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A multivariate analysis of the risk of iron deficiency in plateletpheresis donors based on logistic regression

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ABSTRACT

Background: The purpose of this study was to analyze the application of individual factors, blood cell related indicators, and blood donation frequency in predicting the risk of iron deficiency of plateletpheresis donors.
Methods: A total of 801 plateletpheresis donors were included in this study. The relationship between risk factors and iron deficiency was retrospectively analyzed by univariate analysis and logistic regression analysis. The application of Hb, MCHC, RDW-CV and blood donation frequency combined prediction of iron deficiency risk among plateletpheresis donors was evaluated.
Result: The rate of iron deficiency in this study was 31.5 % (241/766). The age, gender (the ratio of male donors), red blood cell related indicators, blood donation frequency were statistically different between the normal and iron deficiency group (all $P < 0.05$). Age, gender, the reciprocal of Hb and MCHC, RDW-CV, total number of blood donation and number of plateletpheresis donation in the past year, these indicators to predict the risk of iron deficiency area under the curve (AUC) were 0.558, 0.672, 0.785, 0.717, 0.599, 0.621, 0.646, respectively. The AUC of these indicators combined to predict the risk of iron deficiency was 0.877, higher than all single indicators. The sensitivity and specificity of these indicators combined in prediction of iron deficiency were 88.89 % and 81.57 %, respectively.
Conclusion: Age, gender, the reciprocal of Hb and MCHC, RDV-CV, blood donation frequency are associated with the risk of iron deficiency in plateletpheresis donors. The combination of these indicators has high value in predicting the risk of iron deficiency.

1. Introduction

Iron deficiency refers to the reduction of the total body Iron (TBI), which is the most common nutrient deficiency. It is estimated by WHO that about 1/3 of the world population has iron deficiency [1]. In 2012, China's "Health Examination Requirements for Blood Donors" adjusted the number and interval of plateletpheresis donation. The annual number of plateletpheresis donation increased from 12 to 24 times, and the interval of blood donation shortened from 4 weeks to 2 weeks. With the increase in the frequency of blood donation and the shortening of the interval between blood donations, the cumulative loss of red blood cells in the process of blood donation increases. Studies have reported that during a single plateletpheresis process, about 80–100 mL of whole blood was lost due to the retention of test specimens and the remaining red blood cells in the consumable pipeline [2–6]. Based on this calculation, the maximum annual total blood loss of regular plateletpheresis donors can be up to 2400 mL, which is equivalent to 4–6 whole blood donations, significantly higher than the current red blood cell loss for whole blood donation in China. It increases the risk of iron deficiency among donors. Without intervention, this will seriously affect the health of regular plateletpheresis donors and further affect the regular plateletpheresis donors population and the clinical supply of plateletpheresis [7]. Studies on the influencing factors of iron deficiency in plateletpheresis donors have been carried out in different countries and regions, but the research results in different regions are not the same, and there is still a lack of information in Hangzhou, Zhejiang, China.

In this study, a multivariate analysis was conducted on iron deficiency among plateletpheresis donors in Hangzhou, Zhejiang, China, to

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provide data and theoretical basis for the formulation of iron deficiency intervention strategies in the later period.

2. Materials and methods

2.1. Donors and baseline information collection

A total of 801 plateletpheresis donors at the Blood Center of Zhejiang Province from January 2020 to July 2020 were included in this study. The inclusion criteria for plateletpheresis donors were as follows: (1) age 18–60 years, (2) body weight ≧ 50 kg, (3) not taking drugs for anti-platelet aggregation or inhibiting platelet metabolism (such as aspirin, vitamin E, and penicillin) within one week, (4) not taking iron supplementation within three months, (5) in good health, without any significant illness, (6) interval of PP≧ 2weeks, and (7) at least 1 year since last whole blood donation. Health examination was in accordance with the Health examination criteria of blood donors established by the Ministry of Health and Family Planning in China.

The characteristics of the donors was collected from the donors, including age, gender, Body Mass Index (BMI), professional, level of education, experience of donation.

