

Original Article

Non-invasive haemoglobin measurement as an index test to detect pre-operative anaemia in elective surgery patients – a prospective study

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Summary

Non-invasive haemoglobin measurement using absolute values lacks the precision to be the sole basis for the treatment of pre-operative anaemia. However, it can possibly serve as a screening test, indexing 'anaemia' with high sensitivity when values remain under prespecified cut-off values. Based on previous data, non-invasive haemoglobin cut-off values (146 g.l⁻¹ for women and 152 g.l⁻¹ for men) detect true anaemia with 99% sensitivity. An index test with these prespecified cut-off values was verified by prospective measurement of non-invasive and invasive haemoglobin pre-operatively in elective surgical patients. In 809 patients, this showed an estimated sensitivity (95%CI) of 98.9% (94.1–99.9%) in women and 96.4% (91.0–99.0%) in men. This saved invasive blood tests in 9% of female and 28% of male patients. In female patients, a lower non-invasive haemoglobin cut-off value (138 g.l⁻¹) would save 28% of invasive blood tests with a sensitivity of 95%. The target 99% sensitivity would be reached by non-invasive haemoglobin cut-off values of 152 g.l⁻¹ in female and 162 g.l⁻¹ in male patients, saving 3% and 9% of invasive blood tests, respectively. Bias and limits of agreement between non-invasive and laboratory haemoglobin levels were 2 and – 25 to 28 g.l⁻¹, respectively. Patient and measurement characteristics did not influence the agreement between non-invasive and laboratory haemoglobin levels. Although sensitivity was very high, the index test using prespecified cut-off values just failed to reach the target sensitivity to detect true anaemia. Nevertheless, with respect to blood-sparing effects, the use of the index test in men may be clinically useful, while an index test with a lower cut-off (132 g.l⁻¹) could be more clinically appropriate in women.

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Introduction

Pre-operative anaemia is independently associated with subsequent transfusion and postoperative morbidity and mortality [1, 2]. One central pillar of patient blood management programmes is the pre-operative diagnosis and treatment of pre-operative anaemia [3–5]. However,

studies report low pre-operative screening and treatment rates in patients at risk of bleeding during surgery [6–8]. Consequently, major efforts should be made to improve diagnosis and treatment of pre-operative anaemia in patients undergoing major surgery. The main reason for moderate implementation of pre-operative anaemia

diagnostics is that it requires planning weeks before surgery [9]. In addition, the standard laboratory-based haemoglobin concentration test causes patient discomfort, delay until results are reported and raises costs. Therefore, the ideal method for pre-operative anaemia screening should be: easy to perform; fast; non-invasive; cost effective; and accurate. Theoretically, non-invasive haemoglobin measurement could fulfil these criteria; however, previous studies have demonstrated that the agreement between non-invasive haemoglobin concentration (SpHb) and haemoglobin measured by a laboratory haematology analyser (labHb) cannot be the sole determinant of clinical decisions, such as administration of iron therapy in anaemic patients [10–12]. Nevertheless, SpHb measurement could be helpful in the pre-operative setting if SpHb values were not considered as accurate, but rather as an index test highlighting that anaemia is likely and that an invasive control measurement is required. As stated at the 2018 Patient Blood Management Consensus Conference, due to a lack of evidence, it is unknown whether a specific haemoglobin cut-off (index test) vs. another haemoglobin cut-off (comparator test) can be used to diagnose pre-operative anaemia [3]. Therefore, this study aimed to examine if SpHb measurement is useful as an index test, using prespecified SpHb values indexing anaemia with high sensitivity, and whether laboratory haemoglobin measurements could be avoided.

Methods

This prospective study was approved by the local ethics committee (Rhineland-Palatinate, Germany) and written informed consent was obtained from all participating patients. The study was conducted in the pre-anaesthetic clinic of the University Medical Centre of the Johannes Gutenberg-University, Mainz, Germany. All adult patients attending the pre-operative anaesthetic clinic before elective surgery were eligible.

