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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Does the neutrophil-to-lymphocyte ratio have any importance between subjects with obstructive sleep apnea syndrome with obesity and without obesity?

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SUMMARY

Does the neutrophil-to-lymphocyte ratio have any importance between subjects with obstructive sleep apnea syndrome with obesity and without obesity?

Introduction: *An increase in the incidence of OSAS (obstructive sleep apnoea syndrome) has been seen due to the reported association between OSAS and obesity. Subjects are predisposed to cardiovascular disease due to systemic inflammation caused by the interactions between obesity and OSA. Inflammatory markers could be used to predict the degree of systemic inflammation, which could be a prognostic factor for future adverse events such as metabolic risks. One marker that has recently started being used as an indicator of systemic inflammation is neutrophil-to-lymphocyte ratio (NLR).*

Materials and Methods: *The aim is to evaluate NLR, which is a easily measured parameter of systemic inflammation in OSAS subjects with and without obesity. 155 subjects were assigned to four different groups according to their body mass indices. Comparisons of white blood cell, neutrophil, lymphocyte, NLR values and anthropometric measurements were done for each group.*

Results: *The NLR and neutrophil counts of group 4 were statistically significant and higher than those of groups 1, 2 and 3. The lymphocyte counts of group 4 were the lowest amongst all groups, these values were lower than the lymphocyte counts of groups 1,*

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2 and 3 with statistically significant differences (p< 001). A positive correlation was found between the body mass index and lymphocyte count values of obese OSAS subjects (r= 0.027, p= 353).

Conclusion: *The NLR ratio was found to be increasing by obesity grade and reveals that the associated inflammatory response also increases. The NLR ratio might be used as an inflammatory marker in obese OSAS subjects.*

Key words: *Obesity, OSA, Neutrophil-to-lymphocyte ratio*

ÖZET

Obez olan ve olmayan OSAS'lı olgularda nötrofil lenfosit oranının önemi var mı?

Giriş: *Obezite ve obezite ile ilgili hastalıklar, özellikle gelişmiş ülkelerde olmak üzere dünya çapında artmaktadır. Obstrüktif uyku apne sendromu (OUAS) ve obezite arasındaki ilişkinin bildirilmesine bağlı olarak OUAS insidansında bir artış görülmüştür. Obezite ile OUAS arasındaki etkileşimlerin yol açtığı sistemik inflamasyon, metabolik değişiklikler ve endokrin anomalilere bağlı olarak ateroskleroz ve kardiyovasküler hastalıklara yatkınlık vardır. Sistemik inflamasyon derecesini tahmin etmek için inflamatuar markerlar kullanılabilir; bunlar, metabolik riskler gibi gelecekteki advers etkiler için prognostik bir faktör olabilir. Yakın zamanda sistemik inflamasyonun bir göstergesi olarak kullanılmaya başlanan bir belirteç de nötrofil-lenfosit oranı (NLR)'dir. Amaç, obezite olan ve olmayan OUAS'lı hastalardaki sistemik inflamasyonun kolayca ölçülebilen bir parametresi olan NLR'yi değerlendirmektir.*

Materyal ve Metod: *155 hasta beden kitle indeksine göre dört farklı gruba ayrıldı. Her grup için lökosit, nötrofil, lenfosit, NLR değerleri ve antropometrik ölçümler karşılaştırıldı.*

Bulgular: *Grup 4 (obez OUAS grubu)'ün NLR ve nötrofil sayıları grup 1, 2 ve 3' ten istatistiksel olarak anlamlı derece daha yüksekti. Grup 4'ün (obez OUAS grubu) lenfosit sayıları tüm gruplar arasında en düşük olup, bu değerler grup 1 (kontrol grubu), 2 (normal ağırlık OSAS grubu) ve 3 (aşırı kilolu OSAS grubu) lenfosit sayılarına göre istatistiksel olarak anlamlı şekilde düşüktü (p< 0.001). Vücut kitle indeksi ile obez OUAS'lıların lenfosit sayıları arasında pozitif bir korelasyon vardı (r= 0.027, p= 353).*

