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NON-BLOOD ANEMIA DETECTION: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Anemia is a serious global health problem that may result in hemorrhage, premature birth, Low Birth Weight, and fetal development disorder. To this day, detection for anemia in midwifery care is still invasive, despite the fact that it has some drawbacks, including the need for blood sampling, expensive cost, the need for skillful health care personnel, and the need for laboratory facility. All these drawbacks make people less interested in undergoing examination. The WHO recommends hemoglobin (Hb) screening using non-invasive methods.

Method: This systematic review is based on the PRISMA protocol with searches from the database of Google Scholar, Pubmed, and Science Direct for publications published from 2010 to 2019. The keywords used were: "Early Detection for Anemia", "Screening for Anemia", and "Non-Invasive Anemia Detection" with inclusion criteria of publications written in English and Bahasa Indonesia, and those published between 2011 and 2019, which resulted in 16 selected publications.

Results: Searches for publications landed 302 published publications, 16 of which meet the criteria. These 16 selected publications consist of 10 publications detecting anemia using fingers, and the remaining six, detect anemia using conjunctiva.

Conclusion: Non-invasive methods are deemed effective in detecting anemia because they are easy to implement, do not require blood sampling, affordable, and do not need skillful health care personnel to administer them, as well as having less possibility for infection. These advantages make non-invasive methods applicable in midwifery care.

Keywords: Early Detection for Anemia, Screening for Anemia, Non-Invasive Anemia Detection

INTRODUCTION

Anemia is a condition of lower hemoglobin concentration in red blood cells. Hemoglobin functions to take oxygen to all body tissues. Hence, lack of it results in fatigue, dizziness, and breathing difficulty. Factors affecting hemoglobin level include age, sex,

environmental factors, smoking, and pregnancy. Meanwhile, the most common causes of anemia include iron deficiency and communicable diseases such as Tuberculosis (TBC) and Human Immunodeficiency Virus (HIV) ⁽¹⁾.

The World Health Organization (WHO) has set standard hemoglobin level for children

aged 6 - 59 months to be 11 gr/dL, women aged 15 - 49 years who are not pregnant nor breastfeeding to be 12 gr/dL and pregnant women to be 11gr/dL, respectively. Estimated prevalence of anemia among pregnant mothers is at 40%, while among children under the age of 5 is at 42% (1). In terms of region, Asia Pacific recorded an increase from 34% to 35% from 2015 to 2016. Meanwhile, prevalence of anemia in Indonesia in 2016 was at 42% (2). The WHO targets a 50% decrease in anemia prevalence from the figures today by 2025 by developing guidelines for prevention, control, and treatment for anemia (3).

Anemia is a serious global health problem, especially when young children and pregnant mothers are affected as it may result in hemorrhage, premature birth, Low Birth Weight, and fetal development disorder (1). Hemorrhage contributes to Maternal Mortality Rate (MMR) in Indonesia by as much as 30.3% (4). One of the measures to reduce maternal and infant mortality rate is improving Antenatal Care (ANC) both by detecting and preventing causes of death (5).

To this day, detection for anemia still uses invasive method of taking blood samples from patients. However, this method certainly has drawbacks, especially when it comes to patients not comfortable with syringe (6). Other than that, invasive method is expensive, and may cause infection for either the health care personnel or the patient, it takes skillful health care professional to administer, and it is really a problem when a rural area facility does not have proper laboratory facilities, which results in lengthy processing to obtain results of examination due to distance from a proper laboratory (7,8). Therefore, the WHO recommends hemoglobin screening using non-invasive methods, that in turn may play a role in improve global health condition (9).

Mannino (10) mentioned that anemia can be qualitatively correlated to subjective evaluation, such as nails, conjunctiva, and creases on the palm. There numerous methods of non-invasive hemoglobin measurement, including pulse oximetry, diffuse reflectance, spectroscopy, photoplethysmography, digital photography and image processing. These may serve as solution to reduce discomfort patients may feel from blood sampling, and they also reduce the risk of

possible infection (7,11). Some researches comparing invasive and non-invasive methods show that results obtained from non-invasive methods are equal to those taken using invasive methods, in terms of sensitivity and specificity. Therefore, it is evident that non-invasive methods can be applied for future health care services (7,12,13).

