



Impact of Smoking on Hematologic and Biochemical Predictors of Coronary Artery Disease in Iraqi Male Population

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Abstract

Background: Smoking is a well-known risk factor for coronary artery disease (CAD) and other cardiovascular conditions, including coronary heart disease (CHD). Blood cell components and biomarkers such as white blood cells (WBCs), haemoglobin (Hb), fibrinogen, high-sensitivity C-reactive protein (hs-CRP), D-dimer, and ferritin have been implicated in the pathogenesis of CAD. This study aimed to identify key predictors of CAD in smokers by assessing these hematologic and biochemical parameters. **Methods:** This study included male smokers with hypertension, excluding those with diabetes or dyslipidaemia, and compared them to a control group of healthy nonsmokers. Parameters assessed included complete blood count (CBC) and blood-based biomarkers (hs-CRP, D-dimer, fibrinogen, and ferritin). The predictive value of the fibrinogen-to-D-dimer ratio was also analyzed. Statistical analysis was conducted using GraphPad Prism 9.5.0 with a 95% confidence level. **Results:** Significant differences were observed between smokers and nonsmokers in WBC count, Hb level, and packed cell volume (PCV). Smokers exhibited higher levels of hs-CRP, fibrinogen, D-dimer, and ferritin. However, the fibrinogen-to-D-dimer ratio was not

a significant predictor of CAD. **Conclusion:** The study found that elevated WBC count, Hb level, PCV, and biomarkers (hs-CRP, D-dimer, fibrinogen, ferritin) are strong predictors of CAD in smokers. These findings suggest the potential for developing a predictive panel for CAD risk in smokers, though the study's small sample size is a limitation.

Keywords: Smoking, Coronary Artery Disease, Hematologic Biomarkers, Biochemical Predictors, Inflammation

1. Introduction

Coronary artery disease (CAD) is one of the most common causes of mortality worldwide, accounting for ~17.8 million deaths (~31% of total deaths) annually (Azdaki et al., 2024; Brown et al., 2024). It affects the populations of low- and middle-income countries the most (Brown et al., 2024; Hosseini et al., 2021). Atherosclerosis of the coronary arteries is the main characteristic of CAD and is usually asymptomatic. Patients with CAD experience various disabling events such as stroke, myocardial infarction (MI), and amputations, and have a high risk of coronary heart disease (CHD) (Ralapanawa & Sivakanesan, 2021; Vanassche et al., 2020).

The occurrence of CAD is regulated by risk factors such as a sedentary lifestyle, poor dietary habits, alcohol consumption, smoking, and substance abuse, while obesity, diabetes, and hypertension increase the risk (Dwivedi, 2010; Ralapanawa & Sivakanesan, 2021; Vanassche et al., 2020; Wilson et al., 1998).

Significance | This study showed the significant influence of smoking on key predictors of CAD, emphasizing its role in cardiovascular risk assessment.

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Sociodemographic factors such as age, race, and sex are also correlated with CAD (Lima Dos Santos et al., 2023). Males have been reported to have a higher likelihood of CAD compared to females. However, the use of contraceptives and hormonal imbalances must be reviewed to reduce bias in the inference (Araujo et al., 2006; Hosseini et al., 2021). Other medical conditions that increase the risk of CAD include diabetes, dyslipidaemia, hypertension, and smoking, which share complex mechanisms of interaction that affect CAD severity (Chen et al., 2023; Duncan et al., 2022; Jiang et al., 2021; Lee et al., 2015; Neaton, 1992).

