



Complete Blood Count Parameters in Apheresis Platelet Donors According to ABO and Rh Blood Groups

Aferez Trombosit Donörlerinde ABO ve Rh Kan Gruplarına Göre Tam Kan Sayımı Parametreleri

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Abstract

Objective: Data about the effects of blood groups on complete blood count parameters are limited. We aimed to examine the relationship between complete blood count parameters and ABO-Rh blood groups in this study.

Method: Three thousand volunteer apheresis donors were examined. The records of these cases were evaluated retrospectively and age, gender, complete blood count parameters, and ABO and Rh blood groups were recorded. Statistical evaluations were made by the SPSS 21 program.

Results: A significant correlation was found between the ABO blood group and erythrocyte distribution width-standard deviation and plateletcrit values ($p=0.01$, $p=0.009$, respectively). Neutrophil and mean erythrocyte hemoglobin concentration values were statistically significantly higher in Rh-negative cases than in Rh-positive cases ($p=0.04$, $p=0.01$, respectively). Neutrophil count was lower in the A blood group than in the non-A blood group ($p=0.03$). Lymphocyte count was significantly higher in cases with the B blood group than in cases with the non-B blood group ($p=0.002$).

Conclusion: We found a significant relationship between ABO and Rh blood groups and some complete blood count parameters. Therefore, one of the factors affecting hemogram parameters may be ABO and Rh blood group.

Keywords: ABO blood group, hemoglobin, lymphocyte, neutrophil, platelet, Rh blood group

Öz

Amaç: Kan gruplarının tam kan sayımı parametreleri üzerindeki etkilerine ilişkin veriler sınırlıdır. Bu çalışmada tam kan sayımı parametreleri ile ABO-Rh kan grupları arasındaki ilişkiyi incelemeyi amaçladık.

Yöntem: Üç bin gönüllü aferez başışçısı incelendi. Bu olguların kayıtları geriye dönük olarak değerlendirilerek yaş, cinsiyet, tam kan sayımı parametreleri, ABO ve Rh kan grupları kaydedildi. İstatistiksel değerlendirmeler SPSS 21 programı ile yapıldı.

Bulgular: ABO kan grubu ile eritrosit dağılım genişliği-standart sapma ve plateletcrit değerleri arasında anlamlı bir ilişki bulundu (sırasıyla $p=0,01$, $p=0,009$). Nötrofil ve ortalama eritrosit hemoglobin konsantrasyonu değerleri Rh negatif olgularda Rh pozitif olgulara göre istatistiksel olarak anlamlı derecede yüksekti (sırasıyla $p=0,04$, $p=0,01$). Nötrofil sayısı A kan grubunda A olmayan kan grubuna göre daha düşüktü ($p=0,03$). Lenfosit sayısı B kan grubuna sahip olgularda B olmayan kan grubuna sahip olgulara göre anlamlı olarak daha yüksekti ($p=0,002$).

Sonuç: ABO ve Rh kan grupları ile bazı tam kan sayımı parametreleri arasında anlamlı bir ilişki bulduk. Bu nedenle hemogram parametrelerini etkileyen faktörlerden biri de ABO ve Rh kan grubu olabilir.

Anahtar kelimeler: ABO kan grubu, hemoglobin, lenfosit, nötrofil, Rh kan grubu, trombosit



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Introduction

In addition to the history and physical examination findings, laboratory tests play an important role in the diagnosis and follow-up of the diseases. Complete blood count (CBC) is the most commonly used diagnostic hematological laboratory test in clinical practice. It provides information about the numbers of erythrocyte, leukocyte, and platelet, their shapes, and structural features. CBC is used for both diagnosis and follow-up of diseases such as anemia, leukemia, infection, and bleeding disorders. CBC containing more than 20 sub parameters can be performed by the auto analyzers in a very short time.

The results of the CBC parameters are evaluated according to the reference ranges determined by the manufacturer. However, age, race, gender, hunger status, altitude, pregnancy, technical equipment used, and environmental factors may affect CBC parameters (1-4). It is reported that dietary habits also affect the reference ranges of hemogram parameters (5). For this reason, determining the factors affecting the CBC parameters and arranging the reference ranges according to these factors provide an accurate interpretation of CBC parameters. The International Federation of Clinical Chemistry and Laboratory Medicine and the Clinical and Laboratory Standards Institute recommend that each laboratory establish its reference range for the CBC test.