Haemoglobin concentration was measured in all patients using the SpHb measurement device Pronto Radical 67[®] (DCI[®]-mini sensor; Masimo Corporation, Irvine, CA, USA). Two measurements were performed in close succession and the sensor was replaced for the second measurement. The sensor clip was placed on the little finger of the non-dominant hand and if measurement was not possible it was measured on either another finger of the non-dominant hand, a finger of the dominant hand or a toe. The blood sample for haemoglobin measurement using a haematology analyser (labHb, reference method, Siemens Advia[®]2120, Munich, Germany) was taken in the surgical ward, within 24 h of the non-invasive measurement. If the

blood sample was not taken within this timeframe, the SpHb measurement was repeated. If the blood sample was not taken at all, the patient's data were removed from the primary endpoint. Clinical information was available for SpHb but not labHb measurements and SpHb results were not available for the labHb measurements.

The primary endpoint of the study was to determine if prespecified SpHb cut-off values serve as an index test that detects true anaemia (labHb < 120/130 g.l⁻¹) with 99% sensitivity. True anaemia was defined as a labHb < 120 g.l⁻¹ in women and < 130 g.l⁻¹ in men, according to the World Health Organization [13]. The index test works as follows: 'no anaemia' (SpHb measurements > prespecified SpHb cut-off values index) and 'anaemia' (SpHb measurements ≤ prespecified cut-off values index; invasive haemoglobin control measurement should be done). Based on previous data, SpHb cut-off values that detect true anaemia with a high sensitivity were defined for women and men [10]. The cut-off values for SpHb were prespecified using published information on differences between SpHb and labHb. For each sex, we calculated the 99% quantile of the difference, assuming a normal distribution with mean and SD as reported by Khalafallah et al. [10]. These quantiles were then added to the sex-specific critical values, thus resulting in SpHb cut-off values that we expected to produce 1% false-negative findings (i.e. 99% sensitivity). The cut-off values for SpHb were 146 g.l⁻¹ in women and 152 g.l⁻¹ in men.

We intended to measure at least 103 anaemic patients of both sexes, showing that, given a 99% true sensitivity, we can reject the null hypothesis that sensitivity is at most 94%, with 90% power at a significance level of 5%. An assumed prevalence of 30% required a total of 344 patients to be recruited [1]. We decided to recruit 400 patients of each sex to account for uncertainty of true prevalence. Multiple testing correction was not performed, as the two sexes represent two independent subsets of data.

Secondary endpoints were: calculation of further SpHb cut-off values with different sensitivities; cost analysis; calculation of SpHb cut-off values that exclude anaemia (i.e. detects non-anaemic patients) with a specificity of 99%; agreement between SpHb and labHb measurement; the influence of patient and measurement factors on the accuracy of SpHb; and the reliability of SpHb measurements. For the secondary endpoints, we report the 95% and 99% quantiles of SpHb values of patients with true anaemia. For minor surgeries, it might be sufficient to exclude severe anaemia (labHb ≤ 100 g.l⁻¹). We therefore calculated area under the curve (AUC) values and cut-off values that could correctly diagnose severe anaemia with

sensitivity of at least 90%. We used Bland–Altman analysis to define the accuracy of SpHb, which determines the bias (mean difference between the reference and alternative methods) and limits of agreement (LOA) resulting from the bias ± 1.96 times the SD of the bias [14, 15]. According to Rice et al., LOA were taken as an accuracy metric of the Bland–Altman method [16]. The proportion of outliers for SpHb was calculated. The manufacturer of the non-invasive method lists an accuracy of $\pm 10 \text{ g.l}^{-1}$ [17]. Accordingly, the percentage of outliers was defined as the proportion of the measurements that showed a difference of $> 10 \text{ g.l}^{-1}$ relative to the reference method measurements. Finally, root mean square error (RMSE) was calculated:

$$\text{RMSE} = \sqrt{\frac{1}{N} \sum (x_i - y_i)^2},$$

where x_i , y_i denote two different measurements taken simultaneously from the same patient. The effects of: sex; age; bodyweight; ASA physical status; fasting; perfusion index; SpO_2 ; heart rate; blood pressure; pre-existing illnesses; and labHb, on the accuracy of SpHb (measured as absolute difference between SpHb and labHb) were tested using linear regression analysis. Similarly, we tested the effect on measurement bias (measured as difference between SpHb and labHb) with linear regression analysis. Perfusion index is the pulsatile signal indexed against the non-pulsatile signal, which is an indication of localised blood perfusion. For all SpHb calculations, we took the first of the two SpHb measurements, except for the calculation of AUC values and the reliability of SpHb (mean of the two measurements). Area under the curve values were reported with 95% CIs using the approach of DeLong [18]. DeLong's test for (correlated) receiver operating characteristic (ROC) curves was used to compare AUC. The reliability of SpHb was tested by Pearson correlation coefficient of first and second measurements. All tests for the secondary endpoint were performed with exploratory intention, hence p values were descriptive in nature. Nevertheless, we accepted $p < 0.05$ as indicative of statistical significance.