Studies have shown that smoking exacerbates asymptomatic and stable CAD, creating a predisposition for angina, MI, and sudden death events (Bouabdallaoui et al., 2021; Khera et al., 2016; Vanassche et al., 2020), and have also found associations between CVH, smoking, and metabolic syndrome. Neaton *et al.* (1992) analysed the relationship between blood pressure, smoking habits, and serum cholesterol levels to CHD incidence in white males. The study showed that mortality due to CHD was higher in males, with elevated serum cholesterol and increased systolic (>110 mmHg) and diastolic (>70 mmHg) blood pressure. The study revealed that smoking, along with dyslipidaemia and hypertension, increased the mortality rate by ~20 times as compared to nonsmoking and healthy males (Neaton et al. (1992). Bouabdallaoui *et al.* (2021) observed an increased risk of future cardiovascular events and mortality due to smoking in patients with stable CAD compared to nonsmokers, which strongly contradicts the smoker's paradox (Bouabdallaoui et al., 2021). Another study of patients with CAD who had undergone coronary revascularization by balloon angioplasty or stent deployment (percutaneous coronary intervention, PCI) showed that smoking increased the frequency of repeat PCI and the mortality rate (Wu et al., 2022).

In addition to blood pressure and serum cholesterol levels, newer panels of blood-based biomarkers have been identified for the diagnosis of CAD. Since CAD is characterized by atherosclerosis, studying the activation of inflammatory proteins, such as C-reactive protein (CRP), coagulation proteins, and fibrinolytic pathways, is essential. The coagulation factor fibrinogen, a precursor of fibrin clots, plays a crucial role in the development of atherosclerosis. Fibrinogen serves as a biomarker for the diagnosis of CAD, hypertension, and stroke and is also a prognostic marker in patients after PCI. Bai et al. (2020) noted that patients with stable CAD had a high serum D-dimer level, which could improve the prediction of long-term mortality, cardiovascular events, and cancer Bai et al. (2020). The study emphasized that the D-dimer/fibrinogen ratio (DFR) is a novel biomarker for long-term mortality in patients post-PCI, and an increased DFR indicates a higher incidence of cardiovascular complications and all other causes of mortality (Bai et al., 2020). Also identified is an abnormal complete blood count (CBC), where high red blood cell (RBC), white blood cell (WBC),

and platelet counts are associated with an increased risk of CAD and higher morbidity and mortality (Madjid & Fatemi, 2013).

This study aimed to evaluate the influence of smoking and multiple comorbidities on multiple predictors of CAD. This study included nonsmokers and smokers aged 19 to 63 years. The results describe the association between CBC, fibrinogen, D-dimer, high sensitivity CRP (hs-CRP), ferritin levels, fibrinogen to D-dimer (FD) ratio, DFR, smoking status, and other factors like hypertension) on the risk prediction of CAD in smokers.

2. Materials and Methods

2.1 Study design, inclusion, and exclusion criteria

Male patients at the College of Dentistry/University of Anbar were enrolled in the study. Informed consent was obtained from all participants. The study was officially registered with the Ethics Committee of the University of Anbar under reference number 94, on 15/03/2024. The study included male patients aged over 18 years with hypertension and smoking habits and was divided into two groups: nonsmokers (N=18) and smokers (N=28). Patients with hyperlipidaemia, history of diabetes mellitus, or vascular disorders were excluded from the study. A detailed history of smoking habits and hypertension was recorded for all the smokers.

2.2 Sample collection and evaluation

Blood samples (5 mL) were drawn from all participants between May 2023 and October 2023, of which 1 mL was collected in EDTA for CBC estimation, 2 mL in sodium citrate, and 2 mL in a gel tube for serological tests. CBC for all samples was estimated using the automated haematology analyser (Mindray, Korea). Ferritin, D-dimer, and hs-CRP levels were estimated using a fluorescence-based immunoassay analyser, iChroma II (Boditech, Korea). Fibrinogen levels were determined using a fibrinogen assay kit and an automated biochemistry analyser (Mindray, Korea). Furthermore, the FD ratio was calculated to determine the relationship between smoking and the incidence of CAD.

2.3 Statistical analysis

The data collected were compared between smokers and nonsmokers using an unpaired t-test with Welch's correction in GraphPad Prism 9.5.0 (730). Results were represented at mean \pm standard deviation (SD). A confidence interval of 95% and a two-tailed p-value <0.05 was considered statistically significant. The percentage of population outliers was calculated using a logical formula in MS Excel.

