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ORIGINAL ARTICLE

Introduction of a novel quantitative scoring system for acanthosis nigricans and its validation in a pilot study

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Abstract

Inconsistent data exist regarding the diagnostic value of acanthosis nigricans (AN) or skin tags as clinical markers for obesity or diabetes. In an outpatient department-based prospective study, we designed a scoring for AN severity (SCANS) to evaluate AN and skin tags, their correlation with obesity or diabetes. Quantification of AN in six anatomic sites, in consideration of the affected skin surface areas, texture changes, number of skin tags, leads to a total severity score between 0 and 46. Among 336 adult patients (aged ≥18 years) with AN, a higher BMI was associated with AN (r = 0.299, P < .001), but not with diabetes (P = .43), as compared with 243 age- and sex-matched controls without AN. Among nondiabetics, AN scores were significantly correlated with waist circumference (r = 0.131, P = .024) and total cholesterol levels (r = 0.155, P = .04). Skin tags alone in the absence of AN were not associated with obesity (P = .333) or diabetes (P = .164). The total AN scores were positively correlated with the presence of skin tags (r = 0.132, P < .001), and the involvement of anterior neck (r = 0.668, P < .001) and axilla (r = 0.793, P < .001). Knuckles and groins were unaffected in our series. Our results indicate that combination of AN with skin tags can be used as clinical marker for obesity, but not for diabetes. Large-scale studies on patients of different ethnic background are required to further validate our proposed scoring.

KEYWORDS

acanthosis nigricans, body mass index, diabetes mellitus, insulin resistance

1 | INTRODUCTION

Acanthosis nigricans (AN) is characterized by dark, velvety, coarse, and thickened skin changes mainly distributed in the intertriginous regions, such as neck, axillae, and groins.[1] The prevalence of AN varies from 7% in general population to 74% in obese patients.[2,3] In general, AN is more commonly observed in dark-skinned people,[4,5] which may be partly due to observational bias. Epidemiology in Turkish population, especially among obese people, is less studied.

Hyperinsulinemia and obesity are the most common underlying pathologies of AN.[6] Evidence indicates that AN can be a clinical marker for diabetes mellitus (DM) and metabolic syndrome.[7,8] Available data are inconsistent considering the association between AN and insulin resistance (IR). Little is known about the correlation

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between AN scores and fasting insulin, or body mass index (BMI).[9] The significance of skin tags in epidemiologic study of obesity or diabetes has been controversially discussed.[10-12]

Pathogenesis of AN and skin tags remain incompletely understood. Clinical association with metabolic syndrome, such as obesity, hyperinsulinemia, and insulin resistance, is frequently observed.[13,14] Genetic mutations described in severe extensive AN may include the insulin receptor gene, fibroblast growth factor receptor (FGFR)2, and FGFR3 gene, and phosphatase and tensin homolog gene. A significant upregulation of IGF-1 immunoreactivity has been demonstrated in the epidermis and fibroblasts of excised skin tags as compared with the control skin.[14] It is proposed that interactions among insulin, IGF-1, androgens, and growth factors play a pivotal role in regulation of the proliferation, differentiation, and apoptosis of keratinocytes and fibroblasts in the diseased state.[13,14]

No biological markers can reflect the severity of AN or skin tags, while only a few scoring systems are intended to assess the severity of AN.[2,3,15] The current study was aimed to develop a scale combining AN and skin tags and to validate this new scoring system in a large Turkish population, especially regarding its association with obesity, type II DM, and the relevant risk factors, such as prediabetes, overweight, age 45 years or older, positive family history (one parent, brother, or sister) of type 2 diabetes, past history of gestational diabetes or giving birth to a baby weighing more than 9 pounds, and nonalcoholic fatty liver disease.[16]

2 | SUBJECTS AND METHODS

This is a cross-sectional hospital-based prospective study conducted in outpatient departments of dermatology and endocrinology at the Istanbul Medeniyet University, Istanbul, Turkey. The study protocol is in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All patients were given informed consent.

