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Hematological and Platelet Indices Alterations Associated with Khat Chewing Among University Students in Conflict-Affected Yemen: A Cross-Sectional Study

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Abstract

Background: Khat chewing is prevalent among Yemeni youth; however, its impact on hematological parameters in conflict settings remains underexplored.

Objective: To assess the association between khat chewing and complete blood count (CBC) parameters, particularly platelet indices, among university students in Al-Dhale'e, Yemen.

Methods: A cross-sectional study was conducted with 226 undergraduate students. Khat use was assessed using a structured questionnaire, and CBC was analyzed using an automated hematology analyzer. Statistical analyses included independent t-tests, Mann-Whitney U tests, and multiple linear regression adjusted for age, sex, smoking, body mass index (BMI), caffeine intake, and psychological stress score.

Results: The prevalence of khat chewing was 77.9% (176/226). Compared with non-chewers, chewers had significantly higher mean platelet volume (MPV: 9.7 vs. 8.8 fL; $p < 0.001$; d = 0.78), higher platelet distribution width (PDW: 16.1 vs. 15.0%; p = 0.003; d = 0.48), higher white blood cell count (WBC: 7.6 vs. 6.8×10^9/L; p = 0.004; d = 0.46), and lower hemoglobin (13.7 vs. 14.3 g/dL; p = 0.006; d = -0.46). Regression analysis confirmed khat as an independent predictor of elevated MPV (β = 0.85, $p < 0.001$), elevated WBC (β = 0.78, p = 0.008), and reduced hemoglobin levels (β = -0.52, p = 0.012). Trend analysis suggested graded associations with the frequency and duration of use.

Conclusion: Khat chewing is independently associated with elevated MPV and WBC, suggesting a possible proinflammatory state and reduced hemoglobin levels. Routine CBC monitoring should be considered for habitual khat users in resource-limited settings.

Article Info

Keywords:
Khat, Mean Platelet Volume, Platelet Indices, Hematological Parameters, Yemen, University Students, Inflammation, Thrombosis.

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1. INTRODUCTION

The Republic of Yemen continues to endure one of the world's most severe humanitarian crises, characterized by protracted armed conflict, economic collapse, and near-total fragmentation of public health infrastructure [1]. Within this fragile context, populations face profound psychological stress, often leading to coping behaviors, including substance use [2]. Khat (*Catha edulis* Celastraceae) chewing is deeply entrenched in Yemen and the Horn of Africa. The fresh leaves contain psychoactive alkaloids, primarily cathinone and cathine, which produce amphetamine-like stimulant effects, including euphoria and increased alertness [3]. While khat serves social functions and is perceived as stress-relieving, its chronic use has been associated with cardiovascular complications, psychiatric disorders, and gastrointestinal pathologies [4, 5]. A five-year follow-up study of Yemeni university students confirmed that khat chewing prevalence remains high and is associated with multiple health risks [6]. Recent studies have focused on the systemic inflammatory effects of khat. Sympathomimetic compounds can induce sympathetic activation, increasing the heart rate and blood pressure, potentially contributing to endothelial dysfunction [7]. Additionally, oxidative stress during khat metabolism may trigger inflammatory cascades [8]. Hematological parameters, particularly platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW), have emerged as low-cost biomarkers of inflammation and cardiovascular risk factors [9, 10]. Elevated MPV is associated with increased platelet activation and serves as a predictor of thrombotic events in various clinical settings [11]. Similarly, the white blood cell count is a well-established marker of systemic inflammation [12]. Other hematological parameters, including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red blood cell distribution width (RDW), were also examined. In Yemen, where advanced diagnostics are often unavailable owing to resource constraints and conflict-related infrastructure damage, routine hematological parameters represent a pragmatic approach for assessing subclinical inflammation and cardiovascular risk [13]. This study aimed to investigate the association between khat chewing and hematological parameters among university students in Al-Dhale'e Governorate, with particular emphasis on the platelet indices.

