



REVIEW ARTICLE

## Noninvasive hemoglobin monitoring in clinical trials: a systematic review and meta-analysis



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### KEYWORDS

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Oximetry;  
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Meta-analysis

### Abstract

**Background and objectives:** The measurement of Hb by co-oximetry is an innovative technique that offers efficiency and agility in the processing of information regarding the measurement of Hemoglobin concentration (Hb) obtained through continuous, non-invasive and rapid monitoring. Because of this attribute, it avoids unnecessary exposures of the patient to invasive procedures by allowing a reduction in the number of blood samples for evaluation and other unnecessary therapies. It also helps to make decisions about the need for transfusion and how to handle it. The objective of this study is to compare the performance offered to obtain Hb values between the Masimo Corporation (Irvine, CA, USA) instrument and the standard gold tool (laboratory examination).

**Contents:** The study corresponds to a systematic review followed by meta-analysis, which included fully registered full-text clinical trials published from 1990 to 2018. PubMed, Cochrane, Medline, Embase and Web of Science databases were investigated. The mean overall difference found between the non-invasive and invasive methods of hemoglobin monitoring was 0.23 (95% CI -0.16, 0.62), that is, it did not present statistical significance ( $p=0.250$ ). The results of the analysis of heterogeneity within and between the studies indicated high levels of inconsistency ( $Q=461.63$ ,  $p<0.0001$ ,  $I^2=98\%$ ), method for Hb values.

**Conclusions:** Although the mean difference between noninvasive measurements of Hb and the gold standard method is small, the co-oximeter can be used as a non-invasive “trend” monitor in detecting unexpected responses at Hb levels.

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**PALAVRAS-CHAVE**

Espectrofotometria;  
Oximetria;  
Análise química do sangue;  
Monitorização transcutânea dos gases sanguíneos;  
Ensaio clínico;  
Revisão sistemática;  
Metanálise

**Monitorização não invasiva da hemoglobina em ensaios clínicos: uma revisão sistemática e metanálise****Resumo**

**Justificativa:** A medida da Hb por co-oximetria é uma técnica inovadora que oferece eficiência e agilidade no processamento das informações referentes a medida da concentração de Hemoglobina (Hb) obtida por meio de monitorização contínua, não-invasiva e rápida. Por conta desse atributo, evita exposições desnecessárias do paciente a procedimentos invasivos ao possibilitar redução da quantidade de amostras sanguíneas para avaliação e de outras terapêuticas desnecessárias. Além disso, auxilia a tomada de decisões quanto a necessidade de transfusão e quanto ao manejo da mesma.

**Objetivo:** Comparar o desempenho oferecido para a obtenção dos valores de Hb entre medida não invasiva da Hb e a ferramenta padrão ouro (exame laboratorial).

**Conteúdo:** O estudo corresponde a uma revisão sistemática seguida de metanálise, que incluiu ensaios clínicos devidamente registrados com texto completo, publicados a partir de 1990 até 2018. Foram investigadas as bases de dados PubMed, Cochrane, Medline, Embase e Web Of Science. A diferença média global encontrada entre os métodos não invasivo e invasivo de monitorização da hemoglobina foi de 0,23 (95% IC -0,16; 0,62), ou seja, não apresentou significância estatística ( $p=0,250$ ). Os resultados da análise de heterogeneidade dentro e entre os estudos, apontou níveis elevados de inconsistência ( $Q=461,63$ ,  $p<0,0001$ ,  $I^2=98\%$ ).

**Conclusão:** Embora a diferença média entre as medidas não invasivas da Hb e o método padrão ouro sejam pequenas, o co-oxímetro pode ser utilizado como um monitor não invasivo de "tendência" na detecção de alterações inesperadas nos níveis de Hb.