Results

From July to December 2018, SpHb measurements were performed in 817 patients. In eight patients, SpHb measurements failed to be recorded; only one measurement was possible in four patients; and four SpHb measurements were repeated. Of the 809 patients with SpHb measurements, 808 had labHb measurements; hence 808 had both SpHb and labHb measurements (online Supporting Information, Figure S1). There were no adverse

events from performing SpHb or labHb. Patient and measurement characteristics are presented in Table 1. Table 2 shows the performance of the index test with the prespecified SpHb cut-off values. The sensitivity for detecting anaemia of the index test with SpHb cut-off values of 146 g.l^{-1} in women was 98.9% (95%CI 94.1–99.9%) and of 152 g.l^{-1} in men was 96.4% (91–99%) (see Fig. 1).

The alternative SpHb cut-off values, retrospectively calculated, are shown in Fig. 1 for 99%, 95% and 90% sensitivity. To reach the target sensitivity of 99% to detect anaemia, SpHb cut-off values in our study population were calculated as 152 g.l^{-1} in women and 162 g.l^{-1} in men. To detect true anaemia, SpHb values in women of 120 g.l^{-1} and in men of 130 g.l^{-1} have a sensitivity of 58.1% and 60.9%, respectively.

Using the prespecified SpHb cut-off values, the index test would have saved invasive haemoglobin blood tests in 9% of women and 28% of men in this study. The sensitivities and the saving of blood drawing of prespecified and calculated SpHb cut-off values are shown in Fig. 1.

Area under the curve and cut-off values that could index severe anaemia ($\text{labHb} \leq 100 \text{ g.l}^{-1}$), for example, when screening for minor surgery, were calculated. In women, AUC was 0.957 (95%CI 0.931–0.983). A SpHb cut-off value of 118 g.l^{-1} gave a sensitivity of 90.9% (76.4–96.9%) and a specificity of 87.7% (84.0–90.7%) to detect severe anaemia. In men, AUC was 0.934 (0.867–0.998). A SpHb cut-off value of 123 g.l^{-1} gave a sensitivity of 90.5% (71.1–97.3%) and a specificity of 91.5% (88.3–93.9%) to detect severe anaemia.

One Pronto Radical 67 measuring device can perform 1000 measurements, thereafter a new sensor has to be bought which will perform a further 1000 measurements. Comparing only the costs for the measurement device and the laboratory costs, the savings would be 5490 Euros (£4959; \$6428) for a group comprising equal parts men and women, 7720 Euros (£6974; \$9039) in a male-only group and 1260 Euros (£1138; \$1475) in a female-only group. To offset the capital cost of the device in a mixed group of patients, 247 need to be screened (589 patients in a female-only group and 190 patients in a men-only group). This cost analysis is based on the prespecified SpHb cut-off values (women $146/\text{men } 152 \text{ g.l}^{-1}$) and on the following costs: 0.18 Euros (£0.16; \$0.21) per measurement for laboratory materials (two Monovette EDTA, Serum) and 33.81 Euros (£30.52; \$39.59) per measurement for the standard laboratory profile (differential blood count, creatinine, reticulocytes) [19]; and 1.80 Euros (£1.63; \$2.11) per measurement for the Pronto Radical 67 measuring device (Masimo, personal communication, July 2020).

Table 1 Characteristics of patients undergoing non-invasive haemoglobin testing and measurements. Values are mean (SD), number (proportion) or median (IQR [range]).

