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# Review: Non-invasive blood haemoglobin level measurement

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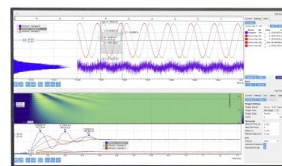
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# Review: Non-Invasive Blood Haemoglobin Level Measurement

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**Abstract.** Blood haemoglobin level measurement is an essential part of a global attempt at reducing anaemia. This review is to elaborate on current advancements in non-invasive methods to measure blood haemoglobin level. This review also elaborates on current established invasive methods for measuring blood haemoglobin level and its role as a reference standard. This review also maps the wavelength used for non-invasive blood haemoglobin level measurement to our observation on blood haemoglobin level control. The research team has obtained Journal or proceeding articles from Google Scholar and Scopus using the keyword "non-invasive haemoglobin" within its titles from 1980 to 2020. The team has grouped the articles by non-invasive methods, invasive reference methods, and the wavelength used by those methods. There are 128 articles gathered from the keywords. There are 88 articles included in this study. There are 26 light source wavelength combinations that the developers use for non-invasive blood haemoglobin level. Most of the wavelength fits neatly in the window between 500 nm to 1000 nm, where the blood-haemoglobin-level control absorbance is low. The researcher has gathered 13 different non-invasive methods for measuring blood haemoglobin level and those commercially available. Most of the articles we have gathered are unregistered trials, and the majority of methods are unproven. We are taking this as a research limitation. The researchers should conduct a further trial for each method listed.

## INTRODUCTION

Anaemia is a condition in which the number and size of red blood cells fall below an established cut-off value. Anaemia consequently impairing the capacity of the blood to transport oxygen around the body. Anaemia is an indicator of both poor nutrition and poor health [1]. There are 29% (496 million) of non-pregnant women and 38%

(32.4 million) of pregnant women aged 15–49 years that were anaemic globally in 2011 [2]. There are 48.9% anaemic expecting mothers in Indonesia in 2018, which is an increase from 37.1% in 2013 [3]. Hence blood haemoglobin level measurement is an essential part of a global attempt at reducing anaemia [1]. Current invasive methods have their risks and limitations [4,5].

Extensive research for safer and more accurate methods to measure blood haemoglobin level is ongoing [6]. That is why the researchers keep developing new methods to non-invasively measure blood haemoglobin level [7].

This review is to elaborate on current advancements in non-invasive methods to measure blood haemoglobin level. This review also elaborates on current established invasive methods for measuring blood haemoglobin level and its role as a reference standard. This review also maps the wavelength used for non-invasive blood haemoglobin level measurement to our observation on blood haemoglobin level control.

## METHOD

The researcher makes use of the PRISMA statement as a reporting standard [8]. The researchers have obtained journal articles and proceeding articles for this review from several indexes such as Google Scholar and Scopus. We have used the string "non-invasive haemoglobin OR haemoglobin" and "non-invasive haemoglobin OR haemoglobin wavelength OR spectroscopy OR spectrophotometry" as the article search keyword. We are gathering both accepted or published development research or clinical trial of non-invasive blood haemoglobin level measurement from 1980 to 2020. The rationale is to ensure that we also have included an unproven concept ready to be trialled. The last searching date is 10 January 2020. The researchers include articles with English as the primary language. However, we also include studies, not in English which the translation is available to maximise the availability of the articles. We have utilised both Docear and Zotero for document indexing [9,10]. The researchers have indexed all included articles using Zotero. Then the researchers use Docear to categorise the articles into four main groups, non-invasive blood-haemoglobin-level measurement methods, reference invasive blood-haemoglobin-level measurement methods, light source wavelengths used for each method, and omitted poor quality articles. The researcher has reported accuracy measurements such as sensitivity, specificity, and accuracy when available.

