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Evaluating the association of ischemic ECG changes and CBC parameters in normal population

Mahdiyeh Yaghooti-Khorasani[1,2#], Naiemeh Varasteh[2#], Hossein Hatamzadeh[3], Sara Saffar Soflaei[1,2], Susan Darroudi[2], Toktam Sahranavard[2], Maryam Allahyari[3], Ehsan Mosa Farkhani[4], Alireza Heidari-Bakavoli[5,6], Hedieh Alimi[5], Azadeh Izadi-Moud[7], Fahime Hosseinzadeh[8,9], Gordon A. Ferns[10], Habibollah Esmaily[8,9], Majid Ghayour-Mobarhan[1,2*], Mohsen Moohebati[5,6*]

1- Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2- International UNESCO Center for Health-Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran
3- Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
4- Department of Epidemiology, Faculty of Health, Mashhad University of Medical Sciences, Mashhad, Iran
5- Vascular and Endovascular Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
6- Department of Cardiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
7- Department of Cardiovascular Diseases, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
8- Department of Biostatistics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran
9- Social Determinants of Health Research center, Mashhad University of Medical Sciences, Mashhad, Iran
10- Brighton and Sussex Medical School, Division of Medical Education, Brighton, UK

[#] Equally first authors
* Equally Corresponding authors

Correspondence:

Majid Ghayour-Mobarhan
International UNESCO Center for Health-Related Basic Sciences and Human Nutrition Mashhad University of Medical Sciences; Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran;
Email: ghayourM@mums.ac.ir

Mohsen Moohebati;
Heart and Vascular Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; Department of Cardiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;
Email: mouhebatiM@mums.ac.ir

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Abstract

BACKGROUND: Finding the relation between complete blood count (CBC) parameters and ischemic electrocardiogram (ECG) changes among a large normal population, for the first time.

METHODS: Participants of the first phase of the MASHAD cohort study were enrolled in this cross-sectional study. Twelve-lead ECGs were taken from participants. According to the Minnesota codes, we divided the ischemic ECG changes into major and minor. Major ischemic changes included major Q-wave changes, minor Q-wave plus ST-T changes, and major isolated ST-T changes. Minor changes included minor isolated Q/QS waves, minor ST/T changes, and ST-segment elevation. The mean of the CBC parameters was compared between individuals with and without ischemic changes. The backward stepwise logistic regression model was implemented to estimate the odds ratios of ECG changes and eliminate confounders. Data were analyzed using SPSS version 20, with significance set at $p < 0.05$.

RESULTS: Among 9,106 participants, 510 individuals (5.6%) had minor and major ischemic changes, with a preference for males. Major ischemic changes were not associated with CBC parameters. However, the odds of having minor ischemic changes increased 1.96-fold with increasing red blood cell (RBC) count (OR = 1.96 [1.31–2.94], p = 0.001); though, they decreased by 0.18 units with increasing hemoglobin (OR = 0.81 [0.73–0.92], p = 0.001). Additionally, high mean corpuscular volume (MCV) increased the odds of minor ischemic changes (OR = 1.05 [1.01–1.08], p = 0.004).

CONCLUSION: Among Mashhad's normal population, major ischemic changes were not associated with CBC parameters. Also, minor and major ischemic changes were positively associated with WBC count.

Keywords: Electrocardiogram; Complete Blood Count; Cardiovascular Disease

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Introduction

Chronic non-communicable diseases have been increasing in recent years due to the aging of the general population and health promotion regarding infectious diseases worldwide[1]. Also, this rising trend in the incidence and prevalence of chronic non-communicable diseases is more prevalent in developing countries, like Iran[1]. Cardiovascular diseases (CVD), as a spectrum of chronic non-communicable diseases, comprise 12% of the global disease burden; it is estimated that the disease burden of CVD will be doubled in 2025 compared to 2005 in Iran[1]. Also, CVD is the leading cause of death globally, accounting for an estimated 17.9 million deaths per year—about 32% of all global deaths, according to the World Health Organization. Identifying the factors that contribute to the incidence of CVD can help reduce their burden by shaping government policies for prevention, early intervention, and treatment strategies[1,2].

