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First report on *ACE* I/D polymorphism and lymphoma susceptibility in Algeria: Clinical and genetic insights

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Abstract: Lymphomas represent a heterogeneous group of malignancies influenced by genetic, clinical, and lifestyle factors, but data from North African populations remain scarce. We conducted a case-control study including 86 patients with Hodgkin and non-Hodgkin lymphomas and 110 matched healthy controls from Algeria to evaluate the demographic, clinical, and genetic determinants of disease risk. Smoking (OR=2.06, 95% CI: 1.48-2.87) and hypertension (OR=3.99, 95% CI: 2.37-6.71) were independently associated with increased lymphoma risk, whereas cardiovascular disease (OR=0.30, 95% CI: 0.14-0.65) and allergies (OR=0.25, 95% CI: 0.15-0.40) showed inverse associations. Genetic analysis revealed that the *ACE* ID genotype was inversely associated with lymphoma (OR=0.18, 95% CI: 0.08-0.38), particularly for non-Hodgkin subtypes. These findings suggest that both modifiable lifestyle factors and genetic variation within the renin-angiotensin system may affect lymphoma risk in the Algerian population. The results represent preliminary, population-specific evidence that should be validated in larger multicenter studies.

Keywords: Hodgkin lymphoma, non-Hodgkin lymphoma, *ACE* I/D polymorphism, risk factors

INTRODUCTION

Lymphomas, encompassing Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), are a heterogeneous group of hematological malignancies characterized by distinct epidemiological and biological features. Globally, they contribute substantially to cancer incidence and mortality, with NHL ranking among the most prevalent cancers in both developed and developing regions [1]. HL typically exhibits a bimodal age distribution and earlier clinical presentation, whereas NHL is more frequent in older adults and is often detected at advanced stages due to its indolent onset [2].

Lymphoma pathogenesis is multifactorial, involving interactions between genetic susceptibility, environmental exposures, lifestyle factors, and comorbidities. Established risk factors include a family history of hematological malignancies, immune dysfunction, chronic infections, and certain autoimmune diseases [3-5]. Increasing attention has been directed toward cardiovascular and metabolic conditions such as hypertension and diabetes, as well as behavioral factors like tobacco use, though associations remain inconsistent across populations [6-8].

Genetic variants within the renin-angiotensin system (RAS), particularly the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism (rs4646994), have been explored for their potential contribution to cancer susceptibility [9,10]. The D allele has been linked to increased ACE activity and elevated angiotensin II levels, promoting angiogenesis, inflammation, and tumor microenvironment remodeling [11-13]. However, data on its relationship with lymphoma risk remain scarce and inconclusive, especially for North African populations.

In Algeria and across North Africa, epidemiological and genetic studies on lymphoma remain limited, despite reports of earlier onset and advanced-stage presentation compared with Western cohorts [14,15].

Population-specific data increases our understanding of disease determinants and guides tailored prevention and management strategies. This study investigated demographic, clinical, and molecular factors associated with lymphoma in an Algerian cohort by focusing on the *ACE* I/D polymorphism, rs4646994. By integrating epidemiological and genetic evidence, it provides novel, population-specific insights into the multifactorial etiology of lymphoma within a North African context, contributing to a broader effort to elucidate disease heterogeneity.

MATERIALS AND METHODS

Ethics statement

The research protocol received approval from the Institutional Ethics board of the University Hospital in Constantine (under approval code EC/CHUC/06/02-2021, issued on 08.02.2021). All participants provided written informed consent before sample collection. The investigation adhered to the principles of the Declaration of Helsinki as well as applicable national guidelines.

Study population

The study population consisted of individuals from eastern Algeria, recruited over two years (2022-2024) at the Hematology Department of Benbadis University Hospital Center, Constantine. A total of 86 patients with a histologically confirmed diagnosis of Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) were included. The control group comprised 110 healthy, normotensive volunteers with no personal or family history of malignancy. Cases and controls were matched by age, sex, and geographic origin to minimize potential confounding. Eligibility criteria for patients included: (i) a histological confirmation of HL or NHL, (ii) no prior chemotherapy, with samples collected before treatment initiation, (iii) willingness to provide a blood sample, and (iv) written informed consent for the use of clinical data and biological material for research purposes. Exclusion criteria were: (i) the presence of another hematologic malignancy distinct from lymphoma; (ii) initiation of chemotherapy before blood collection; and (iii) refusal to provide consent or undergo sampling.

