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Original Article

Determinants for Anemic Retinopathy

Ramesh Venkatesh,[1] Nikitha Gurram Reddy,[1] Chaitra Jayadev,[1] Jay Chhablani[2]

[1]Department of Retina and Vitreous, Narayana Nethralaya, Bangalore, India
[2]Department of Retina and Vitreous, University of Pittsburg Faculty of Medicine, Pittsburg, USA

Abstract

Objectives: To study the prevalence of fundus lesions in anaemics and define the hematological risk factors for retinopathy using the receiver operating characteristic curve analysis.

Methods: For this retrospective study, patients ≥18 years and diagnosed with anemia with dilated fundus examination by a retina specialist from May 2019–April 2020 were included. Anemic retinopathy (AR) was present if hemorrhages in different layers of the retina, Roth's spots, exudates, cotton wool spots, retinal edema, and optic disc changes were noted. Patients with secondary anemia were excluded. Two groups were identified: Group 1: Patients with AR; Group 2: Patients with no AR with normal fundus. Demographic features, fundus findings, and hematological parameters were noted.

Results: 38 (30%) eyes of 23 patients had AR; 90 (70%) eyes of 47 patients had no AR. The mean age in Group 1 and Group 2 was 54.7±18.9 and 58.6±15.3 years, respectively. Low hemoglobin (Hb) [mean = 7.82±1.64 gm/dl, p=<0.001] and hematocrit [mean = 26.93±5.22 %, p=0.002] values were noted in the AR group. AUC values for Hb (0.737) and hematocrit (0.719) were higher for the AR group. Hb < 8.95g/dl could predict AR with 85.8% sensitivity and 68.9% specificity, and hematocrit < 30.5% could predict AR with 80% sensitivity and 53.2% specificity. On regression analysis, Hb (p<0.001) and hematocrit (p=0.000) were associated with AR.

Conclusion: Retinopathy is frequently seen in severe anemic patients. It is recommended that patients having low anemia should undergo a retinal examination.

Keywords: Anemia, anemic retinopathy, hemoglobin, packed cell volume, risk factors

Introduction

The World Health Organization describes anemia as a condition in which the number of red blood cells or the hemoglobin (Hb) concentration within them is lower than normal (1). The optimal Hb concentration required to meet the physiological needs varies with age, sex, high altitude of stay, smoking habits, and pregnancy status (2,3). According to the World Health Organization, anemia is defined as an Hb level <13 g/dL in men and <12 g/dL in women (1). Symptoms of anemia can include fatigue, weakness, lightheadedness, headache, pallor or jaundice, tachycardia, palpitations, chest pain, dyspnoea, cold distal extremities, and claudication (4). These signs and symptoms vary in prevalence and magnitude.

The common ocular features noted with anemia are conjunctival pallor, retinal abnormalities, and posterior pole pallor (5-7). Retinal abnormalities associated with anemia include the presence of hemorrhages in all layers of the retina and choroid, Roth's spots, hard exudates, cotton-wool spots, changes in the retinal vessels, optic disc edema, and pallor (8-13). The exact mechanisms leading to these fundus abnormalities are not completely understood. About 30% of the anemic patients show fundus lesions,

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Address for correspondence: Ramesh Venkatesh, MD. Department of Retina and Vitreous, Narayana Nethralaya, Bangalore, India
Phone: +91 9999712195 **E-mail:** vramesh80@yahoo.com

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and up to 34% of patients having concomitant thrombocytopenia (9,14). These were associated with increasing severity of anemia and thrombocytopenia (9). It has been recommended that all anemic patients, particularly with Hb <10 gm/dl, must undergo routine fundus examinations. The prevalence of anemia varies in different regions worldwide and so is the prevalence of anemic retinopathy (AR). Using the cut-off values of Hb described in Western literature for predicting the presence of AR in the Asian continent may not be appropriate. To the best of our knowledge, there is a lack of data describing the prevalence of AR and its association with varying severity of anemia and other hematological parameters.