Sonuç: *Obezite derecesine göre NLR oranının arttığı ve bununla ilişkili olarakta inflamatuar yanıtın da arttığını görüldü. Obez OUAS'lılarda NLR bir inflamasyon belirteci olarak kullanılabilir ve bu kişiler için metabolik risklerin tahmininde faydalı olabilir.*

Anahtar kelimeler: *Obezite, OSAS, nötrofil lenfosit oranı*

INTRODUCTION

The main characterization of obstructive sleep apnea syndrome (OSAS) is recurrent episodes of partial or complete airway obstruction that occurs during sleep. It is a fairly common sleep disorder that causes disturbed sleep, intermittent hypoxia and daytime sleepiness (1). The prevalence of OSAS within adults is estimated to be around 25% and as high as 45% in obese subjects (2-4). Obesity predisposes to and potentiates OSAS. With the increase in prevalence of obesity, prevalence of OSAS is also likely to increase in a parallel manner (5). According to estimates, 60% of the adult population of industrialized countries is overweight (BMI > 25 kg/m^2) and at least 30% is obese (BMI > 30 kg/m^2) (6). The situation is similar within our country and according to the latest published data the obesity rate has reached 30.3% and the morbid obesity rate has reached 2.9% in our country (7).

The development of altered metabolic, immune and inflammatory system responses are caused and contributed to by chronic airway collapse and recurrent hypoxia. There is also various evidence suggesting that OSA is associated with low-grade systemic inflammation. The occurrence of systemic inflammation is a crucial factor, which links obesity, OSA and the metabolic syndrome (8). Studies with obese subjects have reported elevated levels of the inflammatory marker. Systemic inflammation is further exacerbated in obese subjects due to OSA (9). Pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), which are endogenous mediators of inflammation, are released by activated macrophages due to the cascade of events initiated by OSA (10). There are various markers of systemic inflammation, which are elevated, in obese and non-obese subjects with OSA, including TNF-α, IL-6 and C-reactive protein (CRP).

It is possible to use a wide range of markers to demonstrate systemic inflammation. Due to being cost effective and easily accessible, neutrophil-to-lymphocyte ratio (NLR) has recently been started to be used as a marker as an indicator of the prognosis and systemic inflammation (11-14). We aimed to investigate the correlation of the NLR between subjects with OSA with obesity and without obesity.

MATERIALS and METHODS

This study was designed in a retrospective manner and performed between March 2014 and September 2015 at the Chest Diseases Clinic of the State Hospital. The

study was approved by Faculty of Medicine ethics committee and carried out in accordance with the Helsinki Declaration published in 2000.

A total of 155 subjects (65 females (41.3 percent) and 91 males (58.7 percent)) have met the inclusion criteria and were selected for the study. The inclusion criteria consisted of subjects with symptoms of nocturnal snoring and/or excessive daytime sleepiness and who underwent polysomnographic evaluation. The subjects were divided into two distinct groups according to their apnoea-hypopnea index values. The control group consisted of subjects with AHI < 5 events/h and BMI value of less than 25 (Group 1). The OSAS group consisted of subjects who were having AHI > 5 events/h. The OSAS group was further divided into three groups according to BMI value: group 2 consisted of subjects with normal weight OSAS with an BMI value of less than 25; group 3 consisted of overweight OSAS subjects with an BMI of 25-30; and group 4 consisted of obese OSAS subjects with a BMI value of more than 30.

The exclusion criteria consisted of any known cardiac disease (arrhythmias, ischemic vascular disease and congestive heart failure), lung disease (asthma and chronic obstructive pulmonary disease), diabetes mellitus (defined as fasting plasma glucose > 126 mg/dL and/or antidiabetic treatment), chronic renal or hepatic diseases, malignancies, abnormal hematocrit and/or abnormal white blood cell count and/or abnormal platelet number and subjects receiving anticoagulant or anti-inflammatory drugs or systemic corticosteroids. The complete pre-test blood count data were available for all subjects within their files. The subjects were chosen in accordance to symptoms of daytime sleepiness, sleep apnoea and snoring, as witnessed by the subject's family members. Each subject took part in a questionnaire, which highlighted their demographics and their sleep apnoea related symptoms. The questionnaire also included the Epworth Sleepiness Scale.

