DISSERTATION

Evaluation of the usefulness of Non-invasive Serum Haemoglobin Measurement in a Perioperative Setting: Prospective Observational Study

submitted by

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DECLARATION

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

06.05.2023 Dr.med.univ. Gabriel Honnef eh.

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ABBREVIATIONS AND DEFINITIONS

Hb.....Haemoglobin

SpHb.....spectrophotometric measured Hb

LabHb.....Hb measured with invasive blood sampling

PBM.....Patient Blood Management

CI.....Confidence Intervals

SD.....Standard deviation

WHO.....World Health Organization

CM.....cyanmethemoglobin method

AHA.....automated haematology analyzers

POC.....point-of-care

DO2.....Oxygen delivery to the tissue

SaO2.....saturation of haemoglobin

CO.....cardiac output

PBM..... Patient Blood Management

ROC.....Receiver Operating Characteristics

PI.....Perfusion Index

RBC.....Red blood cells

NSAID.....Non-steroidal anti-inflammatory drugs

PPI.....Proton pump inhibitor

DNA..... Deoxyribonucleic acid

ICU.....Intensive care unit

TTD.....Transfusion Transmitted diseases

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ZUSAMMENFASSUNG AUF DEUTSCH

Einführung: Das Ziel dieser Studie war die Evaluierung der Praktikabilität einer nicht-invasiven Hämoglobinmessung (SpHb) zur präoperativen Erkennung von Patient*innen mit einer Anämie im Sinne des Patient Blood Management (PBM).

Material und Methoden: Es handelt sich um eine prospektive Observationsstudie im Rahmen der präoperativen Narkoseuntersuchung. Bei erwachsenen Patient*innen welche für elektive Operationen präoperativ evaluiert wurden, wurde neben dem Standardlabor auch ein nicht-invasiver Hb Wert gemessen.

Ergebnisse – Resultate: Es wurden 1216 Patient*innen in der präoperativen Narkoseambulanz rekrutiert. Davon wurden 109 (9,3%) mittels invasiver Hb Messung eine Anämie nachgewiesen werden. Die Sensitivität die Erkennung von anämischen Patient*innen mittels SpHb Messung lag bei 0.50 (95% CI 0.37-0.63) bei Frauen und 0.30 (95% CI 0.18-0.43) bei Männern. Die Spezifität lag bei 0.93 (95% CI 0.84-1.0) bei Frauen und 0.97 (95% CI 0.95-0.98) bei Männern. Die Rate der korrekt klassifizierten Patient*innen lag bei 84.7% (Männer) und 89.4% (Frauen). Der positive Prediktionswert für die SpHb Messung lag bei 0.5 (95% CI: 0.35-0.65) bei Männern und 0.40 (95% CI 0.31-0.50) bei Frauen; der negative Prediktionswert lag bei 0.93 (95% CI 0.92-0.94) bei Männern und 0.95 (95% CI 0.94-0.96) bei Frauen.

Diskussion: Aufgrund seiner schlechten Sensitivität und trotz guter Spezifität, ist die SpHb Messung ungeeignet für die Erkennung von Anämie bei Patient*innen beider Geschlechter unter Routinebedingungen.

ABSTRACT IN ENGLISH

Introduction: The objective of this dissertation was to provide a comprehensive analysis of the potential benefits of non-invasive haemoglobin (Hb) measurement devices in identifying preoperative anemia. This change of routine care could help minimizing instances where anemic patients are overlooked in the run-up to surgery, aligning with the principles of a Patient Blood Management(PBM) approach.

Materials and Methods: Prospective observational study conducted in a preoperative clinic, involving adult patients undergoing anesthetic evaluation. Alongside laboratory Hb measurements, these patients also underwent non-invasive measurements.

Results – Findings: 1216 patients were included during their preoperative evaluation. 109 (9.3%) of these patients were found to be anemic by invasive laboratory Hb measurement. The sensitivity of the non-invasive Hb (SpHb) measurement device to detect the anemic patients was 0.50 (95% CI 0.37 to 0.63) in women and 0.30 (95% CI 0.18 to 0.43) in men. Specificity was 0.97 (95% CI 0.95 to 0.98) in men and 0.93 (95% CI 0.84 to 1.0) in women.
This results in a rate of correctly classified patients of 84.7% for men and 89.4% for women. Positive predictive value for SpHb was 0.50 (95% CI: 0.35 to 0.65) in men and 0.40 (95% CI 0.31 to 0.50) in women; negative predictive value was 0.93 (95% CI 0.92 to 0.94) in men and 0.95 (95% CI 0.94 to 0.96) in women.

Discussion: Because of its low sensitivity albeit high specificity, SpHb measurement is poorly suitable for the detection of preoperative anemia in both, male and female patients under real-world conditions.

A. INTRODUCTION

1. Anemia

Anemia is characterized by a decrease in the quantity of red blood cells to a level where their ability to carry enough oxygen becomes insufficient to meet the body's physiological requirements. The specific oxygen demands of the body vary based on factors such as age, gender, altitude of residence above sea level, smoking habits, and various stages of pregnancy.

Anemia is defined as haemoglobin concentration under a specific cut-off value. The WHO defines anemia in children aged under 5 years and pregnant women as a haemoglobin (Hb) concentration <11.0 g/L at sea level, in non-pregnant women as a haemoglobin concentration <12.0 g/L (table 1) and in men as a Hb concentration <13.0 g/L. Smoking and residential elevation above sea level are known to increase Hb levels. This means there can be differences in physiological Hb values from one population to the other. (2) (3)

	Mild	*Moderate*	*Severe*
Children 6 - 59 months of age	10 - 10.9	7 - 9.9	<7
Children 5 - 11 years of age	11 - 11.4	8 - 10.9	<8
Children 12 - 14 years of age	11 - 11.9	8 - 10.9	<8
Non-pregnant women	11 – 11.9	8 - 10.9	<8
Pregnant women	10 – 10.9	7 – 9.9	<7
Men (15 years of age and above)	11 – 12.9	8 – 10.9	<8

Table 1 Classification of Anemia in g dl^{-1} (2)

Anemia is a common disease and therefore a public health problem with a high negative impact on human health as well as social and economic development. The estimate of prevalence of anemia worldwide varies widely because of a lock of accurate data. The WHO Global Database on Anemia for 1993–2005, covering almost half the world's population estimates the number of anaemic people worldwide to be as many as 1,62 billion people (24,8%) with the

major cause being iron deficiency (50%) in developing countries in Africa and Asia.

Strictly numerically, non-pregnant women are mostly affected (468,4 million), but the highest prevalence of the disease is found among children under 5 years (47,4%). (4)
This results in an estimated 115 000 maternal and 591 000 perinatal deaths globally per year because of anemia. (5)
The prevalence of anemia among various populations is determined by a complex interplay of socioecological and biological factors. For example, the prevalence of anemia in a country is inversely correlated with its economic development. (6)

Owing to insufficient medical infrastructure, the detection of anemia in underdeveloped countries can be challenging. According to the cause and speed of onset of anemia, the clinical symptoms and signs may vary. (7)

Frequent symptoms and signs may include but are not limited to:

- Fatigue and dyspnoea during physical activity
- Symptoms of Angina Pectoris and palpitations
- Headaches, vertigo and faintness
- Pallor of the conjunctiva, the nailbeds or generalised
- Hemodynamic signs like tachycardia, low blood pressure and cardiac failure

1.1. Pre-operative Anemia

The prevalence of anemia in Western Europe , Central Europe and Eastern Europe is estimated to be 11.1%, 15.9% and 15.5% respectively for males, and 15.3%, 20.2% and 27.7% respectively for females. (8)
Pre-operative anemia in various surgical populations however, is much more common than in the general population: (9) (10) (11) (12) (13) (14) (15)

- 19-75% of elective surgery patients
- 24-26% of cardiac surgery patients
- 30-40% of non-cardiac surgery patients
- 19-38% of orthopedic surgery patients
- 70% of colorectal surgery patients

Existing studies have already demonstrated that preoperative anemia is an independent risk factor associated with perioperative transfusion, complications, and mortality. (16) (17) (18)
Patients with pre-operative anemia have a five times higher mortality rate within 90 days after surgery compared to patients with normal Hb levels in the run-up to surgery. (10)
Irrespective of the surgical procedure, the presence of any level of anemia in patients elevates the risk of postoperative events. Additionally, among elderly patients, there is an increase in postoperative mortality over 30 days with each percentage-point decrease in hematocrit. (1) (17)

1.2. Causes of anemia

1.2.1 Anemia due to blood loss

Blood loss and the consecutive reduction of red blood cells (RBC) can be acute or chronic.
Bleeding can have multiple causes, from trauma to surgical complications and gastrointestinal bleeding. The latest being one of the most common causes for anemia due to acute blood loss, as well as chronic bleeding.

Stress-induced mucosal lesions and coagulation dysfunctions are two of the most observed risk factors for relevant bleeding in ICU patients. Peptic ulcer is a disease prevalent in up to 10% of the world`s adult population. It is highly associated with gastric juice pH and a decreased mucosal defense. The most frequent causes of peptic ulcers are chronical use of non-steroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori infection.
They are conventionally easily treated by eradication of Helicobacter pylori, proton pump inhibitors (PPIs) and/or histamine-2 blocking agents. However, chronic and even acute bleeding is not unusual with this chronic disease and is a leading cause of anemia, especially in the elderly population. (8)
Also, occult and visible bleeding in ICU patients is often caused by stress ulcers due to clinical interventions, mechanical ventilation, coagulopathy, brain injury and other risk factors.
Although, clinical significant gastrointestinal bleedings as a complication of stress ulcers have become less frequent as the routine use of histamine-2 receptor antagonists or proton pump inhibitors have become standard of care. These medications however, come with potential side effects themselves, such as worsening of iron absorption and consecutive iron deficiency anemia. (9) (10)

Acute bleeding due to trauma or surgical complications is a major source of blood loss is usually accompanied with some degree of coagulopathy. Coagulopathy can be chronic or acquired due to systemic inflammatory reactions of the body (i.e. disseminated intravascular coagulopathy), consumption of clotting factors or because of preexisting conditions and anti-coagulation medications. (9)
Especially in ICU patients acute bleeding events are a major cause for red blood cell transfusion. A study from Arnold et al. showed that up to twenty percent of ICU patients suffer a major bleeding event lasting a median of four days. (11)

Acute or chronic bleeding and the resulting anemia is associated with considerably higher health care costs and use of resources. Patients suffering from anemia during their hospital stay have been shown to have longer hospital stays, higher mortality and higher costs then non-anemic patients with the same conditions. (12) (13)

1.2.2 Iron deficiency anemia

Despite a decline in recent years, iron deficiency anemia remains the primary cause of anemia worldwide, affecting both developed and low-income countries. Its impact is particularly significant among young children and pre-menopausal women. Previous reports indicate that the prevalence of iron deficiency, in the absence of dietary fortification, is approximately 40% among pre-school children, 30% among menstruating girls and women, and 38% among pregnant women. These figures highlight the heightened physiological requirement for iron during specific life stages and in relation to gender. (14) (15) (16)

A functional iron circuit is crucial for many biological functions in our bodies, including oxygen delivery, cell production, DNA synthesis and cell proliferation.
Iron is initially released into the circulation from duodenal enterocytes (around 1-2 mg of iron per day) and from macrophages, which internally recycle 20-25mg of iron from senescent erythrocytes.
These cells serve as the primary storage site for iron and are responsible for secreting the hormone hepcidin, which helps maintaining normal levels of total-body iron. This mechanism prevents both iron deficiency and iron excess. (14) (17)
Iron deficiency refers to a depletion of iron stores, which can lead to the production of small (microcytic), hypochromic red blood cells and finally resulting in iron deficiency anemia. Iron-restricted erythropoiesis indicates impaired delivery of iron to immature red blood cell precursors, regardless of the level of iron stored in the body.
While iron deficiency anemia is commonly observed in individuals with low iron stores, it can also occur in those with normal iron levels due to the sequestration of iron in cases of chronic inflammation, commonly seen in patients with autoimmune disorders, cancer, infections, and chronic kidney diseases. (18) (19)

The causes of iron deficiency anemia vary depending on the geographical region and the economic status of the population. In developing countries, it is often a consequence of inadequate dietary intake, blood loss (such as intestinal worm infestations), or a combination of both factors.
In high-income countries, the most common causes of iron deficiency anemia are dietary habits (such as vegetarianism), pathologic conditions (such as malabsorption) and the higher median age of population. (20)

1.2.3 Folate and Vitamin B12 deficiency anemia

Vitamin B12 or B9 (commonly called folate) deficiency anemia occurs when there is an insufficient amount of vitamin B12 or folate in the body, leading to the production of unusually large red blood cells that are unable to function effectively. (21)

The leading cause of macrocytic anemia is mostly attributed to cobalamin (vitamin B12) deficiency. This deficiency is primarily linked to the lack of intrinsic factor, a protein responsible for binding to dietary vitamin B12 and facilitating its transport to the terminal ileum for absorption. Intrinsic factor deficiency is commonly associated with atrophic body gastritis, a condition characterized by the destruction of the oxyntic mucosa and the subsequent loss of parietal cells. Parietal cells play a crucial role in the production of both, hydrochloric acid and intrinsic factor.

This form of anemia is called pernicious anemia. (22)

Pernicious anemia can also occur in patients with poor diet over a long period of time and in combination with such medications as anticonvulsants and proton pump inhibitors.

Folate deficiency anemia is also principally caused by dietary insufficiency. A balanced diet contains approximately 500 to 700 µg of folate and is therefore sufficient to meet the body's requirements.

Patients with low folate stores usually have a history of weight loss and/or alcohol abuse. Folate deficiency anemia can also occur in combination with drugs, such as methotrexate, sulfasalazine, anticonvulsants, etc.

Maintaining an adequate folate status is especially crucial during pregnancy, as folate deficiency can lead to birth irregularities. (23)

1.2.4 Anemia of chronic diseases

Anemia of chronic disease is primarily driven by immune-related factors. Persistent inflammation and the release of cytokines can trigger alterations in iron regulation, erythroid progenitor cell proliferation, erythropoietin production, and red blood cell lifespan. These changes collectively contribute to the development and progression of anemia in individuals with chronic diseases. (24)

The most common chronic disease to cause anemia is chronic kidney disease, where the decrease in the production of erythropoietin, mediated by renal insufficiency, results in decreased erythropoiesis. (25)

Furthermore, anemia can be caused by proinflammatory cytokines that are produced by tumor cells, which in turn damage erythroid progenitor cells. (24)

Chronic bleeding episodes (especially gastrointestinal bleeding) and hematological diseases (such as myelodysplastic syndrome, rhabdomyolyses, etc) can, over time, also cause chronic anemia.

Anemia caused by the chronic and gradual loss of red blood cell mass is generally better tolerated and compensated for by the body compared to rapid and acute changes in hemoglobin levels, such as those resulting from sudden blood loss.

1.3. Treatment of anemia

Oxygen delivery to the tissues, referred to as DO2, relies on several factors, including the concentration of haemoglobin (Hb), the saturation level of haemoglobin (SaO2), and cardiac output (CO).
These three variables determine the amount of oxygen that can be transported to the body`s tissues.
Haemoglobin concentration has the biggest effect on the total oxygen-carrying capacity of patient`s blood.
The SaO2 indicates the percentage of binding sites occupied by oxygen molecules and CO reflects the volume of total blood pumped by the heart per unit of time and determines the rate at which oxygen-rich blood is circulated throughout the body.
The combinations of these factors define the ability of the body to meet the tissue`s oxygen demands.

$DO2 = Hb \times \%SaO2 \times CO$

When the delivery of oxygen is reduced below a critical level, there is a mismatch of oxygen consumption and delivery in the tissue; the result is a shift to anaerobic metabolism. It is reasonable to assume that restoring the appropriate level of oxygen delivery results in improved clinical outcomes.

