Precision was defined as acceptable if the percentage error was less than 30 % as Critchley and Critchley concluded [7].

2 Methods

We conducted this systematic review and meta-analysis following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Appendix 1) [8].

2.1 Eligibility criteria

The eligibility criteria for the included studies are defined as the following: (1) published studies comparing: CO that was measured using commercially available minimally-invasive CO monitoring systems and CO that measured by an accepted reference method including dilution technique (PAC, transpulmonary thermodilution and pulse dye densitometry), Fick principle, two-dimensional (2D) echo Doppler method, and transit time ultrasound measurements. (2) Studies reporting extractable bias for CO, SD of the bias (or 95 % limits of agreement [LOA]), and mean percentage error between tested and reference method. (3) Studies conducted in children (age <18 years) that report demographic data (age, weight, patient characteristic, study setting, sample size, and data points). (4) Studies performed in the clinical settings (operating room, intensive care unit, catheterization room, and general ward). (5) Studies published as a full paper in English, French and Japanese. (6) If the same study was indexed in multiple databases, only the PubMed version was included. EndNote® software (Version X7.1, Thomson Reuters, New York, NY, USA) was used to filter the duplications between databases. (7) No restriction in publication date.

2.2 Information sources and search

We conducted a comprehensive search of the medical literature in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) from its inception to June 11, 2014, analyzing all manuscripts that assessed the accuracy and precision of minimally-invasive CO monitoring systems in children and were compared with an accepted reference method for measuring CO. Additionally, we searched the Cochrane Library of Clinical Trials (http://onlinelibrary.wiley.com/cochranelibrary/search/), Web of Science (http://apps.webofknowledge.com/) and Scopus (covers all journals included in PubMed/MEDLINE and EMBASE from 1996) (http://www.scopus.com/) to supplement the PubMed results. To establish the search strategy, we created a list of major keywords, MeSH (Medical Subject Headings) terms, and search concepts. We ran the initial search using this list on PubMed and applied the search strategy to the remaining databases with no publication date restriction. We excluded studies that were not performed on children (birth-18 years), were non-English except French and Japanese as coauthors are fluent (n = 493), and were not published as full journal articles focusing on retaining items comprising primary data (e.g., letters, editorials, and conference papers). The following is the PubMed/MEDLINE search strategy.

1. Cardiac output OR heart Output OR stroke volume OR Cardiac index
2. (hemodynamics OR haemodynamic) AND (measurement OR measure OR measured OR measuring OR monitor OR monitoring OR monitored OR monitors OR determined OR determination OR determining OR determine)
3. #1 OR #2
4. (Esophageal OR oesophageal OR espophagus OR oesophagus OR transesophageal OR transoesophageal) AND (Doppler OR ultrasound OR ultrasonography OR sonography OR echocardiography)
5. MRI OR Magnetic Resonance Imaging OR Thermodilution OR Thermodilutions OR Fick principle OR pulmonary artery catheterization OR pulmonary artery catheter OR PAC
6. Electrical cardiometry OR bioimpedance OR Thoracic Electrical Bioimpedance OR pressure recording analytical method OR PRAM OR partial CO2 rebreathing OR waveform analysis OR electrical velocimetry OR ultrasound dilution OR Bioreactance
7. #4 OR #5 OR #6
8. PiCCO OR LiDCO OR Vigileo-FloTrac OR "Vigileo Flo Trac" OR Vigileo OR FloTrac OR MostCare OR Pulsioflex OR Nexfin OR Cardiac Q OR USCOM OR NICOM OR AESCULON OR ECOM OR BioZ OR NICO OR ICON OR COstatus
9. #7 OR #8
10. #3 AND #9
11. Neonates OR neonate OR newborn OR newborns OR infants OR infant OR child OR children OR adolescent OR adolescence OR pediatric OR pediatrics OR paediatric OR paediatrics
12. #11 AND #10
13. #10 Filters: Language: English; French; Japanese; Child: 13–18 years
14. [Note: clear all filters first] (#12 OR #13)
15. Letter OR editorial OR news OR comment OR case reports OR review OR note OR conference
16. #14 NOT #15

Variations of the search strategy for the remaining database are available upon request. In addition to the database search, we contacted the manufacturers of clinically available monitors, PiCCO (Pulsion Medical Systems, Irving, TX, USA), LiDCO (LiDCO Ltd, London, UK), Vigileo-FloTrac (Edwards Lifesciences, Irvine, CA, USA), MostCare (Vytech, Padova, Italy), Pulsioflex (Pulsion Medical Systems, Irving, TX, USA), Nexfin (Edwards Lifesciences, Irvine, CA, USA), CardioQ (Deltex Medical Limited, Chichester, West Sussex, UK), USCOM (USCOM Ltd, Sydney, Australia), NICOM (Cheetah Medical, Tel Aviv, Israel), AESCULON (Osypka Medical, Inc. La Jolla, CA, USA), ECOM (ConMed, Irvine, CA, USA), BioZ (CardioDynamics, San Diego, CA, USA), NICO (Novametrix Medical Systems, Wallingford, CT, USA), ICON (Osypka Medical, Inc. La Jolla, CA, USA), COstatus (Transonic System Inc.,Ithaca, NY, USA) for unpublished studies. We also hand-searched references of included studies to identify additional studies that had not initially been identified through our original database search.

2.3 Study selection

Two investigators (K.S. and A.J.) independently screened the titles and abstracts of all citations for relevance using the eligibility assessment checklist. Abstracts were classified as relevant, potentially relevant, or not relevant. Relevant abstracts were selected for a full review of the article. Abstracts of potentially relevant articles were further examined by the two reviewers. If there were any disagreements between the two on the relevancy, a third reviewer (M.C.) made the final decision. After a full review of 51 studies, only 20 were included in our final review because we could not obtain adequate data to complete the meta-analysis. The study selection process is illustrated in Fig. 1.

2.4 Data-collection process and data items

A data abstraction form was used to record information of the article, including main results of the study (bias, SD of the bias, and percentage error), published year, author(s), sample size, data points, patient characteristics (age, gender, height, weight, type of surgery, and with/without intracardiac shunt), study settings (operating room, intensive care unit, catheterization room, and general ward), tested device (device type and device name), and reference method [dilution technique (PAC, transpulmonary thermodilution, and pulse dye densitometry), Fick principle, 2D echo Doppler method, and transit time ultrasound measurement]. For each study, we examined potential bias through thorough documentation of participants, study design, and inadequate reporting of results. Once this was completed, the reviewers (K.S. and A.J.) summarized the full-text of all relevant articles independently. After both reviewers completed their abstraction forms, consensus between all elements of the two reports was reached. All data were then transferred separately to a standard Excel spreadsheet. The minimum data from each study required to conduct a meta-analysis were mean bias, SD of the bias, and mean percentage error.

In this meta-analysis, the mean percentage error was defined as the following [7].

