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ORIGINAL PAPER

A marker of systemic inflammation in hidradenitis suppurativa patients without cardiovascular disease: aortic arch calcification

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Abstract

Background In this study, we aimed to investigate whether there is a relationship between aortic arch calcification (AAC) and hidradenitis suppurativa (HS) in HS patients without cardiovascular disease.

Methods In this study, patients over 18 years of age who applied to the dermatology outpatient clinic between January 2023 and February 2024 were followed up with the diagnosis of HS without cardiovascular disease, and a healthy control group matched in terms of age and gender were included retrospectively.

Results In total, 130 patients with HS without cardiovascular disease and 130 control patients were included in the study. AAC was significantly higher in the HS group compared to the control group ($p=0.028$). In the multivariate analysis, we found that age and HS were independent predictors of AAC (OR: 1.048 (1.009–1.089); $p=0.015$, OR: 3.158 (1.181–8.445); $p=0.022$, respectively). When we divided the groups as having AAC (grade 1–3) and not having AAC (grade 0), the rate of HS disease was significantly higher in the group with AAC compared to the group without AAC (75.0% vs. 47.5% $p=0.010$).

Conclusions AAC is observed more frequently in patients with HS without cardiovascular disease than in healthy individuals. Moreover, HS can be considered as an independent predictor of AAC. AAC may contribute to developing treatment strategies in HS patients without cardiovascular disease.

Keywords Aortic arch calcification · Hidradenitis suppurativa · Systemic inflammation · Cardiovascular disease

Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent inflammatory skin disease characterized by the development of deep-seated nodules, abscesses, fistulas, and scars mainly in the axilla, inguinal and anogenital regions [1]. The estimated prevalence of HS is approximately 1–4% and it is associated with cardiovascular risk factors such as obesity, hypertension, dyslipidemia, insulin resistance, diabetes, and metabolic syndrome, as well as high CRP levels and systemic inflammation [2–8]. Systemic inflammation is associated with an increased risk of cardiovascular disease. Studies have shown an increased prevalence of subclinical atherosclerosis in patients with HS compared to controls [9, 10]. Some antibiotics and biologic agents with anti-inflammatory properties are used in treatment according to the stage of the disease [11]. Considering that the severity of inflammation is an important parameter in terms of disease prognosis, low-cost markers that practically show this severity have gained importance in recent years.

Inflammation plays a central role in the development of atherosclerosis and vascular calcification. Although vascular calcification was initially considered a degenerative process, recent studies show that vascular calcification involves complex pathophysiological processes [12, 13]. Vascular calcification, particularly aortic arch calcification (AAC), is an independent risk factor for cardiovascular events and all-cause mortality in patients with cardiovascular disease [14–16]. To the best of our knowledge, no studies in the literature investigate the relationship between HS and AAC. In light of these available data, this study aimed to investigate

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whether HS is associated with aortic arch calcification in HS patients without cardiovascular disease.

Materials and methods

Patients and study design

The minimum number of patients who needed to be included for an effect size of 0.2 and 90% power was calculated. In this study, patients over 18 years of age who applied to the dermatology outpatient clinic of Zonguldak Bülent Ecevit University Faculty of Medicine between January 2023 and February 2024 were followed up with the diagnosis of HS without cardiovascular disease, and a healthy control group matched in terms of age and gender were included retrospectively. Patients' demographic information, medical history, laboratory test results, and chest radiographs were collected retrospectively from hospital records. Exclusion criteria were individuals under 18 years of age and those with missing laboratory and chest radiograph data in the hospital registration system. In addition, patients with an uncertain diagnosis of HS and those with a history of cardiovascular disease were excluded from the study. In the control group, individuals with a diagnosis of HS and/or a history of other chronic inflammatory diseases or inflammatory skin lesions involving the flexural regions (abscess, furuncle, lymphadenitis, etc.) that could be differentially diagnosed with HS were excluded.