Blood group identification was first made in 1901 by Karl Landsteiner as A, B, and O according to the type of antigen found on the erythrocyte surface (6). Sturli and Von Castelo defined the AB blood group in 1902. Currently, 339 blood group antigens and 33 blood group systems have been listed by the International Blood Transfusion Association study committee. The relationship between the ABO blood group and esophagus, stomach, prostate, colorectal, liver, and prostate cancers was reported (7-10). In addition, the relationship between coronary artery disease (CAD) and the ABO blood group was investigated, and CAD was found to be more common in patients with non-O blood group (11). Increased mean platelet volume (MPV) and platelet distribution width (PDW) values are also potential biomarkers for CAD. For this reason, it is thought that the reason why coronary artery disease is common in some blood groups may be related to PDW and MPV values. Studies investigating the relationship between the ABO blood group and MPV, PDW values were conducted. However, there are a few studies examining the effects of blood groups on all CBC parameters. Therefore, in this study, we aimed to investigate the effects of ABO and Rh blood groups on hemogram parameters.

Materials and Methods

Ethical approval was obtained from the Atatürk University Ethics Committee for this study (date: 17.12.2020, number: B.30.2.ATA.0.01.00/18). The study design was made in accordance with the Declaration of Helsinki. Three thousand volunteer apheresis donors who applied to the blood center of our hospital were analyzed in this study. All of the subjects included in the study were healthy and they had no history of systemic disease, drug use, or active infection. The medical files of all cases were evaluated retrospectively and age, gender, hemoglobin (hb), hematocrit (hct), erythrocyte (RBC), leukocyte (WBC), neutrophil (PNL), lymphocyte, monocyte, eosinophil, basophil, mean erythrocyte volume (MCV), mean erythrocyte hemoglobin (MCH), mean erythrocyte hemoglobin concentration (MCHC), erythrocyte distribution width-standard deviation (RDW-SD), erythrocyte distribution width-coefficient of variation (RDW-CV), plateletcrit (PCT), MPV, PDW, platelet-larger cell ratio (P-LCR) values, ABO and Rh blood groups were recorded. For the CBC test, a blood sample was taken into a tube with ethylenediaminetetraacetic acid (EDTA) and studied by Sysmex XN 1000 (Germany) automatic CBC device. ABO and Rh blood groups of the cases were determined by Galileo Immucor Gamma (Microplate, Germany) device. Cases with positive D antigen were considered as Rh-positive.

Statistical Analysis

Statistical evaluations were made by SPSS 21 windows software (Armonk, NY: IBM Corp). Descriptive data were defined as number and percentage for categorical variables, and mean \pm standard deviation for numeric variables. For the comparison of the two groups, the Student's t-test was used in the presence of a normal data distribution, and the Mann-Whitney U test was used when there was no normal data distribution. Comparison of numeric values among three or more groups was performed using a One-Way analysis of variance (ANOVA) test for the data with normal distribution, and the Kruskal-Wallis test for the non-normally distributed data. A value of $p < 0.05$ was considered as statistical significance.

Results

The mean age of all cases in our study was 33.97 ± 11.04 (18-65) years; 2456 (81.9%) cases were men, and 544 (18.1%) were women. The distribution of ABO and Rh blood groups in all cases is shown in Table 1. A significant correlation between AB in the O blood group and RDW-SD and PCT

values ($p=0.01$, $p=0.009$, respectively) was detected through the ANOVA test. In subgroup comparisons, the RDW-SD value was found to be significantly higher in the A blood group compared to the B blood group and AB blood group ($p=0.03$, $p=0.018$, respectively). PCT value was significantly higher in the A blood group than in the AB blood group ($p=0.04$). A significant relationship was not determined between other hemogram parameters and the ABO blood group (Table 2).

Neutrophil count and MCHC value were statistically significantly higher in Rh-negative cases than in Rh-positive

cases ($p=0.04$, $p=0.01$, respectively) (Table 3). There was no significant relationship between other hemogram parameters and the Rh blood group.

