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Mobile Health (mHealth) and Advances in Noninvasive Diagnosis of Anemia: An Overview

Saúde móvel (mHealth) e avanços no diagnóstico não invasivo de anemia: Uma visão geral

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Abstract

Anemia is a public health problem that can have different causes, such as iron deficiency, vitamin deficiency, inflammation, hemolytic anemias, and anemias associated with bone marrow disease. Anemia shows a decrease in the concentration of hemoglobin, a pigmented molecule in the erythrocytes. The objectives of this review were to highlight the impact of nutritional factors on morbidity and mortality caused by anemia and to present different non-invasive approaches that use a smartphone to analyze hemoglobin levels to detect anemia. According to the records of the Brazilian Unified Health System (SUS, in the Portuguese acronym), ~ 440,000 people checked in hospitals due to anemia between January 2015 and April 2020, with 215,000 deaths. The government spent ~ 294 million Brazilian Reais (more than 50 million US dollars) on anemia hospitalization cases during this period. There is a worldwide search to provide noninvasive diagnostics and mobile health (mHealth) tools to help diagnosing anemia. The smartphone appears to be a viable device to detect anemia by a camera with colorimetric analysis of images providing a quantitative, instantaneous, and noninvasive result. These images can be obtained as a photograph or extracted from video frames. The review presents three different methods of detecting anemia using a smartphone: *i*) photoplethysmograph from video obtained from the tip of the index finger, *ii*) photo of the palpebral conjunctiva, and *iii*) fingernail photo app. Therefore, it seems urgent that these approaches may be applied in routine clinical diagnosis to allow remote, needy, low-tech locations to have access to anemia screening.

Keywords

- anemia
- coronavirus infections
- micronutrient deficiency
- mobile health (mHealth)
- smartphone

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Resumo

A anemia é um problema de saúde pública que pode ter diversas causas como, por exemplo, deficiência de ferro, deficiência de vitaminas, inflamação, anemias hemolíticas e anemias associadas a doenças da medula óssea. A anemia apresenta uma diminuição na concentração de hemoglobina, uma molécula pigmentada nos eritrócitos. Os objetivos desta revisão foram destacar o impacto dos fatores nutricionais na morbidade e mortalidade causadas por anemia, e apresentam diferentes abordagens não invasivas que usam smartphone para analisar os níveis de hemoglobina, para detecção de anemia. De acordo com os registros do Sistema Único de Saúde brasileiro (SUS), 440 mil pessoas foram internadas em hospitais com anemia, entre janeiro de 2015 e abril de 2020, com 215.000 óbitos. O governo gastou 294 milhões de reais (mais de 50 milhões de dólares) em casos de hospitalização por anemia durante esse período. Existe uma busca mundial para o desenvolvimento de ferramentas não invasivas para diagnóstico e uso de saúde móvel (mHealth) para ajudar na detecção de anemia. O smartphone surge como um dispositivo viável para detectar anemia utilizando a câmera por meio de análise colorimétrica de imagens, fornecendo uma análise quantitativa, instantânea e um resultado não invasivo. Essas imagens podem ser obtidas na forma de fotografia ou extraídas dos frames do vídeo. Essa revisão apresenta três métodos diferentes para detecção de anemia usando um smartphone: i) fotopletismografia obtida a partir de um vídeo da ponta do dedo indicador, ii) foto da conjuntiva palpebral e iii) aplicativo que fotografa e analisa as unhas das mãos. Portanto, nota-se que é urgente que essas abordagens sejam aplicadas no diagnóstico clínico de rotina para permitir que locais remotos, carentes e com pouca tecnologia, tenham acesso a exames para detectar anemia.

Palavras-chaves

- anemia
- infecções por coronavirus
- deficiência de micronutrientes
- saúde móvel
- smartphone

Introduction

Anemia is a public health problem that affects the entire world. This condition affects about a third of the world's population. Nutritional deficiencies of iron are closely related to the development of anemia. Iron deficiency is the leading cause of anemia and, when it affects children, can lead to a delay in mental and psychomotor development. Also, it increases the rate of child and maternal morbidity-mortality during and after pregnancy.[1] Additionally, there are different causes of anemia, such as micronutrient deficiency (folate, riboflavin, vitamins A, and B12), acute and chronic infections (malaria, dengue, schistosomiasis, tuberculosis, and HIV), cancer, autoimmune diseases, genetic disorders, hemoglobinopathies, (most common examples are sickle-cell anemia, thalassemia),[2] and, more recently, the novel coronavirus disease 2019 (COVID-19).[3–5]

Anemias can worsen the health condition of a person, leading to hospitalization and death. Furthermore, this group of diseases can also cause financial impacts on the health system. To understand the Brazilian situation about the number of deaths, number of hospitalizations cases, and total cost with hospitalization due to anemias, our group conducted a detailed survey from the Brazilian Health Information Department (DATASUS, in the Portuguese acronym), an online platform of the Brazilian Ministry of Health (MoH) with records of the Unified Health System (SUS, in the Portuguese acronym).