A qualified dermatologist diagnosed HS patients based on clinical examination and diagnostic criteria, including a history of recurrent inflammatory nodules, abscesses, and drainage of sinuses in inverted areas [17]. Hurley staging system was used to classify disease severity in HS patients. In this staging system, disease severity was classified as mild (Hurley-1), moderate (Hurley-2) and severe (Hurley-3) according to the presence and degree of scar and sinus tract formation [18].

Patients were considered to have metabolic syndrome if any three of the following criteria were present:1-Impaired fasting glucose: Serum fasting glucose ≥ 100 mg/dl and/or receiving treatment for this reason and/or being diagnosed with type 2 diabetes mellitus. 2-Hypertension: Systolic/diastolic blood pressure ≥ 130/85 mmHg and/or receiving treatment for this reason. 3-Hypertriglyceridemia: Serum triglyceride > 150 mg/dl and/or receiving treatment for this reason. 4-Low HDL cholesterol: Serum HDL < 50 mg/dl in women, < 40 mg/dl in men, and/or receiving treatment for this reason. 5-Waist circumference: ≥35 inches in women and ≥ 40 inches in men [19]. Triglyceride glucose (TyG) index was calculated as ln [fasting TGs (mg/dL) × FPG (mg/dL)/2] [20]. Data on smoking was collected with dichotomized (yes or no) questionnaires.

This study was conducted in accordance with the Declaration of Helsinki, and informed consent was taken from all patients. Ethical approval was obtained from Zonguldak Bülent Ecevit University Clinical Research Ethics Committee (Date: 24/04/2024, No: 2024/08).

Assessment of aortic arch calcification

All study patients received routine posterior-anterior chest X-rays (AXIOM Aristos MX, SIEMENS, Germany) or portable chest X-rays (MUX-200D, SHIMADZU, Japan) upon admission. AAC for each patient was assessed by two independent, experienced cardiologists in a blinded fashion. The AAC extent was divided into four grades (Fig. 1): grade 0, no visible calcification; grade 1, small spots of calcification or a single thin area of calcification of the aortic knob; grade 2, one or more areas of thick calcification; grade 3, circular calcification of the aortic knob [21].

Statistical analysis

The conformity of continuous variables to normal distribution was evaluated by visual examination of histograms and Q-Q curves and Kolmogorov Smirnov and Shapiro-Wilks tests. Continuous variables with normal distribution were expressed as mean (± standard deviation), continuous variables without normal distribution were expressed as median (interquartile range), and categorical variables were expressed as numbers and percentages. Continuous variables that fit the normal distribution between the two groups were compared by Student's t test, those that did not fit the normal distribution were compared by Mann-Whitney U test, and categorical data were compared by Chi-square or Fisher exact test. The relationship between HS and AAC was evaluated by univariate and multivariate logistic regression analysis. A two-way p-value < 0.05 was considered statistically significant in all comparisons. IBM SPSS software was used for all statistical analyses (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

Results

In total, 130 patients with HS without cardiovascular disease and 130 control patients were included in the study. Basic demographic, clinical, and laboratory characteristics between the groups are shown in Table 1. Although traditional cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia were higher in the HS group, they did not reach statistical significance. However, smoking and