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**Background**

The word monitoring comes from the Latin *monere*, and comprises the meaning of valuing safety by follow-up and counseling. In 2008, the market introduced a pulse CO-oximeter with technology capable of measuring total Hb fast, continuously and non-invasively. Therefore, the monitor provided an innovating tool for decision making on blood transfusion management and detection of occult bleeding. The method depicts the trend of changes in Hb concentration values, which highlights its use in procedures with potential blood loss, improving patient safety and reducing costs.<sup>1-4,6-8</sup>

The reference method for analyzing Hb concentration uses either venous or capillary blood samples. The method requires collecting samples of arterial or venous blood and is associated with unavoidable delay (sample collecting time, transportation to laboratory, analysis of material and sample validation, time for results to reach the anesthesiologist), and this may delay transfusion management, leading to unnecessary transfusions (before receiving results), increasing risks to patients' health (related to delay or inadequate transfusions), and increase in hospital costs.<sup>4-7,9,10</sup>

Therefore, the objective of the present study was to compare the performance for obtaining Hb values by CO-oximetry and by the gold-standard tool (laboratory test).

**Method**

The present systematic review and meta-analysis was prepared in compliance with the guidelines established in the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses, (PRISMA).<sup>11</sup>

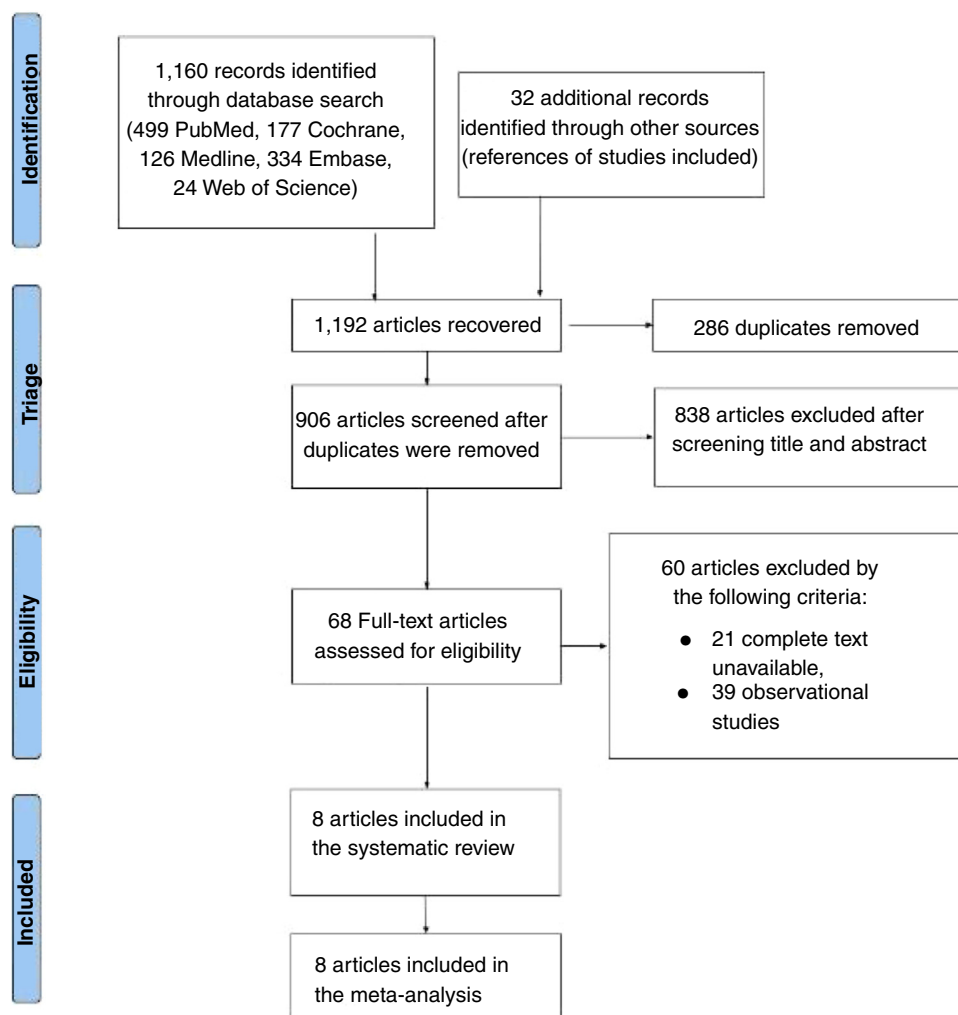
The inclusion criteria established for selecting the studies were articles registered as clinical trials published from 1990 to 2018, focusing on non-invasive hemoglobin monitoring, and comparing it to the gold-standard (laboratory test) for adult and children populations, except neonates.