METHOD

This study uses PRIMA systematic review as guidelines (14).

Search Strategy and Data Source

Literature studied in this research were found from the database of Google Scholar, Pubmed, and Science Direct, covering publications published from 2010 to 2019. The keywords used were “Early Detection for Anemia”, “Screening for Anemia”, “Non-Invasive Anemia Detection”, and 302 publications were found.

Inclusion Criteria

The inclusion criteria for this research are publications written in both English and Bahasa Indonesia published between 2011 and 2019. These publications should also discuss early detection of anemia as intervention, and those that discuss early detection of anemia using non-invasive method. In the meantime, exclusion criteria for this research are; (1) research using blood sampling, (2) research with no effective outcome, (3) research that discuss other diseases, and (4) research that are non-experimental.

Data Extraction

Literature search was performed from January through February 2020. The writers independently search for proper publications and data extraction. Database filtering was then conducted to find publications that meet inclusion criteria. Literatures were reviewed either from their abstracts or full texts to identify the relevant ones. The writers also categorized publications that used non-invasive methods for early detection of anemia, and these selected publications were then further analyzed.

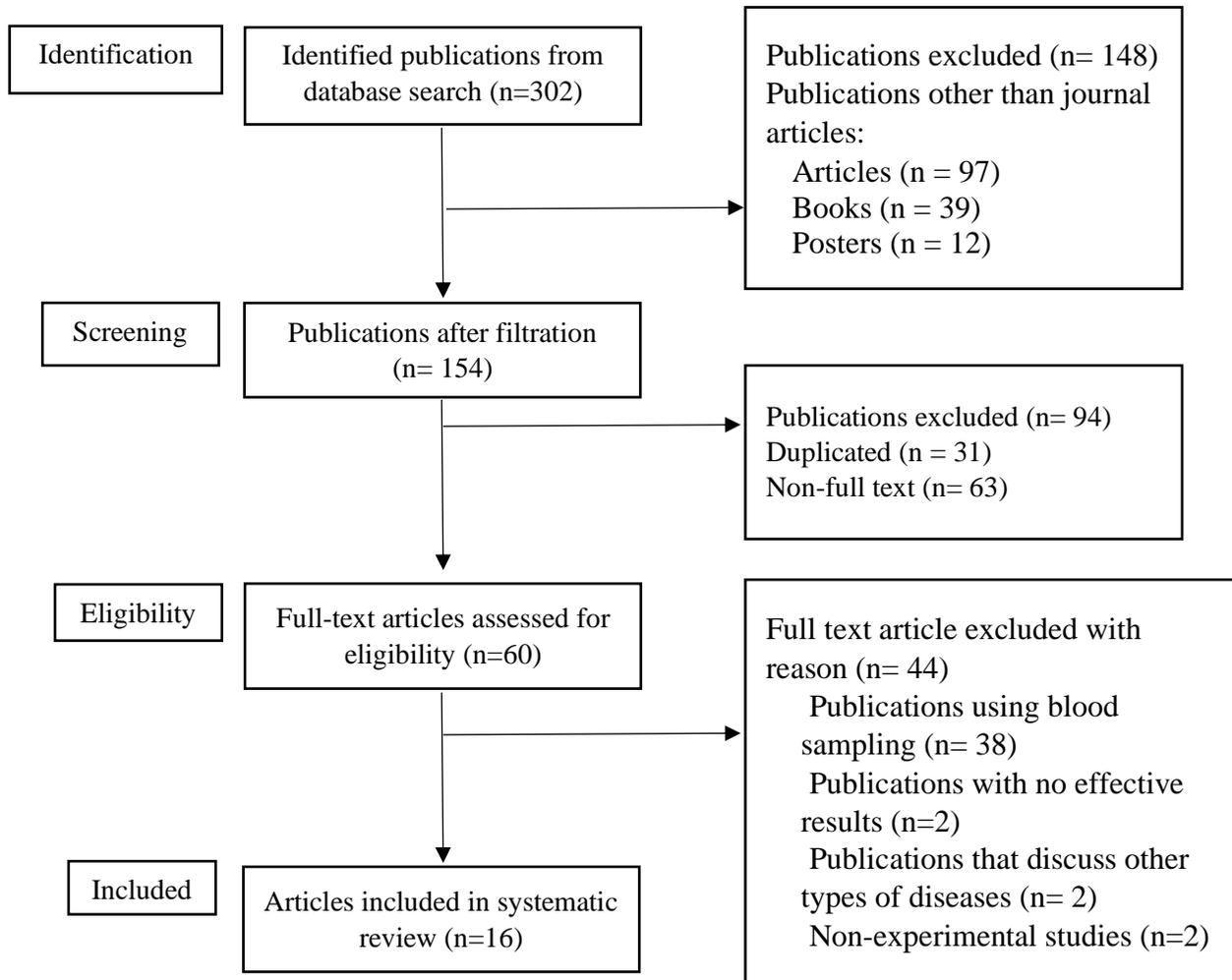


Figure 1 Flowchart of Systematic Review (PRISMA)

RESULTS

Table 1 Early detection for anemia using non-invasive methods

Citation	Name/Year	Title	Sample	Examined Limb	Intervention	Results
(11)	Mallhi, R. S., <i>et al.</i> 2016	<i>Point of Care Hemoglobin Testing in Plateletpheresis Donors: Noninvasive versus Invasive Methods</i>	A total of 500 thrombocyte donor samples at Hb >12.5 g/dl	Thumb	Intervention: Hemoglobin examination was performed using NBM 200 (in which a ring sensor is put on the thumb to temporarily undermine local blood flow whilst the sensor measured transmitted light through the thumb using spectrophotometry). Control: HemoCue measured using SYSMEX KX-21 as standard, in which a drop of blood (capillary blood) taken using sterile blood lancet is put into a cuvette.	NBM 200 was found to be more sensitive (70.59%), specific (98.93%), and precise compared to HemoCue for Hb pre-donation screening in plateletpheresis donation.