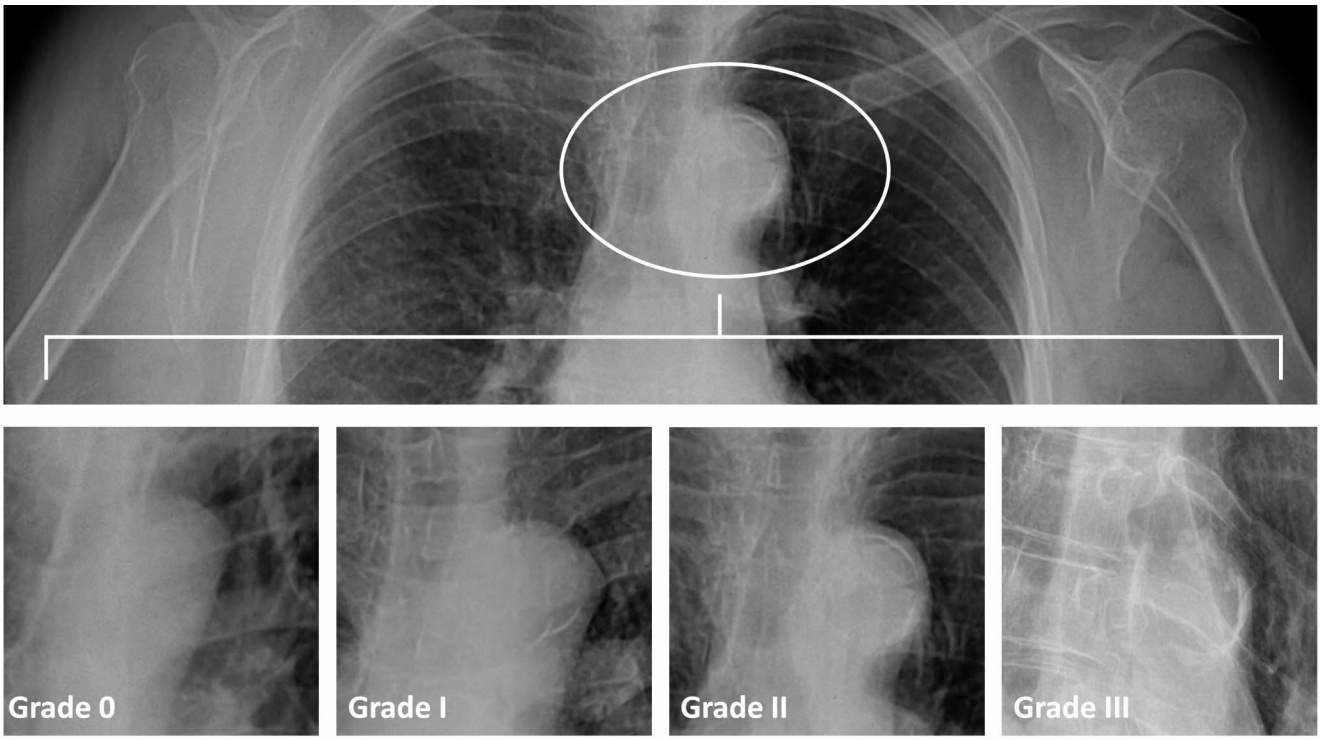

Fig. 1 Grading of aortic arch calcification

metabolic syndrome, which are also known as traditional cardiovascular risk factors, were observed significantly more frequently in the HS group compared to the control group (all $p<0.05$). WBC and CRP values indicating inflammation were significantly higher in the HS group, while albumin, a negative acute phase reactant, was significantly lower in the HS group (all $p<0.05$). Similarly, although LDL cholesterol was significantly higher in the HS group, HDL cholesterol was significantly lower in the HS group (all $p<0.05$). However, TyG index, a valid surrogate marker of insulin resistance, was significantly higher in the HS group compared to the control group ($p=0.041$). In addition, AAC was significantly higher in the HS group compared to the control group ($p=0.028$).

Table 2 presents the clinical findings in HS patients. The median age at onset was 24 years and the median disease duration was 3 years. Of 130 patients with HS, 43 (33.1%) were classified as Hurley stage I, 66 (50.8%) as Hurley stage II, and 21 (16.1%) as Hurley III. The median number of affected sites was 2; axilla and inguinal were the most commonly involved sites.