The average annual deaths of the deadly types of anemias in Brazil recorded from 2013 to 2018 were: aplastic anemias and other bone marrow failure syndromes (837), other nutritional anemias (344), acquired hemolytic anemia (179), iron deficiency anemia (170), and acute posthemorrhagic anemia (133). Also, there are more than 2,000 annual deaths attributed to "other anemias," which do not fit into other anemia categories.

Anemia contributed to the hospitalization of $\sim$ 440,000 people between January 2015 and April 2020 leading to 215,000 deaths. Of 59,202 admissions caused by anemia, 13.4% were due to iron deficiency. Taking into account anemias caused by micronutrient deficiency, there were 3,190 deaths, $\sim$ 14% of the total number of deaths due to anemia in this period.

Although there are a large number of cases of anemia in children, the primary health care services address them with supplementation, and no hospitalization is required. In the mentioned survey that considered hospitalizations, the group of people with the highest number of admissions due to anemia and the population with a higher mortality rate was the elderly. The government spent $\sim$ 294 million Brazilian Reais (over 50 million US dollars) on anemia hospitalization cases in this same period. This amount has a direct impact on SUS. It is clear that anemia directly affects SUS, not only in the use of hospital beds but also regarding the elevated costs of treatments.

For the diagnosis of this group of diseases, some essential laboratory diagnoses, such as complete blood count, are