2. METHODS

2.1. Study Design and Setting

A cross-sectional study was conducted at the Aden Gulf International University, Al-Dhale'e Governorate, Yemen, between May 2 and October 20, 2025. The university serves students from across the governorate, allowing the recruitment of a representative sample of university-attending youth in this conflict-affected region.

2.2. Study Population

The population consisted of undergraduate students enrolled in the 2024/2025 academic year from the faculties of medical and administrative sciences.

Inclusion criteria: registered undergraduate students, age $\geq$ 18 years, voluntary informed consent provided, and presence at the university during data collection.

Exclusion criteria: known chronic diseases (diabetes mellitus, cardiovascular disease, and chronic kidney disease); known hematological disorders (anemia, thrombocytopenia, and leukemia); active infection or recent surgery (within 4 weeks); pregnancy or lactation; use of medications affecting blood counts (anticoagulants, antiplatelet agents, and chemotherapy); and refusal to provide informed consent. Of the 250 individuals initially approached for participation, 24 were excluded based on the prespecified criteria: eight due to known chronic disease (diabetes mellitus, cardiovascular disease, or chronic kidney disease), six due to active infection or recent surgery within four weeks, five due to pregnancy or lactation, three due to use of medications affecting blood counts (anticoagulants, antiplatelet agents, or chemotherapy), and two due to refusal to provide informed consent for blood sample collection. Thus, the final sample comprised 226 participants.

2.3. Sample Size and Sampling

The sample size was calculated using Cochran's formula for finite populations. With a total student population of 500, 95% confidence level, 5% margin of error, and an estimated proportion of 50% to maximize sample representativeness, the required sample size was 218. A total of 226 participants were enrolled using two-stage stratified random sampling, stratified by the faculty and academic year. The response rate was 90.4.

2.4. Data Collection

Questionnaire: A structured, culturally adapted questionnaire was administered by trained research assistants to collect information on demographics, khat chewing habits (frequency, duration, session length, years of use, and age at initiation), tobacco smoking, medical history, and lifestyle factors (diet, physical activity, and sleep). The questionnaire was developed in Arabic, pilot-tested on 20 students, and demonstrated acceptable internal consistency (Cronbach's α = 0.76 for the Khat section). Regarding the control group (non-chewers, n = 50), all participants were university students from the same faculties and academic levels as the khat chewers, with no significant differences in socioeconomic status or dietary habits, as assessed by a brief nutritional questionnaire. The primary reason for non-chewing was personal or family preference rather than economic or health-related factors. However, residual confounding by unmeasured lifestyle factors cannot be excluded.

Blood sample collection and analysis: Approximately 3 mL of venous blood was collected from the antecubital vein into K_2EDTA vacutainer tubes (BD, Franklin Lakes, NJ, USA; Catalog #367841) by trained phlebotomists after an overnight fast ($\geq$ 8 hours). The samples were processed within 2 h. Complete blood count parameters were analyzed using a Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan) following the manufacturer's instructions [14]. Daily quality control was performed using commercial controls (BioRad Liquichek Hematology Control, Catalog #221051), and the laboratory participated in the Yemen Ministry of Health External Quality Assessment Program quarterly.

Parameters measured included: RBC parameters (RBC count, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW), WBC parameters (total WBC, differential count), and platelet parameters (platelet count, MPV, PDW, plateletcrit).

2.5. Statistical Analysis

Data were analyzed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean $\pm$ SD, and categorical variables as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. Group comparisons were performed using the Mann-Whitney U test for all variables, as the assumption of normality was violated for most parameters (assessed using the Shapiro-Wilk test). For multiple group comparisons (trend analysis), the Kruskal-Wallis test with Dunn's post-hoc test was used. Effect sizes were calculated using Cohen's d, where applicable. All data in the tables are presented as median (interquartile range, IQR). Multiple linear regression was used to identify independent predictors of MPV, WBC, and hemoglobin, adjusting for age, sex, smoking status, academic level, body mass index (BMI), self-reported caffeine intake (cups of coffee/tea per day), and brief psychological stress score (4-point scale). Variance inflation factors were assessed to ensure no multicollinearity (all VIF < 5). Sensitivity analyses included outlier exclusion (values > 3 SD from the mean), propensity score matching to balance groups on age, sex, and smoking, and bootstrap confidence intervals (1,000 resamples). Statistical significance was set at p < 0.05.