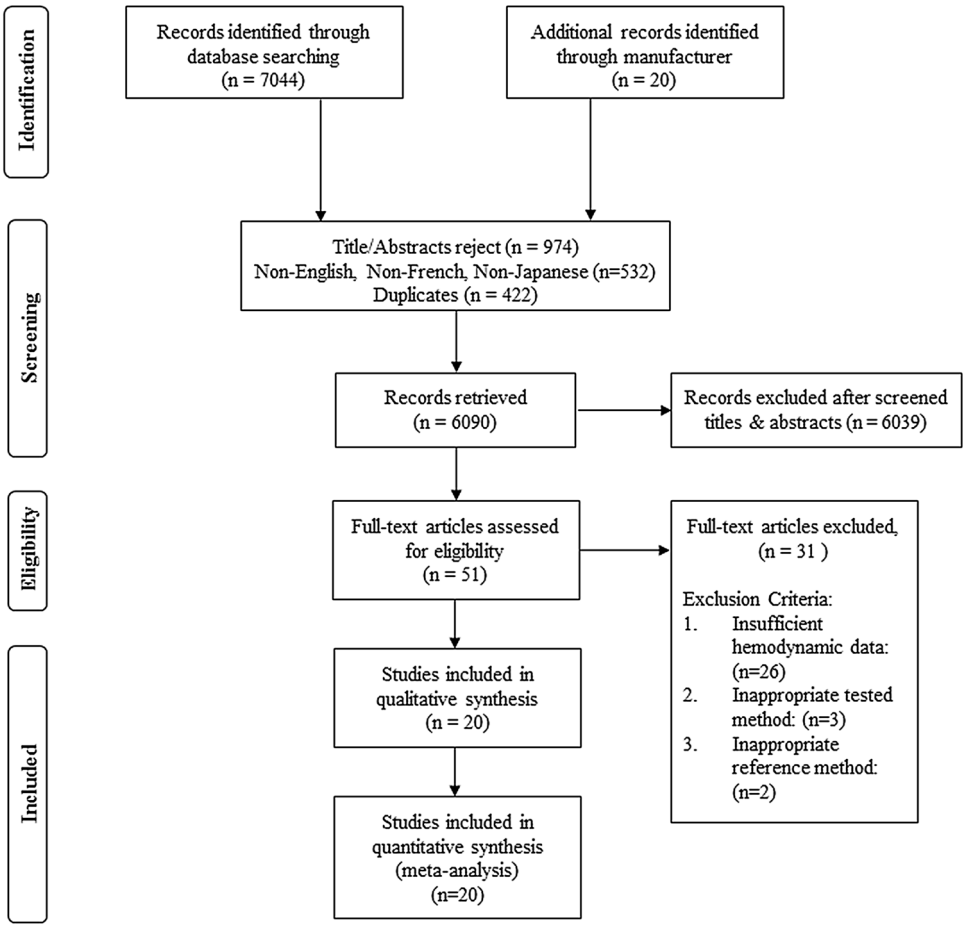

Fig. 1 Flow diagram of the searched process

$$Mean\ percentage\ error = 100 \times 1.96 \times \frac{(SD\ of\ bias\ between\ methods)}{(mean\ CO\ of\ both\ methods)}$$

Mean CO of the reference and tested method was calculated as reported previously [9],

$$Mean\ CO = \sum_{i=0}^{i=N-1} \frac{CO_i \times (n_i - 1)}{\sum_{i=0}^{i=N-1}(n_i - 1)}$$

where CO_i and n_i are the mean CO value of the reference and tested method and number of measurements in study i among N studies, respectively. If a study reported only bias and SD or the mean percentage error was described in a different way, the mean percentage error was recalculated using our definition. We defined the bias as the value of CO measured using the minimally invasive method subtracted from the value of CO measured using the reference method. Once again, if the bias was not presented but necessary data were available the bias was calculated and recorded for each study. Additionally, if a study presented only bias and LOA, SD was calculated as (upper LOA − bias)/1.96. We contacted the authors and ask them to provide the data if their data is insufficient for our meta-analysis.

2.5 Risk of bias in individual studies

For an assessment of the risk of bias in individual studies, we used a modified quality assessment sheet that has been described in two of our previously published meta-analyses [10, 11]. We modified the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) guidelines to focus on method-comparison studies [12]. The quality assessment sheet used in these studies is shown in Appendix 2. The details of the quality assessment sheet were adjusted by K.S., A.J., and M.C. to make it more suitable for our meta-analysis. Initially, a pilot assessment on a set of three papers was conducted independently by two investigators (K.S. and A.J.), and repeated until the assessments by the two investigators became consistent. Subsequently, quality assessment was performed on all included studies using the final modified quality assessment sheet (Appendix 2). As shown, risk for the bias and applicability domains was classified as low, high, and unclear. The disagreement of

the risk between two investigators was resolved by discussion with the third investigator (M.C.).

2.6 Summary measures

Summary measures in our analysis were defined as: (1) accuracy of the tested CO monitoring defined as bias of CO; (2) precision of the tested CO monitoring defined as SD of the bias and the mean percentage error. Mean percentage error was considered to be acceptable if it was less than 30 %, as Critchley and Critchley concluded [7]. We defined the bias and mean percentage error as our primary endpoints.

2.7 Synthesis of results

We utilized random-effects models to make a synthesis of pooled bias and SD, as reported previously [13, 14]. Heterogeneity of bias and SD in included studies was tested using a Q test and shown as an I^2 index (25–50 %: low heterogeneity, 50–75 %: moderate heterogeneity, more than 75 %: high heterogeneity) [15]. When there was moderate or high heterogeneity ($I^2 > 50$ %), sensitivity analysis and meta-regression were performed. Forest plots were created to visualize the data of pooled bias and 2SD.

2.8 Risk of publication bias across studies

Funnel plots were used to assess the publication bias across the included studies. Funnel plot represents the bias of CO against standard error in each study. Egger regression tests were applied to assess the asymmetry of the Funnel plot using a significant level of 0.1 due to the small sample size [16].

2.9 Additional analysis

To assess the causes of heterogeneity, sensitivity analyses were conducted after removing data collected from the studies with high percentage error (>30 %) and high distribution in the SD of the bias (>0.5 l min^{-1}). Additionally, subgroup analyses were conducted based on age (both age ≥1 and age <1 versus only age <1 versus only age ≥1), device (electrical cardiometry versus pulse contour analysis versus ultrasound dilution versus ultrasound Doppler flow), reference method (dilution technique versus Fick principle versus 2D echo Doppler method), setting (operation room versus intensive care unit versus catheterization room versus general ward), invasiveness (invasive versus non-invasive), and intra-cardiac shunt (with intra-cardiac shunt versus without intra-cardiac shunt). Out of the reference methods analyzed in our meta-analysis, the Fick principle, transit time ultrasound method and dye dilution may be more appropriate "gold-standard" methods for the pediatric population when compared to other sources. Therefore we also performed an additional sub-analysis regarding reference method [(Fick principle, dye dilution and transit time ultrasound measurement) versus (thermodilution and two-dimensional echo Doppler method)]. Meta-regression analyses were also conducted to show whether the weighted mean differences between reference and tested methods were modulated by the study characteristics (published year, sample size, intra-cardiac shunt, setting, age, weight, device type, and reference method). We could not conduct a meta-regression analysis regarding gender because of inadequate data.

All the statistical analyses were conducted using Stats Direct version 3.0.121 beta (StatsDirect Ltd, Chesire, UK), StatFlex version 6.0 software (Artech. Co., Ltd, Osaka, Japan), and Microsoft Excel 2010 (Microsoft Corporation). Data are presented as mean ± SD, median ± (Interquartile range [IQR] or range), or bias ± SD. For all analyses, $P < 0.05$ was considered as statistically significant.