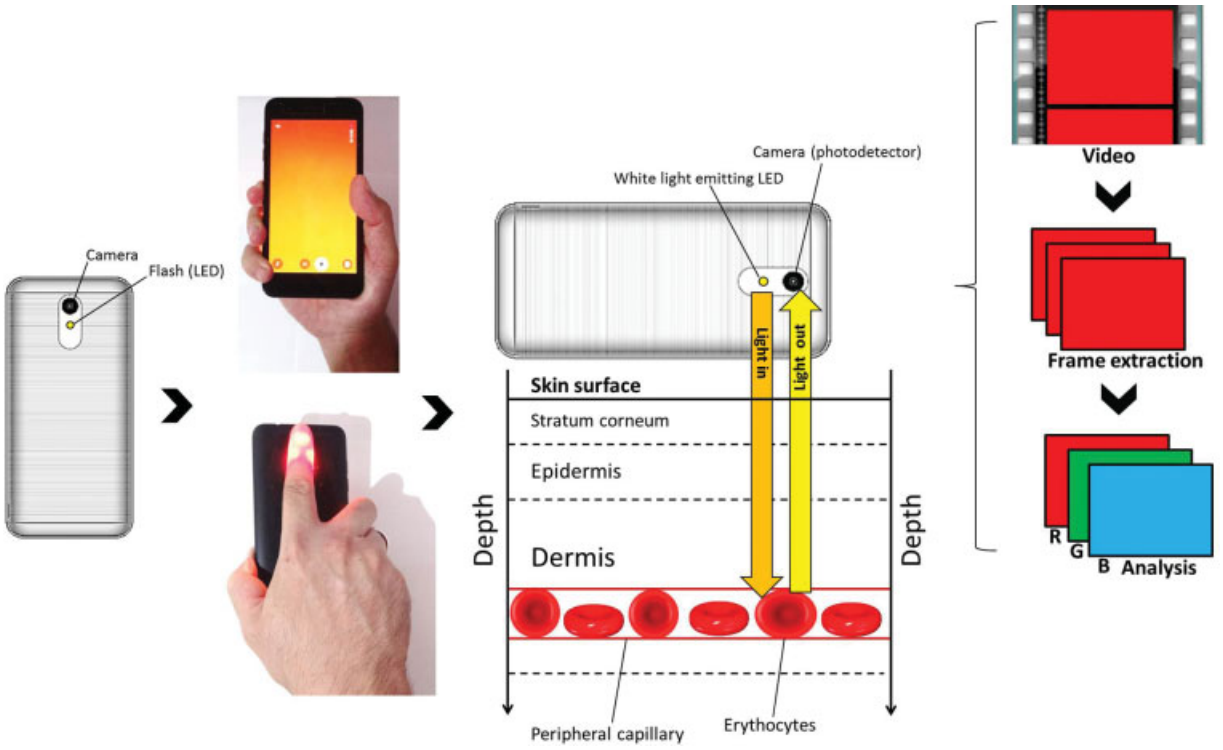

Fig. 1 The sequence of steps applied in smartphone-based photoplethysmography. i) Start by recording a video of the patient's fingertip, covering the entire camera, and with the flashlight on. ii) Light passes through the different skin layers and interacts with blood cells and molecules present in the peripheral capillaries. iii) Part of the light is reflected and captured by the camera. iv) The video is segmented in frames. v) The color intensity of each frame is measured using red, green, and blue analysis.

necessary for the analysis of the red cell series, which includes red blood cell count, mean corpuscular volume, red cell distribution width (RDW), hemoglobin concentration, mean corpuscular hemoglobin and hematocrit, reticulocyte count, as well as hemoglobin electrophoresis.[6,7]

Anemia refers to a decrease in hemoglobin (Hb) concentration,[8,9] a molecule localized inside the erythrocytes (red blood cells). Hemoglobin is a tetramer composed of four subunits: two α subunits and two β subunits. Each protein monomer contains a heme group with a central iron atom, which gives the blood its reddish color.[10]

The inconveniences caused by these laboratory tests include blood collection, use of sharp materials, the time between requesting the trial and obtaining the result. Physical examination should be the first non-invasive way to assess the presence or absence of anemia qualitatively. This examination involves inspecting the conjunctivas, tongue, palms, and fingernails. Visual analysis by medical professionals does not always correlate the low concentration of hemoglobin with the paleness in these areas of the body. Therefore, this method ends up being a subjective analysis, which tends to identify more severe forms of anemias while failing to identify mild and moderate types of the disease.[11]

Noninvasive Diagnosis of Anemia Using the Smartphone

Recent approaches in technology and communication are emerging, and the use of mobile devices, including smartphones and wearable devices, for monitoring health and transmitting clinical information is getting more and more popular. Mobile Health (mHealth) enables instantaneous noninvasive diagnosis, electronic prescriptions, and the most varied possibilities of use in medicine and digital health (eHealth).[12] It is essential to highlight the development observed during the pandemic caused by COVID-19 along with the global recommendations for social isolation, regarding the advances in the use of telemedicine[13] and the importance of mobile health for remote monitoring of COVID-19 patients.[14]

In this scenario, one tool that gained prominence was the smartphone. These devices hold potent cameras and processors that can analyze images and videos that can be very useful for investigating anemia. Hemoglobin is a pigmented molecule, and the colorimetric analysis of images can measure its blood level, providing a quantitative, instantaneous, and noninvasive result. These images can be photographs or extracted from video frames.[15]

Photoplethysmograph (PPG) is used to analyze videos by placing the index finger on the smartphone's camera with the flashlight on, and the camera captures the light deviations per unit of time. When a graph with signal intensity by time is plotted, these series of temporal data are called plethysmographic waves. Hasan et al,[16] in 2017, used this approach to predict the presence of anemia and managed to obtain a strong clinical correlation between the noninvasive method and the Hb levels measured by laboratory methods. The authors obtained a video of the tip of the index finger of the patients and extracted the pixel intensities from each of

