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Erythropoietin treatment in anaemic patients at the Nephrology Unit of the Steve Biko Academic Hospital - a retrospective, cross-sectional study

by

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PLAGIARISM DECLARATION

Full names of student: Elandré Kok

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Topic of work: Erythropoietin treatment in anaemic patients at the Nephrology Unit of the Steve Biko Academic Hospital - a retrospective, cross-sectional study

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CONFLICT OF INTEREST DECLARATION

Tradenames are used in this dissertation as the scientific names for active pharmaceutical ingredients are cumbersome. Recormon® and Mircera® are specifically referred to as these were the products in use by the Nephrology Unit of the Steve Biko Academic Hospital at the time of undertaking this project. I hereby declare that I have no conflict of interest with the pharmaceutical companies who own the rights to these products.

IN MEMORIAM: DR. ANDRÈ MARAIS

Monday 15 June 2020 marked the day my world turned upside down with the receipt of a single text message “Dr Andrè passed away”… Words simply cannot describe how heart-breaking it is to finish off this dissertation knowing you will not be able to share in the joy of the final hand in, yet it came so very close and you were with us till the very end. Suffice to say it is not the ending I conceptualised in my mind and I am shattered by your sudden passing.

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ABSTRACT

Anaemia in chronic kidney disease (CKD) mostly results from a decrease in the production of erythropoietin (EPO) by the failing kidney. CKD progression requires treatment with erythropoiesis-stimulating agents and iron supplementation to ensure sufficient erythrocyte production. Best clinical practice guidelines should be adhered to in managing CKD to reduce morbidity and mortality related to anaemia associated cardiovascular disease. Likewise, guideline deviations create an increased strain on the resources of the treatment facility. It is uncertain to which extent these guidelines are followed by Nephrology Units in the public healthcare sector, or whether the documented international trends are prevalent locally due to the paucity of local data, and therefore further investigation is warranted. This study aimed to assess treatment trends in managing anaemia in CKD patients at the Steve Biko Academic Hospital (SBAH).

Files of patients receiving treatment at the SBAH Nephrology Unit between 2 January 2018 - 31 August 2018 were reviewed. Only individuals with stage 5 CKD receiving either haemodialysis, or peritoneal dialysis were included, while those with less than three months' treatment were excluded. Measured variables included demographical information, current EPO treatment and/or iron supplementation regimens versus serum haemoglobin/iron levels and quantity of administered blood products.

Ninety-seven patients met the inclusion criteria. Haemodialysis accounted for 43% (n = 42), and peritoneal dialysis 57% (n = 55). Intergroup comparison between the number of results where both haemoglobin and iron were within the target range versus the number of results where both parameters fell outside the target range yielded a significant difference ($p = 0.0031$). Patients receiving peritoneal dialysis reached serum haemoglobin and iron levels closer to normal target values compared to those receiving haemodialysis.

Managing anaemia in CKD is a complex process. More stringent iron control, especially for patients receiving haemodialysis, including the administration of long-acting EPO preparations once a month, is proposed. The latter will contribute to the improvement of clinical outcomes of patients with CKD.

Keywords: Chronic kidney disease, anaemia, erythropoiesis stimulating agent, haemoglobin, iron

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ABBREVIATIONS

pH	-log of the $[H^+]$
µg/dl	Microgram per decilitre
µg/l	Microgram per litre
µg/month	Microgram per month
µmol/l	Micromole per litre
χ^2	Chi-squared
ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
AcSDKP	N-acetyl-seryl-aspartyl-lysyl-proline
AKI	Acute kidney injury
APOL1	Apolipoprotein L1
ARB	Angiotensin receptor blocker
BFU-E	Burst-forming unit erythroid
CEO	Chief executive officer
CFU-E	Colony-forming unit erythroid
CHF	Congestive heart failure
CHOIR	Correction of haemoglobin and outcomes in renal insufficiency
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CLP	Common lymphoid progenitor
CMP	Common myeloid progenitor
CrCl	Creatinine clearance
C_{ss}	Steady-state concentration
CVD	Cardiovascular disease
CVEs	Cerebrovascular events
DM	Diabetes mellitus
DOPPS	Dialysis outcomes and practice patterns study
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent

ESRD	End-stage renal disease
Fe	Iron
Fe2+	Ferrous
Fe3+	Ferric
FeSO4	Ferrous sulphate
FSGS	Focal segmental glomerulosclerosis
g/dl	Gram per decilitre
GBD	Global burden of diseases
GFR	Glomerular filtration rate
GMP	Granulocyte monocyte precursors
Hb	Haemoglobin
HCT	Haematocrit
HD	Haemodialysis
H-ESRD	Hypertensive end-stage renal disease
HIFs	Hypoxia-inducible factors
HIV	Human immunodeficiency virus
HSC	Hematopoietic stem cell
IDA	Iron deficiency anaemia
IDMS	Isotope dilution mass spectrometry
IV	Intravenous
KDIGO	Kidney disease improving global outcomes
kg	Kilogram
l/day	Litre per day
l/min	Litre per minute
LVH	Left ventricular hypertrophy
m^2	Square meter
MCH	Mean corpuscular haemoglobin
MDRD	Modification of diet in renal disease
MEP	Megakaryocyte / erythrocyte progenitor
mg	Milligram
mg/day	Milligram per day
mg/kg/day	Milligram per kilogram per day

ml/min	Millilitre per minute
ml/min/1.73m^2	Millilitre per minute per 1.73 square meters of body surface area
MYH9	Myosin heavy chain 9
ng/ml	Nanogram per millilitre
NDD-CKD	Non-dialysis dependent chronic kidney disease
NHLS	National Health Laboratory Service
NKFSA	National Kidney Foundation of South Africa
PD	Peritoneal dialysis
RBCs	Red blood cells
RCC	Red cell concentrate
rhEPO	Recombinant human erythropoietin
SANBS	South African National Blood Service
SAS	Statistical Analysis Software
SBAH	Steve Biko Academic Hospital
SC	Sub-cutaneous
S_{cr}	Serum creatinine
SD	Standard deviation
SEP	Single exit price
SNPs	Single nucleotide polymorphisms
SPSM	Single plasma sampling method
TIBC	Total iron-binding capacity
TREAT	Trial to reduce cardiovascular events with Aranesp therapy
TSAT	Transferrin saturation
ZAR	South African Rand

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1.1. Physiology of the healthy, functioning kidney

One of the main functions of the kidney is to ensure homeostasis of the body's internal milieu. This is achieved by the elimination of waste products, the regulation of blood volume, electrolyte content and the parts of hydrogen (acidity / alkalinity index), thus the pH of the intravascular fluid.[1] In addition to the excretory role of the kidneys to maintain fluid and electrolyte balance, it is also responsible for several endocrine functions including the production and secretion of renin, erythropoietin (EPO) and 1,25-dihydroxycholecalciferol (1,25 Vitamin D3).[2] The basic functional unit of a kidney is the nephron. Each nephron consists of a renal tubule and accompanying glomerulus (Figure 1). Each human kidney consists of approximately one million nephrons.[3]

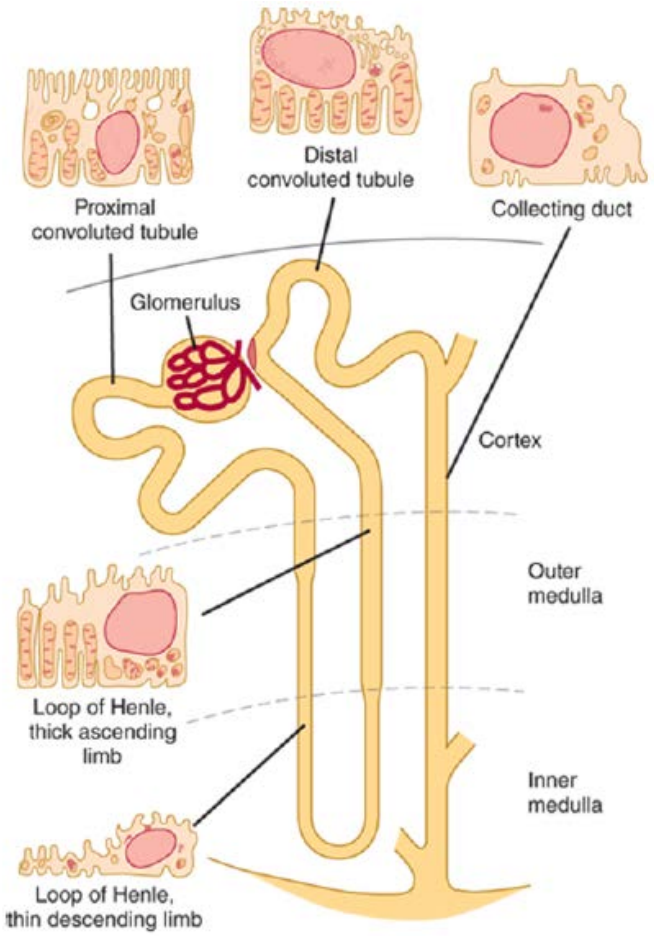


Figure 1: Nephron structure within the kidney, illustrating the renal cortex and medullary layers.[3]

In comparison to other organs, there is a high blood flow to the kidneys, estimated to be approximately 25% of the cardiac output, while at rest.[3,4] The cardiac output for a person weighing approximately 70 kg, while at rest, is estimated at 5 l/min.[5] The expected renal blood flow would therefore be approximately 1.25 l/min. Plasma flowing through the glomeruli results in the production of filtrate that is similar in solute concentration to plasma but differs in that it contains negatively-charged molecules, and high-molecular-weight compounds.[1,4]

1.2. Glomerular filtration rate as an estimate of kidney function

The filtrate produced by each glomerulus, per unit time, is known as the glomerular filtration rate (GFR) and is an indicator of a kidney's physiological excretory function.[3] The normal GFR for a male is approximately 125 ml/min per 1.73 m^2 of body area (or approximately 180 l/day), whereas the normal GFR for a female is approximately 110 ml/min per 1.73 m^2 of body area (or approximately 158 l/day).[3,4] GFR gradually decreases with age due to the steady loss of nephron function.[4] The accurate, direct measurement of GFR is challenging due to the procedures of determination thereof being labour intensive, both at a pre-analytical and analytic level. Some of these challenges include; the need for continuous intravenous (IV) infusions, precise determination of urine production, complicated laboratory analysis which requires specialised staff and equipment as well as costly reagents.[6] In addition, procedures for direct GFR measurement frequently result in an under- or overestimation of the true GFR.[7] Furthermore, GFR is influenced by several factors including renal function, age, sex, diet as well as certain medications.[8] Estimating GFR instead of urinary clearance requires a substance that is freely filtered, non-toxic, not metabolised by the body, not altered during excretion and neither secreted nor reabsorbed by the renal tubules.[3] Some substances used as markers of kidney function are discussed below.

1.3. Markers used for the determination of kidney function

Both exogenous and endogenous substances such as inulin, creatinine, cystatin C (Cys C), iohexol, β-trace protein and blood urea nitrogen (BUN), can be utilised for GFR estimation by monitoring the urinary and/or plasma clearance of these substances.[4]

1.3.1. Inulin

Inulin (Figure 2) is a fructan-type, polysaccharide derived from plants, such as chicory, bananas, garlic, wheat and asparagus.[9,10] β-1,2 glycosidic bonds in the inulin structure prevents its digestion by enzymes, ensuring that it is excreted in an unaltered manner.[11] Inulin is easily filtered by the glomeruli due to its compact structure as well as the abundant hydroxyl groups present in its chemical structure which contribute to its water solubility.[12] Despite being an ideal marker, it is seldom used due to its cost and the difficulty of performing the analytical assay. Furthermore, it is an invasive procedure, requiring continuous infusion coupled with multiple blood sample collections and urinary catheterisation for the entire duration of the procedure.[10]

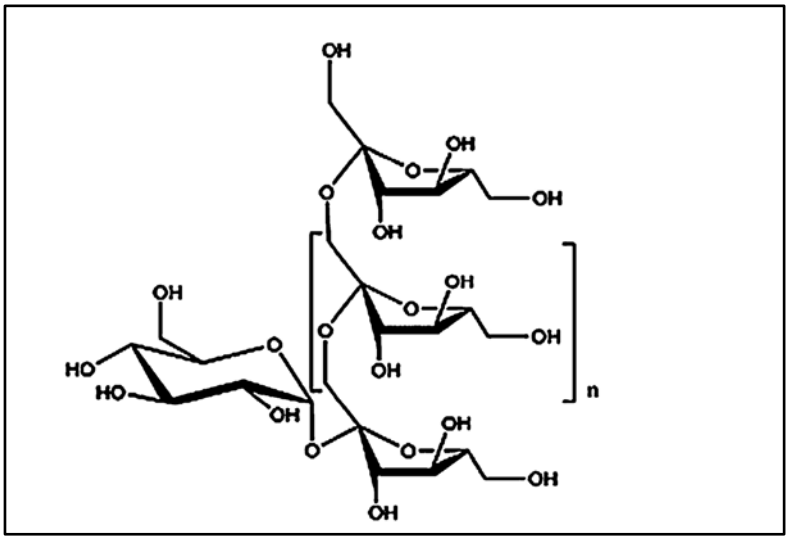


Figure 2: Chemical structure of inulin.[13]

1.3.2. Creatinine

Creatinine (Figure 3) is a breakdown product of creatine phosphate metabolism by the muscle tissue and is freely filtered by the glomeruli. Each day approximately 1-2% of muscle creatine is converted to creatinine, with males generating between 20 - 25 mg/kg/day of creatinine compared to 15 - 20 mg/kg/day in females.[14,15] The difference is attributed to females characteristically having less muscle mass than their male counterparts.[4] Under steady-state concentration (C_{SS}), the rate of creatinine production equals the rate of its excretion. However, renal tubules secrete creatinine to varying extents as it is dependent on muscle function, muscle composition, physical activity, health status (which may include muscular dystrophy, paralysis, anaemia, leukaemia and hyperthyroidism) and diet.[16] These variables may result in the overestimation of GFR.[4] Underestimation of GFR, using creatinine as a marker, may be seen in conditions such as glomerulonephritis, congestive cardiac failure, shock, polycystic kidney disease, dehydration and acute tubular necrosis.[17,18]

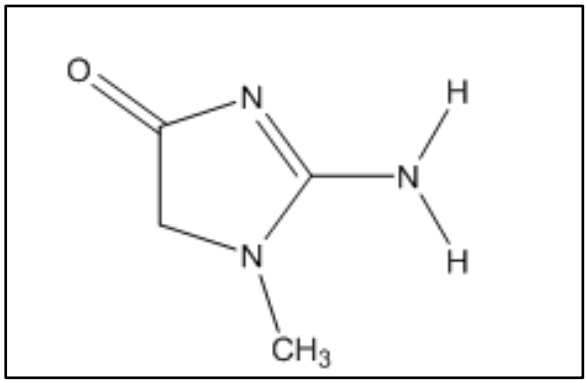


Figure 3: Chemical structure of creatinine.[19]

1.3.3. Cystatin C

Cystatin C (Cys C) is a basic, endogenous peptide (Figure 4) that is secreted by all nucleated cells in the body and is freely filtered by the glomeruli due to its low molecular weight. Over the past decade, Cys C assays have progressed from use as a research tool to possible incorporation into clinical practice, potentially as a confirmatory assay when GFR estimation by creatinine clearance alone is deemed unsatisfactory by the treating physician.[20,21] It is regarded to be a more accurate indicator of GFR than creatinine, as it exhibits more uniformity across different

population groups[22] and is not influenced by variables such as age, sex and muscle mass. However, Cys C is a more costly alternative to assays utilising creatinine, with an estimated cost of 20-fold the amount of a typical creatinine test.[22-24]

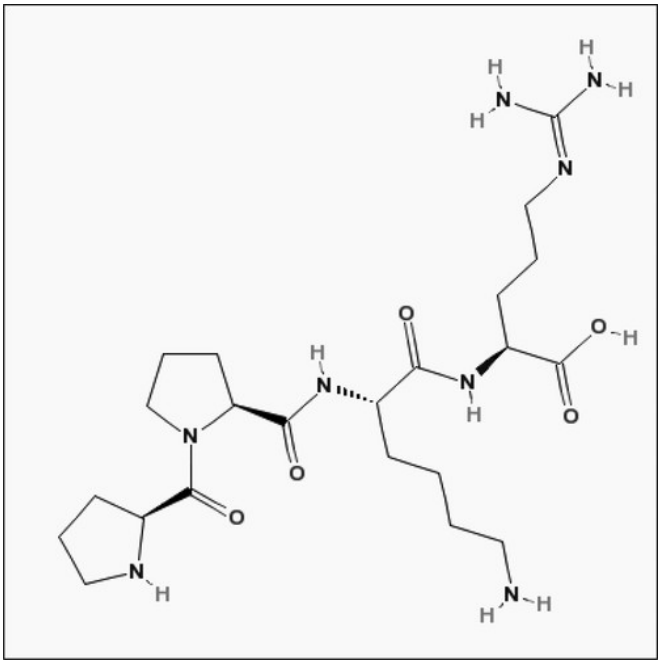


Figure 4: Chemical structure of cystatin C.[25,26]

1.3.4. Iohexol

Iohexol (Figure 5), a non-ionic radiocontrast, has been suggested as a more suitable substitute for inulin in the determination of GFR owing to its chemical properties and relatively low cost. It is water-soluble and is neither secreted nor reabsorbed by the renal tubules and shows negligible plasma protein binding while being non-toxic.[27] As with other assays reliant on exogenous markers, GFR estimation using iohexol relies on bolus IV administration. Either its plasma or renal clearance can be utilised to calculate GFR.[27] A single-plasma sampling method (SPSM) after 4 hours has lapsed has been indicated to accurately estimate GFR when its value is above 60 ml/min/1.73m^2, however, for cases where the GFR is below 60 ml/min/1.73m^2, multiple samples over a more extended time period are required for accurate GFR determination, increasing the cost and labour intensity of this method.[28]

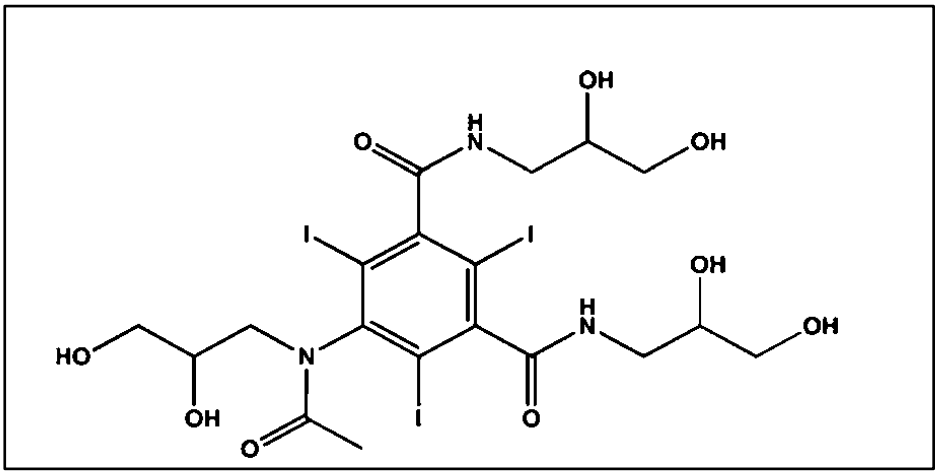


Figure 5: Chemical structure of iohexol.[29]

1.4. Formulae for calculating creatinine clearance / glomerular filtration rate

The following formulae are used to calculate creatinine clearance or GFR.

1.4.1. Cockcroft-Gault equation

In 1976, Cockcroft and Gault were the first researchers to develop a formula to predict creatinine clearance (CrCl) as a function of age, body weight and serum creatinine level of an individual (expressed in millilitre per minute).[30] The formula was derived after the authors noticed a relationship between age and creatinine excreted within 24 hours per unit body weight.[30]

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dl)} \times 72} \ (\times 0.85 \text{ if female})$$

1.4.2. Modification of diet in renal disease

In 1999, Levey *et al*. developed an equation based on data generated by the Modification of Diet in Renal Disease (MDRD) study.[31] The MDRD study was undertaken as the authors realised other factors needed to be incorporated into the equation to improve accuracy in GFR determination, as independent factors were associated with fluctuations.[31] This allowed for the calculation of GFR as a function of creatinine clearance incorporating factors such as race and sex. This equation is employed in the estimation of GFR when the analytical laboratory utilises an isotope

dilution mass spectrometry (IDMS) calibrated method for quantifying serum creatinine concentrations. The constant of 175 is substituted with a value of 186 if the laboratory has not calibrated its methodology to IDMS.[32]

$$GFR\left(ml/min/1.73m^2\right)=175\times(Scr)^{-1.154}\times(Age)^{-0.203}\times (0.742 \text{ if female})\times(1.212 \text{ if African American})$$

Scr: Serum creatinine in milligram per deciliter

1.4.3. Chronic kidney disease epidemiology collaboration

In 2009, through pooling data from multiple studies, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was developed and validated in an attempt to improve the accuracy of the MDRD formula which had been proven inaccurate when the GFR was greater than 60 ml/min/1.73m^2.[33,34] New coefficients coupled with the same variables that are used in the MDRD formula (age, race, sex and serum creatinine level) are used.[35] Overall the CKD-EPI formula has higher accuracy and precision than the MDRD formula and additionally a lower bias when the GFR is greater than 60 ml/min/1.73m^2, yet its accuracy remains comparable to that of the MDRD formula.[36]

$$eGFR = 141 * \min\left(\frac{sCR}{\kappa}, 1\right)^{\alpha} * \max\left(\frac{sCR}{\kappa}, 1\right)^{-1.209} * 0.993^{AGE} * 1.018 * F * 1.159 * B$$

where:

sCR = serum creatinine in mg/dL
κ = 0.7 if female, 0.9 if male
α = -0.329 if female, -0.411 if male
F = 1 if female, 0 if male
B = 1 if Black/African American, 0 otherwise
AGE is measured in years

1.5. Overview of chronic kidney disease

Chronic kidney disease (CKD) is a broad term used to define a group of disorders that impede the normal function and/or structure of the kidneys.[37] The Kidney Disease Improving Global Outcomes (KDIGO) Work Group for CKD has defined it as "abnormalities of kidney structure or function, present for a period longer than three months, with implications for health". Chronic kidney disease is classified according to cause, glomerular filtration rate, and albuminuria category.[38] Ultimately CKD culminates in end-stage renal disease (ESRD) and is a contributing factor to mortality due to comorbid conditions. These conditions include cardiovascular disease (CVD), malignancies and various diverse infections such as gastrointestinal infections (*Clostridium difficile;* colitis), respiratory tract infections (pneumonia), genitourinary tract infections (pyocystitis), musculoskeletal infections (cellulitis and osteomyelitis) and infections of the central nervous system (mucormycosis).[39,40] ESRD signifies the irreversible loss of kidney function and is fatal unless patients receive dialysis or renal transplantation. Fluid retention due to decreased urine output, the resultant uraemia and disturbances in bone mineral density are known complications of ESRD.[41] Figure 6 illustrates the severity and prognosis of CKD, categorized according to GFR and albuminuria severity.

GFR Categories (mL/min/1.73 m²) Description and Range				Persistent Albuminuria Categories Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				ACR <30 mg/g	ACR of 30–300 mg/g	ACR >300 mg/g
	G1	Normal or high	≥90			
	G2	Mildly descreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Figure 6: Prognosis of chronic kidney disease as categorized by glomerular filtration rate and albuminuria severity.[38]

Green = Low risk (in the absence of other markers; implies no chronic kidney disease); Yellow = Moderately increased risk; Orange = High risk; Red = Very high risk.

1.6. Prevalence of chronic kidney disease

Chronic kidney disease has gained notoriety over the past two decades as a significant contributor to the global burden of non-communicable disease. According to the Global Burden of Disease (GBD) study, CKD ranked 27th in 1990 and moved up to the 19th position in 2013 on the list of global death causes.[42] Similar data from the 2016 GBD study highlighted that CKD which was ranked 16th on the list of leading causes of early mortality in that year, but was set to move up to the 5th position by the year 2040.[43] This can be substantiated by the reported rise in the age-standardised annual death

rate where an increase from 15.7 per 100,000 in 1990 to 16.3 per 100,000 in 2010 was noted, amounting to an 82% increase in the years of life lost due to CKD.[44] Jha *et al*. estimated global prevalence rates of CKD in 2013 to be between 8-16% in adults.[45] An estimate by the National Kidney Foundation of South Africa (NKFSA) concluded that nearly 5 million adults in South Africa, (representing approximately 10% of the population) were affected by CKD in 2015.[46] It was further noted that the prevalence may be higher among persons dependant on the public health system.[46] Impoverished populations are at a higher risk of being affected by CKD since it is typically asymptomatic until ESRD manifests. Therefore, a large window of opportunity exists to delay the progression of CKD, which often goes untreated for lengthy periods of time due to the lack of access to adequate healthcare facilities, especially in a rural setting.[45]

1.7. Predisposition to chronic kidney disease

Disease conditions such as hypertension and diabetes mellitus (DM) have been identified as the most common causes of CKD, both in developed and developing countries.[47] Glomerulonephritis and other disorders such as polycystic kidney disease and tubulointerstitial nephritis are more frequently associated with CKD in Asiatic and sub-Saharan African countries.[48] Genetic variations have also been identified as a cause of CKD in individuals of African descent (African Americans).[45,49,50] Single nucleotide polymorphisms (SNPs) in the gene that encodes non-muscle myosin heavy chain (*MYH9*) has been associated with an elevated risk of non-diabetic ESRD of up to four-fold in African individuals in comparison to Europeans.[49] Variations in the gene encoding apolipoprotein L-1 (*APOL1*) has been identified as a risk factor for focal segmental glomerulosclerosis (FSGS) and hypertensive ESRD (H-ESRD) in individuals of African descent.[50-52] Both risk alleles are located on chromosome 22, which has previously been associated with a predisposition to renal disease in individuals of African descent.[49]

1.8. Comorbidities of chronic kidney disease

Renal anaemia develops in almost all CKD patients during the progression of the disease. It is a result of the inability of the kidneys to produce sufficient erythropoietin (EPO).[53] Anaemia is defined as a decrease in the number of circulating erythrocytes, haemoglobin (Hb) and erythrocyte mass.[54] The diminished EPO synthesis by the kidneys contributes directly to the progressively waning production of erythrocyte progenitor cells by the bone marrow and is confounded by impaired iron (Fe) homeostasis.[55,56] The principal effect of anaemia is reduced oxygen delivery to organs and tissues, leading to a vast array of symptoms which include; fatigue, shortness of breath and intolerance to physical exertion.[57] Miscellaneous consequences of anaemia include cognitive decline, sleep disorders, immune suppression, decrease in the quality of life, and less favourable prognoses in CKD patients.[39,55,58] Goodkin *et al*. have found that anaemia occurs in more than 90% of all patients undergoing treatment with haemodialysis (HD).[59] The KDIGO guidelines suggest the initiation of HD when any of the following symptoms appear: inability to control blood volume/pressure, deterioration in nutritional status or cognitive impairment. These symptoms frequently manifest when the GFR diminishes to between 5 and 10 ml/min/1.73m^2.[38]

1.9. Physiological compensation for hypoxia

The systemic response to a continued hypoxic state is initiated by transcription factors known as hypoxia-inducible factors (HIFs). These transcription factors serve to upregulate the expression of several genes of which the summative effect is to offset the hypoxic state at both the cellular and the systemic level.[60] The physiological processes (Figure 7) which result from a decrease in erythrocyte count, translates into a decreased availability of oxygen that does not meet tissue demands. A stimulus, namely a decrease in blood erythrocyte count (implying a decreased availability of oxygen to meet the physiological demand), triggers renal EPO production. Erythropoietin acts on cells within the bone marrow, stimulating the production of erythrocytes, thus restoring the imbalance by increasing the oxygen-carrying capability of the blood.

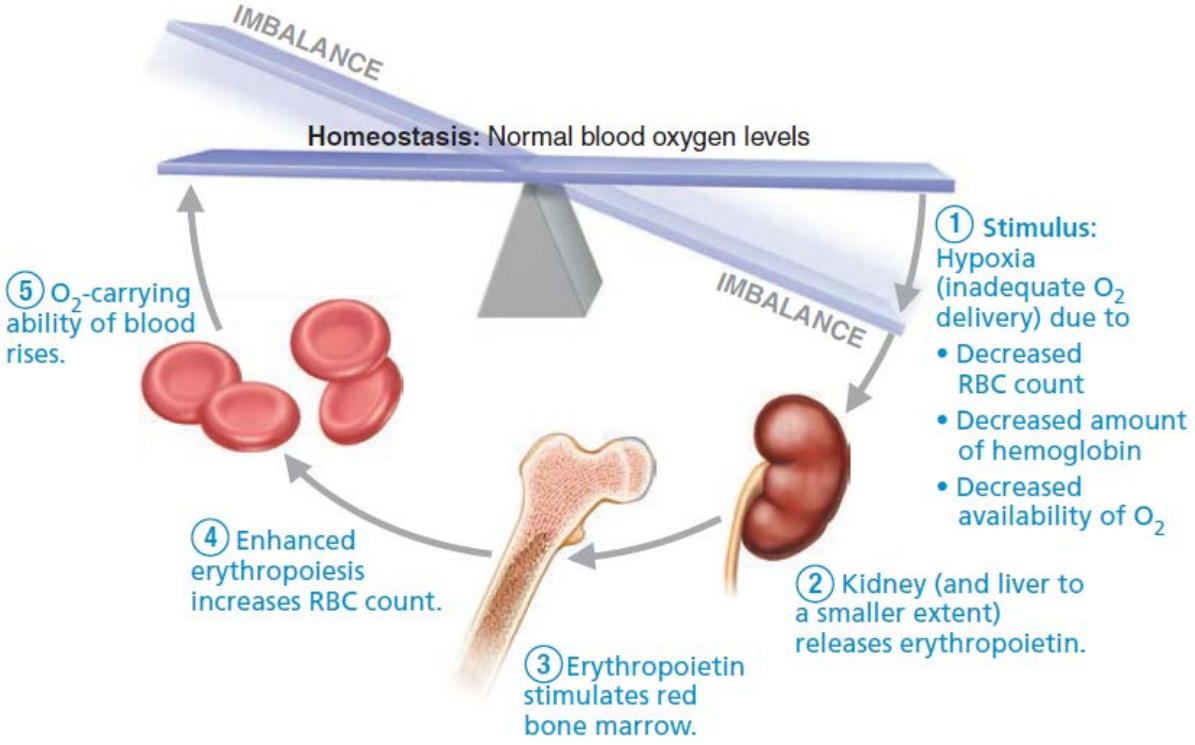


Figure 7: Erythropoiesis as a result of oxygen imbalance.[61] [Reproduced with permission, licence number: 1042847-1]

Stimulation of the bone marrow by EPO gives rise to the production of haematopoietic stem cells (HSCs), the first step in a cascade of events in the erythropoiesis process (Figure 8).[62] Following initial differentiation steps, two erythroid progenitors are formed from HSCs, namely burst-forming unit erythroid (BFU-E) and colony-forming erythroid (CFU-E), illustrating the EPO-dependent phase of the process.[63] Subsequently, in the iron-dependent phase, differentiation of CFU-Es to orthochromatic normoblasts is followed by the formation of reticulocytes.[64] The final step of the process is characterised by the enucleation of reticulocytes where after viable erythrocytes are released into circulation. The duration of the process from HSC to RBC lasts for 7 – 10 days, on average.[62]

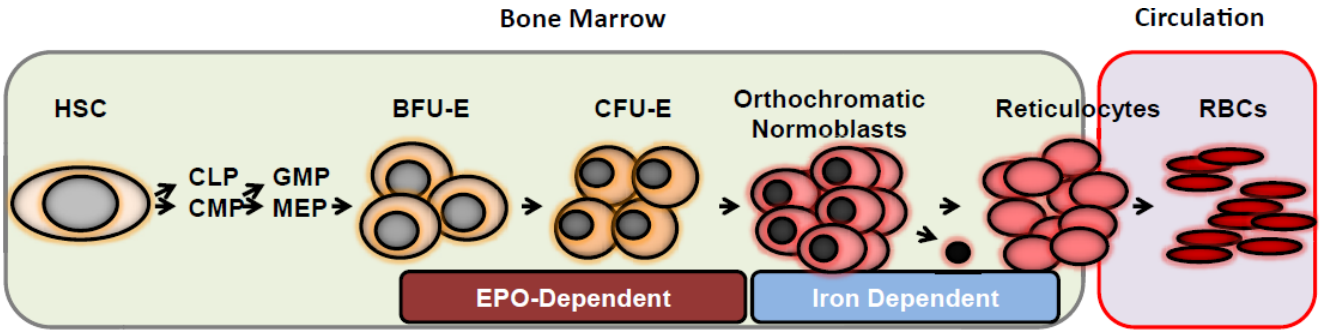


Figure 8: Erythropoiesis from haematopoietic stem cells to mature red blood cells in circulation.[62] [Reproduced with permission, licence number: 4844131412970]

HSC: Haematopoietic stem cell; CLP: Common lymphoid progenitor; CMP: Common myeloid progenitor; GMP: Granulocyte monocyte precursor; MEP: Megakaryocyte/erythrocyte progenitor; BFU-E: Burst-forming unit erythroid; CFU-E: Colony-forming unit erythroid, RBCs: Red blood cells.

Physiological compensatory mechanisms that attempt to counteract the effects of anaemia mainly encompass changes in haematopoiesis, respiration and cardiovascular function. The respiratory rate is increased in order to assimilate more oxygen, with a parallel increase in the cardiac output to promote distribution of oxygenated blood, while the promotion of erythropoiesis serves to improve oxygen saturation and carriage.[65] Chronic compensation by the heart through increased stroke volume (and therefore increased cardiac output), results in significant structural changes to the myocardium. These changes are principally characterised by left ventricular hypertrophy (LVH), ultimately leading to congestive heart failure (CHF).[66] In addition to the elevation of cardiovascular risks, CKD patients are at an increased risk of cerebrovascular events (CVEs).[67]

1.10. Treatment of anaemia

The cornerstone of treating anaemia in CKD patients consists of IV or subcutaneous (SC) administration of erythropoiesis-stimulating agents (ESAs) with co-administration of oral or IV iron supplements to ensure the adequate production of viable erythrocytes.[68,69]

1.10.1. Erythropoiesis stimulating agents

Erythropoietin, an endogenous glycoprotein, produced by the kidneys, stimulates the maturation of erythroid progenitor cells to form new erythrocytes.[1] Biotechnology enables the production of recombinant human erythropoietin (rhEPO) via culturing in mammalian cells.[70] The pharmacokinetic properties of recombinant EPO depend on its degree of glycosylation. Due to variations in glycosylation patterns, recombinant EPO is available in the following forms: α, β, θ and ζ. Novel preparations such as darbepoetin-α (Aranesp®) and methoxy polyethylene glycol-erythropoietin-β (Mircera®) differ from endogenous EPO by their degree of glycosylation. These preparations ensure a longer half-life when treating anaemia, thus requiring less frequent administration and enabling increased compliance.[1] A meta-analysis on the use of various ESAs in patients with CKD failed to prove the superiority of any formulation based on efficacy or safety.[71] Erythropoiesis stimulating agent therapy, however, offers a safer alternative to blood transfusions which inherently carries the risk of bloodborne diseases such as the human immunodeficiency virus (HIV) and hepatitis, accidental miss-transfusions, and augments the possibility of kidney transplantation.[71] Common side effects of ESA therapy include hypertension, renal dysfunction, thrombotic complications and pure red cell aplasia.[72,73]

1.10.2. Iron supplementation

Commonly used biomarkers to assess iron status in CKD patients include: serum iron concentration, transferrin saturation (TSAT) ratio and serum ferritin concentration.[74] Transferrin is an iron-binding plasma glycoprotein which aids in regulating the levels of free iron in the plasma.[75] The majority of iron bound to transferrin is used for Hb synthesis.[76] Serum iron that is not actively used in the synthesis of haem or other iron-containing proteins are bound to ferritin, which acts as a storage protein.[76] Microcytic hypochromic anaemia is commonly noted in individuals with iron deficiency anaemia (IDA).[77] Diagnoses of IDA can further be confirmed by low haematocrit values as well as low mean corpuscular haemoglobin (MCH) concentrations realised from haematology test results.[78]

The TSAT ratio is calculated by dividing the serum iron concentration by the total iron-binding capacity (TIBC).[79] The normal ranges for serum iron concentrations are 70 – 175 µg/dl and 50 – 150 µg/dl for men and women, respectively.[80] Expected TSAT percentages are 10% - 50% and 15% - 50% for men and women, respectively, with the normal range for TIBC indicated as 250 – 450 µg/dl for both men and women.[80] It is estimated that the average per diem iron loss of a healthy person, regardless of sex, is approximately 1 mg/day.[81] This loss increases drastically in individuals subject to frequent blood sampling and HD. It has been estimated to be as high as 3 g of iron per annum.[79] Fluctuations in the iron status of an individual can be ascribed to multiple divergent reasons other than primary iron deficiency, and the cause needs to be investigated. A general guidance algorithm for iron status assessment is provided in Figure 9.