In acute anemia, the body has little time to adapt to and compensate for the reduced delivery of oxygen and shows this quickly. In cases of continuous acute hemorrhaging, and in patients with clinical signs of impaired oxygen delivery (e.g.: tachycardia, low blood pressure or lactatemia), the quickest way to enhance oxygen delivery to the tissue is blood transfusion. (26)

In stable patients without acute blood loss however, other methods of enhancing Hb status are associated with less side effects and costs. Furthermore, with the implementation of Patient Blood Management (PBM) programs, the interest in reducing unnecessary blood transfusion has grown in the last few years. (see chapter 1.3.)

To detect iron deficiency anemia, the serum ferritin level is the most sensitive and specific test (indicated by a level of <30 µg per liter). That said, in the evaluation of iron status, a single test result is insufficient. It is preferable to consider the whole picture (including, for example, transferrin saturation, and higher cut off values for ferritin in patients with heart failure and/or chronic kidney disease).

In cases of severe iron-deficiency anemia where patients exhibit signs of impaired oxygen delivery to tissues, such as cardiovascular symptoms like heart failure or angina, red-cell transfusions are recommended.
This intervention quickly improves oxygen delivery and replenishes iron stores, as each unit of packed red cells provides approximately 200 mg of iron. For stable patients, oral administration of iron sulfate is considered the safest,

most convenient, and cost-effective treatment option.
The recommended daily dosage for adults with iron deficiency is 40 to 60 mg of oral iron. Following this regimen, most patients should experience an increase in hemoglobin (Hb) levels after six to eight weeks. (27)

However, oral iron supplementation is not always well-tolerated. Many patients experience common side effects such as dyspepsia, nausea, vomiting, abdominal pain, constipation, or diarrhea, which can significantly impact patient compliance, especially considering the recommended treatment duration of three to six months to fully restore iron stores. Furthermore, individuals with iron deficiency anemia, who have conditions like malabsorption, helicobacter pylori infection, atrophic gastritis, or a history of gastric or duodenal surgery, as well as those with elevated hepcidin levels due to inflammation, may only partially respond to oral iron treatment, if at all. (28)

In this population, or in patients who require a faster treatment (for example, perioperative patients with scheduled surgery <6 weeks), intravenous iron is the therapy of choice. Intravenous iron is especially recommended in cases where intestinal absorption is suspected to be impaired, when a rapid increase in hemoglobin (Hb) levels is necessary (such as in severe anemia during the second to third trimester of pregnancy), or in instances of chronic bleeding caused by inherited defects. (29)
There is sufficient data that intravenous iron therapy is safe and effective. Therefore, it should be the front-line therapy in patients who don't respond to oral iron and/or who are scheduled for surgery in under 6 weeks. (27)

The exact dose of iron needed for intravenous infusions can be precisely calculated by the following formula:

Iron deficiency(mg) = 200mg per 1g/dl Hb deficiency + 500mg for iron storage

Normally this leads to an iron dose of 500 -1500 mg for an adult that should be administered over 1 hour or in two settings. This therapy will replenish the patients iron stores and lead to an Hb increase in 75% of patients in 10-14 days (peak after three weeks). (27)

The treatment for macrocytic anemia consists of prescribing folate and vitamin B12 supplements where needed along with the evaluation of potential causes (thyroid and liver diseases, chronic alcohol abuse, myelodysplastic syndrome, pregnancy, etc).
In the case of folate deficiency (<1,8 ng/ml) in macrocytic anemia, an oral therapy with 1-5 mg per day of folate acid should be started. In the case of vitamin B12 deficiency, especially where combined with neurological symptoms and/or anemia, an oral therapy of 1 mg of vitamin B12 for at least one month is suggested, with the recommendation of continuing with 125-250 mcg/d. Reticulocytosis should improve within one to two weeks, and anemia should resolve after four to eight weeks. (30)

2. Haemoglobin measurement

2.1. Haemoglobin

Haemoglobin, with a molecular weight of approximately 64,500 daltons, is composed of two types of chains, namely α and β chains, each with a specific sequence of amino acids and incorporating an iron-containing haeme group. These α and β chains combine to form two α-β dimers, which further assemble to create a haemoglobin tetramer. This unique structure allows for the necessary "haeme-haeme" interaction, enabling efficient uptake of oxygen (deoxyhaemoglobin → oxyhaemoglobin) and release of oxygen (oxyhaemoglobin → deoxyhaemoglobin). Haemoglobin is primarily found in red blood cells (erythrocytes), where it transports oxygen from the lungs to the body tissues and carries carbon dioxide in the opposite direction. The affinity of haemoglobin for oxygen is influenced by both the haeme-haeme interaction and pH levels (known as the Bohr effect). It also reflects the number of oxygen-bound haemoglobin molecules relative to the oxygen tension present. The two crucial aspects of haemoglobin synthesis are globin production and haeme synthesis. Globin chains are synthesized in the cytosol of erythrocytes and are regulated by genetic transcription and translation.

Haeme synthesis on the other hand occurs in the cytosol and the mitochondria of erythrocytes and is finished by the binding of a protoporphyrin to an iron ion that then forms the final haeme molecule.

In healthy individuals, the primary type of haemoglobin is HbA, which constitutes approximately 97% of the total haemoglobin in the body. There are variations of these chains. Some of these variations can have relatively normal oxygen affinity and function, whereas others are highly deleterious to the normal function of haemoglobin.
For example, fetal haemoglobin (HbF) which is the dominating Hb molecule in fetuses.

HbF exhibits a higher affinity for oxygen compared to HbA (adult hemoglobin). This characteristic enables efficient transfer of oxygen from the maternal bloodstream to the fetal bloodstream across the placenta. However, following birth, the production of HbF significantly decreases, and it comprises only about two to three percent of the total hemoglobin in adults.

(32) (33) (34) (31)

2.2. Invasive Hb measurement

2.2.1 Blood sampling

Conventional measurement techniques for anemia require direct blood sampling. These methods are therefore time-consuming, costly, invasive and carry potential risks such as an increased chance of infections. (1).
There are three primary sources of blood collection: artery, vein, and capillary.

Arterial blood is most commonly collected from the radial artery in the forearm. This method is less frequently used, as it is more complex and requires a specially trained health care provider to perform it. That said, where the patient already has an arterial line (for example, in intensive care units and in some cases during anesthesia), or when arterial blood gas analyses are required, it can be the method of choice. Arterial blood is oxygenated and has therefore a higher amount of oxygen-bound Hb compared to venous or capillary blood.
Because of its complexity, sampling from the artery is not a field-friendly method of blood collecting in public health population-based field settings. (35) (36)

In comparison with arterial blood, venous blood is easier to collect, and this is therefore the most common form of blood collection in clinical settings and blood banks. Sampling from the veins can provide a relatively large quantity, which makes it possible to asses multiple biological indicators with one sample.

Capillary blood can be collected from the fingertip or heel, as individual drops or as pooled blood. One sample can provide about 50-500 µL of blood, and this is easily drawn in multiple settings, even from newborns.
Capillary blood is acquired from below the dermal layer of the skin, specifically from areas such as the finger and the heel. These regions contain capillary loops, which consist of small arterial and venous blood vessels, as well as interstitial and intracellular fluids.
The blood sampled from these capillaries is therefore a mix of oxygenated and deoxygenated blood. Factors which can compromise the results of capillary blood sampling include excessive squeezing of the finger or the heel, poor circulation, and cold extremities. (37)

2.2.2 Laboratory analysis

The cyanmethemoglobin method (CM) is the globally accepted reference technique for calibrating clinical and field equipment used to measure hemoglobin (Hb) levels and determine Hb concentration in blood.
It is costly and time-consuming, however, and there have been studies examining alternatives to this method. (38) (37)
The principle of the CM, developed for clinical laboratories in the mid-1900s, is to convert Hb into methaemoglobin (MetHb), then to convert metHb into cyanMetHb, and to measure the latter using a photoelectric colorimeter with an absorbance of 540 nm. (39)
Another method that was developed to reduce the cost and time required for Hb testing is to count and size particles using automated hematology analyzers (AHAs). AHAs are currently the most common form of Hb testing in clinical settings because they can also measure other blood indicators including hematocrit. Due to their large size and lack of portability, AHAs are less suitable for field testing, and are more often used by blood banks and clinical laboratories. (40)
Less cumbersome and expensive quantitative methods were later developed; for example the WHO color scale and portable point-of-care (POC) analyzers.. (37)
The threshold evaluation criteria for Hb measurements (i.e., the acceptable difference between methods), as set by the College of American Pathologists, is ±7% of the reference. (41)
In their systematic review of the literature (2019), Whitehead et al. found that, with a few exceptions, the vast majority of studies showed that the various methods of Hb measurement (using AHA as a reference) were within the ±7% mean concentration bias threshold. Three studies compared CM to AHA directly, and all of them showed a variation within the threshold of ±7%. In the Whitehead review, all studies comparing the different types of blood sampling (arterial, venous, capillary) showed mean Hb differences within the ±7% mean concentration bias threshold.
However, it is important to consider that the ±7% threshold may not be the marker of greatest clinical relevance, for, in the studies evaluating diverse testing methods for sensitivity and specificity in the classification of anemic patients. the review found a high range of variation of results. (37)

2.3. Non-invasive Hb measurement

Over the last few decades, the need for rapid, cost-effective, safe and portable means of determining of patients´ Hb status has led to the development of point-of-care (POC) devices.
Current, non-invasive technologies include pulse co-oximetry (Pulse CO-Oximetry™; Masimo Corp., Irvine, CA, USA), occlusion spectroscopy (OrSense™, Ness Ziona, Israel) and transcutaneous reflection spectroscopy (Haemospect, MBR Optical Systems, Herdecke, Germany). (42)

The most studied and used platforms are non-invasive pulse co-oximeters using a finger probe device based on multi-wavelength co-oximetry for the transcutaneous, spectrophotometric estimation of haemoglobin (SpHb). This technique can be used as a spot check measurement method ((Pronto-7™, Rad 67™) and as a continuous measurement method (Radical-7™).
This technique can be used for both spot check ((Pronto-7TM, Rad 67TM) and continuous measurements (Radical-7TM).

Multiple studies have been conducted to assess the accuracy of these devices, comparing them to central laboratory methods (i.e. AHA), in settings ranging from operating rooms to critical care units, emergency departments and blood donor clinics. (1)
In a Meta-Analysis from 2014, including 32 studies and 4425 subjects, Kim et al. found that the overall random-effects pooled mean difference and SD was 0.10 ± 1.37 g/dL (−2.59 to 2.80 g/dL, $I^2 = 95.9\%$ for mean difference and 95.0% for SD) and that between-study heterogeneity for mean differences and SD was high. In consideration of this high variability of results, and in view of the importance of blood transfusion triggers in critical care and the perioperative setting, the authors conclude that "the lack of accuracy and precision in the current generation of these devices may negatively affect clinicians´ decisions about their patients." (43)
Another Meta-Analysis from Hiscock et al. (2015) with 2915 analyzed subjects found an overall pooled mean difference (device versus laboratory) of -0,03 g/dl (95% prediction interval -0.30 to 0.23) and the SD was 1.42 g/dl (associated 95% LOA -3.0 to 2.9 g/dl). (44)
In summary, most of the studies comparing non-invasive Hb measurement to AHA found that while SpHb measurement was a fast, low-cost and safe method for estimating patients´ Hb status, its accuracy was variable.

3 Patient Blood Management

3.1. Background

According to the WHO: "Patient blood management (PBM) is a patient-focused, evidence-based and systematic approach to optimize the management of patient and transfusion of blood products for quality and effective patient care. It is designed to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products." (55)

Essential elements of patient blood management include: "the prevention of conditions that might otherwise result in the need for transfusion (through health promotion and screening for early detection), appropriate diagnosis and optimal treatment, including the use of alternatives to transfusion, good surgical and anesthetic techniques, the use of alternatives to blood transfusion and blood conservation." (55).

In 2010, World Health Assembly Resolution WHA63.12 endorsed PBM, specifically referring to the three-pillar concept, "bearing in mind that patient blood management means that before surgery every reasonable measure should be taken to optimize the patient's own blood volume, to minimize the patient's blood loss and to harness and optimize the patient-specific physiological tolerance of anemia." (56). The resolution urges WHO member states to promote PBM wherever appropriate. (57)

Thus, it is in order to reduce the risk for patients during the perioperative period that Patient Blood Management (PBM) programs have been introduced in recent years. Their introduction has been shown to improve patients` outcomes, to reduce the need for transfusions, and to lessen costs. (58) (55) (59) (60)
PBM thus has three primary goals: optimizing testing and treatment for anemia in the perioperative setting, minimizing blood loss, and maintaining patients´ physiological reserves.

	Optimize Hb	*Minimize blood loss*	*Optimize physiological reserves*
preoperative	• Detect anemia • Identify cause of anemia • Manage disorders • Refer for further evaluation if necessary • Treat iron, vitamin B 12 and folate deficiencies • CAVE: anemia is a contraindication for elective surgery	• Identify and manage bleeding risk • Minimize iatrogenic blood loss • Procedure planning and rehearsal	• Asses/optimize patient's physiological reserve and risk factors • Formulate a patients' specific management plan utilizing appropriate blood conservation modalities
intraoperative	• Time surgery with hematological optimization	• Meticulous hemostasis and surgical techniques • Anesthetic blood conserving strategies • Autologous blood options • Maintain normothermia • Pharmacological/Hemostatic agents	• Optimize cardiac output • Optimize oxygenation and ventilation • Preserve normovolemia •

postoperative	• Optimize erythropoiesis • Be aware of drug interactions that can cause anemia	• Vigilant monitoring and management of postop. bleeding • Avoid secondary hemorrhage • Maintain normothermia • Autologous blood salvages • Minimize iatrogenic blood loss • Hemostasis/anticoagulant agent management • Prophylaxis of upper GIT hemorrhage • Be aware of adverse effects of medications	• Optimize anemia reserve • Maximize oxygen delivery • Avoid/treat infections promptly • Restrictive transfusion threshold

Table 2 The three pillars of PBM (43) (60)

Leahy et al. (2017) assessed the implementation of a PBM program in four hospitals in western Australia. These hospitals already had a relatively restrictive transfusion policy. Over a period of six years, the experiences of 605,046 patients were included in the study. Comparing the base line with the final year of the study, they found that: (60)

- Units of RBCs, FFP, and platelets transfused per admission decreased 41% ($p<0.001$)
- Mean pre-transfusion haemoglobin levels decreased 7.9 g/dL to 7.3 g/dL ($p<0.001$)
- Single-unit RBC transfusions increased from 33.3% to 63.7% ($p<0.001$)
- After adjusting for confounders, the mean length of stay was reduced by 15% ($p<0.001$)
- In-hospital mortality decreased by 28% ($p < 0.001$)

These results demonstrate the importance of careful consideration of the necessity of blood transfusion, as well thorough screening for anemia pre-operatively. Because of studies like the this, guidelines for health care providers emphasize the three pillars of PBM to avoid unnecessary transfusions. A careful pre-operative evaluation of patients' Hb status in the run-up to surgery can play an important role in achieving this goal.