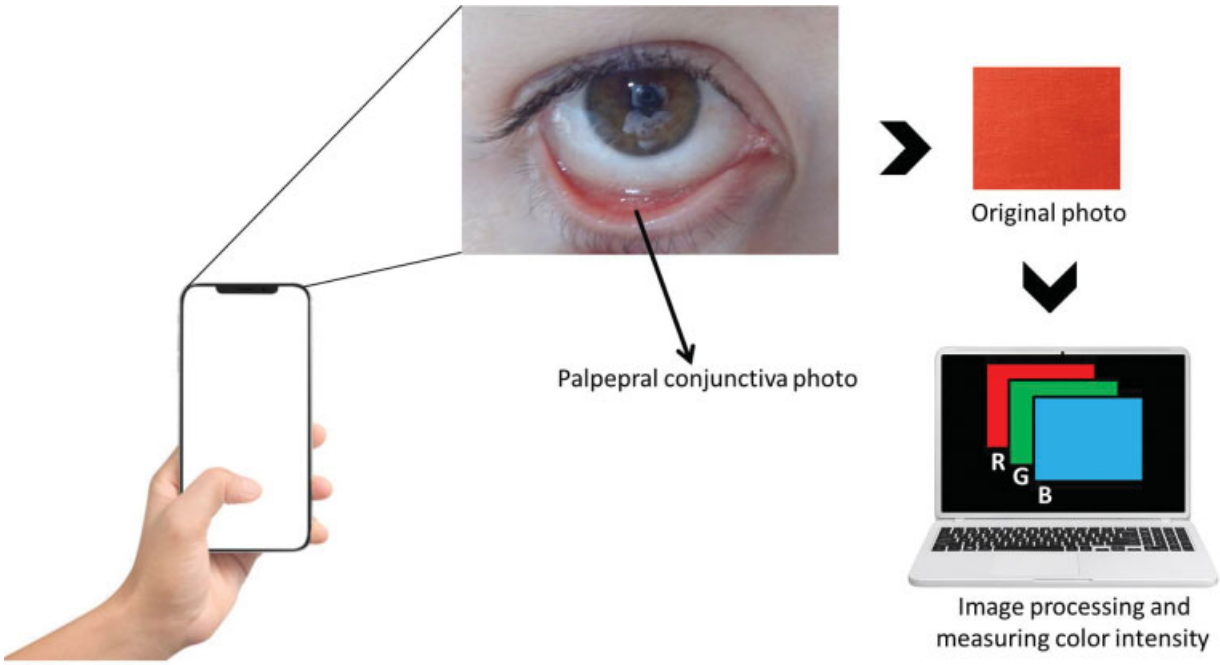

Fig. 2 Detection of anemia from a smartphone photo of palpebral conjunctiva.

the red, green, and blue channels (RGB) of the 100 frames using the algorithms. The hundred histogram images yielded values and the average value of the selected frames recorded. The values obtained by the measurements of the pixels were compared with laboratory-measured results of Hb, presenting a reasonable adjustment of the statistical model, $R^2 = 0.87$. After the extraction and analysis of the color intensity of the video frames, it is possible to notice the color difference that is directly proportional to Hb concentration. This work showed essential advances in the use of smartphones to analyze anemia. To illustrate how this method works, we created a figure based on the representation of the acquisition of the PPG signal reported by Zhao et al.[17] ►**Fig. 1** explains how the smartphone-based PPG method works, which shows the light from the white emitting LED traveling through the skin layers, interacting with erythrocytes, and being detected by the camera (photodetector) by reflection.

Another simple mobile health approach to investigate the presence of anemia makes use of photographs of the palpebral conjunctiva and color intensity analysis in comparison with laboratory dosage. However, lesions or inflammatory eyelid processes can interfere with colorimetric analysis. Algorithms select the region of interest (ROI), filter and process the images, remove the noise, and measure the intensity of the pixels providing a quantitative result. Chen et al[18] tested different algorithms on 100 images of the palpebral conjunctiva, and the algorithms showed sensitivity ranging from 62 to 78% and specificity from 83 to 90%.

Collings et al[19] used the internal rear camera of an Apple iPhone 5S smartphone (Apple Inc., Cupertino, CA, USA) to photograph the palpebral conjunctiva using a calibration card. In total, 47 patients participated in the study, out of whom15 were anemic and 32 non-anemic individuals. The colorimetric analysis runs in the ImageJ software, and the results were compared with the Hb concentration measured by laboratory dosage and also compared with the evaluation of three different clinicians. The results showed good accuracy, measured using the area under the receiver operating characteristic (ROC) curve, (AUC) = 0.86, sensitivity of 93%, and specificity of 66% for the detection of anemia. Also, when compared with the classification performed by the clinicians, the method showed a specificity equal to or higher than that evaluated by two clinicians and sensitivity greater than two of the three clinicians who visually classified the palpebral conjunctiva. ►**Fig. 2** illustrates the detection of anemia from a smartphone using a photo from the conjunctiva palpebral.