CVD includes many types of diseases, such as ischemic heart disease (IHD), cerebrovascular disease, and peripheral artery disease[2]. IHD prevalence is increasing due to the aging population and atherosclerosis formation[2]. IHD includes two process formations: acute ischemic diseases (myocardial infarction [MI] and unstable angina) and chronic ischemic diseases (stable angina)[3]. One of the low-cost tests for CVD diagnosis is the electrocardiogram (ECG). Also, not all CVDs change the ECG; chronic stable angina does not usually cause ECG changes at rest[4]. Besides, not all ECG changes indicate CVD, such as ECG changes seen in electrolyte disorders[4]. Additionally, some ECG changes occur in an asymptomatic, normal population; for instance, Krishnan et al. showed the prevalence of ST-elevation ≥ 2 mm in V2,3 leads as 7% in men and 0.25% in women in the general population of South India[5]. However, Soliman et al. showed a lower risk of CVD incidence in people with normal ECG findings in a 13.2-year follow-up study[4]. Krittayaphong et al. demonstrated that a pathologic Q-wave was an independent predictor for major adverse cardiovascular events (MACE) in atherosclerotic patients in a cohort study; also, the pathologic Q-wave was identified in 21.3% of the sample size[6]. While T-wave inversion was prevalent in 20% of their study population, it did not predict MACE[6].

Cardiovascular risk factors include aging, diabetes mellitus, hypertension, dyslipidemia, obesity, and genetic factors[2]. In addition to these factors, some previous studies have examined complete blood count (CBC) parameters as risk factors for CVD occurrence[7–13]. For instance, Mozos et al. introduced reduced red blood cell (RBC) count and elevated red blood cell distribution width (RDW) as two CVD risk factors[10], while Madjid et al. showed that leukocytosis (increase in white blood cells [WBC]) was a risk factor for CVD incidence[11]. In addition, Pizzulli et al. demonstrated that an increase in mean platelet volume (MPV) increased CVD occurrence in stable and unstable angina patients; however, a decrease in platelet count enhanced CVD incidence only in unstable angina patients[12].

Although previous studies have examined the relationship between CBC parameters and the occurrence of CVD, the association between CBC parameters and ECG findings—as indicators related to CVD—has not been specifically assessed. Therefore, we investigated the association between ischemic ECG changes and CBC parameters.

Methods

Study population

This is a cross-sectional study on a sub-population of the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study, in which a total of 9,704 participants were recruited during the first phase of the MASHAD study (2010), as described previously[14]. It was conducted in Mashhad City, the second-largest city in Iran. Community leaders who were familiar with the families in the community also assisted with the identification and recruitment of potential participants. After identifying eligible participants, they were contacted to arrange an appointment for the formal physical examination (the sampling was

conducted house by house). Mashhad citizens aged between 35 and 65 years were enrolled in the study. Subjects with a confirmed history of CVD, and whose ECGs were either unavailable or uninterpretable, were excluded from the current study. The final analysis was performed on 9,106 subjects (3,646 [40.0%] men and 5,460 [60.0%] women). All participants signed an informed consent form approved by the relevant Human Research Ethics Committee (ethics code: IR.MUMS.MEDICAL.REC.1399.384).

Sample size calculation

At a 95% confidence level and a power of 80%, the required sample size was calculated using the following formula, based on the mean and standard deviation (SD) of RBC counts in two groups as reported by Kiliçli-Çamur et al[15], The mean and SD of RBC in the stable angina group were 4.58 ± 0.53 ($\times 10^6/mm^3$), and in the control group, 4.61 ± 0.46 ($\times 10^6/mm^3$). According to the formula, the minimum sample size required was estimated to be 4290 participants per group. However, due to the availability of blood samples and ECG interpretations from the first phase of the cohort study, the entire dataset from 9704 participants was included in the analysis.

