Development and Validation of remote Photoplethysmography (rPPG) Technology for Blood Pressure and Hemoglobin Level Assessment in the Preoperative Assessment Setting

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Abstract

Background: Various studies have been written about noninvasive, remote photoplethysmography-based measurement of blood pressure (BP) and, to a lesser extent, hemoglobin (Hb) concentration. Widespread applicability has yet to be achieved due to limitations with agreement and correlation. There is also limited data on rPPG BP and Hb measurement evaluation in representative populations at the preoperative evaluation clinic (PEC) setting, such as hypertensive patients and patients with diverse, varying skin tones.

Objective: We assessed the accuracy of rPPG technology in noninvasive systolic BP (SBP) and diastolic BP (DBP) measurements compared to automated cuffed blood pressure measuring devices (BPMD). Additionally, we compared the accuracy of rPPG Hb concentration measurement to that of clinical laboratory testing.

Methods: Nervotec rPPG telehealth and smartphone software utilizes the principle that reflected light from various skin areas is affected by the volume of blood under the skin, which varies according to arterial pulsations and blood flow. This principle allows for an optical measurement technique that measures these variations. The measurements are then analyzed with signal processing algorithms which generate physiological measurements such as BP and Hb. The study was conducted at Singapore General Hospital (SGH) from 15 February 2023 to 6 December 2024. The participants were recruited in two phases. The first group, used for training and evaluating the algorithm, consisted of 100 patients with a mean age of 52.9 ± 13.1 years. In this group, 59% of patients had concomitant medical diseases such as hypertension (HTN) and diabetes mellitus (DM). The second group, used for validation of the algorithm, consisted of 65 patients with a mean age of 55.15 ± 17.27 years. 43% of the patients had concomitant medical conditions such as HTN, DM and ischemic heart disease (IHD). Both groups had an even distribution of males and females, as well as a diverse range of skin tones (1-10) classified according to the Monk Skin Tone (MST) scale. The primary analysis was focused on assessing the accuracy of rPPG BP measurements compared to BPMD BP measurements. The secondary analysis aimed to evaluate the accuracy of rPPG Hb concentration measurement compared to clinical laboratory testing.

Results: Our study demonstrated an accuracy of 83.84% for SBP and 90.55% for DBP, with mean absolute percentage errors (MAPE) of 16.16% for SBP and 9.45% for DBP. Furthermore, the model could predict Hb concentration with an accuracy of 88.41%. MAPE was 11.59%, with an error bias of 0.54 g/dL and an error SD of 1.82 g/dL.

Conclusions: Our study is the first to evaluate contactless rPPG BP and Hb concentration measurements in a diverse, heterogeneous study population. The model achieved a DBP accuracy rate of 90.55% with a MAPE of 9.45%. We recorded a MAPE of 16.16% for SBP, and a MAPE of 11.59% for Hb concentration. Quartile evaluation indicated stronger correlations in mid-quartile ranges for DBP (70-74 mmHg) and Hb (13.2 - 14.4 g/dL), confirming the model's reliability in detecting moderate

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Keywords: blood pressure; hemoglobin; noninvasive; remote; telehealth; remote photoplethysmography; smartphone; hypertension; anemia; mHealth; mobile health

Introduction

Population growth and aging, combined with technological advances and treatment perspective changes, will significantly increase the demand for surgical services. [1,2] One of the clinical areas which may subsequently face increased demand for services is the preoperative evaluation clinic (PEC). Patients needing elective procedures and surgery requiring anesthesia usually undergo a standard preoperative evaluation. This is traditionally done in person at the preoperative evaluation clinic situated within the hospital. [3] Novel possibilities for mobile health (mHealth) have emerged due to the rapid advances in mobile communication devices such as smartphones and tablets. With over 1 billion smartphones and 100 million tablets worldwide, these devices have great potential to become valuable healthcare management tools. [4] Furthermore, telemedicine has grown incrementally in recent years and continues to do so with expansive speed and scale. [5] Telemonitoring is a viable future adjunct that could improve patient care and the effectiveness of treatment in a rapidly aging population with an increasing number of chronic health conditions.[6,7] Implementing a mHealth and telemedicine-based preoperative anesthesia evaluation process can translate into higher patient satisfaction scores and cost savings without increasing day-of-procedure case cancellations. [8]