3 Results

3.1 Study selection

As of June 11, 2014, we obtained a total of 6090 articles from the database searches and manufactures after removal of duplicates. Next, 6039 studies were excluded by two investigators (K.S. and A.J.) after title and abstract screening. We contacted the authors of the remaining 51 papers and ask them to provide the data if their data is insufficient for our meta-analysis. The authors of three papers gave the data, however the others did not. The name of authors who gave the data are listed in the acknowledgement section. From the remaining 51 full-text papers, 31 papers [17–47]. were excluded after assessing for more detailed eligibility. The reasons for exclusion are shown in Appendix 3. Finally, the remaining 20 studies [4–6, 48–64]. were included in the meta-analysis (Fig. 1).

3.2 Study characteristics

A total of 624 patients were included. Notably, one study [61] had two different groups of patients (healthy children and children with congenital heart disease) and was therefore divided into two separate groups resulting in a total of 21 groups (from 20 studies) being included in the final analysis. All groups had small sample sizes (median 28, range 7–64). Among them, 12 studies [4, 6, 48–50, 52, 53, 57, 59–61, 63] had large distributions of age (including both age less than 1 year and more than 1 year). Regarding the clinical setting, the study by Lindberg et al. [60] was

done both in the operating room and the intensive care unit. Among the remaining 19 studies, five were conducted in the operating room [52, 53, 61–63], seven in the intensive care unit [4–6, 51, 56, 57, 64], five in the catheterization room [48–50, 54, 59], and two [55, 58] were conducted in a general ward. Electrical cardiometry [50, 52, 55, 56, 58, 61, 63] was most frequently used, followed by pulse contour analysis [4, 6, 53, 62], ultrasound dilution [54, 57, 59, 60], ultrasound Doppler flow [48, 49, 51, 64], and partial CO_2 rebreathing method [5]. In the reference methods, seven were conducted using dilution technique [4, 48, 49, 52–54, 62], three using the Fick principle [50, 57, 59], nine using 2D echo Doppler method [5, 6, 51, 55, 56, 58, 61, 63, 64], and one using transit time ultrasound measurement [60]. Patient characteristics of included studies are shown in Table 1.

3.3 Risk of bias in individual studies

The results of quality assessment of included studies are shown in Appendix 4. The study by Linton et al. [4] was at high risk of bias in the flow and timing domains. The remaining 19 studies were at low risk in all domains.

3.4 Synthesis of results

Bias, 95 % LOA, and percentage error for the included studies are shown in Fig. 2. The overall random-effects pooled bias and percentage error were 0.13 ± 0.44 l min^{-1} (95 % LOA: -0.74 to 0.99 l min^{-1}) and 29.1 %, respectively. Significant inter-study heterogeneity was detected for both bias ($P < 0.0001$, $I^2 = 98.3$ %) and SD ($P < 0.0001$, $I^2 = 99.9$ %).

3.5 Risk of publication bias across studies

Funnel plot to detect the risk of publication bias across the included studies is shown in Fig. 3. Egger regression test showed no significant P value ($P = 0.518$).

3.6 Additional analysis

3.6.1 Sensitivity and subgroup analyses

Sensitivity analysis after deletion of the data from high percentage error (>30 %) studies [4, 5, 48–53, 55, 57, 61–64] did not reduce heterogeneity across studies ($I^2 = 93.6$ %). Also, significant residual heterogeneity was found in the sensitivity analysis after removal of the data from the studies [5, 48, 49, 51–53, 58, 62–64] with high distribution of SD (>0.5 l min^{-1}) of the bias ($I^2 = 97.0$ %). The results of subgroup analyses are shown in Table 2. Moreover, we continued to find significant residual heterogeneity after conducting subgroup analysis based on the various study characteristics (age, device, reference method, settings, invasiveness, and intra-cardiac shunt).

3.6.2 Subgroup analysis by age

Specific age distribution was not mentioned in one study [64] and therefore deleted from the subgroup analysis by age. Appendix 5 shows the results from this subgroup analysis; group 1: patients of both age less than 1 year and more than 1 year, group 2: patients of age less than 1 year, and group 3: patients of age more than 1 year. The pooled mean bias and percentage error were 0.07 ± 0.44 l min^{-1} and 32.1 %, 0.08 ± 0.08 l min^{-1} and 33.2 %, and 0.14 ± 0.66 l min^{-1} and 31.8 % for groups 1, 2, and 3, respectively. We still found high heterogeneity after subgroup analysis accounting for age distribution.

3.6.3 Subgroup analysis by device type

In Appendix 6, the results of the subgroup analysis by device type are shown. The pooled mean bias and percentage error were -0.03 ± 0.33 l min^{-1} and 23.6 % for electrical cardiometry, 0.32 ± 0.64 l min^{-1} and 33.0 % for pulse contour analysis, 0.04 ± 0.32 l min^{-1} and 30.3 % for ultrasound dilution, and 0.10 ± 0.90 l min^{-1} and 53.4 % for ultrasound Doppler flow. There was still high heterogeneity after subgroup analysis accounting for device type.

3.6.4 Subgroup analysis by reference method

The results of the subgroup analysis by reference method (dilution technique versus Fick principle versus 2D echo Doppler method) are shown in Appendix 7. The pooled mean bias and percentage error were 0.15 ± 0.79 l min^{-1} and 41.5 % for dilution technique, 0.06 ± 0.34 l min^{-1} and 37.9 % for Fick principle, and 0.13 ± 0.37 l min^{-1} and 24.4 % for 2D echo Doppler method. We also performed a sub-analysis with respect to reference method (Fick principle, dye dilution and transit time ultrasound measurement versus thermodilution and two-dimensional echo Doppler method), the results of which are shown in the Table 2. However, the heterogeneity was still high after subgroup analysis accounted for reference method.

3.6.5 Meta-regression

Meta-regression coefficients were not statistically significant when analyzing published year, sample size, intra-