3. Results

3.1 Analysis of CBC between smokers and nonsmokers

The study included 46 healthy male participants: 28 smokers and 18 healthy nonsmokers, aged between 19 and 63 years (median age 40.75 years). The statistical analysis of age and CBC values for smokers and nonsmokers is provided in Table 1. The age difference

between the two groups was not statistically significant ($p=0.68$). The WBC count was higher in smokers and was statistically significant ($p<0.05$). Platelet counts did not differ significantly between the groups ($p=0.5439$). Several participants in the smoker group showed skewed CBC values (Table 2), with 21.4% having WBC counts >11000 cells/mL, and 3.6% having platelet counts $>450 \times 10^9$ /mL. In contrast, only one nonsmoker had an elevated WBC count (12000 cells/mL), and platelet counts were within the normal range for all nonsmokers.

Haemoglobin level (Hb) ($p<0.0001$) and packed cell volume (PCV) ($p<0.0001$) were significantly higher in smokers than in nonsmokers.

Hb and PCV values were within the normal range for all nonsmokers. The percentage of participants with values higher than the normal range was 71.4% (>16 mg/dL) and 75% ($>48\%$) for Hb and PCV, respectively (Table 2). The skewed values for Hb and PCV overlapped in 95% of participants.

3.2 Differences in biomarker levels between smokers and nonsmokers

Significant differences were observed in the serum levels of biomarkers such as hs-CRP ($p<0.0001$), fibrinogen ($p<0.0001$), D-dimer ($p<0.0001$), and ferritin ($p<0.0001$) between smokers and nonsmokers (Table 1). The FD ratio ($p<0.05$) also showed a statistically significant difference between the two groups (Table 1). The difference in the DFR between the two groups was not statistically significant (Table 1). Table 2 lists the minimum and maximum values observed for each parameter in the two groups. While nonsmokers had all these parameters within the normal range, some participants in the smoker group had values greater than the normal range. For hs-CRP, 35.7% of the participants had values of >10 mg/dL (Table 2). Similarly, the percentages of participants in the smoker group with higher D-dimer, fibrinogen, and ferritin levels were 46.4%, 67.9%, and 60.7%, respectively (Table 2). Six participants showed increased values of all four biomarkers (hs-CRP, D-dimer, fibrinogen, and ferritin). Approximately 25% of the smokers reported hypertension and showed an increase in one or more parameters.

4. Discussion

CAD is a lifestyle disorder that is a major cause of mortality worldwide. A lack of physical activity, dyslipidaemia, hypertension, and other comorbidities such as diabetes mellitus and obesity contribute to CAD. Alcohol abuse and smoking have also been reported as risk factors contributing to fatal diseases. Smoking is known to exacerbate CAD by altering various parameters, thereby increasing the risk of disease onset and complications. Various studies have reported an association between smoking and CAD, with and without existing comorbidities (Ambrose & Barua, 2004; Bouabdallaoui et al., 2021; Chen et al., 2023; Jeong et al., 2017; Lee

et al., 2015; Neaton, 1992; Oshunbade et al., 2021). The present study incorporated different blood and biochemical parameters in smokers and nonsmokers from Iraq to elucidate the predictors of CAD in the smoking population. Hematologic parameters (WBC, platelet count, and haemoglobin level) and smoking status were analysed. Additionally, the biochemical parameters, including D-dimer, hs-CRP, fibrinogen, and ferritin, were evaluated in the two groups to determine whether their skewing was related to smoking status and risk for cardiovascular complications.