Data collection

Methods of evaluation of baseline characteristics, including demographic and anthropometric data and laboratory tests were described previously by Asadi et al.[2]. Biochemical factors were assessed by auto-analyzer BT-3000, and CBC parameters were assessed by cell-counter system. Ghazizadeh et al. described the evaluation of metabolic syndrome, diabetes mellitus, hypertension, and dyslipidemia[16].

ECG data collection

Twelve-lead ECG of each MASHAD study participant was taken. The ECGs were read using an application, which was designed by the bioinformatics department, by five cardiology residents and was randomly rechecked by three cardiologists. The application's codes were fixed to the Minnesota codes[17]. We assessed the ischemic ECG changes according to the Minnesota codes as follows: major ischemic changes were 1) Major Q-wave changes (old prevalent MI): codes 1-1, 1-2; 2) Minor Q-wave plus ST-T changes (possible old MI): codes 1-3 plus 4-1, 4-2, 5-1, 5-2; 3) Major isolated ST-T changes: codes 4-1, 4-2, 5-1, 5-2. Minor changes were 1) Minor isolated Q/QS waves: code 1-3; 2) Minor ST/T changes: codes 4-3, 4-4, 5-3, 5-4; 3) ST-segment elevation: code 9-2.

Statistical analysis

SPSS software version 24.0 was used for analysis. The Kolmogorov-Smirnov test was used to assess the normality status; independent samples t-tests and the Mann-Whitney test were used to compare means for normally distributed and non-normally distributed variables, respectively. Qualitative variables were tested using the chi-square test. For quantitative variables, we reported the mean ± standard deviation (SD), while for qualitative variables, we used frequencies expressed as n (%). Backward stepwise logistic regression was implemented to eliminate confounders. Variables entered into the backward stepwise model were sex, age, weight, body mass index (BMI), job, marital and smoking status, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, low- and high-density lipoprotein (LDL and HDL), cholesterol, triglyceride, WBC, RBC, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet, RDW, platelet distribution width (PDW), and MPV. Data were reported using odds ratios (OR) and 95% confidence intervals (95% CI). We divided the ischemic ECG changes into major and minor changes; thereafter, the total population was divided into four groups: individuals with major ischemic changes (group A), individuals with minor ischemic changes (group B), individuals with both major and minor ischemic changes (group C), and individuals without any ischemic changes (group D). We found the associations between CBC parameters and the presence/absence of ischemic ECG

Table 1. Comparison of baseline characteristics of the MASHAD study population between individuals with or without ischemic ECG changes

Variable		Major Ischemic ECG changes (group A) (N= 507)	Minor Ischemic ECG changes (group B) (N= 619)	Major and minor Ischemic ECG changes (group C) (N= 510)	Without Ischemic ECG changes (group D) (N= 7470)
Age (year)		48.47 ± 8.07	47.60±8.28	47.54±8.09	48.20 ± 8.24
Sex	**male**	224 (44.2) *	271 (43.7) *	206 (40.3)	2945 (39.42)
	Female	283(55.8)	348(56.3)	304(59.7)	4525(60.58)
Job	**Students**	1 (0.1)	5 (0.8)	0 (0)	14 (0.1)
	Employment	203 (40.0)	269 (43.4)	187 (36.6)	2723 (36.4)
	Unemployed	253 (49.9)	291 (47.0) ***	281 (55.0)	3947 (52.8)
	Retired	50 (9.8)	54 (8.7)	41 (8.0)	783 (10.4)
Marriage status	**Single**	3 (0.5)	3 (0.5)	6 (1.1)	45 (0.6)
	Married	478 (94.2)	571 (92.2)	477 (93.5)	6957 (93.1)
	Divorced	4 (0.7)	4 (0.6)	4 (0.7)	113 (1.5)
	Widowed	22 (4.3)	41 (6.6)	23 (4.5)	355 (4.7)
Smoking status	**Non-smoker**	346 (68.2)	425 (68.6)	349 (68.4)	5152 (68.9)
	Ex-smoker	53 (10.4)	48 (7.7)	56 (10.9)	737 (9.8)
	Current smoker	108 (21.3)	146 (23.5)	105 (20.5)	1581 (21.1)
Weight (Kg)		73.39±13.10**	72.76±12.76*	72.63±13.70	71.67±12.80
BMI (Kg/m²)		28.27±4.67	28.01±4.89	28.08±4.94	27.86±4.70
Hypertension		159 (31.3)	189 (30.5)	163 (31.9)	2326 (31.2)
Diabetes mellitus		75 (14.8)	88 (14.2)	76 (14.9)	1047 (14.0)
Dyslipidemia		390 (76.9)	437 (70.5) ***	392 (76.8)	5763 (77.1)