3.2. Risks of blood transfusions

The most common and fastest way to increase haemoglobin levels is RBC transfusion. One third of ICU patients receive at least one unit of RBCs. (61)
However, RBC transfusion is not only costly, but also associated with a 40% increase in 30-day morbidity and increased 30-day mortality. (62) In a systematic review Marik et al. found that in most studies included, the risks of transfusion outweighed the benefits and that RBC transfusion was an independent risk factor for nosocomial infections, multi-organ dysfunction and acute respiratory distress syndrome developing. (63)

Adverse events triggered by blood and blood product transfusion can include:

- **Transfusion Transmitted diseases (TTD):**
  The risk of TTD has decreased in the last decades as screening methods have improved. The risk of transmission of Human Immunodeficiency Virus (HIV) and Hepatitis C by blood transfusion is estimated to be 1:1 215 000 for HIV and 1:1 935 000 for Hepatitis C, per unit transfused. However, not all potential pathogens are detectable by modern screening methods. (64) (65)

- **Non-infectious complications:**

  Acute reactions within a 24-hour period are divided into two categories:
  Immune mediated reactions, such as allergic reactions, transfusion-related acute lung injury (TRALI), acute hemolytic transfusion reaction (AHTR) and *non-immune mediated reactions*, such as transfusion-associated circulatory overload (TACO)

  Delayed reactions (>24h):
  Transfusion immunomodulation (TRIM), Transfusion-associated graft versus host disease (TA-GVHD), Post-transfusion Purpura and iron overload (66)

With an incidence of 8.1 (95% CI, 4.4-14.9) cases per 100 000 units of blood components transfused, TALI is one of the most identified causes of transfusion-associated mortality and morbidity. Risk factors for TRALI are the number of transfused units of blood, age, illness severity and time on cardiopulmonary bypass. (67) (68) (9)

Typical symptoms of TRALI include pulmonary edema, hypoxemia, respiratory newly identified bilateral pulmonary infiltrates occurring within a small timeframe after transfusion. (69)
In 2011, Toy et al. found in their prospective study of cardiac surgery patients, that patients who developed TRALI had longer ICU stays, higher mortality rates and underwent more time under mechanical ventilation then patients who received at least one unit of RBC but did not develop TRALI. (70) Therefore, although TRALI is a rare disease, it is a serious condition that significantly effects patients` outcomes and morbidity. (9)

The second most commonly reported cause of transfusion-related adverse events is TACO. Symptoms of the disease mostly include elevated jugular venous pressure, dyspnea, orthopnea, wheezing, coughing, hypertensive episodes and tachypnea. TACO can be developed by patients who are unable to deal with rapid infusions of blood products. Patients at risk of developing TACO include patients who have a history of volume overload, such as those with renal failure, congestive heart failure who are in need of multiple transfusions. (9)

Even though transfusion transmitted diseases are have been less common in the last couple of years because of the improvement of screening methods, evidence from varying sources has indicated that allogenic blood transfusion can cause clinically significant immunosuppression in the recipient.
It is not entirely clear how RBC transfusion interacts adversely with the immune system, but it is likely that multiple factors initiate a cascade of adverse events that lead to a down regulation of the patients' immune function.
This reduction of resilience can cause higher rates of infections and therefore morbidity and mortality. (71) (9)

4. Aim of this study

From the preceding, it is clear that reliable Hb measurement plays an important role in the implementation of PBM programs. Standard methods of Hb measurement, however, are relatively invasive, requiring direct blood sampling (finger prick, venous blood sampling, arterial blood sampling). They are also costly, time-consuming and potentially harmful for staff and patients (e.g., on account of the risk of infection).

New guidelines for reducing both unnecessary testing and unwanted side-effects have been published in the last few years. These guidelines place a priority on performing invasive blood sampling to assess anemia only in patients with higher ASA (American Society of Anesthesiologists) physical health status classification scores and those undergoing moderate to major surgical procedures. This approach is based on the understanding that the prevalence of anemia in ASA 1 and 2 patients (who have relatively better physical health) is lower compared to older individuals or those with more severe health conditions. (72) (1) (73)

Recommendations for specific surgery grades (minor, intermediate, and major or complex) and ASA grades:

	ASA 1	***ASA 2***	***ASA 3 or 4***
Minor surgery	Not routinely	Not routinely	Not routinely
Intermediate surgery	Not routinely	Not routinely	Consider depending on co-morbidities
Major surgery	Yes	Yes	Yes

Table 3 ASA grades According to the NICE guidelines 2016 (72)

Non-invasive Hb measurement methods are fast, inexpensive and have no known side-effects. They could therefore reduce both the unwanted aspects of invasive blood sampling and the number of non-recognized anemic patients in the run-up to surgery.

In recent decades, the need for rapid, cost-effective, safe and portable solutions for the determination of patients´ Hb status has led to the development of SpHb measurement devices utilizing a finger.

Based on the aforementioned description, these devices utilize spectrophotometric estimation of haemoglobin and are designed for both continuous SpHb measurement and spot-check SpHb measurement.(1)

The accuracy of these tests and their comparability with central laboratory Hb (LabHb) has been discussed in the first three chapters. To our knowledge, however, no study to date has assessed the reliability of SpHb measurement devices in the evaluation of patients preparing for elective surgery under real-world conditions (1)

The aim of this study is, to assess the reliability of non-invasive SpHb measurement devices in the estimation of patients preparing for elective surgery under real-world conditions.
"With reliable cut-off values, SpHb levels could potentially serve either as a replacement for LabHb testing or as a pre-test for patients who would normally not receive a complete preoperative lab-test, to further minimize the risks of undetected preoperative anemia. We thus hypothesize that SpHb measurement is useful in preoperative screening for anemia." (1)
SpHb measurement could therefore be used as an index or pre-test for a patient population where anemia is frequent but invasive blood sampling is not recommended by current guidelines. For example, a potential application is the pre-operative evaluation of women preparing for gynaecological and obstetric surgeries. While this patient population is more likely to be classified as <ASA 3 because their relative youth and health, the prevalence of anemia in this group is nevertheless higher than in others. In this situation, there is an enhanced risk of missing the anemia diagnosis. (74)
In such a patient population, the addition of SpHb measurement to clinical routine could help to detect anaemia where it might otherwise pass unnoticed.

5. Research questions

Research question 1: Can we use non-invasive Hb measurement as a pre-test to detect anemia in patients who would normally not undergo central laboratory testing?

Research question 2: For patients preparing for various kinds of surgery, how accurate is SpHb in comparison to the gold standard?

Research question 3: Can we establish cut-off values for SpHb in a pre-operative setting?

5.1. Hypothesis

Null Hypothesis h01a: The addition of SpHb measurement does not provide any significant benefits to the pre-operative evaluation of patients undergoing surgery.

Alternative Hypothesis ha1a: SpHb measurement offers a convenient and safe method to identify anemic patients in a pre-operative setting who may otherwise be overlooked by current clinical routine.

Null Hypothesis h02b: SpHb measurement does not have the capability to detect anemic patients who would typically be missed by the preoperative evaluation protocols recommended by current guidelines.

Alternative Hypothesis ha2b: SpHb measurement has the potential to identify anemic patients who might otherwise go undetected during the pre-operative evaluation process, as outlined by current guidelines.

B. Materials and Methods

1. Study design and patient population

This study was conducted as a single-center, prospective observational study in the preoperative clinic at the Medical University of Graz, Austria, Department of General Anesthesiology, Intensive care- and Emergency medicine.

We included consecutive patients who were preparing for elective surgery and were therefore evaluated by an anesthesiologist between January and October of 2020. Patients preparing for plastic, orthopedic, urological, general, and gynecological surgery were included.
The patient population in our pre-anesthetic clinic consist of patients from the age of 18 upwards. The distribution between sexes is fairly equal, although because of the placement of our study devices (one at the central pre-anesthetic clinic with a mixed population and one at the gynecological pre-anesthetic clinic with mainly female patients) we expected to include more women than men.

As part of the standard preoperative clinic procedures, participating patients were evaluated by an anesthesiologist following national and international guidelines. Additionally, during the routine clinical evaluation, all participants had their Hb levels measured non-invasively by a trained healthcare provider.
This intervention was already part of clinical practice for some patients in the local pre-operative clinic, especially when health care professionals suspected anemia in patients (because of abnormalities in the clinical evaluation) where guidelines did not recommend invasive blood sampling.

SpHb values were recorded in the documentation software already in use at the clinic. (1)

2. Study setting

Our study took place at the Medical University Hospital of Graz, an academic teaching hospital with more than 1,500 beds in Graz, the capital of the province of Styria, Austria.

Patients undergoing elective surgery in the areas of plastic surgery, orthopedic surgery, urological surgery, general surgery, and gynecological surgery were enrolled in this study during their regular preoperative evaluation. The routine care and medical services were provided by healthcare professionals of the Department of General Anesthesiology, Intensive care- and Emergency medicine (head: Univ. Prof DDr. Philipp Metnitz).
There were two inclusion sites: one SpHb measurement device was located at the general pre-operative evaluation station (plastic, orthopedic, urological, general) of the Department of General Anesthesiology, Intensive care- and Emergency medicine and a second was located at the pre-operative clinic for gynecological surgery.

Several circumstances combined to make this an ideal setting for our study:

- Because the SpHb device was already part of the clinical routine at these sites if health care providers thought that it could add benefits to the evaluation of a preoperative patient.
- A second circumstance, especially relevant with respect to gynecological surgery, is the following: because patients undergoing elective gynecological surgery are often young and healthy, they have lower ASA grades, while their rate of preoperative anemia is considered to be high. This combination of low ASA grade and a high rate of preoperative anemia increases the risk of anemia being undetected preoperatively; thus, the SpHb device is already considered advantageous.
- All patients undergoing elective surgery at our hospital must be evaluated preoperatively by an anesthesiologist. This gives us a simple method of informing them about the planned study, and offers an opportunity to ask for informed consent ahead of surgery.

Screening for study inclusion was conducted by health care providers during der routine preoperative evaluation at the anesthetic preoperative clinic.
During their routine checks (EKG, blood sampling, blood pressure measurement), and after informed consent was obtained, patients had their SpHb measured according to the instructions of the manufacturers of the devices, by health care providers trained for this task. (1)
No other study specific interventions were taken during the preoperative evaluation of patients.

3. Ethics approval and consent to participate

The study was registered at clinicaltrials.gov (NCT04391517).

Approval by the ethics committee of the Medical University of Graz (IRB00002556, chairperson Univ. Prof. Dipl. Ing. Dr. Josef Haas) was given on the 5th of December 2019 (decision number 31-482 ex 18/19).

During their preoperative evaluation, patients received comprehensive information about the study from an anesthesiologist both, verbally and trough a written patient information document approved by the ethics committee. The purpose, intervention, and protocol of the study were clearly explained to the patients. They were also provided with a consent form (see appendix) and given the opportunity to ask questions or seek clarification.

It was emphasized that patients had the right to withdraw their consent for the use of their data at any time during the study, in accordance with the relevant Austrian and European legislation. No specific reasons were required for withdrawing consent. (1)

4. Inclusion and exclusion criteria

All patients preparing for elective surgery that were evaluated at our study sights in the study period were screened for inclusion for our study. Patients under the age of 18, emergency surgeries, patients who refused to participate and patients with missing data were excluded.

These exclusion criteria were chosen because of legal requirements and feasibility in our routine preoperative clinic.

The criteria for inclusion and exclusion are listed here:

Inclusion criteria	**Exclusion criteria**
Age ≥ 18 years	Age < 18 years
Patient planned for elective surgery	Documented patient refusal
Patient undergoing pre-operative evaluation by an anaesthesiologist	Emergency surgery
Informed consent	No central laboratory available

Table 4 Inclusion and exclusion criteria (1)

5. Measurements and data management

5.1. LabHb measurement

Haemoglobin measurements were conducted following the standard operating procedure of our preoperative clinics. As part of routine clinical practice, laboratory tests for haemoglobin levels were performed unless the assessing clinicians determined them to be unnecessary in specific cases.

In the case of most patients (i.e., those who did not have recent and/or valid laboratory tests available), the LabHb value was obtained with venous blood sampling in the same session by trained health care providers.

The blood samples were collected using vacuum PET plastic blood collection tubes (VACUETTE® system, Greiner Bio-One International, Kremsmünster, Austria) through peripheral venipuncture, following standard clinical procedures at our pre-anesthetic clinic. All collected samples were promptly send to the central laboratory of the Clinical Institute of Medical and Chemical Laboratory Diagnostics (chair: Univ. Prof. Dr. Markus Herrmann), which operates 24/7. The transportation of samples was carried out using routine methods such as tube mail or courier services, as appropriate.

The measurements were conducted by the routine laboratory of the Clinical Institute of Medical and Chemical Laboratory Diagnostics using a Sysmex XN-1000 analyzer (Sysmex K.K., Kobe, Japan). These measurements were performed within two hours of blood sampling, ensuring timely analysis of the samples.

For patients who had a recent laboratory test (not older than one month) available and were in a stable condition (without active bleeding or hematological disease), the LabHb value from that test was used, following the standard procedure at our preoperative clinic. Patients without a suitable laboratory Hb measurement were not included in the study population. (1)

5.2. SpHb measurement

Non-invasive Hb measurements were performed in the same session with patients who met our inclusion criteria. The measurement took place at our preoperative clinic, along with other standard preoperative tests (blood pressure measurement, EKG, blood sampling, etc).
Before the study started, health care providers were trained to use the SpHb measurement device according to the manufacturer's specifications. Apart from this, clinical routine during the preoperative evaluation was not altered in other means then the additional SpHb measurement.

Rad-67™ Spot-check Pulse CO-Oximeters® (Masimo corporation, Irvine, CA, USA) finger-probe devices, which are based on multi-wavelength co-oximetry for the spectrophotometric estimation of haemoglobin (SpHb), were used according to manufacturer specifications and SpHb values were obtained within 30-60 seconds.

The estimated variability of measurement by the manufacturer (Masimo corporation) is 1 g/dl and the range of measurement should be from 8 to 17 g/dl. (75)

The obtained SpHb values were documented in our clinic's documentation system. The system was specifically adapted for our study to include SpHb values (table 4). (1)

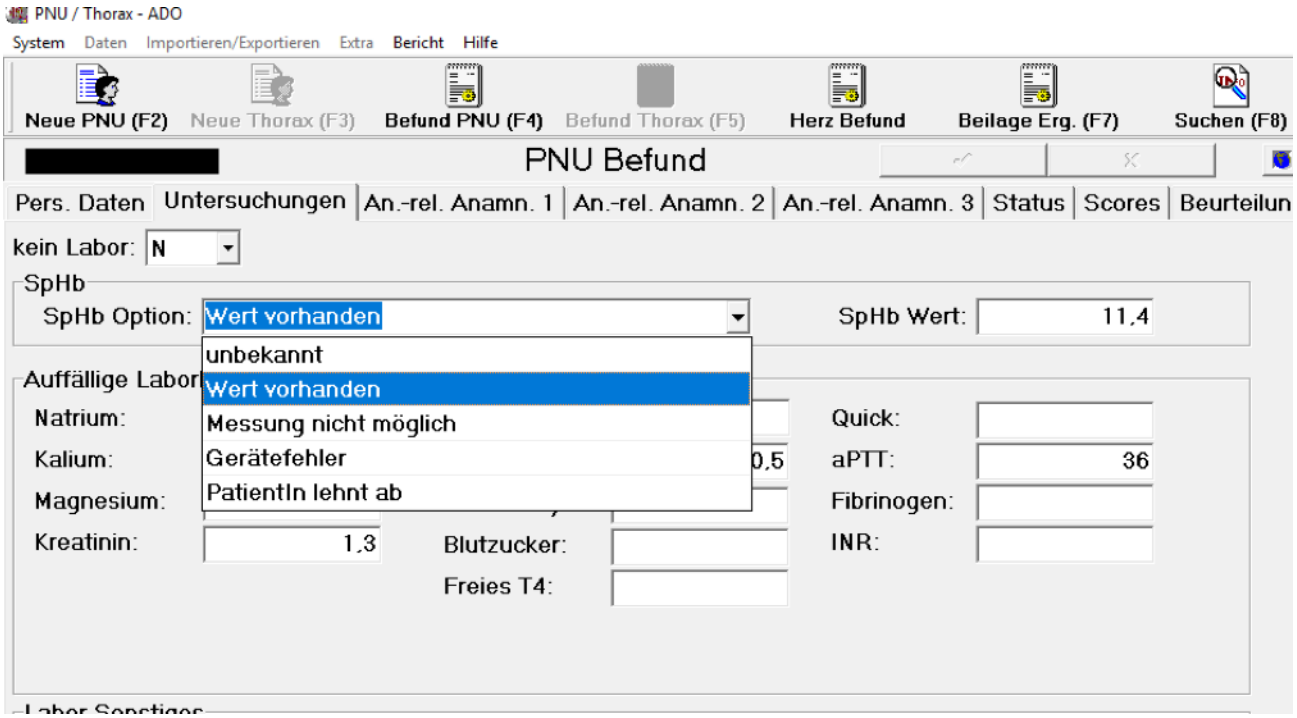

Figure 1 Documentation system

6. Sample-Size Calculation

"Sample size was calculated based on a two-sided confidence interval with a confidence level 1-α of 95%, an expected proportion of 0.85 and a distance of proportion to limit of 0.05. With an expected prevalence of preoperative anemia of 14.1% (54), required sample size was calculated to be 1392." (1)

The sample size calculation was performed by the "statistic ambulance", an institution at our university where statistical professionals help clinicians with the statistical part of their studies.