Blood pressure (BP) and hemoglobin (Hb) concentration are two essential physiological measurements taken during the preoperative evaluation process. Preoperative hypertension is associated with increased perioperative risk. [9] An estimated 1.28 billion adults aged 30-79 years worldwide have hypertension, yet only 1 in 5 people have well-controlled hypertension. [10] The overall pooled prevalence estimate of hypertension for urban Southeast Asian populations is 33.82%. [11] Ambulatory blood pressure monitoring (ABPM) is currently considered the gold standard for accurately diagnosing hypertension. [12] Home BP mHealth monitoring or telemonitoring may lead to better control of ambulatory BP, especially among those with inadequate BP control. [13] [14] [15] Nevertheless, clinic BP measurement has a validated role in medical practice and is the basis on which the majority of literature is founded upon. [12] Hb concentration is one of the most essential components of perioperative blood testing. Preoperative anemia is common and is associated with increased one-year mortality. [3] [16] Anemia is also one of the strongest risk factors for perioperative blood transfusions, which could bring further complications. [17]

Currently, the automated cuffed blood pressure measuring device (BPMD) is the most widely used BP measurement method. [18] Hb concentration is traditionally measured with an invasive blood test. The ideal alternative is noninvasive, contactless physiological monitoring based on remote photoplethysmography (rPPG), an emerging technology that could lead to a positive disruption in healthcare. rPPG technology relies on a ubiquitous, consumer-grade smartphone camera for detection and does not require skin contact, potentially revolutionizing the domain of telemonitoring and mHealth. [19,20] It works on the principle that reflected light from the various regions of the skin is affected by the volume of blood under the skin. [21] By applying this principle, rPPG technology allows for an optical measurement technique that quantifies peripheral blood volume and flow variations. [22] These measurements are then analyzed with signal processing algorithms which then generate physiological measurements, such as blood pressure (BP). [23] In the context of the PEC, the development and validation of contactless rPPG BP and Hb concentration assessment have immense potential applications for telemedicine and mHealth-based preoperative evaluation. A strategic pivot to contactless rPPG vital sign measurement could lead to less strain on healthcare workers and physical resources, allowing optimal allocation of hospital assets that would ordinarily be poured into traditional in-person vital sign measurements. [24] Vital signs monitoring via a contactless smartphone-enabled rPPG platform could potentially enable a higher fidelity telemedicine-based PEC evaluation.

Despite the potential advantages of contactless rPPG vital sign monitoring, there are currently some important limitations that our study aims to address. Most early studies on contactless rPPG based BP measurement were performed in a non-clinical setting. [25] Moreover, they have primarily been conducted on healthy, normotensive subjects with similar skin tones. [23,26] We surmise that these limitations must be addressed for rPPG technology to achieve rapid widespread, commercially viable usage in the clinical setting. Our study aims to develop and validate a rPPG technology

platform for remote BP monitoring and Hb concentration estimation across a representative range of BP readings and skin tones in the Asian population. Such a platform could promote elevated individual patient experience due to increased convenience, reduced entry-level costs and earlier access to healthcare.

Methods

Study Design

The study was conducted at Singapore General Hospital (SGH) from 1 March 2023 to 27 March 2024. Our study used a prospective feasibility design to compare contactless rPPG BP and Hb concentration measurements, with BPMD BP and clinical laboratory Hb concentration measurements.

Participants

The study was approved by the SingHealth Centralised Institutional Review Board (CIRB Ref: 2023/2042) from 15 February 2023 to 6 December 2024 and is registered on ClinicalTrials.gov (Trial number: NCT06320847). All patients who presented to the PEC at SGH during the study period were screened for eligibility. Inclusion criteria were: (1) all patients aged above 21 years (2) presenting for any surgery except head and neck surgery and (3) with the ability to give informed consent. Exclusion criteria were: (1) patients less than 21 years old (2) inability to give informed consent or (3) patients undergoing head and neck surgery. Participation was voluntary and written informed consent was obtained from all participants.

Data Collection

Patients were seated comfortably in the PEC with Nervotec's contactless rPPG vital signs measurement technology and equipment for standard reference measurements (automated cuffed BPMD and pulse oximeter), as illustrated in Figure 1 below. Patients were situated in a private room and positioned comfortably with their arms placed at a 90-degree angle on the table. Two individual measurements were obtained sequentially using both the Welch Allyn Connex® machine and Nervotec's rPPG technology. Nervotec, our technical partner, is a Singaporean digital health and artificial intelligence (AI) company that has successfully used rPPG technology in telehealth and mHealth applications to allow for the collection of rPPG waveforms via smartphones. Their base technology measures heart rate (HR), heart rate variability (HRV), respiration rate (RR) and blood oxygen saturation (SpO2) levels through signal processing techniques of a quick facial scan via the smartphone camera.