With this background, the aim of our study was to calculate the prevalence of fundus lesions in anemic patients, and define the risk factors such as Hb, hematocrit, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration and platelet count for retinopathy using the receiver operating characteristic curve analysis.

Methods

All patients, ≥18 years of age, who visited a tertiary eye care hospital in South India for an ophthalmic examination from May 2019 to April 2020 and were diagnosed with anemia during their laboratory check-ups were included in this retrospective cohort study. These also included cases who were planned for routine cataract surgery, diagnosed with anemia on laboratory investigations and had undergone a dilated fundus examination by a fellowship-trained retinal specialist. Anemia was defined as per the World Health Organization's definition (1). The criteria for diagnosing AR included the presence of any of the following features on retinal examination: hemorrhages that can present at all levels of the retina and choroid, Roth's spots, exudates, cotton wool spots, retinal edema, venous tortuosity, optic disc edema or pallor (8). Roth's spots are described as white-centered hemorrhages, though not exclusively associated with anemia (11). Patients with other co-existent systemic diseases like diabetes mellitus, hypertension, and other blood dyscrasias such as leukemia and lymphomas were excluded from the study. All other causes of retinopathies mimicking AR, like diabetic or hypertensive retinopathies, were excluded from the study. In addition, AR occurring as a secondary manifestation in patients with known systemic diseases such as cancer, infections, or autoimmune diseases were excluded from the study. Patients developing AR following treatment with radiation or chemotherapy for other systemic malignancies were also excluded from the study.

The medical records of all the eligible patients were reviewed, and the following data were collected: age, gender, involved eye, best-corrected visual acuity, and clinical features on retinal examination. Blood parameters such as levels of Hb in gm/dl, hematocrit in percentage, mean corpuscular volume in femtolitre, mean corpuscular Hb in picograms, mean corpuscular Hb concentration in percentage, and platelet count in lakhs/microlitre were recorded at the time of examination. Peripheral smear examination findings and the type of anemia were noted where available. Patients having poor media quality, thereby not allowing the proper description of the retinal findings, were excluded.

All data were collected and analyzed by following per under the policies and procedures of the local Institutional Review Board (EC No.: C-2020-09-04; dated September 24, 2020) and the tenets outlined in the Declaration of Helsinki. Because the study was a retrospective analysis, a waiver for informed consent was obtained.

Based on the identification of the features of AR on fundus examination, patients were classified into two Groups: Group 1: Patients with anemia with AR and Group 2: Patients with anemia with a normal fundus examination.

Statistical Analysis

All data were analyzed with GraphPad Prism software (version 8.4.2 [679] for Windows, San Diego, CA). The Kolmogorov–Smirnov normality test showed the data sets to be of the non-parametric variety, and hence only non-parametric statistical tests were used in this study. Visual acuity data were converted to logMAR for statistical analysis. Quantitative variables between the two groups (Group 1 and Group 2) were analyzed using the Mann–Whitney U test. The chi-square test was used to compare the categorical data between the two groups. The area under the receiver operating characteristic curve was calculated to judge the ability of each hematological index in predicting the occurrence of AR. The cut-off values from the receiver operating characteristic curve were obtained for the highest possible sensitivity and specificity for different indices. Univariate and multivariate logistic regression analyses were performed with the presence of AR as the dependent variable and the different hematological markers as independent variables. $P<0.05$ were considered statistically significant.

