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Research article

Reticulocyte hemoglobin content associated with the risk of iron deficiency anemia

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ABSTRACT

Background/Objective: Reticulocyte hemoglobin content (MCHr) was recognized as a rapid and reliable marker for investigating iron deficiency (ID). We hypothesized that MCHr was associated with the risk of iron deficiency anemia in adults.

Methods: This is a dual-center case-control study. A total of 806 patients and healthy individuals were recruited from Ruijin Hospital and Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine between January 2021 and December 2021. The participants were categorized into iron deficiency anemia (IDA) group (n = 302), non-IDA group (n = 366), and healthy control group (n = 138). According to the MCHr level, the participants were divided into two groups, i.e. normal MCHr (≥25 pg) and decreased MCHr (<25 pg) group. Multivariate logistic regression analysis and adjusted subgroup analysis were conducted to estimate the relative risk between MCHr and IDA, with confounding factors including age, sex, hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Hematocrit (HCT), serum iron (Fe), ferritin (Ferrit), and total iron binding capacity (TIBC).

Results: Compared with the non-IDA, the MCHr level with IDA decreased significantly. ROC curve analysis showed that MCHr had the largest area under the AUC curve. After comprehensive adjustment for confounding factors, individuals with normal level of MCHr exhibited a decreased risk of IDA (OR = 0.68 [0.60, 0.77], $P < 0.01$), while the risk of IDA was up to 5 times higher for those with decreased MCHr.

Conclusion: Our findings supported the hypothesis that MCHr was associated with the risk of IDA in adults and could serve as an indicator of IDA severity. MCHr holds clinical value as an auxiliary diagnostic indicator, providing valuable insights into whether invasive examinations are warranted in the assessment of IDA.

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1. Introduction

Iron deficiency anaemia (IDA) poses a significant health challenge, impacting one-third of the world population, including children, women, and the elderly [1,2]. The overall prevalence of IDA in the Chinese population was high characterized by moderate to severe degrees of IDA. IDA arises from insufficient iron to produce an adequate quantity of hemoglobin [3,4]. Reduced iron levels and low iron utilization have multiple negative effects and may be responsible for fatigue, organ dysfunction, and other diseases [5,6]. The mean reticulocyte hemoglobin content (MCHr), a laboratory parameter used in evaluating iron utilization, also reduces in consistency due to the reticulocyte release of human blood after the post 24–48 h after developing into red blood cells. Clinical challenges included the timely diagnosis of IDA, as a delayed intervention may lead to a missed optimal treatment window. This was particularly critical for vulnerable groups like children, pregnant women, and the elderly [7]. Accurate diagnosis and differentiation of anemia types became imperative in such cases. It's crucial to note that assessing iron deficiency status may be compromised in the presence of infection, inflammation, or malignancy, as serum iron level could be affected by acute phase-reactive proteins under these conditions [8]. Studies [9,10] have shown that MCHr served as a valuable indicator for assessing recent iron utilization and erythropoiesis status, potentially surpassing traditional methods like bone marrow iron staining. It was proposed as an effective and accurate tool for monitoring iron status and iron therapy effectively and accurately at the same time [11]. Nevertheless, it was unclear whether the incidence and severity of IDA between normal and decreased MCHr level in the Chinese population.

In this case-control study, we assessed the association between MCHr and the occurrence and severity of IDA. We employed multivariate logistic regression to explore this association, taking into account various confounding factors including sex, age, hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hematocrit (HCT), serum iron (Fe), ferritin (Ferrit), and total iron binding capacity (TIBC). After adjustment of all these confounders, the relationship between MCHr and IDA allowed us to obtain a comprehensive understanding of how MCHr relates to IDA occurrence and severity, providing insights into its potential as a reliable and informative biomarker in assessing iron status.