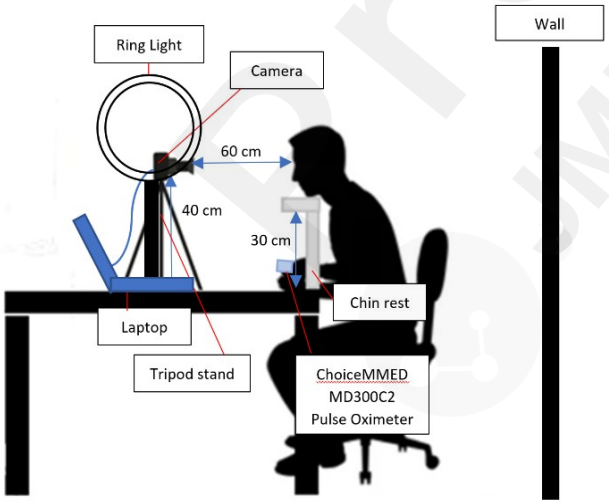


Figure 1. Equipment set-up for vital signs monitoring with Nervotec rPPG in the preoperative clinic

The study team administered a pulse oximeter in conjunction with the Welch Allyn Connex® Vital Signs Monitor 6000 Series™, which serves as the standard equipment within the preoperative clinic setting. Simultaneously, the vital signs, including HR, RR, SpO2, HRV, and BP estimates, were captured using Nervotec's rPPG technology, recorded via the laptop and webcam setup. A synchronized measurement process lasting 3 minutes was conducted to collect these parameters. Furthermore, Hb levels were retrospectively derived from the rPPG scans, comprehensively evaluating each patient's physiological state.

Information on age, height, weight, gender, ethnicity, Monk Skin Tone Scale (MST Scale), relevant medical history and routine preoperative blood investigation results (full blood count, renal panel, anemia panel, coagulation, thyroid function) were collected from the patient's electronic medical records. The Monk Skin Tone Scale is a validated alternative to prior skin tone scales (e.g. Fitzpatrick Scale), which has been adopted for multiple uses, including artificial intelligence and machine-learning. [27] Data collected using the rPPG were non-identifiable, and only numerical data was collected. No photographic face recognition data was stored. The regions of interest captured by the rPPG were the forehead and bilateral cheeks, as indicated in Figure 2 below.

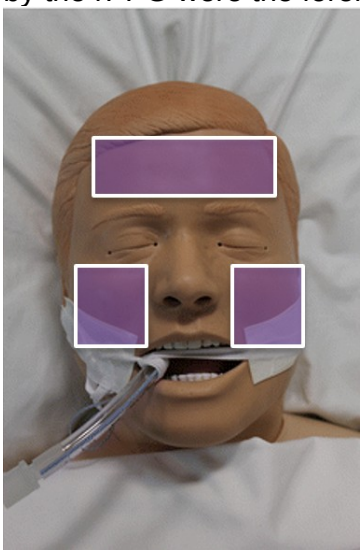


Figure 2: Regions of interest for rPPG technology.

Data Pre-Processing

The dataset was pre-processed to train the model. This was done by slicing the entire dataset into small windows of 60 frames. Each rPPG scan, typically captured over 60 seconds at 30 frames per second using Nervotec's proprietary software NervoScan, was divided into smaller windows of 256 frames [28] Each window spanned 8.53 seconds, aligning with the pragmatic goal of achieving real-time estimates within each scan segment's duration. [29] This window size ensured computational efficiency and captured at most three heartbeats, providing sufficient data granularity for a robust analysis. The selected size balanced the need for detailed data with the requirements for real-time processing, which was critical for accurately monitoring BP and Hb levels changes. Given the limited dataset size, this segmentation also facilitated necessary data augmentation for efficient AI model training.

Training and evaluation datasets

After data pre-processing and data augmentation, the AI model was trained to predict the SBP, DBP and Hb concentration from the respective BPV signals. Our data consisted of a primary and secondary dataset. The primary dataset was used for both training and evaluation, and the secondary dataset was used for the final validation of the AI model. Table 1 shows the data distribution for training (train and validation) and testing (test) the AI model.

Data distribution from primary dataset (n=100)	
Train	72%
Validation	8%
Test	20%
Data distribution from secondary dataset (n=65)	
Test	100%

Table 1: Data distribution for training and evaluating the AI model.

The network was trained on the given data as shown in Table 1 with a split of 72% and 8% (80%) from the first dataset. The trained model was then evaluated on the test data, which was 20% of the total dataset, independent of the train and validation set.