Results

The demographic features, retinal features, and hematological indices noted at the time of examination between the 2 Groups (Group 1: Patients with anemia with AR and Group 2: patients with anemia with normal fundus examination) were analyzed and compared. In this study, 128 eyes of 70 eligible patients diagnosed with anemia and who met the inclusion criteria were analyzed. On the retinal examination, 38 (30%) eyes of 23 patients had AR, while in the remaining 90 (70%) eyes of 47 patients, no features of AR were identified on fundus examination (Figs. 1a-d). The

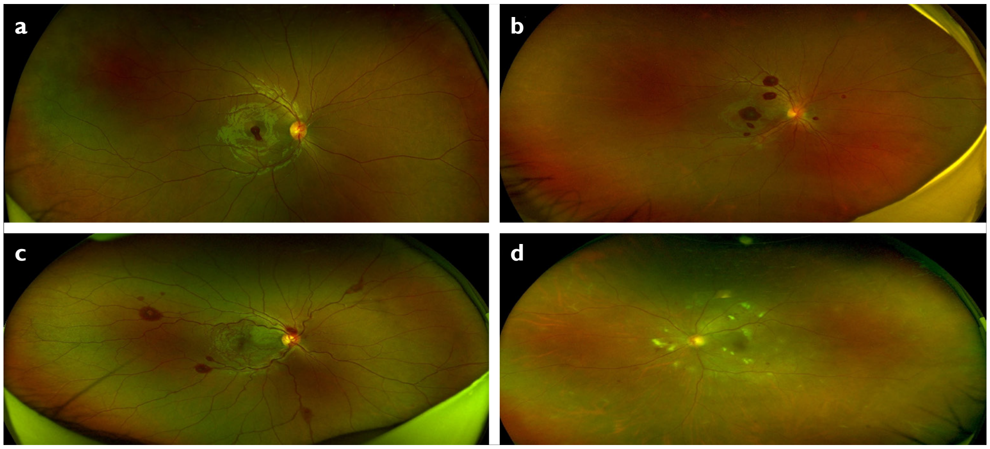

Figure 1. (a-d) Colour fundus images demonstrating the various retinopathy features in anaemic patients.

prevalence of AR was 29.6% in our study. The mean age of the participants in Group 1 and Group 2 was 54.7±18.9 and 58.6±15.3 years, respectively. Table 1 compares the demographic, clinical, and hematological features between the two groups. Sub-internal limiting membrane (ILM) bleeding was the most common clinical finding noted in 18 of the 38

Table 1. Demographic, clinical and haematological features between eyes with AR and without AR

	Anemia with AR (n=38/23)	Anemia without AR (n=90/47)	p
Age (years)	54.7±18.9	58.6±15.3	0.283
Gender (M:F)	12:10	23:25	0.081
Type of anemia (no. of patients)	Normochromic normocytic anemia – 6	Normochromic normocytic anemia – 5	
	Microcytic hypochromic anemia – 5	Microcytic hypochromic anemia – 3	
	Macrocytic anemia – 2		
Study eye (RE:LE)	20:18	47:43	
Spherical equivalent (D)	–0.457±1.53	–1.12±3.94	0.547
Visual acuity (logMAR)	0.352±0.324	0.330±0.332	0.728
Clinical fundus features (N/%)	Vitreous hemorrhage – 1 (2.6)	Normal – 90 (100)	
	Sub ILM bleed – 18 (47.3)		
	Retinal haemorrhages – 8 (21)		
	Roth Spots – 5 (13.1)		
	Dilated and tortuous veins – 1 (2.6)		
	Hard exudates – 4 (10.5)		
	Sub retinal bleed – 5 (13.1)		
	Optic disc edema – 4 (10.5)		
	Optic disc pallor – 5 (13.1)		
Hb (gm/dl)	7.82±1.64	9.24±1.03	<0.001
PCV (%)	26.9±5.22	31.2±3.54	0.002
MCV (fl)	81.9±19.9	77.2±10.6	0.623
MCHC (%)	30.6±3.26	29.9±2.47	0.341
MCH (pg)	25.5±8.52	23.4±4.56	0.604
Platelet count (lakhs/μl)	2.67±1.23	2.86±0.917	0.443

AR: Anaemic retinopathy; M: Male; F: Female; RE: Right eye; LE: Left eye; Hb: Hemoglobin; PCVL: Packed cell volume; MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration; MCH: Mean corpuscular hemoglobin; ILM: Internal limiting membrane.