Table 1 Summary of included studies

References	Device type	Device name	Sample size	Patient characteristics	Setting	Age, mean (SD) or median [IQR* or range]	Gender M/F	Reference method	Bias ± SD (l min^{-1})	PE (%)
Linton et al. [4]	Pulse contour analysis	LiDCO	17	ICU patients	ICU	1.3 [3 weeks–9 years]	N.A.	PICCO	0.1 ± 0.31	31.8
Botte et al. [5]	Partial CO_2 rebreathing	NICO	21	ICU patients	ICU	7.89 years [2.9–16.8 years]	12/9	2D echo Doppler method	0.61 ± 0.94	43.1
Calamandrei et al. [6]	Pulse contour analysis	Mostcare	48	ICU patients	ICU	19 months [1–204 months]	29/19	2D echo Doppler method	0.12 ± 0.27	20.4
Knirsch et al. [48]	Ultrasound Doppler flow	USCOM	24	Cardiac catheterization	CR	7.6 years [0.1–16.7 years]	N.A.	PAC	−0.13 ± 0.67	36.4
Knirsch et al. [49]	Ultrasound Doppler flow	CardioQ	40	Cardiac catheterization	CR	8.2 years [0.5–16.7 years]	18/22	PAC	0.66 ± 0.91	54.3
Norozi et al. [50]	Electrical cardiometry	AESCULON	32	Cardiac catheterization	CR	0.675 year [0.03–17.8 years]	N.A.	Fick principle	−0.01 ± 0.23	33.1
Schubert et al. [51]	Ultrasound Doppler flow	CardioQ	26	Post-cardiac surgery	ICU	3.5 years [1–17.5 years]	13/14	2D echo Doppler method	0.36 ± 0.85	78.0
Tomaske et al. [52]	Electrical cardiometry	AESCULON	50	Cardiac catheterization	OR	7.5 years [0.5–16.5 years]	22/28	PAC	0.66 ± 0.76	44.7
Teng et al. [53]	Pulse contour analysis	FloTrac	31	Cardiac catheterization	OR	9 [0.66–16 years]	19/12	PAC	2.7 ± 2.8	84.2
Crittendon et al. [54]	Ultrasound dilution	COstatus	28	Cardiac catheterization	CR	8 years [1–17 years]	14/14	PAC	−0.004 ± 0.4	25.4
Noori et al. [55]	Electrical cardiometry	AESCULON	20	Healthy neonates	GW	1 day	10/10	2D echo Doppler method	0.004 ± 0.12	43.7
Weisz et al. [56]	Electrical cardiometry	NICOM	10	NICU patients	NICU	Neonates	3/7	2D echo Doppler method	0.15 ± 0.06	25.8
Floh et al. [57]	Ultrasound dilution	COstatus	35	Post-cardiac surgery	ICU	147 days [11–216 days]*	N.A.	Fick principle	0 ± 0.38	97
Rauch et al. [58]	Electrical cardiometry	ICON	64	Obese children	GW	12.5 years [7.9–17.6 years]	28/36	2D echo Doppler method	−0.15 ± 0.53	20.3
Boehne et al. [59]	Ultrasound dilution	COstatus	26	Cardiac catheterization	CR	6.2 years [8 months–17 years 4 months]	18/8	Fick principle	0.26 ± 0.47	25.9
Lindberg et al. [60]	Ultrasound dilution	COstatus	21	Cardiac surgery	OR/ ICU	8.1 months [6 days–27 months]	N.A.	TTU	−0.02 ± 0.15	29.7
Sun et al. [61]	Electrical cardiometry	NICOM	28	General surgery	OR	24.0 months [6.5–36.0 months]*	17/11	2D echo Doppler method	0.03 ± 0.20	22.4
	Electrical cardiometry	NICOM	32	General surgery	OR	18.0 months [10–36 months]*	22/10	2D echo Doppler method	0.31 ± 0.44	45.1
Terada et al. [62]	Pulse contour analysis	esCCO	7	Kidney transplant surgery	OR	9.4 years (3.1 years)	4/3	Dye dilution	−0.27 ± 0.91	37.5
Vergnaud et al. [63]	Electrical cardiometry	NICOM	30	Neurosurgery	OR	50.0 months (43.0 months)	N.A.	2D echo Doppler method	−0.11 ± 0.67	56.9
Wongsirimetheekul et al. [64]	Ultrasound Doppler flow	USCOM	34	ICU patients	ICU	7.86 years (5.78 years)	15/19	2D echo Doppler method	−0.53 ± 1.23	59.3

N.A. not available, *SD* standard deviation, *IQR* interquartile range, *PE* percentage error, *ICU* intensive care unit, *2D* two-dimensional, *OR* operating room, *CR* catheterization room, *PAC* pulmonary artery catheter, *NICU* neonatal intensive care unit, *GW* general ward, *TTU* transit time ultrasound measurement

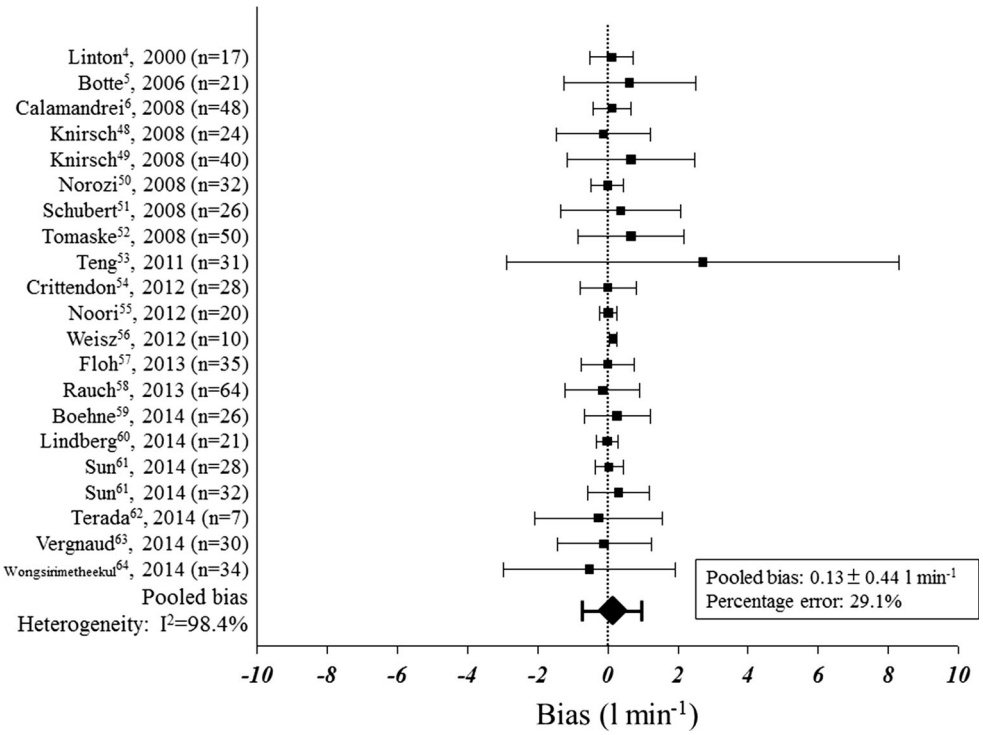

Fig. 2 Forest plot showing the bias, 95 % limit of agreement, and *percentage error* for the included studies. The overall random-effects pooled bias, and percentage error were 0.13 ± 0.44 l min^{-1} (95 % limit of agreement: -0.74 to 0.99 l min^{-1}) and 29.1 %, respectively. Significant inter-study heterogeneity was detected for both bias ($P < 0.0001$, $I^2 = 98.3$ %) and SD ($P < 0.0001$, $I^2 = 99.9$ %)

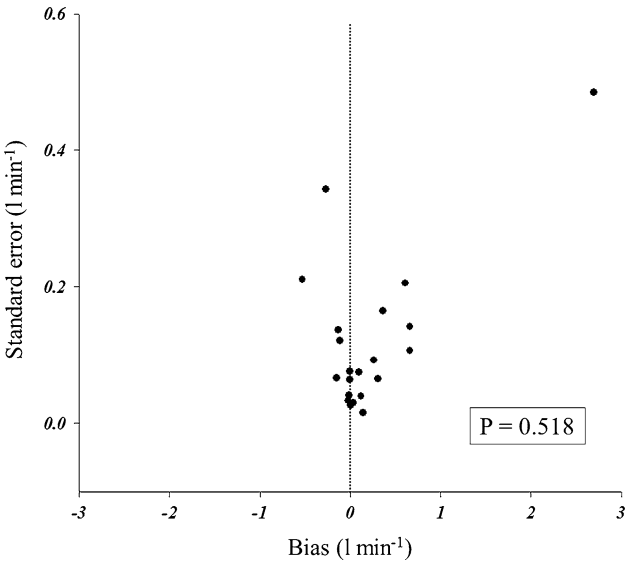

Fig. 3 Funnel plot to detect the risk of publication bias across the included studies. Egger regression test showed no significant *P* value ($P = 0.518$)

cardiac shunt, setting, age, gender, weight, device type, and reference method. There were no independent effects of study characteristics on weighted mean differences between reference and tested methods. We continued to find significant residual heterogeneity after conducting meta-regression analysis based on the above study characteristics.