2. Materials and methods

2.1. Subjects

In this study, 806 adult participants were enrolled between January 2021 to December 2021 at Ruijin Hospital (north), Xinhua Hospital and Ruijin Hospital affiliated to the Shanghai Jiao Tong University School of Medicine. 302 participants were diagnosed as IDA according to the 2018 hematology diagnosis and efficacy criteria, 366 non-IDA patients were selected as the disease control group including small cell anemia alone, megaloblastic anemia, pure erythrocyte aplastic anemia, hemolytic anemia, and aplastic anemia and 138 healthy people with physical examination as the control group. Exclusion criteria: patients with acute, chronic leukemia, malignant tumor diseases, hepatobiliary disease, renal function disease, gout, and others. This study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University Medicine [Ethics No.: (2019) (54)] and all subjects gave informed consent.

2.2. Methods

5 mL of fasting venous blood were collected for all subjects in the morning and placed in SST (serum separator tube) serum isolation gel vacuum extraction vessels and EDTA-K2 anticoagulant tubes within 1 h, respectively. The testing instruments were BC-6800Plus automatic blood analyzer (China Mindray), AU-5800, and DXI-800 automatic biochemical and immunity analyzer (Beckman Coulter, USA).

2.3. Diagnostic criteria

The diagnostic criteria of IDA are as follows: (1) microcytic hypochromatic anemia; Male Hb $<$ 120 g/L, female Hb $<$ 110 g/L and pregnant woman $<$100 g/L; MCV $<$80 f1; MCH $<$27 pg; MCHC $<$320 g/L; (2) Ferritin $<$12 μg/L, serum iron $<$8.95 μmol/L, ferritin saturation $<$0.15, and total iron binding capacity$>$ 64.44 μmol/L (3) Free erythrocyte protoporphyrin $>$0.9 μmol/L or Zinc-protoporphyrin$>$ 0.96 μmol/L, or Free erythrocyte protoporphyrin/HB $>$ 4.5 μg/g (4) serum-soluble ferritin receptor (soluble transferrin receptor, sTfR) $>$ 26.5 nmol/L (5) Iron staining on bone marrow smear showed the absence of stainable iron in the bone marrow. Iron pellet erythrocytes were $<$15 %. For the diagnosis of IDA, it must meet the first criteria (1) and one or more of the other four criteria (2–5). According to the Hb level, the IDA was divided into three subgroups: mild IDA (91 g/L-120 g/L), moderate IDA (61 g/L-90 g/L), and severe IDA (30 g/L-60 g/L). According to the value of MCHr, the IDA group was also divided into the normal (MCHr $\geq$25 pg) and decreased group (MCHr $<$25 pg) as reported [12].

2.4. Statistical method

Statistical analysis was performed using the R language software and Graphpad Prism9 software for drawing. Data are expressed as mean (SD) for continuous variables and percentage (%) for dichotomous variables. The comparison of the differences among the groups was analyzed using a one-way analysis of variance (ANOVA). Measurement data use (%), pairwise comparison use χ^2 checkout.

Test for interaction in the logistic-regression model was used to compare odd ratios between the analyzed subgroups according to sex, age, and grade of anemia. Univariate Logistic regression was used to assess the risk factors of MCHr, age, sex, Hb, MCV, MCH, MCHC, HCT, Fe, Ferrit, and TIBC in IDA, and multivariate Logistic regression was used to analyze the independent effect of MCHr in IDA after correcting confounding factors. ROC curves were made to calculate the AUC and cut-off values. $P < 0.05$ was statistically significant.

3. Results

In this case-control study, Fig. S1 is a flow chart of participant recruitment. The basic information is described in Table 1. The average age of 302 IDA patients and 365 non-IDA patients and 138 healthy people was 49.96 ± 14.71, 51.96 ± 19.43, and 50.74 ± 11.07 years old, respectively. There was no significant difference between the groups ($P > 0.05$). It is noteworthy that the proportion of women with IDA was significantly higher than that in the non-IDA group (90.40 % vs 56.01 %, $P < 0.01$). A comparison of IDA patients with non-IDA patients and healthy people showed significant differences in Sex, MCHr, Hb, MCV, MCH, MCHC, HCT, Fe, Transferrin saturation (TS), Ferrit, and TIBC levels, except for age (Table 1).