*P value: 0.01 – 0.05
**P value: 0.001 – 0.01
***P value <0.001
The reference group was participants "without Ischemic ECG changes".
Data were presented as numbers (%). Quantitative data were presented as mean ± SD. Abbreviations: BMI (body mass index).

changes and reported the OR of each variable using the backward stepwise model. P-values <0.05 were considered statistically significant for all analyses.

Results

Among the 9,106 participants, 40% were men and 60% were women. Based on the presence and type of ischemic ECG changes, participants were classified into four groups:

- Group A: individuals with major ischemic changes (507 participants)
- Group B: individuals with minor ischemic changes (619 participants)
- Group C: individuals with both major and minor ischemic changes (510 participants)
- Group D: individuals without any ischemic changes (7,470 participants)

The distribution of ischemic ECG abnormalities across these groups, as well as their sex-based breakdown, is summarized in Table 1. The overall mean age of participants was 48.08 ± 8.26 years.

The comparison of baseline characteristics and CBC parameters between subjects with and without ischemic ECG changes is shown in Table 1. The percentage of men was higher in groups A, B, and C than in group D (p-value < 0.05). Also, the weight of individuals in groups A (p-value < 0.01) and B (p-value < 0.05) was higher than in group D. The percentage of unemployed subjects was lower in group B (p-value < 0.001) than in group D. Also, the percentage of participants with dyslipidemia was lower in group B (p-value < 0.001) than in group D.

The comparison of the mean biochemical and CBC parameters is shown in Table 2. LDL was lower (p-value < 0.01) and HDL was higher (p-value < 0.05) in group B than in group D. However, HDL was lower in group A than in group D (p-value < 0.05). Among CBC parameters, WBC count was higher in group C than in group D

Table 2. Comparison of the mean of biochemical and CBC parameters of the MASHAD study population between individuals with or without ischemic ECG changes

Variable	Major Ischemic ECG changes (group A) (N= 507)	Minor Ischemic ECG changes (group B) (N= 619)	Major and minor Ischemic ECG changes (group C) (N= 510)	Without Ischemic ECG changes (group D) (N= 7470)
FBG (mg/dl)	92.22±40.53	95.03±42.49	93.59±40.50	92.66±39.20
LDL (mg/dl)	116.92±36.77	112.11±32.59**	117.15±32.20	116.77±35.69
HDL (mg/dl)	41.77±9.56*	43.64±9.99*	42.80±9.97	42.79±9.97
Total cholesterol (mg/dl)	192.14±39.99	188.59±36.16*	190.29±37.79	191.65±39.46
Triglyceride (mg/dl)	151.53±102.26	137.91±95.94	141.44±91.48	142.73±91.43
WBC (10^3/M)	6.11±1.63	6.11±1.91	6.22±1.55*	6.04±1.51
RBC (10^6/M)	4.88±0.50	4.87±0.49	4.87±0.56	4.84±0.48
Hemoglobin (g/dl)	13.79±1.54	13.69±1.51	13.83±1.61	13.71±1.82
Hematocrit (%)	41.39±4.06	41.43±4.06	41.32±4.03	41.19±3.93
MCV (fL)	84.82±5.88	85.04±5.66	84.84±5.92	84.95±6.10
MCH (pg)	28.35±2.74	28.28±2.78	28.41±2.53	28.35±2.66
MCHC (g/dl)	33.30±2.45	33.10±1.83	33.46±1.37**	33.23±1.63
Platelet (10^3/UL)	228.72±60.91	230.53±65.54	230.48±61.57	229.22±60.85
RDW (%)	13.87±1.39	13.78±1.19	13.68±1.37	13.80±1.50
PDW (fl)	12.84±2.10	12.73±2.06	12.76±1.92	12.77±2.00
MPV (fl)	10.07±1.06	10.26±4.94	10.05±0.86	10.08±1.77