Since Grade 2 and Grade 3 AAC were not commonly observed in the groups, we considered Grade 0 AAC as absent and Grade 1–3 AAC as present. We performed univariate and multivariate regression analyses to find the independent predictors of the presence of AAC and the results are shown in Table 3. We included the significant ones in the univariate analysis in the multivariate analysis. Diabetes was not included in the multivariate analysis because it is a subset of the metabolic syndrome. In the multivariate analysis, we found that age, HS, and duration of HS were independent predictors of AAC (OR: 1.048 (1.009–1.089); $p=0.015$, OR: 3.158 (1.181–8.445); $p=0.022$, OR: 1.095 (1.002–1.197); $p=0.045$, respectively).

When we divided the groups as having AAC (grade 1–3) and not having AAC (grade 0), the rate of HS disease was significantly higher in the group with AAC compared to the group without AAC (75.0% vs. 47.5% $p=0.010$) (Fig. 2).

Discussion

This study not only confirmed the association between smoking, metabolic syndrome, insulin resistance, inflammatory markers, and cholesterol parameters, which are associated with HS in previous studies, but also showed that AAC was significantly more common in patients with HS. However, these results provide new evidence that patients with HS are more likely to develop AAC. The risk of developing AAC in patients with HS without cardiovascular disease is more than three times higher than in healthy individuals.

HS is a chronic, inflammatory, recurrent, and debilitating disease of the pilosebaceous unit. The disease usually affects young adults, mostly starts to be seen after puberty and its frequency decreases in elderly people [22]. It predominantly affects the intertriginous regions, axillae, inguinal,

Table 1 Baseline demographics, clinical, and laboratory findings

Variables	Controls ($n=130$)	Patients with HS ($n=130$)	p-value
Age, years	31 (23–40)	30 (23–41)	0.876
Female, gender	55 (42.3)	53 (40.8)	0.801
Alcohol	7 (5.4)	13 (10.0)	0.163
Smoking	30 (23.1)	53 (40.8)	**0.002**
Hypertension	13 (10.0)	14 (10.8)	0.839
Diabetes mellitus	11 (8.5)	17 (13.1)	0.230
Dislipidemia	19 (14.6)	21 (16.2)	0.731
Metabolic syndrome	4 (3.1)	13 (13.0)	**0.024**
Laboratory values			
White blood cells (10^9/L)	8.1 (6.2–9.8)	8.5 (7.0-10.1)	**0.039**
CRP (mg/L)	6.1 (2.5–12.1)	8 (4.4–14.6)	**0.037**
Albumin (g/dL)	4.5 (4.3–4.7)	4.3 (4.0-4.6)	**< 0.001**
LDL-c (mg/dl)	101.2 ± 30.9	115.3 ± 30.3	**< 0.001**
HDL-c (mg/dl)	47.3 ± 11.6	44.4 ± 8.6	**0.027**
Total cholesterol (mg/dl)	184.3 ± 40.9	190.4 ± 33.6	0.191
Triglycerid (mg/dl)	140.8 (109.8–192)	138.5 (111.8–193)	0.922
Uric acid (mg/dl)	5.1 (4.4–5.7)	5.1 (4.4–5.8)	0.320
FPG (mg/dl)	99 (89.8–111)	101.6 (90-127.3)	0.103
TyG index	8.8 (8.6–9.1)	9.0 (8.7–9.3)	**0.041**
AAC			**0.028**
Grade 0	124 (95.4)	112 (86.2)	
Grade 1	6 (4.6)	16 (12.3)	
Grade 2	0 (0)	2 (1.5)	
Grade 3	0 (0)	0 (0)	

Data presented as mean ± SD, median (interquartile range), or number (%). AAC, aortic arch calcification; CRP, C-reactive protein; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; HS, hidradenitis suppurativa; LDL-c, low-density lipoprotein cholesterol; TyG, triglyceride-glucose index

