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Original article

A CROSS-SECTIONAL STUDY OF IMMUNOLOGICAL CHANGES LINKED TO ELECTRONIC CIGARETTE USE IN MALE UNIVERSITY STUDENTS

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ABSTRACT

The growing popularity of electronic cigarettes (e-cigarettes), especially among young adults, is concerning due to the possible impacts on immune system function. This study evaluates the effect of e-cigarette usage on the immunological profile in a sample of 80 male university students aged 18 to 24 years. Participants were divided into two groups of 50 electronic cigarette users and 30 non-electronic cigarette users as the control. Key immunological parameters, including C-reactive protein (CRP), Interleukin 6 (IL-6), Antinuclear Antibodies (ANA), Cardiolipin Antibodies, and White Blood Cells (WBC) counts and differentials, were examined. Electronic cigarette users had significantly elevated ANA positivity (98% vs. 3.3%; p=0.0001), Cardiolipin antibodies (31.70 ± 0.882U/mL vs. 17.61 ± 0.928 U/mL; p=0.0001), indicating possible autoimmune activation, and IL-6 levels (50.546 ± 12.622 pg/mL vs. 17.616 ± 0.928 pg/mL; p=0.0001), which suggested systemic inflammation. CRP (1.159 ± 0.144mg/L vs. 1.170 ± 0.184mg/L; p=0.9567) did not differ significantly. The groups' WBC counts and differentials (neutrophils, lymphocytes) were similar (p > 0.05). These results show that electronic cigarette use is associated with a pro-inflammatory state (IL-6) and an autoimmune association (ANA and cardiolipin), but it did not affect acute-phase response (CRP). To investigate long-term immunological effects, further investigation is necessary.

KEYWORDS: Electronic Cigarette, IL-6, ANA, Inflammation, Cardiolipin Antibodies

1. INTRODUCTION

E-cigarettes, also known as electronic cigarettes, are portable electronic devices that produce aerosols or vapors from e-cigarette liquid (E-liquid) without burning. They have become a well-liked substitute for traditional tobacco smoking (Chen, *et al*., 2019). The first contemporary e-cigarette was created in China in 2003 by Hon Lik, a Chinese chemist (Yang *et al*., 2025). Although the prevalence of electronic cigarette use is still lower in Asia than in Western countries, the use of e-cigarettes is increasing, particularly among young people. Teenage and adolescent e-cigarette use is rapidly increasing in the United States and other developed countries (e.g., Canada, Germany, and the United Kingdom) (Chien *et al*., 2019). The Kurdistan Region of Iraq is seeing a rise in youth e-cigarette use. Among students at Hawler Medical University, the prevalence was 15.7%. This is in line with larger Middle Eastern trends of urban youths adopting e-cigarette use at an increasing rate and being less aware of the health risks (Ahmed, 2024).

Three ingredients make up e-liquids: a humectant, like vegetable glycerin (VG) or propylene glycol (PG); a medication, like nicotine, tetrahydrocannabinol (THC), or cannabidiol (CBD); and a flavoring agent to aid in aerosol inhalation tolerance. An atomizer with wick and heating element, battery, and microprocessor are parts of electronic devices (Ramadhan *et al.*, 2017; Kalininskiy *et al.*, 2021). It is critical to comprehend how electronic cigarettes may affect immunological markers that could signify inflammation, autoimmunity, and immune dysregulation as its prevalence increases (Zima *et al.*, 2025). Key markers of systemic inflammation and immune response include a number of immunological parameters (Hamad & Raziq, 2020; Mangoni *et al.*, 2024). C-reactive protein (CRP), an acute-phase reactant generated by the liver, is one of the main markers of systemic inflammation. There is worry about the inflammatory potential of long-term e-

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cigarette use because elevated CRP levels have been linked to autoimmune disorders and cardiovascular disease (Al-Bayaty *et al.*, 2025). One important mediator of the acute-phase response and a key player in immune regulation is the pro-inflammatory cytokine interleukin-6 (IL-6).

Exposure to e-cigarettes may raise IL-6 secretion, which could affect systemic inflammation and make users more susceptible to chronic inflammatory diseases (Singh *et al*., 2019; Boss *et al.*, 2024).