3. RESULTS

3.1. Participant Characteristics

A total of 226 undergraduate students enrolled. The mean age was 22.4 ± 2.8 years (range 18-39). Male participants comprised 73.5% (n = 166) and females 26.5% (n = 60). Among the students from the Faculty of Medical Sciences, 60.2% (n = 136) participated, while 39.8% (n = 90) were from administrative sciences. The academic year distribution was balanced across the first to fourth years. The prevalence of khat chewing was 77.9% (n = 176). Among the chewers, 20.5% (n = 36) were also tobacco smokers, compared to only 6.0% (n = 3) among non-chewers (p = 0.017). The primary reason for not chewing reported by participants was personal or family preference rather than economic or health-related factors. All non-chewers were from the same faculties and academic levels as the chewers, with no significant differences in socioeconomic status or dietary habits, as assessed by a brief nutritional questionnaire.

3.2. Comparison of Hematological Parameters by Khat Chewing Status

Table 1 presents a comparison of the hematological parameters between khat chewers and non-chewers. Khat chewers had significantly higher MPV (9.7 vs. 8.8 fL; p < 0.001; d = 0.78), higher PDW (16.1 vs. 15.0%; p = 0.003; d = 0.48), higher total WBC (7.6 vs. 6.8×10^9/L; p = 0.004; d = 0.46), and lower hemoglobin (13.7 vs. 14.3 g/dL; p = 0.006; d = -0.46). Differential counts showed significantly higher neutrophil (4.5 vs. 3.9×10^9/L; p = 0.008) and monocyte (0.51 vs. 0.44×10^9/L; p = 0.023) counts in chewers. No significant differences were observed in the RBC count, hematocrit, MCV, MCH, MCHC, RDW, or platelet count.

3.3. Sex-Stratified Comparisons by Khat Chewing Status

To maintain analytical balance as required by the journal, Table 2 presents the hematological parameters stratified by sex and khat chewing status separately. Males had significantly higher hemoglobin and MPV than females, regardless of khat status. Among males, khat chewers showed lower hemoglobin (14.0 ± 1.3 vs. 14.6 ± 1.1 g/dL; p = 0.018) and higher MPV (10.0 ± 1.2 vs. 9.2 ± 1.0 fL; p<0.001) than non-chewers. Among females, similar trends were observed but did not reach statistical significance, likely due to the small sample size of female non-chewers (n = 26) and female chewers (n = 34). Due to this imbalance, the statistical power for sex-stratified analyses and the gender interaction finding (interaction p = 0.042) was limited, and these results should be interpreted cautiously.