DNA extraction

Genomic DNA was extracted from peripheral blood leukocytes using the standard inorganic NaCl-based salting-out method. Approximately 5-7 mL of peripheral venous blood was collected under sterile conditions by venipuncture into ethylenediaminetetraacetic acid (EDTA)-coated vacutainer tubes to prevent coagulation. DNA concentration and purity were assessed spectrophotometrically using the NanoDrop 8000 instrument (Thermo Scientific).

Molecular testing

Genotyping of *ACE* I/D rs4646994

The *ACE* I/D (rs4646994) variant was genotyped by polymerase chain reaction (PCR) using the following primer sequences: forward 5′-CTG CAG ACC ACT CCC ATC CTT TCT-3′ and reverse 5′-GAT GTG GCC ATC ACA TTC GTC AGA T-3′. Amplification was performed in a 10-µL reaction volume containing template DNA, $MgCl_2$ (50 mM), deoxynucleotide triphosphates (dNTPs; 0.2 mmol/L final concentration), and primers (100 ng/µL). PCR reactions were run on a Veriti™ 96-Well Fast Thermal Cycler under the following conditions: initial denaturation at 95°C for 5 min, 35 cycles of denaturation at 94°C for 30 s, annealing at 63°C for 45 s, and extension at 72°C for 30 s, followed by a final elongation step at 72°C for 5 min. PCR products were resolved on 2% agarose gels stained with ethidium bromide and visualized under UV illumination. The insertion (I) allele produced a 490 bp fragment, whereas the deletion (D) allele generated a 190 bp fragment. Accordingly, genotypes were classified as II (490 bp band), DD (190 bp band), or ID (both 490 bp and 190 bp).

Quality control

Genotyping reproducibility was verified by re-genotyping 10 randomly selected samples in independent PCR assays, achieving 100% concordance. The overall genotyping call rate was 100%. Each PCR

run included a positive control (known as the *ACE* genotype), a negative control (no template), and a molecular weight marker to confirm fragment sizes.

Statistical analysis

All statistical analyses were performed using SPSS software (IBM Corp., Chicago, IL, USA) (version 23.0). Continuous variables were expressed as the mean±standard deviation (SD), while categorical data were summarized as absolute numbers and percentages. Group comparisons for categorical variables were performed using the chi-square (χ^2) or Fisher's exact test, while continuous variables were analyzed using the Student's t-test or one-way ANOVA. Hardy-Weinberg equilibrium in the control group was assessed using the chi-square goodness-of-fit test. Associations between ACE (rs4646994) genotypes/alleles and lymphoma risk were estimated using odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate logistic regression models were used to adjust for potential confounders and to identify independent predictors. A P value <0.05 was considered statistically significant.

RESULTS

This study aimed to evaluate demographic, clinical, and genetic determinants of lymphoma risk in an Algerian cohort with a specific focus on the *ACE* I/D (rs4646994) polymorphism.

Demographic and clinical characteristics of patients and controls

A comparative analysis of demographic and clinical characteristics is summarized in Table 1. Although the mean age and sex distribution did not differ significantly between groups, the age distribution varied markedly (P<0.001): Hodgkin lymphoma

Table 1. Demographic and clinical characteristics of Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and control groups