(47.3%) eyes with AR. Other clinical findings were retinal hemorrhages (21%), sub-retinal bleed (13.1%), Roth Spots (13.1%), optic disc pallor (13.1%), hard exudates (10.5%), optic disc edema (10.5%), and vitreous hemorrhage (2.6%). Significantly low Hb (mean = 7.82±1.64 gm/dl, p=<0.001) and hematocrit (mean = 26.93±5.22 %, p=0.002) values were noted in the AR group compared to the no AR group. Peripheral blood smear examination showed normochromic normocytic anemia in 11 cases, microcytic hypochromic anemia in 8 cases and macrocytic anemia in two cases. The visual acuity between the two groups were comparable (p=0.728).

From the receiver operating characteristic curve analysis, the area under curve values were calculated for each hematological parameter. The area under curve values for Hb (0.737) and hematocrit (0.719) were higher for the AR group. From the receiver operating characteristic curve analysis, our aim was to derive cut-off values for each index so as to predict the occurrence of AR with the maximum possible sensitivity and specificity. For instance, a value of Hb < 8.95 could predict AR with 85.8% sensitivity and 68.9% specificity while a value of hematocrit < 30.5 could predict AR with 80% sensitivity and 53.2% specificity (Table 2 and Fig. 2). Univariate logistic regression analysis identified Hb (p<0.001) and hematocrit (p=0.000) to be associated with predicting AR (Table 3 and Fig. 3). However, multivariate logistic regression analysis of these statistically significant variables could not identify a sole important index in predicting AR (p=0.752) (Table 4).

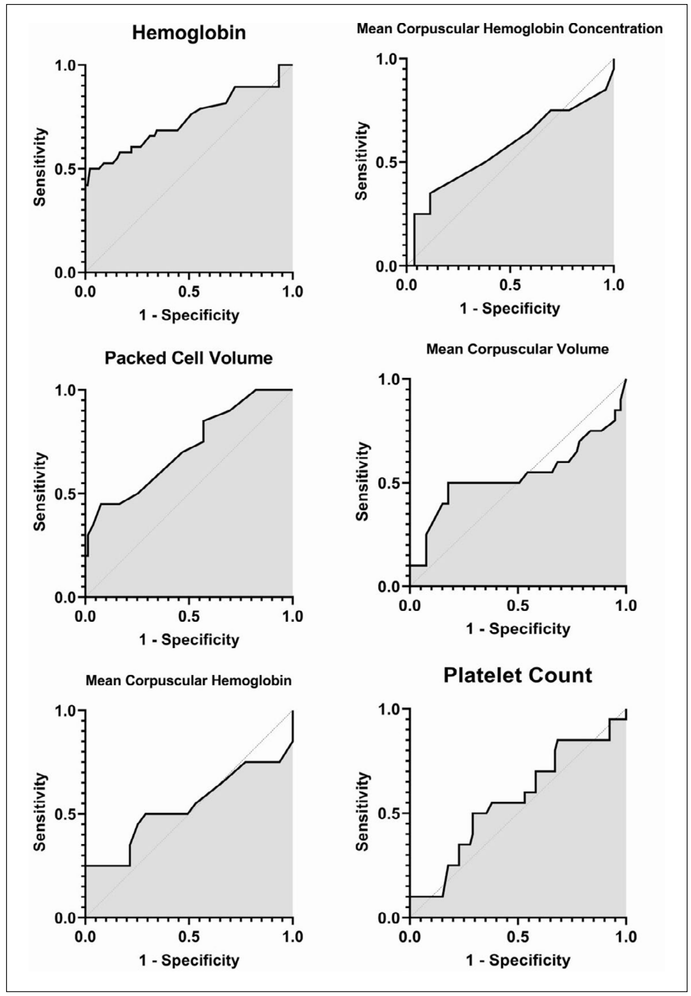

Figure 2. ROC curve analysis graphs showing the AUC of different blood parameters.