Table 1. Hematological parameters by khat chewing status

Parameter	Khat Chewers (n=176) Median (IQR)	Non-Chewers (n=50) Median (IQR)	p-value	Cohen's d
RBC Parameters				
RBC ($\times 10^{12}$/L)	5.10 (4.70–5.50)	5.02 (4.62–5.42)	0.321	0.16
Hemoglobin (g/dL)	13.7 (12.8–14.6)	14.3 (13.5–15.1)	0.006	-0.46
Hematocrit (%)	41.0 (38.5–43.5)	42.0 (39.5–44.5)	0.127	-0.24
MCV (fL)	80.2 (75.8–84.6)	81.1 (76.7–85.5)	0.412	-0.13
MCH (pg)	26.8 (25.2–28.4)	27.3 (25.7–28.9)	0.183	-0.21
MCHC (g/dL)	33.4 (32.6–34.2)	33.7 (32.9–34.5)	0.108	-0.26
RDW (%)	13.1 (12.2–14.0)	12.8 (11.9–13.7)	0.194	0.21
WBC Parameters				
WBC ($\times 10^{9}$/L)	7.6 (6.2–9.0)	6.8 (5.5–8.1)	0.004	0.46
Neutrophils ($\times 10^{9}$/L)	4.5 (3.5–5.5)	3.9 (3.0–4.8)	0.008	0.46
Lymphocytes ($\times 10^{9}$/L)	2.4 (1.9–2.9)	2.2 (1.7–2.7)	0.112	0.26
Monocytes ($\times 10^{9}$/L)	0.51 (0.38–0.64)	0.44 (0.32–0.56)	0.023	0.42
Eosinophils ($\times 10^{9}$/L)	0.17 (0.10–0.24)	0.14 (0.08–0.20)	0.098	0.27
Platelet Parameters				
Platelet Count ($\times 10^{9}$/L)	266 (218–314)	254 (208–300)	0.287	0.17
MPV (fL)	9.7 (9.0–10.4)	8.8 (8.1–9.5)	< 0.001	0.78
PDW (%)	16.1 (14.4–17.8)	15.0 (13.3–16.7)	0.003	0.48
Plateletcrit (%)	0.26 (0.21–0.31)	0.23 (0.18–0.28)	0.011	0.46

Data are presented as median (interquartile range, IQR). P-values were calculated using Mann-Whitney U test for all variables, as the assumption of normality was violated for most parameters (assessed by Shapiro-Wilk test). Cohen's d indicates effect size (small: 0.2, medium: 0.5, large: 0.8). Abbreviations: RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; WBC, white blood cells; MPV, mean platelet volume; PDW, platelet distribution width.

Table 2. Selected hematological parameters by sex and khat chewing status

Parameter	Male Chewers (n=142) Median (IQR)	Male Non-Chewers (n=24) Median (IQR)	p-value (males)	Female Chewers (n=34) Median (IQR)	Female Non-Chewers (n=26) Median (IQR)	p-value (females)
Hemoglobin (g/dL)	13.9 (13.0-14.8)	14.5 (13.7-15.3)	0.018	12.6 (11.8-13.4)	12.9 (12.1-13.7)	0.312
MPV (fL)	9.9 (9.2-10.6)	9.1 (8.4-9.8)	<0.001	9.0 (8.3-9.7)	8.6 (7.9-9.3)	0.118
WBC ($\times 10^{9}$/L)	7.8 (6.4-9.2)	7.0 (5.7-8.3)	0.046	7.2 (5.8-8.6)	6.7 (5.4-8.0)	0.287

Data are presented as median (interquartile range, IQR). P-values represent comparisons between khat chewers and non-chewers within each sex group, calculated using the Mann–Whitney U test. Abbreviations: MPV, mean platelet volume; WBC, white blood cells.

3.4. Trend Analysis of Khat Use Patterns

Table 3 presents the trend analysis based on the frequency of use, session duration, and years of use. The actual quantity (weight in grams) of khat leaves consumed per session was not measured; therefore, these findings represent exploratory trends rather than definitive dose-response relationships. A graded association

Table 3. Selected hematological parameters by sex and khat chewing status

Exposure Category	n	MPV (fL) Median (IQR)	WBC ($\times 10^9$/L) Median (IQR)	Hemoglobin (g/dL) Median (IQR)
Frequency of Use				
Daily	94	10.0 (9.3-10.7)*	8.1 (6.7-9.5)*	13.5 (12.7-14.3)*
3-6 days/week	52	9.5 (8.8-10.2)	7.5 (6.1-8.9)	13.8 (13.0-14.6)
1-2 days/week	30	9.0 (8.3-9.7)	7.0 (5.7-8.3)	14.0 (13.2-14.8)
Non-chewers	50	8.8 (8.1-9.5)	6.8 (5.5-8.1)	14.3 (13.5-15.1)
Session Duration				
$\geq$ 6 hours	48	10.2 (9.5-10.9)*	8.4 (7.0-9.8)*	13.4 (12.6-14.2)*
4-6 hours	76	9.6 (8.9-10.3)	7.6 (6.2-9.0)	13.7 (12.9-14.5)
< 4 hours	52	9.2 (8.5-9.9)	7.2 (5.8-8.6)	13.9 (13.1-14.7)
Years of Use				
$\geq$5 years	68	10.1 (9.4-10.8)*	8.2 (6.8-9.6)*	13.5 (12.7-14.3)*
3-5 years	74	9.6 (8.9-10.3)	7.6 (6.2-9.0)	13.8 (13.0-14.6)
1-3 years	34	9.1 (8.4-9.8)	7.1 (5.7-8.5)	14.0 (13.2-14.8)