We used PubMed, Cochrane Library, Embase, Medline and Web of Science databases for searching the articles.

In order to develop the search strategy, the major terms related to the topic focused were highlighted. Thus, the terms selected were Total Hemoglobin, tHb, Hb, Measurement, Oximeter, Co-oximeter, Co-oximetry, Spectrophotometric, Spectrophotometry, SpHb, Noninvasive Hemoglobin Monitoring, Continuous, Noninvasive, Real-time, Beat-to-beat, Occlusion Spectroscopy, MASIMO, Rad-57, Rad-87, Radical-7 and Monitor.

Following, we carried out the literature search strategy in each of the databases selected, by restricting the period (we chose studies between the years of 1990 and 2018), type of study (only clinical trials), and type of population (human population trials).

Three surveyors (DPSW, TZ and ESMD) selected the potentially eligible studies, read titles and abstracts, and thereafter excluded articles unrelated to the topic of interest. Following, they searched full-texts of the remaining articles and assessed eligibility according to the inclusion criteria previously established. In case of questions or disagreements during the selection of a specific study, a fourth surveyor (KM) was contacted to proceed to the final decision.



**Fig. 1** Flowchart of article selection process. Source: Research data, 2018.

DPSL, TZ and ESMD collected data from studies independently. After this, KM revised all data previously collected. Information taken into account was country or origin of the study, experiment environment, demographic characteristics, name and version of software of monitoring devices and non-invasive Hb sensor, name of central lab analyzer, number of patients included in the analysis, and total number of paired samples.

In this way, data were extracted from the selected articles based on the difference of the means observed between non-invasive and invasive measurements of Hb. The standard deviation was obtained using the Confidence Interval formula (95% CI). Then, data were entered and analyzed on RevMan version 5.3 software.

The meta-analysis used the inversion of variance method for random effects. Standardized differences of means with Confidence Intervals of 95% were calculated. Overall statistical significance obtained was analyzed using the z test.

Heterogeneity within and among studies was analyzed using Cochran's  $Q$  statistical calculation (which follows Chi-Square distribution) and  $I^2$  index, in addition to  $\tau^2$  statistics. A sensitivity analysis was performed to study causes of heterogeneity.

Publication bias was assessed by building a funnel chart. In this way, symmetry of publications was evaluated. If no bias was found, studies would take over the aspect of a symmetric inverted funnel.

To perform quality assessment of the studies included in the meta-analysis we built charts following Quality Assessment of Diagnostic Accuracy Studies, QUADAS-2, guidelines.<sup>12</sup> The risk for each polarization and applicability domain was considered as low, high or unclear. According to these criteria established, two surveyors (DPSW and TZ) analyzed the independent quality of each study. Following, disagreements were solved by a third surveyor (KM).

## Results

The database and manufacturer search recovered 1,192 articles. After excluding duplicates, 906 remained for assessment. Three investigators excluded 838 studies based on title and abstract analysis. The 68 full-text articles remaining were recovered and assessed as to eligibility. After full-text review of the articles, 60 studies were excluded because of non-compliance to inclusion criteria or insufficient data, despite efforts to contact the authors for data. Finally, 8 studies were included in the meta-analysis (Fig. 1).

**Table 1** Characteristics of studies included in the meta-analysis on comparison of the invasive (laboratory) and non-invasive (pulse CO-oximetry) methods to measure Hb.