(10)	Mannino, R. G., <i>et al.</i> 2018.	<i>Smartphone App for Non-Invasive Detection of Anemia Using Only Patient-Sourced Photos</i>	Intervention: Involving 377 samples consisting of 170 males and 167 females. Control: 100 samples	Thumbnail	Intervention: anemia detection using non-invasive smartphone app by taking a picture of the thumbnail for > 1 minute. Thumbnail pictures were taken instantly after 4 weeks of device calibration. Control: Blood sampling using the complete blood count (CBC) assessment.	This application is much better than the point of care (POC) screening device already available such as HemaApp and conjunctiva analysis from pictures, with the same accuracy as with CBC. This app has a 97% sensitivity.

(15)	Bauskar, S., et al. 2019	<i>A Noninvasive Computerized Technique to Detect Anemia Using Images of Eye Conjunctiva</i>	Involving 99 picture samples taken from 48 anemia patients and 51 pictures taken from non-anemia patients.	Conjunctiva	Sample pictures were taken using Support Vector Machine (SVM) standard camera modified using K-fold cross-validation manually to extract eye conjunctiva and to observe Region Of Interest (ROI) prior to further extraction.	Modified SVM resulted in an accuracy of 93%, sensitivity of 100%, and specificity of 88%.
(16)	Hasan, Md. Kamrul., et al. 2019	<i>Smartphone -based Human Hemoglobin Level Measurement Analyzing Pixel Intensity of a Fingertip Video on Different Color Spaces</i>	Involving 79 samples consisting of 5 hemoglobinopathy patients, and 74 adult normal patients made up of 19 men and 44 women.	Point of finger	Intervention: Five hemoglobinopathy patients took video of their fingertips prior to and after blood transfusion using Google Nexus 4.0 (LG) smartphone, with its camera covered by the finger tip. Control: Fingertip video was taken for 10 seconds each, from 74 healthy individuals.	This non-invasive hemoglobin prediction model using fingertip video in a smartphone is capable of predicting Hb concentration with an accuracy of 95%.
(17)	Yamani, Asma Z., et al. 2019.	<i>A Proposed Noninvasive Point-of-Care Technique for Measuring Hemoglobin Concentration</i>	Involving 75 samples	Fingertip	Intervention: Close up videos of finger tips were taken at the LED wavelength of Samsung Galaxy 6 smartphone with the results then undergoing regression using an Anemeter app. Control: Blood sampling using the complete blood count (CBC) assessment.	This app is capable of providing accurate results at all range of Hb concentration with an accuracy of 95%.

