Article published online: 2024-03-21

The Role of Reticulocyte Hemoglobin Content in Diagnosing Iron Deficiency in Childhood Cancer

Murti Andriastuti[1] Anisa Dwi Fathinasari[2] Afifa Fahriyani[1] Kanthi Soraca Widiatmika[2] Khansa Salsabila[2] Fitri Primacakti[1]

[1] Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[2] Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Ind J Med Paediatr Oncol 2024;45:396–401.

Address for correspondence Murti Andriastuti, Sp.A(K), Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jalan Pangeran Diponegoro No. 71, Kenari, Senen, Central Jakarta 10430, DKI Jakarta, Indonesia (e-mail: murtiandri@yahoo.com).

Abstract

Background The prevalence of iron deficiency (ID) and iron deficiency anemia (IDA) in children with cancer is not well studied. The detection of ID and IDA using sensitive laboratory tools may facilitate early diagnosis and treatment in this cohort. In this regard, reticulocyte hemoglobin (Ret-He) content serves as a cost-effective measurement that remains unaffected by inflammation, unlike the ferritin test.

Aim The objective of this study is to analyze the role of Ret-He as a diagnostic tool to identify functional and absolute ID and IDA in children with cancer.

Methods We conducted a cross-sectional study in children aged 0 to 18 years. Blood samples were collected to compare Ret-He values with iron status, reflected by hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), serum iron (SI), total iron binding capacity (TIBC), and ferritin and transferrin saturation. The overall discriminative power of Ret-He in detecting ID and IDA was assessed using receiver operating characteristic analysis.

Results Of the 135 children included in the study, 58 (43.0%) had anemia. Among them, 20 (14.8%) had IDA (8 [5.9%] absolute and 12 [8.9%] functional), while 25 (18.5%) had ID (16 [11.9%] absolute and 9 [6.7%] functional). The Ret-He value was significantly related to iron status ($p \leq 0.002$). Ret-He was also shown to have a significant correlation with the abovementioned hematological parameters ($p = 0.000$), except TIBC. Multivariate analysis revealed a significant relationship between Hb ($p = 0.051$), MCH ($p = 0.000$), and MCHC ($p = 0.001$) and Ret-He. Ret-He values of 33.7, 32.7, 32.4 and 28.6 pg were established as optimal cut-off values to identify functional ID, absolute ID, functional IDA, and absolute IDA, respectively.

Conclusion Ret-He is a reliable diagnostic tool for absolute and functional IDA in children with cancer.

Keywords
- absolute ID
- absolute IDA
- childhood cancer
- functional ID
- functional IDA
- hemoglobin
- Ret-He

Introduction

Children suffering from chronic diseases, such as cancer, are more susceptible to both iron deficiency (ID) and iron deficiency anemia (IDA). A study conducted by the European Cancer Anemia Survey (ECAS) revealed that 39% of children with cancer were anemic at the study's onset. This value increased to 67% after chemotherapy. Moreover, 42% were identified as iron deficient.[1,2]

article published online
March 21, 2024

DOI https://doi.org/10.1055/s-0044-1779047.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Anemia in cancer patients can arise from factors like malnutrition, malabsorption, chronic inflammation, bleeding, therapy-induced myelosuppression, bone marrow infiltration, hemolysis, hypersplenism, and ID. The disrupted iron homeostasis and metabolism in cancer patients are primarily due to chronic inflammation, which leads to iron sequestration in macrophages, causing limited iron availability for red blood cell production in the bone marrow.[3,4]

IDA can adversely affect physical performance, leading to general weakness and fatigue and potentially reducing the effectiveness of chemotherapy/radiotherapy against tumors.[3] Thus, the early detection of ID is crucial to address it with simple treatments like iron supplementation or erythropoietin and limit the need for packed red cell transfusion in cancer patients.