In 2018, a very innovative approach to noninvasively diagnose anemia was the creation of an application that allows estimating the Hb concentration using only a photo of the fingernails of the patients.[20] The patient can download the app and take a picture of the nails for the application to analyze. In this application, some algorithms filter out distortions, such as reflections from lights, and allow a reliable analysis of the image. During processing, the app asks the patient to select the regions of interest corresponding to the nails for analysis. This tool allowed colorimetric detection of Hb levels < 12.5 - mg/dL (± 2.4 mg/dL), sensitivity of 97%, and excellent accuracy, measured using the AUC, AUC = 0.88. This approach emerges as a very innovative way that allows different applications. Anemia screening and rapid treatment in needy and low-resource regions, anemia screening at-risk patients, monitoring of chronically anemic patients, as well as of self-monitoring of Hb levels are a few examples of the potential of this approach. ►**Fig. 3** illustrates the four different applications mentioned.

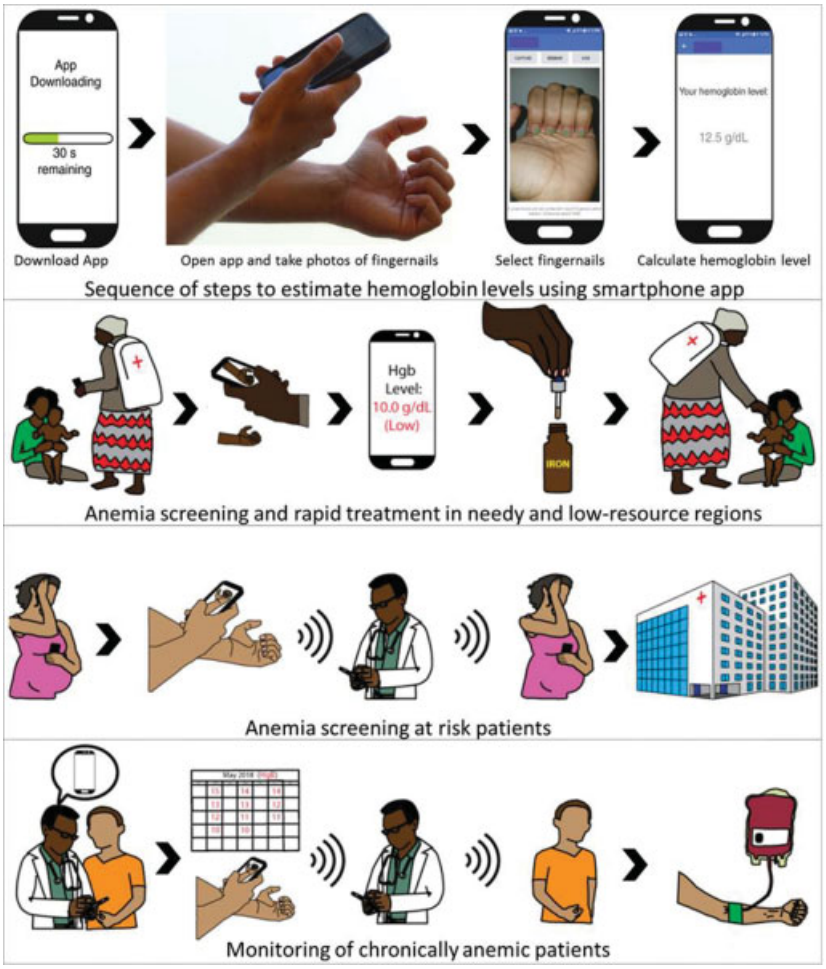

Fig. 3 The sequence of steps to estimate hemoglobin levels using smartphone App and the patient-sourced photos of fingernails for different applications. Reproduced from Mannino RG et al. Smartphone app for noninvasive detection of anemia using only patient-sourced photos. Nat Commun. 2018;9(1):2–11,[20] with permission by Creative Commons Attribution 4.0 International License (For interpretation of the references to color in this figure legend, please refer to the web version of the present article.).

Final Considerations

There is a broad worldwide appeal for the use of noninvasive technologies for diagnosis, and many of them may be possible within a short period. Anemias are one of the most common diseases, and rapid screening can be beneficial in clinical routine. Although several countries invest heavily in health technology, Brazil still invests very little in this field. In this scenario, the use of the smartphone and its accessories, such as camera and flashlight, combined with image analysis and artificial intelligence techniques, will provide great potential for these approaches applied in noninvasive diagnostics of anemia and can be incorporated, soon, in a health system like SUS.

These noninvasive methods using only smartphones are cheaper, faster, user-friendly, easily accessible, portable, and very useful. They can be applied in primary care services to screen anemia; evaluation of supplementation therapy with micronutrients, such as iron; monitoring anemia in critically ill patients admitted to SUS; controlling Hb levels after blood transfusion; self-monitoring of chronically anemic patients, and even be useful for assessing disease progression in patients diagnosed with COVID-19. Early detection of anemia allows a head start of treatment, a decrease in the rate of hospitalizations, less occupation of SUS hospital beds, and a shortened hospital stay. Moreover, the adoption of smartphones allows an instantaneous exam result, greatly reducing the time invested in clinical decisions.