Elevated WBC and platelet counts are associated with the incidence of CAD. Various studies have reported that WBCs play a crucial role in the onset of atherosclerosis via cellular injury to the endothelial lining caused by proteolytic enzymes, increased WBC aggregation, and increased thrombus formation. Thus, high WBC counts have been indicated in predicting future cardiovascular events (Çiftçiler et al., 2019; Dabbagh et al., 2019; Madjid & Fatemi, 2013). Similarly, increased platelet count can be associated with CAD because of its role in increased thrombosis and inflammation and permitting adherence of neutrophils and monocytes to the endothelial membrane in the coronary blood vessels (Madjid & Fatemi, 2013). The results of the current research supported previous studies that reported higher WBC and thrombocyte counts among smokers (Çiftçiler et al., 2019; Dabbagh et al., 2019; Gallucci et al., 2020). Therefore, we concluded that higher WBC and platelet counts may be predictors of CAD in smokers. High haemoglobin levels have been implicated in the development of CAD as they lead to an increase in serum triglyceride and cholesterol levels (Madjid & Fatemi, 2013). Elevated PCV has been associated with increased blood viscosity, and research results have shown that high haematocrit may increase the risk of thrombosis and atherosclerosis, one of the key symptoms of CAD (Çiftçiler et al., 2019; Dabbagh et al., 2019).

CRP is an inflammatory biomarker. High CRP levels indicate systemic inflammation. Studies from different research groups and population studies have shown that patients with CVDs exhibit high levels of CRP (Batta, 2015; Madjid & Fatemi, 2013; Salimi et al., 2023; Zakynthinos & Pappa, 2009). Smoking also causes an increase in CRP levels (Azdaki et al., 2017; Çiftçiler et al., 2019). Reports suggest that CRP alone is a nonspecific predictor of future CAD and other cardiovascular events (Madjid & Fatemi, 2013). Danesh *et al.* (1998, 2004) conducted a meta-analysis of several prospective studies. They deduced that increased CRP levels and WBC counts were strong predictors of future cardiovascular events (Danesh et al., 1998, 2004). The data from the current study correlate with earlier studies in smoker groups, indicating that high hs-CRP and WBC levels can be used to predict the onset of CAD in these participants. However, in the present study, only one smoker had higher-than-normal WBC and hs-CRP values.

Table 1. Comparison of age, hematologic, and biochemical parameters between smokers and nonsmokers

Parameters	Smokers (N=28)	Nonsmokers (N=18)	p-value
Age (years); median	42	39.5	-
WBC (cells/mL); mean ±SD	8479 ± 3050	6967 ± 1928	0.0454
Hb (g/dL); mean ±SD	16.51 ± 1.185	13.68 ± 1.100	<0.0001
Platelets (×10 ⁹ /mL); mean ±SD	242 ± 71.2	256 ± 74.8	0.5439
PCV (%); mean ±SD	50.28 ± 4.005	42.23 ± 1.635	<0.0001
hs-CRP (mg/dL); mean ±SD	8.156 ± 4.254	2.299 ± 1.502	<0.0001
Fibrinogen (mg/dL); mean ±SD	502.6 ± 163.7	172.8 ± 35.76	<0.0001
D-dimer (ng/mL); mean ±SD	466.2 ± 159.9	138.9 ± 79.62	<0.0001
Fibrinogen to D-dimer ratio; mean ±SD	1.168 ± 0.4382	1.681 ± 0.9719	0.0472
DFR; mean ± SD	0.9951 ± 0.4332	0.8220 ± 0.4543	0.2076
Ferritin (ng/mL); mean ±SD	382.6 ± 103.2	117.6 ± 63.88	<0.0001

Abbreviations: WBC, white blood cells; Hb, haemoglobin; PCV, packed cell volume; hs-CRP, high sensitivity CRP; DFR, D-dimer/fibrinogen ratio; SD, standard deviation

Table 2. Minimum and maximum values of each parameter tested and the number of participants showing skewed values in smoker and nonsmoker participants

Parameters	Normal range	Smokers (N=28)			Nonsmokers (N=18)		
		Min. value	Max. value	No. of outlying participants	Min. value	Max. value	No. of outlying participants
WBC (cells/mL)	4000-11000	4000	14800	6	4500	12000	1
Hb (g/dL)	12-16	12.7	18.2	20	12.2	15.7	0
Platelets (×10 ⁹ /mL)	150-450	156	455	1	156	400	0
PCV (%)	38-48	39	56	21	39	45	0
hs-CRP (mg/dL)	<10	1.45	16.54	10	0.56	6.54	0
Fibrinogen (mg/dL)	160-400	177.3	803.4	19	123.4	220.4	0
D-dimer (ng/mL)	<500	115.7	765.8	13	37.6	342.6	0
Fibrinogen to D-dimer ratio	-	0.4689	2.219	-	0.5554	3.306	-
DFR	-	0.4507	2.132	-	0.3025	1.800	-
Ferritin (ng/mL)	30-350	146.5	567.3	17	55.32	245.2	0