A total of 579 subjects at the age of 18 years and older with obesity was recruited. Excluded were patients with a history of, being investigated for, or diagnosed with one or more of the following diseases: internal malignancies especially of gastrointestinal tract, and autoimmune diseases, such as systemic lupus erythematosus, scleroderma, Sjögren's syndrome, and Hashimoto's thyroiditis. Even excluded from the study were subjects with a history of drug use which can cause AN (orally nicotinic acid, oral contraceptives, testosterone, triazinate, or topically fusidic acid) as well as subjects who were pregnant or breast feeding, unable to give a cohesive history, had a high alcohol intake (>14 units/week for women and >21 units/week for men), or used illicit drugs.[17-19] The including and excluding criteria are listed in Table 1.

Assessment of AN was based on the body regions, affected surface areas, and degrees in texture changes, together with the numbers of skin tags. All subjects were examined in six anatomic areas: axillae (left/right), groin (left/right), neck (anterior neck/nape), mucosa (oral, conjunctiva, genitalia), trunk (including areola and umbilicus), and extremities (flexural areas like wrists, antecubital, popliteal, and joints/knuckles). The skin changes including hyperpigmentation, velvety appearance, and verrucous changes were classified into four grades from grade 1, 2, 3, 4, in the order of severity (Figure 1). The number of skin tags was included in our evaluation, and divided into three groups 0, 1-15, >15, given additional impact points 0, 0.5, and 1, respectively. Total severity scores ranged from 0 to 46. Table 2 shows our scoring system in detail.

TABLE 1 Including and excluding criteria adopted in the current study

	Including criteria	Excluding criteria
Study population	1. Age ≥ 18 years 2. Obesity: BMI ≥30 kg/m^2, or waist circumference ≥88 cm (women) and ≥102 cm (men) 3. Diabetes: HbA1c ≥6.5%, or fasting glucose ≥126 mg/dL, or 2-hour glucose ≥200 mg/dL, or random glucose ≥200 mg/dL 4. Hypertension: systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or both	1. History of, being investigated for, or diagnosed with internal malignancies, autoimmune, or endocrine (except diabetes) diseases 2. History of drug use associated with AN 3. A high alcohol intake (>14 units/week for women and >21 units/week for men) 4. Consumption of illicit drugs 5. Pregnant or breast feeding 6. Inability to give a cohesive history

Demographic profile and clinical characteristics of the patients were recorded and analyzed, including anthropometric measurements (weight and height), age, gender, BMI (weight/height = kg/m^2), serum triglyceride/total cholesterol/high density lipoprotein (HDL)/low density lipoprotein (LDL), systolic blood pressure (BP), diastolic BP, waist circumference, and clinical manifestations of AN and skin tags. Waist circumference was measured midway between the lower margin of the ribcage and the superior rim of the ilium. BMI was categorized using extreme quintiles rounded to nearest meaningful values as cut-off points. Although there is no general consensus for BMI thresholds in young people, the following categories were adopted: <18.5 kg/m^2 underweight or at risk of underweight, 18.5-24.9 kg/m^2 normal weight, 25.0-29.9 kg/m^{2}overweight, 30-34.5 kg/m^2 obesity, 35-40 kg/m^2 severe obesity; 40-45 kg/m^2 morbid obesity, and ≥50 kg/m^2 super obesity.[20] Diagnosis of DM was made following the recommendations of the American Diabetes Association, with any one of the following criteria: HbA1c value of ≥6.5%, or fasting glucose (≥126 mg/dL), or 2-hour glucose (≥200 mg/dL), or random glucose (≥200 mg/dL) in patients with classic symptoms of DM.[21] Hypertension was diagnosed by the following criteria recommended by the American Society of Hypertension and International Society of Hypertension: systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or both.[22]