Subsequently, to further evaluate the model's performance, we collected vital signs from another 65 participants with diverse characteristics, specifically to further evaluate and validate the performance of our BP and Hb predictive models. Table 2 shows the demographics and characteristics of the participants in both datasets (n= 100 + 65). Our patient characteristics are representative and reflective of the PEC patient population. The majority of patients had concomitant medical conditions such as prehypertension, HTN, DM and IHD. The study population also consisted of an ethnically diverse mix of patients, which reflects Singapore's population demographics accurately. Additionally, our study population included patients with 10 varying skin tones, classified according to the MST scale.

Results

Baseline Characteristics

The study involved two datasets for validating predictive models of BP and Hb, with 100 participants in the training set and 65 in the evaluation set. These participants reflect the diversity of the PEC patient population.

In the training dataset, participants had an average age of 52.9 years (SD 13.1), from under 40 to over 60 years, with a balanced gender distribution of 46% females and 54% males. The ethnic composition was predominantly Chinese at 75%, with other ethnicities including Malay, Indian, and others making up the remainder. Skin tones varied widely, with 38% falling within the lightest range (1-3 on the Monk-Skin Tone scale) and a significant representation in darker tones. Clinically, 28% had hypertension and 13% had diabetes, among other conditions.

The evaluation dataset showed a slightly older average age of 55.15 years (SD 17.27) and a higher proportion of females at 54%. This group was also predominantly Chinese at 81.5% and similarly showed a broad distribution of skin tones, primarily in the mid-range. Medical conditions were comparable to those of the training dataset, with hypertension present in nearly 31% and prehypertension in 40%, highlighting the dataset's clinical relevance.

Characteristic	*A. Training Dataset (n=100)*	*B. Evaluation Dataset (n=65)*
No. participants analyzed	100	65
Age (mean ± standard deviation)	52.9 ± 13.1 years	55.15 ± 17.27 years
Age groups	<40 years: 16 (16%)	<40 years: 17 (26%)

	40-59 years: 51 (51%) ≥ 60 years: 33 (33%)	40-59 years: 15 (23%) ≥60 years: 33 (51%)
Gender Distribution	Females: 46 (46%) Males: 54 (54%)	Females: 35 (54%) Males: 30 (46%)
Race/ethnicity: n, %	Chinese: 75 (75%) Indian: 9 (9%) Malay: 10 (10%) Eurasian: 1 (1%) Filipino: 3 (3%) Others: 2 (2%)	Chinese: 53 (82%) Indian: 3 (5%) Malay: 7 (11%) Eurasian: 1 (2%) Filipino: 1 (2%)
Monk-Skin Tone (MST)	1-3: 38 (38%) 4: 18 (18%) 5: 17 (17%) 6: 13 (13%) 7: 6 (6%) 8: 4 (4%) 9-10: 4 (4%)	1-3: 1 (1%) 4: 17 (26%) 5: 31 (47%) 6: 12 (18%) 7: 3 (4%) 8: 1 (1%) 9-10: 0 (0%)
Underlying medical conditions	None: 59 (59%) Diabetes Mellitus: 13 (13%) Hypertension: 28 (28%)	None: 37 (57%) Diabetes Mellitus: 12 (18%) Hypertension: 20 (31%)

Table 2: Patient characteristics of the primary training and evaluation dataset, n=100 (A) and the secondary evaluation dataset, n=65 (B)

Specifically, Table 3 shows the blood pressure distribution for systolic and diastolic for the evaluation dataset in comparison to the ANSI/AAMI/ISO 81060-2:2013 guidelines.

	Required minimum as per ANSI/AAMI/ISO 81060-2:2013 guidelines	*Training dataset (n=100)*	*Evaluation dataset (n=65)*
Reference SBP (mmHg), mean ± SD (min–max)			
≥160 mmHg (%)	5	4	8
≥140 mmHg (%)	20	22	15
≤100mmHg (%)	5	9	8
Reference DBP (mmHg), mean ± SD			

(min–max)			
≥100 mmHg (%)	5	0.5	0
≥85 mmHg (%)	20	21	14
≤60 mmHg (%)	5	2	5

Table 3: Blood Pressure distribution for Evaluation Dataset in comparison to ANSI/AAMI/ISO 81060-2:2013 guidelines