Polysomnograpy testing was performed using Respironics ALIS 5, 55 channel polysomnograph, sleepware G3 (USA). Polysomnography entailed the following recordings: electroencephalogram, electro-oculogram, submental and leg electromyograms, electrocardiogram, airflow (measured by oronasal thermistor), thoracic and abdominal respiratory movements, oxygen saturation (measured by fingertip pulse oximeter), snoring (using a tracheal microphone placed on the neck) and body position during sleep. The digitized signals were then stored on a personal computer. Scoring was performed according to the recommendations of Rechtschaffen and Kales and the American Academy of Sleep Medicine (AASM) rules (15,16).

Decrease in 3% or more capillary oxygen saturation was accepted as desaturation and airflow cessations of at least 10-second duration were considered as apnoea. Hypopnea was accepted as an episode of reduced airflow by at least 50% during sleep lasting 10 seconds or longer with an arousal or desaturation. Apnoea-hypopnea index was determined based on the number of apneas and hypopneas per hour. The number of scored desaturations divided by the estimated sleep duration (time in bed-waking times) result in the oxygen desaturation index (ODI). As indices of nocturnal hypoxemia, the mean SaO_2 and the minimal value recorded during sleep (SaO_2 min) were studied; the thresholds to identify obstructive sleep-related disorder were chosen as an AHI ≥ 15.

All pre-test blood counts calculated white blood cell (WBC), neutrophil, lymphocyte and NLR values in al cases. The Beckman Kolter was chosen to complete the blood count analysis. The WBC, neutrophil, lymphocyte and NLR values were compared in each group and between groups. NLR was calculated by dividing neutrophil count by lymphocyte count.

Statistical Analysis

The mean (SD), or number (%) was used to summaries subject characteristics. To begin with, numerical data were tested for normality and then Kruskal Wallis-test and Mann-Whitney U test was used for variables to compare groups. Chi-square test or Fisher exact chi-square test was used to analyze categorical data. All analyses were done using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). A p-value less than 0,05 was considered statistically significant.

RESULTS

In total, 155 subjects (58.7% male; 41.3% female) were included in the analysis. As Table 1 illustrates, the mean ages and gender of the groups were not statistically different (p= 0.923, p= 0.846). In addition to this, there wasn't any significant differences in total sleep time and total sleep efficiency (p= 0.127, p= 0.338) (Table 2). However, the minimum and average values of SpO_2 values of group 4 (obese OSAS group) were statistically significant, lower than those of groups 1, 2 and 3 (p< 0.001) (Table 2). Desaturation index values of group 4 (obese OSAS group) were also statistically significant higher than those of groups 1, 2 and 3. (p< 0.001) (Table 2).

Table 1. Demographic and anthropometric characteristics of the patients

	Group 1 Control	Group 2 Normal OSA	Group 3 Overweight OSA	Group 4 Obesity OSA	p
Sex [male/female; n (%)]	25/17 (59.5/40.5)	20/16 (45.6/44/4)	21/17 (55.3/44.7)	25/14 (64.1/35.9)	0.846
Age (years)	44.02 ± 11.35	42 ± 11.24	43 ± 7.16	43.69 ± 7.42	0.923
BMI (kg/m^2)	23.31 ± 1.62	23.34 ± 1.54	27.82 ± 1.24	36.29 ± 2.29	0.001
Neck circumference (cm)	33.76 ± 1.67	37.86 ± 1.85	39.05 ± 2.86	41.54 ± 2.91	0.001
Waist circumference (cm)	92.76 ± 1.41	93.12 ± 1.82	98.99 ± 1.39	103.81 ± 1.99	0.001
Hip circumference (cm)	102.46 ± 2.09	102.43 ± 2.28	107.30 ± 1.84	108.64 ± 1.26	0.001
Waist to hip ratio	0.95 ± 0.02	0.90 ± 0.02	0.89 ± 0.13	0.95 ± 0.023	0.001