Antinuclear antibody (ANA) and anticardiolipin antibody tests can be used to measure autoimmunity, another component of immune dysregulation (Chighizola *et al.*, 2021). Because ANAs are frequently raised in autoimmune diseases like systemic lupus erythematosus, their presence in e-cigarette users may indicate an aberrant immune activation (Niemczyk *et al*., 2023). Similarly, autoimmune diseases and elevated clotting risks are linked to anticardiolipin antibodies, which belong to the antiphospholipid antibody family. The identification of these antibodies in e-cigarette users may suggest a connection between autoimmune pathogenesis and vaping (El Hasbani *et al*., 2024).

Furthermore, a thorough examination of the body's cellular immune response can be obtained from the differential white blood cell (WBC) count. Changes in WBC differentials, including neutrophils, lymphocytes, eosinophils, monocytes, and basophils, can indicate the activation or suppression of the immune system. Prior research has observed alterations in WBC profiles in e-cigarette users and those exposed to airborne pollutants, indicating that e-cigarette vapour may have a comparable impact on leukocyte distribution and function (Wang *et al*., 2022). This cross-sectional study intends to shed light on the biological effects of e-cigarette users by clarifying the relationship between e-cigarette use and changes in immunological parameters. We evaluate potential variations in inflammation, autoimmunity, and cellular immune response between e-cigarette users and non-e-cigarette users in order to ascertain whether e-cigarette users are associated with appreciable immunological risks.

2. MATERIALS AND METHODS

Material:

In this cross-sectional study, immunological markers were compared between e-cigarette users and non-e-cigarette users (controls) using an observational design. Fifty male e-cigarette users between the ages of 18 and 24 were included in the study, with 30 male non-e-cigarette users (controls), who were matched for age and sex as controls. The sampling method used to choose the participants was convenience. Inclusion criteria for e-cigarette users were (1) regular use of e-cigarettes for at least six months, (2) having no history of traditional tobacco use, and (3) showing no chronic metabolic or immunological disorders. Both groups had to meet the following exclusion criteria: (1) recent infections (within the previous month), (2) immunosuppressive medication use, and (3) pre-existing respiratory or cardiovascular conditions. Members of the research population were interviewed in person to complete a questionnaire form intended to match the study's need for more precise data collection. During the interview, the subjects were asked about their socio-demographic status, including their age, gender, address, length of e-cigarette use, occupation, and marital status. Additionally, anthropometric measurements were used to determine the participants' BMI. Along with clinical data questions about e-cigarette use-related complications like heart/vascular issues, respiratory issues, inflammation issues, and other issues that are documented, the questionnaire also asked about the family history of disease. The social histories of the individuals included regular exercise, smoking, hookah use, and medication use. The appendices section included a demonstration of the questionnaire form.

Blood Samples Collection:

At Raparin University, sterile, single-use needles were used to draw blood (7 mL total) from e-cigarette users and non-e-cigarette user controls between October and December 2024. The blood was distributed into three tubes: 3 mL in a yellow-top gel tube (for serum), 2 mL in a lavender-top tube (sodium citrate anticoagulant), and 2 mL in a blue-top tube (EDTA anticoagulant)**.** To combine with anticoagulants, the lavender and blue-top tubes were gently inverted five to ten times. Every tube was delivered to Ranya City's Smart Laboratory in a cold box. The lavender and blue-top tubes were shaken for 15 to 20 minutes at the lab. The yellow-top tubes were left undisturbed to allow for clotting before the blue-top tubes, and the yellow-top tubes were centrifuged for 15 to 20 minutes at 4500 rpm. Following centrifugation, serum samples that were clear and pale yellow were chosen for analysis; samples that were hemolyzed, lipemic, or icteric were not. Red blood cells were not mixed with plasma or serum.