*P value: 0.01 – 0.05
**P value: 0.001 – 0.01
***P value <0.001
Reference group was participants "without Ischemic ECG changes".
Data were presented as mean ± SD. Abbreviations: FBG (fasting blood glucose), LDL (low-density lipoprotein), HDL (high-density lipoprotein), WBC (white blood cell), RBC (red blood cell), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), RDW (red blood cell distribution width), PDW (platelet distribution width), MPV (mean platelet volume).

(p-value < 0.05). MCHC was higher in group C than in group D (p-value < 0.01).

As shown in Table 3, the significant ORs of variables from the backward stepwise model are presented. The presence of major ischemic ECG changes in females was decreased by 23% compared to the normal population (OR: 0.77; 95% CI: 0.63–0.94; p-value: 0.008), while none of the CBC parameters changed the odds of having major ischemic changes (p-value > 0.05). Students had 4.6 times the odds of having minor ischemic changes compared to retired individuals (OR: 4.61; 95% CI: 1.58–13.43; p-value: 0.005). Employment was associated with 1.43 times the odds of having minor ischemic changes (OR: 1.43; 95% CI: 1.04–1.97; p-value: 0.02), and 1.27 times the odds of having either minor or major ischemic changes (OR: 1.27; 95% CI: 1.03–1.55; p-value: 0.024) compared to retired individuals. Participants with dyslipidemia had 0.21 lower odds of having minor ischemic changes than participants without dyslipidemia (OR: 0.79; 95% CI: 0.64–0.95; p-value: 0.012). The presence of either minor or major ECG changes increased by 0.014 for each unit increase in BMI (OR: 1.014; 95% CI: 1.001–1.027; p-value: 0.029).

Finally, after eliminating the effect of confounders using a logistic regression model, the following CBC parameters showed significant associations with ischemic ECG changes. Increasing one unit of RBC count increased the odds of having minor ischemic changes by 1.96 times (OR: 1.96; 95% CI: 1.31–2.94; p-value: 0.001); however, increasing one unit of hemoglobin decreased the odds to 0.82 (OR: 0.82; 95% CI: 0.73–0.92; p-value: 0.001). An increase in MCV raised the odds of having minor ischemic changes by 5% (OR: 1.05; 95% CI: 1.01–1.08; p-value: 0.004). Increasing one unit of WBC count elevated the odds of having either minor or major ischemic changes by 7% (OR: 1.07; 95% CI: 1.01–1.14; p-value: 0.018). Additionally, elevating MCHC by one unit increased the odds of having both ischemic changes by 17% (OR: 1.17; 95% CI: 1.07–1.29; p-value: 0.001), while the odds decreased by 6% with an increase in

Table 3. Relationship between variables and ischemic ECG changes using Backward Stepwise regression logistic model