Table 2. Sleep characteristics of the patients

	Group 1 Control	Group 2 Normal OSA	Group 3 Overweight OSA	Group 4 Obesity OSA	p
Total sleep time (mean ± SD; mins)	324.57 ± 69	327.75 ± 42.22	304.59 ± 63.16	327.15 ± 57.78	0.127
Sleep efficiency (mean ± SD; %)	79.42 ± 12.66	76 ± 12.03	79.63 ± 10.85	79.60 ± 8.89	0.338
AHI (events/hour)	4.01 ± 1.83	58.11 ± 30.62	59.19 ± 27.89	57.73 ± 27.28	0.001
Average SpO_2 (%)	95.10 ± 1.76	92.56 ± 2.53	93.55 ± 2.43	92.5 ± 2.85	**0.001**
Minimum SpO_2 (%)	89.21 ± 2.83	78.28 ± 11.64	76.32 ± 9.49	76.36 ± 10.46	**0.001**
ESS score (mean ± SD)	8.21 ± 2.75	11.31 ± 3.01	10.13 ± 2.05	10.85 ± 2.54	**0.001**
DSI (mean ± SD)	1.7 ± 0.17	41.7 ± 4.1	49.7 ± 4.3	47 ± 4.2	**0.001**

TST: Total sleep time, AHI: Apnea hypopnea index, ESS: Epworth Sleepiness Scale, DSI: Desaturation index.

Table 3. Full blood count of the groups.

	Group 1 Control	Group 2 Normal OSA	Group 3 Overweight OSA	Group 4 Obesity OSA	p
Neutrophil count (mean ± SD; $10^3/\mu$)	3.57 ± 0.28	4.43 ± 0.27	4.67 ± 0.37	6.34 ± 0.57	**0.001**
Lymphocyte count (mean ± SD; $10^3/\mu$)	2.31 ± 0.15	2.76 ± 0.17	2.59 ± 0.27	2.12 ± 0.063	0.001
Leukocyte count (mean ± SD; $10^3/\mu$)	6.84 ± 0.35	7.27 ± 0.47	8.46 ± 0.32	9.46 ± 0.36	**0.001**
NLR (mean ± SD)	1.55 ± 0.16	1.59 ± 0.15	1.83 ± 0.30	2.98 ± 0.29	**0.001**

NLR: Neutrophil-to-lymphocyte ratio, WBC: White blood cell.

The statistically significant differences were revealed after comparison of NLR values between group 4 (obese OSAS group) and groups 1 (control group), 2 (normal weight OSAS group), 3 (overweight OSAS group). The NLR values of group 4 (obese OSAS group) were also statistically significant higher than those of groups 1, 2 and 3. A positive correlation was observed between the desaturation index and NLR values of obese OSAS subjects (r= 0.027, p= 0.002) (Table 2, Figure 1). The neutrophil counts of group 4 (obese OSAS group) were statistically significant higher than those of groups 1 (control group), 2 (normal

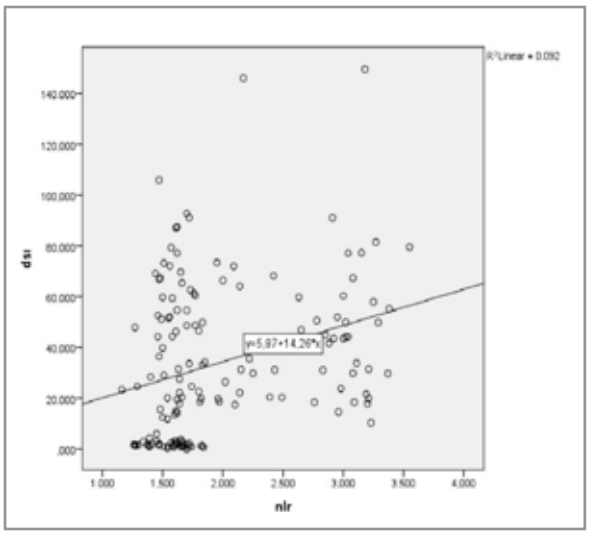

Figure 1. A positive correlation was observed between the body mass index and lymphocyte count values of obese OSAS subjects

weight OSAS group) and 3 (overweight OSAS group). The lymphocyte counts of group 4 (obese OSAS group) were the lowest among all groups; these values were lower than the lymphocyte counts of groups 1 (control group), 2 (normal weight OSAS group) and 3 (overweight OSAS group) with statistically significant differences ($p< 0.001$) (Table 3).