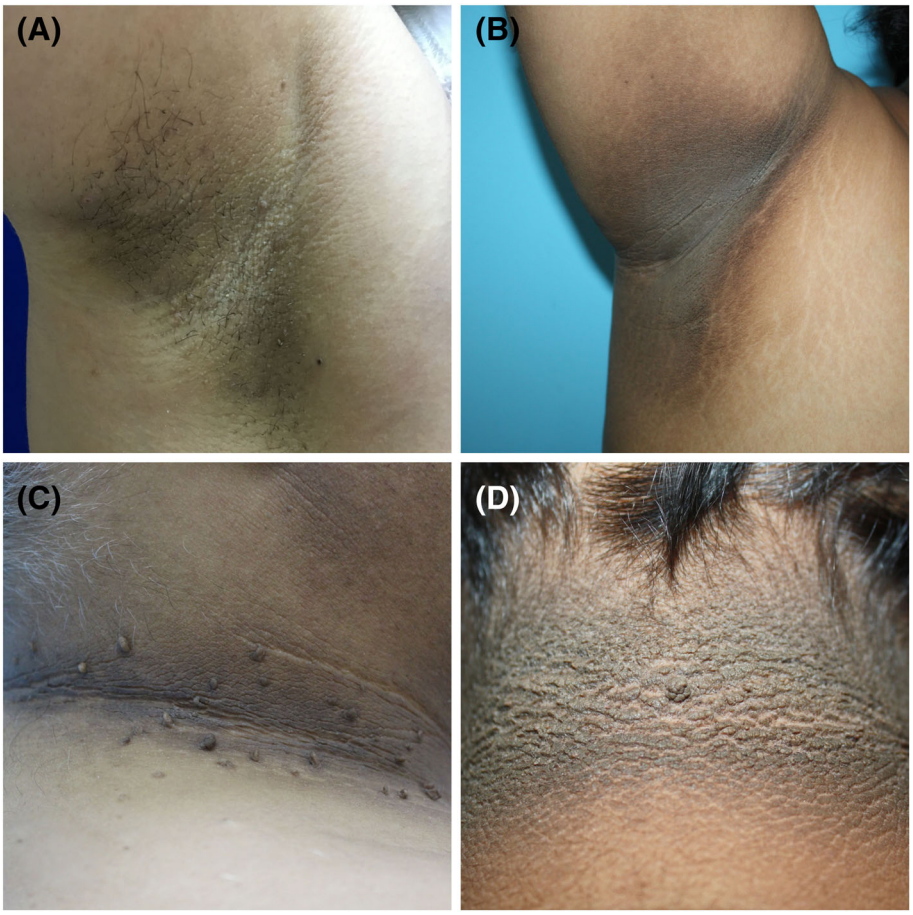

FIGURE 1 Severity of acanthosis nigricans in grading, from grade 1 (A), grade 2 (B), and grade 3 (C) to the highest grade 4 (D)

TABLE 2 Scoring for Acanthosis Nigricans Severity (SCANS) proposed by Karadag and Chen

Severity Localization	Grade 1	Grade 2	Grade 3	Grade 4	Skin tags 0: +0 ≤15: +0.5 >15: +1
Axilla (right)					
Axilla (left)					
Groin (right)					
Groin (left)					
Anterior neck					
Nape					
Mucosa					
Trunk					
Upper extremities					
Lower extremities					
Subtotal					
Total (range 0-46)					

Note: Severity grades: Grade 1 (+1): Hyperpigmentation ≤50% of the skin surface area; Grade 2 (+2): Hyperpigmentation >50% of the skin surface area; Grade 3 (+3): Grade 2+ velvety change of the skin; Grade 4 (+4): Grade 3+ verrucous/papillomatous change of the skin. Skin tags (skin tags): 0: +0; ≤15: +0.5; >15: +1. Anatomic sites: axillae (left and right), groin (left and right), anterior neck, nape, mucosa (oral, conjunctiva, genitalia), trunk (including areola, umbilicus), upper extremities (knuckles, wrists, antecubital), and lower extremities (knees, popliteal). Mucosal involvement: + 4 Truncal involvement: +4 Upper extremity involvement: +4 Lower extremity involvement: +4.

The subjects were divided into four groups for comparison and analysis: diabetic vs nondiabetic, and with vs without AN. Association between diabetes-related risk factors and AN scores were investigated.

2.1 | Statistical analysis

Data were analyzed with SPSS version 16.0 (SPSS Inc., Chicago, Illinois). Descriptive statistics was calculated, including the mean and SD for quantitative variables and percentages for qualitative variables. The magnitude of the association between quantitative variables was evaluated with Spearman's correlation coefficient (rho), while the Mann-Whitney *U* test was used to compare independent variables. The power of these tests was calculated with the effect size detected in the study. A level of significance of 5% ($P < .05$) was established to reject the null hypothesis.