Table 2 Clinical findings in patients with hidradenitis suppurativa

Variables	Patients with HS ($n=130$)
Duration of HS, years	3 (2–6,25)
Age of onset, years	24 (19–35)
Hurley stage	
1	43 (33.1)
2	66 (50.8)
3	21 (16.1)
Number of affected sites	2 (1–3)
Affected sites	
Axilla	88 (35.3)
Inguinal	71 (28.5)
Abdomen	8 (3.2)
Buttocks	24 (9.6)
Breast	20 (8.0)
Perineal	24 (9.6)
Scalp	12 (4.8)
Genital	2 (0.8)

data presented as median (interquartile range) or number (%). HS, hidradenitis suppurativa

inframammary, and anogenital regions. Typical HS lesions include deep-seated, inflammatory nodules, abscesses, and draining inflammatory tunnels that develop into large, rope-like scars [22]. Skin lesions are associated with severe, chronic pain and itching, persistent purulent discharge with a foul odour, and skin contractions with impaired movement due to extensive scarring [23, 24].

HS is associated with numerous concomitant cardiovascular risk factors including hypertension, insulin resistance, diabetes and metabolic syndrome, obesity, and smoking [6–8]. In our study, hypertension and diabetes mellitus were observed to be higher in HS patients, although not reach statistical significance. However, metabolic syndrome, insulin resistance, and smoking were found to be significantly higher in the HS group. TyG index, a new biomarker, correlates significantly with insulin resistance measured by hyperinsulinemic-euglycemic clamp test and HOMA-IR. TyG index has been shown to be a reproducible, reliable, and valid insulin resistance marker [20, 25]. In our study, TyG index was used as an insulin resistance marker differently from previous studies, and TyG index was found to be significantly higher in the HS group.

In addition to the fact that concomitant cardiovascular risk factors such as obesity, hypertension, diabetes, metabolic syndrome, and hyperlipidemia accompanying HS contribute to the development of atherosclerosis, there are also studies showing that the disease alone poses cardiovascular risk in HS patients even in the absence of cardiovascular risk factors and comorbidities [26]. The mechanisms underlying this relationship have not yet been elucidated, but it is thought to be a systemic inflammatory disorder [7, 27]. There is a potential for increased risk of cardiovascular disease in patients with HS and therefore, screening for modifiable cardiovascular disease risks and undiagnosed cardiovascular diseases should be performed and efforts should be made to detect and treat these diseases before a life-threatening condition develops. The need for a holistic approach to patients with HS demonstrates the need for close cooperation between dermatologists and cardiologists. Therefore, it is particularly important to identify factors that predict the risk of cardiovascular disease. These factors can be used for risk stratification and may contribute to the determination of appropriate treatment and improvement of prognosis.

Atherosclerotic plaques in the aortic arch are an important predictor of cardiovascular events [28]. AAC has been suggested to be a suitable index for the burden of atherosclerosis in the aortic arch [29]. However, studies are also focusing on inflammatory markers and arterial calcification, especially AAC [30–32]. Although computed tomography

Table 3 Multivariate regression analysis for potential predictors of aortic arch calcification

	Univariate analysis		Multivariate analysis	
Variables	OR (CI 95%)	*p*	OR (CI 95%)	*p*
Age, years	1.056 (1.020–1.094)	**0.002**	1.052 (1.016–1.090)	**0.005**
Female, gender	1.817 (0.726–4.546)	0.202		
Smoking	0.867 (0.345–2.179)	0.761		
Metabolic syndrome	3.431 (1.02311.510)	**0.046**	1.928 (0.520–7.126)	0.326
Hypertension	2.560 (0.871–7.526)	0.088		
Diabetes mellitus	3.242 (1.266–9.018)	**0.024**		
Dislipidemia	0.768 (0.218–2.708)	0.682		
CRP (mg/L)	1.017 (0.997–1.038)	0.102		
Triglycerid (mg/dl)	0.995 (0.988–1.002)	0.133		
White blood cells (10^9/L)	0.899 (0.741–1.090)	0.279		
TyG index	0.475 (0.201–1.123)	0.090		
LDL-c (mg/dl)	1.000 (0.986–1.013)	0.982		
HDL-c (mg/dl)	0.999 (0.959–1.041)	0.954		
Total cholesterol (mg/dl)	0.997 (0.986–1.009)	0.667		
FPG (mg/dl)	0.990 (0.972–1.009)	0.304		
HS	3.321 (1.274–8.663)	**0.014**	3.156 (1.180–8.439)	**0.022**
Duration of HS, years	1.102 (1.015–1.195)	**0.020**	1.095 (1.002–1.197)	**0.045**
Age of onset, years	1.014 (0.972–1.058)	0.519		