	Women n = 401	Men n = 408	Total n = 809
Age; y	59 (17)	61 (16)	60 (17)
Height; cm	165 (7)	177 (17)	171 (10)
Weight; kg	72 (17)	86 (15)	79 (17)
BMI; m.kg ⁻²	27 (6)	27 (5)	27 (5)
ASA physical status			
1	28 (7%)	43 (11%)	71 (9%)
2	217 (54%)	191 (47%)	408 (50%)
3	146 (36%)	150 (37%)	296 (37%)
4	10 (3%)	24 (6%)	34 (4%)
LabHb; g.l ⁻¹	131 (120-138 [70-186])	142 (129-152 [72-176])	135 (124-146 [70-186])
Patients with anaemia using labHb	92 (23%)	110 (27%)	202 (25%)
Patients with labHb < 100 g.l ⁻¹	29 (7%)	16 (4%)	45 (6%)
SpHb; g.l ⁻¹	130 (122-138 [87-188])	142 (131-149 [90-180])	135 (125-146 [87-188])
Failed SpHb measurements	4 (1%)	4 (1%)	8 (1%)
Duration of measurement; s	17 (16-17 [11-34])	17 (15-17 [14-30])	17 (15-17 [11-34])
Sensor localisation and number of measurements	1*: 400 2†: 3 3‡: 2	1*: 410 2†: 0 3‡: 2	1*: 810 2†: 3 3‡: 4
SpO ₂	98% (97-99 [82-100])%	97% (97-98 [47-100])%	98% (97-98 [47-100])%
Heart rate; bpm	76 (68-84 [48-128])	74 (64-83 [32-130])	74 (66-84 [32-130])
Perfusion index	4 (2-7 [0-20])	5 (3-7 [0-16])	5 (3-7 [0-20])
Reliability; correlation coefficient (95%CI)	0.86 (0.84–0.89)	0.89 (0.88–0.92)	0.89 (0.89–0.91)

Sensor localisation: 1* – little finger of the non-dominant hand; 2† – other finger of the non-dominant hand; 3‡ – any finger of the dominant hand.

Table 2 Performance of non-invasive haemoglobin measurement as an index test for anaemia with SpHb cut-off values 146 and 152 g.l⁻¹. True anaemia: labHb < 120 g.l⁻¹ (women) and labHb < 130 g.l⁻¹ (men). Index test anaemia: SpHb ≤ 146 g.l⁻¹ (women) and SpHb ≤ 152 g.l⁻¹ (men). Values are number.

	Women		Men	
	True anaemia	Index test anaemia	True anaemia	Index test anaemia
True normal	307	58	298	77
True low	93	92	110	106
False normal		1		4
False low		249		221

The SpHb cut-off values that detect non-anaemic patients with a specificity of 99% (99% of non-anaemic patients have a SpHb higher than this value) were 110 g.l⁻¹ (99.3%, CI 97.7–99.9%) for women and 115 g.l⁻¹ (99.0%, CI 97.1–99.8%) for men.

Figure 2 shows the agreement of SpHb with labHb by a Bland–Altman diagram including bias and LOA. Bias, LOA, RMSE, percentage of outliers and ROC with CIs are shown in online Supporting Information, Table S1. Bias and LOA for

the whole sample (men and women) between SpHb and labHb were 2 and –25 to 28 g.l⁻¹. The R² SpHb/labHb showed no relevant effects of: sex; age; weight; ASA physical status; fasting; perfusion index; SpO₂; heart rate; blood pressure; pre-existing illness; and labHb, on the accuracy of SpHb. Taking the average SpHb of both measurements instead of the first measurement did not improve accuracy of the index test (see online Supporting Information, Table S2). While accuracy was not affected by