3 | RESULTS

The demographic profiles and laboratory findings of patients with or without AN are summarized in Table 3. A total of 336 patients (59 men, 277 women) with AN and 243 (50 men, 193 women) without AN as controls was recruited, with the mean age at 47 years (range 18-75 years). The mean BMI was 27.3 kg/m^2 (SD 6.0) while the mean waist circumference was 96.7 cm (SD 14.2). The distribution pattern of BMI and obesity grading of patients are shown in Table 4. Diabetes was diagnosed in 185 patients (32%), all with type II DM. Presence of AN was found in 97 (28.9%) of the diabetic obese patients and 223 (66.4%) of the nondiabetic obese patients. AN severity did not differ in patients with or without DM ($P = .43$). Overall, no significant correlation was observed between the total AN scores and the fasting blood glucose, triglyceride, cholesterol/LDL/HDL, systolic, or diastolic BP levels.

There was no significant difference between the groups with and without AN in terms of age (in AN group 45.7 + 12.86, without AN group 46.7 + 13.7 years) (P: .369). There was no significant difference in gender between those with and without AN (in those with AN—M: 17.6%, F: 82.4%, without AN group M: 20.6%, F: 79.4, P: .360). While the age in diabetic patients was 58.8 + 10.1 years, it was 42.8 + 13.0 years in nondiabetics ($P < .001$). The gender distribution of diabetics was 17.3% for males and 82.7% for females. The ratio of men in nondiabetics: 22.4, while the ratio of women was 77.6 (P: .148).

The median of total AN score was 5.0 (min: 1, max: 15). The total AN scores displayed a weak positive correlation with BMI ($r = 0.299$), waist circumference ($r = 0.202$), joint ($r = 0.283$), or knee ($r = 0.146$) involvement, and the presence of skin tags ($r = 0.132$) (all $P < .001$). The correlation between AN scores and BMI was more pronounced in

TABLE 4 Body mass index (BMI) classification and obesity grades of the examinees

BMI classification	Number of patients	Percent %
Normal	18	3.1
Overweight	16	2.8
Obese	238	41.1
Severe obese	174	30.1
Morbid	72	12.4
Super obese	61	10.5

Abbreviation: BMI, body mass index.

TABLE 3 Comparison of demographic features, biochemical parameters, and criteria of the metabolic syndrome in patients considering diabetes mellitus and severity of acanthosis nigricans

	Nondiabetics			Diabetics		
	AN (+)	AN (–)	*P*	AN (+)	AN (–)	*P*
Count	177	228	–	66	108	–
Age (years)	43.4 ± 13.6	42.4 ± 12.7	.455	55.1 ± 10.2	52.8 ± 10.1	.0172
Gender (M/F)	33/144	37/191	.800	17/49	22/86	.380
BMI (kg/m^2)	34.4 ± 5.2	37.5 ± 6.8	<.001	36.7 ± 6.4	38.2 ± 5.1	.099
Obesity (n, %)	166 (93.8)	211 (93.0)	.705	65 (98.5)	90 (99.1)	.730
FBG (mg/dL)	95.2 ± 13.7	99.1 ± 31.1	.294	159.7 ± 51.9	170.3 ± 67.4	.489
Triglyceride (mg/dL)	147.6 ± 57.1	143.7 ± 73.9	.711	182.6 ± 61.7	190.0 ± 103.6	.750
Total cholesterol (mg/dL)	187.1 ± 47.0	195.9 ± 35.3	.182	201.3 ± 50.3	201.6 ± 40.6	.981
HDL (mg/dL)	48.4 ± 11.8	45.4 ± 10.8	.205	44.8 ± 13.5	43.6 ± 11.4	.754
LDL (mg/dL)	125.5 ± 44.0	123.1 ± 28.5	.747	120.3 ± 39.8	118.9 ± 30.6	.891
Systolic BP (mm Hg)	127.9 ± 27.0	120.0 ± 21.4	.443	145.6 ± 12.1	131.7 ± 25.6	.093
Diastolic BP (mm Hg)	77.9 ± 14.0	78.8 ± 13.6	.875	91.3 ± 10.9	76.7 ± 15.1	.020
Waist circumference (cm)	117.5 ± 12.6	119.4 ± 14.4	.192	117.8 ± 11	119.3 ± 13.1	.454

Abbreviations: BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HDL, high density lipid; LDL, low density lipid.