Primary analysis - SBP and DBP

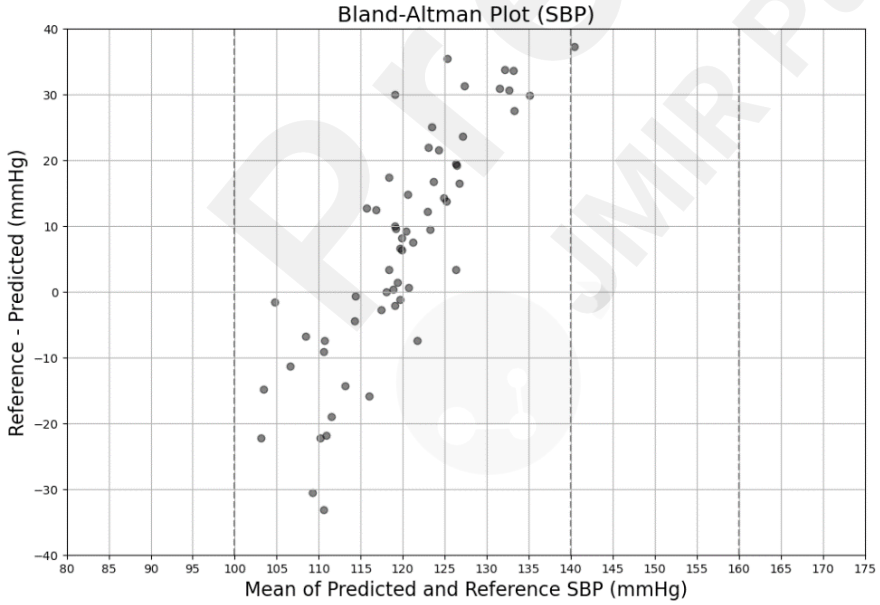
Our study demonstrated an accuracy of 83.84% for SBP and 90.55% for DBP, with mean absolute percentage errors (MAPE) of 16.16% for SBP and 9.45% for DBP. The mean NervoScan Systolic Blood Pressure (SBP) was 116.33 mm Hg (SD 4.86 mm Hg), and the mean reference SBP was 127.45 mm Hg (SD 20.16 mm Hg). The difference between the NervoScan and reference SBP measurements was -11.12 mm Hg (SD 21.30 mm Hg).

For DBP, the mean test DBP was 84.87 mm Hg (SD 4.08 mm Hg), while the mean reference DBP was 75.08 mm Hg (SD 8.90 mm Hg). The mean difference was 9.80 mm Hg (SD 9.45 mm Hg), showing that the test method tends to measure higher compared to the reference method.

We evaluated model performance in terms of agreement using a Bland–Altman plot (Fig. 3). Overall, BPs in the lower end of the range tended to be overestimated and those at the higher end of the range tended to be underestimated for both SBP and DBP.

For SBP, predictions were best for reference blood pressures in the range of 100 to 120 mmHg, where the mean absolute difference between predicted and actual measurements was about 6.07 mmHg. For DBP, the accuracy of the predictions were the highest in the range of 80 to 100 mmHg, with a mean absolute difference of only 4.84 mmHg. These values are below the 6.93mmHg threshold for SBP and the 6.84mmHg threshold for DBP, thus satisfying ANSI/AAMI/ISO 81060-2:2013 standard criterion for both systolic and diastolic pressures.

A



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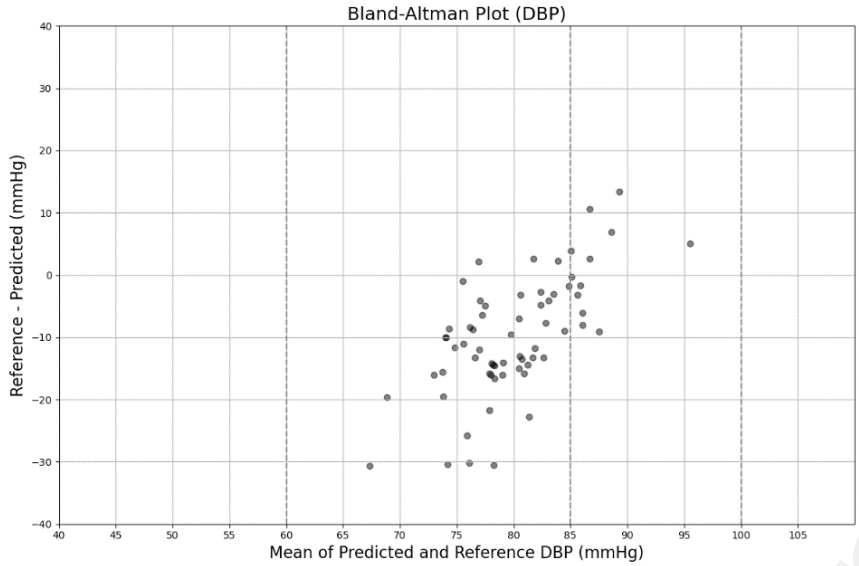