Although the gold-standard diagnostic tool for ID is bone marrow staining with Prussian blue, this method is invasive and expensive.[5] In 2010, the American Academy of Pediatrics (AAP) stated that ID can be diagnosed by evaluating ferritin and c-reactive protein levels or measuring reticulocyte hemoglobin (Ret-He), with low hemoglobin levels indicating IDA.[6] However, ferritin is an acute-phase protein that can increase under inflammatory conditions, including malignancy. The European Society for Medical Oncology (ESMO) guidelines define ID in cancer patients as ferritin levels <100 ng/mL or transferrin saturation (TS) $< 20\%$.[3,5]

In recent years, the potential of Ret-He content as an early marker for ID has been highlighted. Reticulocytes are immature erythrocytes released from the bone marrow that can reflect the erythropoiesis status over the preceding 3 to 4 days.[7,8] Unlike ferritin, Ret-He is not influenced by inflammation as it is not an acute-phase protein.[6,9] The hemoglobin content in reticulocytes can be assessed through measures such as Ret-He content (CHr or Ret-He), both utilizing flow cytometry and reported in picograms.[8,10,11] The Ret-He laboratory test can be performed alongside routine blood tests without the need for additional blood samples.[9,12]

Research to determine the optimal Ret-He cut-off values for ID and IDA in pediatrics, particularly pediatric cancer patients is ongoing.[12–14] In this study, we investigated the diagnostic value of Ret-He in identifying ID and IDA in children with cancer to facilitate the simple detection of these conditions.

Materials and Methods

Subjects

A cross-sectional study was conducted in Cipto Mangunkusumo Hospital from March to June 2021. Hospitalized and outpatient children aged 0 to 18 years with cancer were selected as participants. Patients with a history of iron therapy or blood transfusion in the past month were excluded. Written consent and assent were obtained from the subjects' parents or legal guardians and adolescent patients.

Inclusion and Exclusion Criteria

The inclusion criteria for this study comprised children between the ages of 0 and 18 years with cancer who were either hospitalized or received outpatient treatment. Patients who received iron therapy or blood transfusion within the past month were excluded. No oral iron therapy was initiated for IDA patients.

Laboratory Methods

Venous blood samples (6 mL) were obtained from the subjects. Iron parameters, including hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte hemoglobin (Ret-He), ferritin, serum iron (SI), and total iron binding capacity (TIBC), were measured via standard techniques. TS was calculated using the formula SI/TIBC $\times$ 100. All parameters were analyzed in the Clinical Pathology Laboratory of Cipto Mangunkusumo Hospital.

Iron Status Definition

The World Health Organization defines anemia as a low Hb value according to age: Hb <11 g/dL in children aged 6 to 59 months, <11.5 in 5 to 11-year-olds, <12 g/dL in 12 to 14-year-olds, <12 g/dL in unpregnant girls aged ≥ 15 years, and <13 g/dL in boys aged ≥ 15 years.[15] In this study, ESMO criteria were used to evaluate iron status in children: (1) absolute IDA with low Hb and ferritin <100 ng/mL, (2) functional IDA with low Hb and TS $<20\%$ and normal ferritin ≥ 100 ng/mL, (3) absolute ID with normal Hb and ferritin <100 ng/mL, and (4) functional ID with normal Hb and TS $<20\%$ and ferritin ≥ 100 ng/mL.[16]

Primary and Secondary Outcomes

The primary outcome of this study was the establishment of optimal Ret-He cut-off values for different types of absolute and functional ID or IDA, with their respective sensitivities, specificities, and predictive values. The secondary outcome was the evaluation of iron status in children with cancer, including the prevalence of ID and IDA. Laboratory indices, such as Hb, MCV, MCH, MCHC, SI, ferritin and TS, and their relationship with Ret-He, were also analyzed.