Data are presented as median (interquartile range, IQR). Asterisks (*) indicate p < 0.05 compared to non-chewers (reference group) using Kruskal-Wallis test with Dunn's post-hoc test. The actual quantity of khat leaves consumed in grams per session was not measured; therefore, these findings represent exploratory trends rather than definitive dose-response relationships. Abbreviations: MPV, mean platelet volume; WBC, white blood cells.

was observed for MPV, WBC, and hemoglobin, with daily users, those with longer session durations ($\geq$ 6 hours), and long-term users ($\geq$5 years) showing the most pronounced alterations compared with non-chewers. For example, daily users had MPV of 10.0 fL (IQR: 9.3-10.7) compared to 8.8 fL (IQR: 8.1-9.5) in non-chewers ($p < 0.001$), while occasional users (1-2 days/week) showed intermediate values (9.0 fL, IQR: 8.3-9.7) that did not differ significantly from non-chewers. Similarly, a session duration of $\geq$ 6 hours was associated with an MPV of 10.2 fL (IQR: 9.5-10.9) compared to 9.2 fL (IQR: 8.5-9.9) for sessions < 4 hours.

3.5. Multiple Linear Regression Analysis

After adjusting for age, sex, smoking, academic level, BMI, caffeine intake, and psychological stress score, khat chewing remained an independent predictor of elevated MPV (β = 0.85 fL, 95% CI: 0.52–1.18, $p < 0.001$), elevated WBC (β = 0.78 × 10^9 cells/L, 95% CI: 0.21–1.35, p = 0.008), and reduced hemoglobin (β = -0.52 g/dL, 95% CI: -0.92 to -0.12, p = 0.012). Male sex was also independently associated with higher MPV (β = 0.62 fL, $p < 0.001$) and hemoglobin levels (β = 1.32 g/dL, $p < 0.001$). Smoking, age, BMI, caffeine intake, and psychological stress score were not significant independent predictors in these models. The model R^2 values were 0.15 for MPV, 0.08 for WBC, and 0.22 for hemoglobin.

3.6. Sensitivity Analyses

Sensitivity analyses confirmed the robustness of the primary findings. After removing six participants with extreme values (> 3 SD from the mean), all primary associations remained statistically significant (MPV: $p < 0.001$; WBC: p = 0.011; hemoglobin: p = 0.008). After propensity score matching (48 khat chewers matched to 48 non-chewers by age, sex, and smoking), the associations persisted for MPV ($p < 0.001$), WBC (p = 0.022), and hemoglobin (p = 0.031). Bootstrap confidence intervals (1,000 resamples) confirmed the stability of the regression coefficients.

3.7. Prevalence of Abnormal Parameters

Elevated MPV (>11.0 fL) was observed in 21.6% (38/176) of khat chewers compared to 6.0% (3/50) of non-chewers (p = 0.009; relative risk = 3.60, 95% CI: 1.37–9.45). Elevated WBC (>11.0×10^9 cells/L) was observed in 15.9% of the chewers versus 6.0% of the non-chewers (p = 0.072). Any abnormal hematological parameter (low hemoglobin, elevated WBC, elevated MPV, or elevated PDW) was present in 50.6% (89/176) of the tobacco chewers versus 30.0% (15/50) of the non-chewers (p = 0.009; relative risk = 1.69, 95% CI: 1.14–2.51).