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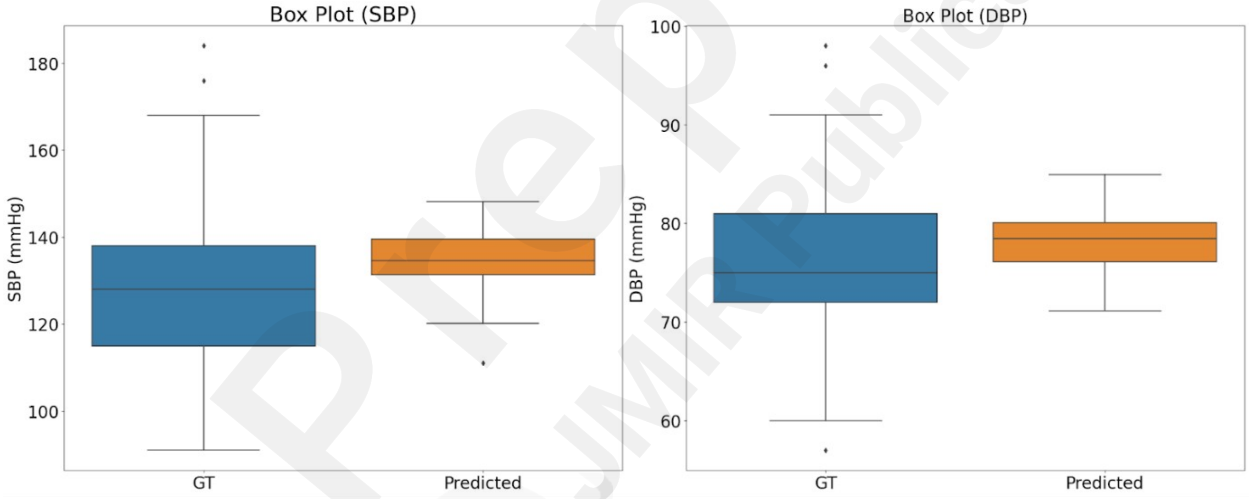

Fig 3. Bland-Altman plots comparing measurements of (A) SBP and (B) DBP between the predicted and standard reference measurements and box plots (C) comparing measurements of (A) SBP and (B) DBP between the predicted and standard reference measurements. The error bias and standard deviations (SD) were 6.12 ± 22.99 mmHg for SBP and 2.38 ± 8.32 mmHg for DBP, respectively.

Secondary analysis - Hb concentration

Our model was able to predict Hb concentration with an accuracy of 88.41%. MAPE was 11.59%, with an error bias of 0.54 g/dL and error SD of 1.82 g/dL. The Hb measurements in 65 participants indicated that the mean test Hb was 13.85 g/dL (SD 0.74 g/dL) and the mean reference Hb was 13.31 g/dL (SD 1.73 g/dL). The mean difference was 0.54 g/dL (SD 1.80 g/dL). Predictions for Hb were best in the range of 13-14 g/dL with a mean absolute error of 0.2.