Variables		B	S.E.	OR (95% CI)	p-value
Major Ischemic ECG changes (group A)					
Sex (female)		**-0.293**	0.100	0.768 (0.632-0.935)	0.008
BMI		**0.020**	0.010	1.020 (1.000-1.041)	0.054
Minor Ischemic ECG changes (group B)					
Job	**Students**	1.529	0.545	4.611 (1.584 – 13.427)	0.005
	Employment	0.359	0.163	1.432 (1.041 - 1.971)	0.027
	Unemployed	0.123	0.167	1.131 (0.816 - 1.568)	0.461
	Retired	Ref.	Ref.	Ref.	Ref.
Marriage status	**Single**	Ref.	Ref.	Ref.	Ref.
	Married	0.188	0.599	1.207 (0.373-3.908)	0.754
	Divorced	-0.844	0.837	0.430 (0.083-2.219)	0.314
	Widowed	0.590	0.623	1.804 (0.532-6.113)	0.343
Dyslipidemia#		-0.251	0.099	0.788 (0.640 - 0.946)	0.012
RBC (106/M)		0.674	0.206	1.961 (1.309 – 2.939)	0.001
Hemoglobin (g/dl)		-0.202	0.061	0.817 (0.725 - 0.920)	0.001
MCV (fL)		0.044	0.016	1.045 (1.014 - 1.078)	0.004
Major and minor Ischemic ECG changes (group C)					
WBC (103/M)		0.071	0.030	1.074 (1.013- 1.139)	0.018
MCH (pg)		-0.062	0.031	0.939 (0.884 - 0.998)	0.043
MCHC (g/dl)		0.162	0.048	1.175 (1.069 - 1.293)	0.001
Major or minor Ischemic ECG changes (group E)					
Sex (female)		-0.299	0.090	0.795 (667-0.948)	0.011
Job	**Students**	0.828	0.499	2.290 (0.861 - 60.89)	0.097
	Employment	0.235	0.104	1.265 (1.031 - 1.552)	0.024
	Unemployed	0.278	0.118	1.32 (1.047 - 1.665)	0.019
	Retired	Ref.	Ref.	Ref.	Ref.
Marriage status	**Single**	Ref.	Ref.	Ref.	Ref.
	Married	-0.921	0.456	0.398 (0.163-0.973)	0.043
	Divorced	-0.117	0.351	0.889 (0.447 - 1.678)	0.738
	Widowed	-0.244	0.328	0.783 (0.412 - 1.491)	0.457
Dyslipidemia#		-0.127	0.068	0.881 (0.770 – -1.007)	0.063
BMI (Kg/m2)		0.014	0.006	1.014 (1.001 - 1.027)	0.029
WBC (103/M)		0.033	0.018	1.033 (0.997 - 1.071)	0.072

Abbreviations: LDL (low-density lipoprotein), HDL (high-density lipoprotein), WBC (white blood cell), RBC (red blood cell), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration).
Variable entered on Backward Stepwise regression logistic model: Sex, age, BMI, job status, marriage status, smoking status, HTN, DM, dyslipidemia, WBC, RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, platelet, RDW, PDW, MPV.

MCH (OR: 0.94; 95% CI: 0.88–0.99; p-value: 0.043).

Discussion

In this study, we assessed the relationship between ischemic ECG changes and CBC parameters in a large population study, for the first time. Major ischemic changes were not associated with any CBC parameters; however, minor ischemic changes were positively associated with RBC count and MCV, and negatively associated with hemoglobin. The presence of both ischemic changes was associated with increased WBC count and MCHC, and lower MCH.

Previous studies have examined the associations between CBC parameters and CVD occurrence[7-12]. Additionally, some have investigated the associations between CVD incidence and ECG changes, particularly major ECG abnormalities[4], or reported the prevalence of ECG changes in the general population[5]. However, none have specifically addressed the relationship between ischemic ECG changes and CBC parameters. Therefore, we report these associations in a large population for the first time.