2.2. Laboratory analysis

Two specimens were collected from every donor during pre-donation testing. Peripheral blood sample (2 mL) in ethylene diamine tetraacetate (EDTA) was drawn from each donor for complete blood count (CBC), such as hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin(MCH), mean corpuscular hemoglobin concentration (MCHC), coefficient of variation in red cell distribution width (RDW-CV). Peripheral blood sample (5 mL) in procoagulant tubes was drawn from each donor for serum ferritin (SF), C-reactive protein (CRP) and acid glycoprotein (AAGP2). CBC were tested using a hematology analyzer (XS-900i, SYSMEX, Kobe, Japan) according to the manufacture's instruction. SF and CRP were tested using an automatic biochemical analyzer (BS-430, Mindray, Shenzhen, China) according to the manufacture's instruction. And AAGP2 was tested using an automatic biochemical analyzer (Cobas6000-c501, Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacture's instruction. All tests were done by trained staffs.

2.3. Iron deficiency criteria

The determination criteria of iron deficiency were based on the Chinese health industry standard "Criteria and Values for Screening Iron Deficiency in Population". The serum ferritin combined with CRP and AAGP2 values were used to determine iron deficiency. Iron deficiency was defined as serum ferritin $<$ 25 mg /L when CRP$\leq$ 5 mg/L and AAGP2 $\leq$ 1 g/L, plasma ferritin $<$ 32 mg /L when CRP $>$ 5 mg/L or AAGP2 $>$ 1 g/L, and serum ferritin $<$ 46 mg /L when CRP $>$ 5 mg/L and AAGP2 $>$ 1 g/L.

2.4. Statistical analysis

Statistical analyses were performed using the SPSS 25.0 software (IBM Corp., NY, USA). Data is presented as number of cases, mean ± standard deviation (SD), and count (percentage). The values of the parameters different groups were compared with the t test. A multivariate analysis of the risk of iron deficiency among blood donors was performed using logistic regression analysis. The discriminative power of the predictive value was assessed by area under the receiver operating characteristic (ROC) curves. *P*-value $<$ 0.05 was considered statistically significant.

3. Results

3.1. Donor baseline characteristics

A total of 801 plateletpheresis donors at the Blood Center of Zhejiang Province from January 2020 to July 2020 were included in this study. However, 35 cases are identified as outliers by a combination of Z-score recognition and actual clinical significance of the data. The baseline characteristics of 766 donors are shown in Table 1.

3.2. Comparison of data between iron deficiency group and normal group of plateletpheresis donors

In this study, the plateletpheresis donors who met the screening criteria for iron deficiency in the Chinese population were classified as the iron deficiency group (31.5 %) and the others as the normal group (68.5 %). Comparison of data between iron deficiency group and normal group of plateletpheresis donors are shown in Table 2.

3.3. Multivariate analysis of iron deficiency in plateletpheresis donors

The above univariate analysis showed that gender, BMI, degree level, Hb, HCT, MCV, MCH, MCHC, RDW-CV, total number of blood donations, and the number of plateletpheresis donation in the past year were associated with the risk of iron deficiency in plateletpheresis donors. Thus, the impact of these factors on iron deficiency in blood donors were evaluated by binary logistic method. Among the 11 independent variables included in the model, age, gender, Hb, MCHC, RDW-CV, total number of blood donation and previous times of plateletpheresis donation in one year were statistically significant(as shown in Table 3). Thus, we derived the following prediction equation of blood donation indicators combined to predict iron deficiency by logistic regression analysis (stepwise regression):Logistic (P) = 14.553 − 0.035 × age + 1.961 × gender - 0.060 × Hb - 0.037 × MCHC + 0.345 × RDW-CV + 0.008 × total number of blood donations + 0.151 × the number of donated blood components in the past year. The obtained Logistic model

Table 1
Donor baseline characteristics.