Then we conducted a univariate analysis for IDA risk and found that sex, MCHr, Hb, MCV, MCH, MCHC, HCT, Fe, TS, Ferrit, and TIBC may have a strong relationship with the risk of IDA (Table S1). Based on the grade of peripheral hemoglobin content, stratified analysis and separate regression analysis showed that MCHr was a protective factor against age, sex, and grade of anemia, but there was no significant interaction between the groups in age, sex, and grade of anemia ($P > 0.05$) (Fig. 1). We also found that as the degree of anemia increased, the level of MCHr decreased (Table 2).

Furthermore, multivariate regression analysis was applied to investigate the effects of MCHr on IDA. Without adjusting for confounding factors, results showed a protective effect of normal MCHr on IDA occurrence (OR = 0.64, CI [0.60,0.68], $P < 0.01$). After fully adjusting the confounding factors of demographic information and laboratory indicators, we obtained a similar conclusion. Based on MCHr exposure conditions, the risk of IDA for decreased MCHr patients was five times higher compared to the normal MCHr group (Table 3).

Cut-off values for best sensitivity and specificity were acquired using ROC for each indicator (Fig. 2). ROC curve analysis showed that the cut-off value of MCHr diagnostic IDA was 26.7 pg, corresponding to a sensitivity of 80.00 % and a specificity of 93.38 %, in the areas under the curve (AUC) was 0.94, CI: (0.92–0.95) (Fig. 2).

4. Discussion

The current understanding of the utility of MCHr in the evaluation of the association between MCHr and IDA risk was limited. Our study sought to address this knowledge gap and found that declined MCHr was a risk factor for the occurrence of IDA in the Chinese population. This association was significantly modified by demographic information and laboratory indicators. In addition, no significant interaction was found in age, sex, or the grade of anemia groups.

Currently, the screens and diagnosis of IDA relied on a combination of laboratory indicators, including routine CBC measures, reticulocytes, and iron metabolism markers. While iron was an essential trace element for the human body, parameters related to iron metabolism were not specific for IDA. The diagnosis challenges of IDA raised since standard biomarkers might be altered in a complex patient population with conditions such as cancer [13], inflammatory diseases like Inflammatory Bowel Disease (IBD) [14], or other chronic diseases [9,15,16]. Our study explored whether MCHr was a potential alternative rapid indicator for the diagnosis and monitoring of IDA [13]. The dual center case-control study was designed to investigate the relation between MCHr and IDA since

Table 1
Baseline characteristics of the study participants.

