

Ferritin and transferrin saturation cannot be used to diagnose iron-deficiency anemia in critically ill patients

Piotr F. Czempik*, Michał P. Pluta, Łukasz J. Krzych

Department of Anesthesiology and Intensive Care, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

Abstract

Introduction: Iron-deficiency anemia (IDA) is the most common anemia globally. The frequency of IDA among critically ill patients is not known. The aim of our study was to analyse performance of standard iron metabolism parameters for diagnosis of IDA in the critically ill.

Material and methods: We performed a retrospective analysis of consecutive anemic patients admitted to the intensive care unit. We based on various cut-off values for ferritin and/or transferrin saturation (TfS), determined the incidence of IDA.

Results: The population consisted of 27 (53%) men and 24 (47%) women. The median hemoglobin concentration was 96 [interquartile range (IQR) 87–109] g/L. The studied population had markedly increased concentrations of C-reactive protein [119 (IQR 44–196) mg/L], and ferritin [686 (385–1,114) µg/L], whereas iron concentration and TfS were below reference values. Depending on the cut-off value chosen IDA could be diagnosed in between 7.8% (ferritin <100 µg/L + TfS <20%) and 56.9% (TfS <20%) of patients.

Conclusions: Ferritin and transferrin saturation cannot be used for a precise diagnosis of IDA caused by absolute or functional iron deficiency in the critically ill.

Key words: ferritin, intensive care unit, iron-deficiency anemia, transferrin saturation

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Introduction

Anemia constitutes a global healthcare challenge [1]. The incidence of anemia among patients admitted to the intensive care unit (ICU) reaches up to 66% [2], in a prospective cohort study by Thomas et al. even 98% [3]. As a result of disease processes and iatrogenic blood loss due to laboratory testing [4, 5], many patients develop anemia during ICU hospitalization. Anemia has several negative consequences: tissue hypoxia, myocardial infarction,

ischemic stroke, infection, and increased mortality [6]. Therefore, timely diagnosis of anemia is a fundamental component of patient blood management (PBM) – the concept of conservation of a patient's own blood through multiple interventions [7]. The cause of anemia should be established and appropriate treatment introduced. IDA is the most common anemia globally [1, 8]. The frequency of IDA among critically ill patients is not known. Although algorithms for differential diagnosis of preoperative anemia have been proposed [9, 10], there are no algorithms for

*Address for correspondence: Piotr F. Czempik, Department of Anesthesiology and Intensive Care, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Medyków 14, 40–752 Katowice, Poland; e-mail: pczempik@sum.edu.pl



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diagnosis of IDA in critically ill patients. Ferritin concentration and transferrin saturation are standard tests used for diagnosis of ID in most guidelines according to a recent systematic review [11]. However, these proteins are acute phase reactants and their concentration may fluctuate when systemic inflammation is present. In the acute phase ferritin concentration rises, whereas transferrin saturation in both directions. Systemic inflammatory response is frequently encountered in ICU patients [12]. As ferritin and transferrin are produced in the liver, liver dysfunction may also have impact on their concentration. Apart from true IDA, many critically ill patients may have functional ID [13, 14]. Functional ID is defined as inappropriately low iron stores in the setting of inflammation [15]. Functional ID is caused by inflammatory cytokines and is a hallmark of anemia of inflammation (AI), previously known as anemia of chronic disease [16]. AI may accompany acute and chronic inflammatory states such as critical illness, obesity or advanced cancer [17]. All these factors make iron metabolism diagnostics complicated in critically ill patients.

Using concurrent determination of ferritin and transferrin saturation, attempts have been made to distinguish between absolute and functional ID [9, 15]. The aim of this study was to assess the usefulness of ferritin and transferrin saturation in diagnosis of IDA in a population of critically ill patients.

Material and methods

We performed a retrospective analysis of consecutive anemic patients admitted to the intensive care unit of a university-affiliated medical center between January and July 2020. Anemia was defined as hemoglobin (Hb) concentration below 130 g/L in both sexes, as it was postulated in the perioperative setting [9]. Exclusion criteria were as follows: blood loss within 120 days (n =11), RBC transfusion within 120 days (n =15), iron supplementation within 120 days (n =0), and history of a hematological disorder other than anemia (n =0). Basic demographic and laboratory data were retrieved: sex, age, primary diagnosis, iron metabolism parameters (iron, ferritin, transferrin), complete blood count, inflammatory marker [C-reactive protein (CRP)], liver function tests (LFT) [alanine aminotransferase (ALT); aspartate aminotransferase (AST); bilirubin], kidney function tests [creatinine; and blood urea nitrogen (BUN)]. Transferrin saturation (TfS) was calculated according to the formula: $(\text{iron } [\mu\text{g/dL}] / \text{transferrin } [\text{mg/dL}]) \times 71.6$ [%]. All laboratory parameters were determined at the ICU admission. Reference values for all laboratory parameters were as per a local laboratory performing determinations (Tables I, II).