4. DISCUSSION

To our knowledge, this is the first study to comprehensively examine the association between khat chewing and hematological parameters, with particular emphasis on platelet indices, among university students in conflict-affected Yemen. Our results demonstrate that khat chewing is independently associated with notable changes in several hematological parameters, including elevated MPV and WBC and reduced hemoglobin levels. These changes were associated with the frequency and duration of khat use. Our findings are consistent with and build upon previous studies in this field. The most robust finding was the association between khat chewing and elevated MPV, with a large effect size (Cohen's d = 0.78). This finding is consistent with the growing body of literature linking substance use to platelet activation. For example, Koupaei et al. (2022) demonstrated elevated MPV in chronic methamphetamine users, suggesting that sympathomimetic stimulants may share common mechanisms of platelet activation [15]. Similarly, Sadeghian et al. (2021) reported significantly higher MPV in opium users than in controls, with values comparable to those observed in our khat chewers [16]. The MPV values observed in our khat chewers ($9.8 \pm 1.2\,\mathrm{fL}$) were notably higher than those reported in healthy young adult populations. A large multicenter study by Lippi et al. (2020) established reference ranges of 7.5–10.5 fL in healthy European adults, with mean values of approximately 8.5 fL [17]. Our khat chewers' mean MPV falls at the upper end of this range, similar to the values reported in patients with metabolic syndrome ($9.9 \pm 1.1\,\mathrm{fL}$) by Zaccardi et al. (2015) [18] and in patients with type 2 diabetes ($10.2 \pm 1.3\,\mathrm{fL}$) by Demirtunc et al. (2022) [19]. This comparison suggests that the degree of platelet activation in young khat users may be comparable to that in older adults with established metabolic risk factors. In contrast, a study from Ethiopia by Gebremedhin et al. (2021) examining khat chewers found no significant difference in MPV, although their sample was smaller (n = 120) and included a higher proportion of occasional users [20]. This discrepancy may be explained by differences in chewing intensity; our sample included a higher proportion of daily users (53.4% vs. 35% in the Ethiopian study). This underscores the importance of exposure intensity in the detection of hematological alterations. The mechanisms linking khat consumption to elevated MPV have been explored in experimental studies. Al-Motarreb et al. (2019) demonstrated that cathinone, the active alkaloid in khat, directly induces platelet aggregation in vitro via the activation of α2-adrenergic receptors [21]. Chronic exposure may lead to increased platelet turnover, with megakaryocytes releasing larger and more reactive platelets. Furthermore, a recent systematic review by Hassan et al. (2023) concluded that khat-induced oxidative stress and endothelial dysfunction are the key drivers of cardiovascular pathology [22]. However, without direct measurements of platelet aggregation or inflammatory cytokines in our study, these mechanisms remain to be elucidated. The finding of elevated WBC in khat chewers (7.8 ± 2.1 vs. $6.9 \pm 1.8 \times 10^9/\mathrm{L}$), driven by neutrophils and monocytes, is consistent with a low-grade inflammatory state. This pattern has been described for other substance use disorders. For instance, a meta-analysis by Wang et al. (2022) found that chronic stimulant users have significantly higher WBC counts than non-users, with effect sizes similar to ours (d = 0.42–0.51) [23]. Experimental studies have provided mechanistic insights into this process. A randomized controlled trial by Alsanosy et al. (2021) found that acute khat chewing increased circulating levels of IL-6 and TNF-α within 2 h of consumption, with levels remaining elevated for up to 6 h [24]. Chronic khat use has been associated with elevated high-sensitivity CRP levels in a dose-dependent manner, as demonstrated in a large cross-sectional study from Saudi Arabia by Mahfouz et al. (2022) [25]. Our finding of elevated monocyte levels is particularly noteworthy, as monocytes play a central role in atherogenesis by migrating into the subendothelial space and differentiating into foam cells. A study by Al-Habori et al. (2020) found that khat extract directly stimulates monocyte chemotaxis and adhesion to endothelial cells in vitro, providing a potential mechanism linking khat use to accelerated atherosclerosis [26]. The observation of reduced hemoglobin levels in khat chewers (13.8 vs. 14.4 g/dL) has been reported inconsistently in the literature. A study from Somalia by Ahmed et al. (2021) found no significant difference in hemoglobin levels between khat chewers and non-chewers, while a study from Yemen by Al-Motarreb et al. (2018) reported lower hemoglobin levels in heavy khat chewers [27, 28]. This discrepancy may be explained by differences in nutritional status across populations. Consistent with our findings, a recent study from Sana'a University by Al-Absi et al. (2024) demonstrated significantly lower hemoglobin concentration, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and packed cell volume (PCV) among Yemeni khat chewers than among nonchewers [29]. The discrepancy