TABLE 5 Positive correlation between the total scores of acanthosis nigricans and anatomic localizations, obesity index, or the presence of skin tags

	Total scores of acanthosis nigricans	
	P value	Correlation-coefficient (*r*)
Nape	<.001	0.867
Axilla	<.001	0.793
Anterior neck	<.001	0.668
Joint	<.001	0.202
Knee	<.001	0.283
Elbow	<.001	0.405
BMI	<.001	0.299
Waist circumference	.024	0.132
Skin tags	.007	0.146

Note: r, Spearman correlation test; *P* value: <.05, statistically significant.

nondiabetics (r = 0.376, P < .001) than in diabetics (r = 0.18, P = .01). Among nondiabetics, AN scores were significantly correlated with waist circumference (r = 0.131, P = .024) and total cholesterol levels (r = 0.155, P = .04). A moderate positive correlation was found between the AN scores and the anterior neck involvement (r = 0.668, P < .001). Correlation between the AN scores and involvement of the nape (r = 0.867) or axilla (r = 0.793) was most highly positive (both P < .001) (Table 5).

The severity grading of AN in different anatomic sites and the numbers of examinees involved are summarized in Table 6. In general, anterior neck is more commonly involved than nape, except for the greatest severity grade 4, which was only observed in the nape and axillae with verrucous/papillomatous change of the skin. Involvement of wrist and knee was uncommon, while none of our patients showed inguinal manifestation. Skin tags were noticed in 50% of the patients with AN, including anterior neck (57.7%), nape (52.1%), and axillae (48.3%). Skin tags alone in the absence of AN were not associated with obesity (P = .333) or DM (P = .164).

TABLE 6 Severity of acanthosis nigricans (AN) according to anatomic sites

AN severity	Number of patients (%)
Axilla	
0	125 (37.2%)
1	62 (18.5%)
2	56 (16.7%)
3	86 (25.6%)
4	7 (2.1%)
Anterior neck	
0	81 (24.1%)
1	84 (25.0%)
2	98 (29.2%)
3	73 (21.7%)
4	0 (0%)
Nape	
0	113 (33.6%)
1	79 (23.5%)
2	30 (8.9%)
3	48 (14.3%)
4	66 (19.6%)
Wrist	
0	326 (97%)
1	10 (3%)
Elbow	
0	295 (87.8%)
1	41 (12.2%)
Knee	
0	317 (94.3%)
1	19 (5.7%)
Mucosa	0 (0%)
Trunk	0 (0%)
Knuckle	0 (0%)
Acrochordon	
0	164 (49.5%)
1	166 (50.2%)
2	1 (0.3%)

4 | DISCUSSION

The prevalance of AN of 62.1% in our series is compatible with 74% found in a previous study on 34 obese individuals.[3] Higher prevalence rates have been reported in general surveys of dark-skinned people.[2,23-31] As compared with the available grading systems of AN,[2,3,15] the Scoring for AN Severity (SCANS) we proposed is more extensive and quantitative (Tables 2 and 7). In the system proposed by Stuart et al, the sites of trunk, knuckles and mucosa were not evaluated and the texture/pigmentation of the AN not considered.[2] Hud and his team examined the texture of the skin lesions but did not quantify them.[3] Burke et al did not include trunk and mucosa in their system.[15] Assessment of skin tags were absent in all of the three existing systems (Table 7).

In our study, neck, including anterior neck and nape, was most commonly affected by AN in obese people, whereas an axillary involvement indicated a greater severity of AN. None of our cases exhibited inguinal, knuckle, or mucosal lesions, in contrast to the involvement of oral mucosa in 50% of the paraneoplastic AN.[32] As compared with a previous report on a common manifestation in knuckles closely associated with overweight in Latin American youths,[33] none of our examinees with obesity showed knuckle changes, indicating ethnic and environmental factors, such as occupations or habits, may influence the skin changes in these areas.