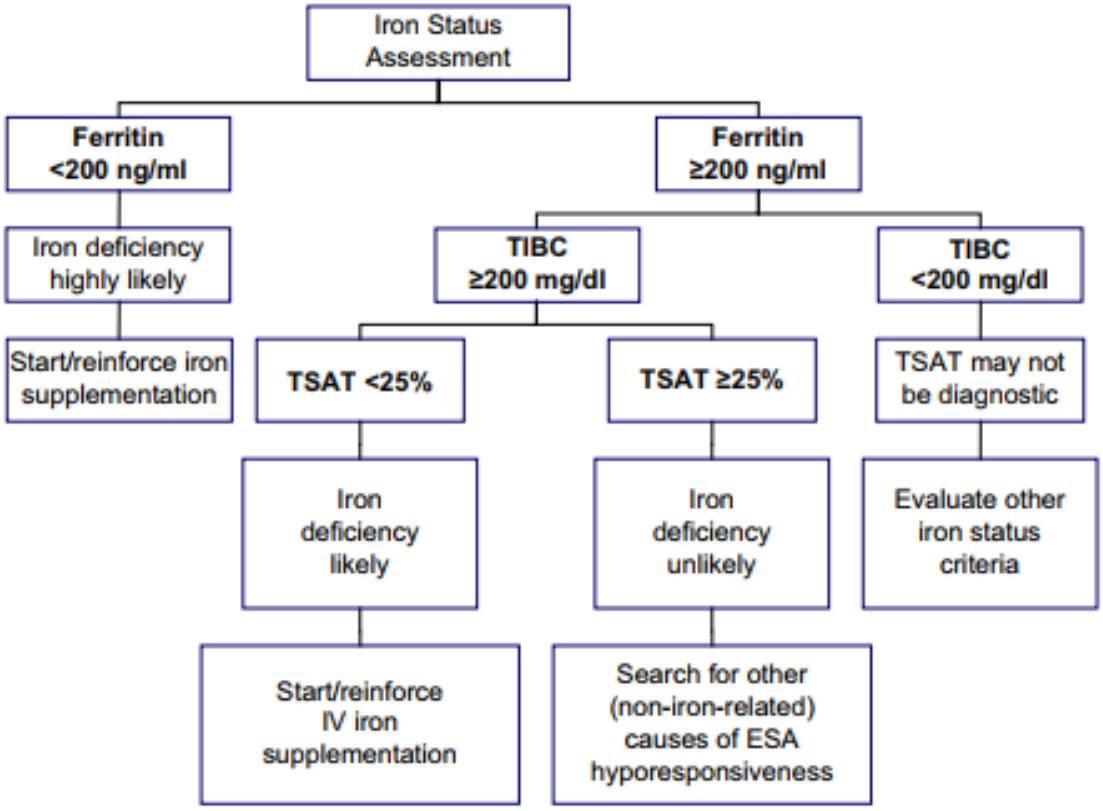


Figure 9: Iron status assessment algorithm.[79] [Reproduced with permission, license number: 4844131071831]

TIBC: Total iron-binding capacity; TSAT: Transferrin saturation; IV: Intravenous; ESA: Erythropoiesis stimulation agent

Oral iron supplements are available as iron sulphate ($FeSO_4$), iron gluconate or iron fumarate, whereas parenteral iron supplements are typically obtainable in the form of ferric carboxymaltose, iron gluconate and iron dextrin. These formulations differ in their ability to be reduced to elemental iron.[82-84] The ferrous form (Fe^{2+}) is more readily absorbed in the small intestine, and absorption is enhanced with increased gastric acidity.[85] Ferric iron (Fe^{3+}) is less soluble, which contributes to its reduced absorption. Furthermore, ferric iron requires reduction to the ferrous form before being absorbed by the small intestine. Therefore ferrous preparations are favoured.[86] Ferrous iron is the physiologically active form that is vital during erythropoiesis as it is incorporated into Hb.[62]

Oral iron supplementation is a low-cost and non-invasive method to correct iron deficiencies. It is routinely prescribed at a dose of 200 mg elemental iron daily but may lead to side effects such as gastrointestinal upsets (including nausea, vomiting, heartburn, abdominal cramps), staining of teeth, an unpleasant taste in the mouth and blackened stools or urine.[82,87] Gastrointestinal upsets may be limited by taking oral iron in conjunction with a meal, yet this further limits the absorption of iron from the small intestine.[59] The limited absorption of oral iron may consequentially result in the maximum recommended dose failing to achieve a normative level. Parenteral iron supplementation should be considered when oral iron fails to correct deficiencies within one to three months.[84,87] Oral doses of ascorbic acid enhance absorption of orally administered iron supplements. A dietary intake of approximately 50 mg of ascorbic acid per main meal is deemed sufficient to ensure optimal iron uptake.[88] In order to obtain 60 mg of elemental iron, 300 mg of ferrous sulphate or 180 mg of ferrous fumarate or 500 mg of ferrous gluconate is required.[89]

Considerations for the use of the various IV iron preparations are based on their dissociation kinetics (i.e. how easily the free iron is liberated from the molecular complex) in order to prevent saturating the binding ability of transferrin which will lead to excessive free iron in the blood and resultant free iron reactions.[84] The intramuscular preparation, iron sorbitol citrate, is not commonly used due to the discomfort at the injection site accompanied by a brown skin discolouration that may persist for a lengthy period.[84]

1.10.3. Treatment guidelines for the commencement of erythropoiesis-stimulating agent therapy

The various international treatment guidelines for treatment initiation are summarised in Table 1.

Table 1: Treatment guidelines for erythropoiesis-stimulating agent therapy initiation.

United States of America[90]	When Hb in adults, who are not on dialysis, exceed 10 g/dl, the dose of ESA should be reduced or interrupted
European Union[91]	In high-risk patients with NDD-CKD, ESA therapy should commence when 9 g/dl < Hb < 10 g/dl For low-risk patients and those who will benefit in terms of quality of life, ESA therapy can be initiated at higher Hb levels
Japan[92]	Initiate ESA therapy when Hb < 11 g/dl following the diagnosis of renal anaemia in patients with NDD-CKD Lower treatment dose/interrupt ESA therapy when Hb > 13 g/dl In cases of CVD/other complications, ESA therapy should be reduced/interrupted when Hb > 12 g/dl
South Africa[93]	ESA therapy should be initiated when Hb < 10 g/dl
KDIGO[38]	Treat symptomatic patients when Hb falls < 10 g/dl

Hb: Haemoglobin; ESA: Erythropoiesis stimulating agent; NDD-CKD: Non-dialysis dependent chronic kidney disease; CVD: Cardiovascular disease; KDIGO: Kidney disease improving global outcomes

1.11. Risks associated with erythropoiesis-stimulating agent therapy

Contradicting findings have emerged between early clinical trials and later studies based on the benefits and risks associated with ESA therapy in anaemic patients. An earlier study advocated more extensive ESA use, including the need to maintain higher Hb levels (> 13 g/dl).[94] Potential benefits included decreased mortality, a lower risk of cardiovascular events, and potentially retarding the disease progression of CKD. [70,94,95] However, later studies have shown that maintaining Hb levels above 13 g/dl, by utilising ESA therapy, is potentially associated with an elevated risk of cardiovascular events and early mortality.[96-98] It has also been suggested that sudden fluctuations in the Hb concentration due to rapid increases and a subsequent concentration exceeding 13 g/dl, may additionally increase an individual's risk of developing adverse cardiovascular events.[99]

In the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) study it was found that target Hb levels of 13.5 g/dl were associated with a higher risk of complications such as venous thromboembolic events in comparison to target Hb levels of 11.5 g/dl.[96] The authors added that the additional risks for events such as myocardial infarction and stroke in conjunction with the higher costs of the treatment outweighed the benefits and that there was no perceivable increase in the overall quality of life for the patients.[96] Pfeffer *et al*. arrived at a similar conclusion in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study.[97,98] Furthermore, the authors of this study alluded to the added risks of ESA therapy in individuals with malignancies, among other an increased mortality rate compared to those who received placebo. This observation was significantly relevant in diabetic patients with concurrent CKD, who were not dependent on dialysis (i.e. 20 ml/min < GFR < 60 ml/min).[97]

Secondary analyses performed on the data generated from the CHOIR and TREAT studies have supported the likelihood of additional risks such as renal events, stroke and mortality in patients that were not responding adequately to ESA therapy, and for whom the doses of ESAs were subsequently increased.[100,101] The authors concluded that the patients in their study, with the most inferior response to the ESA treatment, were at the highest risk for cardiovascular events and early mortality.[100] These findings

have been supported by a study conducted on CKD patients undergoing dialysis with naturally higher Hb levels (thus not receiving ESA therapy) and it was concluded that these patients were not at an increased risk for cardiovascular events nor early mortality.[59]

Constant overstimulation of erythropoiesis by elevated ESA levels results in elevated haematocrit (HCT) values (and therefore increased blood viscosity), contributing to several haemodynamic risks such as venous thromboembolic events.[102] Heinicke *et al.* devised a model for detecting these consequences in transgenic mice that overexpress human EPO genes.[103] No acute cardiovascular events were observed, yet all the mice had a markedly reduced lifespan. Microscopy analyses indicated increased vascularisation and degenerative inflammatory processes in renal and hepatic tissues. The authors concluded that excessive erythropoiesis may lead to multiple organ degradation and reduced life expectancy.[103]

1.12. Angiotensin-converting enzyme inhibitor use in anaemic patients

Angiotensin-converting enzyme inhibitors (ACEIs) are used in the management of hypertension and congestive heart failure, however it has been suggested that ACEIs have a negative effect on erythropoiesis.[104] The use of ACEIs have been shown to preserve residual renal function (RRF), which is an important predictor in the mortality of peritoneal dialysis (PD) patients despite being suspected of having a detrimental effect on erythropoiesis.[105,106] A study by Le Meur *et al.* suggested that ACEI use lead to higher plasma levels of the peptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), a physiological inhibitor or haematopoiesis, due to the dependence of AcSDKP on the angiotensin-converting enzyme (ACE) for degradation.[107] Hayashi *et al.* found that carefully controlled doses of ACEI administered to dialysis patients showed no appreciable effect on haematopoiesis.[108]

1.13. International erythropoiesis-stimulating agent therapy usage trends

The Dialysis Outcomes and Practice Patterns Study (DOPPS) was created to investigate trends in nephrology practice by gathering data from nationally representative, stratified, random samples of patients undergoing treatment in various nephrology facilities across participating countries.[109] Data originating from the first three, separate phases of DOPPS studies indicated significant increases in the ESA usage in eleven out of the twelve participating countries. McFarlane *et al*. concluded that prescribing higher doses with the subsequent Hb levels overshooting treatment targets reflect the broad trend since the first DOPPS study was initiated in 1996.[110] DOPPS has since been extended to a 4th and 5th phase from 2009 to 2012, respectively, with the fifth phase of DOPPS seeing its expansion to all six of the Gulf Cooperation Council countries.[111,112]

Deviations from the recommended treatment guidelines correlate with detrimental effects on a patient's health in the long term as well as an increased financial burden due to the cost of the treatment itself and the management of arising complications. It is uncertain to which extent these guidelines are followed by Nephrology Units in the public healthcare sector, or whether the documented international trends are prevalent locally due to the paucity of local data, and therefore further investigation is warranted.

1.14. Aim and objectives

1.14.1. Study aim

This study aimed to assess treatment trends in the management of anaemia in chronic kidney disease patients at the Nephrology Unit of the Steve Biko Academic Hospital (SBAH).

1.14.2. Study objectives

The objectives of the study were to:

- Obtain demographic data of chronic kidney disease patients undergoing dialysis at the Nephrology Unit at the Steve Biko Academic Hospital.
- Determine if EPO therapy was initiated according to KDIGO and SARS guidelines (evaluated at multiple timepoints based on Hb level < 10g/dl).
- Determine the frequency of iron deficiency at the time of anaemia onset (evaluated at multiple timepoints based on iron status).
- Determine the frequency of iron supplementation (correctly or incorrectly).
- Determine the frequency of ACEI use.
- Provide a summary to the Head of Internal Medicine on where room for potential improvement exists based on the findings of this study.

Exploratory objective

- Determine the economic impact and monetary value of long-term ESA treatment on the allocated resources of the Nephrology Unit at SBAH.

CHAPTER 2: METHODS AND STUDY DESIGN

2.1. Ethical considerations

Approval for the project was obtained from the University of Pretoria, Faculty of Health Sciences, MMed Committee (Appendix 1) as well as the Faculty of Health Sciences Research Ethics Committee (Appendix 2) before commencement of the study. As this was a cross-sectional retrospective study collecting data on medication use in the Nephrology Unit at SBAH, permission was obtained from the hospital Chief Executive Officer (CEO) (Appendix 3) prior to the review of any patient records. The CEO Permission Letter template of the University of Pretoria, Faculty of Health Sciences Research Ethics Committee was used to facilitate the process. No personally identifiable information was collected from the records that were reviewed in the Nephrology Unit, and confidentiality was maintained throughout the conduct of the research.

2.2. Study design

This was a retrospective, cross-sectional, descriptive, observational study. It was conducted by reviewing data obtained from the files of patients undergoing dialysis and/or ESA treatment during the period of data review.

2.3. Study setting

This study was conducted in the Nephrology Unit at the SBAH.

2.4. Study population, record selection and sample size

2.4.1. Study population

Patient files between 2 January 2018 and 31 August 2018 were reviewed. During this period 114 CKD patients were actively enrolled for treatment receiving either HD or PD.

2.4.1.1. Inclusion criteria

- All patients currently receiving active treatment of CKD by either HD or PD
- Stage 5 renal failure where the GFR was below 15 ml/min/1.73m^2
- Anaemic patients (i.e. having serum Hb levels < 10 g/dl)
- Patients with a treatment duration of at least three months

2.4.1.2. Exclusion criteria

- Any patients undergoing treatment due to acute kidney injury (AKI)
- Records for patients no longer receiving active treatment from the Nephrology Unit which included:
    - Deceased patients
    - Relocated or transferred patients
    - Patients receiving renal transplantation
- Patients with incomplete records
- Patients recently added to the treatment program, thus having a treatment duration of less than three months

By applying the aforementioned criteria, seventeen patient files were excluded due to inter alia, not receiving treatment for at least three months, incomplete data or missing values according to the study inclusion criteria. The final dataset consisted of 97 patient files with haemodialysis accounting for 43% (n = 42) of the patients and peritoneal dialysis for the remaining 57% (n = 55). With a final sample size of 97 patient files, the two-sided 95% CI for P, where P remains unchanged from the initial calculation was determined to be within ± 5.97% ≈ 6% of the percentage calculated from the sample.

Sample size calculation was determined using nQuery Advanced (Statistical Solutions Ltd, Cork, Ireland) Release 8.0, and was based on the largest sample possible to give a reasonable approximation with a binomial distribution. The initial sample size calculation was based on the estimation of the percentage, P, cases where the guidelines were not correctly adhered to. It was determined that with a sample size of

139, a two-sided 95% confidence interval (CI) for P would be within ± 5% of the percentage calculated from the sample, assuming that P = 10%.

2.5. Measurements

Objective 1: To obtain demographic data of chronic kidney disease patients undergoing dialysis at the Nephrology Unit at the Steve Biko Academic Hospital.

Demographic data (age, sex, population group, weight and the duration of time undergoing dialysis) was collected from the files of each patient undergoing treatment at the Nephrology Unit of the SBAH.

Objective 2: Determine if EPO was initiated correctly or incorrectly according to KDIGO and SARS guidelines (evaluated at multiple timepoints based on Hb level).

Determining the exact date of treatment initiation with EPO was not possible for all the patients. The focus was placed on the initiation of treatment for new patients who were added to the dialysis program during the period of review. For these patients, parameters which were recorded, included the initial Hb level with or without a documented prescription for EPO, and assessment of whether any EPO had been administered, even in instances where a prescription was not evident on file. The EPO preparations in the subsequent chapters are referred to by their tradenames.

Objective 3: Determine the frequency of iron deficiency at the time of anaemia onset (evaluated at multiple timepoints based on iron status).

As for objective 2, the exact time of anaemia onset could not be determined exactly, as patients typically present to the ward with anaemia as a result of ESRD. To utilise the available results, comparisons were drawn between available laboratory data where either the Hb, serum iron level or both were either controlled or uncontrolled. Further clarification was provided by considering other markers of iron status, such as ferritin, TSAT and TIBC, in order to draw a clinically relevant conclusion.

Objective 4: Determine the frequency of iron supplementation (correctly or incorrectly)

Data on the treatment regimen of the patient was obtained from the patient file and it was determine whether iron supplementation was included therein. Furthermore, the form and dosage of the supplementation prescribed was recorded.

Objective 5: Determine the frequency of ACEI use

Data on the use of ACEIs were obtained from the prescriptions within the patient files.

Objective 6: Provide a summary to the Head of Internal Medicine on where room for potential improvement exists based on the findings of this study.

Feedback from the data analyses was provided to the Head of Internal Medicine as a single page summary (Appendix 4).

Exploratory objective: To determine the economic impact and monetary value of long-term ESA treatment on the allocated resources of the Nephrology Unit at SBAH.

Using data from an online electronic price registry, the estimated cost of each dosage strength of ESA in use was calculated per patient per month. Subsequently, this cost estimate was used to calculate the annual cost of treating the included patients. Furthermore, a comparison was drawn by using a hypothetical scenario in which all patients were placed on a long-acting ESA regimen that would only require monthly dosing as opposed to their current treatment regimen which required dosing three times weekly.

2.6. Statistical analysis

Observed categorical (nominal/ordinal) data were summarized using frequency counts, percentage and cross-tabulations with demographic parameters. Continuous variables such as age, dose of treatment administered, duration of treatment, haemoglobin level versus time, and iron levels versus time, were reported as a mean ± standard deviation (SD), median, minimum and maximum values as well as 95% CI

for mean values.

Association at a bivariate level were assessed using Pearson's Chi-square (χ^2) test or Fisher's exact tests. All statistical procedures were performed in SAS (Statistical Analysis System, SAS institute Inc, Carey, North Carolina, USA) release 9.4, with Microsoft Windows. All statistical tests were two-sided, and p values ≤ 0.05 were considered significant. Statistical analysis was performed by an independent biostatistician, Prof HS Schoeman from Clinstat, Pretoria.

CHAPTER 3: RESULTS

3.1. Demographic information of dialysis patients

The total number of patients assessed was 97, with 43.30% (n = 42) assigned to the HD treatment group and 56.70% (n = 55) to the PD treatment group. The mean age of the patients overall was 38.28 ± 11.10 (Table 2). For the HD treatment group the mean age was 37.98 ± 11.15 years and for the PD treatment group 38.51 ± 11.09 years (Table 2). There was no statistical difference in mean age between the treatment groups (p = 0.81). The average age of the females in the combined group was 35.91 ± 11.28 years and the average age of the males was 40.17 ± 10.61 years. The difference in mean age between the two sexes did not attain statistical significance (p = 0.0592). The youngest patient undergoing treatment was 18 years of age, with the oldest being 67 years of age.

The ethnicity for the population group was 79% (n = 83) African, 12% (n = 13) Caucasian and 1% (n = 1) Coloured (Table 3). Females accounted for 44.33% (n = 43) of the population. Patient weight averaged 68.03 ± 14.66 kg (Table 2), for the combined group with average weights of 62.28 ± 13.27 kg and 72.38 ± 14.26 kg for females and males, respectively. A highly significant difference was noted in the mean weights between the two sexes of the combined group (p = 0.0008). The weights of the patients ranged from 38 to 101 kg (Table 3). The average weight of the HD treatment group was 57.80 ± 11.61 kg and 73.11 ± 15.91 kg for females and males, respectively (Table 4) and the PD treatment group was 64.96 ± 13.69 kg and 71.62 ± 12.61 kg for females and males, respectively (Table 5). A significant difference in weight was noted between the two sexes of the patients in the HD treatment group (p = 0.0022), however the weight difference between the two sexes of patients in the PD treatment group did not attain statistical significance (p = 0.0769). Within the HD treatment group 88.10% (n = 37) of the patients were aged between 18 and 50 years (Table 4) and within the PD treatment group 90.91% (n = 50) of the patients were in the same age bracket (Table 5). The duration of treatment exceeded 24 months for 45.24% (n = 19) of patients in the HD treatment group (Table 4) and 32.73% (n = 18) of patients in the PD treatment group (Table 5).

Table 2: Descriptive statistics for the entire study population, haemodialysis and peritoneal dialysis treatment groups.

	Demographic parameter		
Descriptive parameter	**Age (years)**	**Weight (kg)**	**Treatment duration (months)**
Entire study population			
Mean	38.28	68.03	27.63
SD	11.06	14.66	26.37
95% CI	36.05 – 40.51	65.01 – 71.05	22.04 – 33.21
Minimum	18	38	3
Median	41	65	20
Maximum	67	109	130
Haemodialysis treatment group			
Mean	37.98	67.64	28.02
SD	11.15	16.18	28.67
95% CI	34.50 – 41.45	62.60 – 72.68	19.09 – 36.96
Minimum	20	42	3
Median	39	64	23
Maximum	60	109	130
Peritoneal dialysis treatment group			
Mean	38.51	68.35	27.26
SD	11.09	13.44	24.39
95% CI	35.54 – 41.51	64.57 – 72.13	20.02 – 34.50
Minimum	18	38	3
Median	41	66	19
Maximum	67	101	125

Table 3: Demographic data for the entire study population.

Demographic information	**Female [%, (n)]**	**Male [%, (n)]**	**Total [%, (n)]**
Number of patients	44.33 (43)	55.67 (54)	100.00 (97)
Age (years)			
18 – 30	34.88 (15)	22.22 (12)	27.84 (27)
31 – 40	27.91 (12)	16.67 (9)	21.65 (21)
41 – 50	30.23 (13)	48.15 (26)	40.21 (39)
51 – 60	4.65 (2)	12.96 (7)	9.28 (9)
61 – 70	2.33 (1)	0.00 (0)	1.03 (1)
Population group			
African	90.70 (39)	81.48 (44)	85.57 (83)
Caucasian	9.30 (4)	16.67 (9)	13.40 (13)
Coloured	0.00 (0)	1.85 (1)	1.03 (1)
Weight (kg)			
31 – 40	2.33 (1)	0.00 (0)	1.03 (1)
41 – 50	18.60 (8)	1.85 (1)	9.28 (9)
51 – 60	25.58 (11)	20.37 (11)	22.68 (22)
61 – 70	25.58 (11)	27.78 (15)	26.80 (26)
71 – 80	9.30 (4)	18.52 (10)	14.43 (14)
81 – 90	9.30 (4)	18.52 (10)	14.43 (14)
91 – 100	2.33 (1)	7.41 (4)	5.15 (5)
101 – 110	0.00 (0)	3.70 (2)	2.06 (2)
Not reported	6.98 (3)	1.85 (1)	4.12 (4)
Average time on dialysis (months)			
1 - 3	9.30 (4)	5.56 (3)	7.22 (7)
4 - 6	0.00 (0)	11.11 (6)	6.19 (6)
7 - 9	11.63 (5)	5.56 (3)	8.25 (8)
10 - 12	9.30 (4)	1.85 (1)	5.15 (5)
13 - 24	23.26 (10)	27.78 (15)	25.77 (25)
> 24	37.21 (16)	38.89 (21)	38.14 (37)
Not reported	9.30 (4)	9.26 (5)	9.28 (9)

Table 4: Demographic data for the patient group receiving haemodialysis.

Demographic information	**Female [%, (n)]**	**Male [%, (n)]**	**Total [%, (n)]**
Number of patients	35.71 (15)	64.29 (27)	100.00 (42)
Age (years)			
18 – 30	53.33 (8)	18.52 (5)	30.95 (13)
31 – 40	40.00 (6)	14.81 (4)	23.81 (10)
41 – 50	6.67 (1)	48.15 (13)	33.33 (14)
51 – 60	0.00 (0)	18.52 (5)	11.90 (5)
Population group			
African	80.00 (12)	81.48 (22)	85.57 (34)
Caucasian	20.00 (3)	14.81 (4)	13.40 (7)
Coloured	0.00 (0)	3.70 (1)	2.38 (1)
Weight (kg)			
41 – 50	33.33 (5)	0.00 (0)	11.90 (5)
51 – 60	40.00 (6)	25.93 (7)	30.95 (13)
61 – 70	13.33 (2)	29.63 (8)	23.81 (10)
71 – 80	6.67 (1)	7.41 (2)	7.14 (3)
81 – 90	6.67 (1)	25.93 (7)	19.05 (8)
91 – 100	0.00 (0)	7.41 (2)	4.76 (2)
101 – 110	0.00 (0)	3.70 (1)	2.38 (1)
Average time on dialysis (months)			
1 - 3	6.67 (1)	7.41 (2)	7.14 (3)
4 - 6	0.00 (0)	18.52 (5)	11.90 (5)
7 - 9	20.00 (3)	7.41 (2)	11.90 (5)
10 - 12	6.67 (1)	0.00 (0)	2.38 (1)
13 - 24	33.33 (5)	14.81 (4)	21.43 (9)
> 24	33.33 (5)	51.85 (14)	45.24 (19)

Table 5: Demographic data for the patient group receiving peritoneal dialysis.

Demographic information	**Female [%, (n)]**	**Male [%, (n)]**	**Total [%, (n)]**
Number of patients	50.91 (28)	49.09 (27)	100.00 (55)
Age (years)			
18 – 30	25.00 (7)	25.93 (7)	25.45 (14)
31 – 40	21.43 (6)	18.52 (5)	20.00 (11)
41 – 50	42.86 (12)	48.15 (13)	45.45 (25)
51 – 60	7.14 (2)	7.41 (2)	7.27 (4)
61 – 70	3.57 (1)	0.00 (0)	1.82 (1)
Population group			
African	96.43 (27)	81.48 (22)	89.09 (49)
Caucasian	3.57 (1)	18.52 (5)	10.91 (6)
Weight (kg)			
31 – 40	3.57 (1)	0.00 (0)	1.82 (1)
41 – 50	10.71 (3)	3.70 (1)	7.27 (4)
51 – 60	17.86 (5)	14.81 (4)	16.36 (9)
61 – 70	32.14 (9)	25.93 (7)	29.09 (16)
71 – 80	10.71 (3)	25.93 (8)	20.00 (11)
81 – 90	10.71 (3)	11.11 (3)	10.91 (6)
91 – 100	3.57 (1)	7.41 (2)	5.45 (3)
101 – 110	0.00 (0)	3.70 (1)	1.82 (1)
Not reported	10.71 (3)	3.70 (1)	7.27 (4)
Average time on dialysis (months)			
1 - 3	10.71 (3)	3.70 (1)	7.27 (4)
4 - 6	0.00 (0)	3.70 (1)	1.82 (1)
7 - 9	7.14 (2)	3.70 (1)	5.45 (3)
10 - 12	10.71 (3)	3.70 (1)	7.27 (4)
13 - 24	17.86 (5)	40.74 (11)	29.09 (16)
> 24	39.29 (11)	25.93 (7)	32.73 (18)
Not reported	14.29 (4)	18.52 (5)	16.36 (9)

3.2. Serum haemoglobin concentrations

The baseline mean serum Hb levels recorded for the first month of data collection were 9.31 ± 2.05 g/dl and 10.11 ± 2.48 g/dl for the HD and PD treatment groups, respectively (Figure 10). There was no significant difference ($p = 0.096$) between the groups for this parameter. A downward trend in the mean Hb levels was noted in the HD group over time (monthly), whereas an upward trend in these levels were noted over time (monthly) for the PD treatment group (Figure 10).

The mean serum Hb level over the full study period was 9.23 ± 1.88 g/dl and 10.13 ± 2.35 g/dl for the HD and PD treatment groups, respectively. There was a significant statistical difference ($p = 0.044$) between the two treatment groups for this parameter.

The minimum Hb value noted for any single month within the HD treatment group was 4.05 g/dl with the maximum value being 16.30 g/dl. The corresponding minimum and maximum value for the PD treatment group was 4.60 g/dl and 17.20 g/dl, respectively. An increase in the overall mean Hb level when compared to the baseline value was noted for 50.00% (n = 21) of the HD patients and 56.86% (n = 25) of the PD patients.

Overshooting of the upper serum Hb target level (12 g/dl) was noted for three HD patients and 13 PD patients (Figure 11). Overall, more than 50% of patients had a final mean Hb level below the lower target of 10 g/dl.

The overall group mean serum Hb per month was influenced by the large inter-patient variability as evidenced by the comparison between the overall group mean and the monthly values noted for the first five patients in the HD and PD treatment groups, respectively (Figures 12 and 13). Additional graphs denoting the monthly values per patient in each of the respective treatment groups are provided in Appendix 4 and 5, respectively.

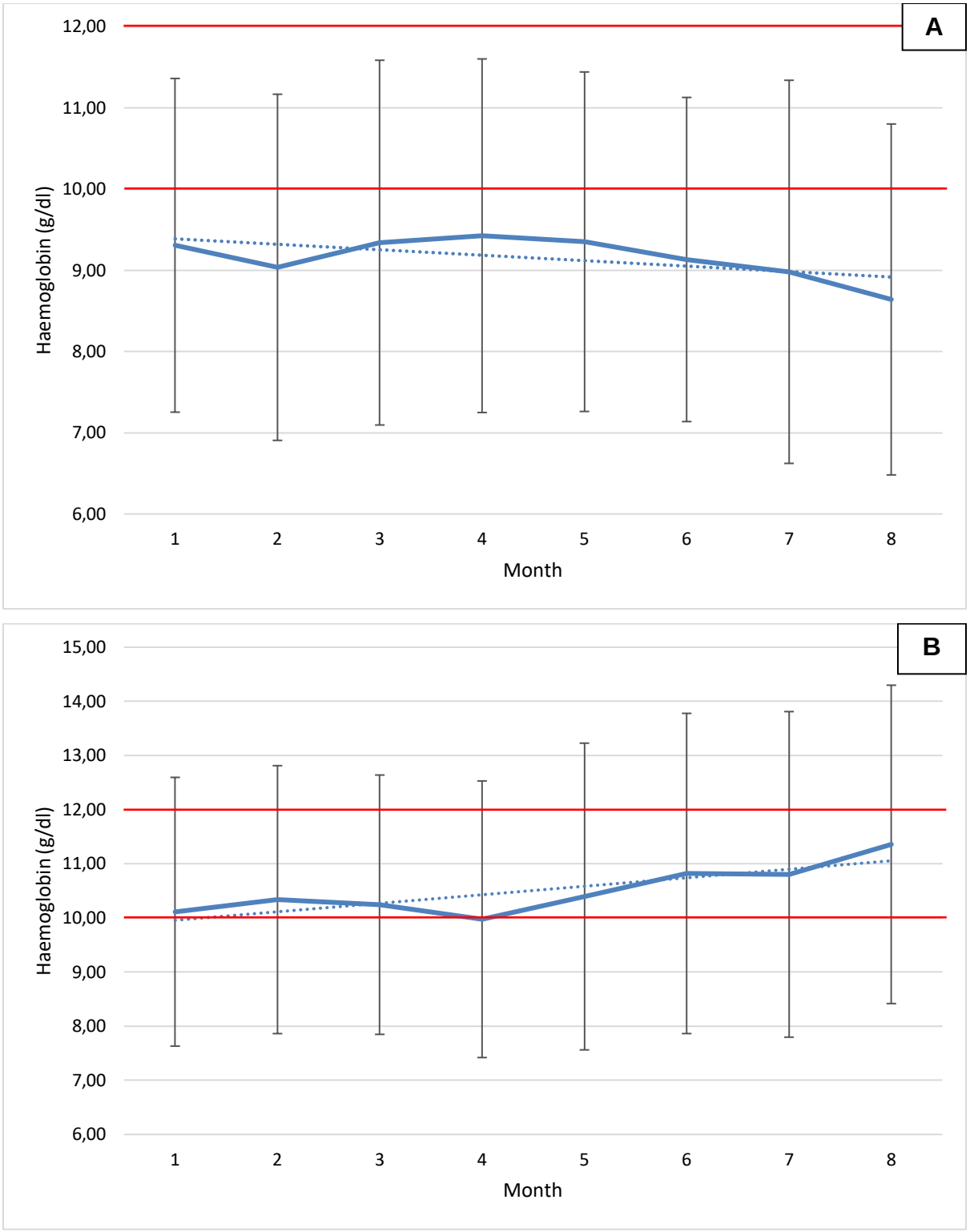


Figure 10: Overall group mean serum haemoglobin level per month of data collected for A) haemodialysis treatment group and B) peritoneal dialysis group. Target levels are denoted by the red lines.

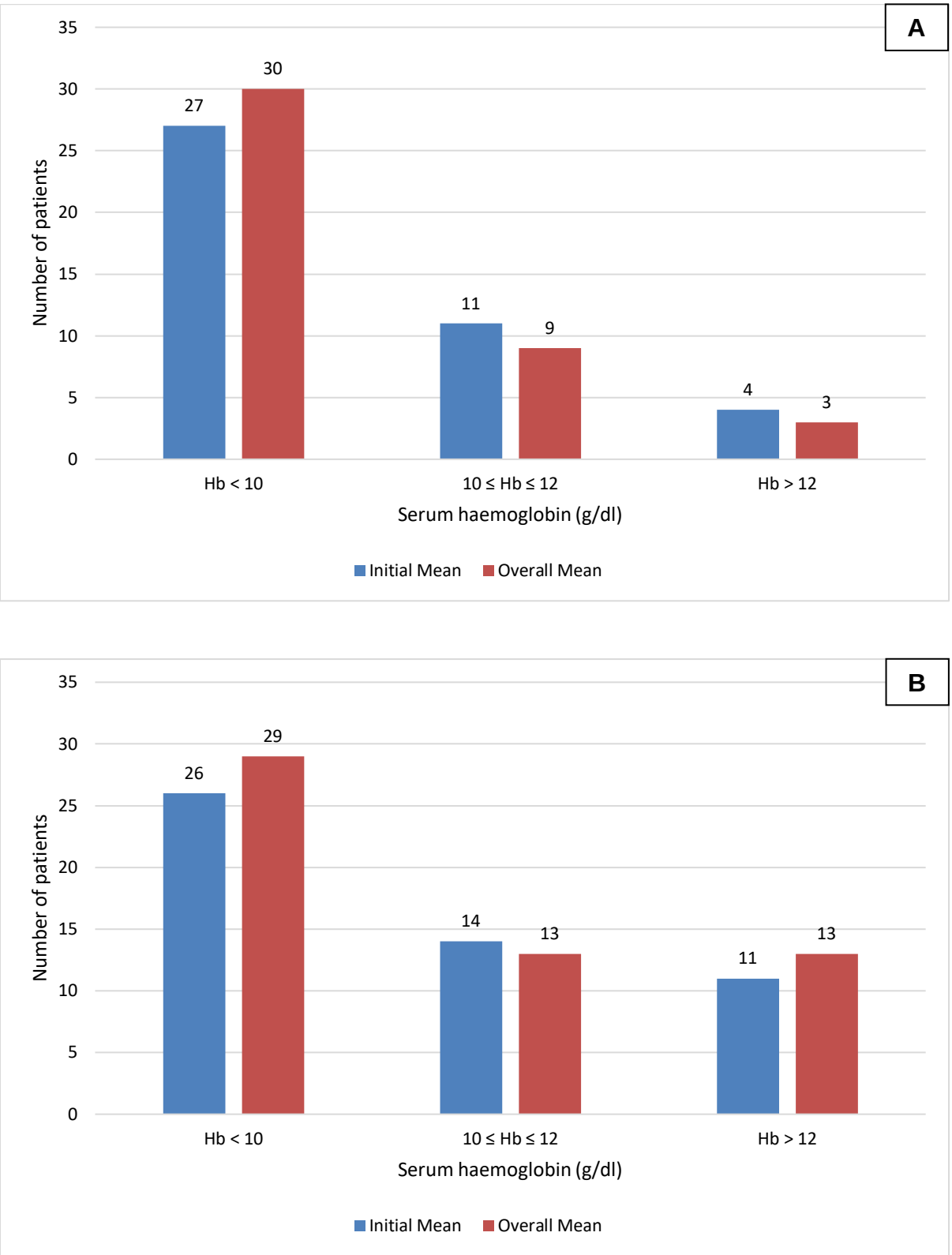


Figure 11: Comparison of initial mean serum haemoglobin level with overall mean serum haemoglobin level for A) haemodialysis treatment group and B) peritoneal dialysis group.

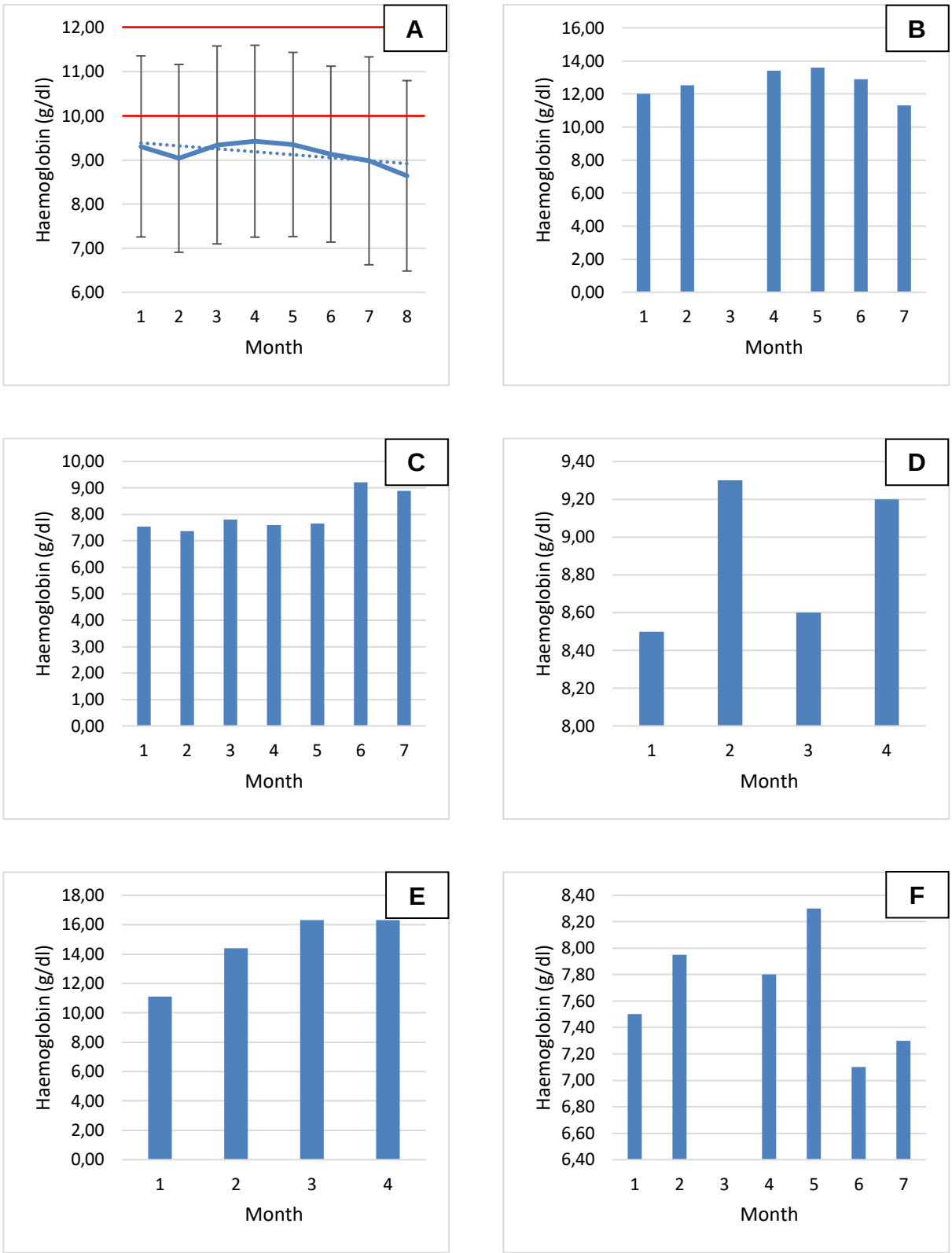


Figure 12: Overall group mean serum haemoglobin level per month of data collected for A) haemodialysis treatment group in comparison to B) through F) the respective monthly values for the first five patients in the haemodialysis treatment group.