Characteristics	n/mean ± SD
Gender, male/female	610/156
Age mean ± SD, year	36.95 ± 9.27
BMI	24.54 ± 2.67
Professional	
Workers, peasants and technicians n (%)	275(35.9)
National staff n (%)	31(4.0)
Student n (%)	57(7.4)
Freelance and others n (%)	403(52.6)
Degree level	
Below High School n (%)	237(30.9)
Junior college n (%)	172(22.5)
Undergraduate and postgraduate n (%)	196(25.6)
Others n (%)	161(21.0)
Blood type	
A n (%)	243(31.7)
B n (%)	204(26.6)
O n (%)	257(33.6)
AB n (%)	62(8.1)
Hb , mean ± SD, g/L	147.1 ± 13.92
HCT , mean ± SD, %	44.68 ± 3.60
MCV	89.79 ± 4.73
MCH	29.55 ± 1.90
MCHC	329.04 ± 9.65
RDW-CV	12.67 ± 0.84
Total number of blood donations, mean ± SD, times	39.37 ± 40.59
The number of plateletpheresis donation in the past year, mean ± SD, times	9.98 ± 6.87

Table 2
Comparison of data between two groups.

Variable	The normal group	Iron deficiency group	χ^2/t	*p*
n	525	241		
Gender，male%	90.5	56	120.94	0
age mean ± SD, year	36.37 ± 9.23	38.21 ± 9.23	-2.567	0.01
BMI, mean ± SD	24.75 ± 2.69	24.05 ± 2.53	3.425	0.001
Professional				
Workers, peasants and technicians n (%)	197 (37.52)	78 (32.37)	4.207	0.24
National staff n (%)	21(4.00)	10 (4.15)		
Student n (%)	43(8.19)	14 (10.37)		
Freelance and others n (%)	264 (50.29)	139 (57.68)		
Degree level				
Below High School n (%)	142 (27.05)	95 (39.42)	12.641	0.005
junior college n (%)	129 (24.57)	43 (17.84)		
Undergraduate and postgraduate n (%)	139 (26.48)	57 (23.65)		
Others n (%)	115 (21.90)	46 (19.09)		
Blood type				
A n (%)	167 (31.81)	77(31.95)	4.58	0.205
B n (%)	130 (24.76)	74(30.71)		
O n (%)	188(35.8)	71(29.46)		
AB n (%)	40(7.62)	22(9.13)		
Hb mean ± SD, g/L	151.67 ± 11.20	137.20 ± 14.11	14.023	0
HCT mean ± SD,%	45.72 ± 3.00	42.39 ± 3.72	12.2	0
MCV mean ± SD, fl	90.10 ± 4.47	89.12 ± 5.21	2.527	0
MCH mean ± SD, pg	29.85 ± 1.74	28.91 ± 2.09	6.066	0
MCHC mean ± SD, g/L	331.24 ± 8.72	324.24 ± 9.85	9.458	0
RDW-CV mean ± SD, %	12.56 ± 0.73	12.91 ± 1.00	-4.803	0
Total number of blood donation, mean ± SD, times	33.67 ± 36.12	52.07 ± 46.75	-5.456	0
The number of plateletpheresis donation in the past year, mean ± SD, times	8.83 ± 6.30	12.54 ± 7.42	-6.779	0

Table 3
logistic regression analysis of blood donation indicators combined to predict iron deficiency.

Variable	B	SE	Wald	*P*	OR (95%CI)
Age	-0.035	0.012	8.065	0.005	0.966 (0.943-–0.989)
Gender, male%	1.961	0.345	32.333	0.000	7.107 (3.615-–13.973)
Hb	-0.060	0.011	27.921	0.000	0.942 (0.921-–0.963)
MCHC	-0.037	0.013	8.238	0.004	0.963 (0.939-–0.988)
RDW-CV	0.345	0.136	6.420	0.011	1.412 (1.081-–1.844)
Total number of blood donations	0.008	0.003	6.018	0.014	1.008 (1.002-–1.014)
The number of donated blood components in the past year	0.151	0.021	53.686	0.000	1.162 (1.117-–1.210)
Constant	14.553	5.191	7.860	0.005	2,089,729.134

was statistically significant, chi-square = 337.156, $P = 0 < 0.05$. The model can classify correctly and 82.6 % of the observations can be correctly classified. Positive predictive value and negative predictive value were 78.4 % and 85 %, respectively. ROC curves were used to verify the predictive function of blood donation index combination in predicting iron deficiency of blood donors, and the results were shown in Table 4 and Fig. 1. When the Youden index had a maximum value, the sensitivity and specificity of blood donation index combination for iron deficiency in blood donors were 78.4 % and 85 %, respectively.