Author	Year	Country	Population characteristics	Age (mean $\pm$ sd), mean (range) or median (range)	Sex	Device tested (version of software, version of sensor)	Hb laboratory analysis	Size of sample/ number of paired measurements	Subgroups (size of sample/ number of paired measurements)	Device tested <sup>a</sup>	Laboratory SMD analysis <sup>a</sup>	SD
Bergek C, Zdolsek JH, Hahn RG <sup>16</sup>	2012	Sweden	Study volunteers, fluid infusion	22 (18–28)	Male 100%	Radical-7 (7.6.0.1, A single use adhesive sensor type R2–25a)	Beckman Coulter Act-5 diff	10/956		NR	NR	-0.07 1.17
Butwick A, Hilton G, Carvalho B <sup>20</sup>	2011	US	Elective C-section	32 (5)	Female 100%	Radical-7 (7.6.0.4, Sensor Rev E)	Coulter LH 750 or LH 780 or CELLDYN Sapphire or CELL-DYN 1800	50/150	Baseline (50/50)	NR	NR	1.22 1.08
Gayat E et al. <sup>17</sup>	2012	US	Emergency Department	57 (43–75)	Male 51.5%	Masimo Pronto-7 (version 2.1.9, Masimo, Sensor Rainbow 4D DC)	ADVIA 2120	272/272	Abdominal pain (21%), Chest pain (13%), dyspnea (12%), sepsis (8%) and bleeding (7%).	NR	13.2 (11.9–14.3) 0.56	1.21

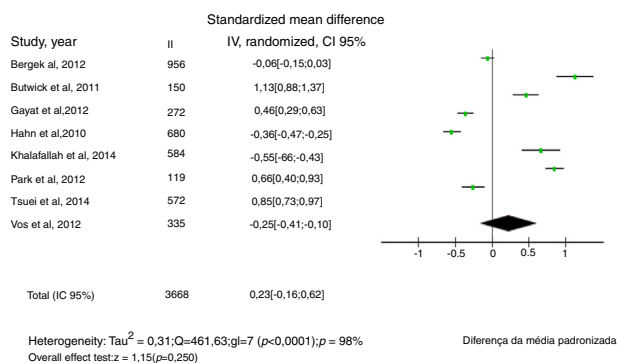
Table 1 (Continued)

Author	Year	Country	Population characteristics	Age (mean $\pm$ sd), mean (range) or median (range)	Sex	Device tested (version of software, version of sensor)	Hb laboratory analysis	Size of sample/ number of paired measurements	Subgroups (size of sample/ number of paired measurements)	Device tested <sup>a</sup>	Laboratory analysis <sup>a</sup>	SMD	SD
Hahn RG, Li Y, Zdolsek J <sup>21</sup>	2010	Sweden	Study volunteers, fluid infusion	22 (19–37)	Male 100%	Radical-7 (7.4.0.9, Sensor handheld R.7.7.1.0, D-station R5.1.2.7)	Cell-Dyn Sapphire	10/680	Group 1: hydrated volunteers, received 5 mL.kg <sup>-1</sup> of Ringer acetate in 15 min. (10/167);  Group 2: dehydrated volunteers, received 5 mL.kg <sup>-1</sup> of Ringer acetate in 15 min. (10/187); Group 3: hydrated volunteers, received 10 mL.kg <sup>-1</sup> of Ringer acetate in 15 min. (10/168); Group 4: dehydrated volunteers, received 10 mL.kg <sup>-1</sup> of Ringer acetate in 15 min. (10/158).	13.425 (0.998)	13.368 (0.862)	-0.37	1.03
Khalafallah AA et al. <sup>14</sup>	2014	Australia	Elective Surgery	Male 65.6 (12)/Female 61.1 (14.9)	Male 50.34%	Masimo Pronto-7 (version 2.1.9, Masimo Corporation, Rainbow 4D Sensor)	Sysmex XE-5000	584/584	Pre-operative: 638 oncological patients with expectation of reduced Hb.	NR	NR	-0.71	1.30

Table 1 (Continued)