Based on cut-off values for ferritin (<100 $\mu\text{g/L}$), transferrin saturation (<20%) and combined ferritin and transferrin saturation (ferritin <100 $\mu\text{g/L}$ and TfS <20% or ferritin <300 $\mu\text{g/L}$ and TfS <20%) reported in literature [18–20],

Table I. Selected laboratory parameters in the study population

Parameter	Me (IQR)	Reference value/range [9]
Hb [g/L]	96 (87–109)	<130
MCV [fL]	92 (88–96)	84–98
MCH [pg]	29 (28–32)	27–31
MCHC [g/dL]	33 (31–34)	32–36
RDW-CV [%]	15 (14–18)	11–16
RDW-SD [fL]	52 (44–57)	39–50
CRP [mg/L]	119 (44–196)	<5
ALT [U/L]	27 (17–68)	<34
AST [U/L]	49 (28–96)	<31
Bilirubin [mg/dL]	0.6 (0.5–0.9)	0.3–1.2
Creatinine [mg/dL]	0.95 (0.79–1.89)	0.84–1.25
BUN [mg/dL]	29 (21–56)	7.9–20

Me – median value; IQR – interquartile range; Hb – hemoglobin; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW-CV – red blood cell distribution width coefficient of variation; RDW-SD – red blood cell distribution standard deviation; CRP – C-reactive protein; ALT – alanine aminotransferase; AST – aspartate aminotransferase; BUN – blood urea nitrogen

we determined the incidence of IDA in our study group. Analysis of associations between ferritin/transferrin and parameters of inflammation and liver function was performed in order to determine the possible impact of systemic inflammation and liver dysfunction on the results obtained.

Statistical analysis was performed using licensed statistical software (MedCalc v.18.2.1, MedCalc Software, Ostend, Belgium). Quantitative variables with normal distribution were presented as means and standard deviations, and with non-normal distribution as medians and interquartile ranges (IQR). The distribution of variables was verified by the d'Agostino-Pearson test. Correlations were assessed based on the Pearson correlation coefficient (normal distribution) or Spearman's rank (non-normal distribution) correlation coefficient. $P < 0.05$ was considered statistically significant.

Due to the observational retrospective character of this study there was no requirement for bioethics committee approval. Patient data have been anonymised.

Results

The study population consisted of 51 patients, 27 (53%) men and 24 (47%) women, median age was 64 (IQR 57–72) years. Primary diagnoses in the study population are presented in Table III. The four most frequent primary diagnoses were subarachnoidal hemorrhage, pneumonia, sudden cardiac arrest, and heart failure (n =29). Selected laboratory parameters in the study population are presented in Table II. The median Hb concentration in the study

Table II. Iron metabolism parameters in the study population

Parameter	Me (IQR) all patients	Me (IQR) women	Me (IQR) men	P value for sex	Reference range
Ferritin [$\mu\text{g/L}$]	686 (385–1,114)	567 (342–826)	773 (521–2,407)	0.2	4.6–204
Iron [$\mu\text{g/dL}$]	37 (18–78)	37 (19–74)	36 (19–81)	0.9	60–180
Transferrin [mg/dL]	159 (118–195)	162 (112–188)	159 (119–203)	0.6	200–360
TfS [%]	16 (9–36)	17 (9–38)	16 (9–35)	0.9	20–45

Me – median value; IQR – interquartile range; TfS – transferrin saturation

Table III. Primary diagnoses in the study population

Primary diagnosis	N
Neurological:	
• subarachnoid hemorrhage	8
• meningitis	2
• intracranial hypertension	2
• brain tumor	1
• cranioccephalic trauma	1
• ischemic stroke	1
• encephalitis	1
• epilepsy	1
Heart failure	6
Post sudden cardiac arrest	7
Gastrointestinal:	
• acute pancreatitis	2
• bowel perforation	1
• peritonitis	1
• bowel obstruction	1
Pneumonia	8
Acute respiratory failure	3
Septic shock	3
Others	2

population was 96 (IQR 87–109) g/L, well below the cut-off value for anemia. The studied population had a markedly increased concentration of CRP, with a median value of 119 (44–196) mg/L. Liver and kidney function tests were within reference ranges. As far as iron metabolism parameters are concerned, ferritin concentration in our patients was more than 3-fold upper limit of normal iron and transferrin saturation were below the reference values. Iron metabolism parameters in the study population are presented in Table II. The number of study subjects diagnosed with IDA based on different reported cut-off values of iron metabolism parameters is presented in Table IV. Depending on the cut-off value chosen, IDA could be diagnosed in between 7.8% (ferritin <100 $\mu\text{g/L}$ + TfS <20%) and 56.9% (TfS <20%) of patients.

We found weak correlations between iron metabolism parameters and parameters of inflammation and LFT (AST).