4. Discussion

Iron in human body is mainly divided into two types, one is the functional state of iron, including hemoglobin iron (67% of the iron in the body), red egg white iron (15% of the iron in the body), transferrin iron. The other is stored iron, including ferritin and hemosiderin. Normal people only need 1–1.5 mg of iron daily from food to maintain iron balance. However, if red blood cell loss is excessive and cannot be corrected over a long period of time, it can lead to reduced iron storage, reduced serum ferritin, and iron depletion (ID). Long-term iron deficiency will lead to anemia and other adverse effects on human body [8, 9], including cognitive dysfunction, fatigue, decreased exercise endurance, etc. [10–17].

In this study, the basic personal information of blood donors and blood donation related information were analyzed by univariate analysis and multivariate analysis.

The results showed that the gender, RDW-CV, total times of blood donation and previous times of blood donation in one year are independent risk factors for the occurrence of iron deficiency. Among these factors, age, Hb and MCHC are protective factors of iron deficiency in blood donors.

4.1. Age and gender

The results of this study suggest that age was a protective factor for iron deficiency in apheresis platelet donors, and donors were less likely to develop iron deficiency with increasing age. Similarly, some scholars have found that young blood donors are more likely to have low ferritin levels[18].

The reason may be that young blood donors have less restriction on their own living habits than the elderly, tend to have irregular diet and work schedule, and pay less attention to their overall health than the elderly, which may cause relatively less intake of iron nutritional food to a certain extent. With the growth of age, the increase of life experience and the establishment of families, people pay more attention to their overall health and nutrition intake, and are less likely to have low iron intake. But Some studies have suggested that older regular plateletpheresis donors are at higher risk of iron deficiency [19].

In addition, the average age of iron-deficient donors in this study was slightly higher than that of the ferritin normal group. Therefore, Our team will also conduct further analysis of iron deficiency in regular plateletpheresis donors of different age levels in the later stage.

The results of this study showed that female blood donors were more likely to develop iron deficiency than male blood donors, and the risk of iron deficiency was 7.107 times that of male blood donors. Other researchers have similarly concluded that women repeat donors are at higher risk of iron deficiency [18]. Studies also have shown that female donors are more likely to have iron deficiency before their first donation than male donors [20]. The main reason may be the high level of androgens in men, and androgens can promote Erythropoietin (EPO) secretion [21]. EPO plays an important role in the formation and maturation of red blood cells [22]. It can promote the proliferation and survival of red progenitor cells and increase the amount of hemoglobin synthesized by each young red blood cell. Therefore, men have higher levels of red blood cells and hemoglobin than women and are less prone to iron deficiency. Moreover, female donors lose blood during

Table 4
Predictive value of blood donation index combination for iron deficiency in plateletpheresis donors.

Variable	ROC-AUC	SE	*P*	Cutoff value	Sensitivity (%)	Specificity (%)
Age	0.558(0.514–0.601)	0.022	0.00	30.5	79.7	30.7
Gender, male%	0.672(0.628–0.716)	0.022	0.01	0.5	44.0	90.5
The reciprocal of Hb	0.785(0.748–0.821)	0.018	0.00	0.0069	68.0	76.2
The reciprocal of MCHC	0.717(0.677–0.757)	0.020	0.00	0.0031	65.6	70.3
RDW-CV	0.599(0.556–0.642)	0.022	0.00	13.5	32.4	81.3
Total number of blood donations(times)	0.621(0.576–0.665)	0.023	0.00	39.5	49.4	73.7
The number of donated blood components in the past year (times)	0.646(0.602–0.690)	0.023	0.00	14.5	44.0	81.9
blood donation index combination	0.877 (0.849–0.904)	0.014	0.00	0.381	78.4	85.0