7. Statistical Analysis

7.1. Data collection

All patient information was collected out of our clinics´ documentation system (Medocs) using a search protocol. We searched for all patients who had a preoperative evaluation in our preoperative anesthetic clinic from January to October 2022 and a recorded SpHb value. We then excluded all patients who did not have a valuable LabHb (i.e. no LabHb available, LabHb older than one month, unstable hematological status).
In all patients found to be anemic by LabHb, we also directly searched for the time distance between blood sampling and the SpHb measurement in our clinics´ documentation system (Medocs).

We than calculated the mean differences between LabHb measurement and SpHb measurement.
The collected data was recorded in a spreadsheet format (.XLSX) using commonly available software (Microsoft Excel® 2019).
After the data collection phase was concluded, the spreadsheet was imported into an IBM SPSS Statistics 2018 file in .SAV format using the built-in import tool. Each variable was adjusted according to its respective data type. Furthermore, manual plausibility checks were performed on the data fields following the conversion of data types.(1)

7.2. Statistical analysis

The statistical analyses were performed using SAS v 9.4 (SAS Institute, North Carolina, USA) and SPSS v 26 (SPSS Inc., Stanford, USA) accessed through Citrix® provided by the Medical University of Graz (https://citrix.medunigraz.at). Graphs were generated using Excel® 2019 (Microsoft Corp., Redmond, USA, 2019) and SPSS v 26 (SPSS Inc., Stanford, USA). The significance level for statistical tests was set at $p < 0.05$, indicating statistical significance.

The patient characteristics, including general demographic information (such as age, gender, and BMI), as well as the American Society of Anesthesiologists (ASA) physical status classification, were described using means and standard deviations (SD) or numbers and percentages (%) as appropriate. (1)

7.3. Patient characteristics

General demographic data (e.g. age, gender, BMI) and American Society of Anesthesiologists (ASA) physical status classification were described with mean and standard deviation (SD) or as numbers and percentages (%), as appropriate. (1)
This information was exported out of our clinics´ documentation system (Medocs).

7.4. Hb measurements

In order to evaluate the reliability of SpHb measurement in identifying anemic patients according to the WHO definition, several metrics were calculated using LabHb values as the gold standard. These metrics include sensitivity, specificity, accuracy, true positive (TP), false positive (FP), true negative (TN), and false negative (FN) rates of the measurements.

Definitions:

True positive (TP) = the number of cases correctly identified as anemic

False positive (FP) = the number of cases incorrectly identified as anemic

True negative (TN) = the number of cases correctly identified as non-anemic

False negative (FN) = the number of cases incorrectly identified as non-anemic

Accuracy: The accuracy of this test refers to its ability to correctly distinguish between anemic and non-anemic cases. To estimate the accuracy of a test, it is necessary to calculate the proportion of true positives and true negatives among all the cases evaluated.
Mathematically, this can be stated as:

Accuracy=TP+TN/TP+TN+FP+FN

Sensitivity: The sensitivity of this test is its ability to determine the anemic cases correctly. To estimate it, the calculation of the proportion of true positive and false negative cases is necessary. Mathematically, this can be stated as:

Sensitivity=TP/TP+FN

Specificity: The specificity of this test is its ability to determine the non-anemic cases correctly. To estimate it, the calculation of the proportion of true negative in non-anemic cases is necessary. Mathematically, this can be stated as:

Specificity=TN/TN+FP
(76) (77)

Accuracy was than calculated, differences between measurements were described according to Bland and Altman. (78) Precision was assessed by determining the mean difference between the measurements and calculating the limits of agreement. (1)

7.5. Subgroup analysis

We performed subgroup analyses in two populations:

- *In patients with moderate to severe anemia (<11 g dl^{-1})*

  → Data from five National Health and Nutrition Examination Surveys (NHANES) in the USA from 2003 to 2012 found a prevalence for anemia of 5.6% and for moderate to severe anemia of 1.4%. In this study five times more non-pregnant women had moderate to severe anemia than men (2.5% vs. 0.5%, p<0.0001). In pregnant women, the rate of moderate to severe anemia was even higher with 3.5% (95% CI: 1.5–5.6%). (79)
  Wu et al. showed in their retrospective cohort study of the VA National Surgical Quality Improvement Program database that with every percentage point decrease in the hematocrit value, the 30-day postoperative mortality increased by 1.6% (95% CI, 1.1%-2.2%).
  They also showed that the adjusted risk of 30-day postoperative mortality and morbidity significantly rose when hematocrit levels fell under a cut-off of 39%. (53)

- *In patients with an ASA score <3*

  → Since these patients may not always have their haemoglobin levels measured according to recommendations. Thus, there is a possibility that anemia could go undetected in this population.

Because of the differences in accuracy of SpHb measurement for men and women described by A.A. Khalafallah et all (80), we primarily analyzed our data stratified by sex.

C. Results

During the study period, patients were carefully evaluated for inclusion in the study based on specific criteria outlined in chapter 2.4. These criteria were used to determine whether patients met the requirements for participation in the study, while also considering any factors that would lead to their exclusion.

Initially, 1284 patients were recruited from the pre-operative clinics of the Department of General Anesthesiology, Intensive care- and Emergency medicine.

All of these patients gave written consent to use their information in this study. However, 68 patients were excluded because of missing data. No patient withdrew consent during or after the study. A study flow chart is presented in figure 2.

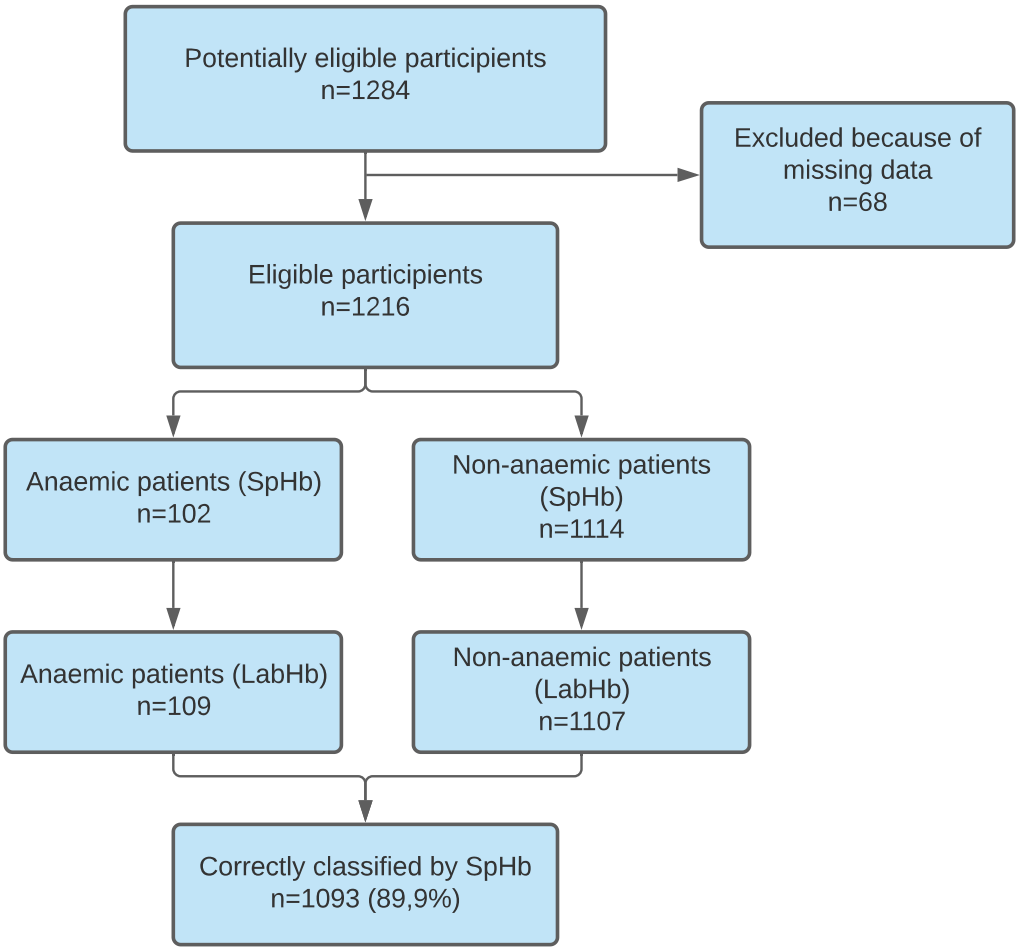

Figure 2 Flow chart reproduced from Honnef et. al. with permission of Scientific Reports (1)

1. Patients characteristics

In our final analysis, we included 1216 patients. In this patient population 660 (54%) were female and 556 (46%) were male. The average age of these patients was 56.0 (SD 16.3) years and the average BMI was 26.9 (SD 5.9).

74% of our study population had an ASA score of under three (ASA one 22%, ASA two 52%) and only 4% (45) had and ASA score of four.

Most recruited patients were planning to undergo orthopedic surgery (27%) followed by gynecological surgery (25%), urological surgery (22%), plastic surgery (14%) and general surgery (9%).

The mean LabHb in women was 13.4 g dl^{-1} (SD 1.3) and 14.9 g dl^{-1} (SD 1.3) in men. The mean SpHb in women was 13.8 g dl^{-1} (SD 1.5) and 14.7 g dl^{-1} (SD 1.4) in men.

In our study population, a total of 109 (9%) patients were found to be anemic by standard laboratory measurement. No significant difference in the prevalence of anemia was observed between sexes [n=53 (49%) men, n=56 (51%) women]. (1)

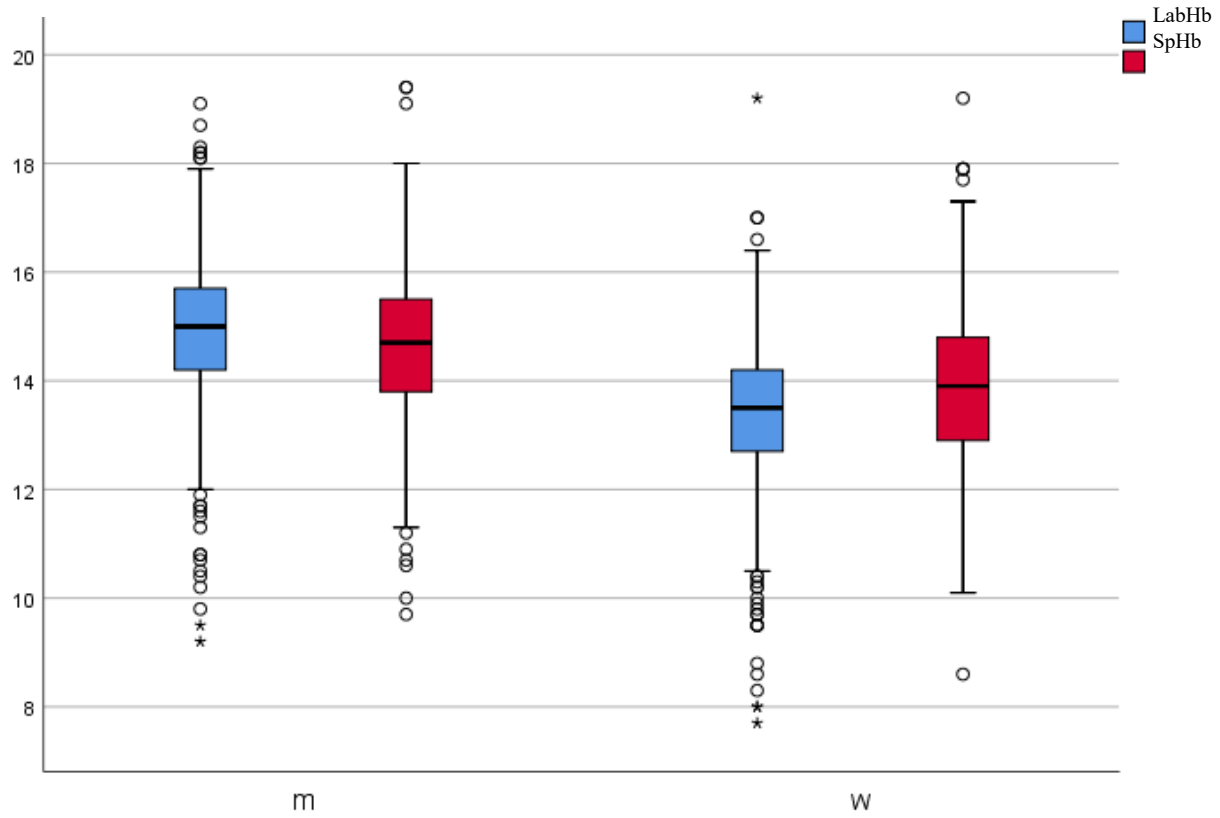

Figure 3 Whiskers boxplot of LabHb and SpHb in both sexes

	overall	*men*	*women*
Patients	1 216	556 (46%)	660 (54%)
Age [years] (mean, SD)	56.0 (16.3)	59.2 (15.5)	52.8 (17.1)
BMI (mean, SD)	26.9 (5.9)	27.8 (5.1)	26.2 (6.6)
Planned surgical procedure (n, %)			
Orthopedic surgery	357 (29%)	183 (33%)	172 (26%)
Gynecological surgery	300 (25%)		294 (45%)
Urological surgery	266 (22%)	234 (42%)	32 (5%)
General surgery	109 (9%)	73 (13%)	44 (7%)
Plastic surgery	167 (14%)	60 (11%)	107 (16%)
Unknown (non-cardiac)	17 (1%)	6 (1%)	11 (1%)
ASA score (mean, SD)	2.1 (0.8)	2.1 (0.8)	2.1 (0.7)
ASA classification (n, %)			
ASA 1	250 (22%)	121 (22%)	129 (20%)
ASA 2	639 (52%)	251 (47%)	378 (57%)
ASA 3	266 (22%)	135 (24%)	131 (20%)
ASA 4	45 (4%)	30 (5%)	15 (2%)
Missing ASA	16 (1%)	7 (1%)	9 (2%)
LabHb [g dl^{-1}] (mean, SD)	14.1 (1.5)	14.9 (1.3)	13.4 (1.3)
SpHb [g dl^{-1}] (mean, SD)	14.2 (1.4)	14.7 (1.4)	13.8 (1.5)

Table 5 Patient characteristics reproduced from Honnef et. al. with permission of Scientific Reports (1)

2. Accuracy of SpHb measurement

With 70 (8.5%) anemic women in our study population, the sensitivity of SpHb to detect anemic patients was 0.50 (95% CI 0.37 to 0.63) in women and with 53 (9.5%) anemic men in our study population sensitivity was 0.30 (95% CI 0.18 to 0.43) in men; specificity was 0.93 (95% CI 0.84 to 1.0) in women and 0.97 (95 % CI 0.95 to 0.98) in men. (Table 5)

The accuracy of a test is its ability to differentiate anemic and non-anemic cases correctly. To estimate the accuracy of a test, the calculation of the proportion of true positive and true negative in all evaluated cases is necessary.
There were 16 true and 16 false positive or 37 false and 487 true negative men in our study population, resulting in an accuracy of 90%.
In women we found that SpHb measurement produced 28 true positive and 42 false positive or 562 true negative and 28 false negative results, resulting in an accuracy of 89%.