Prior studies have shown a higher prevalence of ECG changes in males. For example, Krishnan et al. reported a higher prevalence of all ECG

changes, including ischemic changes, among males in a sample of 4,630 individuals from the normal population of South India[5]. Piwonska et al. evaluated the prevalence of ECG changes in 1,081 participants aged >20 years in Poland; they found that ST depression and negative T-waves were the most prevalent ECG changes among women (>14%), while intraventricular conduction disturbances were most prevalent among men (>11%)[18]. Additionally, Piwonska et al. showed an increasing trend for all ECG changes, particularly ischemic changes, with increasing age[18]. Iannou et al. assessed 4,739 healthy asymptomatic individuals (mean age: 62.8 years) and found that only 68.2% of the population had no ECG changes, with the prevalence of ischemic changes being <19%[19]. They also found that all ECG changes were associated with aging[19]. The difference between our study and those by Piwonska and Iannou et al. regarding the effect of aging on ECG changes may be attributed to the higher mean age in those studies compared to ours. According to studies conducted worldwide, it is suggested that ECG changes, including ischemic changes, might be normal variants in general populations, and dynamic ECG changes are crucial in diagnosing CVD, rather than relying on a single abnormal ECG.

Due to the lack of studies directly investigating the relationship between ECG changes and CBC parameters, particularly WBC count and its subtypes, we referred to previous research exploring the association of these parameters with CVD. However, it should be noted that our study did not assess a direct link with CVD, but rather focused on ECG abnormalities as indicators of ischemia. Given that ECG abnormalities have been shown to be associated with CVD, we could indirectly infer that the observed ECG changes are related to CVD[20-23].

Most previous studies on the relationship between CVD and CBC parameters focused on acute coronary syndrome (ACS), not chronic coronary syndrome (CCS). One study concerning CCS was conducted by Bil et al. among 211 CCS patients with a mean age of 60.5 years[24]. In their study, the WBC count was higher in patients with microvascular coronary spasms than in the control group[24]. In our study, WBC count was positively associated with total ischemic changes. Prior studies have shown a positive relationship between WBC and CVD occurrence. Madjid et al. demonstrated that increases in WBC and neutrophils can elevate the risk of all types of CVD, in a review article[25]. They also showed that the CVD risk ratio associated with WBC was comparable to other inflammatory indices, such as hs-CRP[25]. Rana et al., in a prospective 8-year follow-up study of 16,108 subjects, found that increasing WBC count, particularly neutrophils, was an independent CVD risk factor, whereas lymphocytes and monocytes did not increase the CVD risk[26]. Iranirad et al. demonstrated the predictive value of the neutrophil-to-lymphocyte ratio for IHD severity as an independent predictor in a prospective study of 500 Iranian patients with ACS[27].

To discuss the influence of increased WBC count (particularly neutrophils) on ischemia progression, which causes ischemic ECG changes, prior studies have explained the effects of neutrophils on atherosclerosis formation as an inflammatory biomarker[28]. Neutrophils can cause endothelial injury and further tissue ischemia by secreting inflammatory mediators[28]. They are large, inflexible cells that can adhere to the endothelium, potentially obstructing the restoration of blood flow in capillaries after coronary ischemia. Additionally, neutrophils secrete various bioactive substances that promote platelet aggregation and vasoconstriction, such as thromboxane B2 and leukotriene B4[29]. Neutrophils that gather in ischemic and reperfused areas may release proteolytic enzymes or reactive oxygen species, which can damage surrounding myocytes[29] and cause ECG changes.

Another WBC subtype, named monocyte, is transformed into a macrophage, which is involved in atherosclerosis formation[28], while lymphocytes act as inflammation regulators[28]. Therefore, an increased WBC count, with a predominance of neutrophils and monocytes

and a relative reduction in lymphocytes, causes inflammation and subsequent ischemia[28].

Increasing RBC count and decreasing hemoglobin were associated with minor ischemic ECG changes in this study. Also, the mean RBC count was higher among individuals with either major or minor ischemic changes; however, it was not significant after the elimination of confounders. Overall, reduced hemoglobin, which is called anemia, causes CVD due to hypoxic status[10]. Anemia can also lead to increased cardiac output, increased heart rate, and vasodilation, and if it persists for a long time, it may cause left ventricular hypertrophy and cardiac enlargement, thereby leading to ECG changes[30]. Additionally, anemic patients are at risk of thrombosis due to receiving iron supplements[10]. In terms of pathophysiology, acute anemia decreases the resistance of coronary arteries, whereas chronic anemia enhances the formation of inter-coronary collaterals and leads to increased venous return and decreased afterload (peripheral vascular resistance). The slow progression of severe anemia results in cardiac hypertrophy due to the dilation of blood vessels. In chronic anemia, the heart experiences both dilation and hypertrophy, leading to fatty degeneration caused by disrupted cellular metabolism. The most significant pathological changes occur in the subendocardial layer, especially in the left ventricle. In certain instances of anemia, prolonged conditions may lead to irreversible damage to the heart[31,32].