		Non-IDA	IDA	Normal	F/χ^2 - value	*P*-value
No. of participants, N (%)		366 (45.41 %)	302 (37.47 %)	138 (17.12 %)		
Gender	Male, N (%)	161 (43.99 %)	29 (9.60 %)	84 (60.87 %)	140.8	<0.0001
	Female, N (%)	205 (56.01 %)	273 (90.40 %)	54 (39.13 %)		
age (years), mean (SD)		51.96 ± 19.43	49.96 ± 14.71	50.74 ± 11.07	1.224	0.295
Laboratory results mean (SD)						
MCHr (pg)		31.51 ± 6.69	21.07 ± 3.65$^{*,\#}$	31.42 ± 1.68	506.8	<0.0001
MCV (fl)		88.98 ± 13.92$^{\nabla}$	71.44 ± 8.74$^{*,\#}$	90.29 ± 4.14	253.6	<0.0001
MCH (pg)		28.95 ± 5.45$^{\nabla}$	20.96 ± 3.37$^{*,\#}$	30.92 ± 1.77	386.6	<0.0001
MCHC (g/L)		324.3 ± 16.7$^{\nabla}$	292.6 ± 17.6$^{*,\#}$	342.4 ± 7.85	567.3	<0.0001
HCT (%)		27.58 ± 5.58$^{\nabla}$	28.76 ± 4.53$^{*,\#}$	43.36 ± 4.35	515.6	<0.0001
Hb (g/L)		88.84 ± 19.33$^{\nabla}$	84.41 ± 15.72$^{*,\#}$	148.6 ± 16.55	710.6	<0.0001
FE (umol/L)		10.91 ± 7.38$^{\nabla}$	3.54 ± 1.83$^{*,\#}$	19.96 ± 6.87	389.0	<0.0001
TIBC (umol/L)		54.09 ± 16.18$^{\nabla}$	76.61 ± 10.17$^{*,\#}$	38.58 ± 10.99	446.7	<0.0001
Ferrit (ng/ml)		106.7 ± 217.1$^{\nabla}$	3.86 ± 2.35$^{*,\#}$	147.1 ± 147.4	52.16	<0.0001
TS (%)		21.93 ± 14.86$^{\nabla}$	4.82 ± 2.98$^{*,\#}$	34.88 ± 13.40	362.6	<0.0001

MCHr, mean reticulated hemoglobin content, MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; HCT, hematocrit; Hb, hemoglobin; FE, iron indicators of serum iron; TIBC, total iron-binding capacity; Ferrit, Ferritin; TS, the saturability of iron. *p < 0.05 between IDA group and Non-IDA group; #$p < 0.05$ between IDA group and Normal group.
∇ $p < 0.05$ between the Non-IDA group and control group.

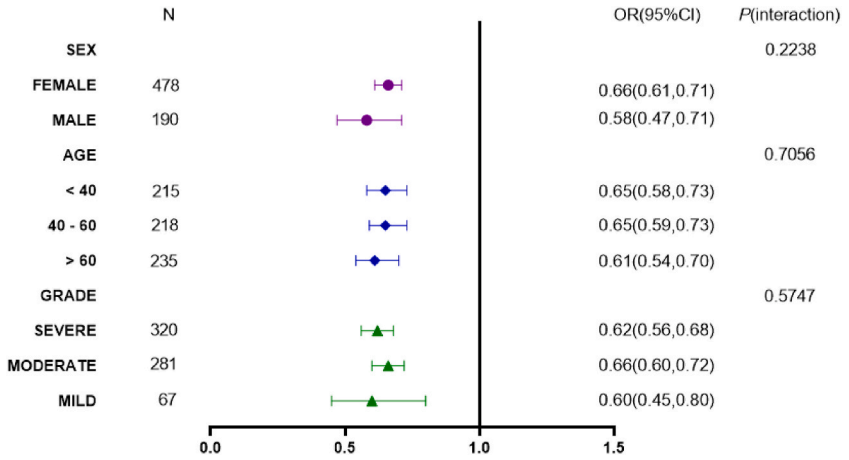

Fig. 1. Forest plot of MCHr. The association between Mchr and anemia according to IDA and Non-IDA.

Table 2
Comparison of MCHr in all groups of IDA patients with mild anemia, moderate anemia, and severe anemia.

Group	Example Number	MCHr (pg)
Mild anemia group	119	21.91 ± 3.382
Moderate anemia group	159	20.97 ± 3.575
Severe anemia group	25	17.78 ± 3.445
F value		14.64
P value		<0.0001

Table 3
Individual effect of MCHr on IDA.