Author	Year	Country	Population characteristics	Age (mean $\pm$ sd), mean (range) or median (range)	Sex	Device tested (version of software, version of sensor)	Hb laboratory analysis	Size of sample/ number of paired measurements	Subgroups (size of sample/ number of paired measurements)	Device tested <sup>a</sup>	Laboratory analysis <sup>a</sup>	SMD	SD
Park YH et al. <sup>18</sup>	2012	South Korea	Neurosurgery, pediatrics	6.4 $\pm$ 3.0	Male 62.5%	Radical-7 (7.6.1.1, Sensor Rev E)	ABL820	40/119	After volume replenishment (NR/47); after administration of colloid (NR/32); after red blood cell replenishment (NR/15); tHb < 9 (NR/NR); 9 $\leq$ tHb < 11 (NR/NR); 11 $\leq$ tHb (NR/NR).	NR	NR	0.9	1.35
Tsuei BJ et al. <sup>15</sup>	2014	US	Surgical ICU	>18	Male 60%	Radical-7 (NR, NR)	iSTAT Abbott Point of Care and CBC LH 780	88/572		CBC	NR	1.49	1.76
Vos JJ et al. <sup>19</sup>	2012	Netherlands	Liver resection	56 (19–76)	Male 27%	Radical-7 (7.6.0.1, Sensor R2-25, Rev E)	ABL 800	15/335	Crystalloid infusion (15/335)	NR	NR	-0.27	1.06

<sup>a</sup> Hb (Mean  $\pm$  SD), Mean (Range) or Median (Range).  
 SMD, Standardized Means Difference; SD, Standard Deviation; NR, Not Reported.  
 Source: Research Data, 2018.



**Fig. 2** Overall analysis forest chart. Source: Research data, 2018.

A total 1,069 individuals were included in the meta-analysis. The features of the individual studies are presented in Table 1. Sample size of studies ranged between 10 and 584 individuals.

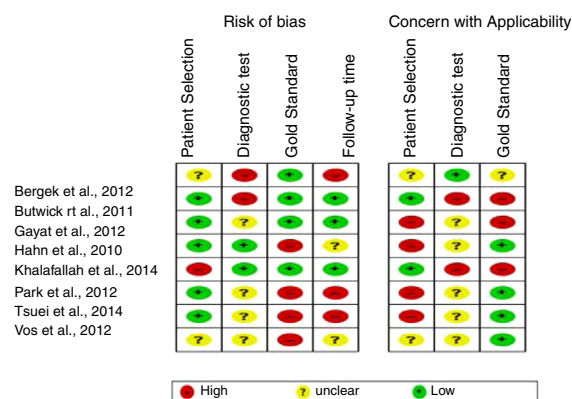
Of the eight studies included in the meta-analysis, two were published in 2014,<sup>13,14</sup> four in 2012,<sup>15–18</sup> one in 2011<sup>19</sup> and one in 2010.<sup>20</sup> Four studies were performed during elective surgeries,<sup>13,17–19</sup> two were performed in volunteers during specific experiments (volume kinetic analysis and hemodilution),<sup>15,19</sup> one was performed at the emergency department<sup>16</sup> and one was performed at the Surgical Intensive Care Unit.<sup>14</sup> Three studies were conducted in the United States,<sup>14,16,19</sup> two in Sweden,<sup>15,20</sup> one was carried out in Austrália,<sup>13</sup> one was performed in the Netherlands, and one was conducted in South Korea.<sup>17</sup>

The mean overall difference found between the non-invasive and invasive method for measuring hemoglobin was 0.23 (95% CI -0.16; 0.62), that is, no statistical significance ( $p = 0.250$ ). In order to interpret this information appropriately, it should be joined by the analysis of heterogeneity within and among studies, which indicated high levels of inconsistency ( $Q = 461.63$ ,  $p < 0.0001$ ,  $I^2 = 98\%$ ) (Fig. 2).