4 Discussion

4.1 Summary of evidence

Our meta-analysis of 20 studies assessing the accuracy and precision of minimally-invasive CO monitoring systems compared with the reference methods shows that the overall random-effects pooled bias and percentage error of CO was 0.13 ± 0.44 l min^{-1} and 29.1 %, respectively. There was significant inter-study heterogeneity for both mean bias and SD. In the sub-group analysis regarding device type, electrical cardiometry demonstrated the lowest percentage error. After removing the data obtained from studies with high percentage errors and large distributions of bias SD, we continued to find high inter-study heterogeneity. Additionally, heterogeneity continued to remain high even after the subgroup analysis by age, device, reference method, settings, invasiveness, and intra-cardiac shunt.

The goal of the current meta-analysis was to provide an overall evaluation of the agreement between minimally-invasive CO monitoring systems and reference methods. CO monitoring has been shown to provide clinicians with beneficial information which leads to improved understanding of hemodynamic status, cardio-respiratory interactions, and assessment of possible hemodynamic interventions [65]. Unfortunately, pediatric specific evidence examining the benefits of CO monitoring in critically ill children is still limited. A low CO state is associated with increased mortality, although it has not been directly proven whether

Table 2 Subgroup analysis by study characteristics

	Number of groups	Number of patients	Bias ± SD (l min^{-1})	95 % LOA (l min^{-1})	Percentage error (%)	I^2 (%)	
						Bias	SD
By age							
Including both age ≥1 and <1	13	414	0.07 ± 0.44	−0.78 to 0.93	32.1	97.5	99.5
Age < 1	2	30	0.08 ± 0.08	−0.09 to 0.24	33.2	85.8	85
Age ≥ 1	5	146	0.14 ± 0.66	−1.15 to 1.43	31.8	79.2	91.5
By device							
Electrical cardiometry	8	266	−0.03 ± 0.33	−0.67 to 0.61	23.6	98.1	99.5
Pulse contour analysis	4	103	0.32 ± 0.64	−0.94 to 1.58	33	89.9	97.3
Ultrasound dilution	4	110	0.04 ± 0.32	−0.59 to 0.66	30.3	63.6	96.7
Ultrasound blood flow	4	124	0.10 ± 0.90	−1.66 to 1.87	53.4	89.7	85.7
By reference method							
Dilution technique	7	197	0.15 ± 0.79	−1.40 to 1.70	41.5	96.2	98.4
Fick principle	3	93	0.06 ± 0.34	−0.61 to 0.73	37.9	59.4	90.5
2D echo Doppler method	10	313	0.13 ± 0.37	−0.59 to 0.86	24.4	96.7	99.6
Fick principle + TTU + dye dilution	5	121	−0.01 ± 0.32	−0.63 to 0.61	34.8	92.4	98.4
Thermodilution + 2D echo Doppler	16	503	0.13 ± 0.49	−0.83 to 1.09	29.6	97.9	99.8
By settings							
Operation room	7	199	0.26 ± 0.51	−0.75 to 1.27	34.0	96.5	99.1
Intensive care unit	8	212	0.10 ± 0.37	−0.63 to 0.83	31.2	95.8	99.6
Catheterization room	5	150	0.19 ± 0.51	−0.81 to 1.19	33.1	91.8	98.8
General ward	2	84	−0.05 ± 0.27	−0.58 to 0.47	13.2	35.8	97.8
By invasiveness							
Invasive monitoring	7	206	0.09 ± 0.37	−0.63 to 0.81	25.5	93.8	98.8
Non-invasive monitoring	14	418	0.22 ± 0.48	−0.73 to 1.17	31.2	98.1	99.7
By intra-cardiac shunt							
With intra-cardiac shunt	4	111	0.12 ± 0.29	−0.45 to 0.69	28.8	89.1	95.6
Without intra-cardiac shunt	17	513	0.11 ± 0.47	−0.82 to 1.04	29	97.9	99.9

SD standard deviation, *LOA* limit of agreement, *2D* two-dimensional, *TTU* transit time ultrasound measurement

correcting poor CO will improve outcomes [66]. Currently, various approaches to CO monitoring in adults have been developed and validated. These include PAC with thermodilution, the Fick principle, trans-pulmonary thermodilution, and, more recently, minimally-invasive techniques based on electrical cardiometry, ultrasound Doppler, and pulse contour analysis [67]. Similar to pediatric outcome analysis, there is still only a small number of studies assessing the accuracy and precision of CO monitoring in pediatric patients. This assessment is the first step in creating an environment where advanced, minimally invasive, CO monitoring can be consistently used in such a vulnerable population. Many cardiac monitoring devices used as reference methods in adults have specific limitations and risks for use in children, such as size and technical constraints, inappropriate algorithms, and a higher incidence of complications [68]. For example, the Fick principle may be unreliable due to commonly uncuffed endotracheal tubes and PAC with thermodilution may be difficult to use due to size limitations. Therefore, in critically ill children, a more reliable, accurate, and safer CO monitoring solution would be a potentially significant contribution to the field. In this study, the pooled percentage error was calculated as 29.1 %, which is within the acceptable limit of 30 %, and is actually lower compared to the previous meta-analysis of CO monitoring in adults [9, 69]. However, based on our results, physicians should remain cautious when making clinical decisions about hemodynamic interventions based on these technologies, as the pooled percentage error is in the gray zone of clinical applicability (around the acceptable limit of 30 %) and there was significant heterogeneity due to a wide range of study characteristics.

In the sub-group analysis, electrical cardiometry (8 studies) is the only approach to demonstrate a small bias (−0.03 l min^{-1}) and relatively low percentage error (23.6 %). Electrical cardiometry is simple, safe, and completely non-invasive technology which has been validated with acceptable reliability in critically ill adults [70, 71].

When used in adults for goal-directed therapy, it has been shown to perform similarly to the more widely accepted esophageal Doppler [72]. However, despite obviously being the most accurate technology in our meta-analysis, electrical cardiometry is of very limited value in the operating room, given the interference with electrocauterization. Additionally, a high heterogeneity was observed in the electrical cardiometry subgroup, which may be caused by the various study characteristics (patient characteristics, study setting and reference method). Therefore, additional validation of electrical cardiometry in the pediatric population is still necessary for the confident clinical application of this technology.

As with most studies of this design, translating our findings directly to the clinical settings may be difficult. However, our findings may have implications for the possible design of future CO monitoring studies in pediatric patients. The included studies in our meta-analysis have a large age-distribution and a wide variation of patient characteristics, which likely lead to a large CO distribution. Of note, the included studies have a variety of reference methods. The significant degree of heterogeneity found in the pooled analysis, even with specific subgroup analyses, suggests that the included studies may have multiple methodological differences in study characteristics including age, weight, settings, device type, reference method, and the presence of intra-cardiac shunt. However, as Kim et al. [11] pointed out in several published meta-analyses [73, 74], including method comparison studies, similar high heterogeneity was found without a discernible cause in spite of strong statistical analyses. Considering this, the established approach to assessing heterogeneity in meta-analysis, including method-comparison studies, may have contributed to the high heterogeneity. In the present meta-analysis, the use of different devices and reference methods in different patient populations is likely contributing to the overall variation. Our results suggested that standardization of data collection and analysis in studies about CO monitoring in children are required to obtain meaningful results which can have an impact on patient care.