BIOCHEMICAL ANALYSIS

Determination of C-Reactive Protein (CRP) Test

An acute-phase protein that is primarily produced by the liver in response to pro-inflammatory cytokines (Rahali *et al.*, 2024)**.** C-reactive protein (CRP) is a well-known marker of inflammation (Sonawane & Nimse, 2017). An immunoturbidimetric assay principle underlies the conventional technique for determining the C-reactive protein (CRP) titer using the Cobras 6000 analyzer. Using a calibration curve, the analyzer automatically determines the CRP concentration; the results are displayed in milligrams per liter. Normal CRP values are less than 10 mg/L, though they may vary depending on the lab reference range. The results are shown on the screen and can be printed. The analyzer automatically calculates the CRP concentration using a calibration curve. Results are

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expressed in mg/L Normal CRP values: <10 mg/L (may vary based on lab reference ranges. The results are displayed on screen and can be printed.

Determination of White Blood Cells (WBC) Counts and Differentials:

White blood cells (WBC) and differentials are measured by the Complete Blood Count (CBC) test (Othman, *et al.*, 2024), which uses an automated hematology analyzer (Medionic 5-part differential analyzer). To categorize WBCs into neutrophils, lymphocytes, monocytes, eosinophils, and basophils, the analyzer uses electrical impedance, flow cytometry, and light-scattering techniques. The results are presented as total WBC count (10^9/L) and 5-part differential (%) and absolute counts (10^9/L).

Assay of Serum Interleukin 6 (IL-6)

Using a commercial sandwich ELISA kit (SunLong Biotech) on an automated ELx800 analyzer, the levels of serum interleukin-6 (IL-6) were determined. Whole blood was clotted at room temperature and then centrifuged to create serum samples. Samples and serially diluted standards (60-5 ng/L, Table 1) were incubated during the assay.

Table 1: Show dilution standards for IL-6

60 ng/L	**Standard No. 1**	**300ul Original Standard+ 150ul Standard diluents**
40 ng/L	Standard No.2	300ul Standard No. 1+ 150ul Standard diluents
20 ng/L	Standard No.3	150ul Standard No.2 -+ 150ul Standard diluent
10 ng/L	Standard No.4	150ul Standard No.3 + 150ul Standard diluent
5 ng/L	Standard No.5	150ul Standard No.4 + 150ul Standard diluent

The IL-6 dilution standards, ranging from 60 ng/L to 5 ng/L, are prepared as shown in the table. Every standard is prepared by serial dilution, which begins with 300 µL of the original standard combined with 150 µL of diluent (60 ng/L), followed by dilutions of the prior standard.

In wells coated with antibodies, then HRP-conjugated detection antibody and TMB substrate. Following the reaction's termination, absorbance at 450 nm was measured, and a standard curve was used to calculate the IL-6 concentrations to guarantee precise measurement of IL-6 in both research groups. The procedure comprised sample dilution (1:5), several washing stages, and controlled incubations at 37°C.

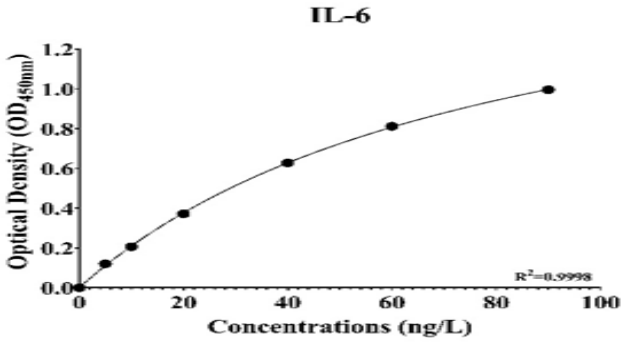

Figure 1: Standard curve for IL-6.

Assay of Serum Human Cardiolipin (CL).

Serum levels of cardiolipin (CL) were measured in e-cigarette users and controls using a sandwich ELISA technique (SunLong Biotech kit). Anti-CL antibody and samples (diluted 5x) or standards (serial dilutions, see Table 2) were pre-coated on the microplate.

Table 2: Shows dilution standards for Cardiolipin.