Shashikala et al. evaluated the prevalence of ischemic ECG changes among anemic patients with hemoglobin <8 g/dl[7]. They showed that the prevalence of ST depression was 50–57% and T-wave inversion was 29–50% among patients with hemoglobin <5 g/dl, while there were no ischemic changes in patients with hemoglobin between 7–8 g/dl[7]. Reducing one unit of hemoglobin is a risk factor for CVD mortality and morbidity[33].

On the other hand, elevated hemoglobin and RBC mass, which is called erythrocytosis, can cause CVD by elevating blood viscosity, reducing blood flow, and leading to thrombosis[34]. Corante et al. showed that the increased CVD risk was 3.63 times higher among erythrocytic individuals than those with normal hemoglobin and RBC mass[35]. Hemoglobin and RBC count have a bidirectional effect on CVD occurrence. Although our mean hemoglobin and RBC count were within the normal range, our results might have been different if we had divided our participants into male/female and anemic/normal/erythrocytic groups. In addition, hemoglobin and RBC count were only related to minor ischemic changes in this study, and they were not associated with major ischemic changes, which are more important for CVD diagnosis.

Another RBC-related parameter significantly associated with major and minor ischemic ECG changes was MCHC, which increased this odds by 1.17 times. Darwish et al. demonstrated higher MCV, MCH, and MCHC in CCS patients compared to individuals without coronary stenosis[36]. Nagula and Iqbal et al. showed higher MCHC in CAD patients; however, in both of these studies, MCV was significantly lower in CAD patients[37,38]. They attributed the high MCHC and low MCV to microcytic anemia[37,38]; therefore, the prevalence of microcytic anemia may have been higher in the populations studied by Nagula and Iqbal et al. than in ours. Additionally, these two studies concerned established angiographic CCS patients, while we evaluated a normal population. Luke et al. showed higher MCHC in 79 ACS patients compared to 112 CCS patients[39]. They suggested that MCHC increased as a result of the inflammatory state and oxidative stress in ACS, and decreased due to reduced intestinal iron absorption caused by inflammation[39]. In our results, major ischemic changes were not related to MCHC; therefore, MCHC might be related to other conditions in the body.

Conclusion

In this study, major ischemic ECG changes, which are more significant for CVD diagnosis, were not related to CBC parameters in a large population of Iranians. While minor ischemic ECG changes

were related to higher RBC count and lower hemoglobin. Also, minor and major ischemic ECG changes were associated with higher a WBC count.

Strengths and limitations

The investigation of the relationship between ischemic ECG changes with CBC parameters for the first time was the strength of this study. Also, the normal population's ECG changes assessment among a large sample size could demonstrate that the presence of ischemic ECG changes does not always show a clinicopathological condition, and these findings may exist as a normal variant in normal people; therefore, dynamic ECG changes are more important for CVD diagnosis. The limitation was the lack of data about WBC subtypes to find the exact influence of each subtype on having ECG changes. Additionally, a lack of dividing hemoglobin and RBC count to anemic/normal/erythrocytic could affect our results.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: MGM; MM
Data Acquisition: MYK; NV; HH; SSS; TS; MA; EMF; AHB; HA; AIM
Data Analysis or Interpretation: HE; SD; FH
Manuscript Drafting: MYK; NV; HH
Critical Manuscript Revision: GAF; MGM; MM
All authors have approved the final manuscript and are responsible for all aspects of the work.

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