Positive predictive value for SpHb was 0.50 (95% CI: 0.35 to 0.65) in men and 0.40 (95% CI 0.31 to 0.50) in women; negative predictive value was 0.93 (95% CI 0.92 to 0.94) in men and 0.95 (95% CI 0.94 to 0.96) in women. (Table 5) (1)

Results can be seen in table 5. The scatterplot for men and women can be seen in figure 4 and 5.

men **n = 556**		**SpHb**		
		Hb < 13.0 g dl-1 n = 32	Hb ≥ 13.0 g dl-1 n = 524	
LabHb	Hb < 13.0 g dl-1 n = 53	true positive n = 16	false negative n = 37	sensitivity 30.2%
	Hb ≥ 13.0 g dl-1 n = 503	false positive n = 16	true negative n = 487	specificity 96.8%
prevalence **9.5%**		positive predictive value 49.9%	negative predictive value 93.0%	accuracy 90.5%
women **n = 660**		SpHb		
		Hb < 12.0 g dl-1 n = 70	Hb ≥ 12.0 g dl-1 n = 590	
LabHb	Hb < 12.0 g dl-1 n = 56	true positive n = 28	false negative n = 28	sensitivity 50.0%
	Hb ≥ 12.0 g dl-1 n = 604	false positive n = 42	true negative n = 562	specificity 93.1%
prevalence **8.5%**		positive predictive value 40.0%	negative predictive value 95.3%	accuracy 89.4%

Table 6 Accuracy of SpHb measurement compared to LabHb. Reproduced from Honnef et. al. with permission of Scientific Reports (1)

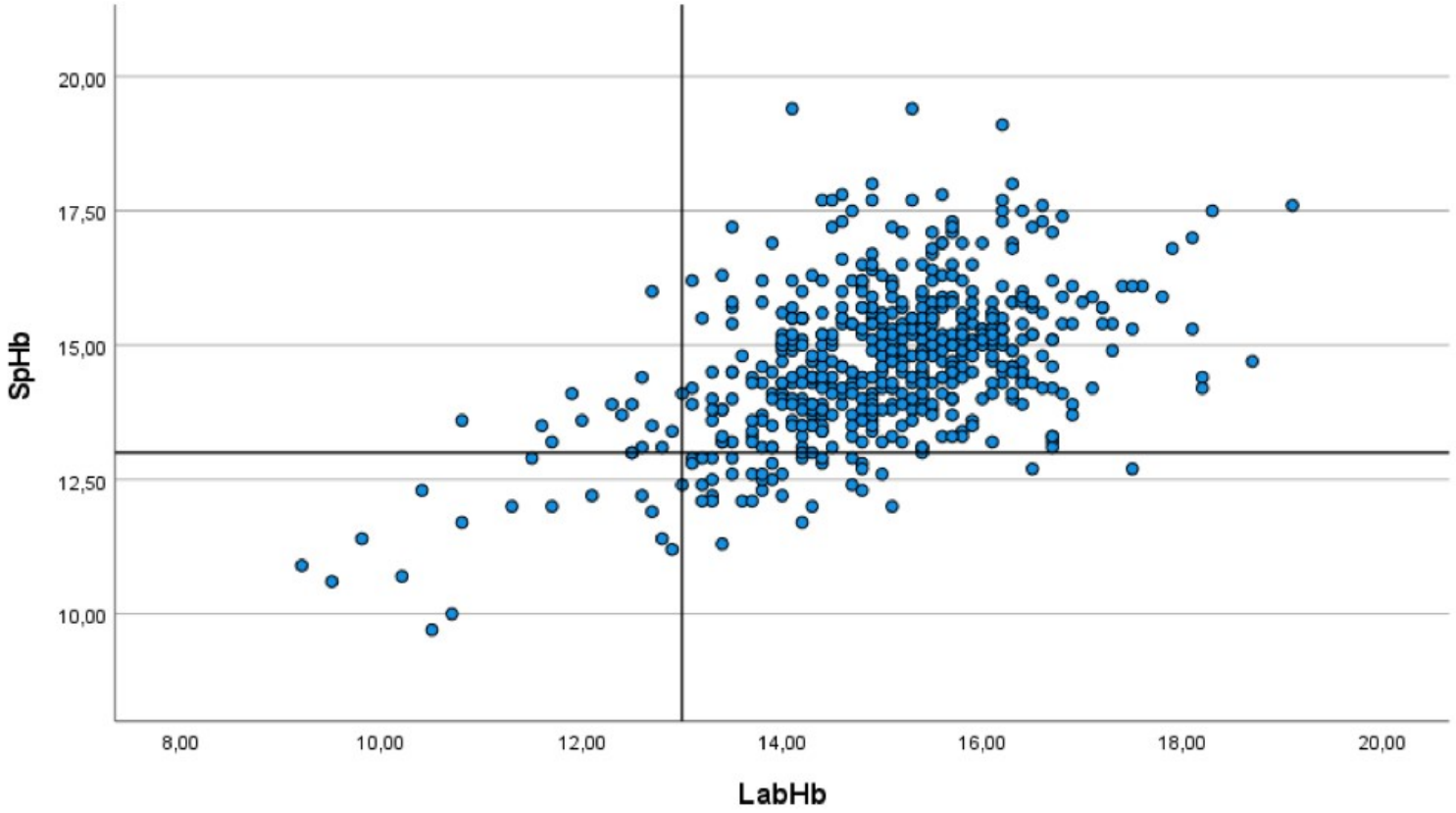

Figure 4 Scatterplots of LabHb (x-axis) and SpHb (y-axis) during preoperative evaluation in men reproduced from Honnef et. al. with permission of Scientific Reports (1)

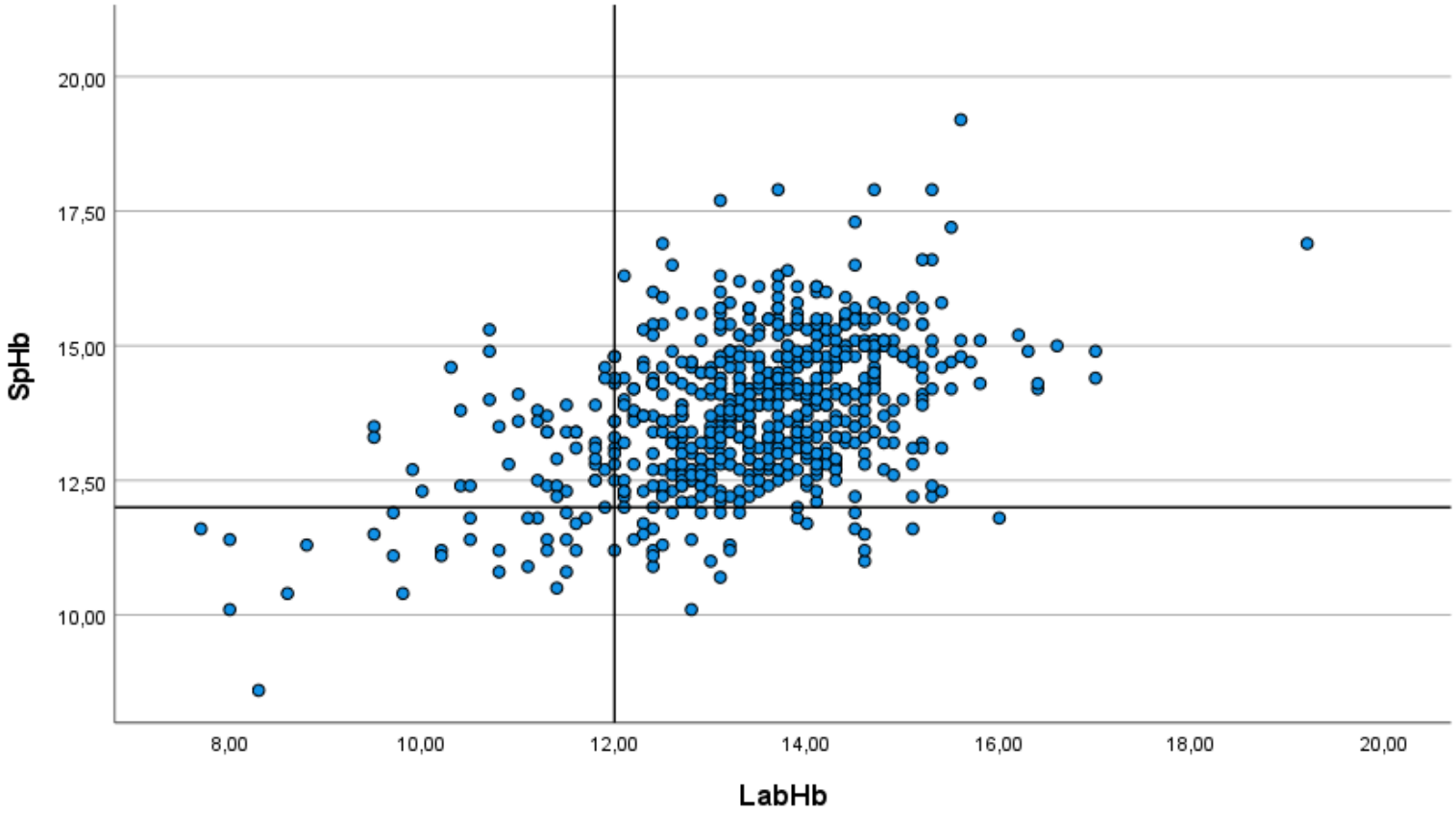

Figure 5 Scatterplots of LabHb (x-axis) and SpHb (y-axis) during preoperative evaluation in women. Reproduced from Honnef et. al. with permission of Scientific Reports (1)

3. Subgroup analysis

3.1. Patients with an ASA score of 1 or 2

In the subgroup of patients with an ASA score <3 (n=889), 7% (n=58) were identified as anemic based on LabHb measurements. Among these 58 anemic patients, 21 (36%) were also detected as anemic using SpHb measurements. The sensitivity of the SpHb device in detecting anemic patients within this subgroup was calculated as 0.45 (95% CI 0.17 to 0.77) for men and 0.40 (95% CI 0.19 to 0.47) for women. This indicates that the SpHb device successfully identified 45% of anemic men and 40% of anemic women in this subgroup.

The specificity of the SpHb device was calculated as 0.98 (95% CI 0.95 to 0.99) for men and 0.98 (95% CI 0.97 to 0.99) for women. This suggests that the SpHb device exhibited a high level of accuracy in correctly identifying non-anemic individuals, with 98% specificity for both men and women in this subgroup. (1)

The scatterplot for men and women can be seen in figure 6 and 7.

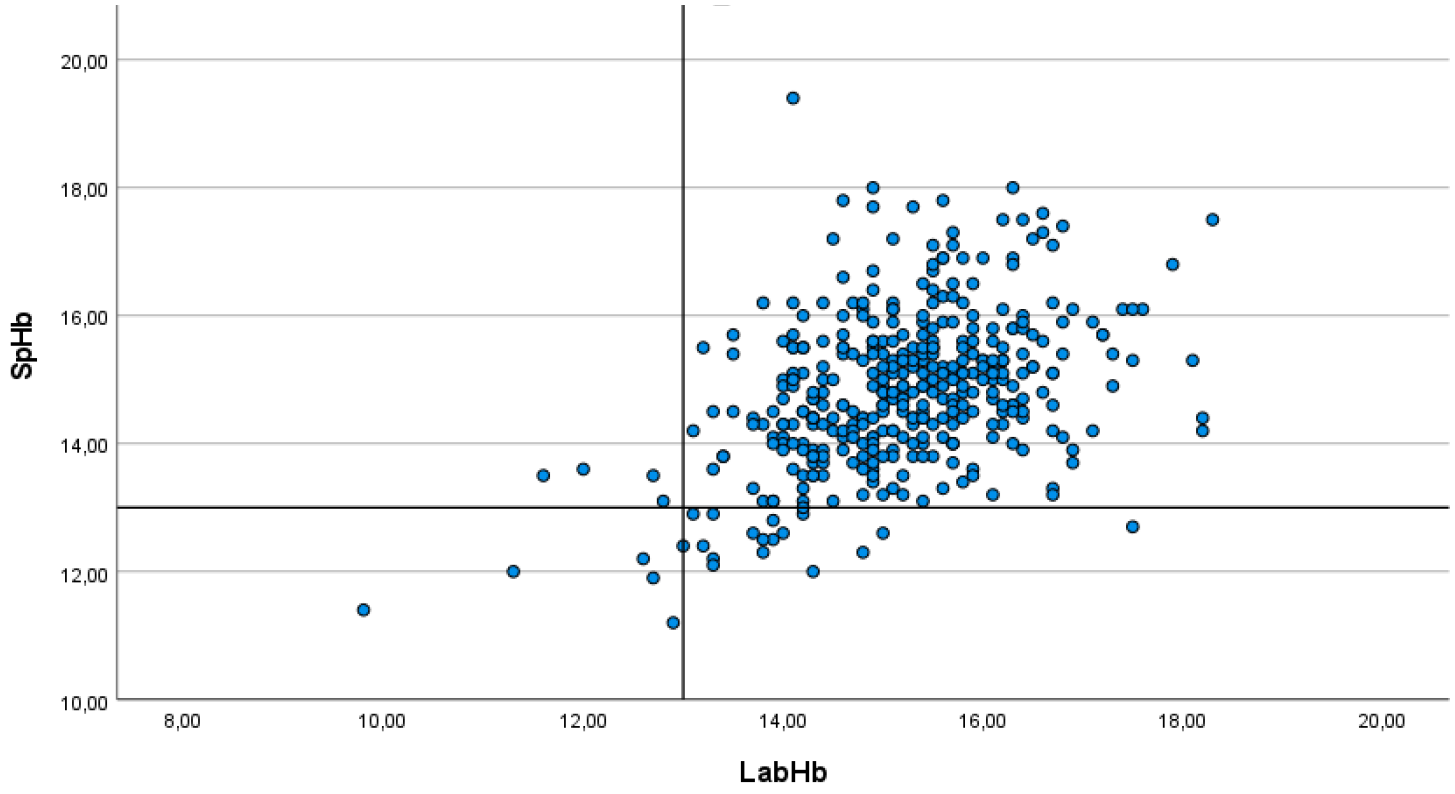

Figure 6 Scatterplots of LabHb (x-axis) and SpHb (y-axis) of male patients with an ASA score <3. Reproduced from Honnef et. al. with permission of Scientific Reports (1)

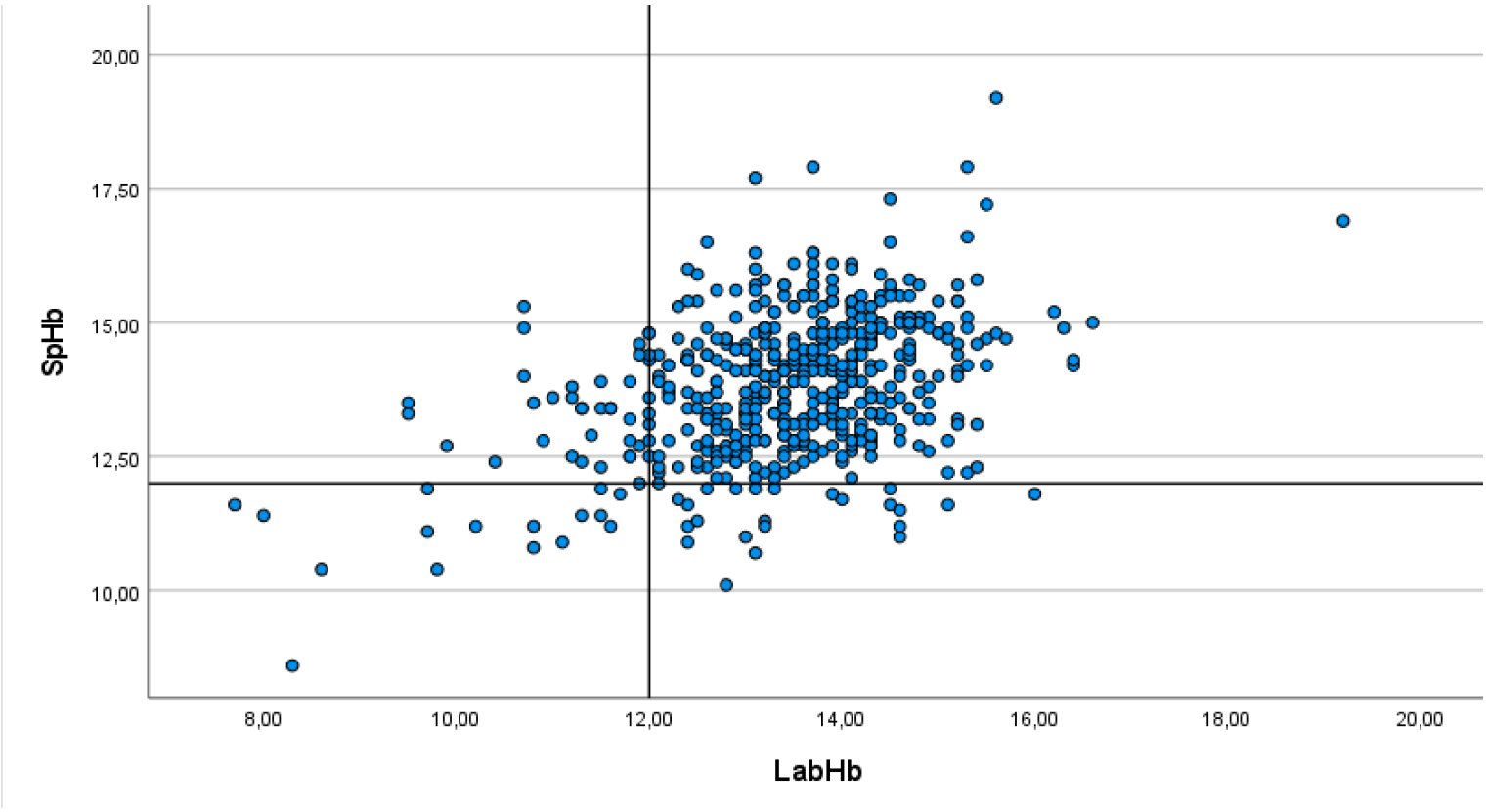

Figure 7 Scatterplots of LabHb (x-axis) and SpHb (y-axis) of female patients with an ASA score <3. Reproduced from Honnef et. al. with permission of Scientific Reports (1)

3.2. Patients with moderate to severe anemia

Within the subgroup of patients with moderate to severe anemia (n=38) (as defined by the WHO < 11 g dl−1) (2), the sensitivity of the SpHb device was calculated as 0.56 (95% CI 0.21 to 0.86) for men and 0.17 (95% CI 0.06 to 0.36) for women.