4.2 Limitations

First, in the present meta-analysis, there is a mixture of different devices, different reference methods, and a variety of patients' characteristics. However, we did subgroup analyses of age, device, reference method, settings, invasiveness, and the presence of intra-cardiac shunt, and found similar results with the overall analysis. The high heterogeneity existing even after sensitivity, subgroup, and meta-regression analyses may be associated with this mixture of different study characteristics. Second, searching in a variety of databases with different search interfaces could lead to different search results. In addition, Scopus does not include MeSH terms. Furthermore, we excluded papers which were not published as full journal articles in order to focus on retaining items comprising primary data. Consequently, all except one of the included papers were at low risk of bias in our quality assessment. Third, in this meta-analysis, we focused on the CO values, not cardiac index (CI) values. As mentioned earlier, the included studies have a wide range of age and weight, which leads to a large CO distribution, and therefore the CI value would appear to be better than CO value to assess accuracy and precision. However, many validation studies about minimally-invasive CO monitoring in children have used CO values rather than CI values, and we could not find enough studies using CI values for meta-analysis. Hence, in this meta-analysis, we utilized CO value and percentage error was calculated to evaluate the results. Fourth, the reference methods included in our meta-analysis have limitations of accuracy and precision. For example, both thermodilution using PAC and CO measurements using 2D echo Doppler method have known precision errors secondary to inter- and intra-observer variability. However, as shown in the previous paper [75], there was a good correlation between CO measured by thermodilution and Fick principle (correlation coefficient >0.8 in 8 papers). Also, in pediatric patients, CO measured by thermodilution technique has shown a low bias and percentage error compared with Fick principle (0.03 l min^{-1} and 19.4 % by Tibby et al. [45], and 0.06 l min^{-1} and 10.8 % by Pauli et al. [37], respectively). Therefore, in this meta-analysis, we include the thermodilution method as a reference method. Similarly, as shown by Chew and Poelaert [76], the precision of pediatric Doppler CO measurements compared to Fick principle, dye dilution and thermodilution is around 30 % with a bias of less than 10 % in the majority of studies. Using the criteria suggested by Critchley and Critchley [7], the accuracy and precision is near the acceptable limit. Hence, 2D echo Doppler method was also included as a reference method. As such, we must recognize this limitation of accuracy of precision in the reference methods. An additional sub-analysis regarding reference method [(Fick principle, dye dilution and transit time ultrasound measurement) versus (thermodilution and two-dimensional echo Doppler method)] was done, because Fick principle, transit time ultrasound measurement and dye dilution may be more appropriate "gold-standard" methods for pediatric population. However, the results were similar with other sub-group analyses and the heterogeneity was still high after this additional subgroup analysis.

Finally, in our meta-analysis, we focused on the accuracy and precision of CO monitoring in pediatric patients, and did not assess the clinical outcomes. In adults, some meta-analyses focused on the clinical outcomes and

complications by hemodynamic interventions using CO monitoring devices [77, 78]. However, in pediatric patients, few meta-analyses have been conducted focusing on the CO measurement, and, to the best of our knowledge, this is the first published paper of meta-analysis assessing the accuracy and precision of minimally-invasive CO monitoring in pediatric population. Further studies are needed to assess the clinical outcomes by conducting hemodynamic interventions using CO monitoring in children.

5 Conclusions

In the present meta-analysis, we found that the overall random-effects pooled bias, and percentage error were 0.13 ± 0.44 l min^{-1} (95 % LOA: -0.74 to 0.99 l min^{-1}), and 29.1 %, respectively. Although the bias was small, the pooled percentage error was in the gray zone (around the acceptable limit of 30 %). Additionally, our results demonstrated a high heterogeneity and a lack of standardization in the way these studies were conducted, and also suggest that when conducting further validation studies of CO monitoring in pediatric population, researchers should standardize the study characteristics including the reference method and patient characteristics in order to obtain meaningful results. Physicians should be careful when making clinical decisions regarding hemodynamic interventions using CO monitoring in children.

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Compliance with ethical standards

Conflict of interest This study does not have any potential conflicts of interest, including no commercial relationships such as consultation or equity interests. Maxime Cannesson is a consultant for Edwards Lifesciences (Irvine, CA), Covidien (Boulder, CO), Masimo Corp. (Irvine, CA), Gauss Surgical (Palo Alto, CA), and Philips Medical System (Suresnes, France). Maxime Cannesson has equity position in Sironis.

Appendix 1

See Table 3.

Table 3 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist

Section/topic	Checklist item
Title	
Title	Identify the report as a systematic review, meta-analysis, or both
Abstract	
Structured summary	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number
Introduction	
Rationale	Describe the rationale for the review in the context of what is already known
Objectives	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)
Methods	
Protocol and registration	Indicate if a review protocol exists, if and where it can be accessed, and, if available, provide registration information including registration number
Eligibility criteria	Specify study characteristics and report characteristics used as criteria for eligibility, giving rationale
Information sources	Describe all information sources in the search and date last searched
Search	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated
Study selection	State the process for selecting studies
Data collection process	Describe method of data extraction from reports and any processes for obtaining and confirming data from investigators
Data items	List and define all variables for which data were sought and any assumptions and simplifications made

Table 3 continued

Section/topic	Checklist item
Risk of bias in individual studies	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis
Summary measures	State the principal summary measures
Synthesis of results	Describe the methods of handling data and combining results of studies, if done, including measures of consistency for each meta-analysis
Risk of bias across studies	Specify any assessment of risk of bias that may affect the cumulative evidence
Additional analyses	Describe methods of additional analyses, if done, indicating which were prespecified
Results	
Study selection	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram
Study characteristics	For each study, present characteristics for which data were extracted and provide the citations
Risk of bias within studies	Present data on risk of bias of each study and, if available, any outcome level assessment
Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot
Synthesis of results	Present results of each meta-analysis done, including confidence intervals and measures of consistency
Risk of bias across studies	Present results of any assessment of risk of bias across studies
Additional analysis	Give results of additional analyses, if done
Discussion	
Summary of evidence	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups
Limitations	Discuss limitations at study and outcome level, and at review-level
Conclusions	Provide a general interpretation of the results in the context of other evidence, and implications for future research
Funding	
Funding	Describe sources of funding for the systematic review and other support; role of funders for the systematic review

Reproduced from Liberati et al. [8]

Appendix 2

See Table 4.