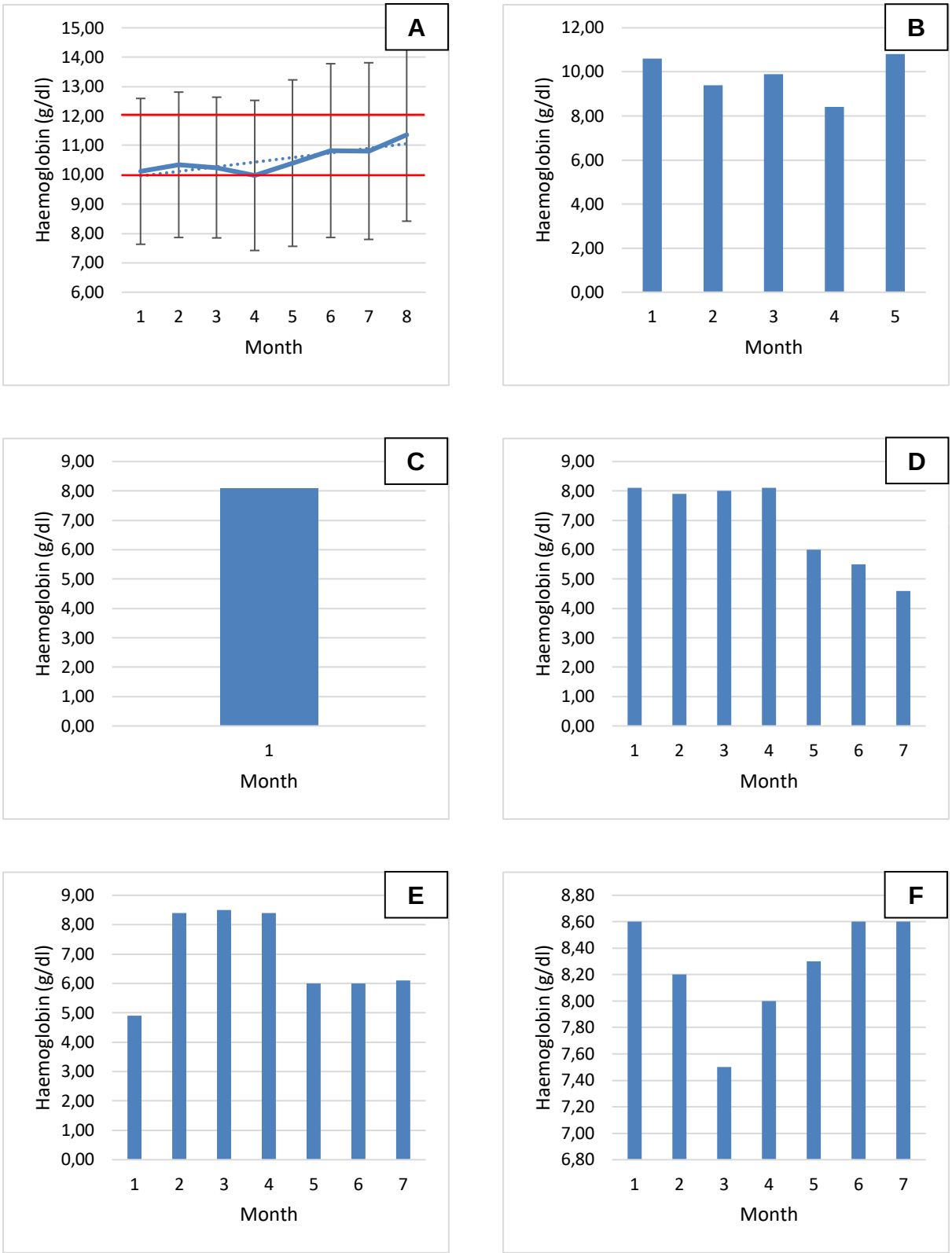


Figure 13: Overall group mean serum haemoglobin level per month of data collected for A) peritoneal dialysis treatment group in comparison to B) through F) the respective monthly values for the first five patients in the peritoneal dialysis treatment group.

3.3. Iron status

The baseline mean serum iron level for the first month of data collection was 11.46 ± 7.78 µmol/l and 12.90 ± 5.81 µmol/l for the HD and PD treatment groups, respectively (Figure 14). These values were however not significantly different (p = 0.576). A similar trend to the mean serum Hb levels, was noted for the mean serum iron levels in the HD (decrease) and PD (increase) treatment groups over time (monthly).

The mean serum iron concentration for the entire period of the study was 9.62 ± 7.67 µmol/l and 12.73 ± 5.69 µmol/l for the HD and PD treatment groups, respectively. The difference in mean serum iron level between the two treatment groups was statistically significant (p = 0.028).

The lowest serum iron value noted for any single month within the HD treatment group was 1.80 µmol/l with the maximum value being 47.70 µmol/l. The minimum and maximum values for the PD treatment group was 5.30 µmol/l and 26.20 µmol/l, respectively.

Only in a single patient was overshooting of the upper serum iron target of 30 µmol/l noted in the HD treatment group. No anomalies were detected for patients within the PD treatment group. Of the HD treatment patients, 80.49% (n = 33) had a mean serum iron level below the lower target of 10 µmol/l. This occurrence was much lower (39.23%; n = 20) in the PD treatment group (Figure 15).

The overall group mean serum Hb per month was influenced by the large inter-patient variability as evidenced by the comparison between the overall group mean and the monthly values noted for the first five patients in the HD and PD treatment groups, respectively (Figures 16 and 17). Additional graphs denoting the monthly values per patient in each of the respective treatment groups are provided in Appendix 6 and 7, respectively.

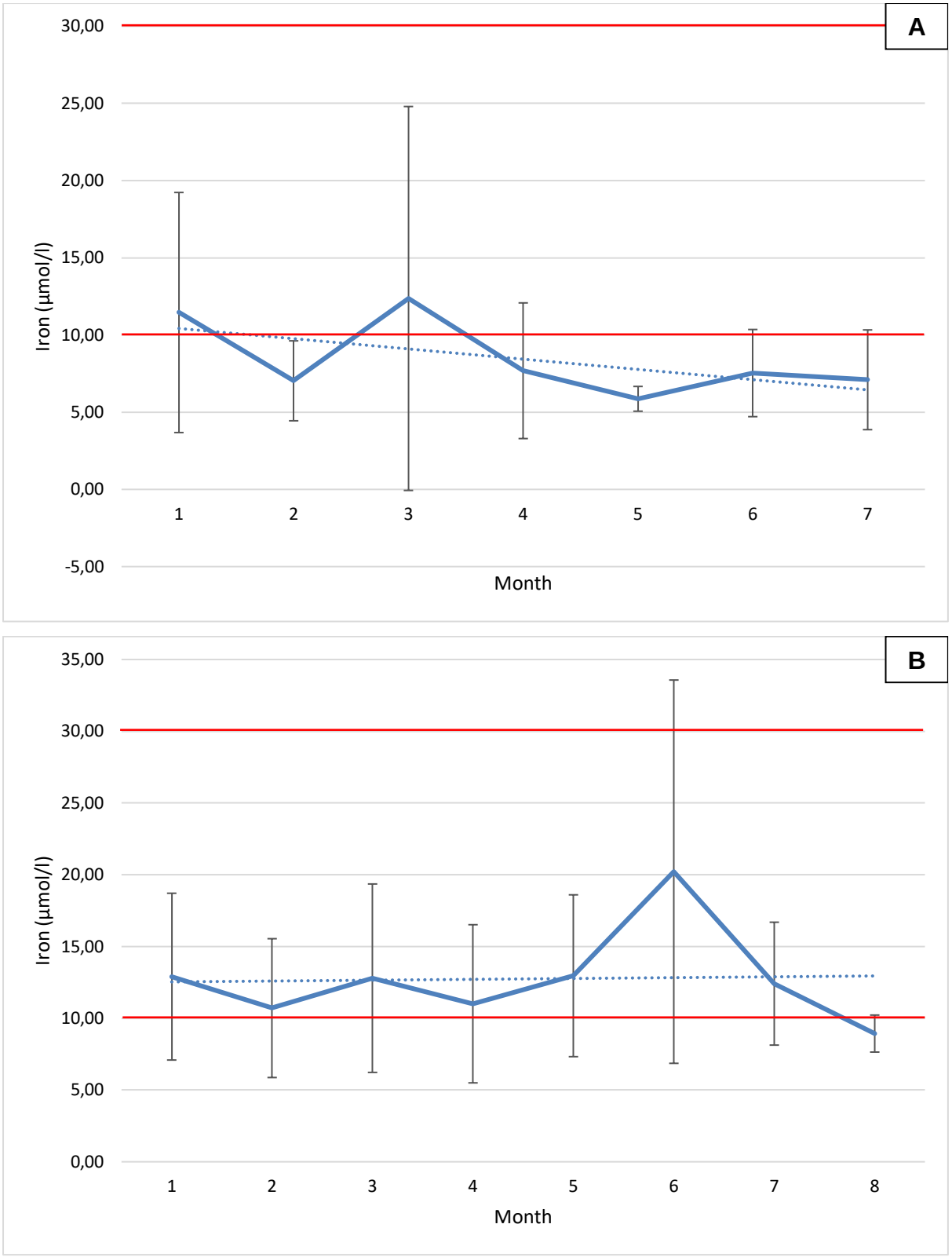
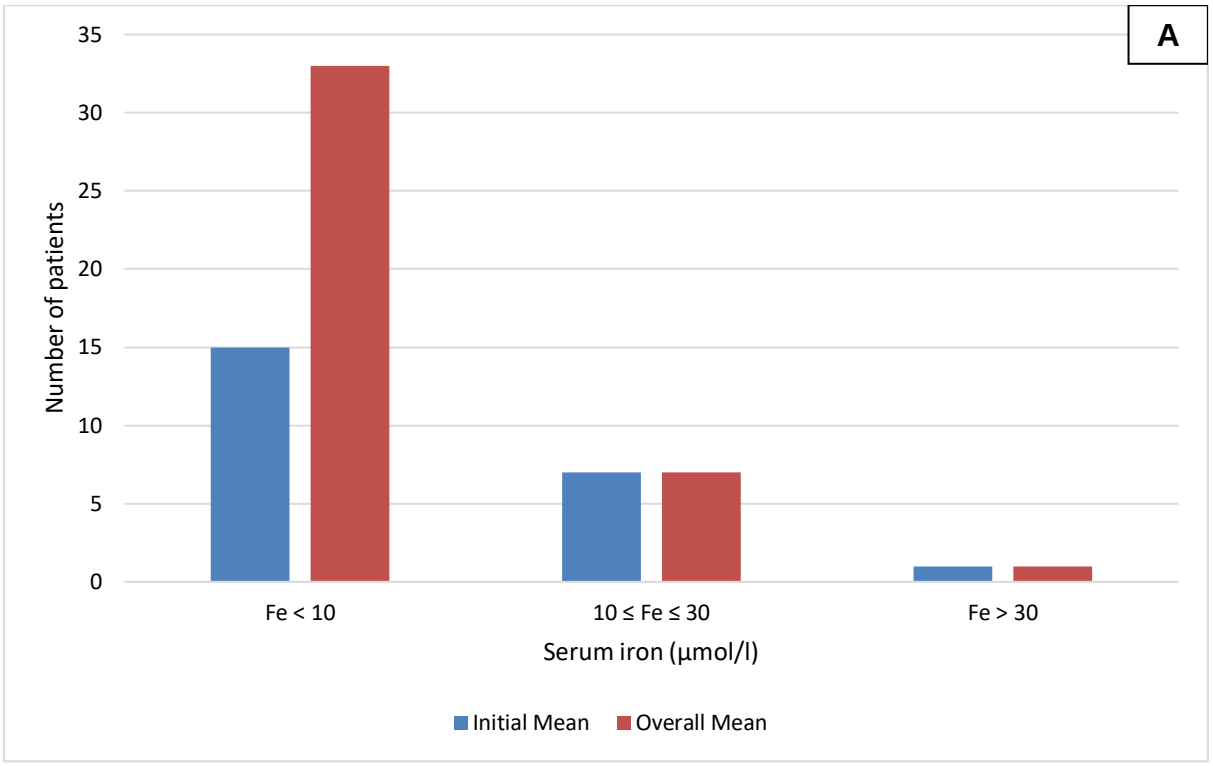


Figure 14: Overall group mean serum iron level per month of data collected for A) haemodialysis treatment group and B) peritoneal dialysis group. Target levels are denoted by the red lines.



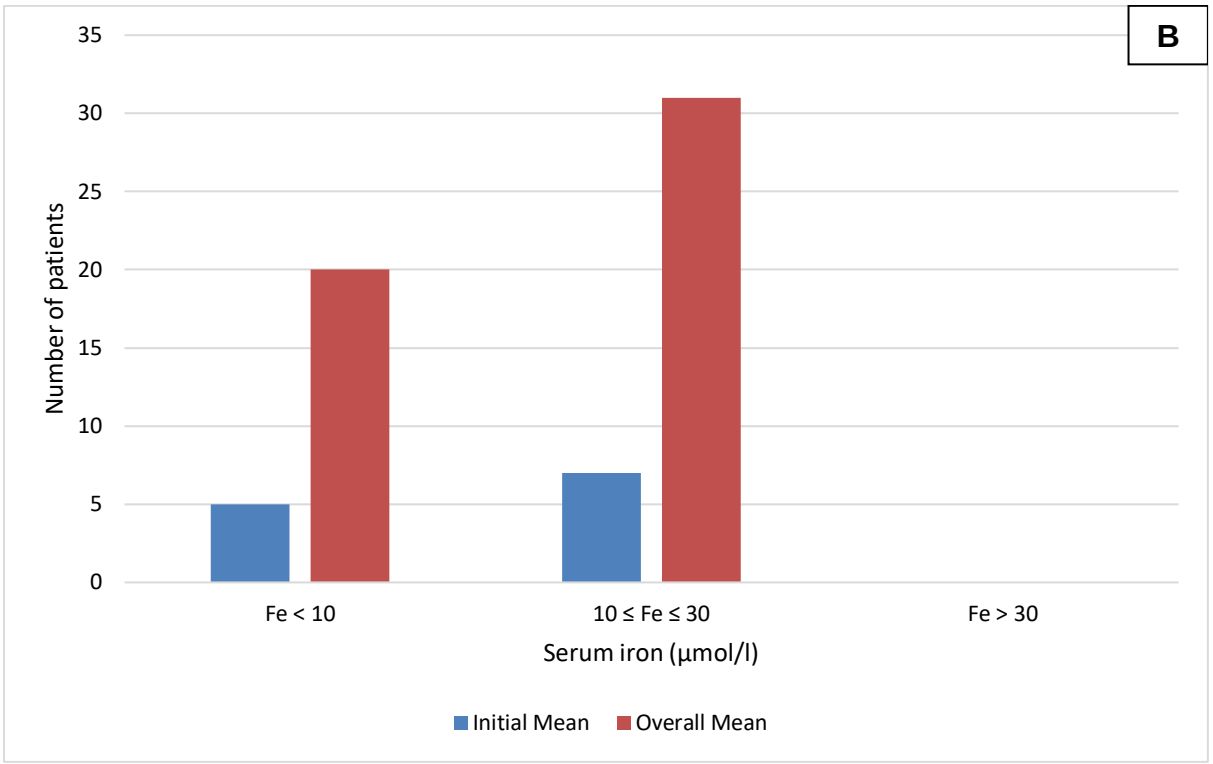


Figure 15: Comparison of initial mean serum iron level with overall mean serum iron level for A) haemodialysis treatment group and B) peritoneal dialysis group.

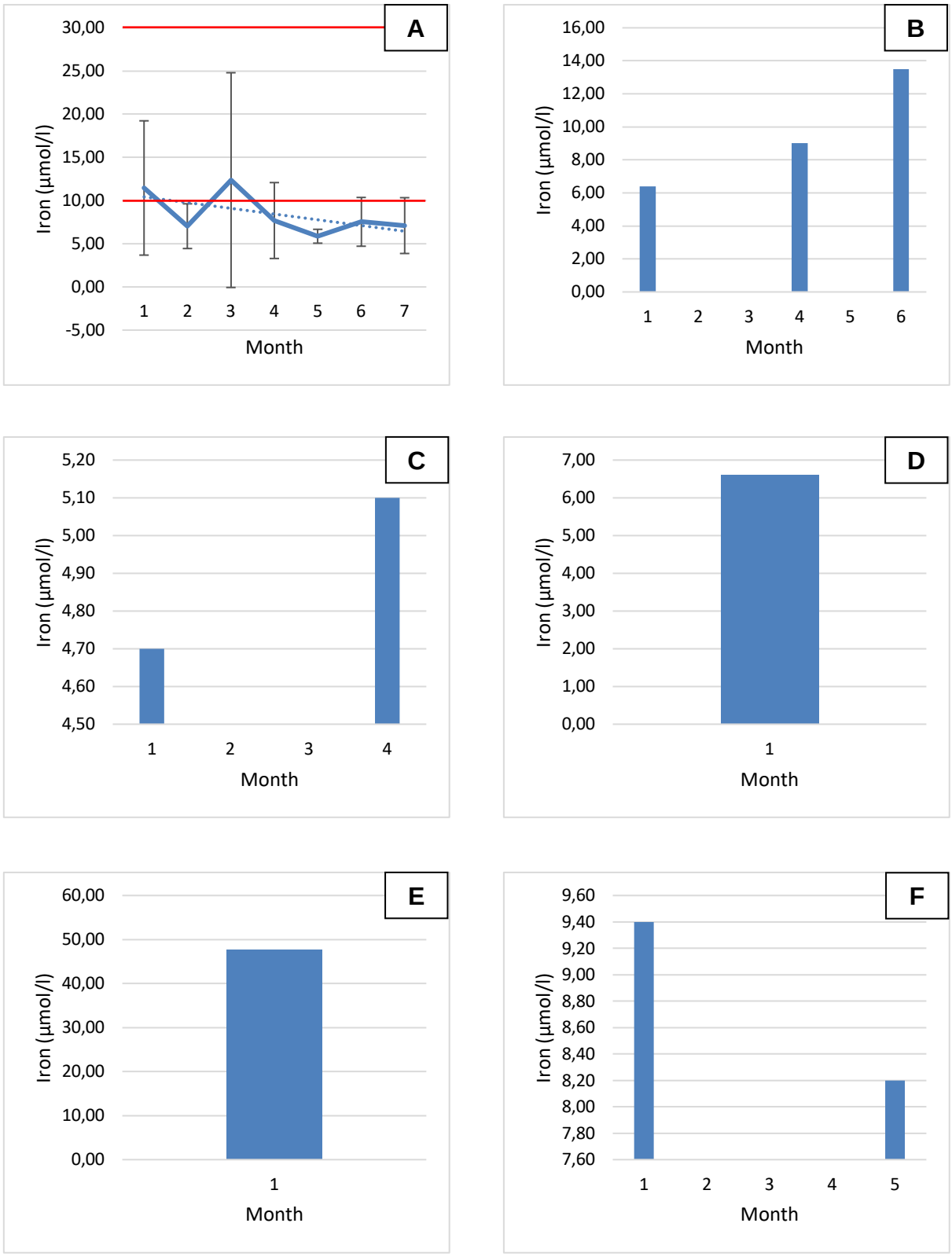


Figure 16: Overall group mean serum iron level per month of data collected for A) haemodialysis treatment group in comparison to B) through F) the respective monthly values for the first five patients in the haemodialysis treatment group.

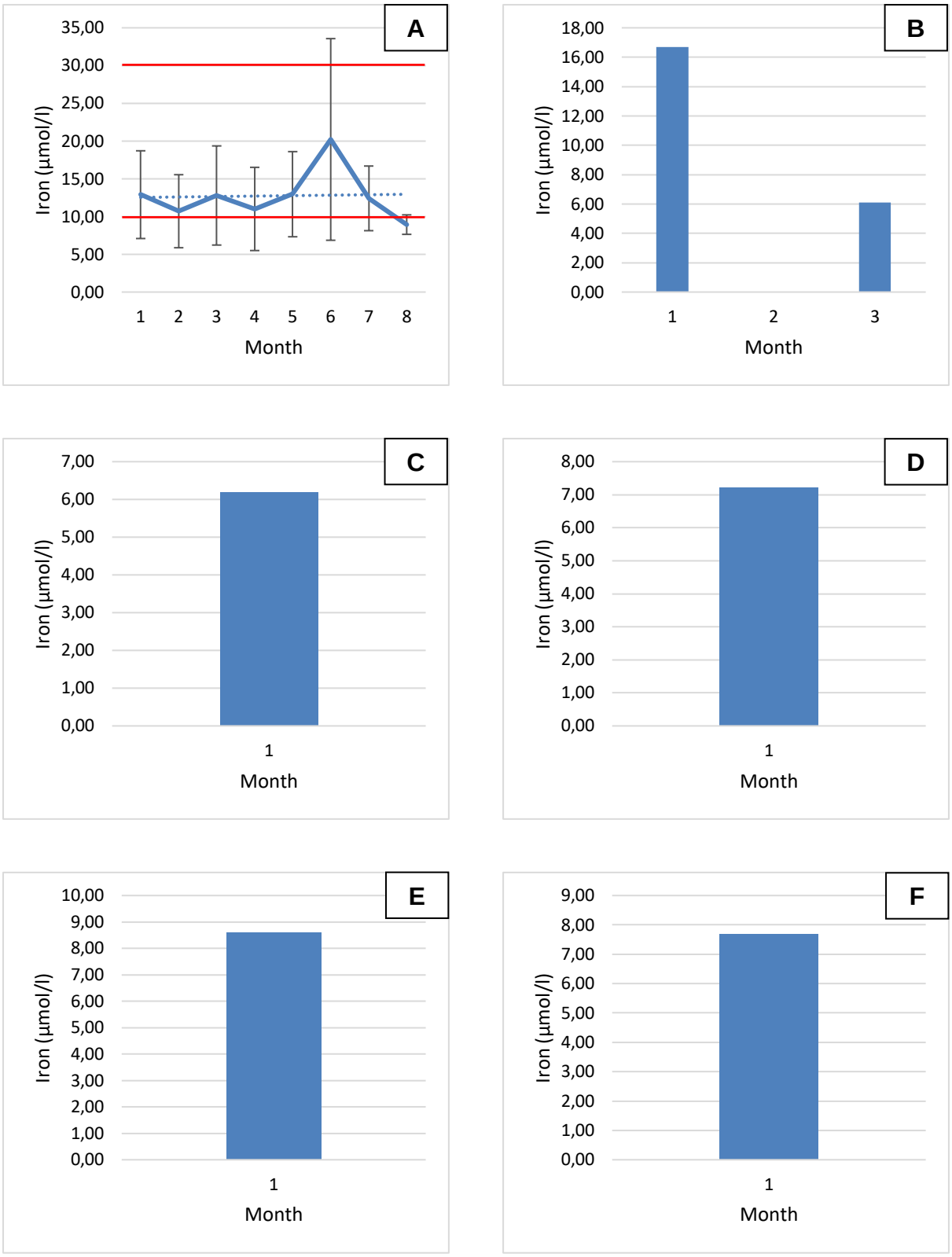


Figure 17: Overall group mean serum iron level per month of data collected for A) peritoneal dialysis treatment group in comparison to B) through F) the respective monthly values for the first five patients in the peritoneal dialysis treatment group.

Key serum markers of iron status, namely, ferritin, TIBC and TSAT were recorded for patients of both treatment groups and factored into the overall iron status determination (Table 6). A comparison of key iron status for patients where parameters were above or below the desired target for each parameter was created (Table 7).

Table 6: Descriptive statistics for serum iron markers for the haemodialysis and peritoneal dialysis treatment group.

	Serum marker		
Descriptive parameter	**Ferritin (µg/l)**	**TIBC (µg/dl)**	**TSAT (%)**
Haemodialysis treatment group			
Mean	519.66	266.11	24.52
SD	879.03	57.02	23.75
Count (n)	41	40	41
95% CI	242.21 – 797.12	247.88 – 284.35	17.03 – 32.02
Minimum	35.50	130.24	7.00
Median	239.33	265.98	17.50
Maximum	5174.00	382.60	123.00
Peritoneal dialysis treatment group			
Mean	461.59	276.94	27.68
SD	670.87	71.70	14.80
Count (n)	52	51	51
95% CI	274.82 – 648.36	256.78 – 297.11	23.52 – 31.84
Minimum	14.00	139.43	9.00
Median	226.75	282.20	24.50
Maximum	3223.33	447.20	87.00

TIBC: Total iron binding capacity; TSAT: Transferrin saturation; CI: confidence interval

Table 7: Comparative summary of values for key serum iron status markers.

Serum Marker	Overall mean [%, (n)]	
Ferritin	**Haemodialysis group**	**Peritoneal dialysis group**
< 200 µg/l	35.71 (15)	45.45 (25)
≥ 200 µg/l	61.90 (26)	49.09 (27)
TIBC		
< 200 µg/dl	14.29 (6)	16.36 (9)
≥ 200 µg/dl	80.95 (34)	76.36 (42)
TSAT		
< 25%	73.81 (31)	50.91 (28)
≥ 25%	23.81 (10)	41.81 (23)

TIBC: Total iron binding capacity; TSAT: Transferrin saturation

The simplified algorithm of Kalantar-Zadeh was used to determine in which patients iron deficiency proved likely, i.e. a serum ferritin value of at least 200 µg/l coupled with a TIBC value of at least 200 µg/dl and a TSAT value of below 25%.[79] Fifteen patients in the HD treatment group and 25 patients in the PD treatment group were found to have ferritin levels < 200 µg/l which, aside from TIBC and TSAT, was indicative thereof that iron supplementation was required. Sixteen HD and ten PD treatment patients had TIBC values > 200 mg/dl, while simultaneously having a TSAT below 25% which signifies that iron deficiency is likely and that IV iron supplementation would be the preferred treatment for correcting the iron status of these patients. Within the latter group (both ferritin and TIBC > 200 ng/ml and 200 mg/dl, respectively), the number of patients with TSAT levels ≥ 25% was four in the HD treatment group and nine in the PD treatment group. As iron deficiency is unlikely in these patients, other causes for ESA hypo responsiveness need to be investigated.

The number of patients with ferritin values ≥ 200 ng/ml as well as a TIBC below 200 mg/dl were five and eight for the HD and PD treatment groups respectively, indicating that TSAT may not be an appropriate diagnostic measure and that other iron status criteria must be considered to draw an accurate conclusion. The results of applying the algorithm for ferritin, TIBC and TSAT was used to categorise the patients on HD and PD treatment into groups where iron deficiency was likely and unlikely (Table 8).

Table 8: Likelihood of iron deficiency based on ferritin, total iron binding capacity and transferrin saturation.

Treatment group	**Iron deficiency likely (n)**	**Iron deficiency unlikely (n)**
Haemodialysis	16	4
Peritoneal dialysis	10	9

Instances where the serum ferritin level alone is < 200 µg/l, indicates that there is a high likelihood of iron deficiency. It was determined that 77.50% (n = 31) of the HD and 68.62% (n = 35) of the PD treatment patients bear a high likelihood of iron deficiency. The monthly group means for the HD and PD treatment groups for each of the three iron status markers, namely ferritin (Figure 18), TIBC (Figure 19) and TSAT (Figure 20) are provided below.

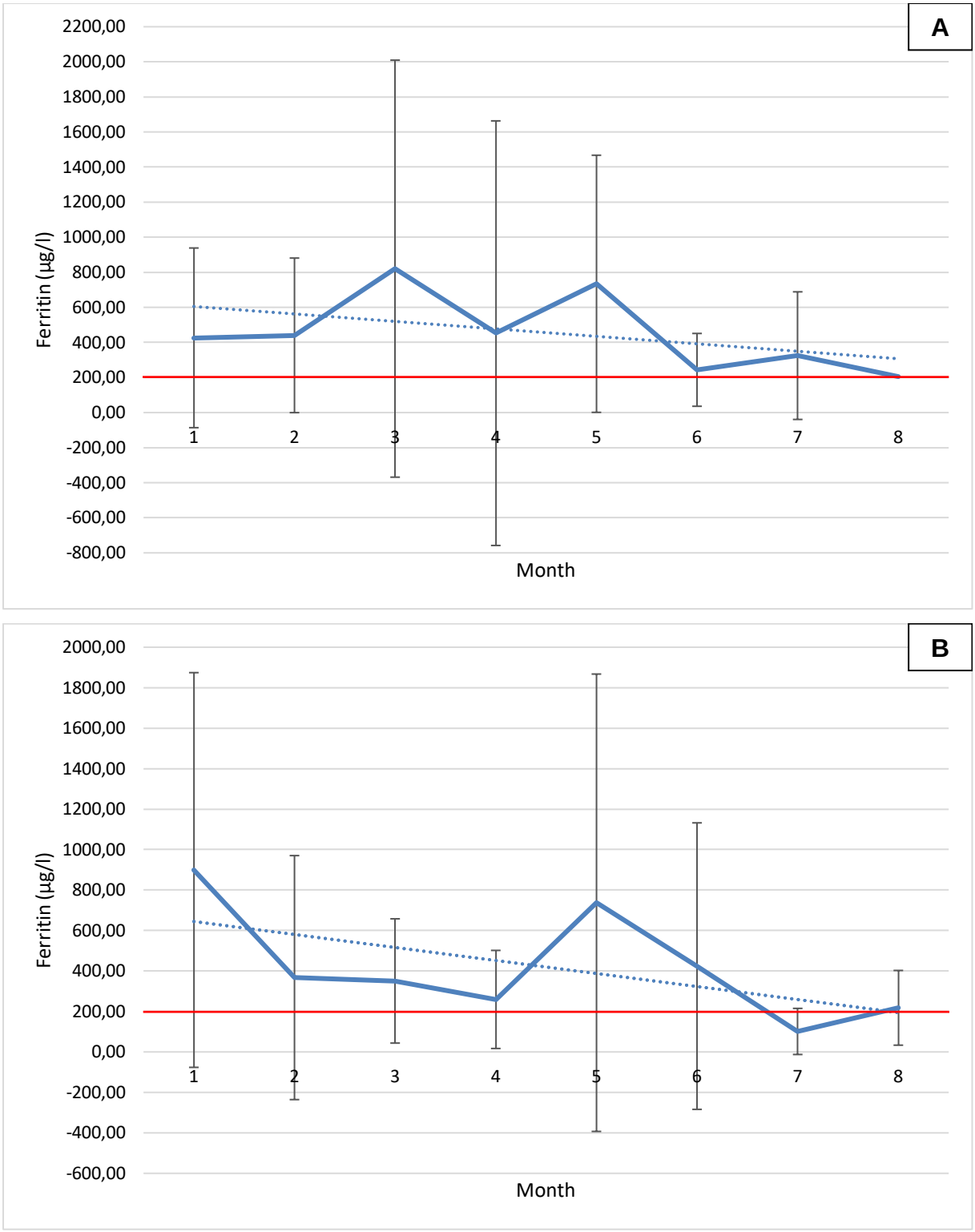


Figure 18: Overall group mean serum ferritin level per month of data collected for A) haemodialysis treatment group and B) peritoneal dialysis group. The target level is denoted by the red line.

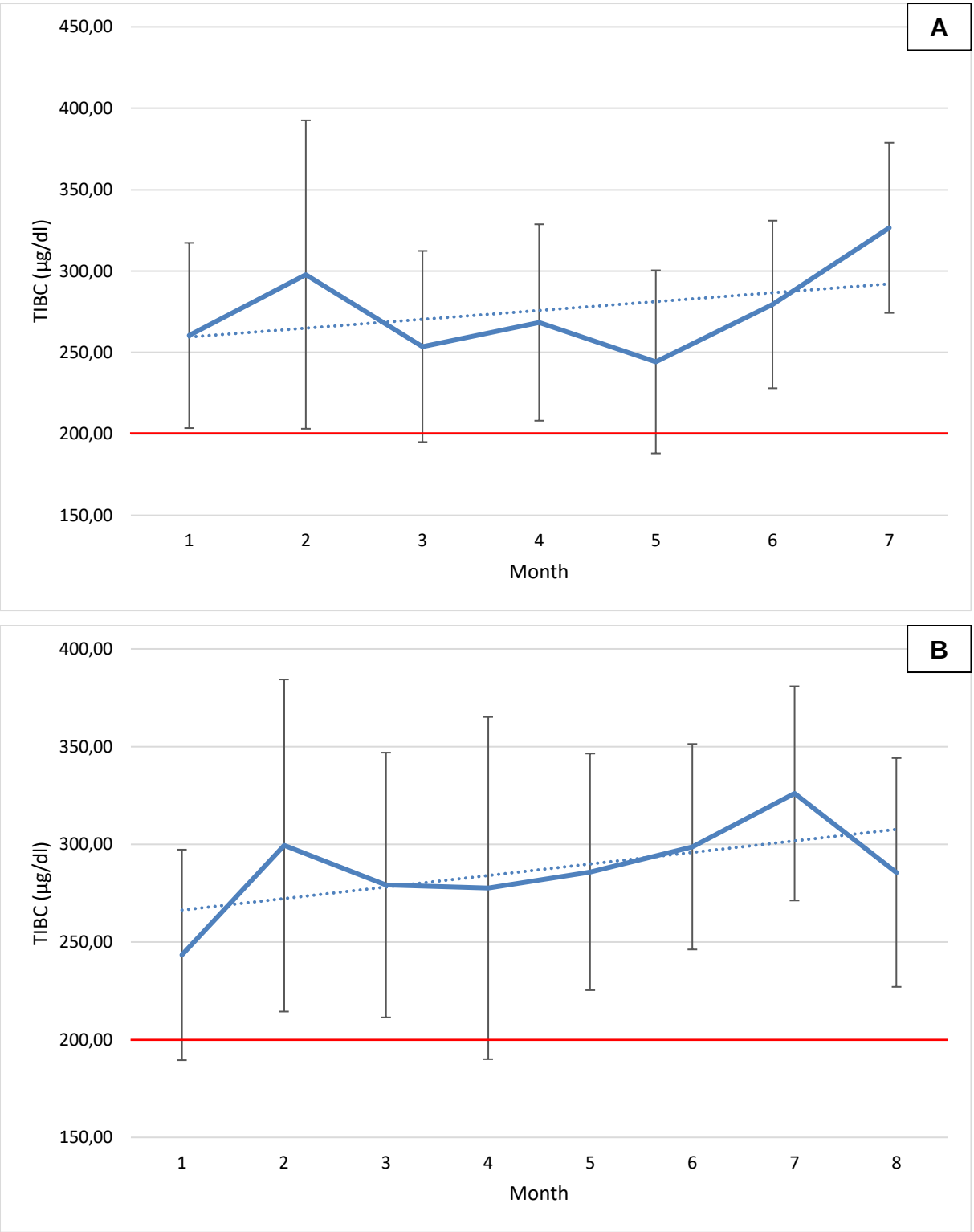


Figure 19: Overall group mean serum total iron binding capacity level per month of data collected for A) haemodialysis treatment group and B) peritoneal dialysis group. The target level is denoted by the red line.

TIBC: Total Iron Binding Capacity

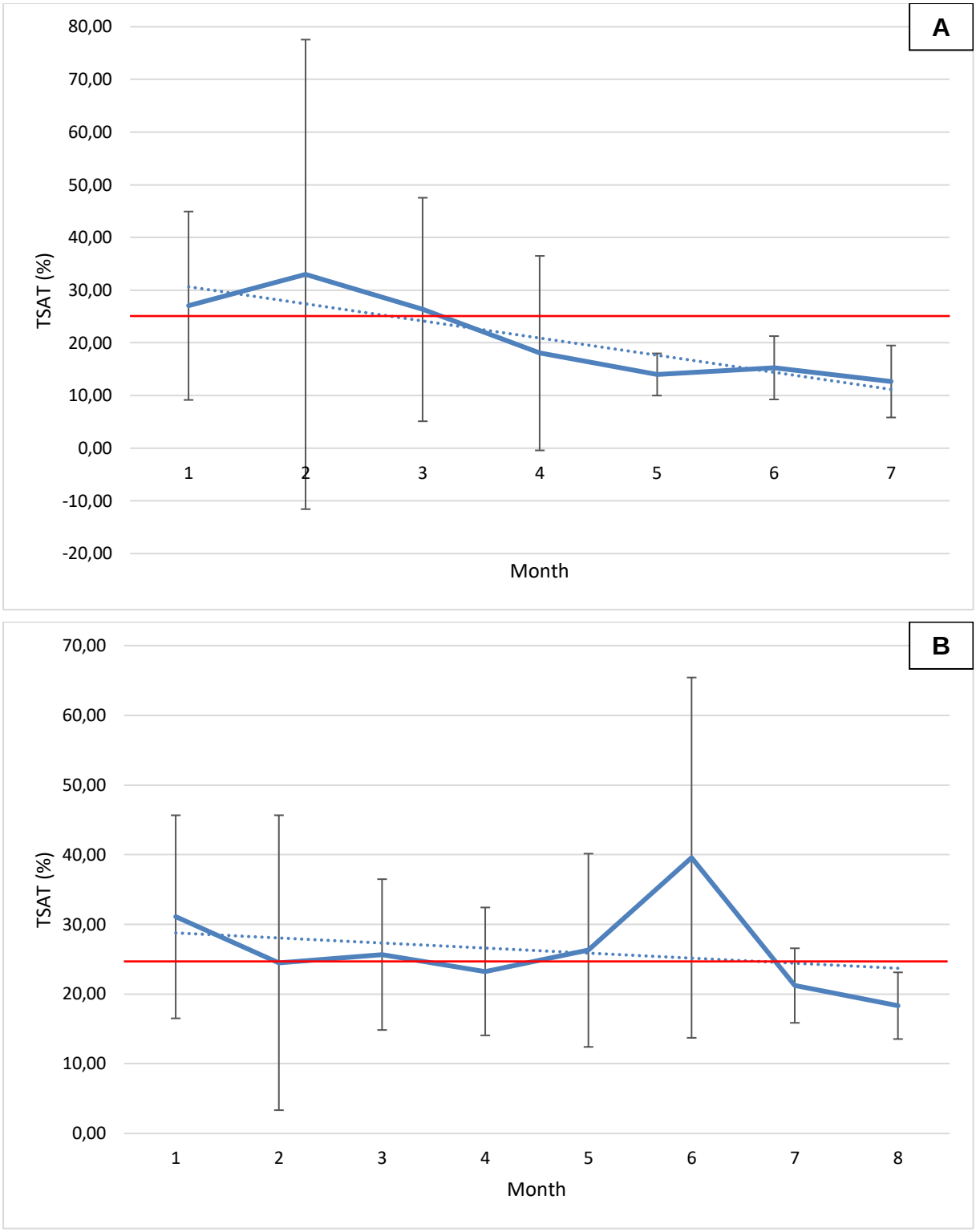


Figure 20: Overall group mean transferrin saturation level per month of data collected for A) haemodialysis treatment group and B) peritoneal dialysis group. The target level is denoted by the red line.