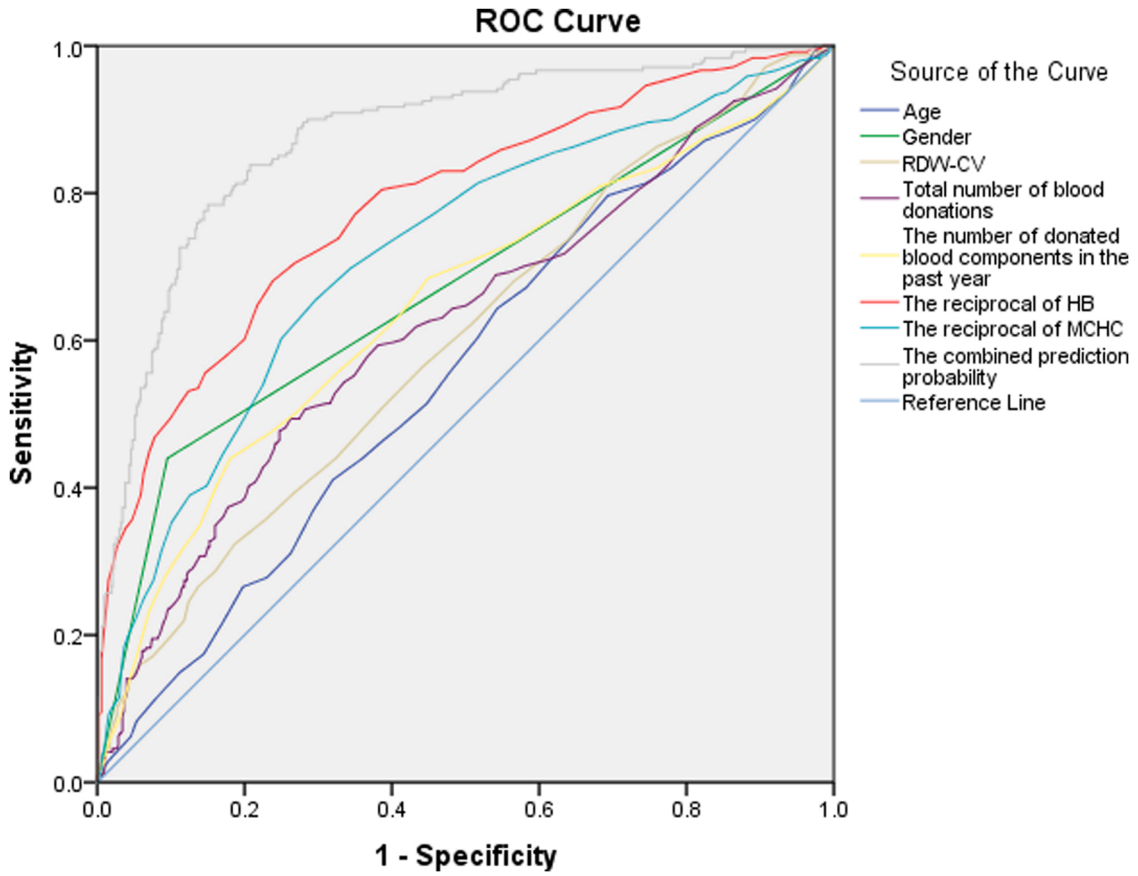

Fig. 1. Receiver operating characteristic curves of blood donation index combination for iron deficiency in plateletpheresis donors.

menstruation, which can also contribute to iron deficiency. In addition, female blood donors pay more attention to external image than male blood donors. In order to keep slim, some female blood donors control their dietary intake and even go on a diet to lose weight, resulting in insufficient iron intake.

Therefore, more attention needs to be paid to iron nutrient levels of women and young blood donors during blood collection.

4.2. Hb, MCHC and RDW-CV

The results of this study showed that the mean values of Hb, HCT, MCHC and other red blood cell related indicators were significantly different between the normal iron nutrition group and the iron deficiency group. Moreover, the results of multivariate analysis suggest that Hb and MCHC are protective factors of iron deficiency in blood donors, while RDW-CV is an independent risk factor. It indicates that donors with low Hb and MCHC levels and high RDW-CV levels have a higher risk of iron deficiency. And the risk of iron deficiency increases by 0.412 times with 1% increase in RDW-CV level.