WBC: white blood cells; Hb: haemoglobin; PCV: packed cell volume; hs-CRP, high sensitivity CRP; DFR, D-dimer/fibrinogen ratio

D-dimer is a protein that is active in fibrin clot turnover. Elevated D-dimer levels correlate with various disorders with excessive coagulation activation, contributing critically to CAD progression (Al-Dahy & Abed, 2022; Danesh et al., 2001; Gong et al., 2016). Excessive activation of coagulation events can lead to increased fibrinogen levels, as observed in smokers (Maresca et al., 1999). Previous studies indicate that smoking tends to increase clot formation, leading to a higher incidence of coronary arterial plaques (Azdaki et al., 2017, 2024; Bouabdallaoui et al., 2021; Cho et al., 2015; Danesh et al., 1998; Gallucci et al., 2020; Koenig et al., 2001; Maresca et al., 1999; Soomro et al., 2016; Wong & Tse, 2021). Studies have emphasized the importance of fibrinogen and D-dimer levels in predicting CAD (Lowe & Rumley, 1999). The present study collected data on these markers in smokers to predict CAD events. The DFR is an emerging marker for risk stratification of CVD and cardiovascular events (Bai et al., 2020). However, a previous investigation has indicated that the FD ratio fails to predict CAD in individuals with or without slow coronary flow (Indrajaya et al., 2020). Data from the current study also show a significant difference between smokers with PSP and CAD. Further women who become smokers in future pregnancies have also shown a similar difference. However, this could not be used to predict future CAD.

Elevated serum ferritin levels have been positively correlated with smoking status. Shivasekar *et al.* (2018) found that smokers had higher serum ferritin levels than nonsmokers (Shivasekar et al., 2018). Another study also showed increased levels of ferritin, D-dimer, and fibrinogen in smokers compared to nonsmokers (Meneke & Emin Düz, 2023). High serum ferritin levels are associated with increased coronary artery calcification and CAD onset (Sung et al., 2012). However, Reyes *et al.* (2020) reported that elevated serum ferritin levels did not indicate a higher CAD risk in the Mediterranean population (Reyes et al., 2020). The current study also shows that smokers have higher ferritin levels than nonsmokers, with many participants showing higher-than-normal levels. The limitations of this study employed a small sample size of smokers and nonsmokers limiting the strength of the conclusions. Additionally, the inclusion of only male participants introduces a sex bias in the study, as no data were available for the female population.

5. Conclusion

This study determined significant differences in hematologic and biochemical parameters between male smokers and nonsmokers, emphasizing the role of elevated WBC counts, PCV, Hb, hs-CRP, D-dimer, fibrinogen, and ferritin levels as potential predictors of coronary artery disease (CAD). The findings suggest that these biomarkers, particularly in smokers, may serve as reliable indicators of future CAD events. However, the FD ratio, while differing

significantly between smokers and nonsmokers, did not prove to be an effective predictor of CAD. The study's limitations, including a small sample size and the exclusion of female participants, suggest that further research with a more diverse and larger population is needed to strengthen these conclusions and explore gender differences in CAD risk factors. Despite these limitations, the study contributes valuable insights into the relationship between smoking and CAD risk.

Author contributions

T.I.M. conceptualized the study. D.A.A. conducted the research, provided resources, and handled data. E.H.A. wrote the article after conducting a thorough data analysis and interpretation. All authors reviewed and approved the final version, taking responsibility for the content and similarity index.

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Competing financial interests

The authors have no conflict of interest.

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