CI, confidence interval; CRP, C-reactive protein; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; HS, hidradenitis suppurativa; LDL-c, low-density lipoprotein cholesterol; OR, odds ratio; TyG, triglyceride-glucose index

is accepted as the standard criterion for the evaluation of AAC, it is expensive and difficult to use in routine clinical practice [33]. Chest radiography is one of the most common radiological examinations and can provide reliable information about AAC [34].

In light of these data, we hypothesized that the frequency of AAC may be higher in HS patients without cardiovascular disease than in normal healthy individuals and that there may be a relationship between HS and AAC. In our study, the frequency of AAC was significantly higher in HS patients compared to the control group. In addition, we found HS as an independent predictor of AAC in multivariate analysis. The mechanism of the relationship between HS and AAC is not well understood. However, inflammation is involved in every stage of atherosclerotic lesion development [35]. Elevation of inflammation markers may indicate activation of vascular damage. Inflammatory markers such as CRP and NLR are known to be associated with atherosclerotic diseases [36, 37]. This chronic inflammation resulting from atherosclerosis may ultimately contribute to vascular calcification [38]. The pathological mechanisms described are based on the results of previous studies, so any relationship described in the discussion should be considered only as a hypothesis. A direct causal relationship between HS and AAC cannot be established. Although this study suggests that the increased risk of developing AAC in patients with HS without cardiovascular disease may be used in risk stratification and may contribute to the development of treatment strategies accordingly, randomized controlled studies are needed to prove this relationship.

Some limitations of our study should be mentioned. (1) Since our study is single-center and retrospective, it is relatively weak. (2) The number of patients is relatively small. (3) AAC was only assessed by chest X-ray and is a semi-quantitative assessment. Therefore, the actual calcium deposition in the aortic wall may have been underestimated. (4) Since ACC assessment is primarily visual, the quality of the chest radiograph (under-penetration/over-penetration) may have influenced the result. (5) Parameters such as body mass index and waist circumference could not be included in the analyses due to lack of data in hospital records. (6) We could not include scoring systems such as the Sartorius score and the International Hidradenitis Suppurativa Severity Scoring System used to assess HS severity in these analyses due to missing data. (7) Family history of cardiovascular disease could not be evaluated due to incomplete data. (8) The race of the patients included in the study may affect the results. Therefore, generalizations cannot be made.

Conclusion

AAC, which occurs due to systemic inflammation and atherosclerosis, is observed more frequently in patients with HS without cardiovascular disease than in healthy individuals. HS can be considered an independent predictor of AAC. AAC may contribute to the development of treatment strategies and prognosis by contributing to risk stratification before the development of cardiovascular diseases in HS patients without cardiovascular disease.