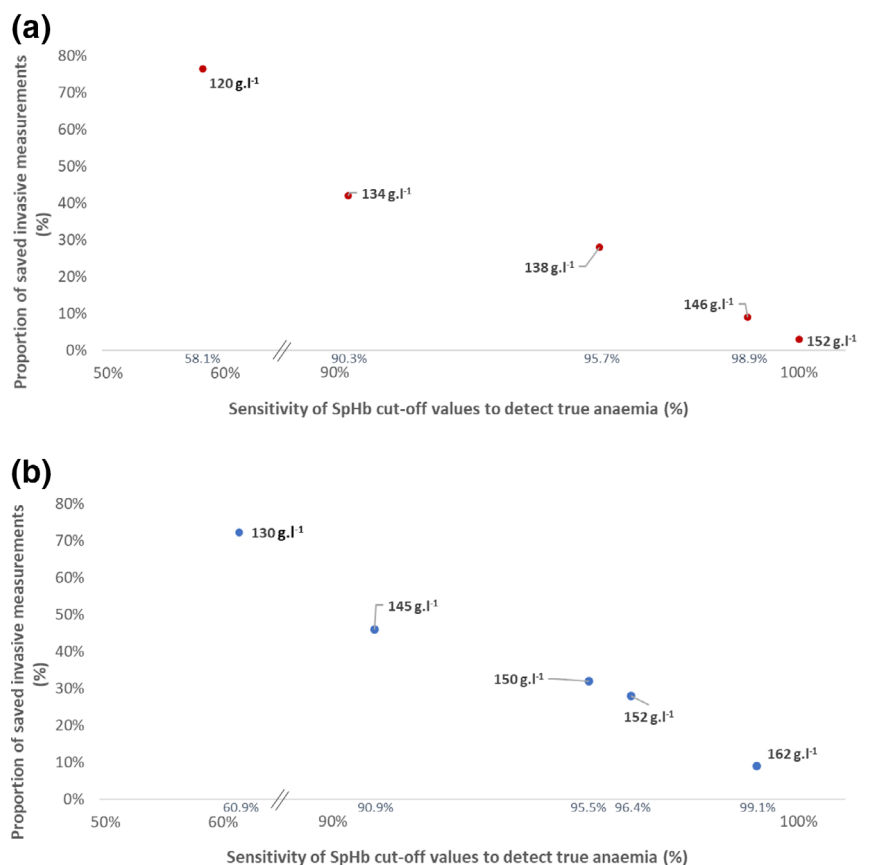


Figure 1 Sensitivities of SpHb cut-off values for men and women to detect true anaemia and proportion of invasive haemoglobin blood tests saved in (a) women and (b) men. SpHb, non-invasive haemoglobin concentration.

the variables, the direction of bias was associated with the following variables: labHb was associated with a negative bias in measurement difference in both sexes; perfusion index was associated with a positive bias in both sexes; and diastolic blood pressure was associated with a negative bias in men, with only a faint trend seen in women. Similarly for heart rate, we observed an association with a positive bias in men, but not in women (Table 3).

Discussion

Our study has shown that the index test with the verified SpHb cut-off values (women 146, men 152 g.l⁻¹) has high sensitivity, especially in women. However, it just failed to meet the target sensitivity of 99%. Sensitivity of the index test was high in women, but the blood sparing effect was low. In contrast, sensitivity was lower in men, but the blood-sparing effect was higher. Our data suggest that the clinical benefit of an index test with SpHb cut-off values reaching 99% sensitivity is low because of poor blood-sparing effect. Therefore, the use of the verified cut-off values for male

patients may be clinically useful, while for female patients, a lower cut-off value might be suitable.

The sensitivity of the index test with the prespecified SpHb cut-off values to detect anaemia was 98.8% for women and 96.4% for men and therefore below the target sensitivity of 99%. In our study population, this level of sensitivity means that five true anaemic patients were not identified as anaemic by the index test. At the same time, one-fifth of the patients would not have needed invasive haemoglobin blood tests. Interestingly, men would especially benefit from the application of the index test; 28% would not have needed blood tests, while four would not have been identified as anaemic. In women, the blood sparing effect of the index test is much less (9%); only one would not have been identified as anaemic. We conclude that the index test with the prespecified SpHb cut-off value of 152 g.l⁻¹ in men makes sense for clinical application as its sensitivity is still high and the blood-sparing effect is large enough to justify costs and efforts of SpHb measurement. For women, the index test with the prespecified SpHb cut-