In only male cases, a significant relationship was found between the ABO blood group and RBC, RDW-SD values ($p=0.01$, $p=0.01$, respectively). In the subgroup examination, the RDW-SD value was found to be significantly higher in the A blood group than in the B blood group ($p=0.026$), and the RBC value in the AB blood group was significantly higher than in the A blood group ($p=0.008$). Neutrophil and MCHC values in Rh-negative cases were significantly higher than in Rh-positive cases ($p=0.03$, $p=0.01$, respectively). In male cases, no significant relationship was found between other hemogram parameters and ABO, Rh blood groups.

In only female cases, a significant association between hb, hct values, and ABO blood group was determined ($p=0.004$, $p=0.002$, respectively). In the subgroup evaluation, the hb value in the A blood group was found to be significantly higher than in the B, AB, and O blood groups ($p=0.004$, $p=0.012$, $p=0.039$, respectively). Hct value was also found significantly higher in the A blood group compared to B, AB, and O blood groups in accordance with the hb value

Table 1. The distribution of blood groups

Blood group	Male n (%)	Female n (%)	Total n (%)
A Rh(+)	885 (29.5%)	165 (5.5%)	1050 (35%)
A Rh(-)	157 (5.2%)	31 (1%)	188 (6.3%)
B Rh(+)	352 (11.7%)	78 (2.6%)	430 (14.3%)
B Rh(-)	60 (2%)	13 (0.4%)	73 (2.4%)
AB Rh(+)	162 (5.4)	60 (2%)	222 (7.4%)
AB Rh(-)	38 (1.3%)	7 (0.2%)	45 (1.5%)
O Rh(+)	602 (20.1%)	147 (4.9%)	749 (25%)
O Rh(-)	200 (6.7%)	43 (1.4%)	243 (8.1%)

Table 2. CBC parameters according to the ABO blood group

CBC parameters	Blood group					p
	A	B	AB	O	Total	
WBC (μL)	8155 \pm 1709	8314 \pm 1692	8115 \pm 1754	8203 \pm 1800	8194 \pm 1741	0.31
Lymphocyte (μL)	2803 \pm 751	2885 \pm 768	2805 \pm 784	2767 \pm 0.734	2805 \pm 752	0.42
Neutrophil (μL)	4496 \pm 121.8	4576 \pm 1279	4446 \pm 1297	4568 \pm 1358	4529 \pm 1295	0.32
Monocyte (μL)	630 \pm 174	628 \pm 163	637 \pm 194	638 \pm 175	633 \pm 174	0.63
Eosinophil (μL)	179 \pm 127	177 \pm 121	182 \pm 139	181 \pm 142	180 \pm 132	0.95
Basophil (μL)	46 \pm 21	46 \pm 23	43 \pm 21	45 \pm 21	45 \pm 21	0.33
RBC (μL)	5511 \pm 421	5533 \pm 418	5539 \pm 437	5489 \pm 440	5510 \pm 4290	0.17
Hb (g/dL)	16.05 \pm 1.22	16.06 \pm 1.25	16.03 \pm 1.28	15.98 \pm 1.25	16.03 \pm 1.24	0.53
Hct (%)	47.2 \pm 3.2	47.29 \pm 3.38	47.2 \pm 3.3	47.07 \pm 3.32	47.21 \pm 3.31	0.46
MCV (fL)	85.9 \pm 3.8	85.5 \pm 3.8	85.39 \pm 4.1	85.9 \pm 4.2	85.81 \pm 3.98	0.09
MCH (pg)	29.1 \pm 1.6	29.08 \pm 1.66	29 \pm 1.88	29.18 \pm 1.78	29.15 \pm 1.71	0.32
MCHC	33.9 \pm 1.25	33.98 \pm 1.3	33.95 \pm 1.3	33.96 \pm 1.25	33.96 \pm 1.26	0.98
RDW-SD	39.47 \pm 2.56	39.11 \pm 2.57	39.33 \pm 2.59	39.56 \pm 2.66	39.43 \pm 2.6	0.01
RDW-CV	12.62 \pm 0.78	12.57 \pm 0.83	12.66 \pm 0.77	12.66 \pm 0.84	12.63 \pm 0.81	0.16
PLT (μL)	270853 \pm 53594	269918 \pm 54323	264940 \pm 50275	270599 \pm 58214	270143 \pm 55092	0.58
MPV (fL)	10.07 \pm 0.81	10.16 \pm 0.83	10.08 \pm 0.87	10.11 \pm 0.83	10.10 \pm 0.83	0.3
PCT (%)	0.27 \pm 0.05	0.27 \pm 0.05	0.26 \pm 0.05	0.27 \pm 0.05	0.27 \pm 0.05	0.009
PDW	11.64 \pm 1.72	11.84 \pm 1.83	11.66 \pm 1.93	11.72 \pm 1.79	11.70 \pm 1.78	0.33
P-LCR	25.80 \pm 6.47	26.44 \pm 6.64	25.80 \pm 7.18	26.23 \pm 6.49	26.04 \pm 6.58	0.49