We have conducted The FTIR spectrophotometry observational study. The process took place in Laboratorium Teknik Pengolahan Pangan dan Hasil Pertanian, Faculty of Agricultural Engineering, IPB University, in August 2019. The research team has used three biomimetic blood haemoglobin level control (6.3 g/dl, 12.2 mg/dl, 15.2 mg/dl) (Lyphocek Assayed Chemistry Control, Bio-Rad Laboratories, Inc., USA). The researchers then combine the result with the data from our other research [11,12]. We are using R, RKward, and RStudio for data analysis [13,14].

## RESULTS AND DISCUSSION

### Review Process

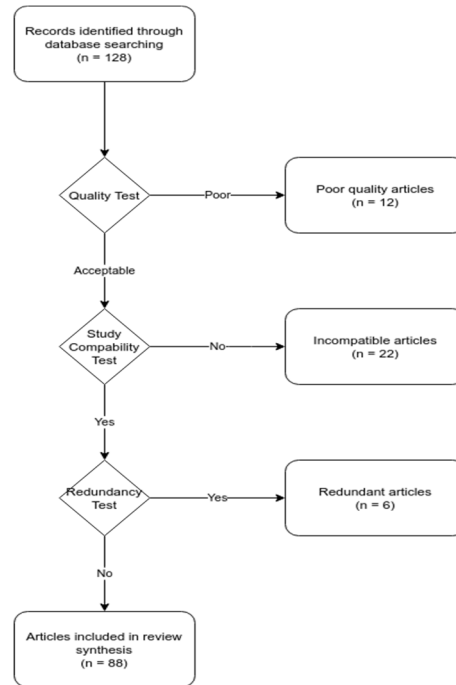
There are 128 articles gathered from the keywords. We have omitted 12 articles due to poor quality. The researchers omitted further 22 articles due to incompatibilities with this study, and the next six articles due to redundancy. There are 88 articles included in this study (Fig. 1).

### Non - Invasive Blood Haemoglobin Level Measurement Methods

Photoplethysmography (PPG) is a simple optical technique used to detect volumetric changes in blood in the peripheral circulation. There so many ongoing research on non-invasive blood haemoglobin level measurement based on this principle. Examples include research by Timm, Doshi, Sharma, Nirupa, Desai, Pavithra, Padma, and Yuan, which not adequately trialled [15–22]. Kraitl unregistered trial for 43 subjects yields a correlation of 0.918 against silver standard HemoCue [23]. Kavsaoglu et al. unregistered trial against 33 subjects yields a correlation of 0.9711 and root means squared error of 0.0833 g / dl against Hemocue Hb-201TM [24]. Unregistered trial by Yuan et al. to 91 subjects against undisclosed reference standard yield relative root means squared error of 6.08% [25]. Rochmanto et al. have conducted an unregistered clinical trial 78 subjects against gold standard Sysmex KN-21, with a sensitivity of 44.4% and specificity of 72.5%. The accuracy is 69.2% [26].

Geer et al. proposed a blood-haemoglobin-level measurement technique utilising blood hematocrit value in the equation. They have been trialled the methods to Siemens Advia 2120 analysers (Spectra Labs, Milpitas, CA, USA)

as a reference standard. The methods proved 93% sensitive and 70% specific, from 310 measurements from 47 patients in an unregistered clinical trial [27].



**FIGURE 1.** Prisma Flowchart of Review on Non-Invasive Blood Haemoglobin Level Measurement Methods

A method proposed to use computer vision/image processing techniques to quantify blood haemoglobin level on human skin [28,29]. Suner et al. have conducted a clinical trial out of 65 patients against SE 9500, Sysmex Corporation Ltd., Kobe, Japan, in an unregistered clinical trial. The correlation is 0.634 [30].

The commercial pulse oximetry device works by temporarily occluding the blood flow through a pneumatic finger cuff and reading the transmitted light by a multi-wavelength sensor. The methods gain 0.45 correlation to undisclosed automatic haematology analyser from an unregistered clinical trial [31].