Characteristic	HL (N=39) n (%)	NHL(N=47) n (%)	Control (N=110) n (%)	P value
Age (years, mean± SD)	43.02 ± 19.73		43.05 ± 9.57	0.999
Age categories (years)				**<0.001**
< 30	24 (61.6)	4 (8.5)	10 (9.1)	
30-44	13 (33.3)	12 (25.5)	44 (40.0)	
45-59	0 (0.0)	9 (19.2)	56 (50.9)	
≥ 60	2 (5.1)	22 (46.8)	0 (0.00)	
Gender				0.965
Female	14 (35.9)	18 (38.3)	42 (38.2)	
Male	25 (64.1)	29 (61.7)	68 (61.8)	
Sex ratio (M/F)	1.69		1.62	
Smoking status				**0.043**
Yes	22 (56.4)	18 (38.3)	37 (33.6)	
No	17 (43.6)	29 (61.7)	73 (66.4)	
Hypertension				**<0.001**
Yes	1 (2.6)	18 (38.3)	17 (15.5)	
No	38 (97.4)	29 (61.7)	93 (84.5)	
Diabetes				**0.016**
Yes	2 (5.1)	12 (25.5)	13 (11.8)	
No	37 (94.9)	35 (74.5)	97 (88.2)	
Thyroid disease				**0.033**
Yes	1 (2.6)	5 (10.6)	2 (1.8)	
No	38 (97.4)	42 (89.4)	108 (98.2)	
Cardiovascular disease				**0.043**
Yes	0 (0.0)	3 (6.4)	14 (12.7)	
No	39 (100)	44 (93.6)	96 (87.3)	
Allergy				**<0.001**
Yes	3 (7.7)	0 (0.0)	26 (23.6)	
No	36 (92.3)	47 (100)	84 (76.4)	
Surgical history				0.335
Yes	7 (17.9)	15 (31.9)	28 (25.5)	
No	32 (82.1)	32 (68.1)	82 (74.5)	
Personal history of Cancer				0.359
Yes	0 (0)	1 (2.1)	-	
No	39 (100)	46 (97.9)	-	
Family history of Cancer				**0.041**
Yes	26 (66.7)	21 (44.7)	-	
No	13 (33.3)	26 (55.3)	-	
Ann Arbor stage				
I + II	20 (51.3)	11 (23.4)	-	**0.007**
III + IV	19 (48.7)	36 (76.6)	-	

F – female, M – male, SD – standard deviation. The P values for quantitative variables were assessed using the Mann-Whitney U-test for non-parametric and asymmetrically distributed variables, while the $\chi 2$ test was used for qualitative variables. P<0.05 was considered significant.

(HL) patients were predominantly younger, with more than 60% diagnosed before the age of 30 years, whereas nearly half of non-Hodgkin lymphoma (NHL) patients were aged 60 years or older. In contrast, most controls were concentrated in the 45-59-year age group. The gender distribution was balanced across all groups (P=0.965).

Smoking habits differed significantly (P=0.043), with HL patients showing the highest prevalence of tobacco use. Among comorbidities, arterial hypertension (P<0.001), diabetes mellitus (P=0.016), and thyroid disease (P=0.033) were more frequent in NHL cases compared to HL and controls. Conversely, cardiovascular disease was unexpectedly more common among controls (12.7%) than in NHL patients (6.4%) and was absent among HL cases (P=0.043).

A striking difference was also observed for allergic conditions (P<0.001), which were absent in NHL, less frequent in HL, but present in nearly one-quarter of controls. The surgical history did not differ significantly between groups (P=0.335); the personal history of cancer was rare in all participants, and the family history of malignancy was significantly higher among HL patients compared to NHL (P=0.041).

Regarding disease stage, HL cases were nearly equally distributed between early (I+II, 51.3%) and advanced stages (III+IV, 48.7%). In contrast, most NHL cases were diagnosed at advanced stages (III-IV, 76.6%) rather than at earlier stages (23.4%), showing a statistically significant difference (P=0.007).

ACE I/D genotypes and allele distribution

The distribution of *ACE* I/D (rs4646994) genotypes and allele frequencies is presented in Table 2. In the control group, genotype frequencies deviate from the Hardy-Weinberg equilibrium (P=0.0007). Among all lymphoma patients, the DD genotype was more prevalent (89.5% vs 79.1% in controls), whereas the ID genotype was significantly underrepresented (3.5% vs 15.5%, OR=0.20, 95% CI: 0.06-0.71, P=0.006), suggesting a potential protective effect. No significant differences were observed for the II genotype or overall allele frequencies.