between studies may be explained by differences in nutritional status, chewing intensity, and sample characteristics of the populations. The mechanism underlying the reduction in hemoglobin levels may be multifactorial. First, khat is anorexigenic. A nutritional assessment study by Hassan et al. (2022) found that chronic khat chewers had significantly lower dietary iron and folate intakes than non-chewers [30]. Second, chronic inflammation can lead to anemia of chronic disease via hepcidin-mediated iron sequestration. A study by Ganz (2019) demonstrated that IL-6 upregulates hepcidin production, reducing iron absorption and release from macrophages [31]. Third, a toxicological study by Alsalahi et al. (2020) found that high-dose khat extract administered to rats for 12 weeks resulted in dose-dependent reductions in RBC count and hemoglobin, suggesting possible direct bone marrow suppression [32]. The graded association observed in our study, with daily users and those with ≥ 5 years of use showing the lowest hemoglobin levels, supports a cumulative effect and argues against random variation. Our findings have several implications for clinical practice and public health in Yemen. First, the association between khat chewing and elevated MPV, a marker of platelet activation, suggests that habitual khat users may be at increased cardiovascular risk, although this remains to be confirmed by prospective studies. Second, in resource-limited settings where advanced cardiovascular risk assessment is unavailable, routine CBC parameters, particularly MPV, represent pragmatic, low-cost biomarkers for identifying individuals who may benefit from further risk assessment. Third, the graded associations observed suggest that reducing khat exposure (frequency and session duration) may mitigate hematological abnormalities, supporting harm-reduction approaches. Our findings suggest that routine CBC monitoring could be a pragmatic approach for habitual khat users in resource-limited settings, particularly given the observed alterations in MPV, WBC, and Hb levels. This is consistent with the broader WHO recommendations for monitoring substance use-related health consequences in conflict-affected populations [33], although specific guidance on hematological monitoring of khat users is not explicitly detailed in that report. This study has several limitations. First, the cross-sectional design precludes the establishment of causality or temporal sequence between khat chewing and hematological alterations. Second, khat use was assessed via self-report, which may be subject to recall bias or underreporting; biological verification (e.g., urine cathinone levels) was not performed in this study. Third, although the analysis was adjusted for multiple confounders, including age, sex, smoking, BMI, caffeine intake, and psychological stress, residual confounding by unmeasured factors (e.g., detailed nutritional status, sleep quality, physical activity, and socioeconomic status) cannot be entirely excluded. Fourth, although the control group (non-chewers) was selected from the same faculties and academic levels, and non-chewing was attributed to personal or family preference rather than socioeconomic factors, we cannot completely rule out differences in lifestyle and nutritional habits. Fifth, while we observed WBC elevation, we did not directly measure inflammatory cytokines (e.g., CRP, IL-6) or perform platelet function assays that would confirm inflammatory mechanisms or definitively establish a pro-thrombotic state; therefore, interpretations regarding inflammation and thrombosis remain speculative. Sixth, the actual quantity of khat consumed (weight in grams) was not measured; therefore, the graded associations presented represent exploratory trends rather than definitive dose-response relationships. Seventh, the predominance of male participants (73.5%) and the small number of female khat chewers (n = 34) limit generalizability to female populations and reduce statistical power for sex-stratified analyses; the gender interaction finding (p = 0.042) requires confirmation in larger, balanced studies. Eighth, the study was conducted at a single university, and the findings may not be generalizable to non-university-attending youth or other cultural contexts. Ninth, the absence of direct inflammatory markers (CRP, IL-6) means we cannot confirm that the observed hematological changes are mediated by inflammation rather than other mechanisms. Longitudinal studies are needed to establish causality and determine whether hematological abnormalities normalize after khat cessation. Research directly measuring inflammatory cytokines (CRP, IL-6, TNF-α), platelet activation markers (P-selectin, soluble CD40 ligand, platelet aggregation assays), and oxidative stress biomarkers would clarify the underlying mechanisms. Studies linking khat-associated hematological alterations to clinical cardiovascular events (myocardial infarction and stroke) are needed to establish their prognostic significance. Comprehensive nutritional assessments would help determine whether the observed hemoglobin reductions are attributable to khat-induced nutritional deficiencies or anemia of chronic disease. Finally, larger, balanced studies with adequate female representation are needed to confirm sex-specific effects.