Machine learning is an umbrella of computing methods to find a pattern between measurement using computing or intelligent agent. Ding et al. have designed 9 LED non-invasive blood-haemoglobin-level measurement devices powered with backpropagation artificial neural networks. They clinically trialled the device to 109 subjects and an undisclosed automatic blood analyser, with the correlation coefficient of 0.94 and a standard error of 11.01 g/l. The trial is unregistered [32]. Lakshmi et al. have designed a similar device, using an undisclosed regressive machine learning. The system attains an absolute bias of 0.73 g/dl in an unregistered clinical trial with 47 pregnant women against lab measurement [33].

The advancement of mobile technology and prevalence has created new methods to measure blood haemoglobin level. Ahsan, Venkata, Padma, and Dewantoro have proposed these methods, which have yet to adequately trialled [21,34–36]. Another attempt by Santra yields an accuracy of 91% from 20 subjects against lab measurement in an unregistered clinical trial [37].

Raman spectrophotometry is a measurement technique. The operator used the light to measure vibrational modes of molecules. One of such work combines Raman spectroscopy in 785 nm wavelength with principal component analysis and support vector machine to measure blood haemoglobin level. It gains 100% sensitivity and between 60% to 100% specificity out of 86 subjects in an unregistered clinical trial. They did not disclose the reference standard [38].

Dynamic Spectrum methods proposed as spectrophotometry methods to measure a range of wavelength as opposed to discrete wavelength, before converting it to measurement value. Wang et al. have proposed the usage of wavelength range 600.22 nm to 1000.60 nm in the continuous form to measure blood haemoglobin level. Wang et al. have conducted two non-registered trials. The first one is using Dynamic Spectrum methods combined with BackPropagation Artificial Neural Network. It attains the correlation coefficient of 0.907 out of 60 subjects, but the reference standard

is undisclosed [39]. They then repeat the trial for 110 subjects with a similar result against undisclosed reference standard [40].

Researchers have tried simple Bert-Lambert methods for measuring blood haemoglobin level. Teng, Timm, and Netz have proposed these methods, which are not yet adequately trialled [19,41–44].

Several researchers proposed a simplified non-invasive blood-haemoglobin-level measurement system with only one led — the device work with similar principles of photoplethysmography. Examples are works by Al Baradie using 670 nm LED and Abhisek using 950 nm LED. Neither method has been adequately trialled [45,46].

Zhang et al. modify simple Bert-Lambert methods. They have to put four sensors around the light source with 660 nm and 850 nm wavelength to measure reflection from blood haemoglobin level on human skin. This method is not yet adequately trialled [47].

Magnetic plethysmograph (MPG) is obtained by exposing a section of the body with magnetic flux and delineating the component of flux that interacts with blood volume changes. This method is not yet adequately trialled [48].

Phillips et al. proposed a method to measure blood haemoglobin level by estimating the value from optical absorbance change occurring over the cardiac cycle divided by a corresponding change in measured blood volume during the cycle measured from peripheral tissue. They call the method as electro-optical plethysmography. This method is not yet adequately trialled [49].