WBC: White blood cell, RBC: Red blood cell count, hb: Hemoglobin, hct: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-SD: Erythrocyte distribution width-standard deviation, RDW-CV: Erythrocyte distribution width-coefficient of variation, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet-larger cell ratio

(p=0.009, p=0.007, p=0.005, respectively). Basophil, MCH and MCHC values were low in Rh-positive group compared to Rh-negative group (p=0.04, p=0.04, p=0.009, respectively). In female cases, there was no significant relationship between other CBC parameters and ABO, Rh blood groups.

The cases were compared as A Rh(+) and A Rh(-), B Rh(+) and B Rh(-), AB Rh(+) and AB Rh(-), O Rh(+) and O Rh (-). In addition, the cases were compared as A Rh (+) and non-A Rh (+), B Rh(+) and non-B Rh(+), O Rh(+) and non-O Rh(+), AB Rh(+) and non-AB Rh (+), A Rh(-) and non-A Rh (-), B Rh (-) and non-B Rh(-), O Rh(-) and non-O Rh(-), AB Rh(-) and non-AB Rh (-). Statistically significant results were shown in Tables 4, 5, respectively.

The cases were also grouped as A and non-A, B and non-B, AB and non-AB, and O and non-O blood groups. The neutrophil count in the A blood group (4496±121.8 µL) was significantly lower than in the non-A blood group (4613±1304 µL) (p=0.03). The lymphocyte count was found significantly higher in the B blood group (2885±768 µL) than in the non-B blood group (2697±757 µL) (p=0.002). There was no relationship between other hemogram parameters and these blood groups.

Table 3. CBC parameters according to Rh blood group

CBC parameters	Rh-positive	Rh-negative	p
Leukocyte (µL)	8167±1744	8314±1726	0.07
Lymphocyte (µL)	2804±756	2810±735	0.86
Neutrophil (µL)	4506±1287	4631±1326	0.04
Monocyte (µL)	630±174	644±177	0.09
Eosinophil (µL)	179±135	181±120	0.77
Basophil (µL)	45±22	46±21	0.43
RBC (µL)	5510±425	5512±444	0.9
Hb (g/dL)	16.02±1.24	16.07±1.23	0.41
Hct (%)	47.24±3.34	47.08±3.21	0.31
MCV (fL)	85.86±3.94	85.59±4.16	0.14
MCH (pg)	29.13±1.69	29.22±1.79	0.25
MCHC (g/dL)	33.92±1.26	34.13±1.28	0.01
RDW-SD	39.45±2.59	39.33±2.63	0.35
RDW-CV	12.63±0.81	12.64±0.81	0.84
PLT (µL)	273370±53543	271250±55825	0.41
MPV (fL)	10.11±0.83	10.14±0.76	0.46
PCT (%)	0.27±0.05	0.27±0.05	0.83
PDW	11.73±1.77	11.77±1.64	0.71
P-LCR	25.99±6.7	26.24±6.13	0.5

RBC: Red blood cell count, hb: Hemoglobin, hct: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-SD: Erythrocyte distribution width-standard deviation, RDW-CV: Erythrocyte distribution width-coefficient of variation, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet-larger cell ratio