TSAT: Transferrin saturation

3.4. Intergroup comparison of serum haemoglobin and iron

A total of 735 data points for both the serum Hb and iron levels were collected over the study period. The proportion of data points for the HD treatment group amounted to 46.94% (n = 345) with the remainder accounting for the PD treatment group (53.06%; n = 390). The data was further categorized into two groups, i.e. where both the Hb and iron levels were within the target range or where both these values were above or below the range for both treatment groups (Table 9).

Table 9: Categorisation of haemoglobin and iron values into those that fell within target range and those out of range.

Haemoglobin versus Iron			
Haemoglobin (g/dl)	**Iron (µmol/l)**		**Total**
	≥ 10 and ≤ 30	**< 10 or > 30**	
Haemodialysis treatment group			
≥ 10 and ≤ 12	79	129	208
< 10 or > 12	216	266	482
Total	295	395	690
Peritoneal dialysis treatment group			
≥ 10 and ≤ 12	128	120	248
< 10 or > 12	270	262	532
Total	398	382	780

Values for both treatment groups were subjected to significance testing using Chi-Square (χ^2) analysis. For neither of the parameters in the groups was statistical significance noted. The χ^2 statistic values were 2.77 and 0.05 for HD and PD treatment groups, respectively, rendering respective p-values of 0.10 and 0.82.

Intergroup comparison of the number of results where both Hb and iron levels were within the target range versus the number of results where both parameters fell outside the target range is provided in Table 10. Fisher's exact test indicated a highly significant difference (p = 0.0031) between the two groups (within and out of target range).

Table 10: Intergroup comparative categorisation where both haemoglobin and iron values fell within target range and where both were out of range.

Haemoglobin and iron			
	Haemodialysis group	**Peritoneal dialysis group**	**Total**
Both within range	79	128	207
Both out of range	266	262	528
Total	345	390	735

3.5. Erythropoiesis stimulating agent treatment initiation and maintenance

Data were obtained for seven new patients (i.e. having received treatment for three months) during the period of review, three of whom resorted under the HD treatment group and the remainder under the PD treatment group. Five patients (71.43%) had Hb values below 10 g/dl (two in the HD group and three in the PD group). Treatment with ESAs had been prescribed and initiated for three of the new patients, one in the HD group and two in the PD group. In a single new case, an HD patient had not been prescribed any ESA therapy due to a contraindication. Therefore, the treatment options were limited to blood transfusions for the patient, however, for the remaining three patients with a Hb value below 10 g/dl, the reason for not initiating ESA treatment could not be ascertained at the time of review.

Recormon® with a dosage strength of 4000 IU, to be taken three times per week, is the ESA preparation most frequently prescribed by the Nephrology Unit. The dosage strengths prescribed to the associated number of patients in the HD and PD groups for all patients were noted (Table 11).

Table 11: Dosage strength of erythropoiesis-stimulating agent prescribed.

Recormon® dose prescribed (IU)	Patients (n)
Haemodialysis treatment group	
None	6
2000	2
4000	25
6000	8
8000	1
Peritoneal dialysis treatment group	
None	8
2000	5
4000	40
6000	1
8000	1

3.6. Haemoglobin resolution time and target level overshoots

Overshooting the upper limit of 12 g/dl, based on the overall mean Hb, was noted for 7.14% (n = 3) and 23.64% (n = 13) of the HD and PD patients, respectively. The number of individuals where the monthly means were above target were determined to be 24 and 87 for the HD and PD treatment groups, respectively.

Seven (25.93%) HD and nine (34.62%) PD patients with an initial mean Hb < 10 g/dl were able to reach a Hb value > 10 g/dl for at least a single month during the period under survey. The mean resolution time was determined to be 2.57 ± 1.40 months for the individuals in the HD group and 2.11 ± 1.27 months for individuals in the PD group (Table 12). There was no statistical significance (p = 0.502) between the mean resolution times for these groups.

Table 12: Descriptive statistics for haemoglobin resolution time in the haemodialysis and peritoneal dialysis treatment groups.

	Resolution time per treatment group	
Descriptive Parameter	**Haemodialysis (months)**	**Peritoneal dialysis (months)**
Mean	2.57	2.11
SD	1.40	1.27
Count (n)	7	9
95% CI	1.28 – 3.86	1.14 – 3.09
Minimum	1.00	1.00
Median	3.00	2.00
Maximum	5.00	4.00

SD: Standard deviation, CI: Confidence interval

3.7. Iron supplementation

Parenteral iron supplementation is the treatment of choice for the HD group with 73.89% (n = 31) of patients administered 100 mg of iron sucrose during the weekly visit. In addition, 19.56% (n = 9) of the HD patients receive iron supplementation in the form of ferrous sulphate, with 16.67% (n = 7) of patients given both oral and parenteral iron supplementation. Oral ferrous sulphate is the supplement of choice for PD patients, with 58.18% (n = 32) having prescriptions for oral iron. Two patients (4.76%) were able to maintain an overall serum iron level > 10 µmol/l without any iron supplementation, whereas six patients (14.29%) not receiving iron supplementation were noted to have a serum iron level < 10 µmol/l. In the PD group, thirteen patients (23.64%) were able to maintain an overall serum iron level > 10 µmol/l without any iron supplementation, while seven patients (12.73%), not receiving iron supplementation had a serum iron level < 10 µmol/l.

3.8. Blood product administration

During the period of review, a total of 141 units of red cell concentrate (RCC) was administered to 21 (50%) patients in the HD treatment group. No records of blood product administration were found for the PD group. Two distinct cases were noted within the HD group where ESA therapy was either contraindicated or did not achieve the desired efficacy; therefore these patients were treated with RCC alone.

3.9. Angiotensin-converting enzyme inhibitor use

A total of 49 patients (50.52%) in the study population had prescriptions for an ACEI class antihypertensive agent. This amounted to 54.76% (n = 23) and 47.27% (n = 26) for the HD and PD treatment groups, respectively.

3.10. Economic impact of long-term erythropoiesis-stimulating agent therapy on the resources of the Nephrology Unit

Single exit prices (SEPs) of current medication, sourced from an online medicine price registry, were used as indicative prices for each of the prescribed dosage strengths of Recormon® in use by the Nephrology Unit (Table 13).[113]

Table 13: Single exit price of Recormon® pre-filled syringes (each).

Dosage strength (IU)	Price (ZAR)
2000	167.18
4000	334.37
6000	491.12
8000*	668.74

*Note that a dosage strength of 8000 IU is not available as a pre-filled syringe, therefore two vials of 4000 IU are used which implies double the cost of the 4000 IU dosage strength.

Taking the above-mentioned costs into account and applying this to the thrice weekly dosing regimen employed in the Nephrology Unit, the expected weekly and monthly costs could be calculated for the commonly used dosage strengths (Table 14).

Table 14: Calculated weekly and monthly cost of Recormon® treatment.

Dosage strength (IU)	Cost/week (ZAR)	Cost/month (ZAR)
2000	501.54	2 006.16
4000	1 003.11	4 012.44
6000	1 473.36	5 893.44
8000	2 006.22	8 024.88

A dose based quick reference for transitioning to a Mircera® regimen for patients already receiving ESA therapy was extracted from the Mircera® package insert (Table 15).[114]

Table 15: Mircera® starting doses for patients currently receiving an erythropoiesis-stimulating agent.

Previous weekly EPO α dose (units/week)	Previous darbepoetin α dose (µg/week)	Mircera Dose	
		Once monthly (µg/month)	Once every two weeks (µg/ every two weeks)
< 8000	< 40	120	60
8000 – 16000	40 – 80	200	100
> 16000	> 80	320	180

The quick reference as well as the prices obtained from the online price registry were used to calculate the starting dose of Mircera® required if all patients were changed to a regimen consisting of the long-acting ESA preparation (Table 16).[113]

Table 16: Calculated Mircera® dose and monthly cost.

Recormon® pre-filled syringe (IU)	Calculated Mircera® dose required (µg/month)	Calculated Mircera® cost/month (ZAR)
2000	120	2 905.26
4000	200	3 669.99
6000	200	3 669.99
8000	360	5 548.25

It was apparent that the cost savings for a months' treatment with Recormon® compared to a months' treatment with Mircera®, was negligible for patients receiving Recormon® at a dosage strength of 4000 IU. It was determined that it would be more expensive to replace the 2000 IU of Recormon® with 120 µg of Mircera® per month. The most noteworthy cost saving would occur if patients were to be prescribed 360 µg of Mircera® per month instead of 8000 IU of Recormon® (Table 17).

Table 17: Calculated cost difference when changing treatment regimen from Recormon® to Mircera®.

Recormon® pre-filled syringe (IU)	Calculated cost/month (ZAR)	Calculated Mircera® dose required (µg/month)	Calculated cost/month (ZAR)	Cost impact (Recormon® – Mircera®)
2000	2 006.16	120	2 905.26	-899.10*
4000	4 012.44	200	3 669.99	342.45#
6000	5 893.44	200	3 669.99	2223.45#
8000	8 024.88	360	5 548.25	2 476.63#

* denotes higher cost per month; # denotes cost saving per month

By taking the known dosage strengths of ESA administered to the patients in the HD treatment group and the calculated prices thereof into account, the total cost for the Recormon® treatment was determined at ZAR 159 495.72 per month, whereas the treatment with Mircera® was determined at ZAR 132 468.44 per month. This amounts to an expected saving of ZAR 27 027.28 per month when patients are treated with a

Mircera® regimen. The same calculation was performed for the patients in the PD treatment group, and it was determined that the monthly cost for Recormon® treatment was ZAR 184 446.72, whereas the estimated cost for treatment with Mircera® was ZAR 170 544.14 per month, which implies an estimated saving of ZAR 13 902.58 per month. The calculated costs per annum for treatment with Recormon® versus Mircera® for the entire study population was carried out (Table 18). The cost saving was determined to be ZAR 491 158.32 when only Mircera® was prescribed for ESA therapy for all patients. However, as the appropriate Mircera® regimen for patients currently receiving 2000 IU of Recormon® three times per week has been calculated to cost more, the maximum cost saving was calculated to be ZAR 566 682,72 per annum if only patients who receive 4000 IU to 8000 IU of Recormon® were to be placed on a Mircera® regimen.

Table 18: Calculation of treatment cost per annum for the entire study population.

Recormon® dosage strength (IU)	**Recormon® cost per annum (ZAR)**	**Mircera® cost per annum (ZAR)**	**Cost impact (ZAR)**
2000	168 517.44	244 041.84	-75 524.40*
4000	3 129 703.20	2 862 592.20	267 111.00#
6000	636 491.52	396 358.92	240 132.60#
8000	192 597.12	133 158.00	59 439.12#

* denotes a higher cost per month when utilising Mircera®; # denotes a lower cost per month when using Mircera®

CHAPTER 4: DISCUSSION

4.1. General treatment considerations

The dialysis clinic of the Nephrology Unit is open six days per week, Monday through Saturday (closed on Sunday's and Public Holidays). The principal difference in patient management between the two treatment modalities stems from the short "in-patient" visits by the HD patients as opposed to the mostly self-care treatment of the PD patients. Haemodialysis patients attend their dialysis sessions for approximately four hours, three times per week; where two sessions are available per day in the clinic, namely in the morning and afternoon. In contrast the PD patients attend monthly visits for a clinical examination, to obtain blood specimens for routine assessments inter alia Hb levels and iron status determination as well as for resupplying them with their take-home medication which includes dialysate, ESA regimen, iron supplementation regimen and other chronic medications.

The difference in the number of patients assigned to each of the treatment modalities, (as explained by the staff of the Nephrology Unit) is due to the capacity of the Unit. Ideally, the number of HD patients should be kept at forty or below at any given time point. However, the demand typically exceeds the ideal target, and some additional patients are accommodated. The ideal target for the PD group should not differ from that of the HD group, however it is simpler to accommodate more patients for this treatment modality, as the number of patients attending the PD portion of the clinic is considerably lower on any given day. Additional flexibility is afforded to the PD patients in terms of scheduling the resupply/follow-up visits within a given window and the opportunity for planning in advance is a more definite possibility for this group. If a patient knows that they will only be able to re-attend in two months, sufficient supply can be dispensed in advance to facilitate uninterrupted treatment. This difference is evidenced by the data rendered from this study where the number of patients included is approximately in a 1:1.2 ratio for the HD to PD treatment groups.

The decision of treatment of PD patients is clinician directed, with patient preference having a negligible influence on the clinical direction. According to the SARS Guideline for the optimal care of patients on chronic dialysis in South Africa treatment, the

decision regarding treatment should be based firstly on whether there is a history of major abdominal surgery, which renders a patient unsuitable for PD, and secondly whether the patient has residual renal function (RRF) [although the exact range is not specified].[115]

4.2. Patient demographics

The demographic data of the population group were compared to information noted in the most recent South African Renal Registry (SARR) annual report, dated 2017.[116] Per this report, the median age of the registered patient population was 52.6 years. In this study the median age of the entire study population was 41 years. To note, the report does state that on average, the patient age in the public sector is younger than in the private sector.[116] Although the mean ages noted in the two treatment groups of this study are similar, this was purely coincidental, yet approximately half of the patients undergoing dialysis (49.49%; n = 48) were aged between 18 and 40 years. The manifestation of CKD in early adulthood may be attributable mostly to congenital anomalies of the kidney, damage caused by nephrotoxic exogenous substances, autoimmune disorders, diabetes mellitus, obesity and hypertension.[117,118] Neild *et al.* has stated that congenital abnormalities are associated with approximately half of all ESRD cases worldwide.[119] Accurate statistics are not available for South Africa in lieu of the proportion of young adults suffering from CKD due to congenital abnormalities.[120] Per the SARR annual report of 2017, hypertension and diabetes were the leading causes of ESRD in adults in South African, however, in 31.9% of the diagnosed cases, the exact cause was unknown.[116] In the absence of disease, the renal function, more specifically the filtration capacity of glomeruli is known to wane at a rate of 1% per annum above the age of 40.[121] Despite the sizeable inter-individual variability, the estimated decrease in GFR is approximately 8 ml/min/1.73 m^2 per decade after the fourth decade of life[122].

Even though women are thought to be at a higher risk for CKD, approximately 55% of the patients from the entire study population were male.[123] It was documented in the SARR annual report of 2017 that 59.6% of CKD patients in South Africa at the time were male.[116] This may be attributable to the statistics showing that women are more likely to seek medical attention than males, thus males may present to a clinician when

already in stage 5 of CKD as the majority of CKD cases are asymptomatic until at an advanced stage.[124,125] Given the increased predisposition of individuals of African and Asiatic descent for CKD and the confirmation by the SARR annual report of 2017 that African individuals account for more than 50% of CKD patients in South Africa,[45,116] it was anticipated that the majority of the patients would be African. This was indeed the case, as ~ 86% of the study population were self-reported African. These findings are however not representative of the national prevalence rate, instead, it is more reflective of the national demographic distribution per population group as per the SARR annual report where it was estimated that approximately 80% of the national population is African.[116] A highly significant ($p = 0.0008$) difference was noted between the mean weight for men and women in this study, with the mean weight for men being 72.38 ± 14.25 kg and the mean weight for women being 62.28 ± 13.27 kg.

4.3. Haemoglobin status

Blood tests for determining serum Hb levels for new patients were conducted weekly whereas it was monthly for established patients, which is in accordance with the SARS guidelines.[115] The mean serum Hb for the HD treatment group fell shy of the recommended lower target of 10 g/dl for each of the months' data collected. The mean was negatively skewed by the 30 patients with an overall mean Hb level below the target, however in most instances this was only marginally. In contrast, the mean serum Hb for the PD treatment group was above the recommended lower treatment target for seven of the eight months studied. This was however positively skewed by the 26 patients where the overall average serum Hb level overshot the recommended upper treatment target of 12 g/dl. Approximately 50% of the patients in each treatment group exhibited an improvement in Hb level when the mean level for the first month was compared to that obtained over the duration of the study.

In the group of new patients, approximately 72% presented to the Nephrology Unit with a mean Hb level of < 10 g/dl (in the first month). Quantification of the exact number of patients who present for dialysis while already anaemic could not be determined. It was established, in a study undertaken in the United Kingdom, that between 40 and 50% of patients commence renal replacement therapy (RRT) with a Hb level below 10 g/dl.[126,127] Richardson *et al.* reported that 85% of new patients were able to maintain

a serum Hb level ≥10 g/dl within six months of commencing ESA therapy.[122] Furthermore, the authors found that 49% of HD and 48% of PD patients were able to consistently maintain a Hb within the target range although the average dose of ESA was higher for the HD patients at 9204 IU per week versus 6080 IU per week for the PD patients.[126] In the current study, none of the new patients with a serum Hb level < 10 g/dl were able to reach the recommended target, however a single PD patient had a Hb level of 9.8 g/dl by month two on treatment. With regard to ESA therapy, it should be kept in mind that HD patients receive their treatment (doses) during dialysis sessions at the clinic, whereas PD patients are reliant upon self-administration at home. When considering the month to month data for serum Hb levels in each of the treatment groups and comparing it to the overall means, the number of patients with Hb levels below the lower target increased by three patients in each treatment group. Furthermore, the number of participants with a Hb level within target range decreased by two in the HD group and by one in the PD group. The number of patients with a target overshoot decreased by one in the HD group and increased by two in the PD group.

4.4. Iron status

Blood tests for iron status determination were undertaken monthly for new patients and thereafter quarterly for established patients. Observed trends for iron levels matched those of Hb levels in the patients, although the variability in these levels were more pronounced. In the HD treatment group serum iron levels, on average, remained above subminimum for all but a single month. A target overshoot in the mean serum iron level was noted for only a single HD patient, with none occurring in PD patients. To note is the difference in the formulation and administration of iron supplementation between the patient groups, IV for HD treatment patients which is administered during the clinic visit versus oral ferrous sulphate preparations given to PD patients which is taken at home. Additional oral iron supplementation, and whether taken in conjunction with sufficient simultaneous ascorbic acid, could not readily be determined for the HD treatment patients although it was noted that seven of these patients appeared to receive both oral and parenteral iron supplementations. The possibility of PD patients receiving parenteral iron supplementation when attending scheduled clinic visits does exist, however, this could not readily be quantified.

Given the multifactorial and complex nature of iron status determination in anaemic CKD patients, in conjunction with the fact that serum iron level alone is not the absolute measure of iron status, the calculations for overall iron status were directed by the simplified algorithm of Kalantar-Zadeh *et al.*[74] From a study conducted by Iyawe *et al.* in Nigeria in 2018, it was evident that an iron deficiency of 14% was present in CKD patients.[128] In this study it was noted that 68% (n = 66) of the entire study population had a high probability of iron deficiency, which explains the serum iron level results. In conjunction with the likelihood for iron deficiency, the propensity for a suboptimal response to ESA therapy is exacerbated considerably. The local SARS guidelines propose a dosing rate of parenteral iron at 100 mg/week.[109] Parenteral iron was prescribed for 74% (n = 31) of the HD patients, in accordance with this guideline. Two patients in the HD group maintained both Hb and iron levels within the target range despite not receiving parenteral iron supplementation, one of which only received oral iron supplementation. Goodkin *et al.* reported that a small number of patients have a paradoxical ability to maintain higher Hb levels without pharmacological intervention.[59]

4.5. Blood product administration

According to the information in the patient files of the HD patients, there were occasions where complementary transfusions of red cell concentrate to the ESA treatment was employed in order to provide more instantaneous relief, especially where Hb values had fallen to alarmingly low levels. The administration of RCC however, is a notable cost driver for the Nephrology Unit, and the staff eluded to supply shortages from the South African National Blood Service (SANBS). Instances were noted where patients were not prescribed ESA therapy and were therefore reliant on blood product administration alone, which significantly limits the ability to bring their Hb levels to within the target level. Hypersensitivity to rhEPO and poorly controlled hypertension are key contraindications to treatment with ESA and may likely be the reason for the reliance on blood products for the select few patients.[129]

4.6. Angiotensin-Converting Enzyme inhibitor use

Residual renal function (RRF) has been documented as a predictor of mortality in PD patients and therefore the preservation thereof is of key importance for this group.[105,115] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been documented to play an essential role in preserving RRF despite the controversies cited for using these agents in dialysis patients.[106] Optimal fluid balance with the aid of preserved RRF offer benefits such as a larger degree of control over fluid balance, adequate blood pressure control and a decreased likelihood of left ventricular hypertrophy.[130] In a study on patients with polycythaemia, Ishani *et al.* found that patients receiving ACEI treatment were more likely to develop anaemia.[131] In contrast, Abu-Alfa *et al.* reported that patients who received moderate doses of ACEIs had no appreciable difference in hematologic parameters compared to patients not receiving this treatment.[132] More recently in a meta-analysis conducted on data of 29 061 patients, an association was found between ACEI use and anaemia severity. The authors recommended careful monitoring of hematologic parameters and adjustment of ESA dosage as required.[133]

4.7. Economic impact of long-term erythropoiesis-stimulating agent therapy on the resources of the Nephrology Unit

Management of anaemia in patients with chronic kidney failure is a costly endeavour with the monthly cost of treating the majority of patients who receive 4000 IU of Recormon® three times weekly of approximately ZAR 4012.44. Additionally, it is estimated that the parenteral iron supplementation with Venofer® (iron sucrose) costs an additional ZAR 753.90 per patient per month. It was calculated that the expected Mircera® dose for patients receiving 2000 IU of Recormon® three times weekly would be more expensive. Seven of the patients in the study population were prescribed 2000 IU and 65, 4000 IU of Recormon® three times weekly - in a hypothetical scenario should all patients' treatment have been replaced with appropriate doses of Mircera®, the additional cost for the seven patients receiving the lowest dose of Mircera® would still have been offset by the cost saving of patients receiving higher Mircera® doses.

CHAPTER 5: CONCLUSIONS

The study aimed at assessing treatment trends in the management of anaemia in chronic kidney disease patients at the Nephrology Unit of the SBAH in lieu of Hb and iron marker levels, collected at multiple timepoints and for different treatments.

It was found that 71.43% (n = 30) of HD patients and 52.73% (n = 29) of PD patients had overall mean Hb levels below the desired minimum of 10 g/dl. Similarly, it was found that 73.81% (n = 31) of HD patients and 63.64% (n = 35) of PD patients had a high likelihood of iron deficiency based on key iron status markers.

Owing to the complicated nature of managing anaemia in CKD patients, the results of the study were expected. It is evident that best practice guidelines are adhered to as far as reasonably possible, and there were no instances noted where patients went untreated. Despite the similar treatment approaches to the patients in the HD and PD treatment groups, the critical difference in outcome was underpinned by the dialysis process. The extracorporeal circulation of blood for HD is characterised by blood loss in the dialyser.[134,135] The mechanical damage of erythrocytes through the process is a cause of haemolysis in the hours that follow the dialysis session and determining the extent to which it occurs aside from healthy cell turnover is impossible, yet it may be as high as three litres per annum.[135] This contributes significantly to iron needs of an HD patient and it has been estimated by Kalantar-Zadeh *et al.* that approximately 3 g of iron may be lost per annum due to drawing of blood for analyses and the dialysis process alone.[79] The highly significant difference noted for the intergroup comparison of Hb and iron levels highlighted iron deficiency as the most probable cause of suboptimal response to ESA therapy.

CHAPTER 6: LIMITATIONS AND RECOMMENDATIONS

6.1 Study limitations

Patients records have the propensity to contain errors or be incomplete. The extent to which this affected the project is hard to determine. Due to the vast volume of data, especially for HD patients, records for the previous year are removed and stored in January of the following year, thus in many instances for patients receiving treatment for an extended period of time, the details of initial diagnosis and the treatment interventions immediately taken are no longer available in the file. Therefore, the diagnosis for most patients is noted as CKD or ESRD with the exact aetiology being unknown. The calculation of body mass Index (BMI) for patients could not be performed due to the lack of data on height. The official dialysis start date did not coincide with the first data points available in each patient file. According to the Nephrology Unit staff, there is an acute dialysis period immediately before the commencement of chronic dialysis and data from the former is not kept in the files. As such noting the exact dates of anaemia onset, iron deficiency status at anaemia onset and the date of the first ESA and iron supplementation doses was not possible. The perpetuated effect implies that calculating the exact time from anaemia onset to the time where Hb and iron levels would be adequately corrected was not possible.

As PD patients are reliant on self-administration of the ESA therapy at home, their exact compliance in lieu of the number of pre-filled syringes dispensed versus the number of pre-filled syringes used could not be determined. The financial impact of treating the PD patients was therefore calculated based on prescription data alone and represented a scenario where patients were 100% adherent to their treatment regimen.

In many instances blood samples were rejected by the National Health Laboratory Services (NHLS), citing electronic gatekeeper rules as the reason for rejection. Electronic gatekeeping is a measure implemented to prevent unnecessary repeat testing.[136] Despite the use of the electronic gatekeeper rules as a means of reigning in the cost of analysing samples, it was found by Pema *et al.* that the cost savings by

electronic gatekeeping were moderate.[136] From the data collected, it appeared that iron status tests, especially for anaemic patients, may not be well catered for under the current gatekeeping rules.

As only a single patients' treatment of Recormon® was replaced with Mircera®, shortly before data collection was undertaken, the effect of the change in treatment regimen appeared insignificant, however, this may be confounded by factors such as iron metabolism anomalies or even inborn ESA hypo-responsiveness. No conclusions could be drawn from the data for this specific patient.

The patient sample of 97 fell shy of the target sample of 139 that was determined by the statistician which was required to meet the statistical analysis criteria for the study, however, this merely led to a weakening of ±0.97% for two-sided 95% CI. The shortfall is situational, and given the capacity of the Nephrology Unit at the time, a sample of 139 would not have been achieved.

6.2 Recommendations

Overall, more stringent iron control is proposed for patients of both treatment groups. Ensuring that iron treatment is adhered to in order to maintain appropriate levels is more challenging for PD patients due to less frequent clinic visits, however, ensuring oral ferrous sulphate supplementation is taken with adequate amounts of ascorbic acid to aid in absorption is essential. Adjusting iron dosage for HD patients is simpler, yet has to be optimised in accordance with appropriate testing. The potential to motivate why another blood specimen was sent for testing when receiving pushback due to gatekeeping rules does exist, however, this will only prove valuable in the most troublesome cases.

Switching to a longer-acting ESA preparation such as Mircera® which allows monthly dosing may aid treating physicians to spend more time focussing on iron status management while the ESA component should have less variability owing to Mircera®'s longer half-life. The estimated cost saving by prescribing Mircera® as the primary treatment regimen can be utilised to procure additional supplies for correcting

iron status as required. Initiating any treatment regimen change will have to be conducted in conjunction with more frequent monitoring of Hb levels and may require additional motivation in lieu of gatekeeping rules imposed by the laboratory. With this said it is evident that the potential for long term benefit outweighs the initial efforts. Any apparent benefit or lack thereof stemming from a change in the ESA treatment regimen will be quantifiable by the additional laboratory test results. It is evident that the changes will have to occur in a phased approach, and sufficient time should be allowed for corrections.

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APPENDICES

Appendix 1: Letter of MMed committee approval

University of Pretoria
Faculty of Health Sciences

Department Internal Medicine
Kalafong Hospital
Klinikala Building 2-1
Tel 27-12-373 1075
e-mail: danie.vanzyl@up.ac.za

LETTER OF MMED COMMITTEE APPROVAL

This letter is to confirm that the protocol of student, **Dr E Kok** titled **"Erythropoietin treatment in anaemic patients at the Nephrology Unit of the Steve Biko Academic Hospital – a retrospective, cross-sectional study"** has served at the MMed Committee and was found to be academically acceptable.

Prof DG van Zyl
Chairman: MMed Protocol Committee

Date: June 14, 2018

Please Note that you may now apply to the Ethics Committee for approval.
See http://www.up.ac.za/academic/healthsciences_old/ethics/ for requirements.

Appendix 2: Ethics Committee approval certificate

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IORG #: IORG0001762 OMB No. 0990-0279 Approved for use through February 28, 2022 and Expires: 03/04/2023.

20 July 2020

Approval Certificate
Annual Renewal

Ethics Reference No.: 402/2018
Title: Erythropoietin treatment in anaemic patients at the Nephrology Unit of the Steve Biko Academic Hospital - a retrospective, cross-sectional study

Dear Mr E Kok

The **Annual Renewal** as supported by documents received between 2020-06-18 and 2020-07-15 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 2020-07-15.

Please note the following about your ethics approval:

- Renewal of ethics approval is valid for 1 year, subsequent annual renewal will become due on 2021-07-20.
- Please remember to use your protocol number (402/2018) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

Research Ethics Committee
Room 4-60, Level 4, Tswelopele Building
University of Pretoria, Private Bag x323
Gezina 0031, South Africa
Tel +27 (0)12 356 3084
Email: deepeka.behari@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

Appendix 3: Hospital Chief Executive Officer permission letter

Permission to access Records / Files / Database at Steve Biko Academic Hospital

TO:
The Chief Executive Officer of Steve Biko Academic Hospital

Re: Permission to do research at Steve Biko Academic Hospital

TITLE OF STUDY: Erythropoietin treatment in anaemic patients at the Nephrology Unit of the Steve Biko Academic Hospital - a retrospective, cross-sectional study

This study is approved by the relevant Head of Department, Prof Vanessa Steenkamp:

Signature: Steenkamp

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

I am a student at the Department of Pharmacology at the University of Pretoria. I am working with Dr André Marais, Dr Wesley van Hougenhouck-Tulleken and Prof Vanessa Steenkamp. I herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital grounds. This study involves access to patient records. This study involves clinical research.

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Print Name Elandré Kok Signature
Principal Investigator

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved, on condition that there will be no cost to the hospital.

Title and name of Chief Executive Officer: Dr TS Mangwane

Name of hospital / clinic: Steve Biko academic Hospital

Signature: Date: 28/06/2018

GAUTENG PROVINSIALE REGERING
DEPT VAN GESONDHEID
STEVE BIKO AKADEMIESE HOSPITAAL
STEVE BIKO ACADEMIC HOSPITAL
2018 -06- 28
PRIVAATSAK/PRIVATE BAG X169
PRETORIA 0001
GAUTENG PROVINCIAL GOVERNMENT
DEPT OF HEALTH

Appendix 4: Feedback letter to Head of Internal Medicine

The study entitled: Erythropoietin treatment in anaemic patients at the Nephrology Unit of the Steve Biko Academic Hospital - a retrospective, cross-sectional study, conducted during late 2018 yielded results that are indicative of the inherent benefit to patients in terms of clinical outcomes by using the long acting preparation, methoxy polyethylene glycol-erythropoietin-beta (Mircera®). Files of patients receiving treatment at the Steve Biko Academic Hospital (SBAH) Nephrology Unit between 2/Jan/2018 and 31/Aug/2018 were assessed, with data obtained from 97 patient files comprising 43% (n = 42) haemodialysis patients and 57% (n = 55) peritoneal dialysis patients.

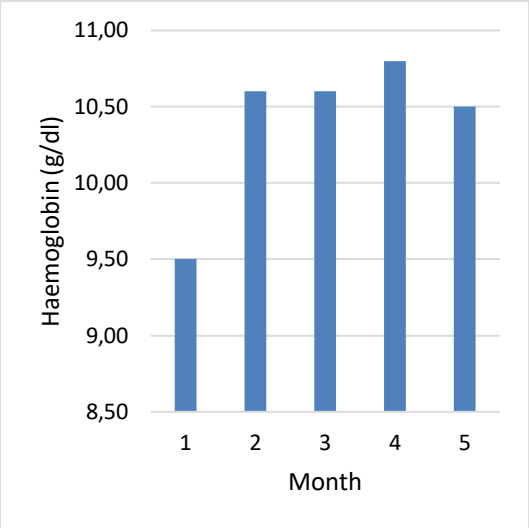
Serum haemoglobin (Hb) and iron levels constituted the key clinical markers under consideration for the study and prescribed treatments were considered in lieu of the guidelines promulgated by the South African Renal Society (SARS) as well as the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.

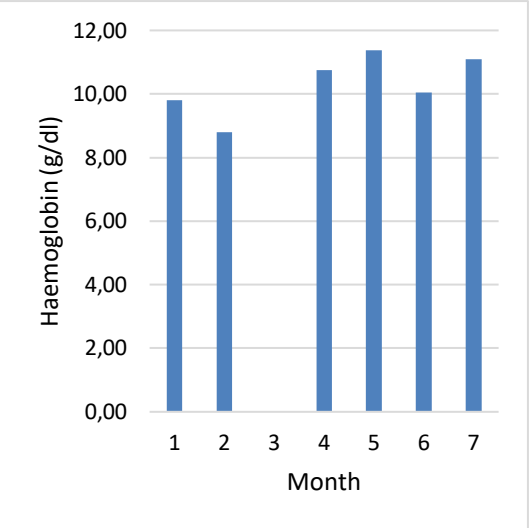
An intergroup comparison between the number of data points where both Hb and iron levels were within the target range versus the number of results where both parameters fell outside the target range yielded a significant difference ($p = 0.0031$). Patients receiving peritoneal dialysis reached serum Hb and iron levels closer to normal target values compared to those receiving haemodialysis.

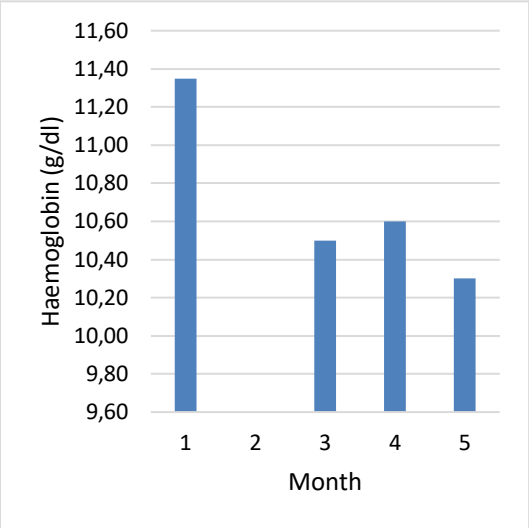
Considering the estimated cost of treating a patient with 4000 IU of Recormon®, three times weekly, amounts to approximately ZAR 4012.00 for 12 administrations per month, the most commonly prescribed dose as observed in the Nephrology Unit (in 67% of those receiving EPO). The routine Recormon® treatment regimen can be substituted with a single, 200 µg dose of Micera® per month (or with 100 µg fortnightly, if required) at an estimated monthly cost of ZAR 3669.99. The cost saving was determined to be ZAR 491 158.32 when only Mircera® was prescribed for ESA therapy for all patients, however as the appropriate Mircera® regimen for patients currently receiving 2000IU of Recormon® three times per week has been calculated to cost more, the maximum cost saving was calculated to be ZAR 566 682,72 per annum if only patients who receive 4000 IU to 8000 IU of Recormon® were to be placed on a Mircera® regimen.

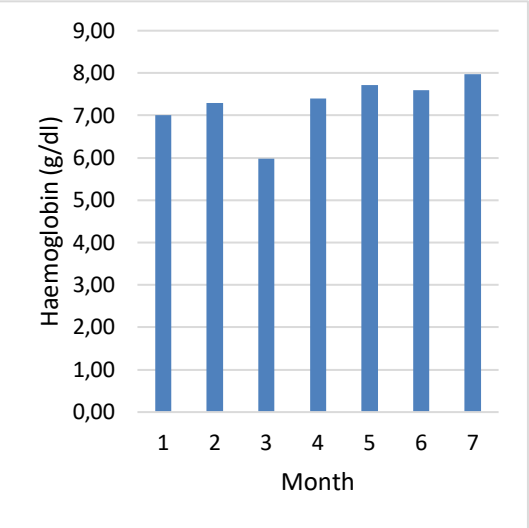
Transitioning to a longer-acting ESA preparation such as Mircera® which allows monthly dosing may aid treating physicians to spend more time focussing on iron status management while the ESA component should have less variability owing to Mircera®'s longer half-life. The estimated cost saving by prescribing Mircera® as the primary treatment regimen can be utilised to procure additional supplies for correcting iron status as required.