Although a sensitivity analysis was performed, heterogeneity did not decrease significantly. The analysis was performed according to the type of procedures to which patients were submitted (surgical/no surgical), age group and sex. According to the QUADAS-2 assessment, the high risk of bias prevailed in the assessment of the gold standard. This was because in some studies it was not clear if lab test results were actually interpreted without previous knowledge of the results of the test studied.<sup>14,17,18,20</sup> The lowest risk of bias was observed in patient selection criteria, given most studies showed either a consecutive or random sample, adequately described the process of patient selection, and executed appropriate exclusions.<sup>14,16,17,19,20</sup> Only two articles were considered low risk<sup>13,19</sup> according to QUADAS-2. The classification of the remaining articles ranged from high to unclear risk (Fig. 3). performed in five subgroups. The subgroups assessed were formed according to age

After the overall meta-analysis of the eight articles included, five new meta-analyses were group, sex, country, comorbidities and elective/non-elective character of the procedures patients were submitted to.

The standardized mean difference found between the non-invasive and invasive Hb measuring methods in the subgroup of articles comprising patients submitted to elective



**Fig. 3** QUADAS-2 chart of results per study. Source: Research data, 2018.

procedures<sup>13,15,19,20</sup> was 0.02 (95% CI -0.43; 0.47) (Fig. 4). This meta-analysis corroborated the result found in the overall meta-analysis, with no statistically significant difference between methods ( $p = 0.910$ ), but with high levels of inconsistency ( $Q = 165.54$ ,  $p < 0.0001$ ,  $I^2 = 98\%$ ).

The standardized mean difference found between the non-invasive and invasive Hb measuring methods in the subgroup of articles comprising patients submitted to non-elective procedures<sup>14,16–18</sup> was 0.43 (95% CI -0.11; 0.96) (Fig. 5). This meta-analysis corroborated the result found in the overall meta-analysis, with no statistically significant difference between methods ( $p = 0.120$ ), but high levels of inconsistency ( $Q = 126.22$ ,  $p < 0.0001$ ,  $I^2 = 98\%$ ).

The standardized mean difference found between the non-invasive and invasive Hb measurement methods in the subgroup of articles that presented patients with relatively similar age groups<sup>14,15,19,20</sup> was 0.38 (95% CI -0.22; 0.99) (Fig. 6). This meta-analysis corroborated the result found in the overall meta-analysis, with no statistically significant difference between the methods ( $p = 0.220$ ), but high levels of inconsistency ( $Q = 295.97$ ,  $p < 0.0001$ ,  $I^2 = 99\%$ ).

The standardized mean difference found between the non-invasive and invasive Hb measurement methods in the subgroup of articles that presented a distribution according to patients' sex<sup>13,14,16–18</sup> was 0.13 (95% CI -0.37; 0.63) (Fig. 7). This meta-analysis corroborated the result found in the overall meta-analysis global, with no statistically significant difference between methods ( $p = 0.600$ ), but with high levels of inconsistency ( $Q = 379.19$ ,  $p < 0.0001$ ,  $I^2 = 99\%$ ).

The standardized mean difference found between non-invasive and invasive Hb measurement methods in the subgroup of articles that presented proximity among sites where studies were conducted (US)<sup>14,16,19</sup> was 0.80 (95% CI 0.47; 1.13) (Fig. 8). This meta-analysis did not corroborate the results found in the overall meta-analysis, presenting a statistically significant difference between the methods ( $p < 0.001$ ), but with high levels of inconsistency ( $Q = 22.28$ ,  $p < 0.0001$ ,  $I^2 = 91\%$ ).