(18)	Dimauro, Giovanni., et al. 2018.	<i>A New Method and a Non-Invasive Device to Estimate Anemia Based on Digital Images of the Conjunctiva</i>	Involving 113 samples Anemia = 29 Non-anemia= 84	Conjunctiva	Intervention: Images of conjunctiva were taken using a smartphone and were then analyzed using an Hb meter app. Control: Hb concentration measured using laboratory examination.	Results show pretty solid correlation (r= 0.726) with results of Hb measurement from blood sampling. This means that this method can be used for anemia filtering.
(19)	Bevilacqua, Vitoantonio., et al. 2016.	<i>A Novel Approach to Evaluate Blood Parameters Using Computer Vision Techniques</i>	Involving 77 samples Anemia = 9 Non-anemia= 68	Conjunctiva	Intervention: Conjunctiva images were taken using a smartphone using computer vision (CV) technique. Control: Hb concentration measured using laboratory methods.	There was significant correlations between values of hemoglobin taken from blood sampling and those resulting from algorithm of this device. The prototypical binary classification algorithm used to measure blood transfusion requirement show proper accuracy (84.4%), specificity (82.4%), and sensitivity (100%). This means that this method can help avoid the need for most blood sampling.
(20)	Hsu, Daniel P., et al. 2016.	<i>Evaluation of a Noninvasive Hemoglobin Measurement Device to Screen for Anemia in Infancy</i>	Involving 110 samples from children age 9-36 months	Toe or thumb	Intervention: Masimo rainbow sensor device is placed on the fingertip using Hemoglobin Spectrophotometry (HbSp) method. Control: Blood samples were taken from the vein using the venipuncture technique to	The practice of non-invasive hemoglobin testing using Masimo Pronto device can be an alternative screening method for anemia among infants in order to avoid the used of invasive methods. This method results in a sensitivity of 82% and specificity of 65%.

					measure complete blood count (CBC).	
(21)	Collings, Shaun. <i>et al.</i> 2016.	<i>Non-Invasive Detection of Anemia Using Digital Photographs of the Conjunctiva</i>	Involving 94 samples taken from both male and female volunteers aged ≥18.	Conjunctiva	Intervention: Conjunctiva images were taken twice (2 times) each using a digital camera (Panasonic DMC-LX5), and smartphone camera (Apple iPhone 5S) and were then digitally analyzed. Control: Blood samples were taken for laboratory tests.	The EI digital method provides a sensitivity of 93%, and specificity of 78% in detecting anemia using Panasonic DMC-LX5.
(22)	Anggraeni, MD., and A Fatoni. 2017.	<i>Non-invasive Self-Care Anemia Detection during Pregnancy Using a Smartphone Camera</i>	Involving 20 samples from pregnant mothers aged 22-36 years.	Conjunctiva	Intervention: Images of conjunctiva palpebral were taken using Asus Zenfone and were then analyzed using ImageJ software to observe conjunctiva color sensitivity. Control: Blood hemoglobin was measured using standard spectrophotometer.	Smartphone cameras can be used to predict anemia with proper correlation ($R^2= 0.814$) between conjunctiva palpebral color intensity and blood hemoglobin concentration.
(23)	Acharya, Soumyadipta., <i>et al.</i> 2019.	<i>Non-Invasive Estimation of Hemoglobin Using a Multi-Model Stacking Regressor</i>	Involving 1583 samples from pregnant mothers aged 17-52 years.	Finger	Intervention: Using photo detector spectroscopy to capture photoplethysmogram (PPGs) signal from fingers. Control: Standard method.	Close correlation between PPG and standard method of 0.81 ($p<0.01$) was measured.
(24)	Ding, Haiquan. <i>et al.</i> 2014.	<i>Non-Invasive Prediction of Hemoglobin Levels by</i>	Involving 109 samples taken from both male and female volunteers aged 23 - 78 years.	Fingertip	Samples of finger spectrum were taken using spectrophotometry, and were then analyzed using Back	The BP-ANN method in combination with PCA has the potential to become a non-invasive method for hemoglobin level as they can come with a correlation