Table 4. CBC parameters in B Rh(+), B Rh(-), AB Rh(+), AB Rh(-), O Rh(+) and O Rh(-) blood groups

CBC parameters	Blood group		p
	B Rh(+) (mean ± SD)	B Rh(-) (mean ± SD)	
Leukocyte (µL)	8339 ±1696	8834±1609	0.025
Neutrophil (µL)	4530±1267	4960±1253	0.010
MCV (fL)	85.44±3.91	86.68±3.71	0.015
MCH (pg)	28.99±1.67	29.59±1.47	0.006
	AB Rh (+) (mean ± SD)	AB Rh(-) (mean ± SD)	
	MCH (pg)	28.86±1.91	
MCHC (g/dL)	33.79±1.31	34.49±1.33	0.002
	O Rh(+) (mean ± SD)	O Rh(-) (mean ± SD)	
	PLT (µL)	273310±60280	
PCT (%)	0.27±0.05	0.26±0.05	0.025
MCV (fL)	86.11±4.09	85.30±4.78	0.016
MCHC (g/dL)	33.91±1.25	34.14±1.27	0.022

MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, PLT: Platelet, PCT: Plateletcrit, SD: Standard deviation, CBC: Complete blood count

Table 5. CBC parameters in B Rh(+), non-B Rh(+), O Rh(+) and non-O Rh(+), B Rh(-) and non-B Rh(-), AB Rh(-) and non-AB Rh(-), O Rh(-) and non-O Rh(-) blood groups

CBC parameters	Blood group		p
	B Rh(+) (mean±SD)	Non-B Rh(+) (mean±SD)	
MCV (fL)	85.44 ±3.9	85.9±4.05	0.041
MCH (pg)	28.99±1.67	29.18±1.73	0.049
RDW-SD	39.09±2.59	39.49±2.62	0.006
PDW	11.87±1.88	11.67±1.76	0.042
	O Rh (+) (mean ± SD)	Non-O Rh(+) (mean ± SD)	
	RBC (µL)	5470±430	
	B Rh(-) (mean ± SD)	Non-B Rh(-) (mean ± SD)	
	Leukocyte (µL)	8281±2377	
Lymphocyte (µL)	2823±1023	2568±1061	0.047
Neutrophil (µL)	4955±1253	4526±1293	0.006
MCH (pg)	29.59±1.47	29.14±1.73	0.032
	AB Rh(-) (mean ± SD)	Non-AB Rh(-) (mean ± SD)	
	MCHC (g/dL)	34.49±1.33	
	O Rh(-) (mean ± SD)	Non-O Rh(-) (mean ± SD)	
	MCV (fL)	85.31±4.77	
MCHC (g/dL)	34.13±1.27	33.94±1.27	0.035
PLT (µL)	261967±50442	270865±55434	0.016
PCT (%)	0.26±0.05	0.27±0.05	0.04

MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-SD: Erythrocyte distribution width-standard deviation, PLT: Platelet, PCT: Plateletcrit, PDW: Platelet distribution width, SD: Standard deviation, RBC: Red blood cell count, CBC: Complete blood count

Discussion

The frequency of ABO and Rh blood groups is affected by ethnicity. In ABO blood group distribution worldwide, A blood group was 41%, O blood group was 47%, B blood group was 9%, and AB blood group was 3% (12). In the United States, the blood group distribution was found as 37.1%, 46.7%, 12.2%, and 4.1% according to the same order (13). Akbay et al. (14) investigated the ABO blood group frequency in Turkey and they determined the distribution of A, O, B, and AB blood groups as 42.84%, 32.67%, 16.46%, and 8.03%, respectively. Eren and Çeçen (15) studied 2198 platelet donors and they found the blood group distribution of these cases as A Rh(+): 37.2%, O Rh(+): 33.3%, B Rh(+): 11.7%, A Rh(-) and O Rh(-): 5.2%, AB Rh(+): 5.1%, B Rh(-): 1.2% and AB Rh(-): 1%. Rh positivity in Turkey was determined as 88.54%. The blood group distribution in our study was A>O>B>AB and this result was similar to blood group distribution in our country. However, we detected Rh positivity in 66.7% of our cases. This rate is lower than in Turkey and around the world. This may be due to ethnic differences. There are more male cases than female cases who voluntarily applied to healthcare institutions to become platelet and erythrocyte donors (16,17). The reason for this condition may be that anemia is more common in women due to menstrual bleeding and pregnancy. In our study, in accordance with the literature, the number of male donors was more than women.