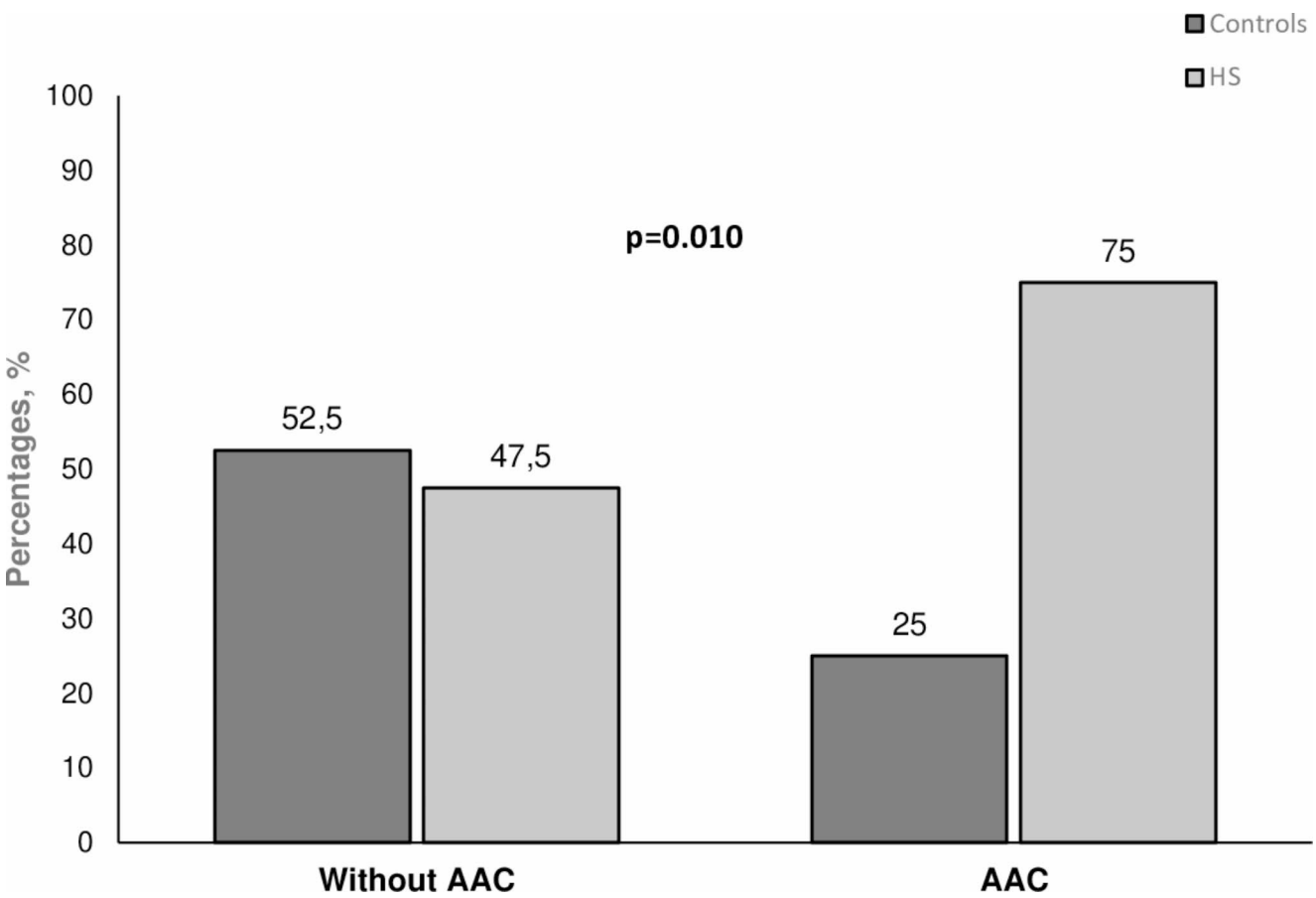

Fig. 2 Patients with hidradenitis suppurativa according to AAC

Author contributions U.K. wrote the manuscript. U.K., P.E.D., I. E., E. H., and N.E.G. designed the research. U.K., P.E.D., I. E., E. H., F. K., and N.E.G performed the research. R.K., and A.A. analyzed the data. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and are accountable for the accuracy and integrity of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study was conducted in accordance with the Declaration of Helsinki, and informed consent was taken from all patients. Ethical approval was obtained from Zonguldak Bülent Ecevit University Clinical Research Ethics Committee (Date: 24/04/2024, No: 2024/08).

Competing interests The authors declare no competing interests.

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