Statistical Analysis

The correlation between iron status and Ret-He was determined with analysis of variance (ANOVA) or the Kruskal–Wallis test, depending on the data distribution. Normality was assessed using the Kolmogorov–Smirnoff test. ANOVA with Tukey's post-hoc analysis was performed. Ret-He was also compared with other laboratory parameters through correlation analysis using the Pearson and nonparametric Spearman methods. Significant variables were subsequently subjected to multivariate analysis using linear regression. The overall discriminative power of Ret-He to detect iron depletion, ID, and IDA was assessed using receiver operating characteristic (ROC) analysis. Cut-off values were determined for each iron status using Youden's index, where (sensitivity + specificity) –1 had the highest value. A p-value of <0.05 was considered statistically significant.

Ethics

The Ethics Committee of the Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, approved this study (No. KET-1010/UN2.F1/ETIK/PPM.00.02/2020) on September 14, 2020. This study did not involve any animals. All the research methods involving humans were performed according to the ethical guidelines established by the responsible committee overseeing human experimentation at the institutional and national levels. They also complied with the 1975 Helsinki Declaration, updated in 2013.

Results

A total of 146 children were initially included in this study. Eleven subjects had incomplete data and were excluded; thus, the final study population comprised 135 children (►**Supp. Fig. 1**). The characteristics of these subjects are shown in ►**Table 1**.

Iron Status in Children with Cancer

In this study, 58 children (43.0%) had anemia. The prevalence of IDA was 14.8% (20/135), while anemia in the remaining subjects had other causes. Absolute IDA was found in 8 subjects and functional IDA in 12 subjects. The prevalence of ID was 18.5% (25/135). Absolute ID was found in 16 subjects and functional ID in 9 subjects. Analysis of laboratory indices showed that Hb, MCH, MCHC, Ret-He, SI, and TS were statistically significantly related to iron status. All the laboratory parameters assessing iron status in the abovementioned subgroups were statistically significant except ferritin, MCV, and TIBC (►**Table 2**).

Diagnostic Performance of Ret-He

The diagnostic performance of Ret-He is shown in ►**Supp. Fig. 2**. The ROC curve revealed Ret-He as a reliable diagnostic tool for functional ID, absolute ID, functional IDA, and absolute IDA, with area under the curves (AUCs) of 72.4% ($p = 0.033$, 95% confidence interval [CI]: 0.54–0.91), 77.8% ($p = 0.001$, 95% CI: 0.65–0.91), 69.7% ($p = 0.034$, 95% CI: 0.50–0.89), and 73.1% ($p = 0.037$, 95% CI: 0.50–0.97), respectively. From the correlation analysis, Ret-He was found to be positively related to transferrin (0.54) and ferritin (0.44), as well as the remaining hematological parameters except for TIBC (►**Table 3**). We also conducted a multivariate analysis to examine the relationship between other hematological parameters and Ret-He. A significant relationship was observed between Ret-He and Hb ($p = 0.051$), MCH ($p = 0.000$), and MCHC ($p = 0.001$); see ►**Table 4**. By assessing Youden's index, we determined the optimal cut-off values of Ret-He with their respective sensitivities and specificities for each group (►**Table 5**). The optimal cut-off values for functional ID, absolute ID, functional IDA, and absolute IDA were 33.7, 32.7, 32.4 and 28.6 pg, respectively. On the contrary, the cut-off values with the highest specificity for the aforementioned groups were 28.4–30.25, 27.85–30.25, 27.85–30.25, and 27.25–30.25 pg, respectively.

Table 1 Characteristics of subjects

Characteristics	Frequency (*n*)	Percentage (%)
Gender		
Male	75	55.6
Female	60	44.4
Age (years), mean ± SD, median (IQR)	8.4 ± 4.7	7 (8)
Cancer type		
ALL	74	54.8
AML	7	5.2
CML	9	6.7
Lymphoma	6	4.4
Solid cancer	39	28.9

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; IQR, interquartile range; SD, standard deviation.