5. CONCLUSION

This study demonstrates that khat chewing among university students in conflict-affected Yemen is independently associated with significant alterations in hematological parameters, including elevated mean platelet volume (suggesting platelet activation), elevated white blood cell count (suggesting low-grade systemic inflammation), and reduced hemoglobin levels. These findings were supported by graded associations according to use patterns and remained robust after adjustment for multiple potential confounders, including age, sex, smoking, BMI, caffeine intake, and psychological stress. The observed hematological alterations indicate that chronic khat use may be associated with a low-grade inflammatory process; however, this interpretation remains speculative in the absence of direct measurements of inflammatory cytokines (e.g., CRP and IL-6) or platelet function assays. The cross-sectional design precludes causal inference, and the clinical significance of these findings, particularly regarding long-term cardiovascular risk, requires confirmation through prospective cohort studies. In resource-limited conflict settings, where advanced diagnostic modalities are often unavailable, routine CBC parameters, particularly MPV, represent pragmatic, low-cost biomarkers for screening purposes. These findings support the consideration of routine CBC monitoring for habitual khat users, integration of khat-related health education into university programs, and the development of culturally appropriate harm-reduction interventions. Future prospective studies with direct inflammatory markers and functional assays are warranted to confirm causality and elucidate the underlying mechanisms.

Declarations

Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ministry of Health Ethics Committee (Reference: MOPHP-DH-IRB-2025-029, dated April 19, 2025). Written informed consent was obtained from all participants prior to enrolment.

Consent to Participate

Informed consent was obtained from all the participants included in the study. All participants were informed of the purpose of the study, the procedures involved, and their right to withdraw at any time without consequences.

Consent for Publication

The authors confirm that informed consent for the publication of the data contained in this article was obtained from all participants.

Conflict of Interest

The authors declare no competing interests.

Competing Interests

The authors have no financial or proprietary interest in any material discussed in this article.

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Availability of Data and Materials

The de-identified dataset generated and analyzed in the current study is available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the study's conception and design. N.T.A., R.S.A., and M.A.H.M. performed statistical analyses and interpreted the data. M.A.Q., A.T., A.S., B.O., M.F., S.A., W.S., A.A., A.A.S., A.N.A., E.M., F.K.F., F.S.T., L.A.H., N.J.A., O.A.Q., Q.A.S., and Y.A.S. collected data and performed laboratory analyses. N.T.A. drafted the manuscript. All authors have reviewed, commented on, and approved the final version of the manuscript.

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Declaration of AI-Assisted Technologies

The authors declare that artificial intelligence (AI) tools were used only for limited purposes, such as language editing, grammar improvement, and formatting assistance. All scientific content, data analysis, interpretations, conclusions, and final manuscript revisions were reviewed and verified by the authors, who took full responsibility for the integrity and originality of the work.

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