Table 4 Quality assessment sheet

Risk of bias is judged as "low," "high," or "unclear." If the answers to all signaling questions for a domain are "yes," then risk of bias can be judged low. If any signaling question is answered "no," potential for bias exists. Review authors must then use the guidelines developed in phase 2 to judge risk of bias. The "unclear" category should be used only when insufficient data are reported to permit a judgment			
Patient selection			
Risk of Bias: Could the Selection of Patients Have Introduced Bias? (Two No = High, Unclear: 2 unclear, 1 No + 1 unclear)	Low	High	Unclear
Signaling question 1: Were subject population of interest and demographic data described?	Yes	No	Unclear
Signaling question 2: Were inclusion and exclusion criteria clearly described?	Yes	No	Unclear
Applicability: Are There Concerns That the Included Patients and Setting Do Not Match the Review Question?	Low	High	Unclear
Index test (Tested method for cardiac output monitoring)			
Risk of Bias: Could the Conduct or Interpretation of Tested Method for Cardiac Output Monitoring Have Introduced Bias?	Low	High	Unclear
Signaling question 1: Was the tested method for cardiac output measurements described clearly (Were calibration, position, and characteristics of monitoring device described clearly?)	Yes	No	Unclear
Applicability: Are There Concerns That the Tested Method for Cardiac Output Monitoring, Its Conduct, or Its Interpretation Differ From the Review Question?	Low	High	Unclear

Table 4 continued

Reference standard (Reference method for cardiac output monitoring)			
Risk of Bias: Could the Reference Method for Cardiac Output Monitoring, Its Conduct, or Its Interpretation Have Introduced Bias?	Low	High	Unclear
Signaling question 1: Is the reference method for cardiac output monitoring likely to correctly measure cardiac output?	Yes	No	Unclear
Applicability: Are There Concerns That the Target Condition as Defined by the Reference Method for Cardiac Output Monitoring Does Not Match the Question?	Low	High	Unclear
Flow and timing			
Risk of Bias: Could the analysis of Flow and Timing Have Introduced Bias? (Unclear: $\geq$ 2 unclear, 1 No + 1 unclear) (High: $\geq$ 2 No), Not applicable = Yes	Low	High	Unclear
Signaling question 1: Were number of patients enrolled and who dropped out clearly described in the result?	Yes	No	Unclear
Signaling question 2: Was the tested method and reference method for cardiac output monitoring measured simultaneously?	Yes	No	Unclear
Signaling question 3: Were the method of acquiring paired measurements well described?	Yes	No	Unclear
Signaling question 4: In case of repeated measurements of cardiac output in patients, did they use statistical analysis for agreement between methods of measurement with multiple observations per individual?	Yes	No	Unclear
Signaling question 5: In the case of the bias being described in both the manuscript and figures, do they match, i.e. both are (tested method minus reference method) or both are (reference method minus tested method)	Yes	No	Not applicable

Appendix 3: List of 31 excluded studies

1. Alverson DC, Eldridge M, Dillon T, Yabek SM, Berman W, Jr. Noninvasive pulsed Doppler determination of cardiac output in neonates and children. J Pediatr 1982;101:46–50.
   Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
2. Braden DS, Leatherbury L, Treiber FA, Strong WB. Noninvasive assessment of cardiac output in children using impedance cardiography. Am Heart J 1990;120:1166–72.
   Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
3. Fakler U, Pauli C, Balling G, Lorenz HP, Eicken A, Hennig M, Hess J. Cardiac index monitoring by pulse contour analysis and thermodilution after pediatric cardiac surgery. J Thorac Cardiovasc Surg 2007;133:224–8.
   Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
4. Ficial B, Finnemore AE, Cox DJ, Broadhouse KM, Price AN, Durighel G, Ekitzidou G, Hajnal JV, Edwards AD, Groves AM. Validation study of the accuracy of echocardiographic measurements of systemic blood flow volume in newborn infants. J Am Soc Echocardiogr 2013;26:1365–71.
   Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
5. Garisto C, Favia I, Ricci Z, Romagnoli S, Haiberger R, Polito A, Cogo P. Pressure recording analytical method and bioreactance for stroke volume index monitoring during pediatric cardiac surgery. Paediatr Anaesth 2014, in press.
   Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
6. Gentles TL, Neutze JM, Caulder AL, Greene ER. Cardiac output measurements in congenital heart disease—Validation of a simple, portable Doppler method. Journal of Ultrasound in Medicine 2001;20:365–70.
   Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
7. Gergely M, Ablonczy L, Kramer S, Szekely EA, Sapi E, Gal J, Szatmari A, Szekely A. Comparison of transpulmonary thermodilution, transthoracic echocardiography and conventional hemodynamic monitoring in neonates and infants after open heart surgery: a preliminary study. Minerva Anestesiol 2012;78:1101–8.
   Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
8. Grollmuss O, Demontoux S, Capderou A, Serraf A, Belli E. Electrical velocimetry as a tool for measuring cardiac output in small infants after heart surgery. Intensive Care Med 2012;38:1032–9.
   Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
9. Grollmuss O, Gonzalez P. Non-invasive cardiac output measurement in low and very low birth weight infants: a method comparison. Front Pediatr 2014;2:16.
   Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).

10. Introna RP, Pruett JK, Crumrine RC, Cuadrado AR. Use of transthoracic bioimpedance to determine cardiac output in pediatric patients. Crit Care Med 1988;16:1101–5.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
11. Jain S, Allins A, Salim A, Vafa A, Wilson MT, Margulies DR. Noninvasive Doppler ultrasonography for assessing cardiac function: can it replace the Swan-Ganz catheter? Am J Surg 2008;196:961–7.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
12. Kim JJ, Dreyer WJ, Chang AC, Breinholt JP, 3rd, Grifka RG. Arterial pulse wave analysis: An accurate means of determining cardiac output in children. Pediatr Crit Care Med 2006;7:532–5.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
13. Levy RJ, Chiavacci RM, Nicolson SC, Rome JJ, Lin RJ, Helfaer MA, Nadkarni VM. An evaluation of a noninvasive cardiac output measurement using partial carbon dioxide rebreathing in children. Anesth Analg 2004;99:1642–7.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
14. McLuckie A, Murdoch IA, Marsh MJ, Anderson D. A comparison of pulmonary and femoral artery thermodilution cardiac indices in paediatric intensive care patients. Acta Paediatr 1996;85:336–8.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
15. Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: comparison with simultaneous thermodilution. Pediatr Cardiol 1987;8:241–6.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
16. Morrow WR, Murphy DJ, Jr., Fisher DJ, Huhta JC, Jefferson LS, Smith EO. Continuous wave Doppler cardiac output: use in pediatric patients receiving inotropic support. Pediatr Cardiol 1988;9:131–6.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
17. Murdoch IA, Marsh MJ, Tibby SM, McLuckie A. Continuous haemodynamic monitoring in children: use of transoesophageal Doppler. Acta Paediatr 1995;84:761–4.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
18. Nguyen HB, Banta DP, Stewart G, Kim T, Bansal R, Anholm J, Wittlake WA, Corbett SW. Cardiac index measurements by transcutaneous Doppler ultrasound and transthoracic echocardiography in adult and pediatric emergency patients. J Clin Monit Comput 2010;24:237–47.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
19. Notterman DA, Castello FV, Steinberg C, Greenwald BM, O'Loughlin JE, Gold JP. A comparison of thermodilution and pulsed Doppler cardiac output measurement in critically ill children. J Pediatr 1989;115:554–60.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
20. Patel N, Dodsworth M, Mills JF. Cardiac output measurement in newborn infants using the ultrasonic cardiac output monitor: an assessment of agreement with conventional echocardiography, repeatability and new user experience. Arch Dis Child Fetal Neonatal Ed 2011;96:F206–11.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
21. Pauli C, Fakler U, Genz T, Hennig M, Lorenz HP, Hess J. Cardiac output determination in children: equivalence of the transpulmonary thermodilution method to the direct Fick principle. Intensive Care Med 2002;28:947–52.
Reason: The tested method is not suitable for our present meta-analysis.
22. Pianosi P, Garros D. Comparison of impedance cardiography with indirect Fick (CO2) method of measuring cardiac output in healthy children during exercise. Am J Cardiol 1996;77:745–9.
Reason: The reference method is not suitable for our meta-analysis.
23. Rein AJ, Hsieh KS, Elixson M, Colan SD, Lang P, Sanders SP, Castaneda AR. Cardiac output estimates in the pediatric intensive care unit using a continuous-wave Doppler computer: validation and limitations of the technique. Am Heart J 1986;112:97–103.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
24. Saxena R, Durward A, Puppala NK, Murdoch IA, Tibby SM. Pressure recording analytical method for measuring cardiac output in critically ill children: a validation study. Br J Anaesth 2013;110:425–31.
Reason: The reference method is not suitable for our meta-analysis.
25. Song R, Rich W, Kim JH, Finer NN, Katheria AC. The Use of Electrical Cardiometry for Continuous Cardiac Output Monitoring in Preterm Neonates: A Validation Study. Am J Perinatol 2014, in press.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).
26. Taylor K, La Rotta G, McCrindle BW, Manlhiot C, Redington A, Holtby H. A comparison of cardiac