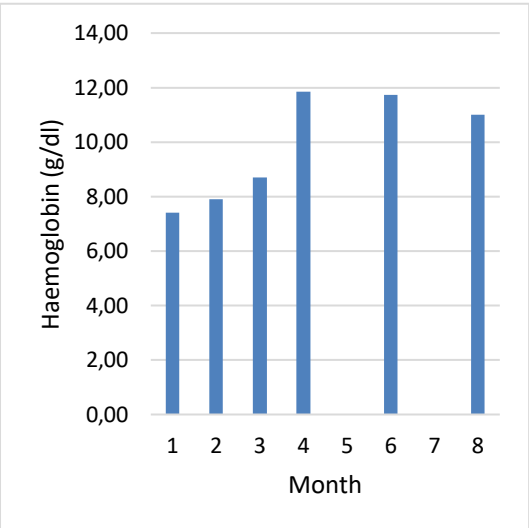
Appendix 5: Additional serum haemoglobin graphs for patients in the haemodialysis treatment group

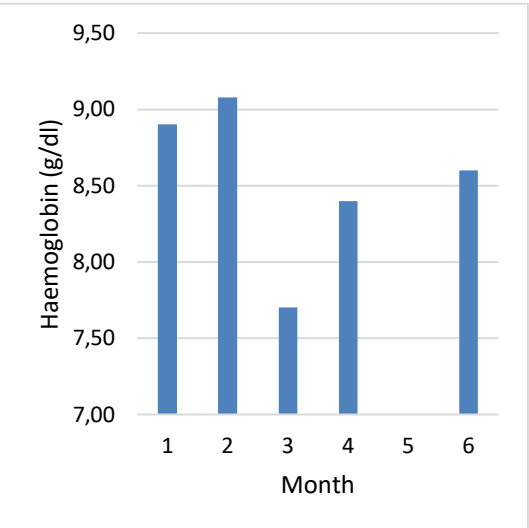


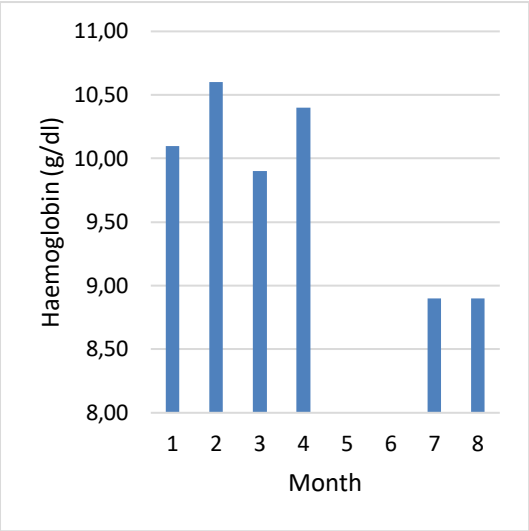








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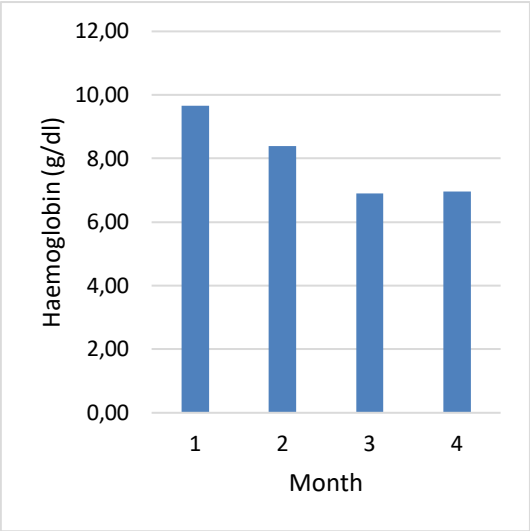
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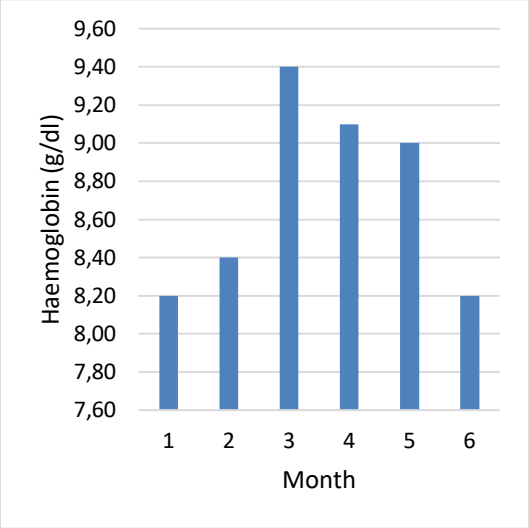
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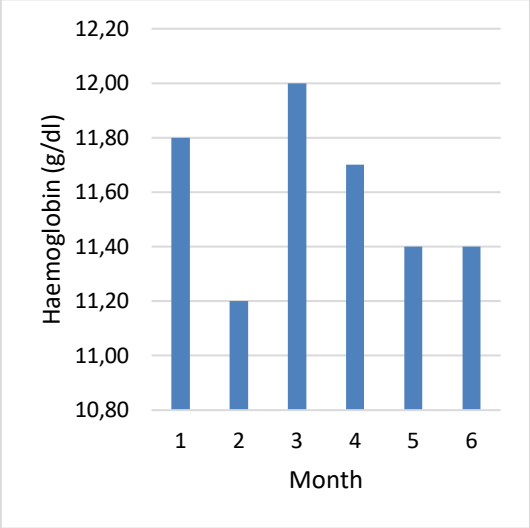
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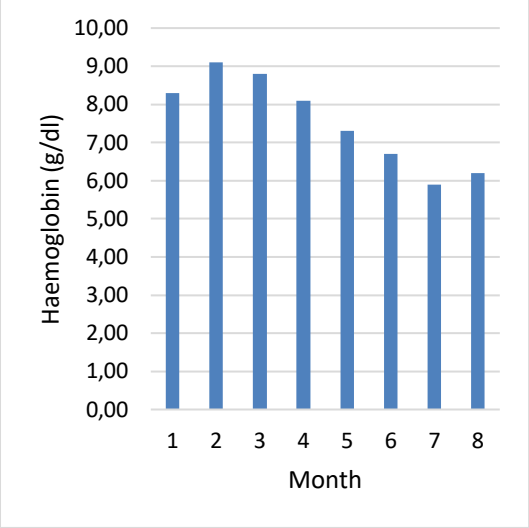
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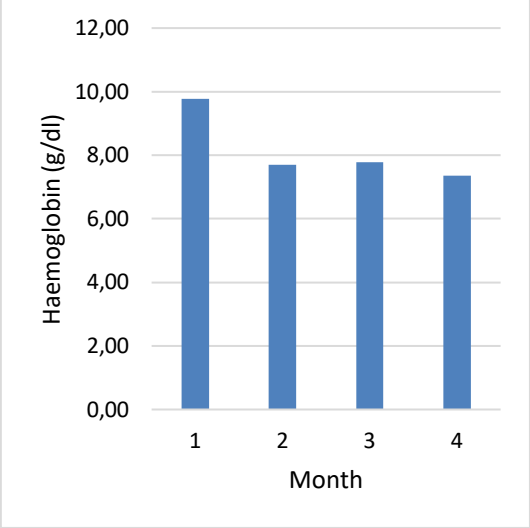
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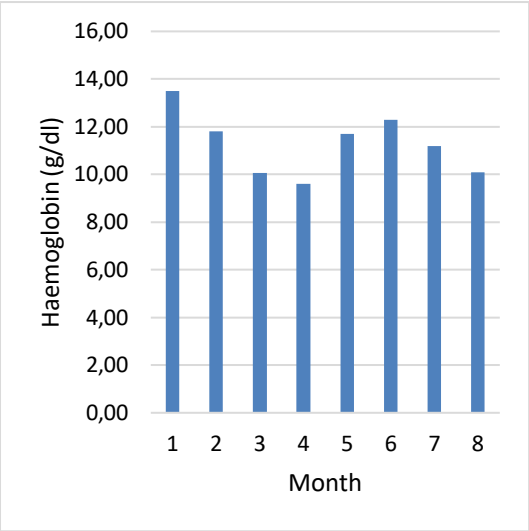
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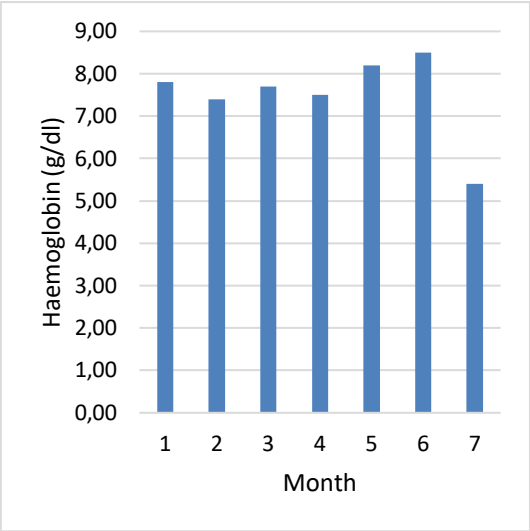
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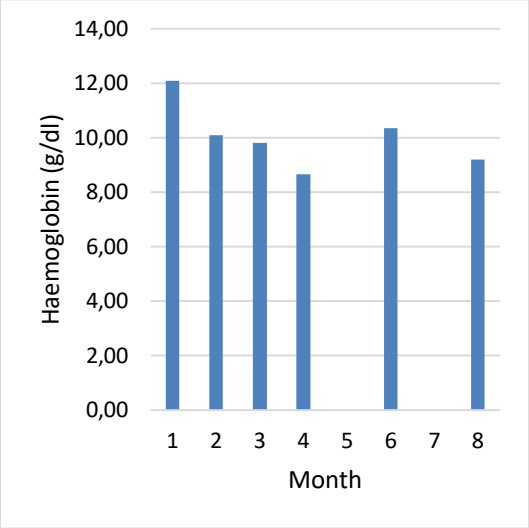
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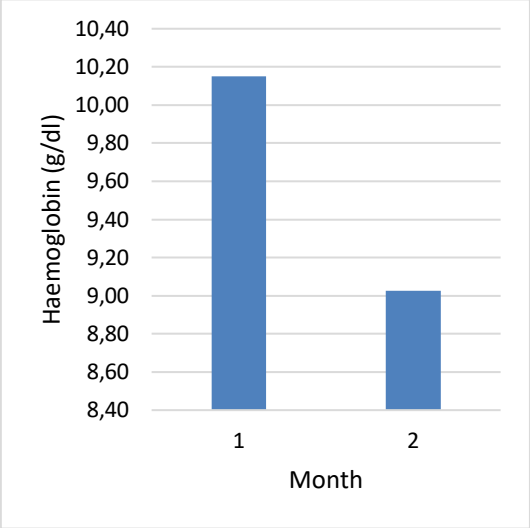
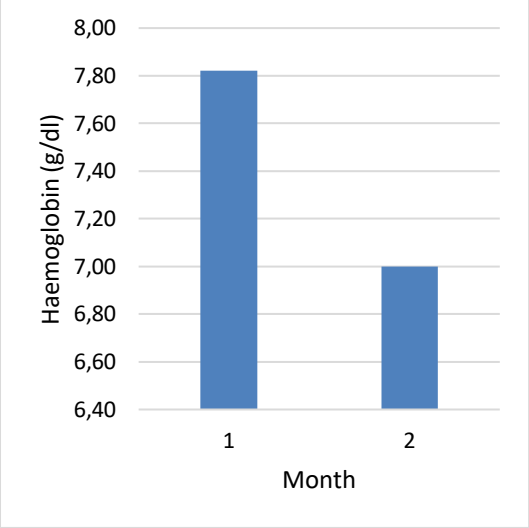
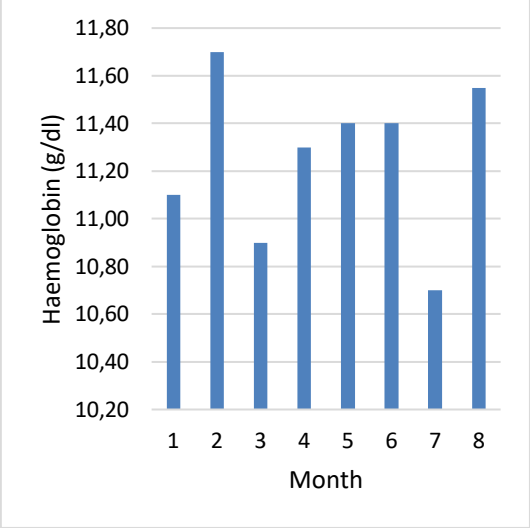
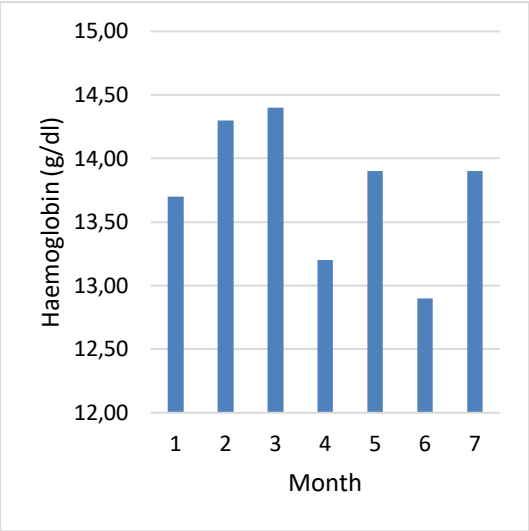
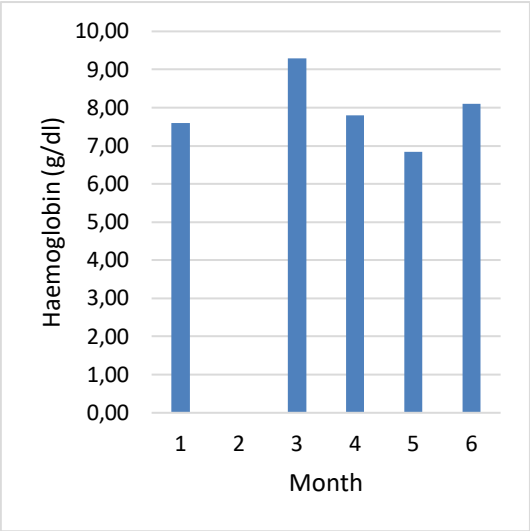
1 2 3 4 5 6 7 8
Month

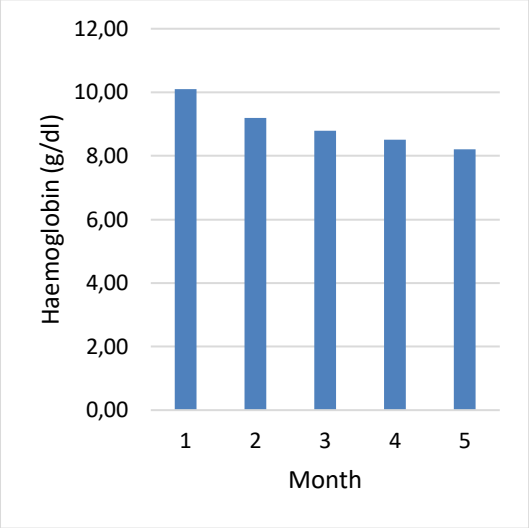

10,40
10,20
10,00
9,80
9,60
9,40
9,20
9,00
8,80
8,60
8,40
Haemoglobin (g/dl)
1 2
Month

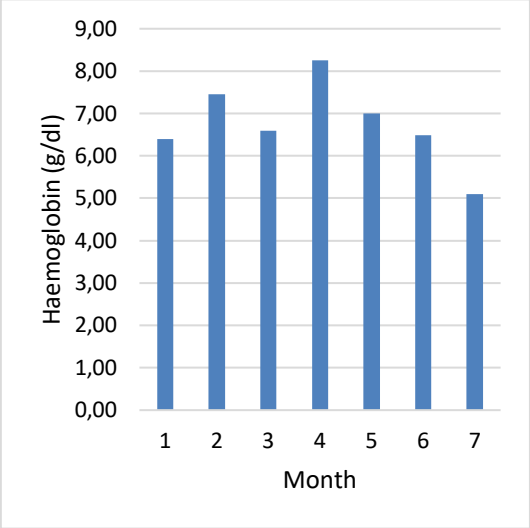

8,00
7,80
7,60
7,40
7,20
7,00
6,80
6,60
6,40
Haemoglobin (g/dl)
1 2
Month

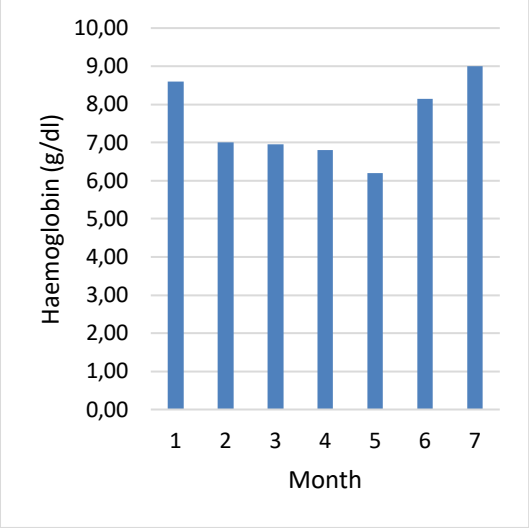

11,80
11,60
11,40
11,20
11,00
10,80
10,60
10,40
10,20
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

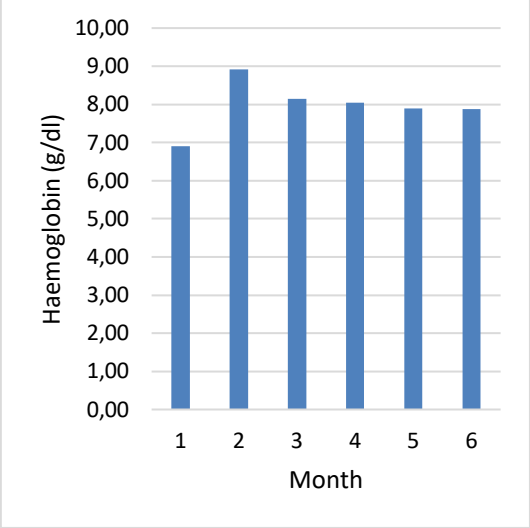

15,00
14,50
14,00
13,50
13,00
12,50
12,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

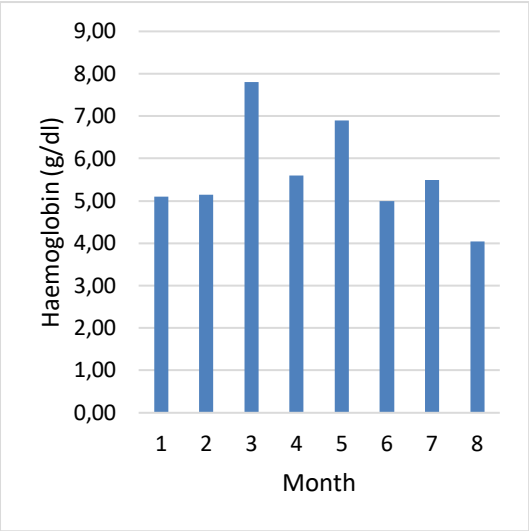

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6
Month

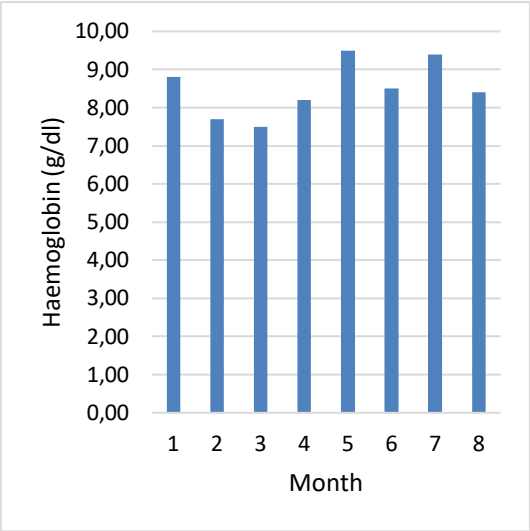

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5
Month

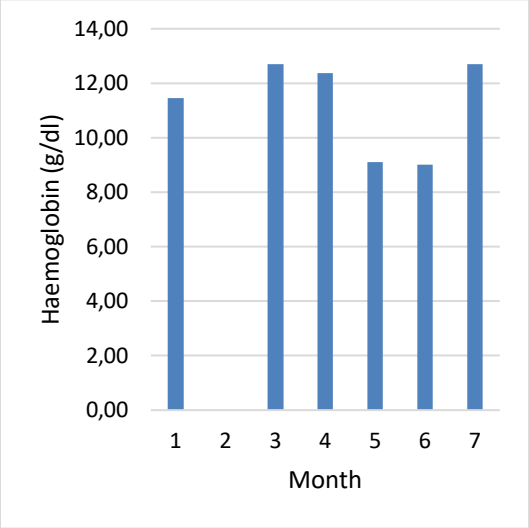

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

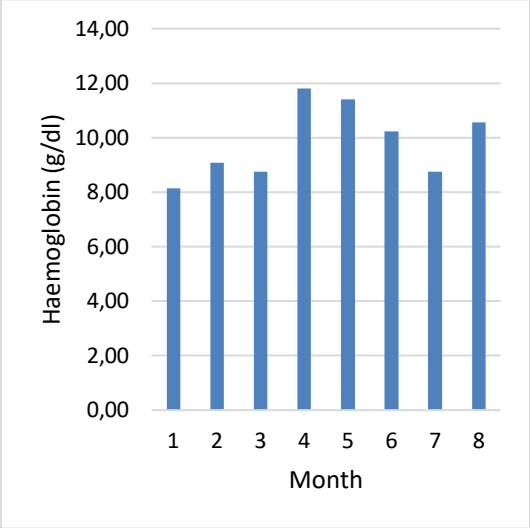

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

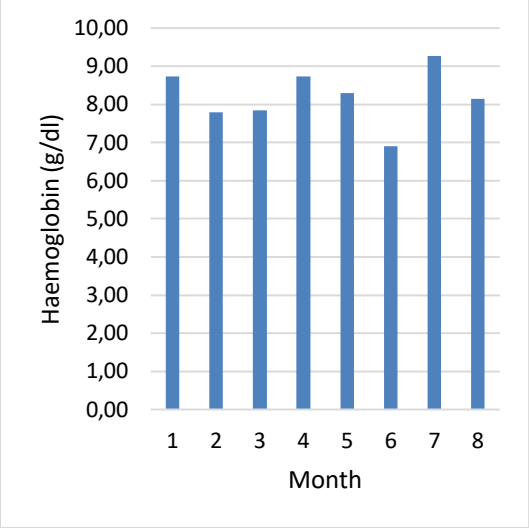

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6
Month

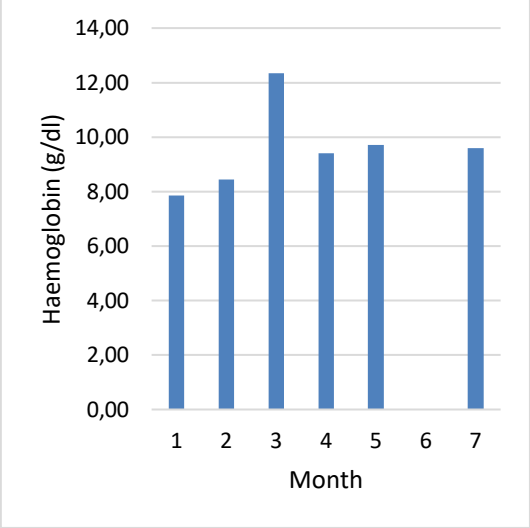

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

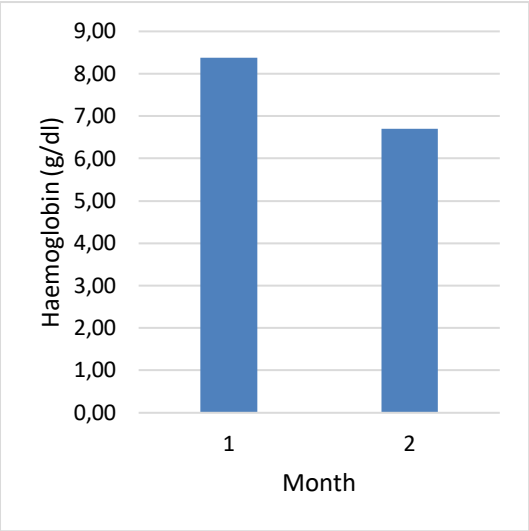

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

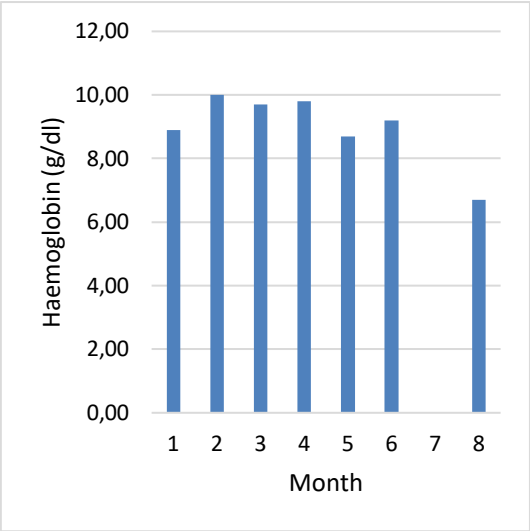

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

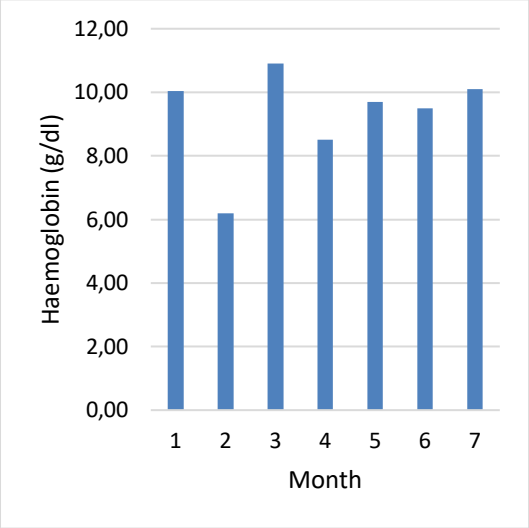

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

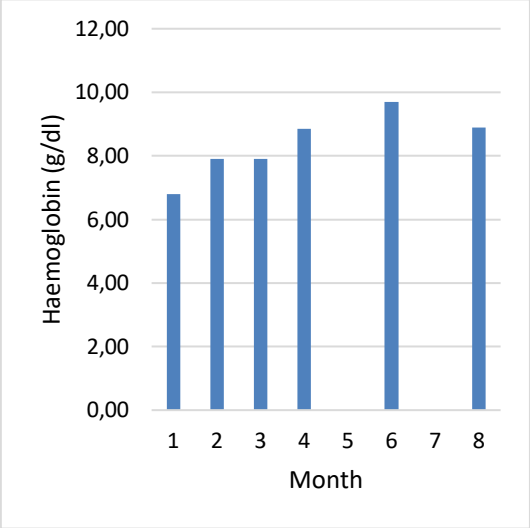

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

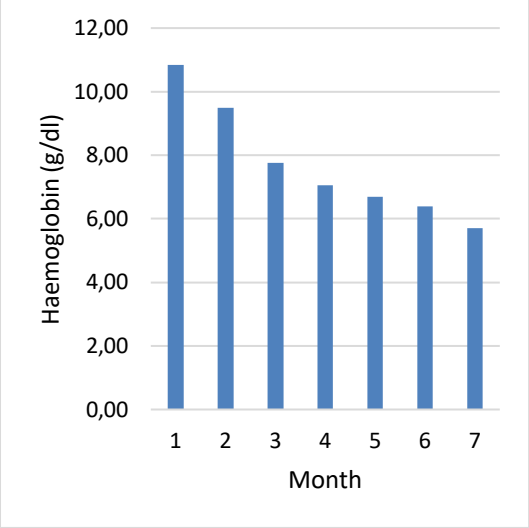

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

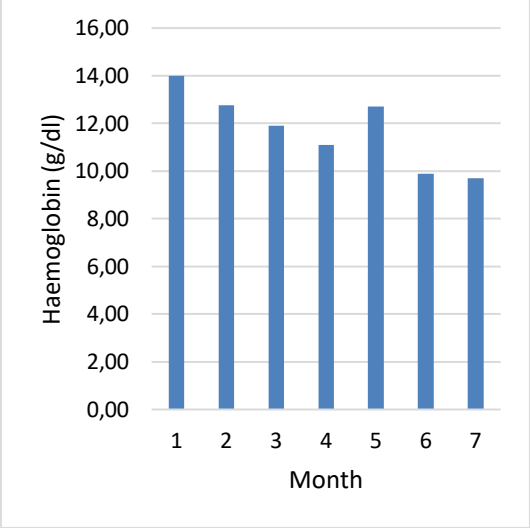

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1
2
Month

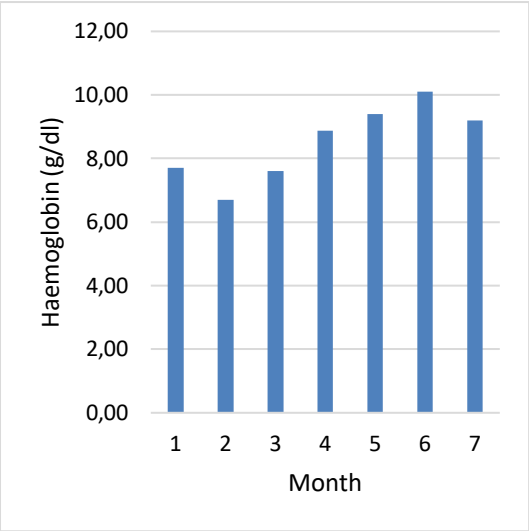

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month


12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

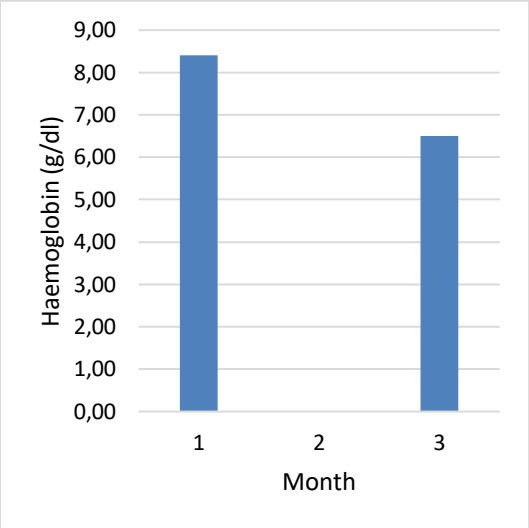

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

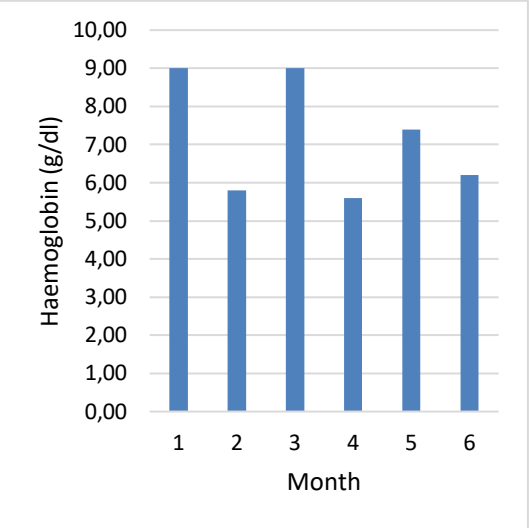

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

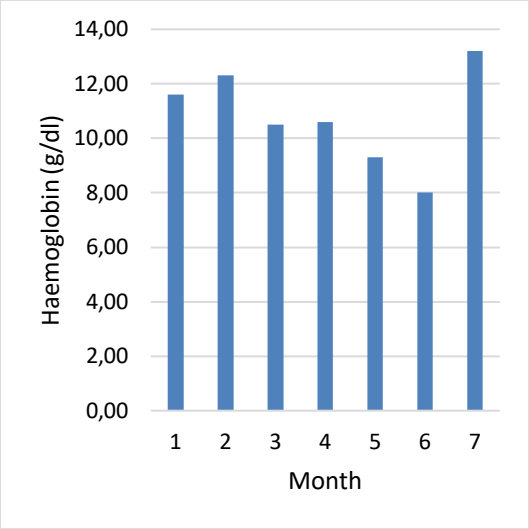

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

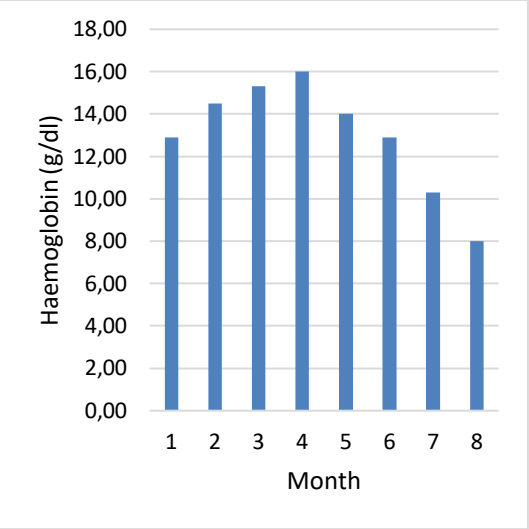

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1
2
3
4
5
6
7
Month

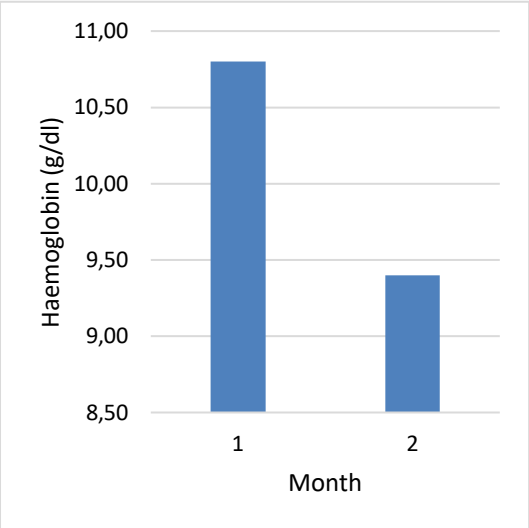
Appendix 6: Additional serum haemoglobin graphs for patients in the peritoneal dialysis treatment group

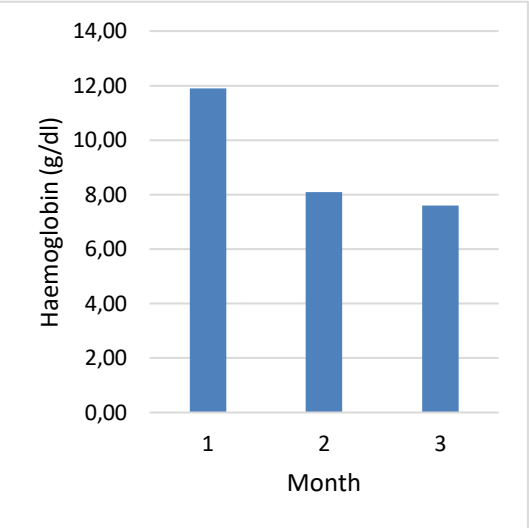


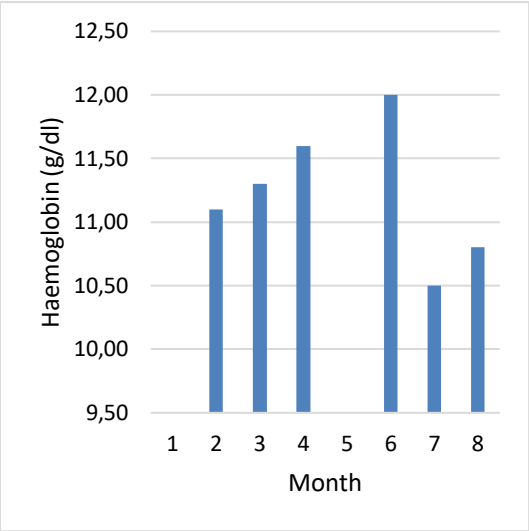


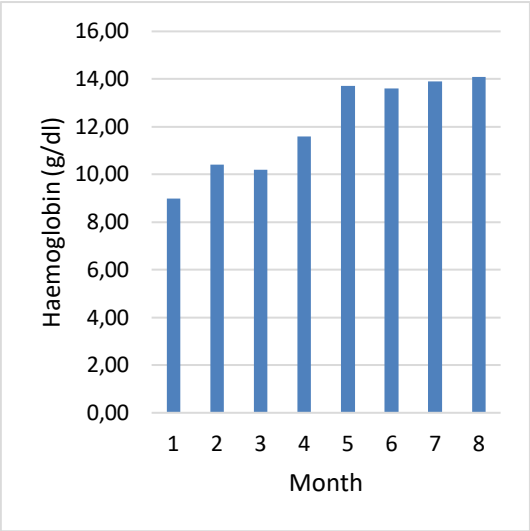


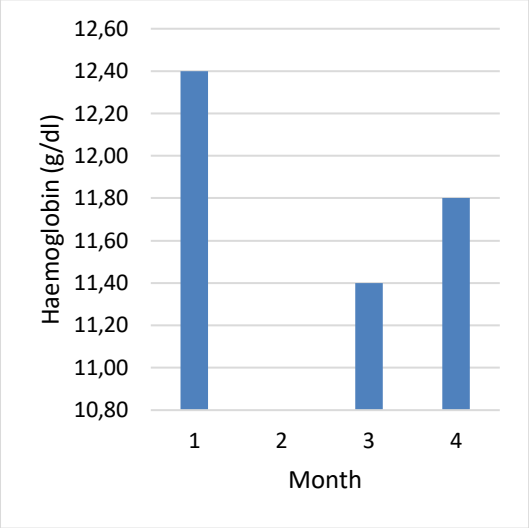


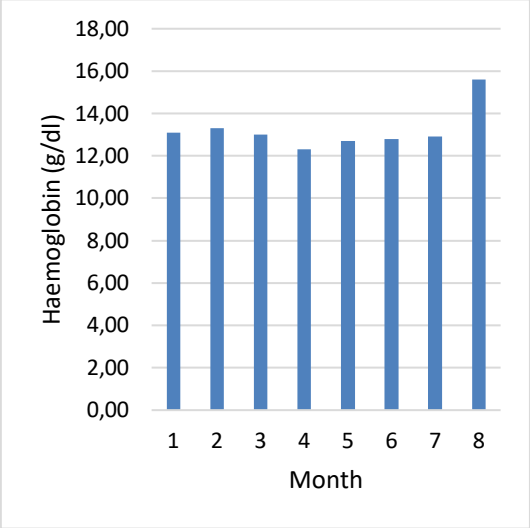


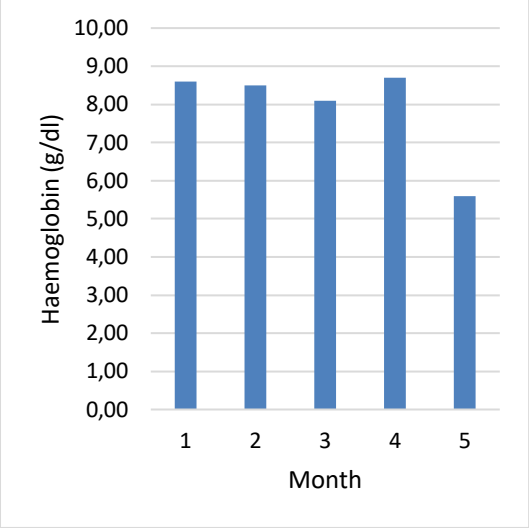


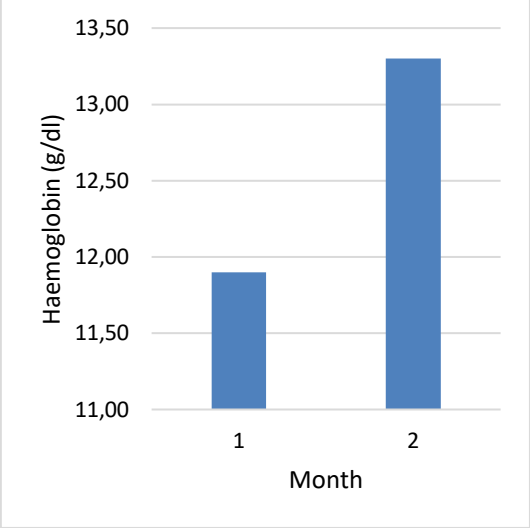

12,50
12,00
11,50
11,00
10,50
10,00
9,50
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