Discussion

Our data analyses suggest that severe anemia, either due to reduced Hb or hematocrit levels played a significant role in the pathogenesis of AR in our set of patients. The prevalence of AR in our study was 29.6%. This is in concordance with other studies reported in the literature (8,9,15,16). From the receiver operating characteristic curve analysis, a cut-off value of Hb < 8.9% and hematocrit count of < 30.5% showed a sensitivity of 85% and 80%, respectively, in predicting the occurrence of AR. The bivariate regression analysis done in our study showed both the Hb and the hematocrit levels to be equally important determinants for AR. No correlation

Table 2. Receiver operating curve analysis corresponding to presence of AR using the different blood indices in patients with anemia

Index	AUC	Cut-off value	Highest possible sensitivity (%)	Highest possible specificity (%)	95% CI	p
Hb (gm/dl)	0.737	<8.95	85.8	68.9	0.628–0.846	<0.001
PCV (%)	0.719	<30.5	80	53.2	0.589–0.849	0.003
MCV (fl)	0.536	>75	50	49.4	0.361–0.712	0.619
MCHC (%)	0.569	>30.5	50	62	0.406–0.732	0.342
MCH (pg)	0.538	>26.5	50	70.9	0.366–0.710	0.601
Platelet count (lakhs/μl)	0.563	<2.27	50	70.9	0.418–0.708	0.388

Hb: Hemoglobin; PCV: Packed cell volume; MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration; MCH: Mean corpuscular hemoglobin; PC: Platelet count; AUC: Area under curve.

Table 3. Univariate logistic regression analysis of different blood indices for predicting the development of anaemic retinopathy

	Best-fit value	SE	95% CI	Odds ratio	95 % CI for odds ratio	Likelihood ratio test		AUC	(Tjur's R square)	p
						Log-likelihood ratio	p			
Age	–0.011	0.012	–0.033–0.012	0.989	0.968–1.01	0.863	0.353	0.537	0.005	0.347
Gender	–0.490	0.368	–1.23–0.223	0.612	0.293–1.25	1.81	0.178	0.560	0.009	0.182
Hb	–0.801	0.168	–1.15—0.489	0.449	0.317–0.613	28.6	<0.001	0.737	0.234	<0.001
PCV	–0.26	0.074	–0.421—0.127	0.771	0.656–0.880	16.4	<0.001	0.719	0.192	0.000
MCHC	0.089	0.094	–0.096–0.275	1.09	0.908–1.32	0.909	0.340	0.569	0.011	0.339
MCH	0.064	0.043	–0.021–0.151	1.07	0.979–1.16	2.19	0.139	0.538	0.031	0.138
MCV	0.026	0.019	-0.011–0.064	1.03	0.99–1.07	1.99	0.158	0.536	0.028	0.157
PC	–0.205	0.265	–0.747–0.300	0.815	0.474–1.35	0.615	0.433	0.563	0.008	0.439

Hb: Hemoglobin; PCV: Packed cell volume; MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration; MCH: Mean corpuscular hemoglobin; PC: Platelet count; AUC: Area under curve; SE: Spherical equivalent.