3ug/ml	Standard No. 1	300kl Original Standard + 150ul Standard diluents
2ug/ml	Standard No.2	300ul Standard No.1+ 150ul Standard diluents
1ug/ml	Standard No.3	+ 150ul Standard No.2 150ul Standard diluent
0.5ug/ml	Standard No.4	150ul Standard No.3 x 150ul Standard diluent
0.25ug/ml	Standard No.5	150ul Standard No.4 -+ 150ul Standard diluent

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Cardiolipin standards were prepared by serial dilution: Standard No. 1 (3 µg/mL, 300 µL original + 150 µL diluent) was diluted stepwise to create Standards No. 2 (2 µg/mL), No. 3 (1 µg/mL), No. 4 (0.5 µg/mL), and No. 5 (0.25 µg/mL). Each of these standards was prepared by mixing equal or specified volumes with a diluent, ensuring a precise concentration gradient.

The TMB substrate and the HRP-conjugated antibody were then introduced. A standard curve was used to determine the CL concentration after the reaction was stopped, and absorbance was measured at 450 nm (Figure 2).

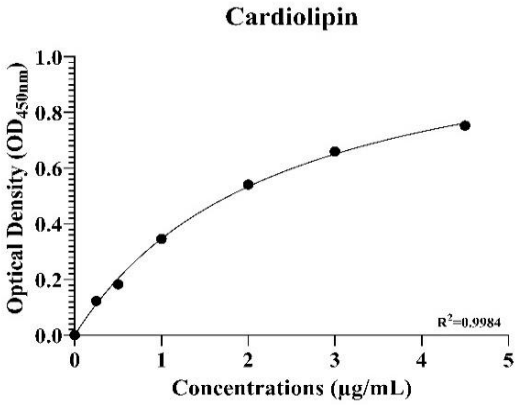

Figure 2: Standard curve for Cardiolipin.

Clotting at room temperature (10–20 min) and centrifuging (4500 rpm, 10 min) were used to create the serum. Following a 30-minute incubation period at 37°C, five washings, and a 15-minute colour development period under light protection, the procedure was terminated. Measurements were made using the ELx800 analyser.

Assay of Serum Anti-Nuclear Antibody:

Using a sandwich enzyme-linked immunosorbent assay (ELISA) kit (SunLong Biotech), the serum anti-nuclear antibody (ANA) levels were measured according to the manufacturer's instructions. In summary, serum samples from controls and e-cigarette users were diluted (1:5) and added to microplate wells that had been precoated with antigen. The samples were then incubated with an antigen conjugated to horseradish peroxidase (HRP). Following washing, the colour changed from blue to yellow when tetramethylbenzidine (TMB) was added as the substrate, and the reaction was halted. An ELx800 analyser was used to measure the optical density (OD) at 450 nm. The mean OD of negative controls plus 0.15 was used to determine the cutoff value; samples with OD values above the cutoff were regarded as ANA-positive, and those below were regarded as negative. Positive controls had to be greater than 1.00 and negative controls less than 0.10 in order for the test to be considered valid. Every step was carried out in accordance with the established protocol, including washing and incubation (37°C, 30 min).

Statistical analysis:

Statistical analyses were performed using GraphPad Prism software (version 9.01, GraphPad, San Diego, CA, USA). Numerous statistical tests that were specific to the data types and parameter distributions were used in the analysis. Depending on the assumptions of normality and homogeneity of variance, either the independent t-test (parametric) or the Mann-Whitney U test (nonparametric) was applied to continuous data (IL-6, Cardiolipin, CRP, WBC, and subgroups). Either the chi-square test or Fisher's exact test was used to analyse categorical data (ANA); Fisher's test was chosen because of the small cell counts. P-values below 0.05 were considered statistically significant for all analyses.

3. RESULTS

Significant differences between electronic cigarette users (case n = 50) and non-e-cigarette users (Controls, n = 30) were found by immunological biomarker analysis, suggesting that electronic cigarette use may affect immune function. Below is a summary of the main findings:

Interleukin-6 (IL-6)

Electronic cigarette users had significantly elevated levels of IL-6 (50.546 ± 12.622 pg/mL) than controls (17.616 ± 0.928 pg/mL), with a statistically significant difference (p=0.0001). This implies that electronic cigarette use is linked to a markedly pro-inflammatory state.