Among the commercially available non-invasive blood-haemoglobin-level measurement device, Masimo is the most well known and well-tested manufacturer. OrSense, Hamamatsu Photonics, and Hutchinson Technology Inc have come after. The most well known Masimo product is Rainbow SET Radical-7 Pulse CO-Oximeter SpHb. In clinical trial NCT01062776, with ten subjects, the accuracy was 1.6%, and the precision was 4.6% against Cell-Dyn Sapphire (Abbott Diagnostics, Abbott Park, Ill., USA) [50]. NCT01108471 with 50 subjects shown that Radical 7 shown significant positive bias against (Beckman Coulter, Inc., Brea, CA, USA) [51]. NCT01060683 with 30 patients, the correlation is 0.5 against Coulter LH 750 or LH 780 haematology analysers (Beckman Coulter, Inc., Brea, CA, USA) [52]. In an unregistered clinical trial by Amano, with 43 pediatric children, the correlation is 0.602 against (Microsemi® LC-667CRP; Fukuda Denshi, Tokyo, Japan) [53]. In an unregistered clinical trial by Khanna with 30 patients, the correlation 0.634 against undisclosed blood gas analyser [54]. Miyashita unregistered trial to 19 subjects shown that the correlation is between 0.83 to 0.93 against (Model ABL700; Radiometer, Copenhagen, Denmark [55]. Broderick unregistered trial to 25 subjects has shown 2.4 g.dl bias to GEM Premier 4000 (Instrumentation Laboratory, Bedford, MA, USA) [56]. In Tokuda unregistered trial to 46 subjects, correlation to Radiometer ABL 850; Radiometer, Copenhagen, Denmark is 0.87 [57]. Von Schweinitz unregistered trial with 135 subjects has shown that the correlation is 0.69 to LH-500 blood cell analyser (Beckman-Coulter, Brea, CA, USA) [58]. The 148 subjects unregistered study by Bhat has shown that the correlation to lab analyser (Nihon Kohden, Celltac F, Japan) is 0.94 [59]. Baulig unregistered study with 46 patients has shown a 0.81 correlation to ABL 825, Radiometer Medical A/S Akandevej 21 DK-2700 Bronshoj, Denmark) [60]. Adel unregistered clinical trial with 70 patients has shown a 0.938 correlation to Automated Haemoglobinn analyser (Coulter LH 750 Beckman) [61].

Panda unregistered clinical trial has shown a 0.44% deviation to (Autoanalyzer - Shenzhen Mindray Bio-Medical Electronics Co. Ltd, BC- 5380, PRC) [62]. Chang et al. have conducted an unregistered trial with 49 patients. They have shown that the correction coefficients between were 0.6946 to blood gas analyser (Stat Profile Critical Care Xpress, Nova Biomedical, Waltham, Mass, United States) [63]. Kadioglu unregistered trial with 48 patients has shown correlation 0.997 to ADVIA 2120/2120i Hematology System [64]. NCT02722759 with 61 measurements has shown that the root means square error to Siemens Advia 2120, Siemens, Munich, Germany) is 1.9 g / dl [65]. The 2nd most used is Masimo Pronto-7 Pulse CO-oximetry. The NCT01321580 and NCT01321593 both by Gayat et al. with 300 patients, the absolute mean difference is 0.56 g / l against ADVIA H 2120 (Siemens Medical Solutions Diagnostics, Zurich, Switzerland) [66]. Al Khabori unregistered clinical trial with 106 subjects has shown 0.46 correlation with CELL-DYN SAPPHIRE (Abbott Diagnostics, USA) [67], but currently disputed [68,69]. ACTRN12611001256965 with 726 subjects has shown sensitivity 92.9% and 81.3% specificity against Sysmex XE w 5000 TM automated haematology analyser (Sysmex Corporation, Kobe, Hyogo, Japan) [70]. Pajares non registered clinical trial with 159 subjects has shown 0.618 correlation against automatic haematology analyser (COULTER® LH 750 System, Beckman Coulter, Brea CA, USA) [71]. Ziaka unregistered clinical trial with 24 subjects has shown 1.9 g / dl deviation against laboratory measurement [72]. von Schweinitz unregistered clinical trial with 135 subjects has reported Masimo Rad-7 0.67 correlation to Beckman-Coulter LH-550 (Brea, CA, USA) [58].

For NBM 200 (Orsense, Nes-Ziona, Israel), in NCT01321580 and NCT01321593 both by Gayat et al. with 300 patients, the absolute mean difference is 0.21 g / l against ADVIA H 2120 (Siemens Medical Solutions Diagnostics, Zurich, Switzerland) [66]. Malukani unregistered clinical trial with 200 subjects has shown a sensitivity of 97.6% and specificity of 88.2% to Sysmex KX 21, Sysmex America, Inc. Lincolnshire) [73]. Pajares non registered clinical

trial with 159 subjects has shown 0.648 correlation against automatic haematology analyser (COULTER® LH 750 System, Beckman Coulter, Brea CA, USA) [71]. Ahankari unregistered clinical trial with 269 pregnant women has shown that the NBM 200 showed low sensitivity 33.7% but high specificity 91.8%; 95% against Sysmex XP-100, Japan [74]. Mallhi unregistered clinical trial with 500 subjects against SYSMEX KX-21 has shown 70.59% sensitivity and 98.93% specificity [75].