		<i>Principal Component and Back Propagation Artificial Neural Network</i>			Propagation Artificial Neural Network (BP-ANN) method.	value of 0.94, which is pretty accurate.
(25)	Hasan, Md Kamrul. <i>et al.</i> 2017.	<i>A Novel Technique of Noninvasive Hemoglobin Level Measurement Using HSV Value of Fingertip Image</i>	Involving 60 samples taken from both male and female volunteers aged 19 - 62 years.	Fingertip	Intervention: Videos were taken using Nexus 4 smartphone for 10 seconds each and high Saturation-value (HSV) was measured using Hue analysis with Partial Least Squares (PLS) algorithm. Control: Standard method	PLS as an Hb measurement device results in prediction accuracy of 0.95, which is pretty high.
(26)	Chen, YM, and Shaou-Gang Miaou. 2017	<i>A Kalman Filtering and Nonlinear Penalty Regression Approach for Noninvasive Anemia Detection with Palpebral Conjunctiva Images</i>	Involving 100 samples. Anemia = 40 and non-anemia = 60	Conjunctiva	Images taken were resized to 500 × 500 pixels using MATLAB before further processed using the Kalman filtering method and linear regression in order to calculate average red blood components of conjunctiva palpebral as recognition features. The algorithm was then used to find nonlinear curve that matches data value and hemoglobin (Hb) concentration.	Comparison between results of Kalman filtering and linear regression showed a sensitivity of 0.8571.
(27)	Wang, EJ., <i>et al.</i> 2016	<i>HemaApp: Noninvasive Blood Screening of</i>	Involving 30 samples from	Fingertip	HemaApp was used for anemia screening from videos of	HemaApp comes with a sensitivity of up to 85.7% and

	<i>Hemoglobin Using Smartphone Cameras</i>	volunteers aged 6-77 years.		fingertips under all kinds of lighting.	specificity of 76.5% under an LED IR lighting.
(28)	Parker, M., et al. 2018	<i>An Evaluation of Hemoglobin Measurement Tools and Their Accuracy When Screening for Child Anemia in Rwanda: a Randomized Study</i>	Intervention: Involving 132 samples. Control: Involving 132 samples. Involving children age 6-59 months	Fingers or toes	Intervention: The non-invasive device (Pronto® Sensor mini DCI™) is a digital clip that comes with a wavelength sensor and calibration equation to measure percentage of total hemoglobin. Control: The micro cuvette photometric Sysmex KN21 (HemoCue®) device can predict hemoglobin concentration in blood. The non-invasive Pronto® and DCI™ mini sensor can come with 72% sensitivity, 84% specificity, and 80% correct classification. Nonetheless, these percentages are still lower from those of HemoCue®

Characteristic Differences

The total number of samples involved is 3559. One publication only used samples from women ⁽²²⁾. Five publications used samples from both men and women ^(10,16,21,24,25). Two publications included samples from infants aged 6-59 months ^(20,26). Six publications included samples from children, teenagers, adults, and seniors ^(21-25,27). Four publications included both anemia and non-anemia samples ^(15,18,19,26). Those characteristic differences results in varied accuracy, sensitivity, and specificity.