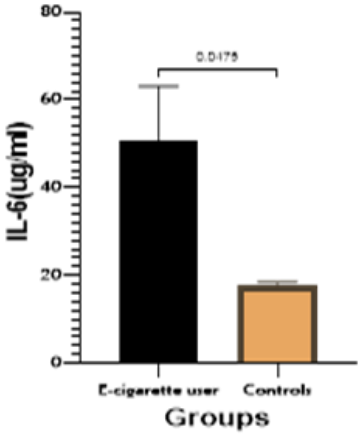

Figure 3: Interleukin-6 (IL-6) level in electronic cigarette users and controls (p <0.05).

Antinuclear Antibodies (ANA)

Forty-nine electronic cigarette users (49/50, 98%) and only one control (1/30, 3.3%) had ANA positivity, with a p-value of 0.0001. This notable distinction suggests a robust correlation between autoimmune reactivity and electronic smoking.

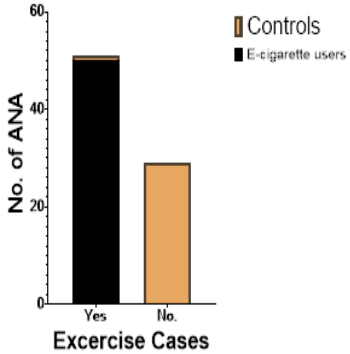

Figure 4:ANA results in electronic cigarette users and controls (p < 0.05).

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Although users had elevated mean levels of cardiolipin antibodies (31.70 ± 0.882 U/mL) than controls (17.61 ± 0.928 U/mL), the difference was statistically significant (p = 0.0001). This implies that there is evidence linking the production of antiphospholipid antibodies to electronic cigarette use.

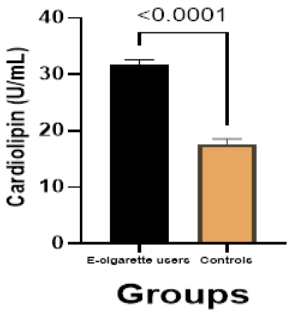

Figure 5: Cardiolipin level in electronic Cigarette users and controls (p < 0.05).

C-Reactive Protein (CRP)

There was no significant difference in CRP levels between the groups (electronic Cigarette users: 1.159 ± 0.144mg/L; controls: 1.170 ± 0.184mg/L; p = 0.9567). The lack of significance might be due to variations in this cohort's systemic inflammation that are not connected to e-cigarette use.

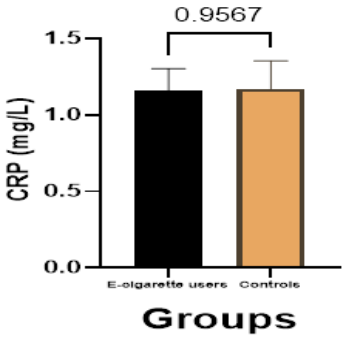

Figure 6: CRP level in electronic Cigarette users and controls (p >0.05).

White Blood Cells (WBC)

The WBC counts of the controls (7.033 ± 0.299 ×10^9/L; p = 0.4223) and e-cigarette users (6.7117 ± 0.195 ×10^9/L) were similar. No significant differences were found in the subgroup analysis of differential counts (neutrophils, lymphocytes, and monocytes), suggesting that the overall leukocyte numbers or distribution were not significantly affected, as indicated by the results in Table 3.

Table 3: Shows White Blood Cells (W.B.C) and differentials results in electronic Cigarette users and controls.

Parameters	Electronic cigarette users n. (50)	Controls n. (30)	P-Value
W.B.C(10^9/L)	6.7117±0.195	7.033±0.299	0.4223
Neutrophil(10^9/L)	3.478±0.135	3.795±0.255	0.4477
Neu%	51.546±1.001	53.173±1.869	0.998
Lymphocyte(×10^3/μL)	2.572±0.092	2.638±0.151	0.8091
Lym%	38.552±0.888	38.34±1.8733	0.9103
Monocyte(10^9/L)	1.2468±0.8055	0.40167±0.0239	0.4476
Mon%	6.5084±0.377	5.8±0.2981	0.2683
Eosinophil (10^9/L)	0.252±0.0687	0.1497±0.0168	0.9704
Eso%	2.6728±0.34739	2.127±0.21	0.9154
Basophil(10^9/L)	0.043±0.0031	0.0387±0.003	0.3822
Bas%	0.6464±0.0436	0.557±0.0456	0.0947

The data is displayed as mean ± standard deviation, group comparisons were conducted using independent samples t-tests (controls: n = 30; e-cigarette users: n = 50). White blood cell counts and group differences did not differ significantly (all p > 0.05). W.B.C. stands for white blood cells, Neu% for neutrophil percentage, Lym% for lymphocyte percentage, Mon% for monocyte percentage, Eso% for eosinophil percentage, and Bas% for basophil percentage.