In subgroup analyses, HL patients did not differ significantly from controls, although the ID genotype was less frequent (5.1% vs 15.5%, OR=0.32, P=0.124) and the II genotype slightly more frequent (12.8% vs 5.5%, P=0.191). In contrast, a marked imbalance was observed among NHL patients: the ID genotype was notably reduced compared with controls (2.1% vs 15.5%; OR=0.11, 95% CI: 0.01-0.88, P=0.013), and the I allele was significantly less frequent (3.2% vs 13.2%; OR=0.22, 95% CI: 0.06-0.73, P=0.007). These findings highlight a potential association between the D allele and increased susceptibility to NHL.

Table 2. Genotype and allele distribution analysis of the *ACE* I/D polymorphism in patients and controls

Group	N	Genotype/Allele	Patients n (%)	Controls n (%)	OR	95% CI	P value
All Patients	86	DD	77 (89.5)	87 (79.1)	-	-	-
		ID	3 (3.5)	17 (15.5)	0.20	0.06–0.71	**0.006**
		II	6 (7.0)	6 (5.5)	1.13	0.35–3.65	0.84
		D allele	157 (91.3)	191 (86.8)	-	-	-
		I allele	15 (8.7)	29 (13.2)	0.63	0.33–1.22	0.17
HL Patients	39	DD	32 (82.1)	87 (79.1)	-	-	-
		ID	2 (5.1)	17 (15.5)	0.32	0.07–1.46	0.124
		II	5 (12.8)	6 (5.5)	2.27	0.65–7.94	0.191
		D allele	66 (84.6)	191 (86.8)	-	-	-
		I allele	12 (15.4)	29 (13.2)	1.18	0.58–2.48	0.627
NHL Patients	47	DD	45 (95.7)	87 (79.1)	-	-	-
		ID	1 (2.1)	17 (15.5)	0.11	0.01–0.88	**0.013**
		II	1 (2.1)	6 (5.5)	0.32	0.04–2.76	0.277
		D allele	91 (96.8)	191 (86.8)	-	-	-
		I allele	3 (3.2)	29 (13.2)	0.22	0.06–0.73	**0.007**

Ref – reference category, n – number of individuals, OR – odds ratio, CI – confidence interval. P was examined by the $\chi 2$ test and considered significant at <0.05.

Multivariate analysis of predictive factors

Multivariate logistic regression analysis, adjusted for age and sex, identified several independent predictors of lymphoma risk (Table 3). The *ACE* I/D genotype remained strongly associated with disease susceptibility (OR=0.18, 95% CI: 0.08-0.38, P<0.001), supporting a protective role of the I allele. Tobacco smoking (OR=2.06, 95% CI: 1.48-2.87, P<0.001) and hypertension (OR=3.99, 95% CI: 2.37-6.71, P<0.001) significantly increased lymphoma risk, confirming their contribution as major modifiable factors.

Conversely, cardiovascular disease (OR=0.30, 95% CI: 0.14-0.65, P=0.002) and allergy (OR=0.25, 95% CI: 0.15-0.40, P=0.035) showed inverse associations with lymphoma, suggesting potential protective effects. Other comorbidities exhibited weaker or non-significant relationships: diabetes showed a borderline association (P=0.073), thyroid disease had no measurable effect (P=0.939), and surgical history was not retained in the model (P=0.198).

These findings delineate distinct clinical and molecular profiles between HL and NHL. Lifestyle factors such as smoking and hypertension, along with the ACE I/D polymorphism, were major determinants of lymphoma risk, while cardiovascular disease and allergy showed inverse association with disease occurrence.

Table 3. Multivariate logistic regression analysis of predictive factors for lymphoma

Variable	P value	Odds ratio (OR)	95% Confidence interval (CI)
ACE genotype	**<0.001**	0.178	0.083 – 0.378
Smoking (tobacco)	**<0.001**	2.064	1.483 – 2.873
Hypertension (HTN)	**<0.001**	3.985	2.369 – 6.706
Diabetes	0.073	1.609	0.956 – 2.707
Thyroid disease	0.939	0.977	0.538 – 1.776
Cardiovascular disease	**0.002**	0.302	0.141 – 0.646
Allergy	**0.035**	0.245	0.150 – 0.402
Surgical history	0.198	1.245	0.892 – 1.737