Table IV. Incidence of iron-deficiency anemia in the study population

Parameter	% of population
Ferritin <100 $\mu\text{g/L}$	11.8
Ferritin <100 $\mu\text{g/L}$ + TfS <20%	7.8
Ferritin <300 $\mu\text{g/L}$ + TfS <20%	15.7
TfS <20%	56.9

TfS – transferrin saturation

Table V. Associations between parameters of iron metabolism and other parameters

Association	Correlation coefficient	P-value
Ferritin–CRP	0.22	0.13
Transferrin–CRP	-0.28	0.04
Ferritin–bilirubin	0.14	0.30
Ferritin–ALT	0.27	0.05
Ferritin–AST	0.31	0.03
Transferrin–bilirubin	-0.21	0.14
Transferrin–ALT	0.02	0.88
Transferrin–AST	-0.09	0.53
Ferritin–MCV	0.25	0.08
Ferritin–MCH	0.26	0.07
Ferritin–MCHC	0.05	0.71
Ferritin–RDW-CV	0.19	0.19
Ferritin–RDW-SD	0.44	0.001
Transferrin–MCV	-0.01	0.92
Transferrin–MCH	0.02	0.90
Transferrin–MCHC	-0.02	0.87
Transferrin–RDW-CV	-0.36	0.01
Transferrin–RDW-SD	-0.40	0.004

CRP – C-reactive protein; AST – aspartate aminotransferase; ALT – alanine aminotransferase; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW-CV – red blood cell distribution width coefficient of variation; RDW-SD – red blood cell distribution standard deviation; in bold: statistically significant associations

There were also some weak correlations between standard iron metabolism and erythrocyte (red blood cell distribution width coefficient of variation/standard deviation) parameters (Table V).

Discussion

In our study, we used standard iron metabolism parameters to diagnose IDA in critically ill patients hospitalized in the ICU. In order to do this, we used different reported in the literature cut-off values for ferritin (<100, <300 µg/L) or TfS (<20%) alone [18–20]. We also combined different cut-off values for both these parameters together. The more than 7-fold disparity in the percentage of patients diagnosed with IDA using the different criteria (i.e. from 7.8% to 56.9%) shows that we were unable to precisely diagnose IDA (absolute or functional ID) in critically ill patients using these standard iron metabolism parameters. The incidence of IDA among patients admitted to the ICU reaches up to 66% [2]. The reason for this disparity lies in the population studied. Systemic inflammatory response is frequently present in patients hospitalized in the ICU and is associated with the following conditions: trauma, surgery, acute pancreatitis, burns, and sepsis. Ferritin is an acute phase reactant and its concentration rises in systemic inflammatory response. Transferrin concentration in an acute phase may change in both directions. Median ferritin concentration in our study was more than double the upper limit of normal (686, IQR 385–1,114 µg/L), thus lowering the number of patients diagnosed with IDA. The high ferritin concentration in our study was due to systemic inflammatory response present in the patients, which was heralded by median CRP concentration well above the reference value (119, IQR 44–196 mg/L). However we did not find any correlation between ferritin and CRP concentration (correlation coefficient 0.22, $p=0.13$). On the other hand, median concentration of iron (37, IQR 18–78 µg/dL) was well below the reference range (60–180 µg/dL) and transferrin concentration was slightly below the reference range (median 159, IQR 118–195, reference 200–360 mg/dL), lowering the calculated TfS, and hence increasing the number of patients diagnosed with IDA.

In order to precisely diagnose IDA in critically ill patients, it is of the utmost importance to accurately assess the amount of iron stored (absolute deficiency) and iron available for erythropoiesis (functional deficiency). Therefore other parameters have been proposed [21]. One of these parameters is the percentage of hypochromic red cells (%HRC), a figure which reflects recent iron reduction [15, 22]. Another is reticulocyte hemoglobin equivalent (Ret-Hb) which reflects functional iron reserve available for immature erythrocytes in the previous 3–4 days [23]. Ret-Hb quickly normalizes with iron supplementation and can be used in treatment monitoring [24]. Another parameter is hepcidin. Hepcidin is a peptide hormone produced in the liver which along with its receptor (ferroportin) regulates iron transport and availability in the body [25, 26].

This is gradually used more frequently in diagnosis of functional IDA [27, 28].

Our study has some limitations. The first might be the number of study subjects. We analysed 51 subjects. However this was a pragmatic study aimed at finding the incidence of IDA in a heterogenous group of our critically ill patients using standard parameters of iron metabolism. We did not diagnose other types of anemia that could be present in our ICU patients (e.g. folate, vitamin B₁₂, vitamin A deficiency, immune hemolytic anemia). Our only goal was to analyze the incidence of IDA in our ICU population based on standard parameters of iron metabolism. Another limitation is that we used only one laboratory parameter of inflammation (CRP), however this has been used previously in the context of anemia and inflammation [9]. Although our study was single-center, wide variability in iron metabolism results obtained from different laboratories was shown, so identical laboratory equipment must be used in multi-center studies. The variability in results obtained in different laboratories can reach as high as 50% [19]. Standard parameters of iron metabolism have diurnal variability. ICU patients are admitted at different times of the day, and this could impact on the results obtained. However some new parameters also have diurnal variability (hepcidin).

Conclusions

Ferritin and transferrin saturation cannot be used for a precise diagnosis of anemia caused by absolute or functional iron deficiency in critically ill patients, due to the systemic inflammatory response frequently encountered in these patients.

Authors' contributions

PFC – design, data collection, final manuscript, MPP – statistical analysis, final manuscript, ŁJK – critical review, final manuscript.

Conflict of interests

None.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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