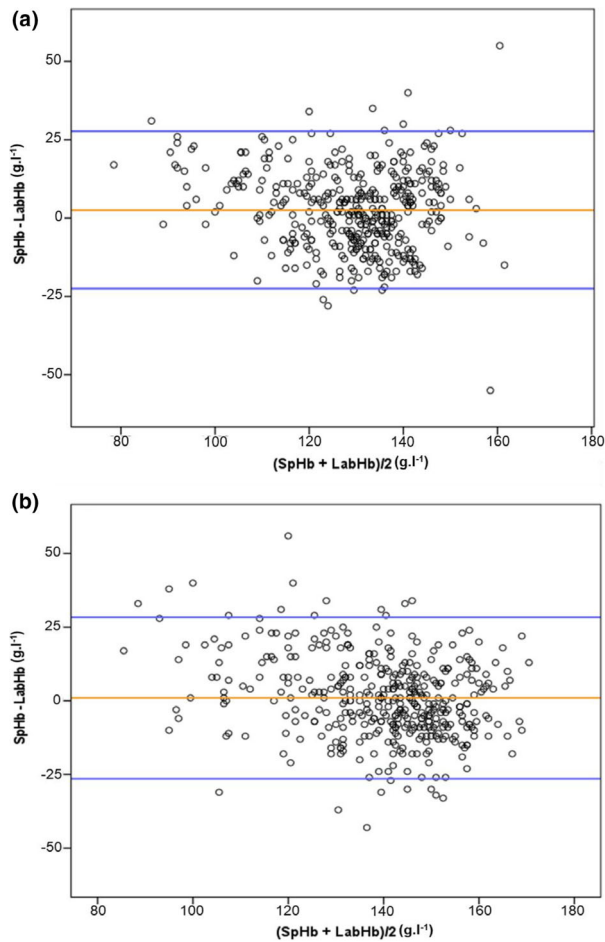


Figure 2 Bland–Altman diagrams showing the accuracy of non-invasive haemoglobin measurement with laboratory haemoglobin measurements in (a) women and (b) men. Bias/limits of agreement (LOA) are (a) 3/-23 to 28 g.l⁻¹ in women and (b) 1/-26 to 28 g.l⁻¹ in men. labHb, laboratory haemoglobin concentration; SpHb, non-invasive haemoglobin concentration.

off value of 146 g.l⁻¹ is not as clinically useful because of its low blood-sparing effect. An index test with a lower SpHb cut-off-value for women has to be found to save more

invasive blood consuming measurements with a still acceptable sensitivity.

If non-invasive anaemia screening is used as the primary tool in the pre-operative clinic, the costs for the Pronto Radical 67 measuring device would be offset well before the 1000 measurements were used up. Using the sex-specific prespecified SpHb-cut-off values, these costs are offset earlier in men compared with women. One could argue that these extra costs could be omitted, as laboratory diagnostics are routinely performed on the day of admission to hospital for surgery. However, early non-invasive haemoglobin screening in the pre-op clinic gives the opportunity to treat potential anaemia and thereby improve the outcome of the patient without delaying their operation [20].

As secondary endpoints, we retrospectively analysed the sensitivity of the index tests with other SpHb cut-off values and their potential for avoiding invasive blood sampling. According to our data, an index test with SpHb cut-off values reaching the target sensitivity of 99% (men 161 g.l⁻¹, women 151 g.l⁻¹) is not useful because the blood-sparing effect is too small. Women could benefit from a lower SpHb cut-off value of 138 g.l⁻¹, which has a 95% sensitivity and would save 25% of invasive blood tests. However, this retrospectively calculated value would require validation by a prospective study. As there are currently no published data comparing the sensitivity of an index test with SpHb cut-off values to detect true anaemia, we cannot compare the sensitivity of our cut-off values with that of other investigations.

As expected, the accuracy of SpHb measurement was not enough to use the Pronto-7 as an exact measurement device for pre-operative haemoglobin and as the basis for clinical decision-making. For both sexes, LOA are too wide to use SpHb interchangeably with the reference method labHb that invasively measures haemoglobin using a haematology analyser. Limits of agreement from -26 or -23 (men and women, respectively) to 28 g.l⁻¹ could lead to unjustified clinical decisions such as: unnecessary intravenous iron therapy; unnecessary

Table 3 Factors associated with bias (SpHb-labHb). Values are number [95%CI].

1 SD increase of:	Women		Men	
	Effect on bias in g.l ⁻¹	p value	Effect on bias in g.l ⁻¹	p value
LabHb	-8.6 [-9.6 to - 7.6]	< 0.001	-8.4 [-9.4 to - 7.4]	< 0.001
Perfusion index	4.4 [3–5.8]	< 0.001	2.8 [1.5–4.1]	< 0.001
Diastolic blood pressure	-1.4 [3–0.1]	0.07	-2.4 [-3.7 to - 1.1]	< 0.001
Heart rate	1.3 [-0.2 to 2.8]	0.08	1.7 [0.4–3]	0.010

labHb, laboratory measurement of haemoglobin.