Discussion

The prevalence of anemia in our pediatric cancer study was 43.0%, comparable to a study by ECAS (39%).[1] In this study, the overall prevalence of IDA was 14.8%, similar to prior studies in healthy school-aged children in Jakarta (13[12] and 14%[17]). Notably, no previous study has examined the prevalence of anemia and ID in children with cancer in Indonesia.

In cancer patients, iron metabolism and regulation are altered due to chronic disease, chronic blood loss, nutritional deficiency, increased consumption by cancer cells, myelosuppressive chemotherapy, and metastases. ID can contribute to DNA damage, genomic instability, and immunological dysfunction during cancer development.[18] The timely diagnosis and treatment of ID are crucial in cancer patients to prevent complications associated with anemia, such as impaired exercise capacity, fatigue, reduced quality of life, and an overall poor prognosis.[4,7,18] While functional ID is typically predominant,[4,16,18–20] absolute ID was more prevalent in this study, indicating reduced iron stores as the main cause. Thus, restoring iron stores through appropriate therapies is essential.

Iron status assessment in cancer patients remains challenging due to the lack of a gold standard and the impact of inflammatory conditions on standard biochemical tests such as SI and ferritin. According to the AAP, Ret-He is the strongest predictor for ID in children.[6] It remains stable compared with other markers and is unaffected by conditions like infection, inflammation, and malignancy.[6,7,21] In our study, Ret-He showed a significant positive correlation with other hematological parameters ($p = 0.000$) except for TIBC. Multivariate analysis revealed a significant relationship between Ret-He and Hb ($p = 0.051$), MCH ($p = 0.000$), and MCHC ($p = 0.001$). The simultaneous analysis of all laboratory parameters in multivariate analysis allows for assessing the effects of variables, as each laboratory parameter represents a specific definition of ID.

Unfortunately, there is no universal cut-off value or guidelines for Ret-He in diagnosing ID or IDA. Prior studies have

Table 2 Comparison of iron status

	Normal ($n = 52$)	Functional ID ($n = 9$)	Absolute ID ($n = 16$)	Functional IDA ($n = 12$)	Absolute IDA ($n = 8$)	*p*-Value
Hb	13.00 ± 0.96	12.33 ± 0.86	12.58 ± 1.45	10.09 ± 1.16	10.44 ± 1.37	<0.001
MCV	85.48 (75–96)	80.39 (75–87)	77.43 (60–85)	84.03 (78–97)	80.05 (71–85)	0.000
MCH	29.85 (25–34)	27.80 (25–30)	27.40 (19–30)	27.90 (26–33)	27.60 (20–29)	<0.001
MCHC	34.75 ± 1.30	34.29 ± 0.93	34.05 ± 1.28	33.93 ± 1.17	32.64 ± 2.19	0.001
Ret-He	34 (26–38)	32.5 (27–36)	31.2 (20–35)	31.50 (17–36)	30 (19–36)	<0.002[a]
Ferritin	709.55 (113–96,773)	191.03 (111–5,039)	38.35 (11–95)	716.79 (187–3,483)	14.68 (1–81)	0.79
SI	93.5 (40–291)	39 (9–54)	73.5 (24–132)	29.5 (10–52)	45 (19–82)	<0.001[a]
TS	40 (21–92)	17 (9–18)	23 (10–40)	15 (5–20)	14.5 (6–26)	<0.001[a]
TIBC	238 (101–258,000)	231 (103–326)	315 (247–389)	214.5 (168–310)	330 (193–382)	0.93

Abbreviations: ANOVA, analysis of variance; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Ret-He, reticulocyte hemoglobin; SI, serum iron; TIBC, total iron binding capacity; TS, transferrin saturation.
Note: Data are presented as mean ± standard deviation or median (min–max).
[a]Kruskal–Wallis for nonparametric analysis as alternative to ANOVA test.