Haematological parameters from 50 e-cigarette users and 30 controls are compared in the table; most measures do not show statistically significant differences. Neutrophils (absolute: p = 0.4477; percentage: p = 0.998), lymphocytes (absolute: p = 0.8091; percentage: p = 0.9103), and white blood cell (WBC) counts (e-cigarette users: 6.7117 ± 0.195; Controls: 7.033 ± 0.299; p = 0.4223) were comparable across groups. While the basophil percentage approached marginal significance (e-cigarette users: 0.6464% ± 0.0436; Controls: 0.557% ± 0.0456; p = 0.0947), monocyte counts seemed elevated in e-cigarette users (1.2468 ± 0.8055 vs. 0.40167 ± 0.0239) but were highly variable (p = 0.4476). Overall, the results point to

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similar haematological profiles; however, the variability of monocyte data calls for more research.

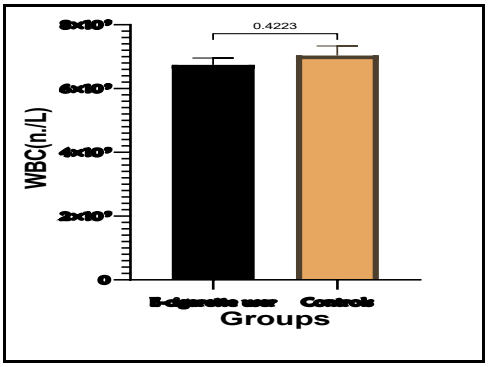

Figure 7: Total WBC counts analysis in electronic cigarette users vs. controls (p >0.05).

Comparable to those in non-e-cigarette users (controls) (7.03 ± 0.30 ×10⁹/L; p= 0.422), indicating no significant difference between groups (unpaired t-test).

These results imply that e-cigarette use has no discernible impact on the overall number of leukocytes or the proportions of their subsets under the conditions under investigation.

Elevated IL-6 levels, Cardiolipin antibodies, and universal ANA positivity were strongly linked to e-cigarette use, suggesting autoimmune activation and systemic inflammation. CRP and total WBC counts, however, did not show any discernible changes. These results highlight how e-cigarette use may interfere with immune homeostasis, especially via autoimmune and pro-inflammatory pathways, that calls for more research into the long-term immunological effects.

4. DISCUSSION

With an emphasis on autoantibodies (ANA, cardiolipin), inflammatory markers (IL-6, CRP), and leukocyte count (WBC), the current study examined the impact of e-cigarette use on immunological traits. The results of the current study indicate that changes in these biomarkers when compared to non-e-cigarette users may indicate that e-cigarette use may be a contributing factor to immune dysregulation.

Autoantibodies and Autoimmunity: anti-nuclear antibodies (ANA) and Cardiolipin antibodies were significantly elevated in e-cigarette users, according to our data, which may indicate autoimmune activation. This is consistent with previous research showing that nicotine and other ingredients in e-cigarettes may cause immunological tolerance to decline (Goniewicz *et al.*, 2018). Notably, it has been demonstrated that two important e-liquid solvents, propylene glycol and vegetable glycerin, can cause oxidative stress and alter self-antigens, which may encourage the production of autoantibodies (Beklen & Uckan, 2021). Additionally, our cohort's elevated anti-cardiolipin antibodies raise concerns regarding thrombotic risk, supporting the findings manifested by Magliah *et al.* (2025), who found that the aerosols from e-cigarettes encourage prothrombotic states and endothelial dysfunction. Recently, research by Graham and Tapson (2020) showed that long-term use of e-cigarettes raises β2-glycoprotein I autoantibodies, which are closely linked to antiphospholipid syndrome. These findings imply that e-cigarettes and traditional smoking may have similar harmful mechanisms for triggering autoimmunity. As indicated by Binder and Litwin (2017), Antiphospholipid antibodies (aPL), such as anti-β2 glycoprotein-I antibodies, are important indicators of antiphospholipid syndrome and have been associated with smoking, According to studies, smoking may exacerbate autoimmunity by encouraging the production of these antibodies, which is comparable to the effects of using e-cigarettes. Hence, more research is needed to pinpoint the precise mechanisms.