Hemoglobin is the main component of red blood cells and accounts for about 97% of the dry weight. Disease conditions can be excluded from apheresis platelet donors who are qualified after health consultation. When Hb and MCHC levels are high in blood donors, it indicates that there is rich functional iron content and no need to use stored iron, so there is no risk of iron deficiency. Iron deficiency occurs when the body's demand and supply of iron are out of balance. According to the severity of iron deficiency, iron depletion (ID), iron deficiency in red blood cells (IDE), and iron deficiency anemia (IDA) occur in sequence. The changes of the three stage indexes were as follows: the serum ferritin concentration decreased with the deficiency of stored iron in ID; IDE serum ferritin (SF), serum iron (Fe) decreased, total iron binding ability (TIBC) increased, transferrin saturation (TS) decreased; In addition to abnormal indicators of the first two stages, hemoglobin (Hb) and hematocrit (Hct) decreased in IDA.Therefore, when other pathological factors can be excluded to cause abnormal blood test results and low levels of Hb and MCHC occur, it indicates that the stored iron in blood donors can no longer compensate for the loss of functional iron and has entered the third stage of iron deficiency. Dugdale Alan E et al. also

showed that RDW-CV and Hb levels can predict iron deficiency anemia [23].

4.3. Number of blood donation: Total times of blood donation and previous times of plateletpheresis donation in one year

The results of this study suggest that the risk of iron deficiency will increase by 0.008 times with each increase in the total number of blood donations. The risk of iron deficiency increased by 0.162 times with each increase in the number of plateletpheresis donations in the past year. The results showed that the decrease in ferritin was significantly correlated with the increase of frequency of blood donation. This result is consistent with Salwa Hindawi's study on iron nutrition status of whole Blood donors in the Mediterranean region and Hella Pfeiffer of University of Erlangen and Huihui Li of New York Blood Center's study on iron nutrition status of plateletpheresis donors [20,24,25].

In conclusion, as the number of blood donation increases, it is easy to lead to iron deficiency among blood donors, which is consistent with the results of most researchers [20]. Since nearly two-thirds of TBI is in hemoglobin, loss of red blood cells must lead to loss of iron.Platelet apheresis procedure may cause the loss of red blood cells in blood donors mainly because of residual blood in the pipeline and loss of some red blood cells in sample test retention [2–6]. Moreover, some red blood cells may be subjected to pressure or osmotic pressure changes when they are centrifugated at high speed or mixed with anticoagulant and other fluids. Hemolysis or rupture may occur with loss of RBC [5]. With the increase in blood donation frequency, the total loss of red blood cells increases.When the loss of red blood cells, such as sample collection of plateletpheresis donors for testing and residual supplies, can not be corrected in time, functional iron loss will result in iron deficiency when the storage of iron in the body is reduced to insufficient to compensate for functional iron.

With the significant increase of clinical demand for plateletpheresis, the establishment of a stable team of regular blood donors can not only effectively guarantee the supply of plateletpheresis, but also reduce the risk of transfusions transmitted infection to the minimum. The healthy and sustainable development of blood donors has become an important topic.

In 2017, the American Association of Blood Banks (AABB) and other academic organizations jointly issued a notice on "Latest Strategies for limiting and preventing iron deficiency among blood donors", which listed high-frequency blood donors as one of the "groups at risk of iron deficiency" [26]. The results suggest that blood collection and supply institutions should not only pay attention to the results of iron metabolism indicators of high-frequency blood donors, but also formulate corresponding measures to prevent iron deficiency in high-frequency blood donors.

In conclusion, we need to pay more attention to ferritin levels in female and high-frequency fixed blood donors, and predict the possible risk of iron deficiency in blood donors based on the results of Hb MCHC RDV-CV. We need to add ferritin test for these people, provide health education and guidance to blood donors, and extend the interval or postpone blood donation if necessary, so as to prevent high-risk groups with iron deficiency from becoming unqualified blood donors and affecting their health.

There are still some shortcomings in this study, which did not follow up and test the iron-related results of blood donors. We have started a prospective cohort study to track the iron-related project level of blood donors from the initial stage.We will accumulate and summarize the data and analyze the iron deficiency risk prediction model to effectively guide the implementation of iron deficiency intervention measures.

CRediT authorship contribution statement

Chunyan Li: Writing - original draft, Data curation, Formal analysis. **Qing Feng**: Experimental design guidance. **Jun Zhang** : Experimental design and data analysis guidance. **Xinyou Xie** : Writing-review & editing.

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