Several studies have been conducted to examine the effects of ABO and Rh blood groups on platelet count and parameters. Eren and Çeçen (15) reported that the platelet count in Rh-positive individuals was higher than in Rh-negative individuals. They detected the platelet count as higher in the O Rh(+) group than in the O Rh(-) group. However, there was no statistically significant difference between the two groups. MPV shows the mean platelet volume and is an important biomarker of platelet activation (18). PDW measures the distribution of platelet sizes and is a marker showing platelet function. Celik et al. (19) evaluated the association between platelet parameters and the ABO blood group of 301 healthy volunteers. They found the MPV value lower in the O and A blood groups than in the AB and B blood groups. On the other hand, PDW value was lower in individuals with O and A blood groups than in cases with B blood group. In our study, a significant relationship was found between the ABO blood group and plateletcrit value. PCT value was significantly higher in the A blood group compared to the AB blood group. Plt and PCT values were lower in the O Rh(-) blood group than in the O Rh(+) and non-O Rh(-) blood groups. In addition, the

PDW value was higher in B Rh(+) individuals than in non-B Rh(+) individuals. We did not find a significant relationship between ABO and Rh blood groups and MPV, P-LCR values.

Khan et al. (20) determined the association between the hb value and ABO, Rh blood groups of 1796 people in Abha city. They did not find a significant relationship between ABO, Rh blood groups, and hb value. In the study conducted by Ramalingam and Raghavan (21) 158 male and 111 female cases were examined. They found that the hb value in O Rh(+) individuals was significantly higher than in A Rh(+) individuals. They also declared that the O blood group had a higher hb value than the A and B blood groups. In our study, we found that individuals in the A blood group had significantly higher hb and hct values than the other groups in only female cases. Seyfizadeh et al. (22) examined 792 healthy pregnant women and found the RBC count higher in the AB blood group than in the A and O blood groups. However, they did not find a significant difference between the groups in terms of hb and hct values. In our study, the RBC count was higher in the AB blood group than in the A and O blood groups in only male cases. Also, the RBC value was lower in the O Rh(+) group than in the non-O Rh(+) group in our study. Ramalingam and Raghavan (21) found the hb value to be lower in the Rh-negative group than in the Rh-positive group. In our study, no relationship was found between the Rh blood group and the hb value. However, we found the MCHC value was higher in the Rh(-) group than in the Rh(+) group. RDW is a test that shows the difference in the size of erythrocytes. It is a parameter used to distinguish between iron deficiency anemia and thalassemia carriage. In our study, we found that the RDW-SD value was significantly higher in the O blood group.

In our study, the neutrophil count in the A blood group was found to be statistically significantly lower than in the non-A blood group. In the B blood group, the lymphocyte count was higher than in the non-B blood group. The results of our study could not be compared with the literature, because there were no studies in the literature about the effect of ABO and Rh blood groups on leukocyte, lymphocyte, monocyte, eosinophil, and basophil counts.

Conclusion

A CBC is a cheap test and it can be performed in any hospital. However, reference ranges for hemogram parameters have not been fully standardized. Therefore, it is recommended that each laboratory establish its reference range for CBC. All factors affecting hemogram parameters should be evaluated to determine reference ranges. In this study, we

detected that ABO and Rh blood groups affected some CBC parameters.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Atatürk University Ethics Committee for this study (date: 17.12.2020, number: B.30.2.ATA.0.01.00/18).

Informed Consent: Patients consent form was waived (not required) because the study was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.S., F.E., Design: E.B., S.S., Data Collection or Processing: G.S., S.S., F.E., Analysis or Interpretation: E.B., Literature Search: G.S., S.S., F.E., Writing: G.S., S.S., E.B., Manuscript Review, and Revision: F.E., G.S., S.S., E.B.

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