Systemic Inflammation: We found that e-cigarette users had elevated levels of IL-6, which is in line with previous studies showing that e-cigarette aerosols cause the release of pro-inflammatory cytokines (Reidel *et al*., 2018). We found no statistically significant difference in CRP between the e-cigarette user and control groups. This disparity could be the result of variations in the study populations, exposure times, or control group attributes. The idea that e-cigarettes may exacerbate chronic inflammatory conditions, albeit less so than traditional cigarettes, is supported by the rise in CRP, a measure of low-grade systemic inflammation (Bozier *et al*., 2020). According to new research, flavoring additives-especially those containing cinnamon and menthol- by triggering NF-κB and raising IL-6 secretion (Allbright *et al*., 2024). However, our study's IL-6 elevation was less severe than that of traditional smokers, which may indicate a gradient of harm. Notably, a recent longitudinal study by (Zięba *et al*. 2024). Discovered that even three months of e-cigarette use resulted in a sustained elevation of IL-6, suggesting that the effects of inflammation may last longer than just the initial exposure.

Leukocyte Count and Immune Response**:** Our findings indicated a modest but no significant increase in WBC count among e-cigarette users, mirroring previous reports that e-cigarette use alters leukocyte profiles as traditional smoking (Flouris *et al*., 2012; Shnawa *et al*., 2020). This may reflect subclinical immune activation, as nicotine is known to stimulate sympathetic nervous system activity, leading to leukocytosis. A study by Bademian *et al*. (2020) revealed that e-cigarette users exhibit elevated neutrophil-to-lymphocyte ratios (NLR), a marker of systemic inflammation and immune dysregulation, further supporting the notion of altered leukocyte dynamics. Additionally, animal models have shown that repeated e-cigarette vapor exposure leads to bone marrow myeloid progenitor cell proliferation, suggesting a potential mechanism for sustained leukocytosis (Sarkar *et al*.,2024). However, the clinical implications of this finding remain uncertain, as long-term studies on e-cigarette-related immune modulation are limited.

Contrast with some studies argue that e-cigarettes are "less harmful" than conventional cigarettes (Kachel, *et al*., 2018; Adebisi & Bafail 2025). Our data suggest that they still exert measurable immunological effects. Notably, the elevation in ANA and cardiolipin antibodies resembles patterns seen in early autoimmune dysfunction, warranting further investigation into whether e-cigarette use could accelerate autoimmune disease onset.

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Limitations and Future Directions: Our study was cross-sectional, limiting causal inferences. Longitudinal studies are needed to assess whether these immunological changes persist or progress to clinical disease. Additionally, variations in e-cigarette constituents (e.g., nicotine concentration, flavorings) may differentially impact immune responses, necessitating component-specific analyses. Recent findings by Farsalinos *et al*. (2018) highlight the need for standardized exposure assessments, as device power settings and puffing topography significantly influence biomarker levels.

CONCLUSION

According to these results, using e-cigarettes is linked to changes in immunological parameters such as leukocyte activation, systemic inflammation, and autoantibody production. The possible risks to immune homeostasis should not be disregarded, even though the effects might not be as bad as those of traditional smoking. Given new data showing that e-cigarettes may contribute to low-grade inflammation and autoimmunity, regulatory and public health policies should take these immunological effects into account when assessing the safety profile of these devices (Farrell, 2024).

Ethical Statement:

The research protocol was evaluated and approved by the Research Ethics Committee at the Koya University Faculty of Health and Science, in accordance with established ethical guidelines (Approval Code: 004 Bio, year 2024).

Author Contributions:

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Q. H. H., and I. S. K.,
Acquisition, analysis, or interpretation of data: Q. H. H., and I. S. K.
Drafting of the manuscript: I. S. K.,

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