output by thoracic impedance and direct fick in children with congenital heart disease undergoing diagnostic cardiac catheterization. J Cardiothorac Vasc Anesth 2011;25:776–9.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
27. Taylor K, Manlhiot C, McCrindle B, Grosse-Wortmann L, Holtby H. Poor accuracy of noninvasive cardiac output monitoring using bioimpedance cardiography [PhysioFlow(R)] compared to magnetic resonance imaging in pediatric patients. Anesth Analg 2012;114:771–5.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
28. Tibballs J. A comparative study of cardiac output in neonates supported by mechanical ventilation: measurement with thoracic electrical bioimpedance and pulsed Doppler ultrasound. J Pediatr 1989;114:632–5.
Reason: Insufficient hemodynamic data (The data of cardiac output are not shown).
29. Tibby SM, Hatherill M, Marsh MJ, Morrison G, Anderson D, Murdoch IA. Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. Intensive Care Med 1997;23:987–91.
Reason: The tested method is not suitable for our analysis.
30. Wippermann CF, Huth RG, Schmidt FX, Thul J, Betancor M, Schranz D. Continuous measurement of cardiac output by the Fick principle in infants and children: Comparison with the thermodilution method. Intensive Care Medicine 1996;22:467–71.
Reason: The tested method is not suitable for our analysis.
31. Wippermann CF, Schranz D, Huth R, Zepp F, Oelert H, Jungst BK. Determination of cardiac output by an angle and diameter independent dual beam Doppler technique in critically ill infants. Br Heart J 1992;67:180–4.
Reason: Insufficient hemodynamic data (The percentage error cannot be obtained from the data).

Appendix 4

See Table 5.

Table 5 Results of quality assessment of included studies

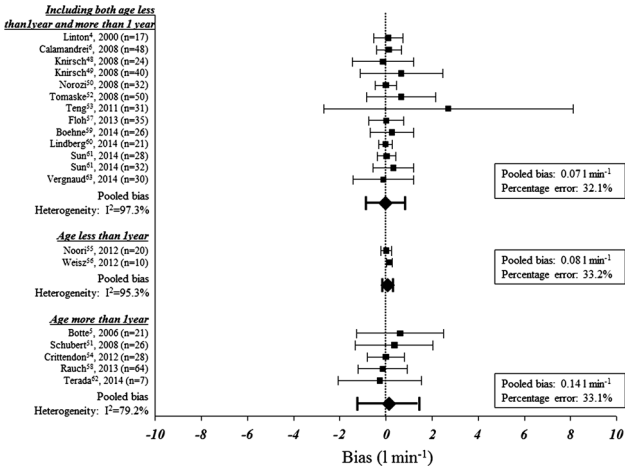
	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Linton et al. [4]	Low	Low	Low	High	Low	Low	Low
Botte et al. [5]	Low	Low	Low	Low	Low	Low	Low
Calamandrei et al. [6]	Low	Low	Low	Low	Low	Low	Low
Knirsch et al. [48]	Low	Low	Low	Low	Low	Low	Low
Knirsch et al. [49]	Low	Low	Low	Low	Low	Low	Low
Norozi et al. [50]	Low	Low	Low	Low	Low	Low	Low
Schubert et al. [51]	Low	Low	Low	Low	Low	Low	Low
Tomaske et al. [52]	Low	Low	Low	Low	Low	Low	Low
Teng et al. [53]	Low	Low	Low	Low	Low	Low	Low
Crittendon et al. [54]	Low	Low	Low	Low	Low	Low	Low
Noori et al. [55]	Low	Low	Low	Low	Low	Low	Low
Weisz et al. [56]	Low	Low	Low	Low	Low	Low	Low
Floh et al. [57]	Low	Low	Low	Low	Low	Low	Low
Rauch et al. [58]	Low	Low	Low	Low	Low	Low	Low
Boehne et al. [59]	Low	Low	Low	Low	Low	Low	Low
Lindberg et al. [60]	Low	Low	Low	Low	Low	Low	Low
Sun et al. [61]	Low	Low	Low	Low	Low	Low	Low
Sun et al. [61]	Low	Low	Low	Low	Low	Low	Low

Table 5 continued

	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Terada et al. [62]	Low	Low	Low	Low	Low	Low	Low
Vergnaud et al. [63]	Low	Low	Low	Low	Low	Low	Low
Wongsirimetheekul et al. [64]	Low	Low	Low	Low	Low	Low	Low

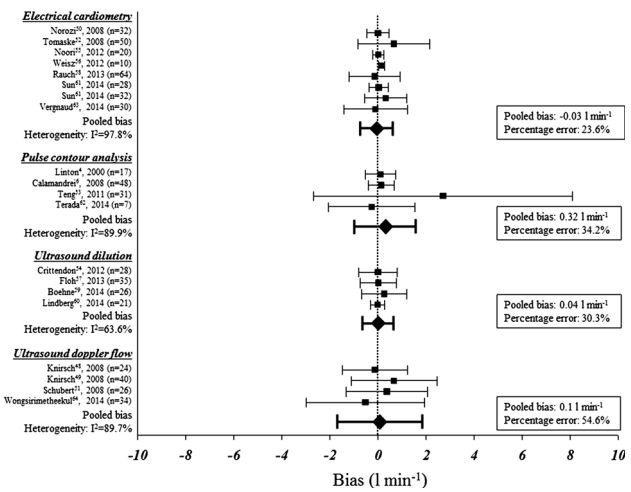
Appendix 5

Forest plot showing the results of subgroup analysis by age



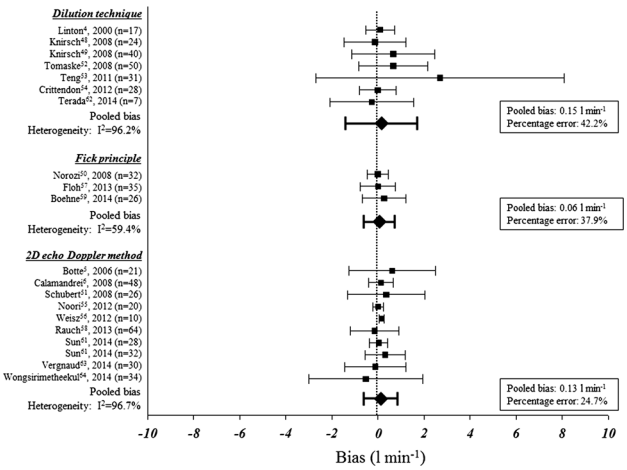
Appendix 6

Forest plot showing the results of subgroup analysis by device type



Appendix 7

Forest plot showing the results of subgroup analysis by reference method



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