Measurements such as the neck, waist and hip circumference of group 4 (obese OSAS group) were significantly higher than those of groups 1 (control), 2 (normal weight OSAS) and 3 (overweight OSAS) ($p< 0.001$). In addition, waist to hip ratio of group 4 (obese OSAS group) was significantly higher than those of group 1, 2, 3 ($p< 0.001$) (Table 1).

DISCUSSION

In the present study, we concluded that, NLR values for obese OSA subjects prove significantly higher when compared to those of the control, and normal weight OSA subjects ($p< 0.001$). The similar trend was seen in overweight OSA subjects as they had significantly higher NLR values compared to the control subjects and normal weight OSA subjects ($p< 0.001$).

OSA typically occurs during sleep and is a result of muscles of the upper airway relaxing, which causes partial (hypopnea) or complete (apnea) obstruction to airflow. As a result of muscle tone the upper airway collapses during sleep, especially if a predisposing factor such as obesity is present (17). Intermittent upper airway obstruction during sleep could have a multifactorial aetiology and in most cases depends on the loss of pharyngeal muscle tone in a subject already at risk with a narrow upper airway, or crowded oropharynx (17). Although a vast majority of subjects suffering with OSA are obese, a high number have an alternative predisposing factor, such as enlarged tonsils, hypothyroidism, retrognathia and neurological condition.

OSAS is also associated with inflammation. OSAS results in the occurrence of apnea, and hypopnea. It also causes hypoxia asphyxia, respiratory acidosis and hypercapnia, which are due to the reoccurring sleep disruptions and leads to the development of local and systemic inflammation (18). Paulsen et al have shown that people with habitual snoring and upper respiratory tract epithelial lymphocyte infiltration in subjects with OSAS and showed increased connective tissue density, and they thought this might be due to the increased vibration trauma due to snoring (19). Even in the absence of clinical signs of rhinitis and sinusitis in subjects with OSAS, it is observed that inflammation increases within the nasal region (20). On the other hand, vibration trauma caused by the persistent snoring leads to increased inflamation within the uvulopalatal region and pharynx (19,21). The obstruction caused by OSAS in the upper airways and the mechanical trauma caused by snoring, which leads to local inflammation is also thought to effect systemic inflammation.

Furthermore, inflammatory markers have been observed to be increased in OSAS subjects and the increase is related to hypoxia duration and disease severity. Studies done with OSAS subjects have shown increase in CRP, leptin, TNF-α, IL-6, vascular endothelial growth factor (VEGF), nuclear factor kappa B (NF-kB), reactive oxygen radicals, intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which shows the presence of systemic inflammation (18).

NLR is an indicator of subclinical inflammation. It is still unclear what elevated NLR indicates; however, it leads to a higher neutrophil count compared with lymphocyte count in response to stress such as inflammation. This easily calculated ratio could may be used as an indicator of the prognosis and systemic inflammation in OSA subjects with obesity.

The number of leukocytes measured and the ratio of their subtypes are regarded as markers of inflammation in obesity (22). Obesity is a condition, which

stimulates reactive leucocytosis. In parallel to this, our study has shown that obese OSAS subjects showed significantly higher values of leukocyte's compared with other groups. In severely obese subjects, along with macrophage accumulation within fatty tissue, cortisol and insulin levels increase in parallel to increased fat tissue, and leucocytosis increases as a result via leptin secretion from adipocytes (23). Other types of immune cells such as neutrophils demonstrate phagocytic and anti-microbial activity by the proteins contained in their granules. Comparison of neutrophils between obese and normal individuals, it has been observed that glucose oxidation and bactericidal capacity is decreased and chemotactic ability is reduced, and these characteristics are correlated with BMI (24-26). It is also observed that monocytes within the immune system of obese individuals have decreased maturation and that oxidative burst is increased. In a study by Atmaca et al. while neutrophil counts of all obese groups were increased, the increase of neutrophil count in severely obese individuals were more marked and statistically significant (22). Similarly, lymphocyte count has increased with increasing BMI. In parallel to this, our study has found a positive correlation between the BMI and lymphocyte count values of obese OSAS patients. This situation was similar for the neutrophil ratio, which, increased in severely obese subjects and that the NLR value was also found to be higher in severely obese subjects. These findings support the opinion that as obesity levels increase inflammation also increases. In a study by Yenigun et al. a positive correlation was found between the severity of OSAS and NLR and it was also shown that as AHI increased NLR also increased (27).