For NIRO 300 oximeter (Hamamatsu Photonics, Hamamatsu City, Japan), Dullenkopf unregistered clinical trial with 40 children reported Sensitivity and specificity 73.1% and 70.0% against ABL 700 blood gas analyser (Radiometer Medical A/S, Copenhagen, Denmark) [76]. For Haemospect, Pajares non registered clinical trial with 159 subjects has shown 0.416 correlation against automatic haematology analyser (COULTER® LH 750 System, Beckman Coulter, Brea CA, USA) [71]. Strydom unregistered clinical trial with 161 subjects has reported that sensitivity is 94.6% to ADVIA2120 [77]. For TouchHb Alpha 1.1- non-invasive, Neogi unregistered clinical trial with 5316 subjects 73.1% sensitivity and 51.5% specificity against Beckman Coulter LH 780 [78]. For Tech4Life, The accuracy of the total sample was 92% whereas the sensitivity and specificity was 89% and 76% respectively. The reference standard is undisclosed [79].

## Reference Invasive Blood Haemoglobin Level Measurement Methods

Three of the most used reference gold standard are automated haematology analyser, blood gas analyser, and laboratory analysis [50,59,61,67,77]. Some research found the use of one of five silver standards. They are commercial portable blood haemoglobin level meter, Sahli's haemoglobin meter, CuSO<sub>4</sub>, photoplethysmography, and haemoglobin colour strip.

Automated haematology analyser performs blood component analysis with minimal human intervention. Several prominent manufacturer include (Sysmex Corporation, Japan) [31,70,73,75,78], (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China) [78], (Siemens, Germany) [27,64–66,72], (Beckman – Coulter, USA) [58,71,80], and (Fukuda Denshi, Japan) [53].

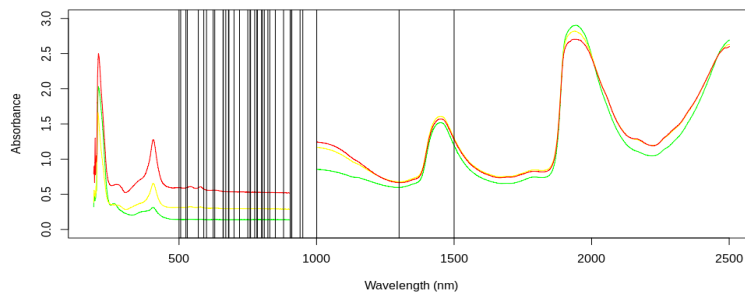
Blood gas analyser measures the number of arterial gases from the measurement sample. Several prominent manufacturers include (Radiometer Medical A/S, Denmark) [52,55,65,76,81,82], (Instrumentation Laboratory, USA) 56, and (Nova Biomedical, USA) [63].

Commercial portable blood haemoglobin level meter uses one - use strip to measure the biomarker. Examples include (HemoCue AB, Sweden) [31,65,71,73,75] and (EKF Diagnostics, USA) [73].

Sahli haemometer is one of the oldest methods to determine blood haemoglobin level. It works by measuring the blood sample colour change due to reaction with acid [74]. CuSO<sub>4</sub> Methods also use similar chemical reaction based principle [73]. Haemoglobin colour strip is the most straightforward methods, which compare the blood colour with provided sample colour images [78].