The specificity was calculated as 1.00 (95% CI 0.99–1.00) in men and 0.99 (95% CI 0.98–1.00) in women. This suggests that the device had a high level of accuracy in correctly identifying non-anemic individuals, with 100% specificity for men and 99% specificity for women in this subgroup.

The scatterplot for men and women can be seen in figure 8 and 9.

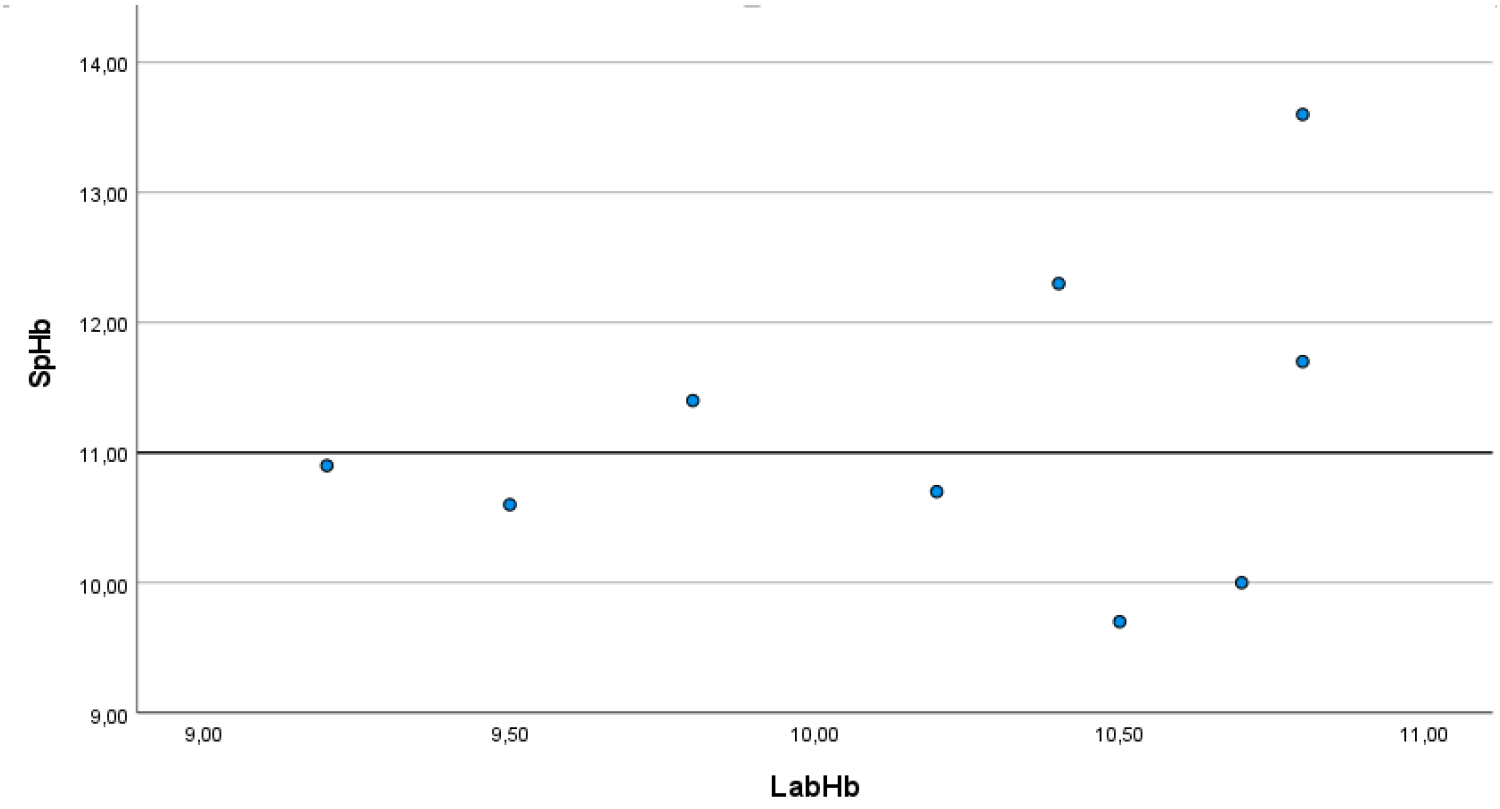

Figure 8 Scatterplots of LabHb (x-axis) and SpHb (y-axis) of male patients with moderate to severe anemia. (1)

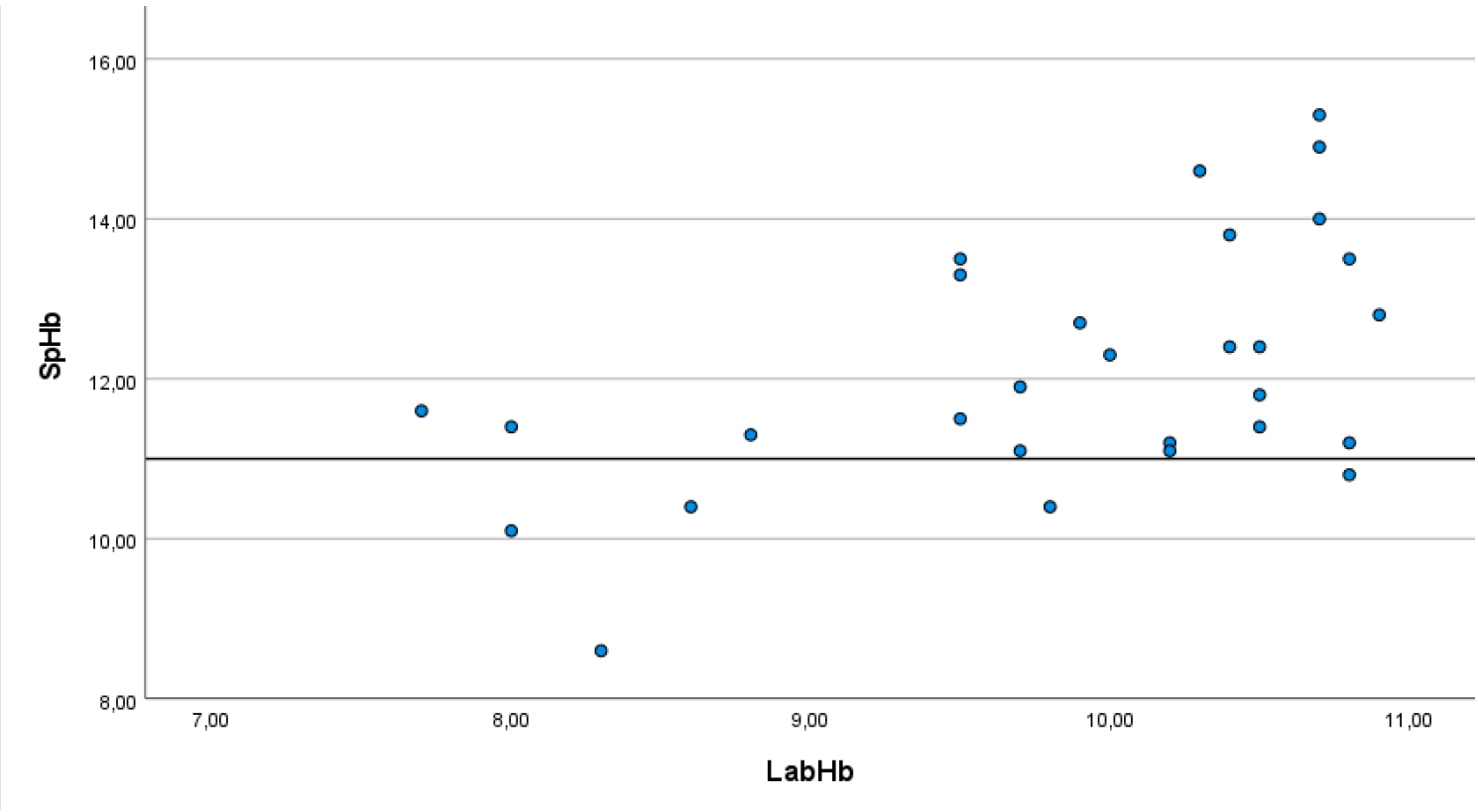

Figure 9 Scatterplots of LabHb (x-axis) and SpHb (y-axis) of female patients with moderate to severe anemia. (1)

4. Correlation

We found that SpHb correlated poorly with LabHb in our study population (Figure 3 and 4). The Pearson correlation coefficient was r=0,5 for men and r=0,45 for women. There was no systematic variation of measurement (Figure 5 and 6).

Mean difference for men was 0.25 ± 1.3 g dl−1 (limits of agreement − 2.5 to 3.0) and − 0.42 ± 1.4 g dl−1 (limits of agreement − 3.2 to 2.4) for women.

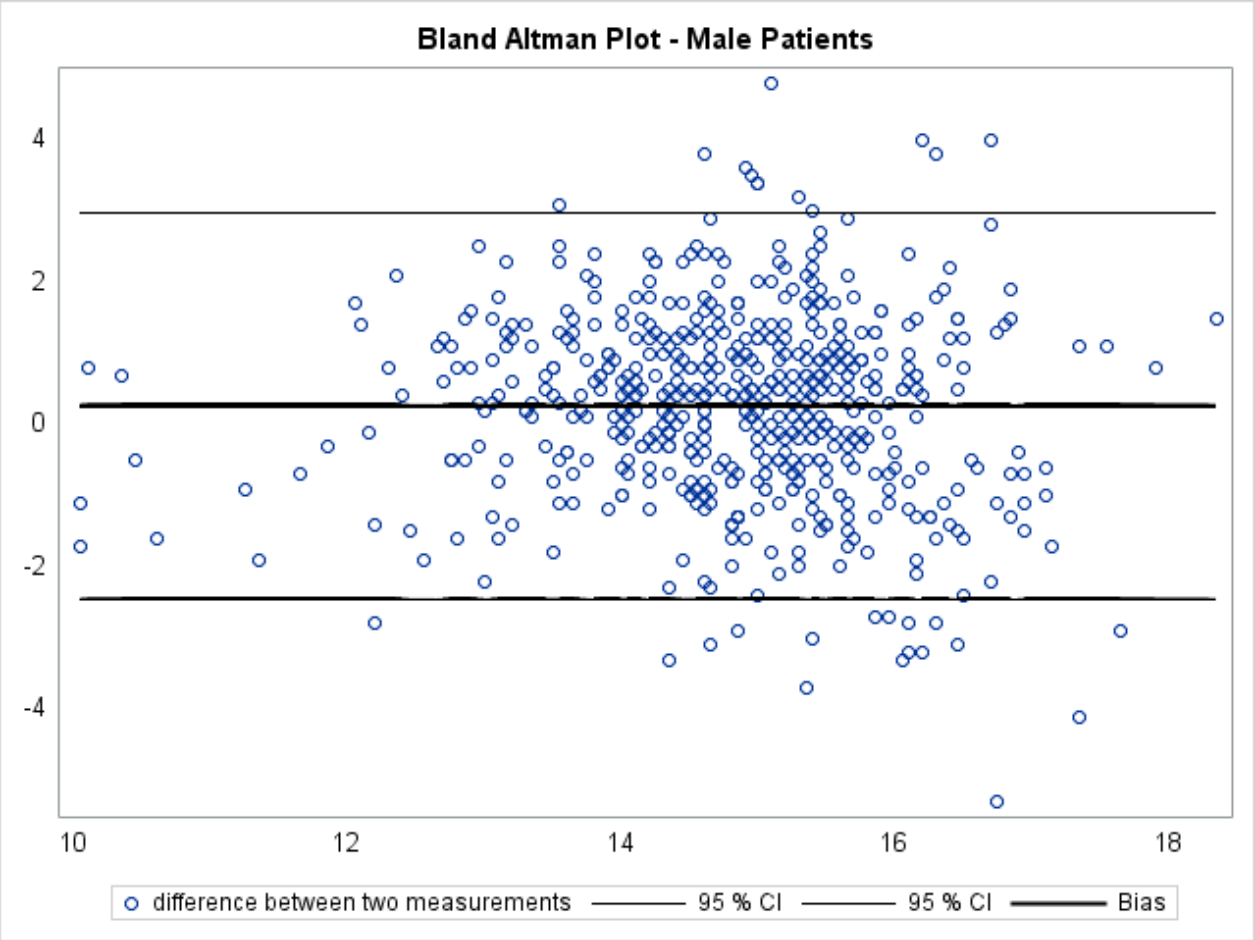

Figure 10 Bland–Altman-Plot for LabHb and SpHb in men; x-axis denote average between two measurements, y-axis denote differences between two measurements, horizontal lines indicate mean differences and limits of agreement between two measurements (=mean deviation±2×standard deviation), respectively. Reproduced from Honnef et. al. with permission of Scientific Reports (1)