Assessment of publication bias was performed by building a funnel chart with the standardized mean differences on the abscissa axis, and the standard error of the standardized mean differences on the ordinate axis. When publication bias is absent, the studies distribute themselves symmetrically in the chart in the shape of an inverted funnel. The



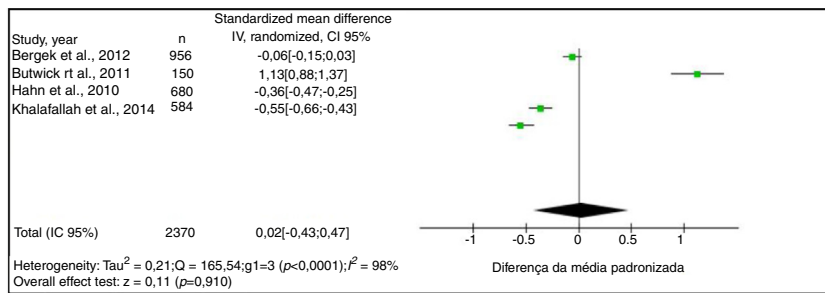


Fig. 4 Subgroup forest chart (elective status patients). Source: Research Data, 2018.

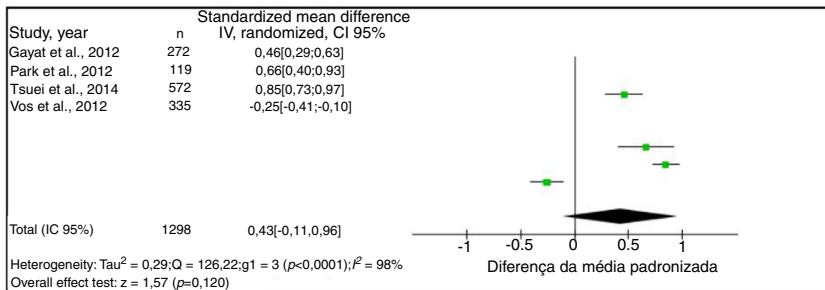


Fig. 5 Subgroup forest chart (non-elective status patients). Source: Research data, 2018.

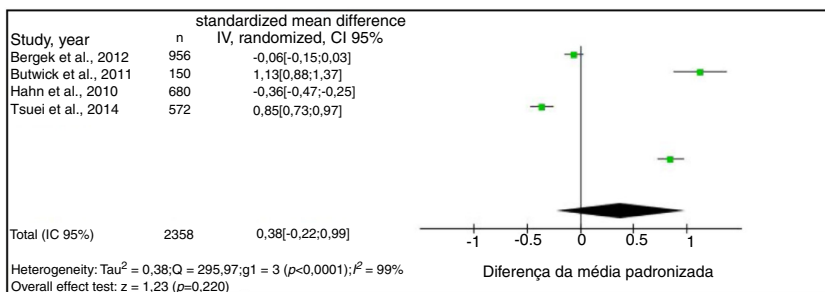


Fig. 6 Subgroup forest chart (age). Source: Research data, 2018.

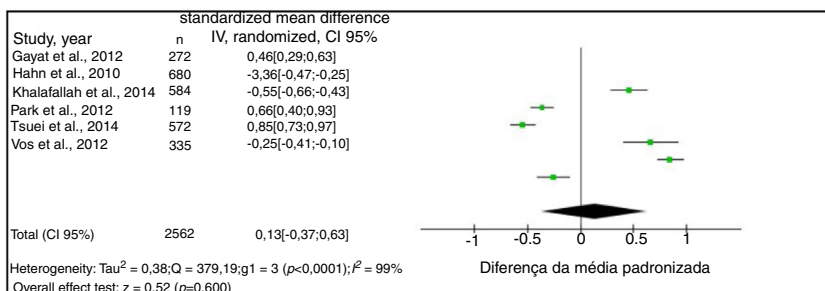


Fig. 7 Subgroup forest chart (both sexes). Source: Research data, 2018.

studies of this review did not present the latter behavior, suggesting the presence of publication bias. (Fig. 9)

## Discussion

Non-invasive Hb monitoring using CO-oximetry is efficient and expedites the processing of information referring to Hb concentration values, which are obtained quickly and continuously during patient care in several settings (partic-

ularly OR, ICU and ER).<sup>13,14,19</sup> Moreover, there is an enormous potential in pediatric populations in which multiple test samplings are less well-tolerated. The non-invasive Hb measurement would also be ideal for patients who have needle phobia.<sup>13</sup>

This study compared the accuracy and precision of non-invasive Hb monitoring with monitoring provided by the lab method (gold-standard) in 1,069 individuals in eight clinical trial articles.