cancelling of elective surgery; or otherwise overlooking of pre-operative anaemia. The accuracy found in our study corresponds to that of the study by Khalafallah et al. [10]. They performed measurements on 726 patients using SpHb with Pronto-7 and compared it with labHb using an automated analyser in pre-operative and oncology clinic patients. Their LOA are in the range of our results. However, they reported that measured SpHb tended to underestimate labHb measurement (negative bias), whereas in our study, non-invasive measurement tended to overestimate labHb (positive bias). As a consequence, their sensitivity to detect true anaemia by measuring SpHb < 120 to 130 g.l^{-1} was higher compared with the present study (75% vs. 58% sensitivity in women, 93% vs. 61% sensitivity in men). A recent retrospective study examining the accuracy of the Pronto device as a secondary endpoint in pre-operative patients found an overall sensitivity of 48% by detecting anaemia measuring SpHb $< 120/130 \text{ g.l}^{-1}$. This is even lower than our reported findings. Comparable with the present study, SpHb tended to overestimate labHb and the authors concluded the device was not precise enough to replace invasive measurements [12]. Another study that examined the usefulness of the Pronto-7 device in the emergency department found even wider LOA (-32.9 to 22.5 g.l^{-1}) [21], indicating that the accuracy of the Pronto-7 device has not improved.

We could not identify a specific factor that influenced the agreement between SpHb and labHb, but we identified factors that predict the direction of bias. The most clinically relevant factor is labHb, which was associated with a negative change in measurement difference in both sexes. Therefore, SpHb tends to underestimate labHb for high labHb values. This is in line with an older study investigating patients in the emergency department [22], where diastolic blood pressure was also characterised as a predictor of bias for all patients. This is in contrast to our results where this was true only for men. In addition, an increase in perfusion index was associated with a more positive change in measurement difference between SpHb and labHb, which is also confirmed for women by Khalafallah et al. [10]. In contrast, we could not identify factors that influence the accuracy (agreement between SpHb and labHb) of the device. Taking the average of two measurements instead of one showed a trend to higher accuracy in men, but the improvement is not clinically relevant. Considering costs and time required for a second measurement, we cannot recommend taking two non-invasive measurements in clinical practice.

The failure rate of measuring SpHb in our patients was 0.97%, which is an improvement on that previously reported. Khalafallah et al. described a 20% failure rate in obtaining a technically satisfactory SpHb reading in pre-operative and oncology patients. A failure rate of 14% was reported in trauma patients [23]. Furthermore, the device improved in terms of reliability. The correlation coefficient between two repeated measurements was 0.89, which is slightly better than has been previously reported (0.78) [24].

There are some limitations to this study. We failed to reach the planned number of female patients with true anaemia, thus theoretically resulting in a minor loss in the study power. Nonetheless, our primary research question (determining the sample size) yielded a significant positive finding in women. Furthermore, we did not measure SpHb and labHb at exactly the same time. There was a 24-h timeframe between the two measurements. However, the primary endpoint was not the accuracy of the non-invasive device. It was the usefulness of non-invasive measurement as an index test to detect pre-operative anaemia. It is common clinical practice that non-invasive measurement in the pre-operative clinic is performed before invasive measurement in the ward. Therefore, this time-frame reflects the clinical reality. In addition, our patients were a typical sample of the pre-operative clinic; hence we believe our results are generalisable.

As non-invasive measurement of pre-operative haemoglobin is too inaccurate to form the basis for clinical decisions, we have investigated if non-invasive haemoglobin measurement can be used as an index test to detect anaemia in pre-operative patients with high sensitivity in order to save invasive blood tests. The index test with prespecified SpHb cut-off values for women of 146 and men of 152 g.l^{-1} reached sensitivity just below the target 99% to detect true anaemia. However, sensitivity was still clinically acceptable for both sexes. The clinical benefit of an index test with SpHb cut-off values reaching 99% sensitivity is low because of a poor blood-sparing effect. Therefore, considering the sufficient blood sparing effect in men, the use of the index test with the SpHb cut-off value of 152 g.l^{-1} in a pre-operative diagnosis of anaemia seems to be clinically useful. However, the blood-sparing effect of the index test in women was too low for clinical application. For them, the retrospectively calculated index test with a lower SpHb cut-off value of 138 g.l^{-1} might be clinically useful.

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Supporting Information

Additional supporting information may be found online via the journal website.

Figure S1. STARD flow diagram.

Table S1. Comparison of non-invasive haemoglobin measurement with the laboratory haemoglobin measurement.

Table S2. Comparison of values obtained from first non-invasive haemoglobin measurement and the mean of two measurements.