Exposure	Non-adjusted		Adjust model I		Adjust model II	
	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P
MCHr	0.64 (0.60, 0.68)	<0.0001	0.64 (0.60, 0.69)	<0.0001	0.68 (0.60, 0.77)	<0.0001
MCHr groups						
≥25	Reference		Reference		Reference	
<25	37.24 (23.99, 57.81)	<0.0001	36.86 (22.81, 59.56)	<0.0001	5.33 (2.45, 11.62)	<0.0001

Adjust model I: Adjusted for age, sex, grade.
Adjust model II: Adjusted for age, sex, grade, Hb,MCV,MCH,MCHC,HCT,Fe,Ferrit and TIBC.

MCHr values can be obtained more easily by complete blood count. To ensure consistency in study selection, we implemented rigorous inclusion and exclusion criteria.

MCHr emerged as a valuable tool for early measurement of response to iron therapy, exhibiting an increase as early as the second day following the initiation of iron therapy [17]. Its rapid response to the status of hemoglobin synthesis in bone marrow erythroid cells made it a sensitive predictor of IDA. MCHr reduction was swift, offering timely and sensitive indications, serving as an indicator of IDA even before hemoglobin and mature erythrocyte parameters began to decline [10]. Related studies [18] suggested that MCHr was not influenced by acute phase reactions, making it a reliable biological marker reflecting the iron reserves in the body. As a marker of the mature erythrocyte stage lasting only 24–48 h, MCHr was particularly sensitive to iron deficiency, enabling early detection [18] and identification of latent subclinical iron deficiency before the onset of full-fledged IDA [19,20]. Its direct reflection of erythropoiesis added to its practicality as it remained unaffected by acute-phase reactions [21,22], which made it a more practical and available reference indicator for the measurement of iron availability. The recent study revealed no difference in patients between MCHr levels determined at 1 month and 3 months after treatment time-points [23]. It showed the cut-off value of MCHr for diagnosing IDA was 26.7 pg, lower than the value of 27.2 pg in our previous study [24]. So, we opted for an MCHr cutoff of 25 pg for diagnosing IDA to align with the reference provided by the value the Mindray BC-6800Plus automatic blood analyzer. It was worth noting that MCHr cutoffs reported or the identification of iron deficiency varied in studies depending on populations [25]. As MCHr thresholds may differ based on demographic and regional characteristics, customizing the cutoff values was recommended, especially for a nuanced understanding of its correlation with IDA risk in Chinese patient populations.

However, the results of this study showed that Hb, MCV, MCH, MCHC, HCT, Fe, TS, Ferrit, and TIBC were all associated with IDA besides MCHr itself. Hematological parameters, including Hb, hematocrit, MCV, MCH, and HCT, exhibited a significant correlation