P<0.05 was considered significant

DISCUSSION

This study provides one of the first comprehensive insights into the demographic and clinical characteristics of lymphoma in an Algerian population. Distinct subtype-specific patterns were observed: Hodgkin lymphoma (HL) occurred predominantly in younger individuals and was more often diagnosed at earlier stages, whereas non-Hodgkin lymphoma (NHL) was largely confined to older adults and typically identified at advanced stages. Over 60% of HL patients were younger than 30 years, while nearly half of NHL cases occurred in individuals aged 60 years or older. Although international studies commonly report a bimodal age distribution for HL, with incidence peaks in young adulthood and later life [16,17], our data revealed a single prominent peak among younger patients. This trend may reflect regional demographic characteristics, differences in environmental exposures, or the influence of sample size. The mean age in our cohort (~43 years) was slightly lower than that generally reported in European and North American populations but aligns with more recent findings from North Africa and the Middle East. For instance, a 2024 epidemiological survey of hematologic malignancies across North Africa reported comparably younger median ages at diagnosis for NHL [18]. Similarly, data from Lebanon indicated a mean age at NHL diagnosis of approximately 53.5 years, still lower than that observed in most Western populations [19]. The male-to-female ratio (~1.6) was in line with global epidemiological data, which consistently demonstrate a modest male predominance in lymphoma [18,20].

Hypertension emerged as a strong predictor, nearly quadrupling the risk of lymphoma. This finding is consistent with mechanistic models implicating chronic inflammation mediated by both innate and adaptive immune responses in the pathogenesis of hypertension and lymphomagenesis [8]. Although the direct relationship between hypertension and lymphoma remains insufficiently characterized, it may partly reflect the influence of antihypertensive treatments or the metabolic profiles of affected individuals. Growing epidemiological evidence supports a broader association between hypertension and cancer risk: for example, a large pooled analysis identified hypertension as an independent risk factor for endometrial cancer [21], while a major cohort study reported increased risks of kidney, lung, breast cancers, and melanoma among hypertensive patients [22]. Nonetheless, data specific to hematologic malignancies remain scarce. Recent studies have linked preexisting hypertension to

poorer survival in diffuse large B-cell lymphoma [23], and global burden analyses have suggested a possible association with Hodgkin lymphoma incidence [24].

In contrast, cardiovascular disease showed an inverse association with lymphoma in our cohort. This finding may partly reflect the influence of medications commonly prescribed for cardiovascular conditions. Statins possess antiproliferative and immunomodulatory properties and have been linked to a reduced incidence of lymphoid neoplasms [25]. Likewise, inhibitors of the renin-angiotensin pathway, such as ACE blockers, have demonstrated anti-angiogenic, anti-inflammatory, and immune-modulating effects [26,27]. These pharmacological mechanisms could plausibly account for the observed decreased risk. However, the apparent protective effect of cardiovascular disease should be interpreted with caution, as it could arise from treatment-related factors rather than a true biological association.

Allergic conditions were also inversely associated with lymphoma risk, aligning with meta-analyses that reported a lower likelihood of NHL among individuals with asthma, hay fever, food allergies, or allergic rhinitis (pooled OR≈0.83) [28-30]. However, large prospective investigations, including Swedish studies, failed to confirm this protective association [29-31]. Although enhanced immune surveillance in allergic individuals provides a biologically plausible explanation, the inconsistencies across studies suggest that recall bias, reverse causation, or residual confounding may also play a role. Therefore, the inverse association observed in our cohort should be interpreted cautiously and confirmed in well-designed prospective studies.

Diabetes demonstrated only a borderline association with lymphoma risk in our analysis. Previous meta-analyses reported a modest elevation in NHL incidence (RR≈1.20) [7,32,33], yet findings from more recent prospective studies have been inconsistent. For instance, a large multiethnic cohort including over 190,000 participants found no significant overall association (HR=1.04; 95% CI: 0.96-1.13), although a slight increase in risk was noted among normal-weight individuals [32]. Likewise, pooled analyses from US cohorts revealed no clear relationship after adjustment for BMI and lifestyle factors [7]. These discrepancies may reflect differences in glycemic control, obesity prevalence, or underlying population-specific characteristics.