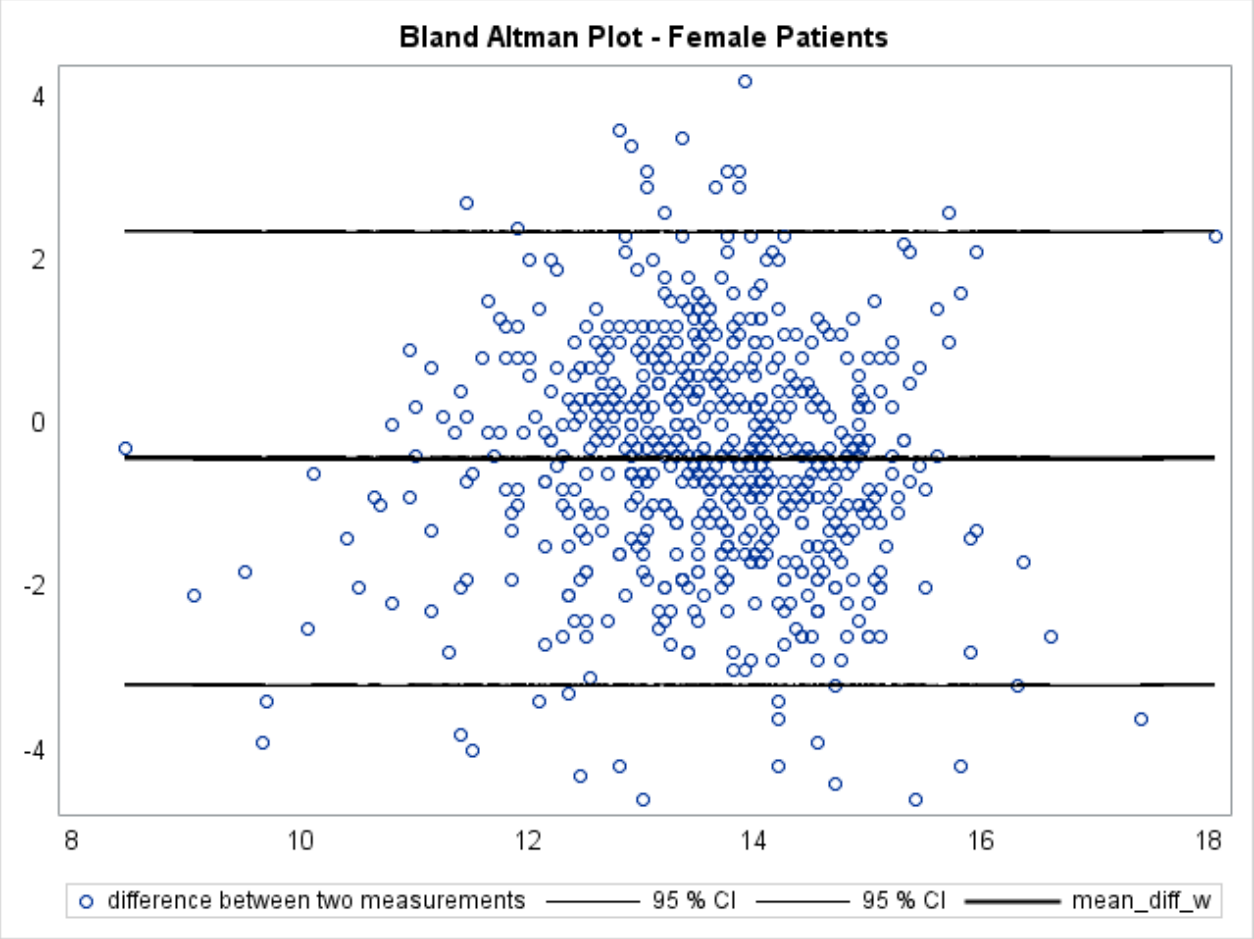

Figure 11 Bland–Altman-Plot for LabHb and SpHb in women; x-axis denote average between two measurements, y-axis denote differences between two measurements, horizontal lines indicate mean differences and limits of agreement between two measurements (=mean deviation±2×standard deviation), respectively. Reproduced from Honnef et. al. with permission of Scientific Reports (1)

D. Discussion

This dissertation and the underlying research project contribute to the to question if non-invasive Hb measurement can add benefits to the perioperative evaluation of patients´ Hb status.
The existing data regarding the accuracy of spot-check SpHb measurement in various settings is both inconsistent and insufficient. There has therefore been a clear need for additional insights on the usability of these devices in a perioperative setting to guide clinicians and researchers in their decision-making process.

1. Answers to research questions

1.1. Research question 1

> Can we use non-invasive Hb measurement as a pre-test to detect anemia in patients who would normally not undergo central laboratory testing?

Previous studies have shown that the risk for anemia in ASA 1 and 2 patients is lower than in other patient populations with more comorbidities.
In a retrospective analysis (2005) Olson et al. found that, of 9584 ASA I and II patients scheduled for elective low risk surgery, only 0,8% (n=75 patients) had an Hb <9 g/dl; nevertheless, perioperative management of anemia occurred in none of these patients. Because of studies like this, guidelines today prioritize preoperative Hb testing in patients with an ASA score >2 and patients scheduled for mediate or high risk surgery. (see chapter 1.3) (73) (72) (81) (82) (83)

With the implementation of PBM programs, designed to reduce the risk of unnecessary blood transfusions, health care providers are now stressing the importance of detection and treatment of preoperative anemia.
Also, there are groups of patients where the rate of anemia in relatively healthy individuals (i.e. ASA<3) is higher than in the overall population (for example patients preparing for gynecological surgeries).
In 2021 Nadia et al. found that, in a Canadian multicenter database, 27.3% out of 4822 of patients preparing for gynecological surgery were anemic; moreover, that anemia was associated with higher rates of intensive care (ICU) admission and adverse outcomes. (84)
For these reasons, an inexpensive, non-invasive and risk-free Hb measurement method could be of great use in

preselected populations. To our knowledge however, to date no study has been conducted to evaluate the usefulness of SpHb measurement under everyday clinical conditions. (1)

In our study, we performed subgroup analysis in patients with an ASA score <3 (n=889). These are patients whose haemoglobin levels, according to recommendations, might not be measured, and whose anemia could thus remain undetected.

While we found that 7% (n=58) of these patients were anemic, we were only able to detect 36% (n=21) of them with SpHb measurement, resulting in a sensitivity of 0.45 (95% CI 0.17 to 0.77) in men and 0.40 (95% CI 0.19 to 0.47) in women. Specificity was 0.98 (95% CI 0.95 to 0.99) in men and 0.98 (95% CI 0.97 to 0.99) in women. (1)
These results correlate well with the rest of our findings and they highlight the fact that under real-world conditions, SpHb is not sufficiently accurate to identify anemic patients in this population.

That said, according to modern perioperative guidelines, these patients would normally not have had their Hb measured at all. With the high specificity of SpHb measurement devices, their lack of side effects, and their low cost, there remains the possibility that these devices could be of use in ruling out anemia in doubtful cases.
Because of the mediocre correlation of SpHb measurement with laboratory measurement and the wide spread of results in our comparison (as represented by wide limits of agreement), a calculation of cut-off values using receiver operating characteristics (ROC) analysis was not possible. (1)

Thus, we conclude that further research is needed to allow definitive conclusions on the question of whether SpHb devices, given their low sensitivity to detect anemia, are advantageous in the preoperative evaluation of these low-risk patient populations

1.2. Research question 2

For patients preparing for various kinds of surgery, how accurate is SpHb in comparison to the gold standard?

In 2015 Khalafallah et al. conducted a study where they also evaluated the accuracy of SpHb measurement compared to invasively measured Hb in a preoperative setting, with a comparable population (i.e., pre-anesthetic clinic patients, n=699) and similar technology. They found that SpHb was useful, at the very least, for detecting anemia in male patients, with a sensitivity of 92% in men, 57% in women and a specificity of 74 in men and 82% in women. (80)
In their study they used an "average of three readings" mode to reduce the influence of inaccurate measurements. Since the aim of our study was to use SpHb measurement to detect anemia in patients in an everyday clinical setting, and the method used by Khalafallah et al.., on account of its cost in time and resources, is not routinely used, we chose not to use their "average of three readings" mode. (1)

Our data (obtained under every day routine clinical conditions) differs vastly from Khalafallah et al., and this highlights one of the problems we have encountered in the evaluation of SpHb devices. (1) (80)

Meanwhile, other studies comparing SpHb devices with invasively measured Hb (AHA, HemoCue), which focused on accuracy of measurement of these devices but not on their ability to detect anemia, found numbers comparable to ours.
In a systematic review and meta-analysis of method comparison studies (SpHb versus LabHb), Hiscock et al. described a low overall mean difference with -0.03 g/dl (95% prediction interval -0.30 to 0.23) but high limits of agreement (-3.0 to 2.9 g/dl). (44)

There have also been studies of the screening of blood donors for anemia with spot-check SpHb measurement devices.
Before blood donors are accepted for donations, they need to be evaluated by health care providers. For donations to be acceptable, European cutoff levels require a Hb level of 12.5 g/dl for women and 13.5 g/dl for men. The method of choice for pre-donation anemia screening has been to take the sample by finger stick (i.e., capillary sampling) and to analyze it with portable photometric measurement devices. (85) (86)
However, capillary blood sampling is problematic on two counts: 1) capillary and venous haemoglobin levels may differ; and 2) the finger stick is reported by blood donors to be one of the worst parts of the whole process. (87) (88)
Therefore, as has been the case with preoperative evaluation of patients' Hb status, a non-invasive and less risky measurement method has led to several studies with blood donors.

Although some of these studies have shown good correlation between SpHb and LabHb, the overall conclusion was that, on account of low sensitivity and high limits of agreements, non-invasive measurement did not sufficiently identify anemic patients in a healthy population. (90) (87)
A study conducted by Ardin et al. found that the main barrier to reliable measurement results was preanalytical variability in sampling. (85)

These results and conclusions correlate well with our findings. (1)

1.3. Research question 3

Can we establish cut-off values for SpHb in a pre-operative setting?

The aforementioned study of Khalafallah et al. compared the performance of SpHb with laboratory Hb measured simultaneously by receiver operating characteristics (ROC) analysis. In their population of preoperative patients, the performance of SpHb for detecting anemia was 0.90 (0.86-0.95) in men, and 0.75 (0.66-0.84) in women (ROC area CI 95%). (80)
However, the authors of this study did not propose cut-off values based on their data.

The ROC plot is one way to evaluate to what extent a test result differs among people who do or not have the condition of interest. This method was developed in the 1950's to evaluate radar signal detection and has been used commonly in medicine since the 1990's.

To obtain a ROC plot, one must calculate the sensitivity and specificity of every measured data point and then plot sensitivity against specificity. A perfectly accurate test would then show up on this graph as a curve that nearly meets the left and top sides of the plot. A test that is considered useless would result in a straight line from the bottom left corner to the top right corner when plotting the obtained data points. However, in clinical practice, there is typically some degree of overlap between the data points of the two groups being compared. This overlap creates a curve that falls between the two extreme scenarios previously described. This indicates that the test has some degree of discriminatory ability, although it may not be perfect in distinguishing between the two groups. (91)

ROC curves can be used to select an optimal cut-off point. A commonly used approach is to select a threshold to give the same weight to sensitivity and specificity by selecting a point that is near to the top-left corner of the ROC curve, which is also known as the Youden Index. (92) In the case of non-invasive Hb measurement, in order to avoid missing anemic patients, it would make sense to give more weight to sensitivity than to specificity. (93)

Unfortunately, in our study population, with a sensitivity <0.50 in both men and women, and given the mediocre correlation of SpHb measurement with laboratory measurement, along with the wide spread of results in this comparison (as represented by wide limits of agreement), we found that a ROC analysis and calculation of cut-off values was neither sensible nor feasible. (1) (94) (91)

SpHb measurement is not as straightforward, rapid and easy as measuring oxygen saturation (Sp02). Environmental factors such as ambient light, heart rhythms, movements, peripheral perfusion and operating inexperience seem to have a greater effect on the success rate of SpHb measurements, however correctly obtained, than the manufacture's declaration would suggest.

Addressing environmental factors during SpHb measurements, as well as methodological adjustments such as the "best of three readings mode," or even future refinements of SpHb devices by the manufacturer might all improve the accuracy of these devices. Greater accuracy could in turn help create reliable cut-off values.

That said, it remains questionable whether the "best of three readings mode," or the time it would take to establish perfect surroundings during the measurement, are realistically applicable in a daily routine work environment.

2. Implications for clinical practice

Although non-invasive methods of Hb estimation and SpHb measurement devices have received considerable scientific interest recently, to our knowledge no recommendations for changes in routine clinical practice in either perioperative medicine or blood donor clinics have been proposed.

It has previously been shown that continuous SpHb measurement and trend monitoring is useful for detecting blood loss intraoperatively and at intensive care units.
Recent studies have demonstrated that continuous measurement of SpHb as a trend monitoring tool can assist healthcare providers in estimating haemoglobin values in different clinical scenarios. This approach has shown potential in reducing the need for unnecessary red blood cell transfusions. By continuously tracking SpHb levels, healthcare providers can make more informed decisions regarding patient management and optimize transfusion practices. (43) (95) (96) (97) (98)

In 2014, Kim et al. conducted a meta-analysis to assess the utility of continuous SpHb measurement for intraoperative assessment of patients' haemoglobin (Hb) status and transfusion triggers. While the study identified certain advantages, it also noted a considerable mean difference and standard deviation (SD) between SpHb measurements and laboratory-based methods. (43)

Conversely, that spot-check SpHb measurement devices are not accurate enough to replace invasive Hb measurement methods has been described sufficiently elsewhere. (43) (99)
Over the last few years, studies such as ours have evaluated the usefulness of SpHb devices as a

pre-test in settings where invasive blood sampling should be avoided, whether on account of the time it takes, its expense, the possibility of negative side effects, or the danger of anemia remaining undetected (for example, in preoperative evaluation of low risk patients, pediatrics, or blood donor clinics). (89) (90) (87) (100)

Neither the NICE guidelines on routine preoperative tests for elective surgery, nor the ASA practice advisory for pre-anesthesia evaluation suggest non-invasive Hb measurement for anesthetic evaluation of patients preparing for elective surgery.

Both guidelines state that, instead of routine preoperative Hb measurements, health care providers should use past medical history, preexisting diseases, and clinical status to identify potential anemic patients. These selected patients should than have their Hb measured by central laboratory. (72) (101)

However, patients' medical histories and the clinical signs of anemia are of varying quality, as they depend on patients' cooperation and the severity of anemia. Therefore, despite mediocre sensitivity, with reliable cut-off values SpHb measurement could still assist health care providers in detecting anemia in the run up to surgery, as well as in other situations where invasive blood sampling is best avoided or is unfeasible.

Previous studies conducted on this topic have shown indifferent results, ranging from good correlation and acceptable sensitivity (especially in men), to high limits of agreement and low accuracy. Therefore, it remains questionable whether SpHb measurements add value in these situations, especially in the evaluation of patients preparing for elective surgery. Our study could not eliminate uncertainty regarding the accuracy of SpHb devices in this setting.

Because of low sensitivity of the SpHb device to detect anemia in our study population, we were also not able to calculate reliable cut-of values for the usability of these devices in a perioperative setting. (1)

What our data shows us is that SpHb measurement is not as straight forward and easy as Sp02 measurement; its accuracy is dependent on numerous aspects of the test environment, including the frequency of measurements in the same patient. In comparison to a somewhat similar study by A.A. Khalafallah, our data, collected under everyday routine conditions, revealed that accuracy and sensitivity were both lower than previously described.

Therefore, health care providers should be aware of the highly variable accuracy of these devices, and should consequently not base their clinical decisions exclusively on SpHb measurements. (80) (1)

3. Implications for future research

In our study, we did not find non-invasive measurements to be more suitable for men than for women like it was previously described. Women in our study population were significantly younger than their male counterparts. This is partly because the vast majority of them were preparing for small gynecological and obstetric surgeries. They were therefore less likely to have comorbidities such as blocked arteries and chronic heart failure.

This, in combination with the association between perfusion index and accuracy in SpHb measurement devices might offer an explanation for the observed differences in our study. (1)

Existing studies have suggested that the perfusion index is linked to the accuracy of SpHb devices. (102) (103) (104) (1)
This finding could potentially help researchers to better understand the differences between the accuracy of non-invasive Hb measurement in the two sexes.

In 2013 Rice et al. published an article called "Noninvasive Hemoglobin Monitoring:

How Accurate Is Enough?," in which they evaluated the existing data on continuous SpHb measurement and questioned whether standard methods of device evaluation can be applied to these new measurement methods. (105)

They stated that the purpose of noninvasive SpHb measurement, especially in the operating room, is to assist health care providers in deciding whether or not to transfuse the patient. They wrote:

"For that reason, we suggest that not only should noninvasive Hb devices and the gold standard method produce statistically similar results, they should also lead to comparable clinical decisions. To that end, a test of decision making around the relevant Hb concentration range of 6 to 10 g/dL should be used." (105)
Their ultimate conclusion was that the published accuracy of continuous noninvasive SpHb measurement was not sufficient to guide health care providers in such decisions. (105)

However, in 2016 Barker et al. published a "Measured Response to a Critical Review," in which they highlighted several studies that showed good trend accuracy of continuous SpHb measurement devices.
They concluded that "SpHb has repeatedly demonstrated clinically usable accuracy in head-to-head comparisons with lab-Hb and similar trend accuracy (precision) as invasive methods," and that it has therefore "been shown to help clinicians reduce RBC transfusions and initiate more timely RBC transfusions when they are needed." (106)

As these reviews show, that researchers have focused on implementing SpHb measurement devices as a tool to help clinicians in their decision-making process regarding transfusion.