## Lightsource Wavelength for Non-Invasive Blood Haemoglobin Level Measurement Method

There are 24 light source wavelength combinations that the developers use for non-invasive blood haemoglobin level. Most of the wavelength fits neatly in the window between 500 nm to 1000 nm. The blood-haemoglobin-level control absorbance is low (Fig. 2, Table. 1).



**FIGURE 2.** Lightsource Wavelength for Non-Invasive Blood Haemoglobin Level Measurement, Superimposed to The Absorbance of Biomimetic Blood Haemoglobin Level Control (Green 6.3 g/dl., Yellow 12.2 g/dl., Red 15.2 g/dl.) Wavelength list in Table 1. This chart has incorporate content from our previous publications [11,12]

**TABLE 1. Lightsource Wavelength for Non-Invasive Blood Haemoglobin Level Measurement**

<b>Wavelength</b>	<b>References</b>
500 nm to 1300 nm	(Bhatia and Singh 2015; J Pajares 2015) [71,83]
506 nm and 860 nm	(J Pajares 2015) [71]
525 nm and 590 nm	(Chaskar <i>et al.</i> 2010) [84]
530 nm	(Desai and Chaskar 2016) [15]
570 nm and 700 nm	(Meinke <i>et al.</i> 2005) [85]
570 nm and 880 nm	(Rana <i>et al.</i> 2018) [31]
600 nm to 1500 nm	(J Pajares 2015) [71]
600.22 nm to 1000.60 nm (Continuous)	(Wang <i>et al.</i> 2010; Wang <i>et al.</i> 2013) [39,40]
600nm to 1050 nm, 9 LED	(Ding <i>et al.</i> 2014) [32]
624 nm and 850 nm	(Nirupa and Kumar 2014) [16]
630 nm and 940 nm	(Chugh and Kaur 2015) [86]
660 nm and 850 nm	(Zhang <i>et al.</i> 2018) [47]
660 nm and 940 nm	(Doshi and Panditrao 2013; Bhatia and Singh 2015; Gupta and Chauhan 2016; Pavithra <i>et al.</i> 2017) [17,18,83,87]
661 nm, 681 nm, 783 nm, 823 nm, 850 nm, 910 nm	(Saltzman <i>et al.</i> 2004) [88]
670 nm	(Al-Baradie and Bose 2013) [45]
670 nm and 940 nm	(Rochmanto <i>et al.</i> 2017; Dewantoro <i>et al.</i> 2018; Venkata Praveen Kumar <i>et al.</i> 2019) [26,34,35]
670 nm, 810 nm, 1300 nm	(Timm, Lewis, <i>et al.</i> 2009; Timm, McGrath, <i>et al.</i> 2009; Timm, Lewis, <i>et al.</i> 2010; Timm, Leen, <i>et al.</i> 2010; Kraitl <i>et al.</i> 2011) [19,23,41,89,90]
680 nm	(Suner, McMurdy, <i>et al.</i> 2007) [28]
758 nm, 794 nm and 850 nm	(Teng <i>et al.</i> 2011; Teng <i>et al.</i> 2012) [42,43]
775 nm, 825 nm, 850 nm, 904 nm	(Dullenkopf <i>et al.</i> 2004) [76]
785 nm (Raman)	(Villa-Manriquez <i>et al.</i> 2017) [38]
810 nm, 880 nm, 940 nm	(Sharma <i>et al.</i> 2013) [20]
940 nm	(Umar and Alyah 2019) [91]
950 nm	(Abhishek <i>et al.</i> 2015) [46]

## CONCLUSIONS

The researcher has gathered 13 different non-invasive methods for measurement of blood haemoglobin level, as well as those commercially available. Most of the articles we have gathered are unregistered trials, and the majority of methods are unproven. We are taking this as a research limitation. The unregistered research amount implicates that the researchers should conduct a further trial for each method listed. We have seen that the wavelength used mostly fits nicely between 500 nm to 1000 nm. The researcher found that in these wavelengths, the absorbance is low. However, the correlation to blood haemoglobin level is quite high, which make them easy to utilise for measurement.

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