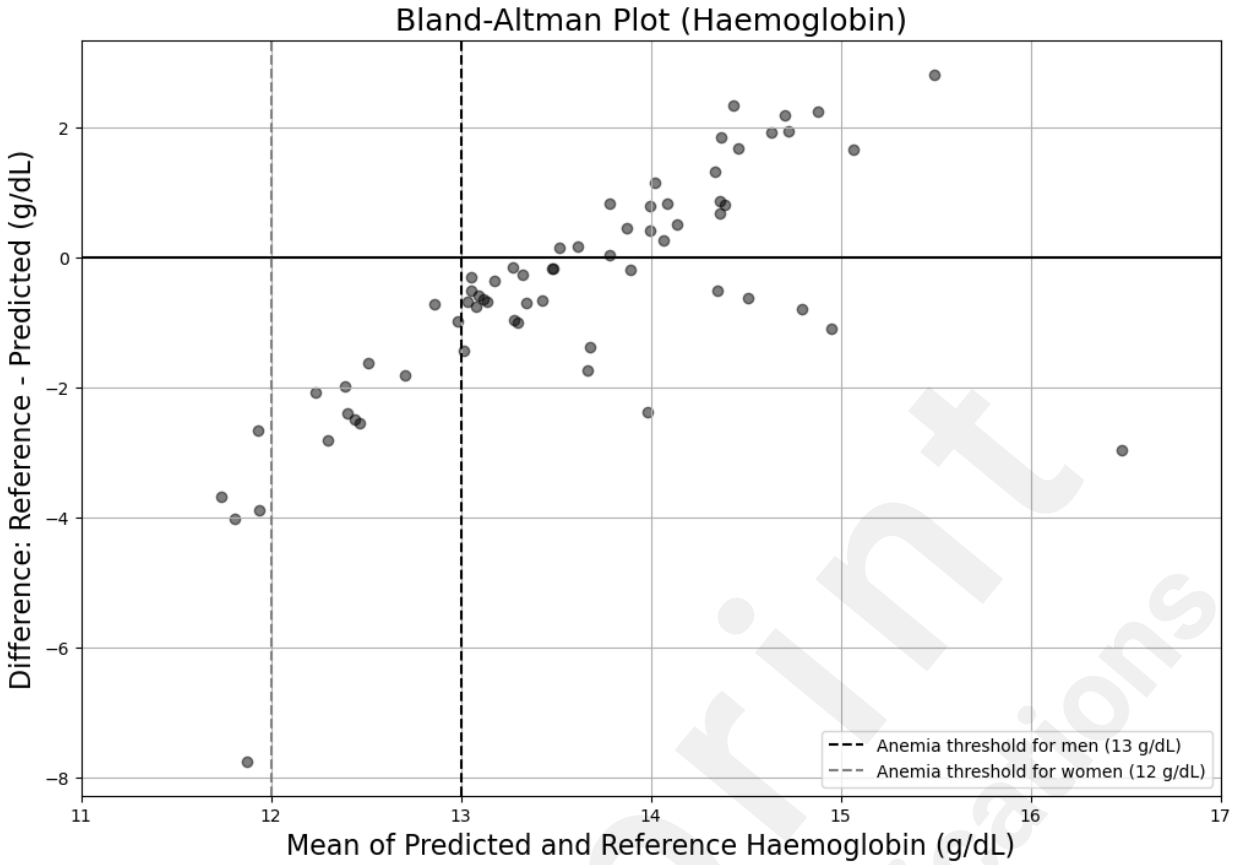

Fig 4. Bland-Altman plot comparing Hb measurements between the predicted and standard reference measurements.

	SBP, mmHg	DBP, mmHg	Hb, g/dL
NervoScan, mean (SD)	116.33 (4.86)	84.87 (4.08)	13.85 (0.74)
Reference Device, mean (SD)	127.45 (20.16)	75.08 (8.90)	13.31 (1.75)
Difference, mean (SD)	11.12 (21.47)	-9.80 (9.53)	-0.5 (1.8)

Table 4. Summary of primary analysis results for SBP, and DBP and Hb

Table 5 summarizes the results of our study:

Measurement	*Accuracy (%)*	*MAPE (%)*
SBP	83.84	16.16
DBP	90.55	9.45

Hb	88.41	11.59

Table 5: SBP, DBP and Hb predictive model results

Discussion

Our study substantiates the efficacy of the rPPG-based model for accurately predicting vital signs, notably BP and Hb measurements. The model achieved a DBP accuracy of 90.55% with a MAPE of 9.45%. We recorded a MAPE of 16.16% for SBP, and a MAPE of 11.59% for Hb concentration. These results are promising, given the diverse and complex demographic characteristics of our study population, which includes patients with a wide range of skin tones and common comorbidities such as prehypertension and hypertension.

The proposed model showed better or increased performance within certain physiological ranges. Specifically, SBP predictions were most accurate within the range of 100 to 120 mmHg and DBP between 80 to 100 mmHg. These findings conform to the ANSI/AAMI/ISO 81060-2:2013 standard criteria, with mean absolute differences of 6.07 mmHg for SBP and 4.84 mmHg for DBP, respectively. Also, the Hb estimates were predicted with a mean absolute error of 0.2 g/dL in the range of 13-14 g/dL. Further analysis through quartile evaluation indicated stronger correlations, particularly in mid-quartile ranges for DBP (70-74 mmHg) and Hb (13.2 - 14.4 g/dL), confirming the model's reliability in detecting moderate deviations from normal physiological states.

As demonstrated in Table 3, the BP distribution of our dataset generally adhered to the ANSI/AAMI/ISO 81060-2:2013 guidelines. However, the study faced limitations due to the small size of our dataset, which comprised 100 subjects for training and 65 for evaluation. This was evident in the distribution of SBP and DBP readings. For instance, in the training dataset (n=100), 4.5% of subjects had SBP ≤ 100 mmHg and only 2.0% had DBP ≤ 60 mmHg. Extreme high values were also underrepresented, with no subjects having a DBP > 100 mmHg. Similarly, in the evaluation dataset (n=65), SBP values > 160 mmHg were present in only 10.76% of cases, and again, no cases of DBP exceeded 100 mmHg. This under-representation at both tail ends of the blood pressure spectrum limited the model's prediction capabilities. The heterogeneity within our existing dataset facilitated an assessment across a substantial range of blood pressure values, albeit with some under-representation or class-imbalance at extreme levels.