Obesity is considered a major risk factor for the development and progression of OSA (28,29). It is should be considered that obesity could be playing role in worsening OSA due to fat deposition at specific sites. Decreased size of lumen and increased collapsibility of the upper airway could be due to fat deposition in the tissues surrounding the upper airway and could lead to apnea (30). Fat could also deposit around the thorax (truncal obesity) reduce chest compliance and functional residual capacity, while increasing oxygen demand in some cases (31). In our study, minimum SpO_2 and average SpO_2 values of group 4 (obese OSAS group) were also statistically significant and lower than those of groups 1, 2 and 3. In addition to this, desaturation index values of group 4 (obese OSAS group) were also statistically significant higher than those of groups 1, 2 and 3. And there was a positive correlation between the desaturation index and NLR.

Visceral obesity is common in subjects with OSA (32). However, there is a complex relationship between OSA and obesity. Although there is evidence showing that obesity and visceral obesity may predispose to OSA and that OSA is improved after weight loss, recent studies suggest that OSA may be causing weight gain itself (33,34). Other factors also play a role in weight gain in subjects with OSA such as reduced activity and increased appetite, especially for refined carbohydrates.

It has been accepted that anthropometric measurements are associated with inflammatory state, and BMI and waist circumference are indicators of inflammation (35). Some studies have shown that BMI and waist circumference are closely associated with inflammation and especially with leukocyte count (35). A study with obese adolescent women showed that leukocyte count positively correlated with body mass index and total fat tissue (35). Similar to this, our study demonstrated that absolute lymphocyte counts have positive correlation with BMI. This observed increase was more apparent in morbid obese individuals. A new indicator, waist-hip ratio, could be accepted for visceral obesity (35). In our study, waist to hip ratio of group 4 (obese OSAS group) was significantly higher than those of group 1, 2 and 3.

The NLR, when compared to inflammatory cytokines, including IL-6, IL-1 and TNF-α, has the advantage of no extra costs. It is simply measured from the complete blood count of peripheral blood. The neutrophil count reflects the inflammatory status, while the lymphocyte count is related to the general stress and nutritional status of the body. Recent studies have claimed that the NLR could potentially be used as a marker of inflammation, both in cardiac and non-cardiac disorders. It is also a potential marker for inflammatory conditions caused by autoimmune conditions or infection (36,37).

As for the limitations of our study, the main one is the lack of other established markers of inflammation as a reference for comparison. Also, the sample size in our study was small and studies with a larger number of subjects are required to confirm any of our findings. Our study has demonstrated that, NLR ratio increases by obesity grade and therefore, by increased fat tissue and reveals that the concomitant inflammatory response increases. The findings suggest that the NLR

will be significant in the clinical follow up of obesity in OSAS subjects. We think that, could be used for obese OSA subjects as an inflammatory marker and could prove helpful in predicting metabolic risks for the subject. The ratio along with treatments for weight loss could be followed up as a method to monitor the effects of the treatment in the prevention of obesity-associated diseases.

Quick Look

Current Knowledge

There is also various evidence suggesting that OSA is associated with low-grade systemic inflammation. The occurrence of systemic inflammation is a crucial factor, which links obesity, OSA and the metabolic syndrome. Obesity predisposes to and potentiates OSAS Systemic inflammation can be measured using a variety of biochemical and hematological markers. Due to being cost effective and easily accessible, neutrophil-to-lymphocyte ratio (NLR) could be an important measure of systemic inflammation.

What This Paper Contributes To Our Knowledge

Our study has demonstrated that, NLR ratio increases by obesity grade and therefore, by increased fat tissue and reveals that the concomitant inflammatory response increases. The findings suggest that the NLR will be significant in the clinical follow up of obesity in OSAS subjects. We think that, could be used for obese OSA subjects as an inflammatory marker and could prove helpful in predicting metabolic risks for the subject.

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