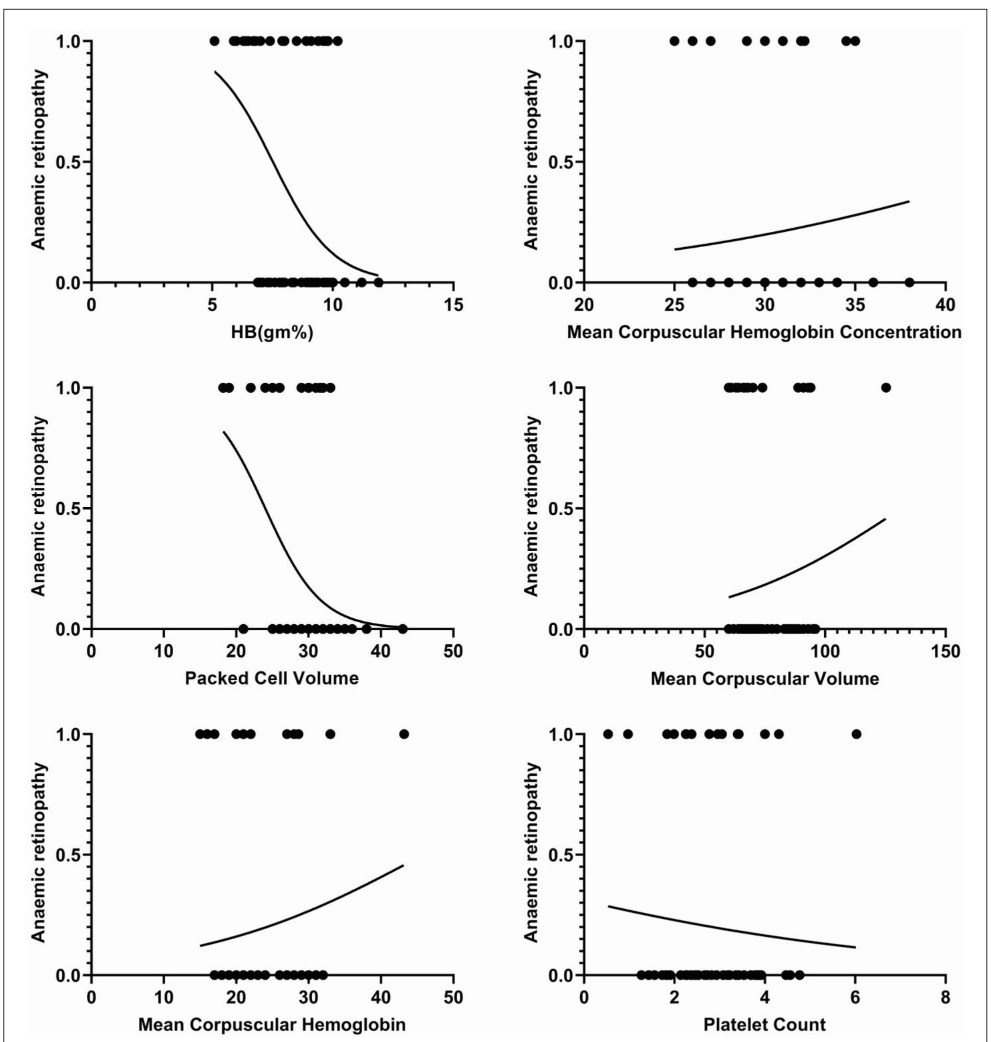

Figure 3. Univariate logistic regression analysis studying the relation of individual blood parameters with AR.

Table 4. Multivariate logistic regression analysis of different blood indices to predict the development of anaemic retinopathy

Variable	Estimate	SE	95% CI (profile likelihood)	Odds ratio estimate	95% CI (profile likelihood	AUC	AICc	Tjur's R square	p
Age	–0.037	0.029	–0.097–0.021	0.964	0.908–1.021	0.904	124.7	0.323	0.752
Gender	–1.182	0.684	–2.603–0.121	0.307	0.074–1.129				
Hb	–1.230	0.797	–2.80–0.318	0.292	0.061–1.374				
PCV	0.030	0.239	–0.468–0.467	1.031	0.626–1.596				
MCV	0.024	0.055	–0.079–0.221	1.000	0.924–1.248				
MCHC	0.081	0.238	–0.427–0.558	1.084	0.652–1.747				
MCH	0.139	0.142	–0.485–0.324	1.150	0.616–1.383				
PC	0.302	0.343	–0.376–0.996	1.352	0.687–2.706				

Hb: Hemoglobin; PCV: Packed cell volume; MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration; MCH: Mean corpuscular hemoglobin; PC: Platelet count; AUC: Area under curve; SE: Spherical equivalent; AICc: Akaike information criteria corrected.

was noted between the other blood indices and the development of AR.