A previous study of noninvasive Hb concentration measurement based on the difference of optical densities induced by cardiac pulsations demonstrated a strong positive correlation between laboratory and noninvasive Hb concentration measurements. However, the study was limited to a small sample of patients with normal Hb values and homogenous characteristics. [30] Another study comparing Hb concentration values obtained with a widely available noninvasive point-of-care device against laboratory testing showed that the noninvasive device was systematically biased and too unreliable to guide transfusion decisions. [31] Our Hb model had a similar limitation to our BP model, where data was sparse below 12.70 g/dL and above 14.40 g/dL. This skewness in data distribution underscores the need for a more balanced dataset that includes the full spectrum of physiological variations. [29]

The potential applications for this technology are vast. Given the current model performance, an important application of our model lies in its potential as a triaging tool within both hospital and population health settings. By stratifying patient readings into distinct zones—normal, caution, and critical—our model can significantly optimize the triaging process, thereby reducing the workload on healthcare professionals and increasing the efficiency of patient management. Our data revealed that the model successfully identified 65% of prehypertension cases and 37.5% of hypertension cases, highlighting its potential utility in detecting critical health indicators within clinical and remote monitoring environments. Furthermore, this model can be integrated into a mobile application (mHealth) that supports the trend towards more individualized and accessible healthcare solutions. Such an application could dramatically enhance ambulatory chronic disease management by enabling continuous monitoring and early detection, potentially reducing emergency visits and associated healthcare costs.

Considering the immense potential of this technology, the results of our study support further data

evaluation and development of clinical applications for the rPPG model. We anticipate that significant advancements in the model's diagnostic capabilities and accuracy can be made if we expand our dataset by including more data points, especially for under-represented values at the extremes of physiological range. This will expand the model's clinical applicability across various settings, providing real-time, actionable insights into patients' health trajectories.

Primary and ambulatory care patients may self-monitor their vital signs continuously and conveniently, which could be used to diagnose hypertension [32] without physically traveling to a health facility. This may allow timely intervention while reducing unwarranted hospital visits and transport costs [33] Apart from hypertension, other common conditions such as diabetes may also be monitored with this technology. [32] For example, rPPG technology could be developed upon to measure glycated Hb to diagnose diabetes mellitus and monitor glucose control in patients known to have diabetes. [34] In-hospital applications would include continuous contactless monitoring in the emergency department, post-anesthesia care unit or intensive care unit and could possibly decrease human errors and improve patient safety. [35] Contact-free monitoring of pulse rate has also been described as a viable method for triage of patients in an emergency setting. [36]

In summary, our study not only advocates for the continued refinement and deployment of the rPPG-based model but also underscores its potential as a vital resource in healthcare, promoting effective medical resource allocation and enhancing patient care outcomes. Our proactive approach to recruiting a broad spectrum of subjects, including those with underlying health conditions, establishes a new standard in the field and demonstrates our commitment to advancing the model's precision and general applicability.

Conclusion

Our study evaluated contactless (rPPG-based) BP and Hb concentration measurements in a diverse, heterogeneous and population. It was also conducted in a practical and real-world setting, similar to the settings where commercially viable devices could be used. The model achieved a DBP accuracy rate of 90.55% with a MAPE of 9.45%. The SBP recorded a MAPE of 16.16%, and Hb concentrations exhibited a MAPE of 11.59%. In addition, the Quartile evaluation indicated stronger correlations particularly in mid-quartile ranges for DBP (70-74 mmHg) and hemoglobin (13.2 - 14.4 g/dL), confirming the model's reliability in detecting moderate deviations from normal physiological states. Our current model performance carries potential as a triaging tool within both hospital and population health settings.

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Author Contributions

Conceptualization, H.R.A. and J.C.; Methodology, H.R.A. and J.C.; Software, validation, formal analysis, M.C. and U.J.; Investigation, S.T., H.R.A and M.C.; Resources, H.R.A., M.C. and U.J.; Data curation, B.T. and B.C.; Writing – original draft preparation, S.T.; Writing – review and editing, S.T., H.R.A., M.C. and U.J.; Supervision, H.R.A. Funding acquisition, H.R.A.

Supplementary Files