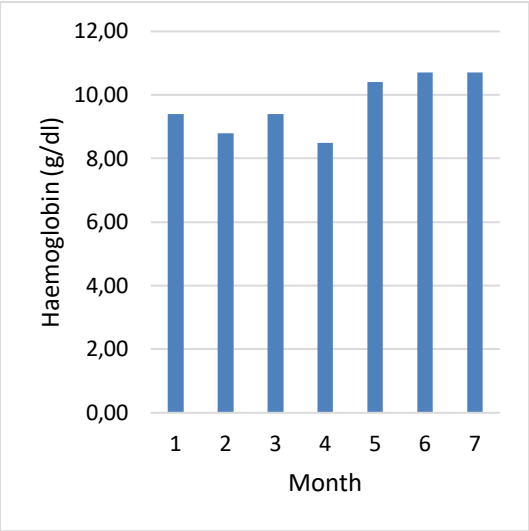

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

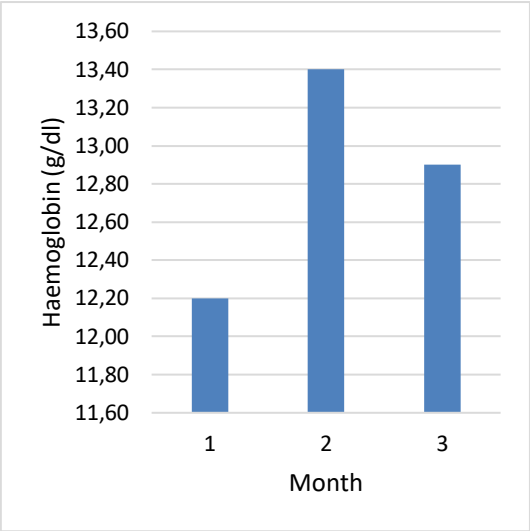

12,60
12,40
12,20
12,00
11,80
11,60
11,40
11,20
11,00
10,80
Haemoglobin (g/dl)
1 2 3 4
Month

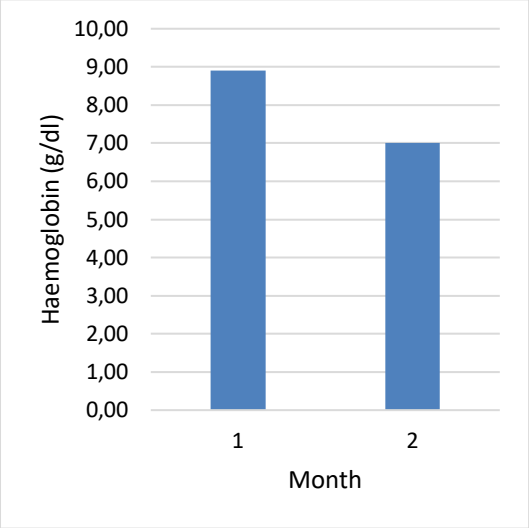

18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

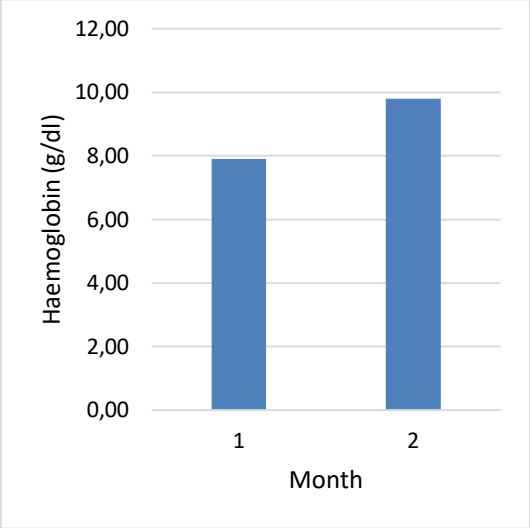

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5
Month

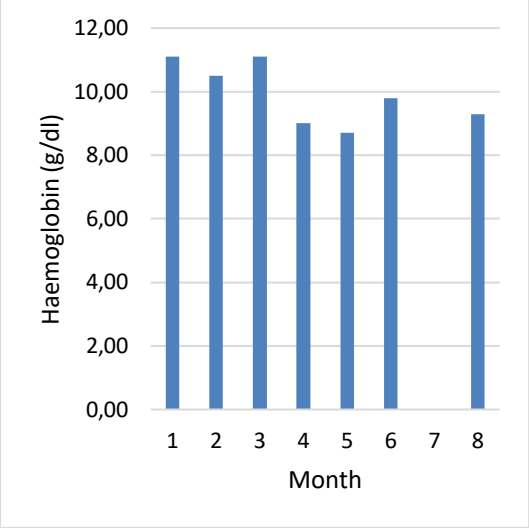

13,50
13,00
12,50
12,00
11,50
11,00
Haemoglobin (g/dl)
1 2
Month

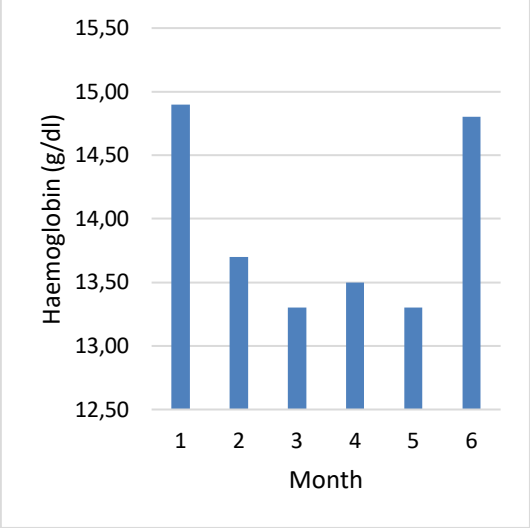

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

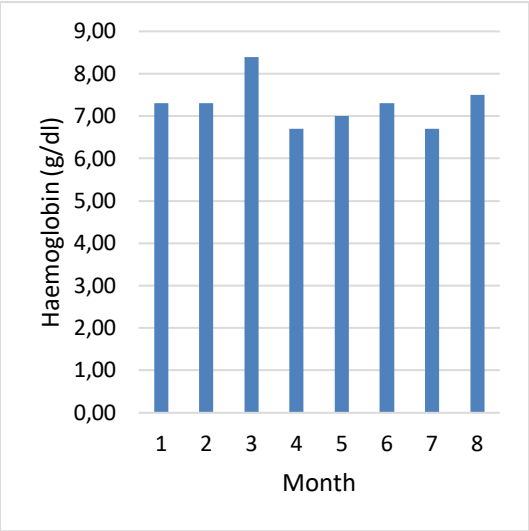

13,60
13,40
13,20
13,00
12,80
12,60
12,40
12,20
12,00
11,80
11,60
Haemoglobin (g/dl)
1 2 3
Month

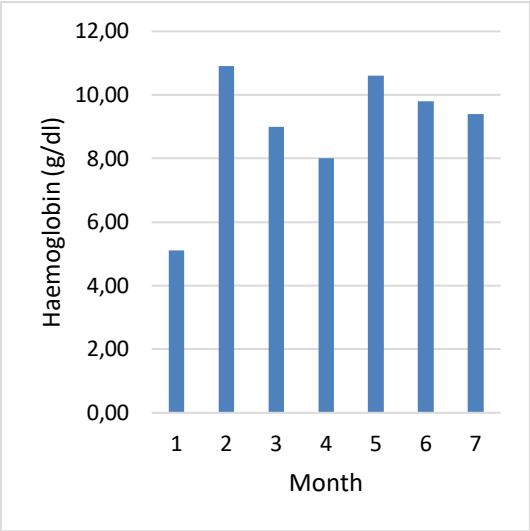

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2
Month

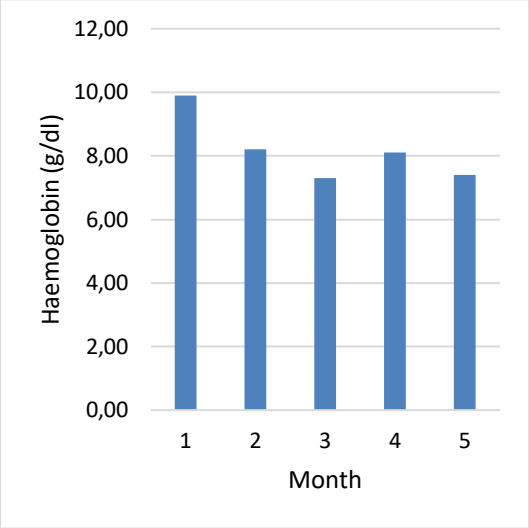

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2
Month

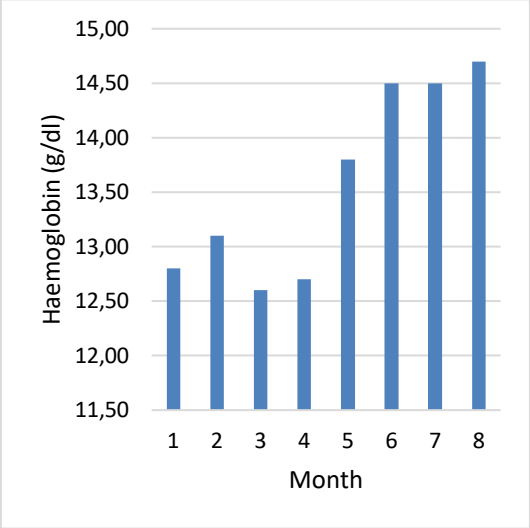

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

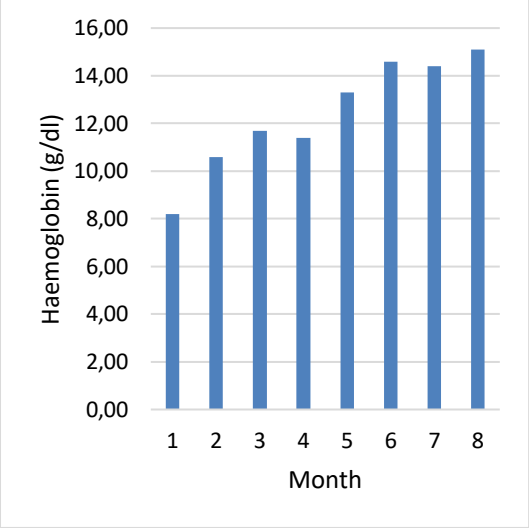

15,50
15,00
14,50
14,00
13,50
13,00
12,50
Haemoglobin (g/dl)
1 2 3 4 5 6
Month

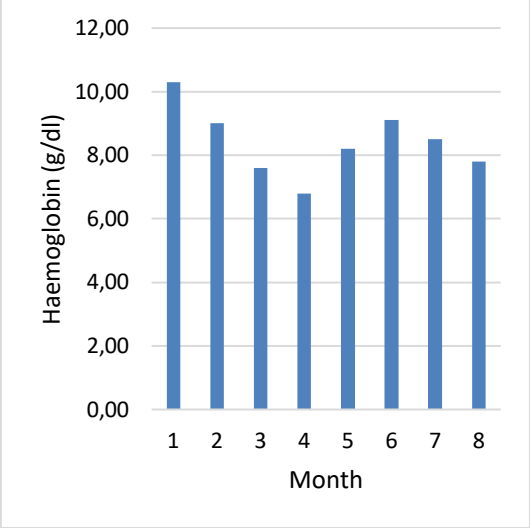

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

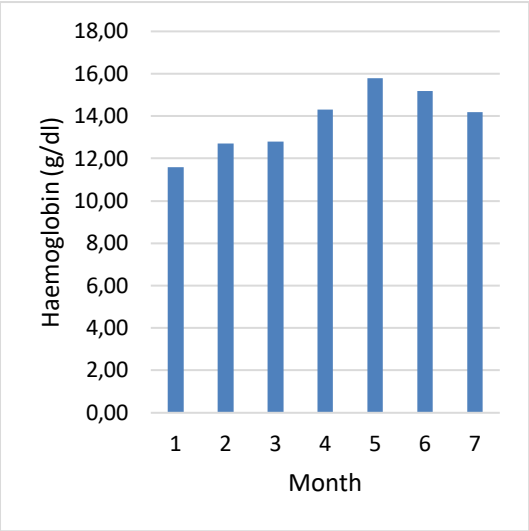

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

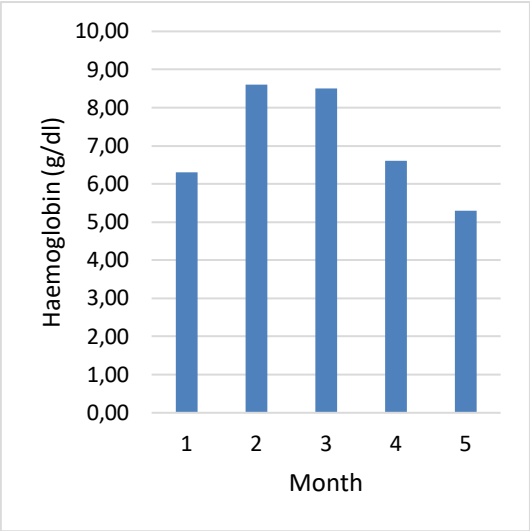

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5
Month

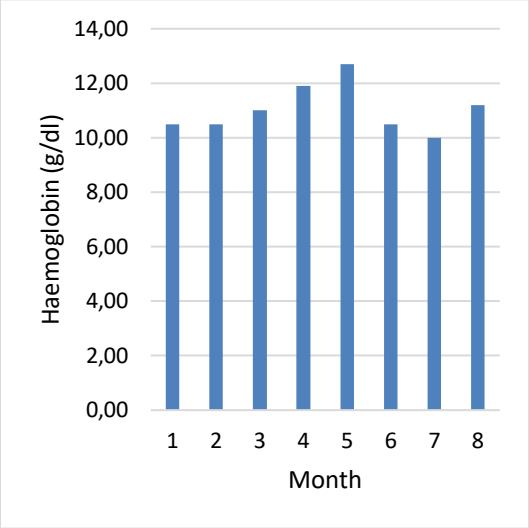

15,00
14,50
14,00
13,50
13,00
12,50
12,00
11,50
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

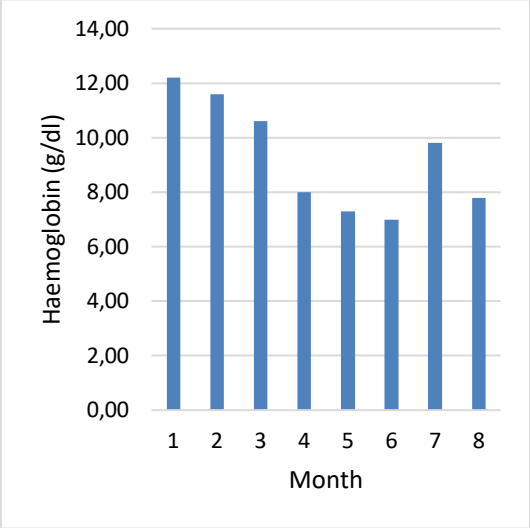

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

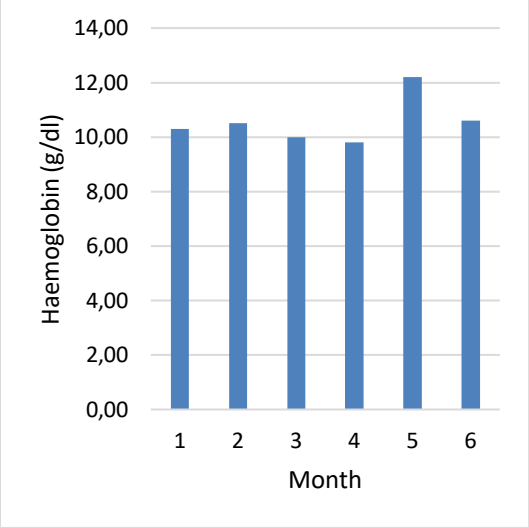

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

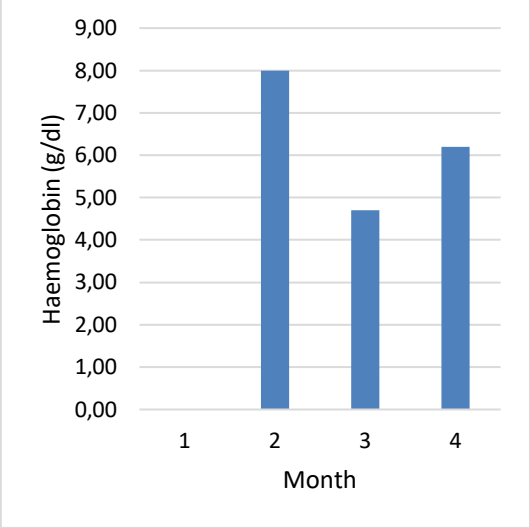

18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

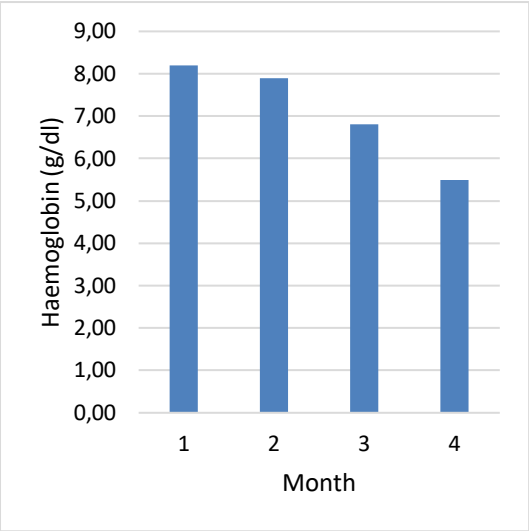

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5
Month

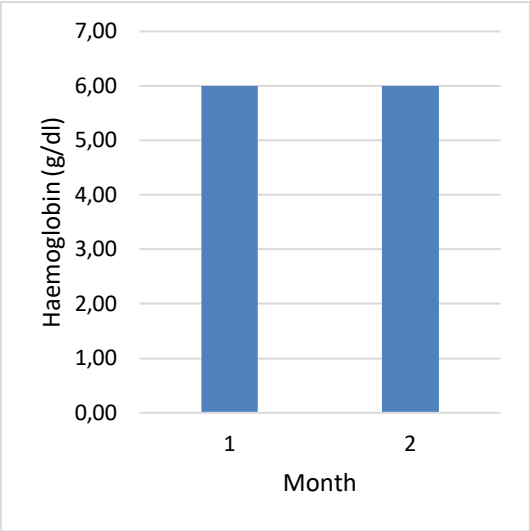

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

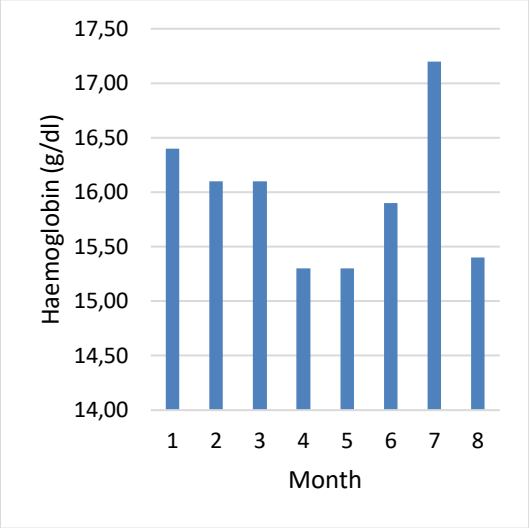

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

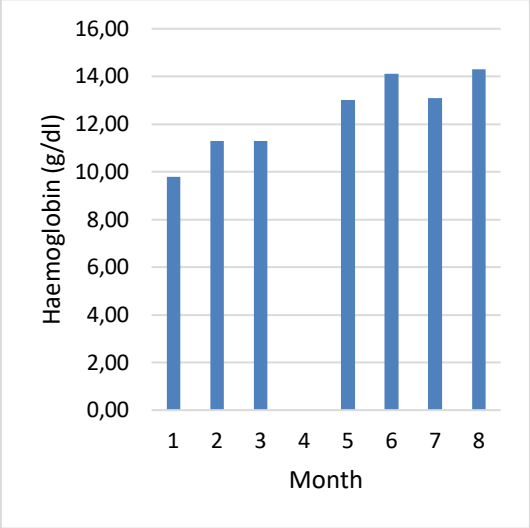

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6
Month

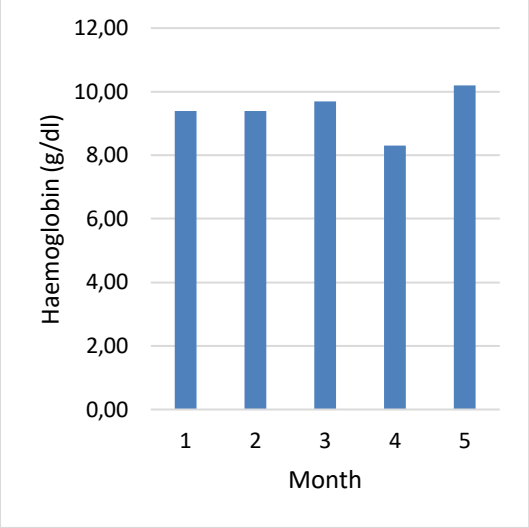

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1 2 3 4
Month

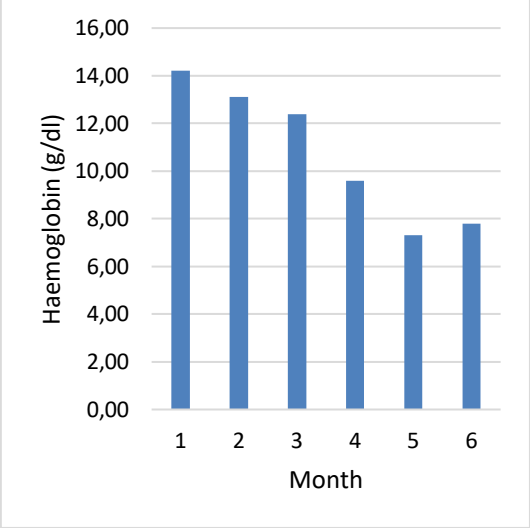

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1
2
3
4
Month

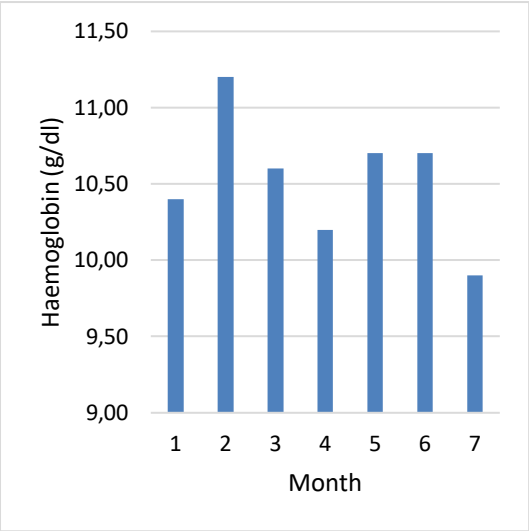

7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Haemoglobin (g/dl)
1
2
Month

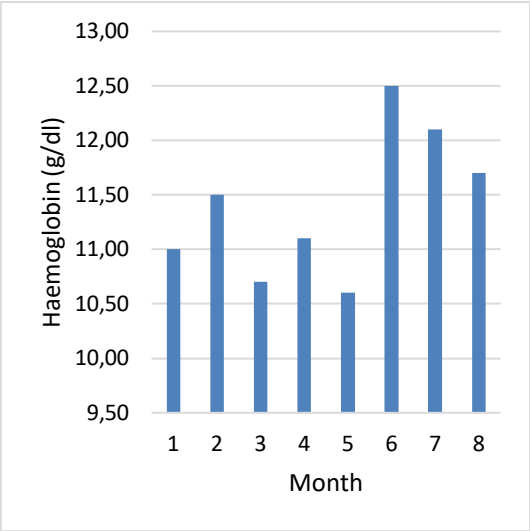

17,50
17,00
16,50
16,00
15,50
15,00
14,50
14,00
Haemoglobin (g/dl)
1
2
3
4
5
6
7
8
Month

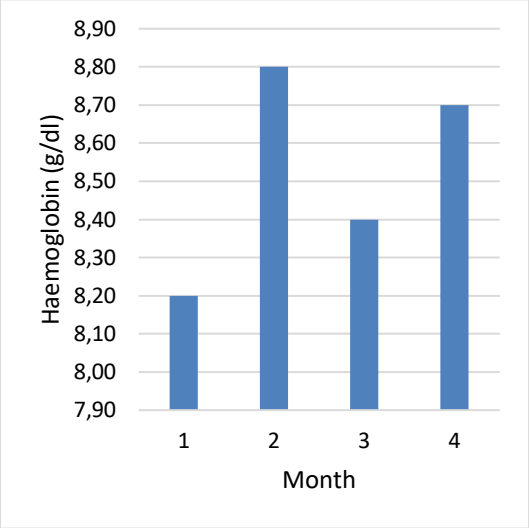

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1
2
3
4
5
6
7
8
Month

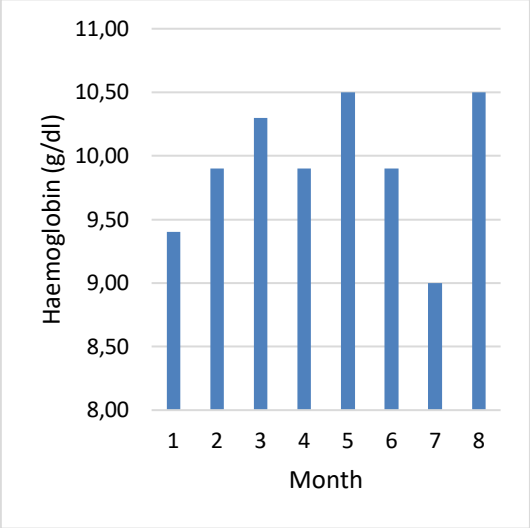

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1
2
3
4
5
Month

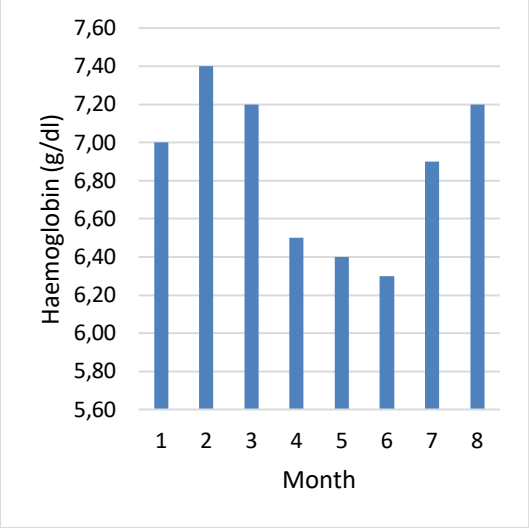

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1
2
3
4
5
6
Month

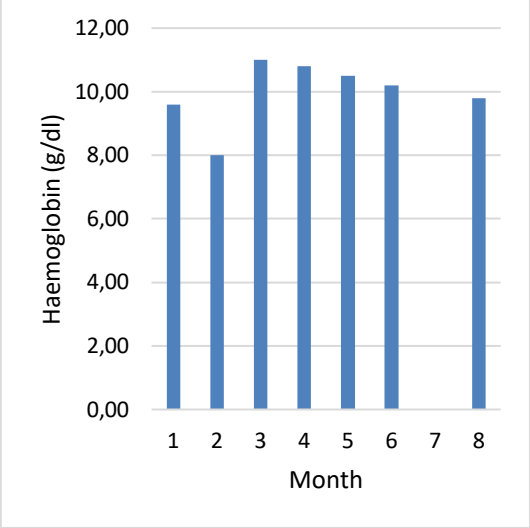

11,50
11,00
10,50
10,00
9,50
9,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

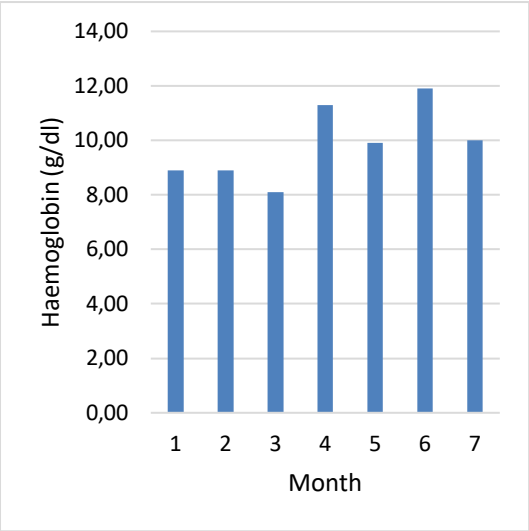

13,00
12,50
12,00
11,50
11,00
10,50
10,00
9,50
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

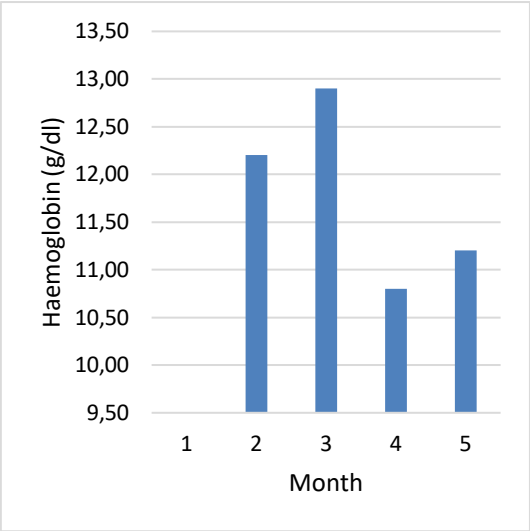

8,90
8,80
8,70
8,60
8,50
8,40
8,30
8,20
8,10
8,00
7,90
Haemoglobin (g/dl)
1 2 3 4
Month

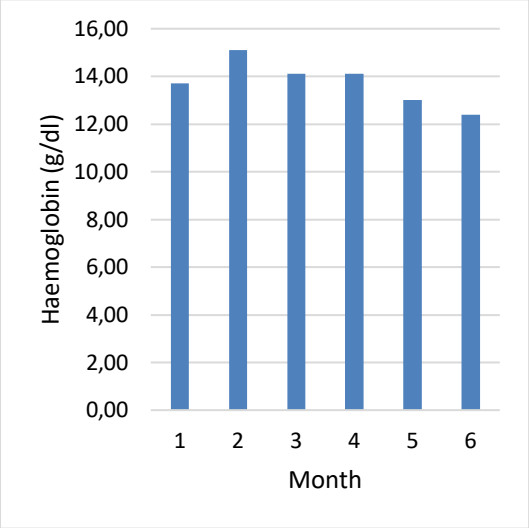

11,00
10,50
10,00
9,50
9,00
8,50
8,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

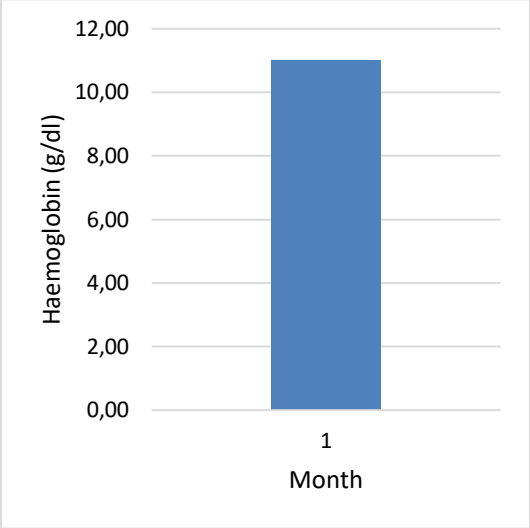

7,60
7,40
7,20
7,00
6,80
6,60
6,40
6,20
6,00
5,80
5,60
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

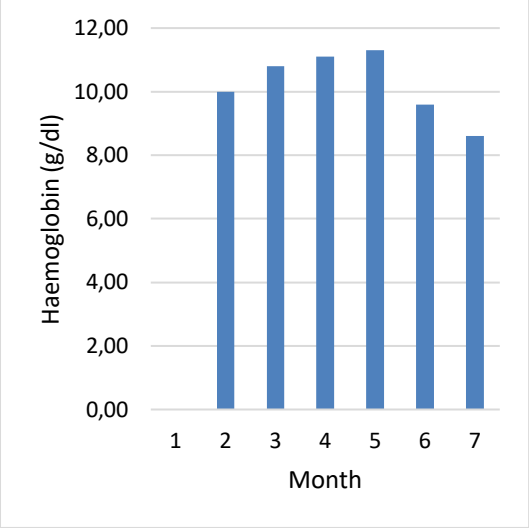

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

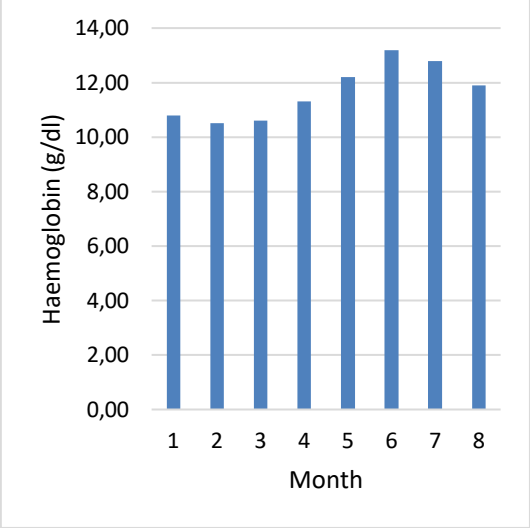

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

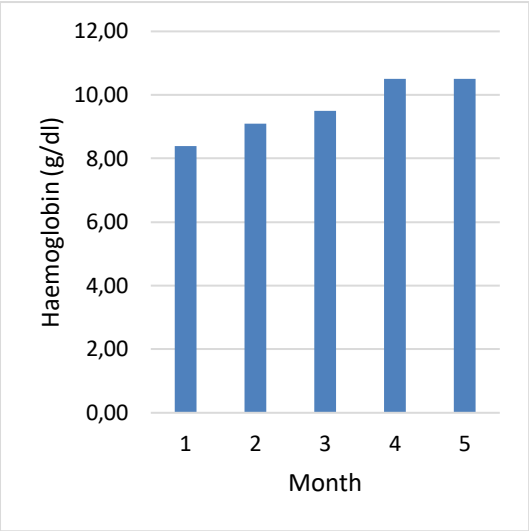

13,50
13,00
12,50
12,00
11,50
11,00
10,50
10,00
9,50
Haemoglobin (g/dl)
1 2 3 4 5
Month