Although thyroid disorders initially appeared more common among patients, this association disappeared after adjustment for age and sex, suggesting that thyroid disease is unlikely to represent an independent risk factor in our population. This finding contrasts with earlier studies linking autoimmune thyroiditis, particularly Hashimoto's disease, to primary thyroid lymphoma [34]. The absence of association in our study may reflect limited clinical detail in the dataset, the small subgroup size, or the aggregation of autoimmune and non-autoimmune thyroid disorders into a single category.

Smoking was a significant predictor, conferring more than a threefold increase in lymphoma risk. This result aligns with previous studies implicating tobacco exposure in immune dysregulation and lymphomagenesis, especially in Hodgkin lymphoma and follicular lymphoma [35,36]. Carcinogens present in tobacco smoke likely promote chronic inflammation and immune alteration, providing biological plausibility for this association.

Although family history of cancer could not be included in multivariate models since no controls reported such antecedents, it remains a well-established risk factor. Large, pooled analyses consistently show that individuals with a first-degree relative affected by lymphoma or other hematological malignancies have a significantly higher risk of developing the disease themselves [3,37-40]. This underscores the contribution of inherited susceptibility and shared environmental exposures to lymphoma etiology, even though our dataset did not permit direct evaluation.

Clinical stage distribution also differed markedly between subtypes. HL cases were nearly evenly divided between early and advanced stages, reflecting its clinical heterogeneity and the influence of B symptoms on earlier diagnosis [41]. In contrast, NHL was predominantly diagnosed at advanced stages (~77%), consistent with its typically indolent onset and rapid dissemination in aggressive subtypes such as diffuse large B-cell lymphoma [2]. Similar findings have been reported in regional studies from Algeria and Tunisia, which also documented a predominance of late-stage presentation [15,42]. This trend may be explained by

diagnostic delays, disparities in healthcare access, or the limited applicability of the Ann Arbor system to NHL due to its frequent extra nodal involvement [43].

Genetic analysis revealed a significant role of the *ACE* I/D polymorphism in susceptibility to lymphoma. The ID genotype was underrepresented among patients compared with controls, suggesting a potential protective effect, whereas the DD genotype was more frequent, particularly in NHL cases. These findings support the involvement of the renin-angiotensin system (RAS) in lymphomagenesis, consistent with prior reports linking the D allele to increased cancer risk [9,10].

This study examined the association between the angiotensin-converting enzyme (ACE) insertion/deletion (I/D, rs4646994) polymorphism and lymphoma risk. The ID genotype was inversely associated with disease, particularly in NHL, whereas the DD genotype was more prevalent among patients. This pattern aligns with previous studies associating the D allele with elevated cancer susceptibility [9,10,44,45].

Mechanistically, these results are biologically plausible given the central role of RAS in oncogenesis. The DD genotype is associated with higher ACE activity and increased production of angiotensin II (Ang II). Ang II binding to the AT1 receptor activates proliferative and anti-apoptotic pathways, notably the PI3K/Akt signaling, as demonstrated in AT1R-positive breast cancer cells [46]. Similar mechanisms have been described in NK/T-cell lymphoma models, where Ang II accelerated tumor growth through PI3K/Akt activation, while pharmacological AT1R inhibition significantly reduced tumor progression *in vivo* [11]. Beyond direct oncogenic signaling, RAS contributes to several cancer hallmarks, including angiogenesis, inflammation, and oxidative stress, through ROS, MAPK, and PI3K pathways, thereby enhancing stromal remodeling and tumor aggressiveness [47,48]. Sustained AT1R stimulation further promotes a tumor-supportive microenvironment characterized by angiogenesis, fibrosis, and immune evasion, effects that can be mitigated by ACE inhibitors or angiotensin receptor blockers (ARBs) in preclinical models [27,49].