Conducting pilot tests at the health units would be a starting point for implementing this innovative approach, in addition to investments in research, to improve these techniques. Application of this method would diminish exams-related costs and, more importantly, it could lead to a decline in the incidence of mortality due to anemia and a reduction in the amount the government spends on hospitalizations.|

The main objective of this review was to highlight the impact of anemia on morbidity and mortality and present some different noninvasive approaches that use the smartphone to analyze Hb levels to detect anemia, contextualizing with the needs and possibility of use in the Brazilian SUS. Therefore, it seems urgent that these approaches may be used within eHealth and be applied in hospitals, primary care services, as well as in remote, needy, vulnerable, low-tech locations to have access to anemia screening.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 André HP, Sperandio N, Siqueira RL, Franceschini SDCC, Priore SE. Food and nutrition insecurity indicators associated with iron deficiency anemia in Brazilian children: a systematic review. Cien Saude Colet 2018;23(04):1159–1167

2 Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann N Y Acad Sci 2019;1450(01):15–31

3 Duarte FB, Lemes RPG, Duarte IA, Duarte BA, Duarte JVA. Hematological changes in Covid-19 infections. Rev Assoc Med Bras (1992) 2020;66(02):99

4 Lippi G, Mattiuzzi C. Hemoglobin value may be decreased in patients with severe coronavirus disease 2019. Hematol Transfus Cell Ther 2020;42(02):116–117

5 Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020;58(07):1131–1134

6 Wallerstein RO Jr. Laboratory evaluation of anemia. West J Med 1987;146(04):443–451

7 Grotto HZW. O hemograma: Importância para a interpretação da biópsia. Rev Bras Hematol Hemoter 2009;31(03):178–182

8 Rosenfeld LG, Malta DC, Szwarcwald CL, et al. . Reference values for blood count laboratory tests in the Brazilian adult population, National Health Survey. Rev Bras Epidemiol 2019;22(Suppl 2): E190003.SUPL.2

9 Dalanhol M, Barros M, Mazuchelli J, Silva PH, Hashimoto Y, Largura Á. Storage effects on peripheral blood samples as identified from automated hemograms. Rev Bras Hematol Hemoter 2010;32(01):

10 Tanaka PP, Tanaka MA. Substâncias carreadoras de oxigênio à base de hemoglobina: situação atual e perspectivas. Rev Bras Anestesiol 2003;53(04):543–554

11 Benseñor IM, Calich ALG, Brunoni AR, et al. . Accuracy of anemia diagnosis by physical examination. Sao Paulo Med J 2007;125 (03):170–173

12 Crico C, Renzi C, Graf N, et al. . mHealth and telemedicine apps: in search of a common regulation. Ecancermedicalscience 2018;12 (853):853

13 Rockwell KL, Gilroy AS. Incorporating telemedicine as part of COVID-19 outbreak response systems. Am J Manag Care 2020;26 (04):147–148

14 Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). Mayo Clin Proc 2020;95 (06):1213–1221

15 Jonathan E, Leahy MJ. Cellular phone-based photoplethysmographic imaging. J Biophotonics 2011;4(05):293–296

16 Hasan MK, Sakib N, Love RR, Ahamed SI. RGB pixel analysis of fingertip video image captured from sickle cell patient with low and high level of hemoglobin. 2017 IEEE 8th Annu Ubiquitous Comput Electron Mob Commun Conf. 2017:499–505

17 Zhao D, Sun Y, Wan S, Wang F. SFST: A robust framework for heart rate monitoring from photoplethysmography signals during physical activities. Biomed Signal Process Control 2017; 33:316–324

18 Chen YM, Miaou SG, Bian H. Examining palpebral conjunctiva for anemia assessment with image processing methods. Comput Methods Programs Biomed 2016;137:125–135

19 Collings S, Thompson O, Hirst E, Goossens L, George A Weinkove R. Non-invasive detection of anaemia using digital photographs of the conjunctiva. PLoS One 2016;11(04): e0153286

20 Mannino RG, Myers DR, Tyburski EA, et al. . Smartphone app for non-invasive detection of anemia using only patient-sourced photos. Nat Commun 2018;9(01):4924