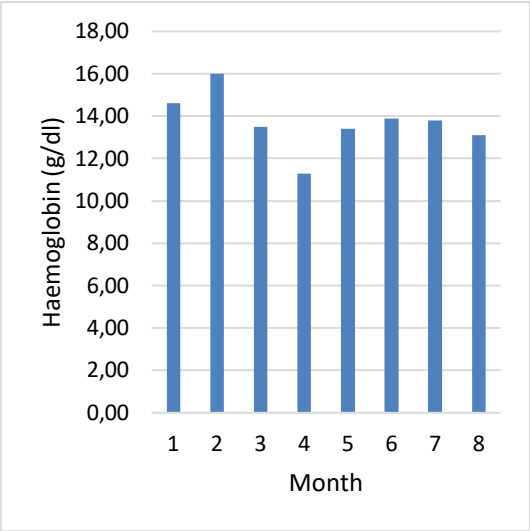

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6
Month


12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1
Month

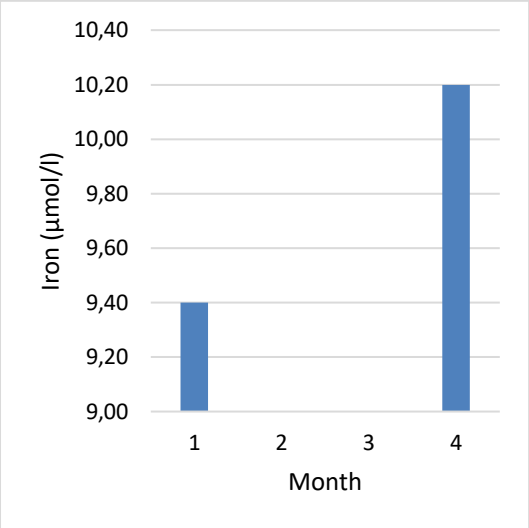

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7
Month

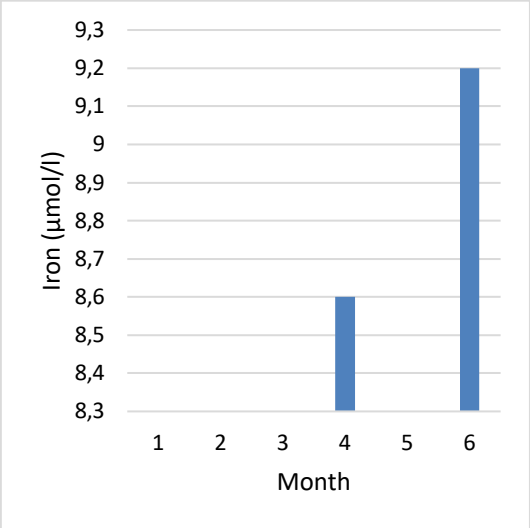

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1 2 3 4 5 6 7 8
Month

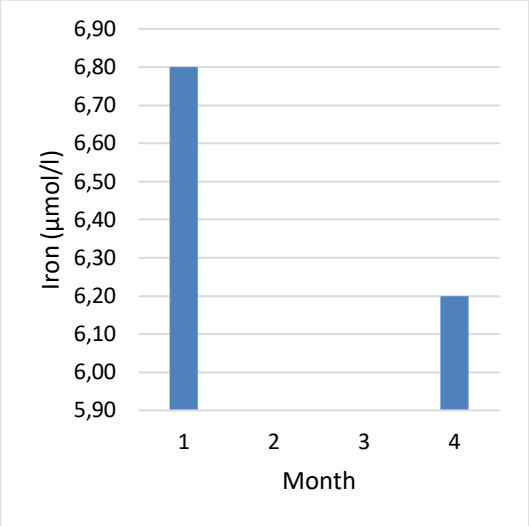

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1
2
3
4
5
Month

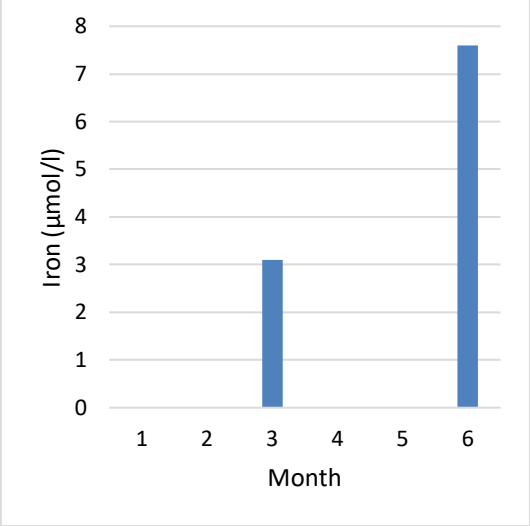

18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Haemoglobin (g/dl)
1
2
3
4
5
6
7
8
Month

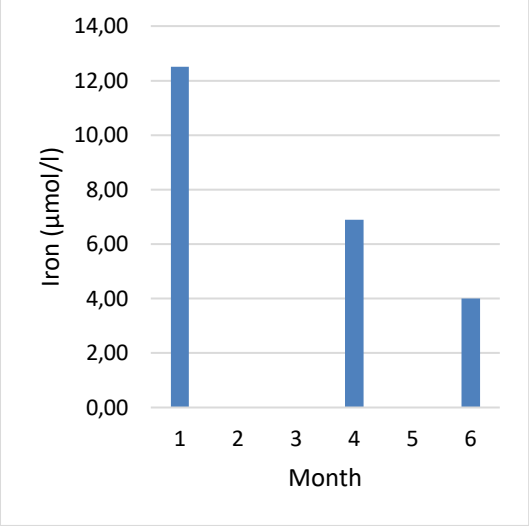
Appendix 7: Additional serum iron graphs for patients in the haemodialysis treatment group

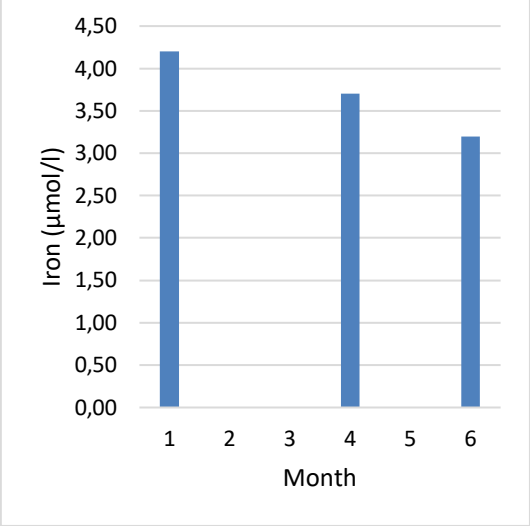


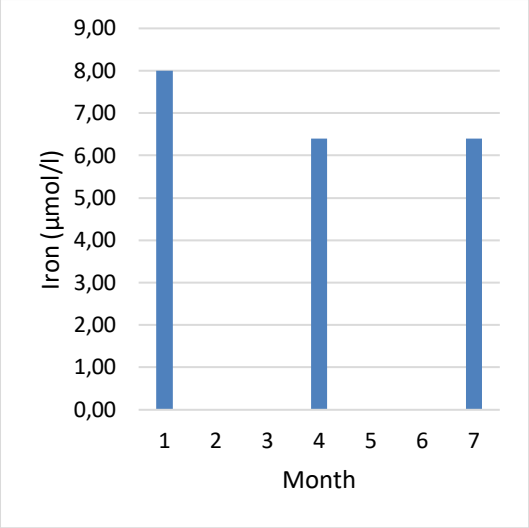


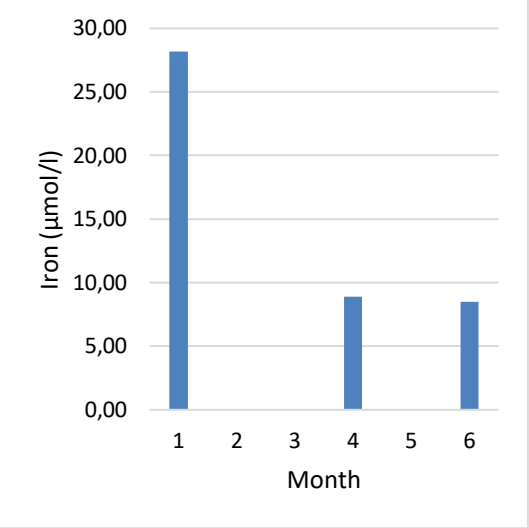


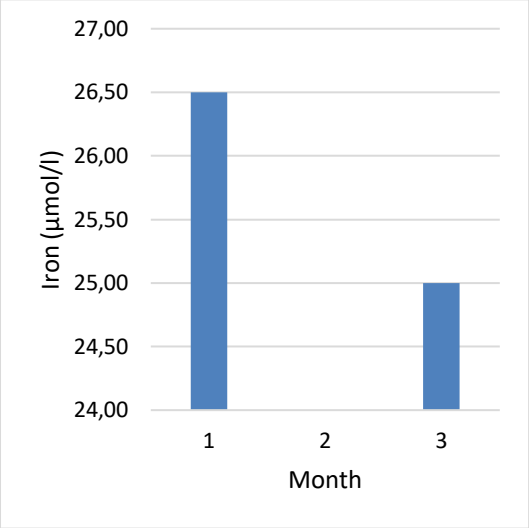


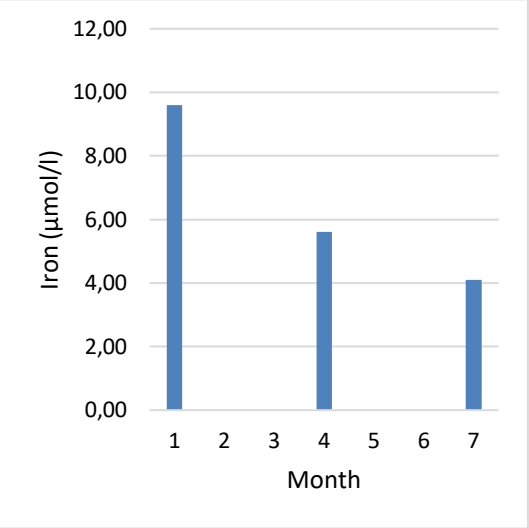


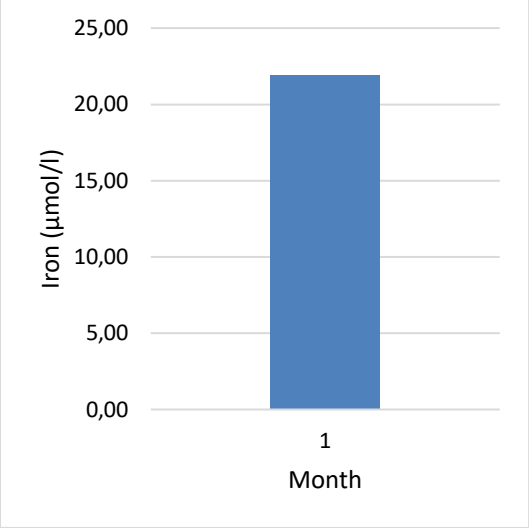


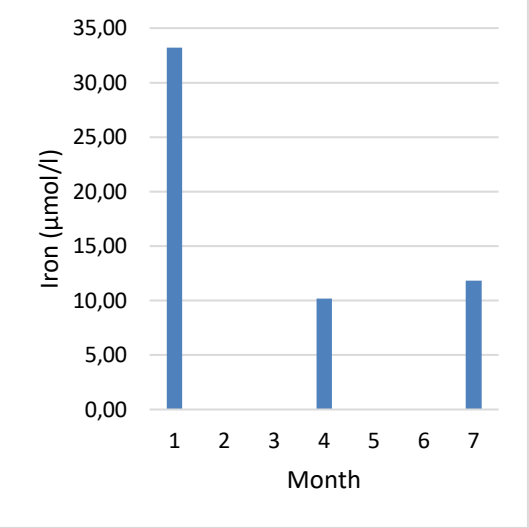

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1 2 3 4 5 6 7
Month

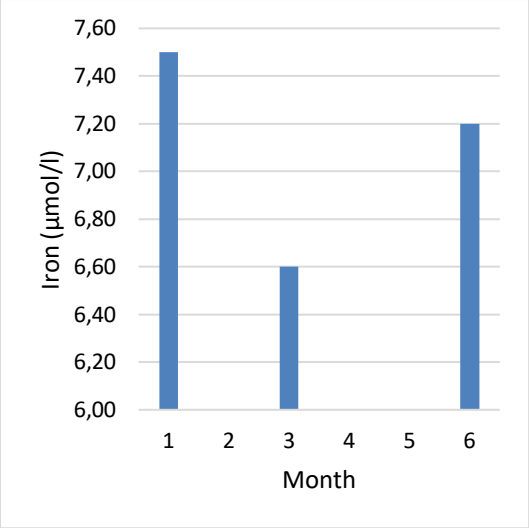

30,00
25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

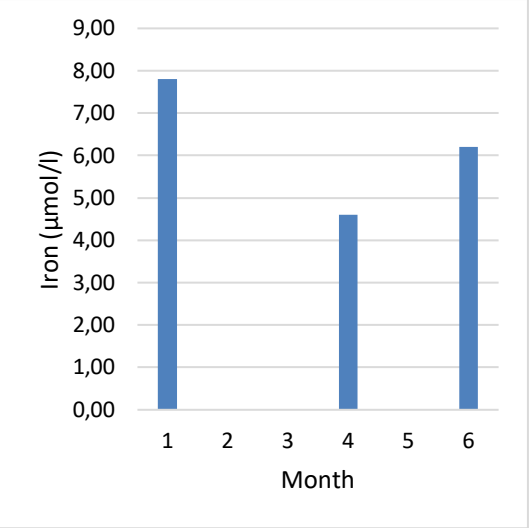

27,00
26,50
26,00
25,50
25,00
24,50
24,00
Iron (µmol/l)
1 2 3
Month

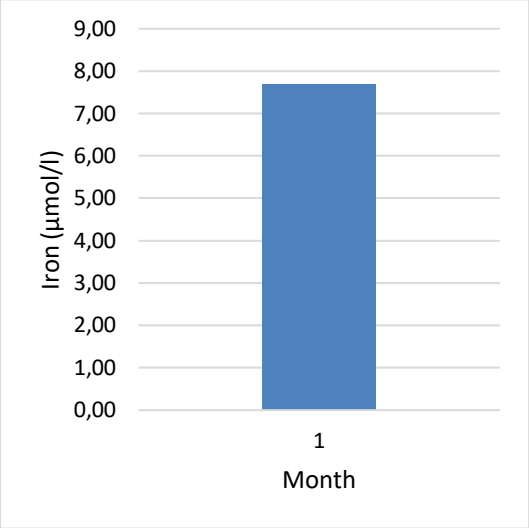

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6 7
Month

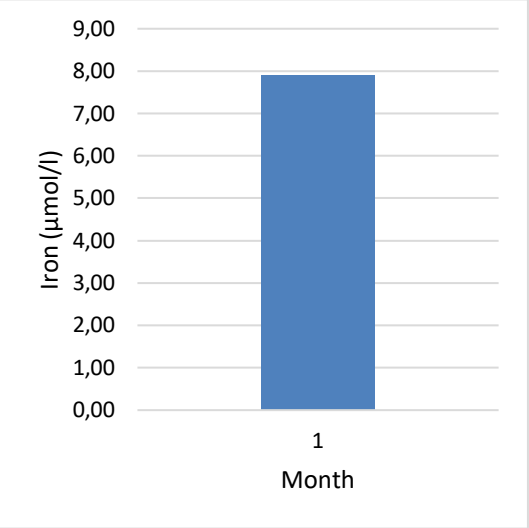

25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
Month

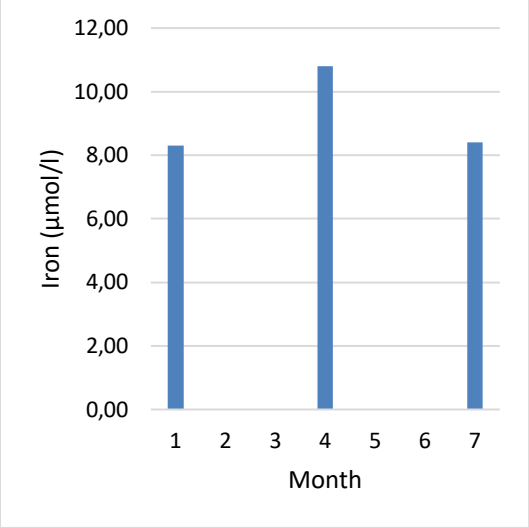

35,00
30,00
25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1 2 3 4 5 6 7
Month

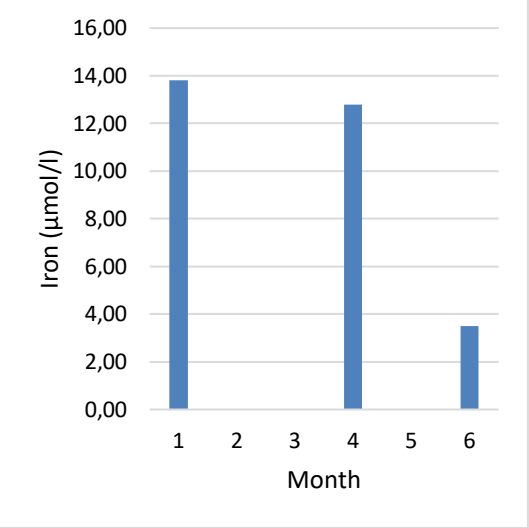

7,60
7,40
7,20
7,00
6,80
6,60
6,40
6,20
6,00
Iron (µmol/l)
1 2 3 4 5 6
Month

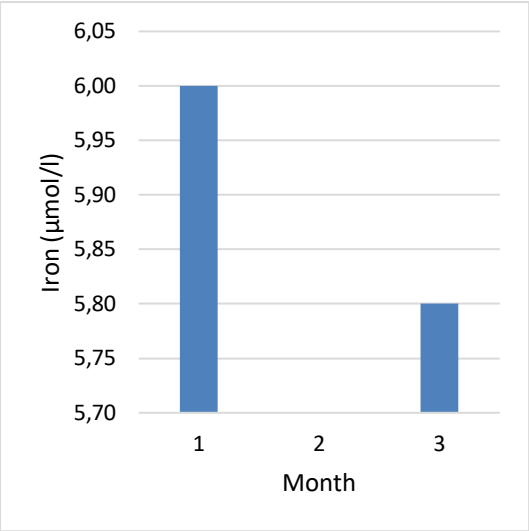

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

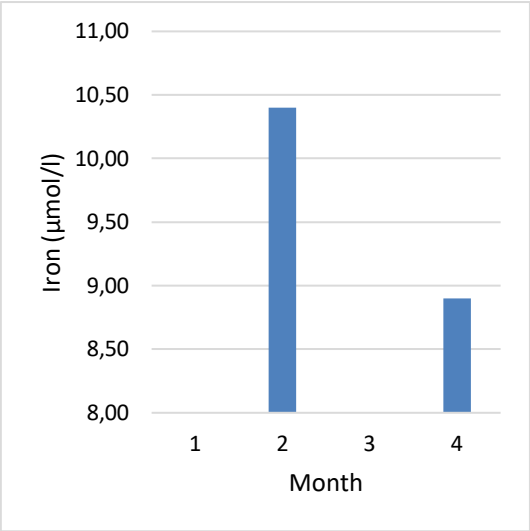

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month

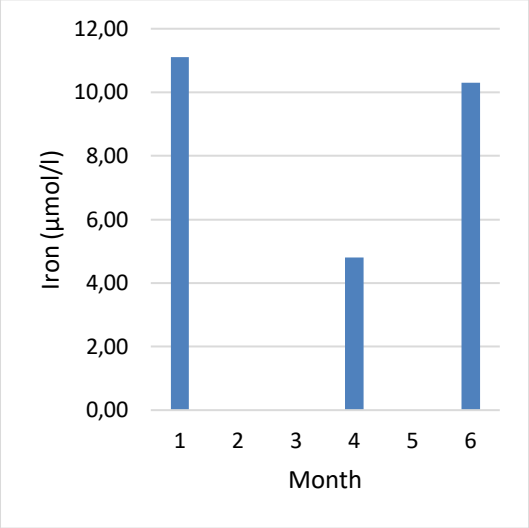

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month

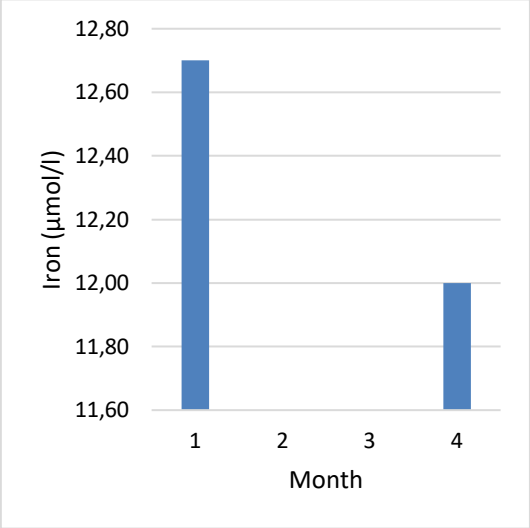

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6 7
Month

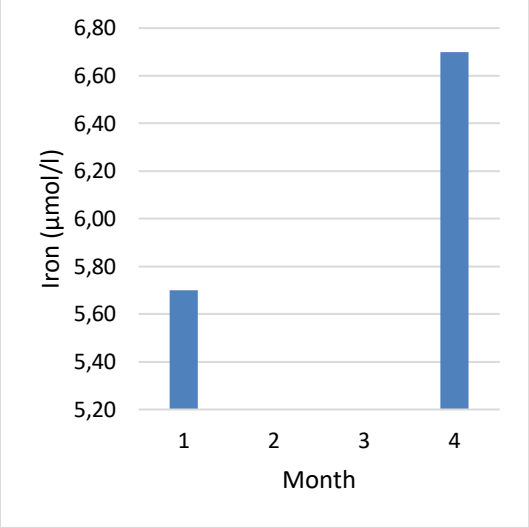

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

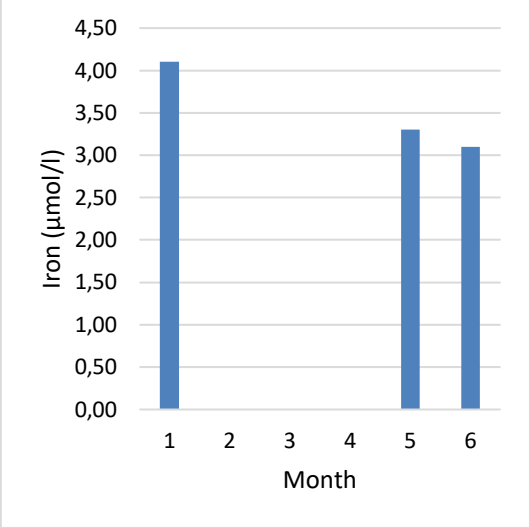

6,05
6,00
5,95
5,90
5,85
5,80
5,75
5,70
Iron (µmol/l)
1
2
3
Month

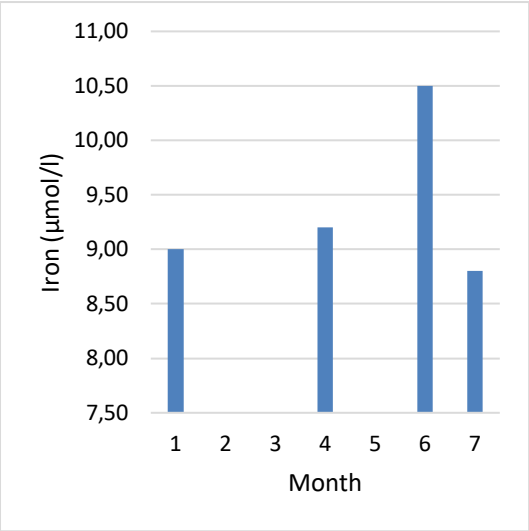

11,00
10,50
10,00
9,50
9,00
8,50
8,00
Iron (µmol/l)
1
2
3
4
Month

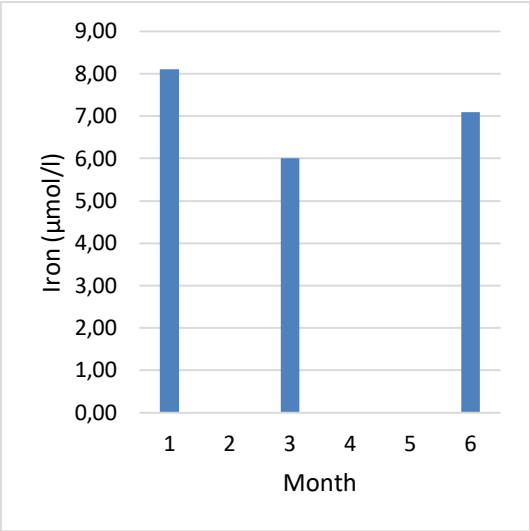

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
2
3
4
5
6
Month

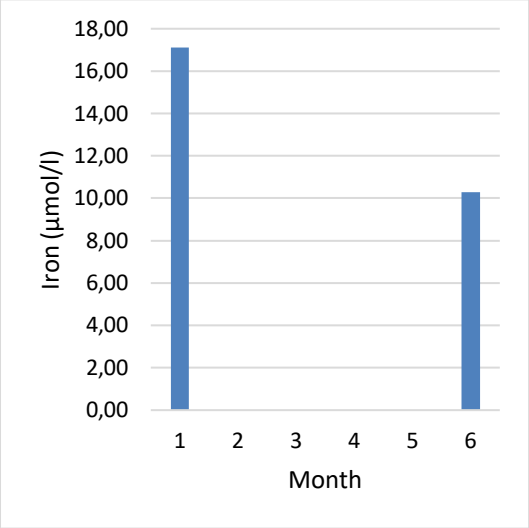

12,80
12,60
12,40
12,20
12,00
11,80
11,60
Iron (µmol/l)
1
2
3
4
Month

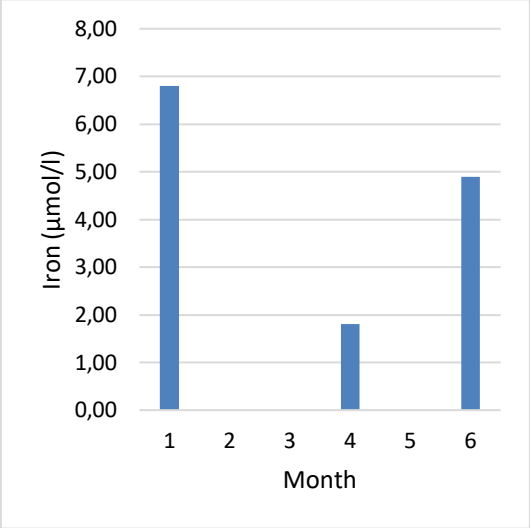

6,80
6,60
6,40
6,20
6,00
5,80
5,60
5,40
5,20
Iron (µmol/l)
1
2
3
4
Month

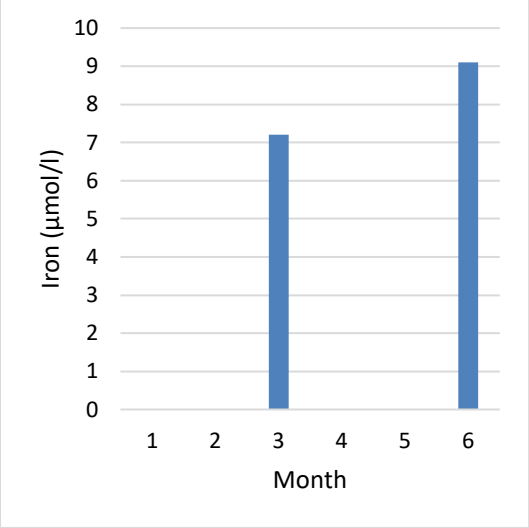

4,50
4,00
3,50
3,00
2,50
2,00
1,50
1,00
0,50
0,00
Iron (µmol/l)
1
2
3
4
5
6
Month

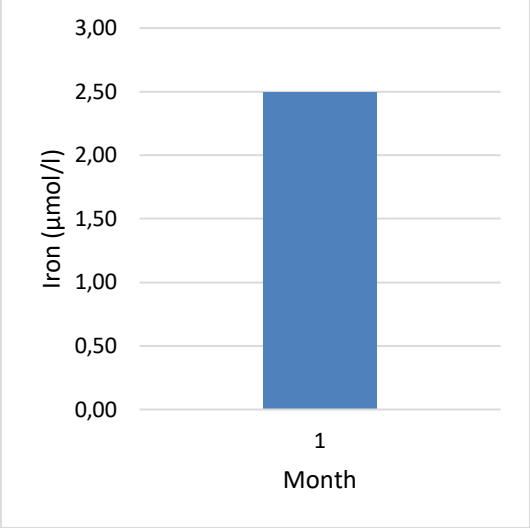

11,00
10,50
10,00
9,50
9,00
8,50
8,00
7,50
Iron (µmol/l)
1 2 3 4 5 6 7
Month

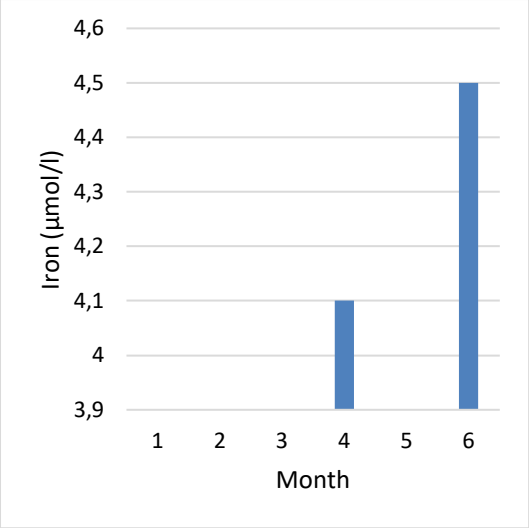

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

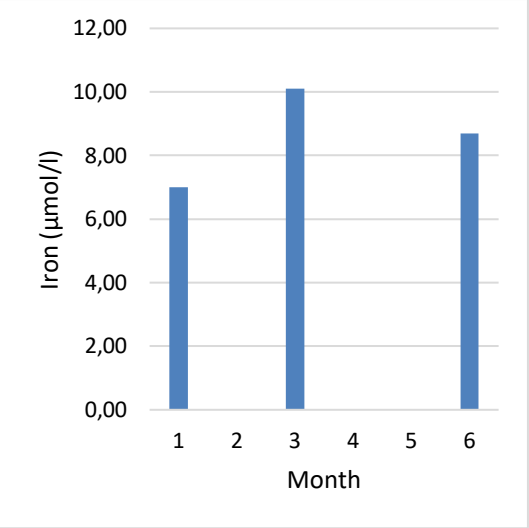

18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

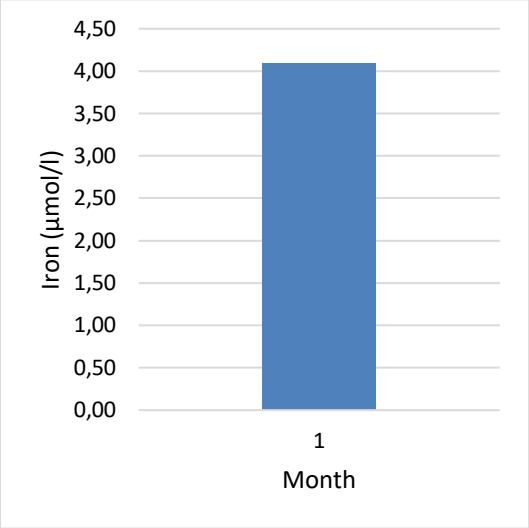

8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

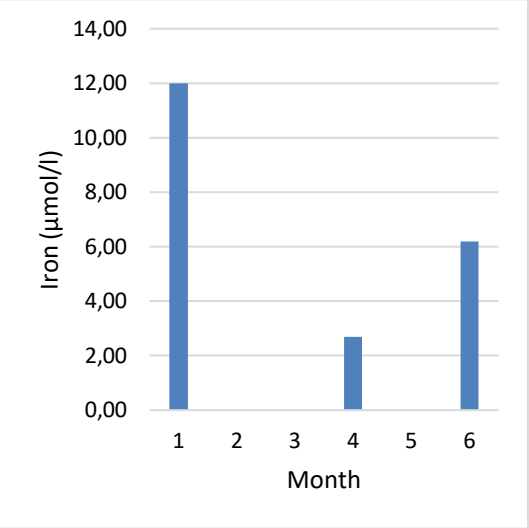

10
9
8
7
6
5
4
3
2
1
0
Iron (µmol/l)
1 2 3 4 5 6
Month

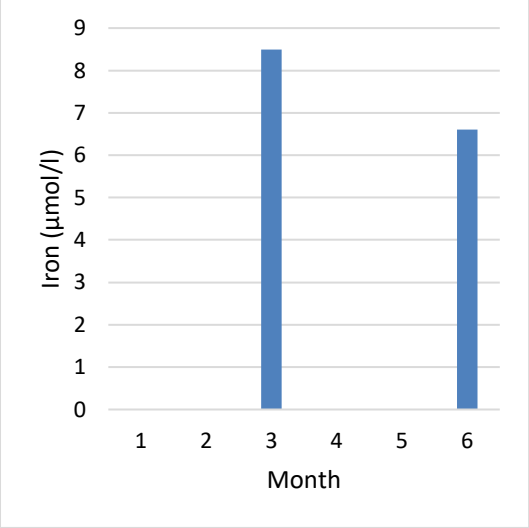

3,00
2,50
2,00
1,50
1,00
0,50
0,00
Iron (µmol/l)
1
Month

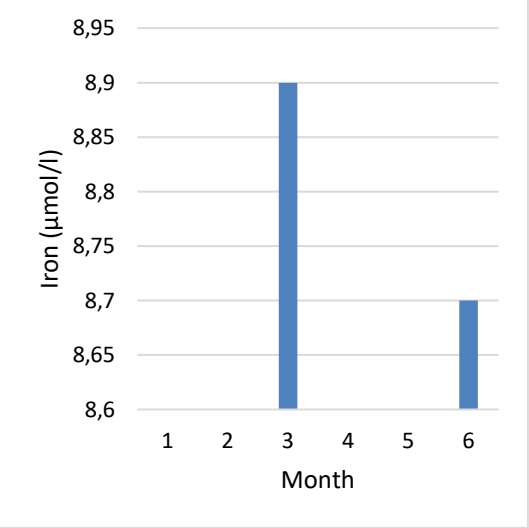

4,6
4,5
4,4
4,3
4,2
4,1
4
3,9
Iron (µmol/l)
1 2 3 4 5 6
Month


12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

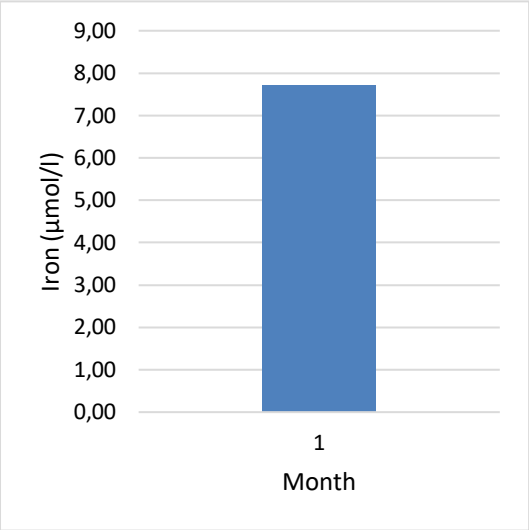

4,50
4,00
3,50
3,00
2,50
2,00
1,50
1,00
0,50
0,00
Iron (µmol/l)
1
Month

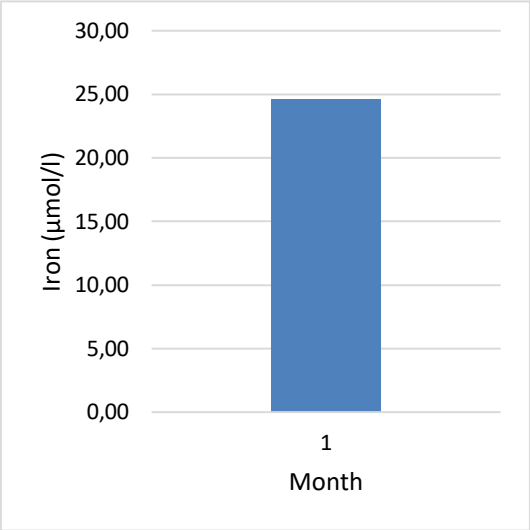

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month

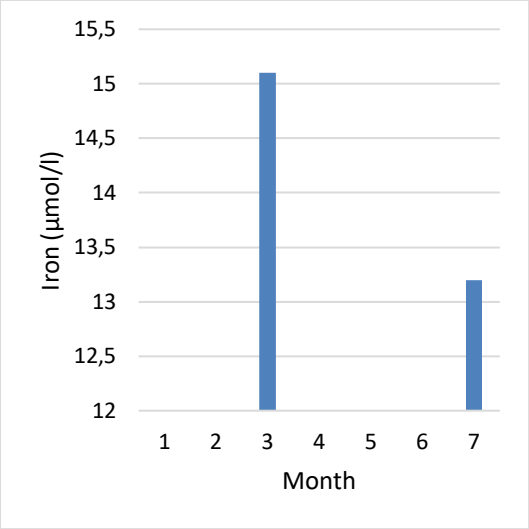

9
8
7
6
5
4
3
2
1
0
Iron (µmol/l)
1 2 3 4 5 6
Month

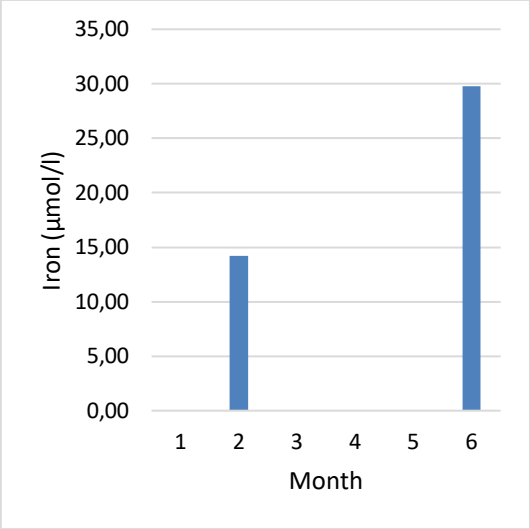

8,95
8,9
8,85
8,8
8,75
8,7
8,65
8,6
Iron (µmol/l)
1 2 3 4 5 6
Month

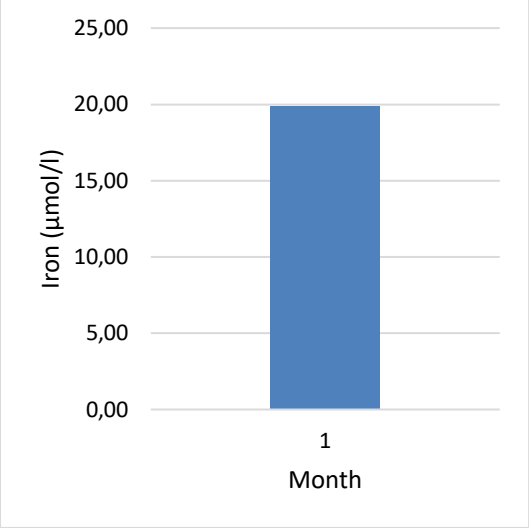
Appendix 8: Additional serum iron graphs for patients in the peritoneal dialysis treatment group