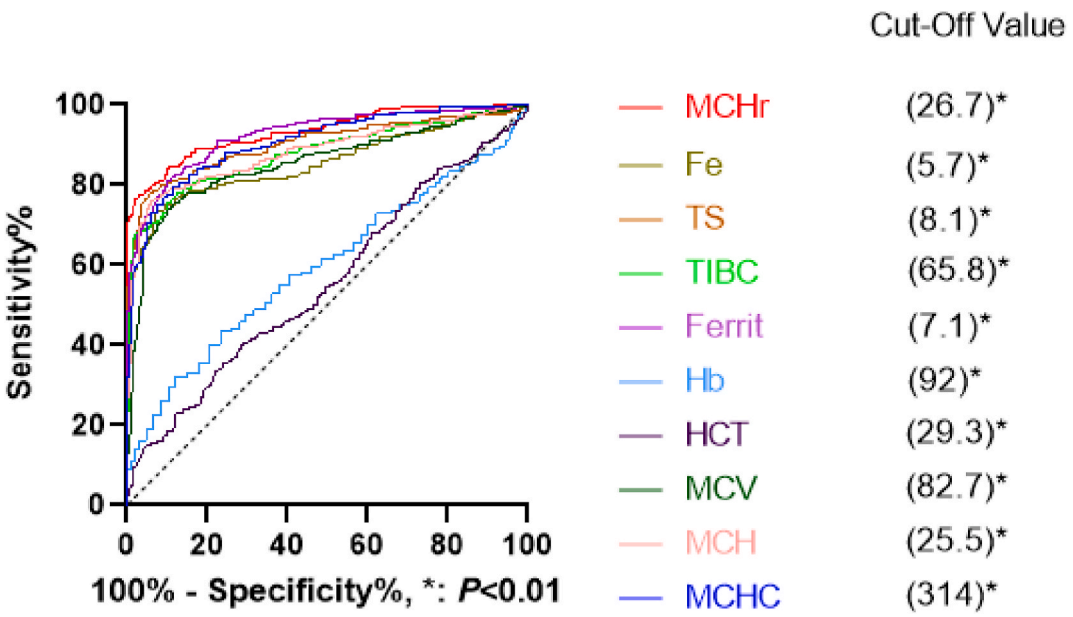

Fig. 2. Sensitivity, specificity, cut-off value, and ROC curve analysis results of the diagnostic IDA for each index.

with MCHr. Similarly, iron status parameters such as Fe, Ferrit, and TIBC, were found to be significantly correlated with MCHr. Interestingly, MCHr was identified as a valuable indicator for assessing the severity of IDA in this study. The study also highlighted the limitation of serum iron concentrations in inconsistently correlating with the severity or clinical stage of iron deficiency. The laboratory data on serum iron indicated that more subjects seemed to experience reduced iron levels in both IDA and general iron deficiency, emphasizing the need for additional indicators like MCHr for a more nuanced assessment. While changes in platelet count (PLT) and platelet parameters were reported in IDA [26], the study did not observe the relationship between iron parameters (Fe, Ferrit, TIBC) and platelet parameters. This underscores the complexity of iron metabolism and the diverse manifestations of iron deficiency, prompting further exploration and understanding of these interactions.

This study had several limitations that should be considered when interpreting the findings. This was a retrospective case-control study conducted to explore the risk factors of IDA for adults in Shanghai, China, in 2021, and to investigate the relationship between multiple risk factors and IDA in adults. One notable limitation was the reliance on an inferred diagnosis of IDA based on biochemical measures and medical record review, lacking access to a gold standard such as bone marrow iron studies. This could introduce uncertainty in the accuracy of the IDA diagnosis, as biochemical measures may not capture all aspects of iron status. Furthermore, this study analyzed cross-sectional data, which inherently restricted the ability to establish a causal relationship between the identified risk factors and IDA. To narrow the focus on patients at risk for iron deficiency, we evaluated MCHr only in patients with orders for CBC and serum iron related measures. This approach might introduce unintended bias into the analysis, as the results were not stratified by specific causes and risk factors for iron deficiency. In this unselected patient population without health control, the results of our data may be slightly different. Other limitations of the study include the patient population was median and limited to participants from two centers in Shanghai, with a distance of over 35 km between them. This geographical restriction might have impacted the diversity and representation of the population, potentially underestimating the prevalence of anemia in the broader population.

The results of a multivariate logistic regression analysis revealed that the risk of IDA in the group with reduced MCHr was five times higher than in the group with normal MCHr level, even after adjusting for other factors. Clinicians are advised to closely monitor changes in MCHr levels, as it may serve as a crucial indicator in the early identification of patients who are at an elevated risk of developing IDA.

5. Conclusion

Decreased MCHr level (<25 pg) is strongly associated with IDA risk. Herein, the literature suggests MCHr values as a rapid and feasible indicator may have a predictive role in monitoring the iron status for clinical management of IDA.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Ning Ding: Writing – original draft, Formal analysis, Data curation. **Yan-Hui Ma:** Writing – review & editing, Formal analysis, Data curation. **Ping Guo:** Writing – review & editing, Data curation. **Tian-Kai Wang:** Data curation. **Lin Liu:** Data curation. **Jian-Biao Wang:** Supervision, Resources. **Pei-Pei Jin:** Writing – review & editing, Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25409.

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