Table 3 Correlation analysis between Ret-He and hematological parameters

Parameters	Correlation coefficient	Sig. (2-tailed)
Hb[a]	0.431	0.000
MCV	0.474	0.000
MCH	0.627	0.000
MCHC[a]	0.668	0.000
SI	0.489	0.000
TIBC	−0.76	0.460
Transferrin	0.540	0.000
Ferritin	0.443	0.000

Abbreviations: Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Ret-He, reticulocyte hemoglobin; SI, serum iron; TIBC, total iron binding capacity.
Note: Remaining data are analyzed with nonparametric Spearman.
[a]Data are analyzed using Pearson correlation.

Table 4 Multivariate logistic regression analysis between Ret-He and hematological parameters

		Unstandardized coefficients		Standardized coefficients	*t*	Sig.
		B	Standard error	Beta		
Ret-He	Hb	0.392	0.198	0.154	1.983	0.051
	MCV	0.009	0.030	0.025	0.313	0.755
	MCH	0.642	0.166	0.427	3.878	0.000
	MCHC	0.841	0.243	0.315	3.466	0.001
	SI	0.007	0.11	0.101	0.599	0.551
	TIBC	−7.131E − 007	0.000	−0.005	−0.072	0.943
	Transferrin	−0.006	0.028	−0.040	−0.231	0.818
	Ferritin	−1.703E − 005	0.000	−0.043	−0.637	0.526

Abbreviations: Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Ret-He, reticulocyte hemoglobin; SI, serum iron; TIBC, total iron binding capacity.

Table 5 Ret-He cut-off to evaluate iron status

Parameter	AUC	Cut-off	Sensitivity	Specificity	*p*-Value
Functional ID					
	72.4%	33.7[a]	88.9	55.8	0.033 (0.54 – 0.91)
		33.65 – 34.65	88.9	32.7 – 55.8	
		28.4 – 30.25	22 – 33	90.4 – 98.1	
Absolute ID					
	77.8%	32.7[a]	81.3	73.1	0.001 (0.65 – 0.91)
		33.4 – 34.05	81.3 – 87.5	44.2 – 57.7	
		27.85 – 30.25	31.3 – 37.5	90.4 – 98.1	
Functional IDA					
	69.7%	32.4[a]	66.7	75.0	0.034 (0.50 – 0.89)
		34.55 – 35.25	83.3	21.2 – 36.5	
		27.85 – 30.25	25 – 41.7	90.4 – 98.1	
Absolute IDA					
	73.1%	28.6[a]	50.0	98.1	0.037 (0.50 – 0.97)
		35 – 35.25	87.5	21.2 – 26.9	
		27.25 – 30.25	37.5 – 50	90.4 – 98.1	

Abbreviations: AUC, area under the curve; ID, iron deficiency; IDA, iron deficiency anemia,
[a]Optimal cut-off based on the highest Youden index.

suggested various cut-offs, ranging from 25 to 29 pg,[22–24] with sensitivities between 70 and 94% and specificities from 72 to 80% in healthy children. Population studies in healthy Indonesian children aged 6 to 18 years and 6 to 12 years found cut-offs of 27.8[12] and 27.8 pg,[14] respectively. In cancer patients, one study in adolescents and adults aged 11 to 94 years reported a higher Ret-He cut-off of 32.0 pg for ID.[7] In our study, cut-offs for functional ID, absolute ID, functional IDA, and absolute IDA were 33.7, 32.7, 32.4, and 28.6 pg, respectively. Studies in children on hemodialysis reported cut-off values of 28.9[25] and 29.0 pg.[26] Both these values are more similar to the cut-offs in healthy children. Besides determining the optimal fixed values to evaluate iron status, we also analyzed a range of cut-offs for clinical utility. We found that higher cut-offs (33.4–35.25 pg) are suitable for screening purposes, while lower values (27.25–30.25 pg) are more appropriate for diagnosis.