The goal of our study was to establish reliable cut-off values for spot-check SpHb measurement, in order to help clinicians reduce the likelihood of anemia going undetected in the run up to surgery.

Because of low sensitivity of the SpHb device to detect anemia (see 4.1. research question 3), this goal was unattainable. It may be, however, that with further refinements of these devices and the optimization of test environments, it will become possible to calculate cut-off values in the future. (1)

In 2021 Wittenmeier et al. evaluated the usefulness of SpHb measurement as an index test to detect pre-operative anemia. They calculated their cut-off values based on previous data and achieved a sensitivity of 99%.
With the cut-off values they calculated—14.6 g/dl in women and 15.2 g/dl in men—they would have "saved" 9% of women and 28% of men from invasive blood testing. In their study population, SpHb performed similarly to our own results, with a sensitivity of 58% in women and 61% in men. With these numbers their cut-off values to detect anemia with a sensitivity of 99% were 16.2 mg/dl in women and 15.2 mg/dl in men. (107)
These results show that the accuracy of current SpHb devices is no sufficient to calculate clinical usable cut-off values for the detection of pre-operative anemia.

However, in a study published in 2023 (that is, after the study on which this dissertation is based was published), with 122 participants, Hornedo-González et al. managed to achieve sufficient accuracy of SpHb measurement to perform a ROC analysis and calculate cut-off values. With a gender-neutral haemoglobin threshold of 12.0 mg/dl to define anemia, the optimal SpHb cut-off point was calculated to be 13.5 mg/dl with an AUC of 0.87, a sensitivity of 86%, and a specificity of 81%.

With this cut-off point, 60% (n=73) of all patients could have safely avoided invasive blood sampling for the detection of pre-operative anemia, while 3 anemic patients would have been missed. (108)

As is currently the case with continuous SpHb measurement devices as a an aid for transfusion decisions, spot-check SpHb measurement devices could help clinicians in their evaluation of preoperative patients and their Hb status. With existing devices and data, however, this method is not sufficiently reliable for the guidance of clinical decisions.

More research, accompanied by technical refinements in measurement, is necessary to assess the usability of spot-check devices in a perioperative setting.

4. Strengths and Limitations

Our ability to reach our planned sample size in the chosen observation period was somewhat restricted by the covid-19 pandemic. As in many institutions, the pandemic occasioned a reduction of surgical schedules, in order to free up anesthetic and intensive care resources. (1)
In addition, the occurrence of anemia observed in our study population was slightly lower than what we would have expected based on the current literature. (54) (109)

That said, our investigation is, to our knowledge, based on the largest cohort of patients so far described in recent literature. The size of the cohort is important, since, given the low occurrence of preoperative anemia, a high number of patients is crucial to properly estimate the sensitivity and specificity of the test in question. Our study thus provides the most comprehensive insight to date into the usability of non-invasive Hb measurement in a preoperative setting. In our subgroup analysis of patients with moderate to severe anemia, the observed study population (n=38) was nevertheless too small to draw reasonable conclusions about the usability of SpHb devices for that group. (1)

In our study population, the proportion of women was significantly higher than would be expected in a normally distributed population. This can be explained by the placement of our SpHb devices (one at the gynecological pre-anesthetic clinic and one at our central pre-anesthetic clinic), where we naturally recruited a high rate of patients preparing for gynecological and obstetric surgery. This should not compromise our findings. (1)

In fact, this particular demographic fits our research questions rather well, as, due to their relatively high rate of anemic patients, gynecological and obstetric surgeries represent a promising area of application for non-invasive Hb measurement.

4.1. Critical reflection on the study method

The standard protocol for preoperative evaluation in our pre-anesthetic clinic is that central laboratory values are accepted if they are not older than six months and the patient is in stable condition. For this reason, not all patients had had their SpHb measured at the same time as their blood was sampled for LabHb. We therefore decided to exclude all patients who had not had a LabHb measurement within a month of the SpHb measurement and patients with unstable hematological status. (1)

This decision was based on clinical feasibility, current literature and guidelines. For example, the NICE guidelines for preoperative testing recommend including the results of tests undertaken in primary care in the preoperative evaluation of patients. (72) (110) (111)

In 2017, in their retrospective study of routine laboratory preoperative tests, Rodríguez–Borja et al. showed that only 2.7% of these tests showed unexpected pathologies based on previously (up to 6 months) performed laboratory analyses, and none of these findings changed anesthetic management. (112)

Among the anemic patients who did not have their measurements performed in the same session (n=27, 25%), it was found that the mean time to central laboratory was 64.4 hours (SD 59.2) and none of these patients were found to have an unstable Hb status. Based on this information, it is unlikely that the difference in the timing of sampling significantly affected the findings of the study. (1)

As mentioned above, non-invasive SpHb measurement devices have been shown to have widely variable accuracy, and thus the studies conducted on them have come to very different conclusions regarding their usefulness in various settings.

For these divergences in accuracy, the three most likely causes are the following:

1. *Perfusion:*

   Miller et al. showed in their 2012 study that increasing the perfusion of the finger used for measurement by means of a digital nerve block could de-crease the variability of measurement, and thus increase the accuracy of non-invasive SpHb measurement devices. They also found that the accuracy of SpHb measurement was related to the perfusion index (PI), which is automatically indicated by some SpHb devices. The authors concluded that the accuracy of these devices is better when the PI is >2.0, and that better perfusion could potentially also be achieved by less invasive methods then digital nerve block (i.e. warming the finger). (102)

2. *Number of measurements:*

   With the use of the "best of three readings" method, A.A. Khalafallah et al. achieved more accurate results of SpHb measurement then we did in our study. (80)
   Also, continuous SpHb measurement as a trend monitoring seems to produce better results than spot-check measurements; this improvement is likely related to the number of consecutive measurements.

3. *Ambient light:*

   SpHb measurement devices use a technology based on multiple wavelength spectrophotometry. Because of the number of wavelengths involved (com-pared to standard pulsoxymeters that only use 2 to 4 wavelengths), these de-vices are more likely than pulsoxymeters to be affected by ambient light. (113)

Our study was intended to evaluate the performance of SpHb measurement devices under conditions of everyday clinical use. Thus, we did not report the perfusion index. Keeping to the standard of care protocol in our pre-anesthetic clinic, we did not intervene to increase the perfusion state of the measurement finger. (A digital nerve block is both invasive and time consuming, and is therefore neither feasible nor sensible in a preoperative setting.) Neither did we use the "best of three readings" mode, nor undertake to reduce the possibility of ambient light compromising the measurement. Our logic here is the following: 'real world conditions' are very different from a laboratory environment, and devices designed for clinical use should be able to perform under such conditions.

5. Conclusion

The results of our study are consistent with existing data on spot-check SpHb measurement in multiple clinical settings.

While non-invasive SpHb measurement could certainly be useful in the perioperative evaluation of patients whose anemia might otherwise go undetected, obtaining consistent and accurate results under everyday clinical conditions with existing SpHb devices, whose results deviate noticeably from laboratory measurement, remains problematic.

Thus, our data suggest that with low sensitivity and good specificity, SpHb measurement is insufficiently accurate to help health care providers make decisions based on a preoperative patient's haemoglobin status, let alone replace invasive blood sampling.

Measurements with the spot-check SpHb devices may, under everyday clinical conditions, deviate noticeably from laboratory measurements and are therefore not useful in a perioperative setting.

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F. Appendix

1. Patient information and consent form

PatientInneninformation und Einwilligungserklärung
zur Teilnahme an der klinischen Studie

Nicht-invasive Hämoglobin-Messung im perioperativen Bereich

(Messung des roten Farbstoffes im Blut ohne Blutabnahme vor einer Operation)

Sehr geehrte Teilnehmerin,
sehr geehrter Teilnehmer!

Wir laden Sie ein an der oben genannten klinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Ihre Teilnahme an dieser klinischen Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Klinische Studien sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie diese Einwilligungserklärung nur

- wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im Klaren sind.

Zu dieser klinischen Studie, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

1. Was ist der Zweck der klinischen Studie?

Der Zweck dieser klinischen Studie ist es, die Genauigkeit und Nützlichkeit sogenannter nicht-invasiver, das heißt ohne Blutabnahme durchführbare, Messmethoden der Konzentration des roten Farbstoffs (Hämoglobin) zur Erkennung von Blutarmut (Anämie) in

der Vorbereitung auf Operationen zu überprüfen.

2. Wie läuft die klinische Studie ab?

Diese klinische Studie wird an der Medizinischen Universität Graz durchgeführt, und es werden insgesamt ungefähr 1500 Personen daran teilnehmen. Für die Teilnahme an dieser klinischen Studie ist keine zusätzliche Anwesenheit Ihrerseits mehr nötig. Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:

Während dieser klinischen Studie wird zusätzlich zu den Routinemessungen lediglich die nicht-invasive (das heißt ohne Blutabnahme) Hämoglobin-Bestimmung durchgeführt. Dafür ist es nötig, dass Sie für 1-3 Minuten ein Messgerät auf den Finger bekommen welches mittels Infrarotlicht die roten Blutkörper in Ihrem Blut bestimmt. Es sind keine weiteren Besuche oder Verpflichtungen mit der Teilnahme an dieser Studie verbunden.

3. Worin liegt der Nutzen einer Teilnahme an der Klinischen Studie?

Es ist möglich, dass Sie durch Ihre Teilnahme an dieser klinischen Studie keinen direkten Nutzen für Ihre Gesundheit ziehen. Die Erkenntnisse aus dieser Studie könnten jedoch in Zukunft dazu beitragen die präoperative Narkoseuntersuchung noch sicherer zu gestalten.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Für die nicht-invasive Hb-Messung sind keine Risiken, Beschwerden oder Begleiterscheinungen beschrieben.

5. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der klinischen Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, müssen Sie diese Ihrem Arzt mitteilen, bei schwerwiegenden Begleiterscheinungen umgehend, ggf. telefonisch (Telefonnummern, etc. siehe unten).

6. Wann wird die klinische Studie vorzeitig beendet?

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden ohne dass Ihnen dadurch irgendwelche Nachteile für Ihre weitere medizinische Betreuung entstehen.

Ihr Studienarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur weiteren Teilnahme an dieser klinischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Studienarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

- Sie können den Erfordernissen der klinischen Studie nicht entsprechen;
- Ihr Studienarzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Studie nicht in Ihrem Interesse ist;

7. In welcher Weise werden die im Rahmen dieser klinischen Studie gesammelten Daten verwendet?

Bei den Daten, die über Sie im Rahmen dieser klinischen Studie erhoben und verarbeitet werden, ist grundsätzlich zu unterscheiden zwischen

- jenen personenbezogenen Daten, anhand derer Sie *direkt identifizierbar* sind (z.B. Name, Geburtsdatum, Adresse, Bildaufnahmen...),
- *pseudonymisierten (verschlüsselten)* personenbezogenen Daten, bei denen alle Informationen, die direkte Rückschlüsse auf Ihre Identität zulassen, durch einen Code (z. B. eine Zahl) ersetzt bzw. (z.B. im Fall von Bildaufnahmen) unkenntlich gemacht werden. Dies bewirkt, dass die Daten ohne Hinzuziehung zusätzlicher Informationen und ohne unverhältnismäßig großen Aufwand nicht mehr Ihrer Person zugeordnet werden können und
- *anonymisierten* Daten, bei denen eine Rückführung auf Ihre Person nicht mehr möglich ist.

Der Code zur Verschlüsselung wird von den verschlüsselten Datensätzen streng getrennt und nur an Ihrem Prüfzentrum aufbewahrt.

Zugang zu Ihren nicht verschlüsselten Daten haben der Prüfarzt und andere Mitarbeiter des Studienzentrums, die an der klinischen Studie oder Ihrer medizinischen Versorgung mitwirken. Die Daten sind gegen unbefugten Zugriff geschützt. Zusätzlich können autorisierte und zur Verschwiegenheit verpflichtete Beauftragte von in- und/oder ausländischen Gesundheitsbehörden und jeweils zuständige Ethikkommissionen in die nicht verschlüsselten Daten Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der klinischen Studie notwendig bzw. vorgeschrieben ist.

Eine Weitergabe der Daten erfolgt nur in verschlüsselter oder anonymisierter Form. Auch für etwaige Publikationen werden nur die verschlüsselten oder anonymisierten Daten verwendet.

Sämtliche Personen, die Zugang zu Ihren verschlüsselten und nicht verschlüsselten Daten erhalten, unterliegen im Umgang mit den Daten der Datenschutz-Grundverordnung (DSGVO) sowie den österreichischen Anpassungsvorschriften in der jeweils gültigen Fassung.

Im Rahmen dieser klinischen Studie ist keine Weitergabe von Daten in Länder außerhalb der EU vorgesehen.

Sie können Ihre Einwilligung zur Erhebung und Verarbeitung Ihrer Daten jederzeit widerrufen. Nach Ihrem Widerruf werden keine weiteren Daten mehr über Sie erhoben. Die bis zum Widerruf erhobenen Daten können allerdings weiter im Rahmen dieser klinischen Studie verwendet werden.

Aufgrund der gesetzlichen Vorgaben haben Sie außerdem, sofern dies nicht die Durchführung der klinischen Studie voraussichtlich unmöglich macht oder ernsthaft beeinträchtigt, das Recht auf Einsicht in die Ihre Person betreffenden Daten und die Möglichkeit der Berichtigung, falls Sie Fehler feststellen.

Sie haben auch das Recht, bei der österreichischen Datenschutzbehörde eine Beschwerde über den Umgang mit Ihren Daten einzubringen (www.dsb.gv.at).

Die voraussichtliche Dauer der klinischen Studie ist ein Jahr. Die Dauer der Speicherung Ihrer Daten über das Ende der klinischen Studie hinaus ist durch Rechtsvorschriften geregelt.

Falls Sie Fragen zum Umgang mit Ihren Daten in dieser klinischen Studie haben, wenden Sie sich zunächst an Ihren Prüfarzt. Dieser kann Ihr Anliegen ggf. an die Personen, die am Studienzentrum für den Datenschutz verantwortlich sind, weiterleiten.

Datenschutzbeauftragte/r des Prüfzentrums:

datenschutz@medunigraz.at

datenschutz@kages.at

8. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten.

Eine Vergütung für die Teilnahme an dieser Studie ist nicht vorgesehen.

9. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Studienarzt und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Patient und Teilnehmer an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

Name der Kontaktperson: **Dr. Gabriel Honnef**

Ständig erreichbar unter: **0316-385-81283**

10. Sollten andere behandelnde Ärzte von der Teilnahme an der klinischen Studie informiert werden?

Es ist nicht notwendig andere behandelnde Ärzte über Ihre Teilnahme an dieser Studie zu informieren.

11. Einwilligungserklärung

Name des Patienten:

Geb.Datum:

Ich erkläre mich bereit, an der klinischen Studie *Nicht-invasive Hb-Messung im perioperativen Bereich* teilzunehmen.

Ich bin von Herrn/Frau ..... ausführlich und verständlich über die klinische Studie, mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Studie, sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 5 Seiten umfasst gelesen. Aufgetretene Fragen wurden mir vom Studienarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile für meine weitere medizinische Betreuung entstehen.

Ich stimme ausdrücklich zu, dass meine im Rahmen dieser klinischen Studie erhobenen Daten wie im Abschnitt „Datenschutz“ dieses Dokuments beschrieben verwendet werden.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Studienarzt.

.....

(Datum und Unterschrift des Patienten)

.....

(Datum, Name und Unterschrift des verantwortlichen Prüfarztes)