The blood is made of 4 important components: plasma, red blood cells, white blood cells and platelets (17). In anemia, there is the reduction in the number of red blood cells or in the Hb concentration within the red blood cells. According to the National Cancer Institute, anemia is graded into mild (Hb > 10gm/dl to the lower limit of normal), moderate (Hb between 8 and 10 gm/dl),and severe (Hb between 6.5 and 8 gm/dl) (18). Hematocrit is a measure of the percentage or proportion of red blood cells in the blood. Thus, a reduction in the hematocrit count is associated with anemia. Red cell indices like mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, and red cell-width distribution are widely used to determine the etiology of anemia (19). Retinal abnormalities associated with severe anemia are well known (15). The retinal changes found in AR are nonspecific and may closely resemble diabetic or hypertensive retinopathy. We excluded anaemic patients having other co-morbidities like diabetes or hypertension from the study.

There are a few reports in literature defining the relationship between anemia and/or thrombocytopenia with the fundus lesions (9,16). Carraro et al. studied the prevalence of AR in patients having anemia and/or thrombocytopenia (9). An increased prevalence in AR was noted in patients having anemia with coexistent thrombocytopenia; however, no reason was given to explain this phenomenon. A cut-off value of Hb < 8 gm/dl and platelet count < 150 × 109/lit was associated with fundus lesions. In our study, no association was seen between the development of AR and the degree of thrombocytopenia. Severe thrombocytopenia is unusual in cases of primary anemia. Anemia that occurs in combination with severe thrombocytopenia may suggest other diagnoses, such as bone marrow failure, Evan's syndrome, aplastic anemia, or malignancy (16,20). We excluded cases with secondary causes of anemia from our study. This could be the explanation for the high cut-off values of Hb and hematocrit in our cohort of cases. The prevalence and the causes of anemia differ with age, sex, and different ethnic populations (21). Nutritional deficiency, parasitic infections, blood loss during menstruation and growth spurt are the common reasons for anemia in children and adolescents (22). A study by Punjabi et al noted the prevalence of AR in pediatric age group to be about 30% (14). A higher prevalence of AR was noted in children with Hb levels below 10 gm/dl. The reasons for anemia in the elderly are chronic disease, iron deficiency, Vitamin B12 deficiency, folate deficiency, gastrointestinal bleeding and myelodysplastic syndromes (23). Thus, the prevalence of AR in our study could have been affected by age and gender in our study. However, univariate analysis of age and gender with the prevalence of AR showed no statistical significance in our study.

Limitations in our study include the small sample size and the disproportionate number of cases between the 2 Groups. Another important limitation was the absence of sub-group analysis between the etiology of anemia and the development of retinal lesions. This is because of the absence of data on peripheral smear examination in most of our cases. Furthermore, assessing the prevalence of AR in children with anemia would have been useful.

Conclusion

The retinopathy is a frequent finding in anemic patients with low Hb and hematocrit levels. It is recommended that all patients having low Hb and low hematocrit values undergo a dilated fundus examination. The presence of low platelet count in primary anemia did not prove to be an important factor. Other blood indices like mean corpuscular volume, mean corpuscular Hb and mean corpuscular Hb concentration showed no association with the presence of the retinal lesions.

Disclosures

Ethics Committee Approval: All data were collected and analyzed by following per under the policies and procedures of the local Institutional Review Board (EC No.: C-2020-09-04; dated September 24, 2020) and the tenets outlined in the Declaration of Helsinki. Because the study was a retrospective analysis, a waiver for informed consent was obtained.

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Conflict of Interest: None declared.

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