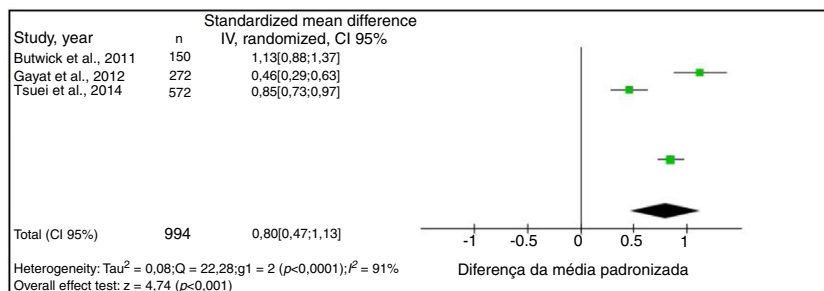


Fig. 8 Subgroup forest chart (country). Source: Research data, 2018.

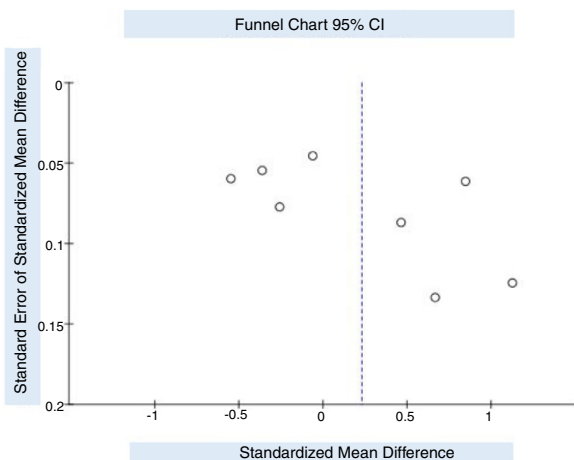


Fig. 9 Funnel chart. Source: Research data, 2018.

Meticulous quality assessment of the articles selected is crucial for meta-analysis.<sup>12</sup> Unfortunately, the result attained by QUADAS-2 in the present study, in which only two studies were considered as presenting low bias risk and applicability, showed the poor quality of the research on the topic approached.

Due to the heterogeneity of data present in the studies included, they were divided into subgroups to provide a more reliable comparison. Subgroup analysis results were concordant with overall analysis results, suggesting that the subgroups did not represent interference factors for the final result.

The articles used in the present study, not only reiterate the issues discussed, but also corroborate the results found in the overall meta-analysis.<sup>21</sup> That is, the present study did not show a statistically significant difference between methods.

Therefore, the discussion on the continuous measurement technique is based on the principle that the technique would especially track the direction of change, that is, the trend of values in real-time. Moreover, the instrument is a useful tool both to decrease unnecessary transfusions and simultaneously signal when an early intervention is required.<sup>2</sup> In this way, it is important to underscore that careful clinical management should be observed when making decisions based only on non-invasive Hb monitoring values, due to underestimation of lower Hb values.<sup>19</sup>

One of the limitations faced by our study was the small number of studies on the topic chosen. There are more

observational studies and the availability of clinical trials is still limited. Moreover, the poor quality of the studies assessed limited the level of consistency of the study performed. Regarding age group, studies concentrate on adults with scarce evidence on the device use in pediatric populations. Last, despite the comprehensive search on several research platforms, many articles selected to be read in full were not available and, therefore, were excluded without extracting data.

The development of criteria that standardize how studies are conducted on a subject can contribute to the development of research with more consistent data. Moreover, we suggest calculating Egger regression to formally assess the existence of publication bias. The development of studies in other subgroups, such as pediatrics, can highlight potential benefits and, thus, further expand the use of the non-invasive method.

## Conflicts of interest

The authors declare no conflicts of interest.

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