Ret-He proved to be a reliable diagnostic tool for functional ID, absolute ID, functional IDA, and absolute IDA, with respective AUCs of 72.4, 77.8, 69.7, and 73.1%. It exhibited the highest diagnostic performance in the absolute ID group, demonstrating high sensitivity and specificity. In the functional ID and absolute ID groups, sensitivity was higher than specificity, indicating its reliability as a screening tool. In the functional and absolute IDA groups, specificity was higher, making Ret-He a reliable diagnostic tool supported by a good negative predictive value. Ret-He has been reported as superior in diagnosing ID in children by Brugnara et al,[23] Andriastuti et al,[12] and Syed et al.[27] Using Ret-He as a diagnostic tool can reduce the need for additional iron studies, improving cost-effectiveness and patient comfort.[28,29]

Our study has limitations that could potentially introduce bias, such as the restriction of the population to subjects who had not received blood transfusions within the past month and the lack of assessment of transfusion frequency and volume. However, from a clinical perspective, the test can effectively be used as a diagnostic tool either at baseline or for new cases, considering the high prevalence of IDA. This study is the first to report the prevalence of ID and IDA in Indonesian children with cancer. Additionally, it is the first to compare Ret-He to other laboratory parameters as a diagnostic tool for pediatric cancer in Indonesia. Further cohort studies are needed to evaluate Ret-He after iron therapy and explore its impact on anemic and iron-deficient children with cancer, including newly diagnosed patients.

Conclusion

The prevalence of IDA and ID in childhood cancer in this study was 14.8 and 18.5%, respectively. Ret-He emerged as a reliable diagnostic tool, showing a significant positive correlation with other hematological parameters. Given the burden of IDA in children, it is important to understand its impact on children diagnosed with cancer. The relationship between IDA and cancer in this context is currently understudied and requires further exploration. The present study provides valuable insights into iron metabolism in cancer. It also supports the existing evidence that Ret-He remains unaffected by inflammation in cancer. However, further research is needed to determine the clinical utility of these tests in this population.

Patient Consent

Patient consent was obtained from every subject.

Funding
This study was supported by the International Indexed Publication (Publikasi Terindeks Internasional or PUTI) Universitas Indonesia research grant.

Conflicts of Interest
None declared.