DISCUSSION

Anemia is one of the many risk factors for maternal and neonatal complications. There have been some research that aim to meet the need of care for non-invasive early detection of anemia for midwifery care ^(5,7).

Non-invasive method does not require blood sampling. There are 16 publications presented here with 6 of them developing instruments to detect anemia by examining eye conjunctiva and the remaining 10 by examining fingers.

There are also studies that compare accuracy, sensitivity, and specificity of non-invasive hemoglobin measurement methods using eye conjunctiva in comparison to standard methods. Most non-invasive methods developed using eye conjunctiva analysis as research object come up with proper sensitivity, specificity, and high accuracy. Bauskar ⁽¹⁵⁾ took images of the eyes using modified standard camera with Support Vector Machine (SVM) and then manually extracting eye conjunctiva images and examining Region of Interest (ROI) prior to further extraction using K-Fold cross-validation. This method results in an accuracy of 93%, sensitivity of 100% and specificity of 88%. Giovanni ⁽¹⁸⁾ also came up with a pretty strong correlation ($r = 0.726$). Bevilaqua ⁽¹⁹⁾ showed that non-invasive techniques can also detect anemia via conjunctiva with the help of Computer Vision (CV), with resulting accuracy of 84.4%, sensitivity of 100% and specificity of 82.4%.

There have also been some instruments devised by camera modification plus image analysis software to examine conjunctiva. Cameras are modified using Support Vector Machine (SVM) and Computer Vision (CV). Nonetheless, non-invasive techniques that observe conjunctiva must still be complemented by image analysis software such as EL digital, ImageJ, Kalma filtering, and linear regression ^(21,22,26), and even an application to analyze conjunctiva images called Hbmeter ⁽¹⁸⁾.

Other than conjunctiva, hemoglobin measurement can also be carried out using fingers as the object in order to analyze accuracy, sensitivity, and specificity of non-invasive methods. Mannino ⁽¹⁰⁾ took images of nails using a smartphone (iPhone 5) to detect anemia with resulting accuracies comparable to those gained using Complete Blood Count (CBC) and has sensitivity of 97%, as well as much better evaluation compared to using point-of-care (POC) screening instrument developed, such as HemaApp and conjunctiva analyses from images.

Mannino ⁽¹⁰⁾ also recommended that finger tips can be used as objects in detecting anemia, as they do not contain melanocyte (skin cell that produces melanin). Some researches that make use of fingertip method also combined it with different evaluation components such as pixel intensity of the fingertip (95% accuracy), finger spectrum sample ($r = 0.94$), High Saturation-Value (HSV) (0.95 prediction accuracy) (72% sensitivity and 84% specificity) and photoplethysmogram signal (PPGs) ($r = 0.81$), as well as Back Propagation Artificial Neural Network (BP-ANN) method ($r = 0.94$) (19-22,24). Meanwhile, there are also researches that use applications to analyze images such as Anemeter and HemaApp ^(17,27). Other parts of the fingers that can be used for hemoglobin measurement include thumb or toe with the help of measurement devices such as digital clip and NBM 200, both of which are equipped with wave and light sensors to measure Hemoglobin Spectrophotometry (HbSp) ^(11,20,28).

In the meantime, limitations associated with early detection for anemia using non-invasive methods include use of different kinds of components and

image analyses that result in various levels of accuracy, sensitivity, and specificity.

CONCLUSION

The sixteen publications studied here show that non-invasive methods are effective in detecting anemia. The researchers recommend non-invasive method for early detection of anemia to be applied in midwifery care for mothers and children as they are easy to use, do

not require laboratory equipment, do not require blood sampling, affordable, and do not require skillful health care personnel to administer, and do not pose any risk of infection.

CONFLICT OF INTEREST

The writers hereby states that there is no conflict of interest whatsoever with any company, publisher, or journal writer concerning this review paper.

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