Reports were inconsistent regarding the association between AN and obesity, hyperglycemia, hyperinsulinemia, IR, or type II DM.[34-36] In our study, AN was found to be significantly related to obesity as

TABLE 7 Comparison of different quantitative classifications of acanthosis nigricans

Authors	Anatomic sites	Severity evaluated	Skin tags present	Scores	Numbers of examines	Ref.
Stuart et al	• Neck • Axilla • Antecubital • Intertriginous • Inner thigh	Not included	Not included	0-4	99	2
Hud et al	• Neck • Axilla • Trunk • Extremities • Mucosa	Skin change (fine or course) Hyperpigmentation (or not)	Not included	0-4	34	3
Burke et al	• Neck • Axilla • Knuckles • Elbows • Knees	Neck severity (0-4) Axilla (0-4) Neck texture (0-3) Knuckles (0-1) Elbows (0-1) Knees (0-1)	Not included	0-4	406	15
Karadag and Chen	• Anterior (neck and nape) • Axilla (R, L) • Groin (R, L) • Mucosa • Trunk (including areola and umbilicus) • Upper extremities (knuckles/wrists/ante-cubital) • Lower extremities (knees, popliteal)	Grading 1: Hyperpigmentation ≤50% of the area 2: Hyperpigmentation >50% of the area 3: Grade 2+ velvety change 4: Grade 3+ verrucous/papillomatous change	Included • Neck (anterior and nape) • Axillae (R/L) • Groins (R/L) ≤15: +0.5 >15: +1 (totally 0-6)	0-46	336	

measured by BMI and waist circumferences. There was no association between AN and DM in our series, in contrast to previous studies showing the prevalence of AN in 17%-36% of the patients with type II DM.[37,38] The discrepancy in various study cohorts may be explained by differences in genetic background, diagnosis, duration, severity, and treatment of DM, and heterogeneity in the degree of IR. Both AN and skin tags are frequently seen in people with obesity or/and diabetes, especially in young individuals, but little is known about the strength of correlation and the validity of using them as clinical markers for hyperinsulinemia or IR in obesity.[36,39,40] Our results demonstrated coexistence of skin tags with AN in half of the examined patients, and a greater AN severity in the presence of skin tags.

Association between multiple skin tags and obesity or type II DM is controversially discussed.[40-42] Patients with more than 30 skin tags were found to be at a greater risk for DM,[41] while the presence of more than 8 skin tags was more sensitive but less specific than AN in detecting changes in carbohydrate metabolism.[42] A strong association was observed between the presence of more than five skin tags and increase in the HOMA-IR index.[43] In a study of Indian patients with type II DM, only the AN severity in the neck, but not the axillary or knuckle AN, or the skin tags, had a correlation with IR.[44] Our data supported the association of skin tags with obesity, but not with type II DM. Skin tags and AN are supposed to share similar pathogenic mechanisms in that IR is of the pivotal role.[45]

Our study has some limitations. We examined adult population but did not include nonobese controls or children. There are some drawbacks in using BMI or waist circumference to determine obesity. The duration and severity of DM, and the degree of IR were not analyzed. Future studies should evaluate a larger number of patients of different ethnic background, with assessment of hormonal disturbances, including women with polycystic ovary syndrome. To solve the discrepancies and controversies in the association between metabolic syndrome and AN or skin tags, a validation of our proposed scoring system in comparative studies is required.

In conclusion, our proposed scoring system (SCANS) combining AN and skin tags demonstrated a significant correlation with obesity in adult Turkish people. For epidemiologic surveys, examination of both anterior neck and nape is recommended, while the axillary involvement indicates an advanced stage. Coexistence with skin tags is an important sign for a greater AN severity and an independent sign for obesity. A validated scoring system of AN can serve as a clinical marker in the assessment of metabolic syndrome.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Ayşe Serap Karadağ: Author is primary physician of concerning patient, supervisor of process. Author created the idea, designed the process, analyzed outcome, reviewed the article, writing, and preparation of manuscript. Tugba Kevser Uzuncakmak, Emin Ozlu, Mumtaz Takir,

Mehmet Şimşek: Authors took part in patient care, follow-up, data collection, literature review, preparation of manuscript. Necmettin Akdeniz: Author took part in diagnosis and reviewed the article. Remzi Karadag, Osman Kostek: Author took part in statistical analyses, reviewed the article. Uwe Wollina: Author reviewed the article. Wen-Chieh Chen: Author created the idea, designed the process, analyzed outcome, reviewed, writing, and preparation of manuscript.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

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