Evidence for ACE expression in tumor-associated macrophages (TAMs) further supports the notion that localized RAS activity contributes to an immunosuppressive tumor microenvironment. In HL, ACE has been detected in macrophages within affected lymph nodes, suggesting a role in the biology of HL lesions [27,50]. Across multiple cancer types, ACE has been implicated in reshaping the tumor microenvironment (TME) by expanding myeloid-derived suppressor cells (MDSCs) and driving TAMs and cancer-associated fibroblasts (CAFs) toward immunosuppressive phenotypes. Pharmacological blockade of RAS with ARBs has been shown to reduce immunosuppressive cytokines (IL-6, IL-10, VEGF), alleviate T-cell inhibition by $CD11b^{+}$ myeloid cells, and enhance antitumor immune responses [51,52]. Conversely, the I allele, associated with lower ACE activity and reduced generation of Ang II, may limit these pro-oncogenic effects, providing partial protection against lymphoma.

For HL, no statistically significant genotype associations were detected, although a trend toward reduced ID frequency was noted. This may reflect biological differences between HL and NHL or a limited sample size that restricts statistical power. The detection of ACE expression in HL macrophages [27,50] suggests possible RAS involvement, though genotype-phenotype relationships remain to be clarified.

The observed deviation from the Hardy-Weinberg equilibrium in the control group deserves cautious interpretation. This deviation is most likely attributable to the hospital-based recruitment strategy, which does not fully represent the general population, and which, combined with the modest sample size, amplifies random variation. To exclude technical errors, a random subset of samples was rechecked, confirming the accuracy of genotyping. Despite this limitation, the strong effect estimates and the narrow confidence intervals support a genuine association between ACE I/D polymorphism and NHL susceptibility. These findings, however, should be regarded as preliminary and validated in larger, population-based cohorts. A pooled analysis of 25 studies found no overall association, though ethnic differences were reported between European and Asian populations [4]. Another meta-analysis of 35 studies similarly identified no global effect but detected significant associations in Caucasians (II *vs* ID+DD: OR 1.43; I *vs* D: OR 1.23) [53]. A Sudanese study also reported no association with acute lymphoblastic leukemia [54]. Collectively, our results provide lymphoma-specific evidence, particularly for NHL, that

may reflect true ethnic or tumor-specific variations, consistent with findings from breast and gastric cancer studies showing significant associations in Asian and Caucasian subgroups [55-57].

This study has several limitations that should be acknowledged. First, the modest sample size, particularly within certain lymphoma subgroups, limited statistical power and may have prevented the detection of weaker associations. This was partly due to the strict eligibility criteria (recruitment of chemotherapy-naïve patients) and the rarity of some lymphoma subtypes. Second, the recruitment was hospital-based, which may introduce selection bias and restrict the generalizability of the findings to the wider Algerian population. Third, some clinical and lifestyle data were based on patient self-reporting, which carries a risk of recall bias and potential misclassification. In addition, logistical constraints such as a limited enrollment period, occasional patient non-participation, and exclusion of low-quality samples further reduced the dataset. Finally, the genetic analysis was restricted to a single variant (*ACE* I/D), while a broader set of genetic and environmental interactions influences lymphoma susceptibility. Overall, these limitations indicate that our results should be interpreted with caution and considered preliminary until validated in larger, multicenter studies.

CONCLUSIONS

This study provides the first data from Algeria on the interplay between clinical risk factors and the *ACE* I/D polymorphism in lymphoma susceptibility. Hodgkin lymphoma was more frequent in younger patients and was often diagnosed at early stages, whereas non-Hodgkin lymphoma was more common in older adults and at advanced stages. Tobacco use and hypertension were associated with increased risk, while cardiovascular disease and allergy appeared inversely related. The *ACE* I/D polymorphism showed a significant association, with the D allele linked to greater susceptibility and the I allele suggesting protection, particularly in NHL. Given the modest sample size, hospital-based recruitment, and reliance on self-reported clinical data, these findings should be considered preliminary and specific to the studied population. They highlight the multifactorial nature of lymphoma and the need to integrate genetic and environmental factors in risk assessment. Future large-scale, multicenter investigations are essential to confirm these associations, refine risk stratification, and inform strategies for early detection and personalized patient care in North African populations.

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Conflict of interest disclosure: The authors declare no conflicts of interest.

Data availability: The data supporting this article are available in the online dataset: https://www.serbiosoc.org.rs/NewUploads/Uploads/Salhi%20et%20al_Dataset.pdf

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