References

1 Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer 2004;40(15):2293–2306
2 Ludwig H, Müldür E, Endler G, Hübl W. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol 2013; 24(07):1886–1892
3 Abiri B, Vafa M. Iron deficiency and anemia in cancer patients: the role of iron treatment in anemic cancer patients. Nutr Cancer 2019; 0(00):1–9
4 Naoum FA. Iron deficiency in cancer patients. Rev Bras Hematol Hemoter 2016;38(04):325–330
5 Uçar MA, Falay M, Dağdas S, Ceran F, Urlu SM, Özet G. The importance of RET-He in the diagnosis of iron deficiency and iron deficiency anemia and the evaluation of response to oral iron therapy. J Med Biochem 2019;38(04):496–502
6 Baker RD, Greer FR, Bhatia JJS, et al; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). Pediatrics 2010;126(05):1040–1050
7 Peerschke EIB, Pessin MS, Maslak P. Using the hemoglobin content of reticulocytes (RET-He) to evaluate anemia in patients with cancer. Am J Clin Pathol 2014;142(04):506–512
8 Elghetany MT, Schexneider KI. Erythrocytic disorder. In: McPherson RA, Pincus MR, ed. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Missouri:: Elsevier; 2017:562
9 Toki Y, Ikuta K, Kawahara Y, et al. Reticulocyte hemoglobin equivalent as a potential marker for diagnosis of iron deficiency. Int J Hematol 2017;106(01):116–125
10 Thomas L, Franck S, Messinger M, Linssen J, Thomé M, Thomas C. Reticulocyte hemoglobin measurement–comparison of two methods in the diagnosis of iron-restricted erythropoiesis. Clin Chem Lab Med 2005;43(11):1193–1202
11 Brugnara C, Schiller B, Moran J. Reticulocyte hemoglobin equivalent (Ret He) and assessment of iron-deficient states. Clin Lab Haematol 2006;28(05):303–308
12 Andriastuti M, Adiwidjaja M, Satari HI. Diagnosis of iron deficiency and iron deficiency anemia with reticulocyte hemoglobin content among children aged 6–18 years. Iran J Blood Cancer 2019;11(04): 127–132
13 Lorenz L, Arand J, Büchner K, et al. Reticulocyte haemoglobin content as a marker of iron deficiency. Arch Dis Child Fetal Neonatal Ed 2015;100(03):F198–F202
14 Rungngu SLP, Wahani A, Mantik MFJ. Reticulocyte hemoglobin equivalent for diagnosing iron deficiency anemia in children. Paediatr Indones 2016;56(02):90
15 World Health Organization. Iron deficiency anaemia: assessment, prevention and control, a guide for program managers. Geneva: World Health Organization; 2001:1–114
16 Aapro M, Beguin Y, Bokemeyer C, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29(February):96–110
17 Andriastuti M, Ilmana G, Nawangwulan SA, Kosasih KA. Prevalence of anemia and iron profile among children and adolescent with low socio-economic status. Int J Pediatr Adolesc Med 2020;7 (02):88–92
18 Fan H, Su Y, Duan C, et al. Iron deficiency in children at the time of initial neuroblastoma diagnosis. Pediatr Investig 2019;4(01): 17–22
19 Hashemi SM, Mashhadi MA, Mohammadi M, Ebrahimi M, Allahyari A, Soleimanzadeh Mousavi SH. Absolute and functional iron deficiency anemia among different tumors in cancer patients in south part of Iran, 2014. Int J Hematol Oncol Stem Cell Res 2017; 11(03):192–198
20 Neoh K, Stanworth S, Pasricha SR, Bennett MI. Estimating prevalence of functional iron deficiency anaemia in advanced cancer. Support Care Cancer 2017;25(04):1209–1214
21 Tantawy AA, Ragab IA, Ismail EA, Ebeid FSE, Al-Bshkar RM. Reticulocyte Hemoglobin Content (Ret He). J Pediatr Hematol Oncol 2020;42(03):e147–e151
22 Mateos ME, De-la-Cruz J, López-Laso E, Valdés MD, Nogales A. Reticulocyte hemoglobin content for the diagnosis of iron deficiency. J Pediatr Hematol Oncol 2008;30(07):539–542
23 Brugnara C, Zurakowski D, DiCanzio J, Boyd T, Platt O. Reticulocyte hemoglobin content to diagnose iron deficiency in children. JAMA 1999;281(23):2225–2230
24 Ullrich C, Wu A, Armsby C, et al. Screening healthy infants for iron deficiency using reticulocyte hemoglobin content. JAMA 2005; 294(08):924–930
25 Davidkova S, Prestidge TD, Reed PW, Kara T, Wong W, Prestidge C. Comparison of reticulocyte hemoglobin equivalent with traditional markers of iron and erythropoiesis in pediatric dialysis. Pediatr Nephrol 2016;31(05):819–826
26 Di Pinto D, Paz M, Adragna M, López L. Clinical usefulness of the reticulocyte hemoglobin equivalent in children on hemodialysis. Arch Argent Pediatr 2020;118(06):411–417
27 Syed S, Kugathasan S, Kumar A, et al. Use of reticulocyte hemoglobin content in the assessment of iron deficiency in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2017;64(05):713–720
28 Chinudomwong P, Binyasing A, Trongsakul R, Paisooksantivatana K. Diagnostic performance of reticulocyte hemoglobin equivalent in assessing the iron status. J Clin Lab Anal 2020;34(06): e23225
29 Hönemann C, Hagemann O, Doll D, Luedi MML, Ruebsam ML, Meybohm P. [Reticulocyte hemoglobin equivalent as a diagnostic marker for the current iron deficiency: old wine in new bottles]. Anaesthesist 2020;69(12):919–925