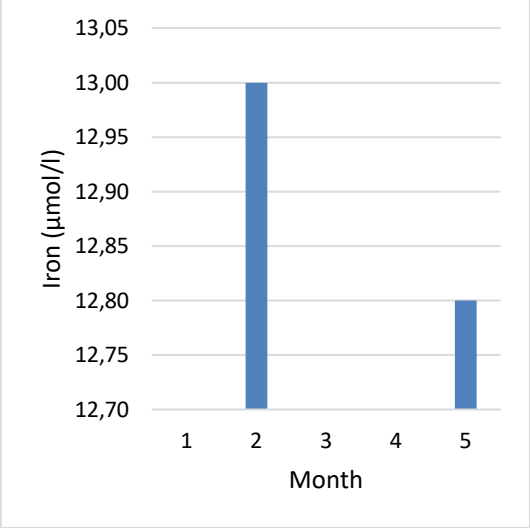


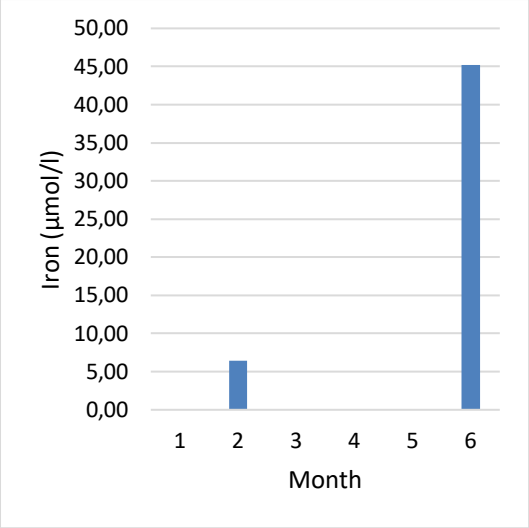


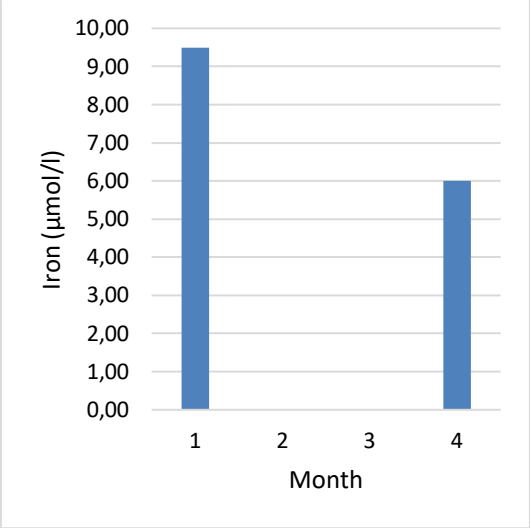


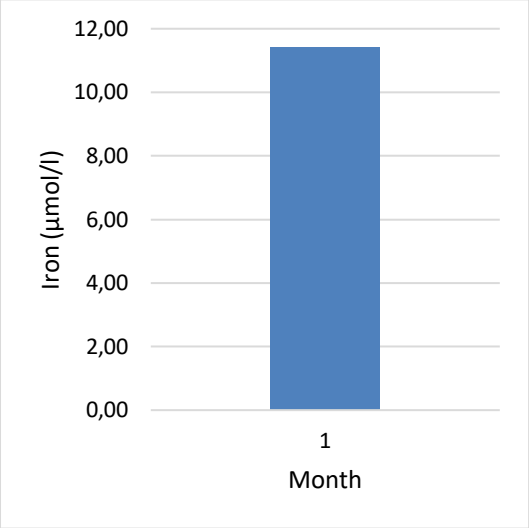


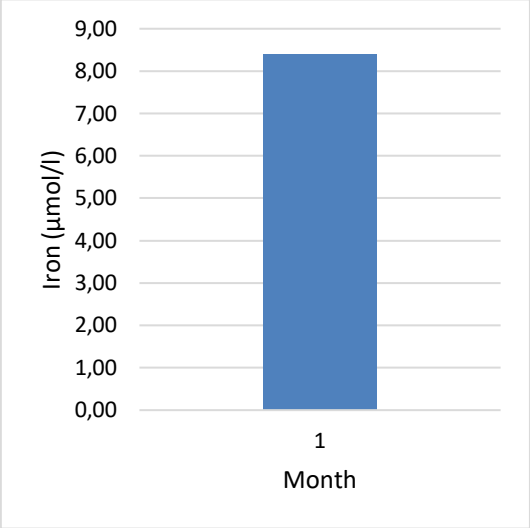


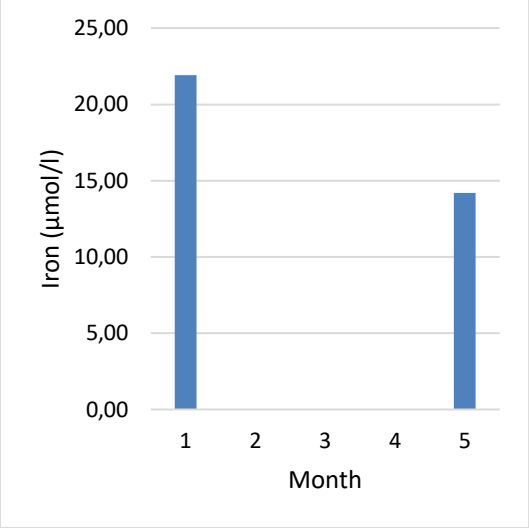


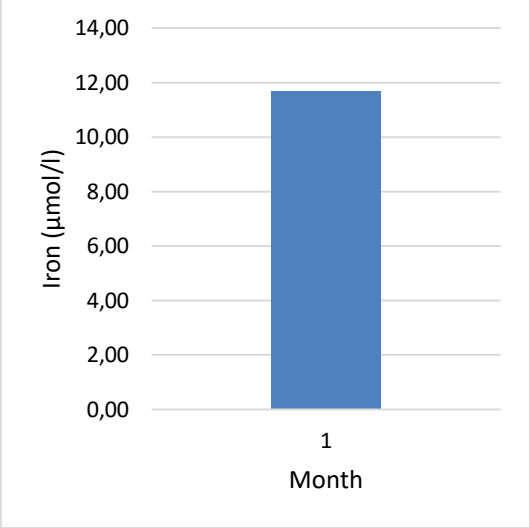

50,00
45,00
40,00
35,00
30,00
25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
2
3
4
5
6
Month

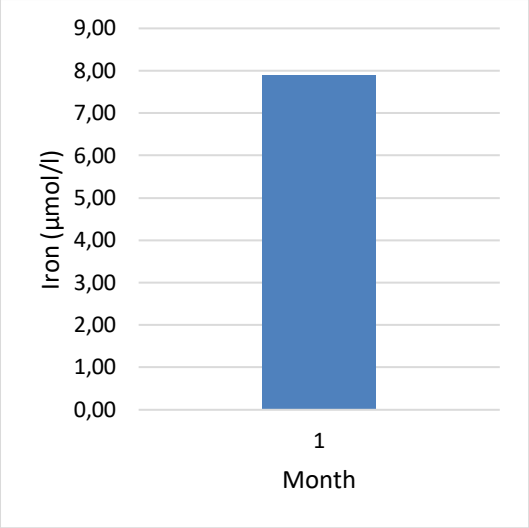

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
2
3
4
Month

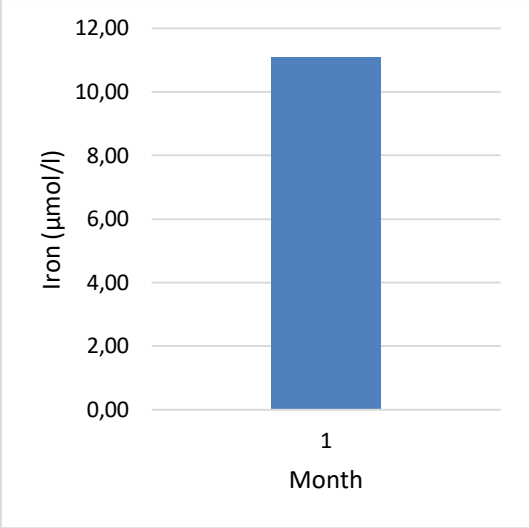

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
Month

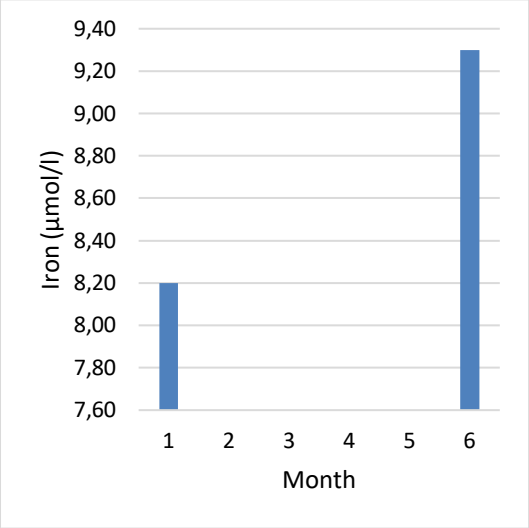

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month

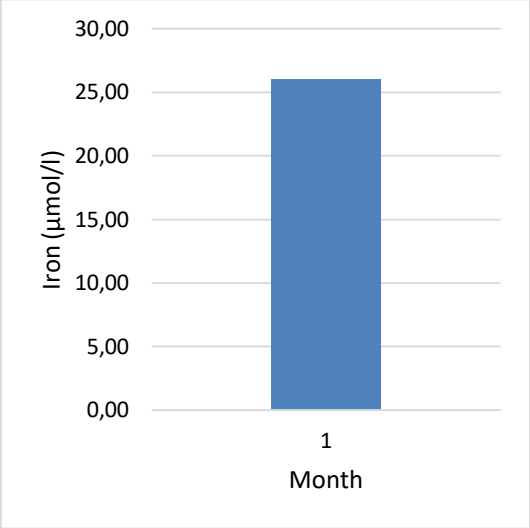

25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
2
3
4
5
Month

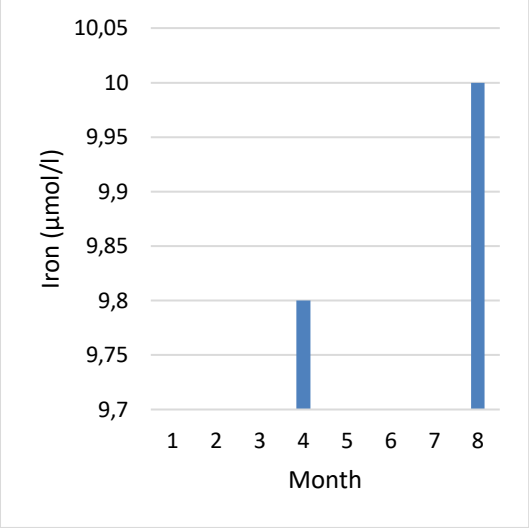

14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
Month

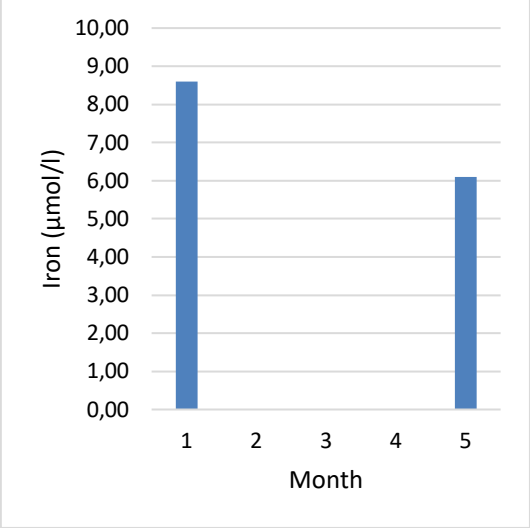

9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month

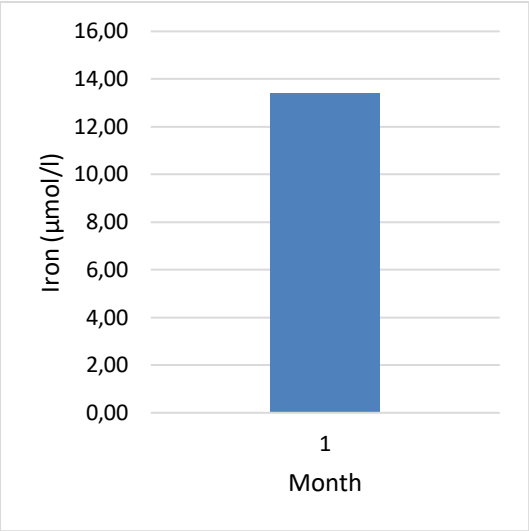

12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
Month

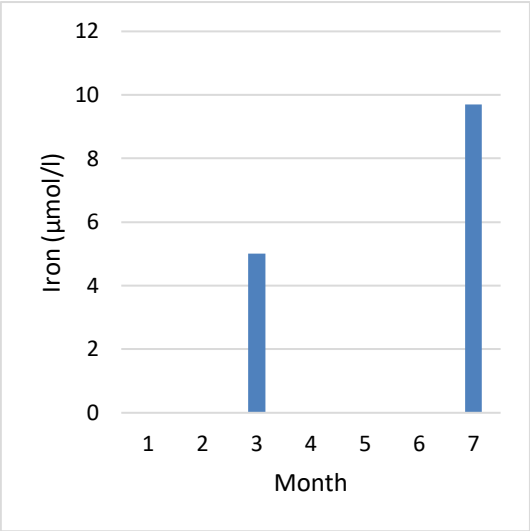

9,40
9,20
9,00
8,80
8,60
8,40
8,20
8,00
7,80
7,60
Iron (µmol/l)
1 2 3 4 5 6
Month

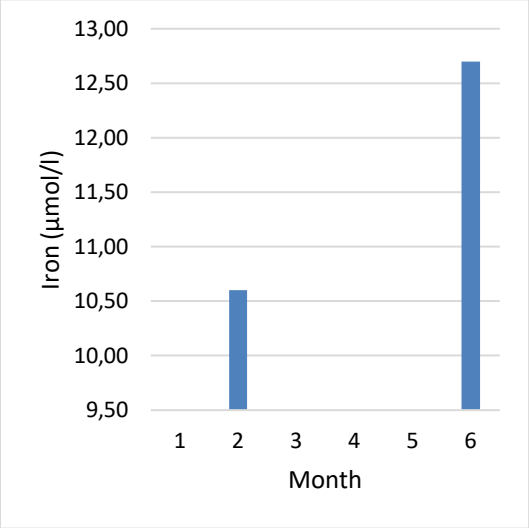

30,00
25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
Month

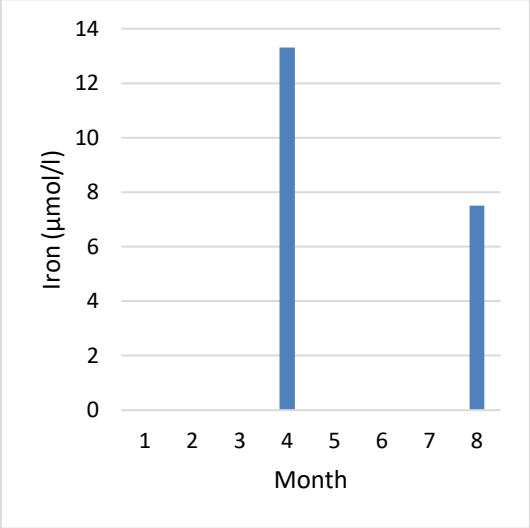

10,05
10
9,95
9,9
9,85
9,8
9,75
9,7
Iron (µmol/l)
1 2 3 4 5 6 7 8
Month

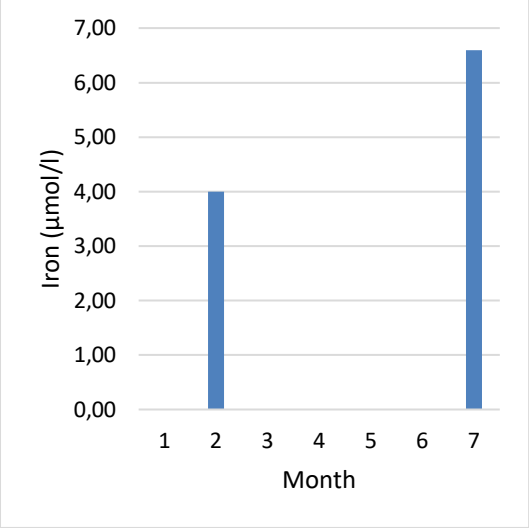

10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1 2 3 4 5
Month

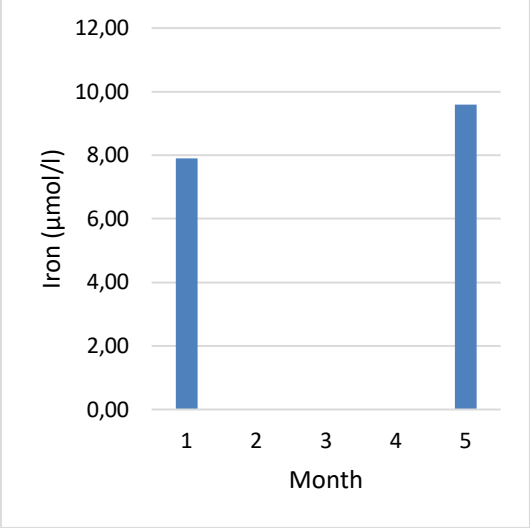

16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
Month

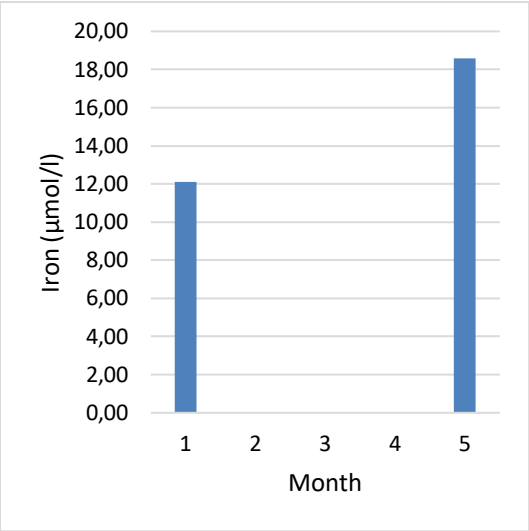

12
10
8
6
4
2
0
Iron (µmol/l)
1 2 3 4 5 6 7
Month

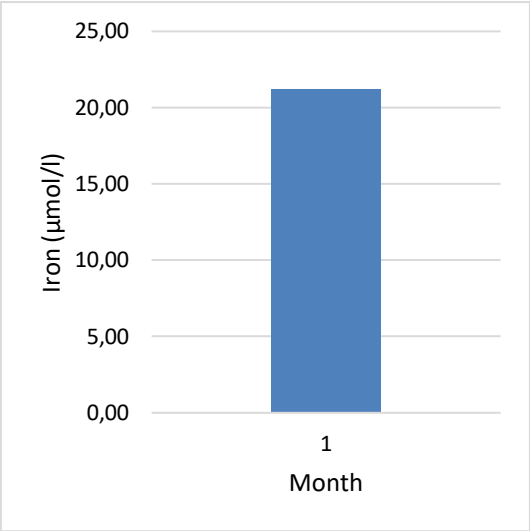

13,00
12,50
12,00
11,50
11,00
10,50
10,00
9,50
Iron (µmol/l)
1 2 3 4 5 6
Month

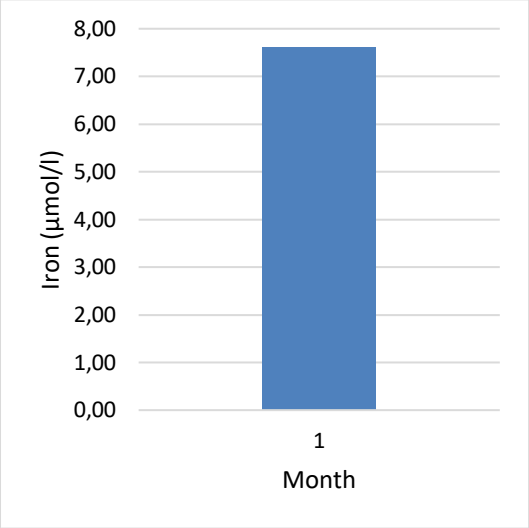

14
12
10
8
6
4
2
0
Iron (µmol/l)
1 2 3 4 5 6 7 8
Month

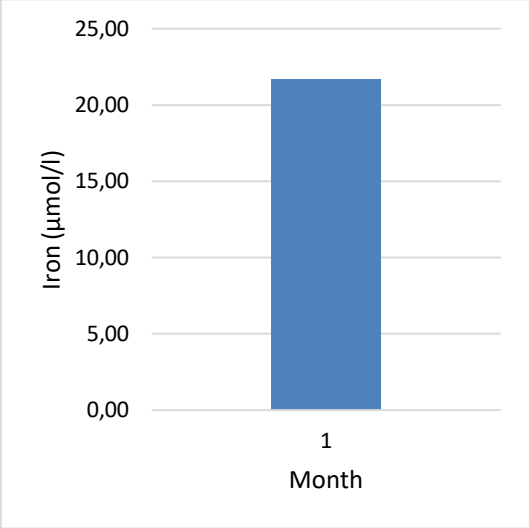

7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1 2 3 4 5 6 7
Month


12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5
Month


20,00
18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
2
3
4
5
Month


25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
Month


8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month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10,00
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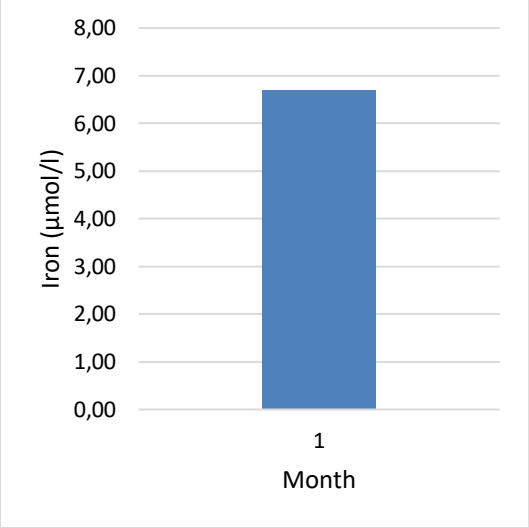
Iron (µmol/l)
1
Month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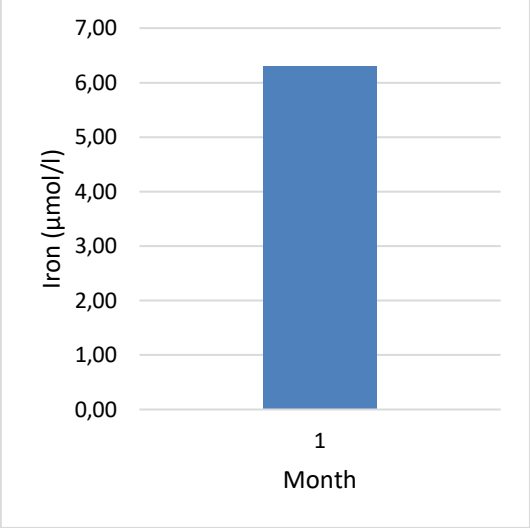
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month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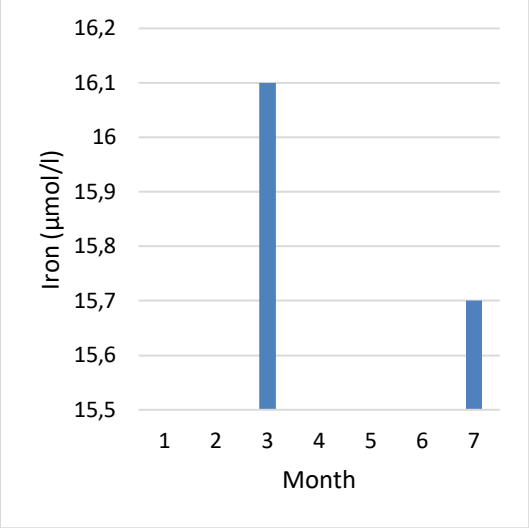
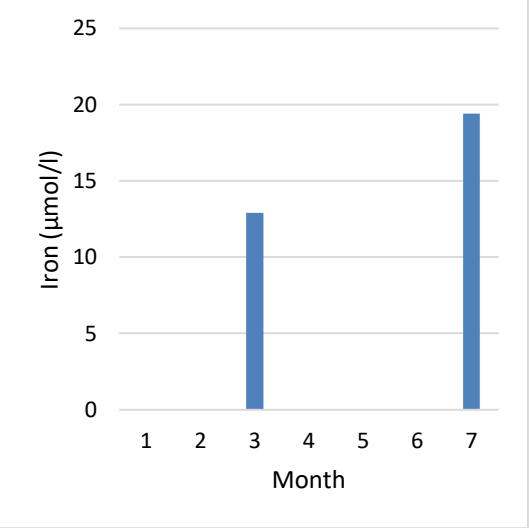
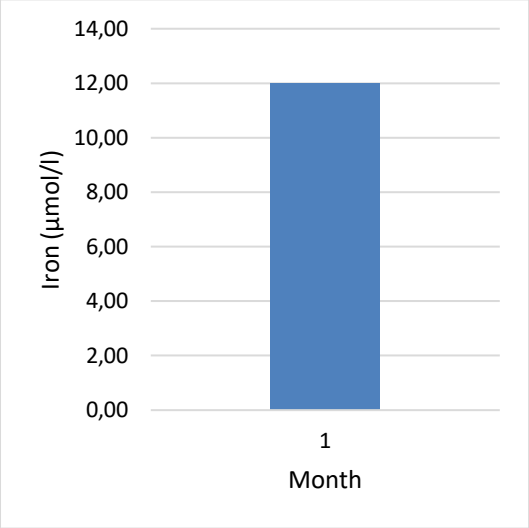
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month


16,2
16,1
16
15,9
15,8
15,7
15,6
15,5
Iron (µmol/l)
1 2 3 4 5 6 7
Month


25
20
15
10
5
0
Iron (µmol/l)
1 2 3 4 5 6 7
Month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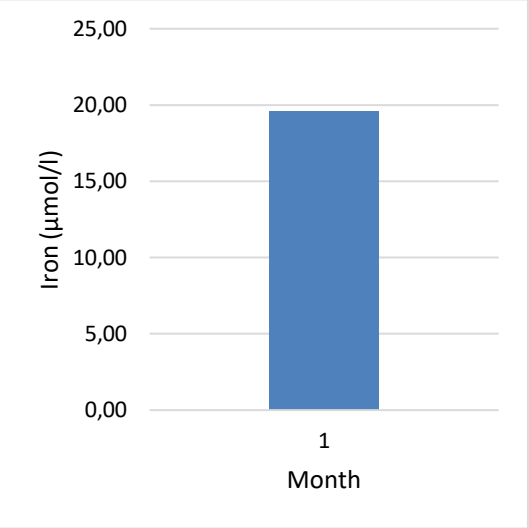
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
Month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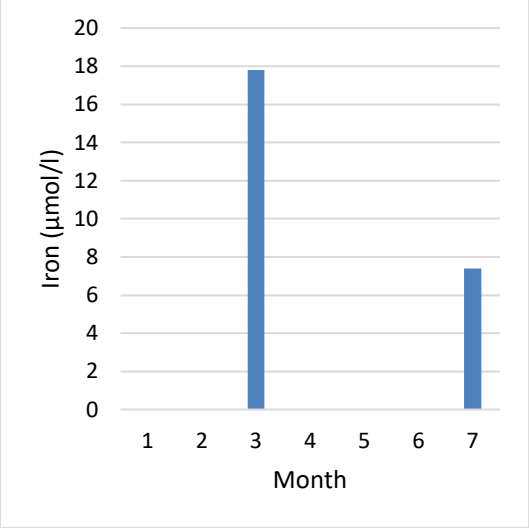
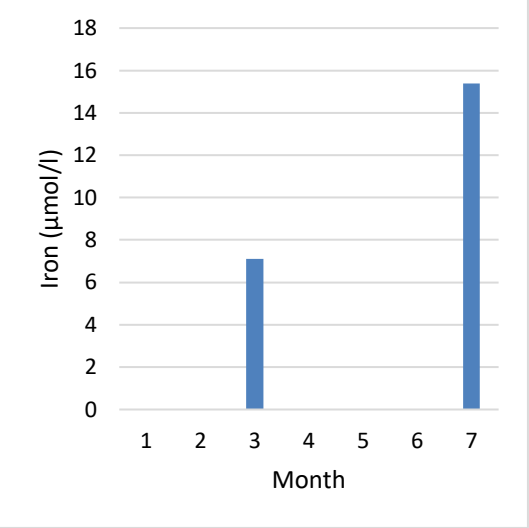
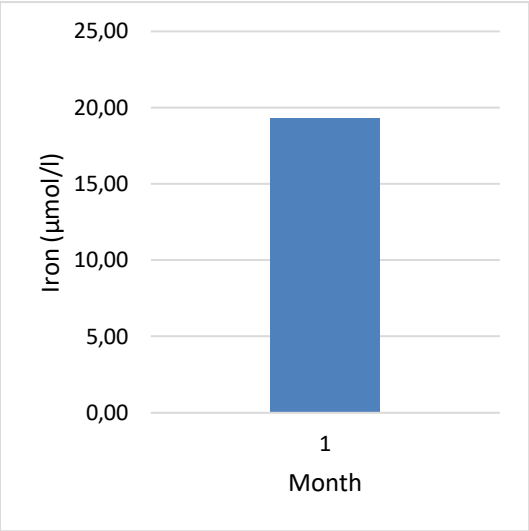
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
Month


20
18
16
14
12
10
8
6
4
2
0
Iron (µmol/l)
1 2 3 4 5 6 7
Month


18
16
14
12
10
8
6
4
2
0
Iron (µmol/l)
1 2 3 4 5 6 7
Month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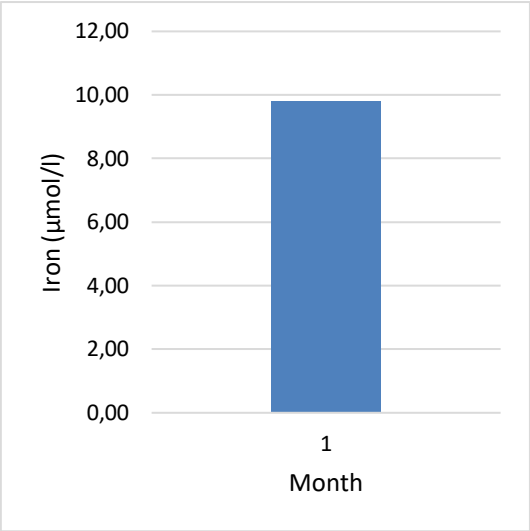
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
Month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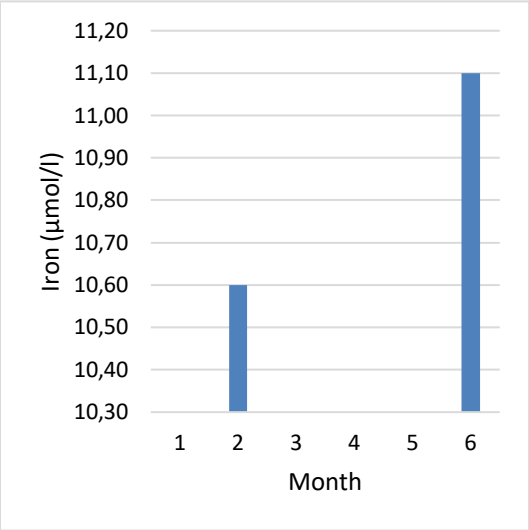
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1
Month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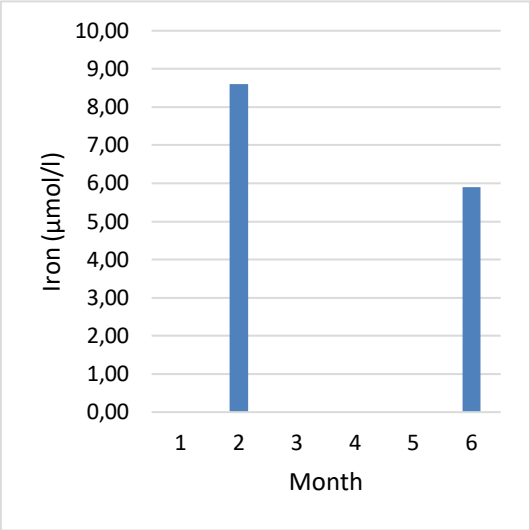
11,10
11,00
10,90
10,80
10,70
10,60
10,50
10,40
10,30
Iron (µmol/l)
1 2 3 4 5 6
Month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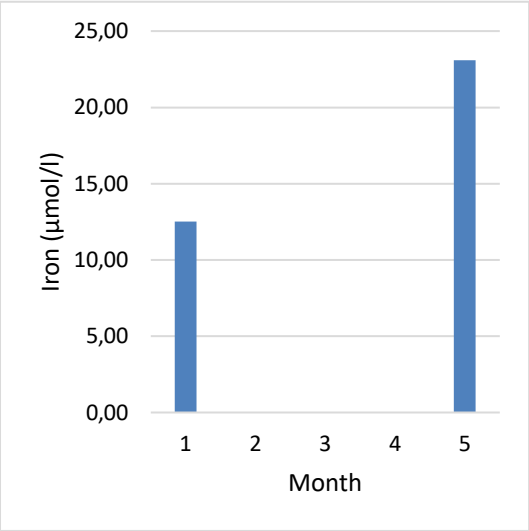
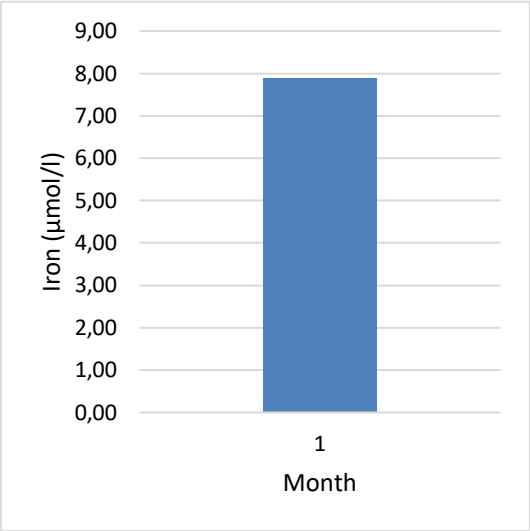
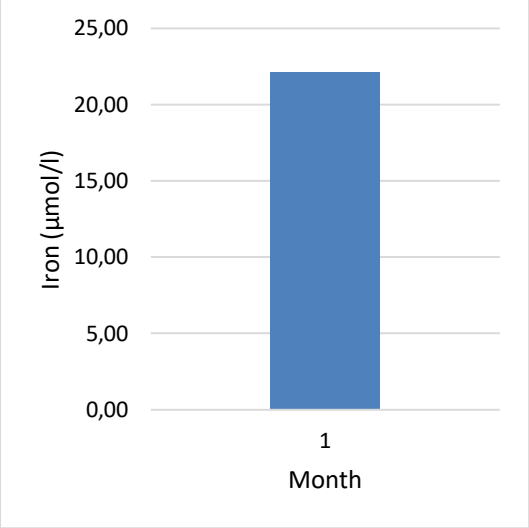
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month


25,00
20,00
15,00
10,00
5,00
0,00
Iron (µmol/l)
1 2 3 4 5
Month


9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month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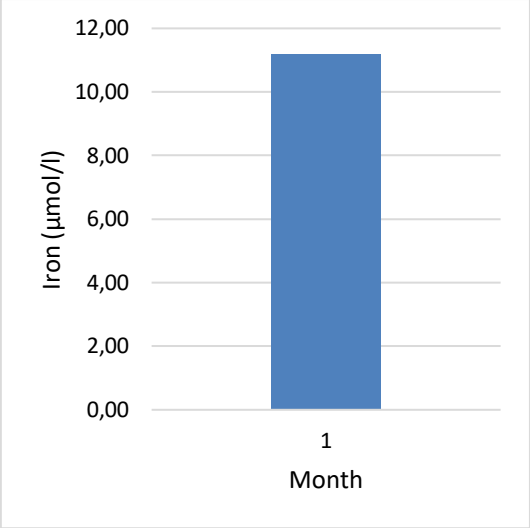
15,00
10,00
5,00
0,00
Iron (µmol/l)
1
Month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6,00
4,00
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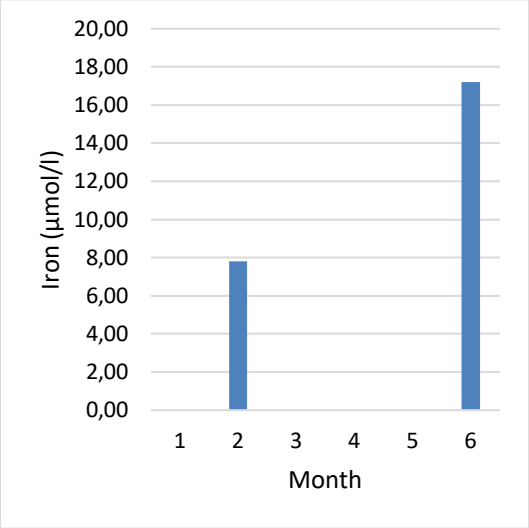
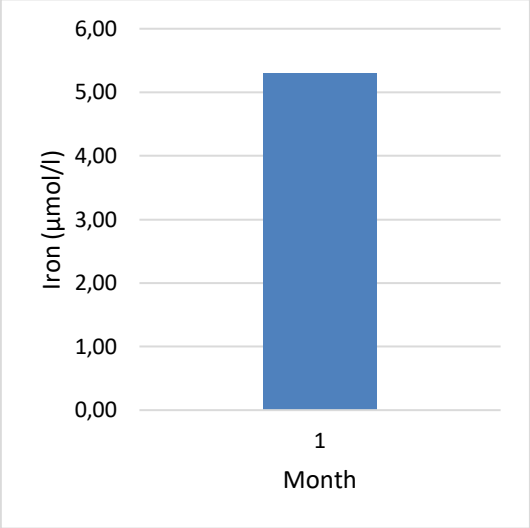
0,00
Iron (µmol/l)
1
Month


20,00
18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6
Month


6,00
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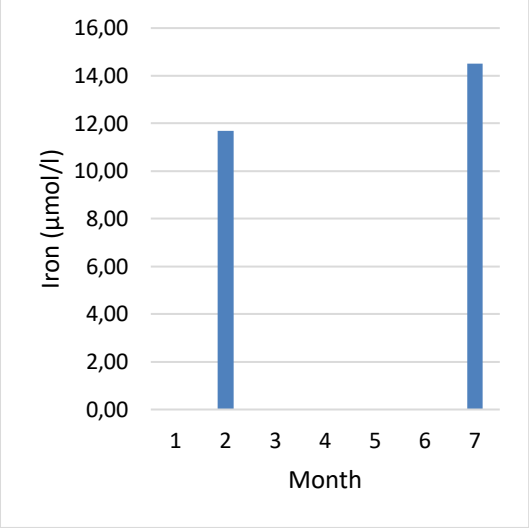
3,00
2,00
1,00
0,00
Iron (µmol/l)
1
Month


16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
Iron (µmol/l)
1 2 3 4 5 6 7
Month