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The Importance of the De Ritis Ratio and Glasgow Prognostic Score in prehypertensive patients

Prehipertansif Hastalarda De Ritis Oranı ve Glasgow Prognostik Skorunun Önemi

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ABSTRACT

Aim: To evaluate Glasgow prognostic score (GPS) and De Ritis ratio in optimal blood pressure and prehypertensive patients, and investigate whether these parameters can predict antihypertensive treatment in the follow-up period.
Methods: A total of 402 patients who were followed up with a 24-hour ambulatory blood pressure with a pre-diagnosis of hypertension between January 2018 and December 2018 were included in the study. Routine laboratory parameters of the patients were recorded in the hospital digital system. The common health system data of the patients was analyzed until June 2020, and those who were started on antihypertensive treatment were recorded.
Results: 402 patients (mean age 40.16 ± 13.01 years, 49% male) were included in the study. 226 of these were in prehypertension group. The mean GPS and the De Ritis ratio, aspartate aminotransferase levels, mean systolic and diastolic blood pressures were different between the groups (p=0.035, p=0.023, p=0.039, p<0.001 and p=0.012, respectively). When patients whose antihypertensive treatment was started and those who did not receive antihypertensive treatment were compared; age, De Ritis ratio and mean diastolic blood pressure differed between the two subgroups (p<0.001, p=0.015 and p=0.040, respectively). Multivariate logistic regression analysis showed that De Ritis ratio and age were, independently, predictors for antihypertensive treatment (OR:3.064, p=0.015 and OR:1.050, p= 0.001 respectively). In ROC curve analysis, both age and De Ritis ratio were successful at predicting the initiation of antihypertensive treatment with an AUC:0.697 and p<0.001 and AUC:0.630 and p=0.018 respectively.
Conclusions: Both GPS and the De Ritis ratio were found to be significantly higher in prehypertensive patients than those with optimal blood pressure. Moreover, the De Ritis ratio, an easily calculated laboratory parameter, can be used as a predictive value for antihypertensive treatment.

Keywords: De Ritis ratio, Glasgow prognostic score, prehypertension

ÖZ

Amaç: Optimal kan basıncı ve prehipertansif hastalarda Glasgow prognostik skoru (GPS) ve De ritis (AST/ALT) oranını değerlendirmek ve bu parametrelerin takip döneminde antihipertansif tedaviyi tahmin edip edemeyeceğini araştırmayı amaçladık.
Yöntemler: Ocak 2018-Aralık 2018 tarihleri arasında kliniğimizde hipertansiyon ön tanısıyla 24 saat ambulatuvar kan basıncı monitörizasyonu ile izlenen toplam 402 hasta çalışmaya dahil edildi. Hastaların rutin laboratuvar parametreleri hastane dijital sisteminden kaydedildi. Hastaların medikasyon verileri ulusal sağlık sisteminden Haziran 2020'ye kadar analiz edilerek antihipertansif tedavi başlanan hastalar kayıt altına alındı.
Bulgular: Çalışmaya 402 hasta (ortalama yaş 40.16 ± 13.01 yıl) dahil edildi (% 49 erkek). Bunların 226'sı prehipertansiyon grubundaydı. Prehipertansiyon grubunda ortalama GPS ve De Ritis oranı, aspartat aminotransferaz seviyeleri, ortalama sistolik ve diyastolik kan basınçları daha yüksek ve istatistiksel olarak anlamlı belirlendi (sırasıyla p = 0,035, p = 0,023, p = 0,039, p = <0,001 ve p = 0,012). Antihipertansif tedavi başlanan ile başlanmayan hastalar karşılaştırıldığında; yaş, De Ritis oranı ve ortalama diyastolik kan basıncı antihipertansif tedavi alan grupta daha yüksek belirlendi (sırasıyla p <0,001, p = 0,015 ve p = 0,040). Çok değişkenli lojistik regresyon analizinde De Ritis oranı ve yaş antihipertansif tedavi başlanması için bağımsız öngördücüler oldukları saptandı (sırasıyla OR: 3.064, p = 0.015 ve OR: 1.050, p = 0.001). ROC eğrisi analizinde, hem yaş hem de De Ritis oranı sırasıyla EAA: 0.697 ve p <0.001 ve EAA: 0.630 ve p = 0.018 ile antihipertansif tedavinin başlamasını öngörmede başarılıydı.
Sonuçlar: Hem GPS hem de De Ritis oranı prehipertansif hastalarda optimal kan basıncına sahip olanlara göre anlamlı olarak daha yüksek bulundu. Ayrıca kolay hesaplanan bir laboratuvar parametresi olan De Ritis oranı, antihipertansif tedavi başlanması için bir tahmin değeri olarak kullanılabilir.

Anahtar Kelimeler: De ritis oranı, Glasgow prognostik skoru, prehipertansiyon

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INTRODUCTION

Hypertension (HT) is the leading component of global disease burden and acts as a major cause of cardiovascular (CV) diseases; a higher mortality in hypertensive population is well known in many countries through national level studies [1].

Pre-HT was defined as a systolic blood pressure (SBP) between 120–139 mmHg or diastolic blood pressure (DBP) between 80–89 mmHg [2]. The definition of HT changed in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines, which caused confusion in the diagnosis and treatment of patients with stage 1 HT, previously referred to as pre-HT [3].

In the presence of pre-HT, the risk of CV events in patients is significantly increased compared to those with normal blood pressure levels. The increase in arterial blood pressure develops over the years, and the diagnosis of pre-HT and HT is mostly made in the 4-5th decades. In patients defined in the pre-HT stage, the development of HT can be prevented by appropriate lifestyle changes and correction of known risk factors for the development of HT. However, although lifestyle changes and risk factors are optimized in some patients, HT develops in patients with progressive increase in blood pressure, and medical treatment is required. The pathophysiology underlying the development of HT is not unique, but more than one factor plays a role. Endothelial dysfunction and chronic inflammation are some of well-determined factors involved in the pathogenesis of HT [4,5]. Tsounis, Huang and Polónia have previously shown that there is a relationship between inflammatory markers / risk scores and endothelial dysfunction in the development of HT [6-8].

It has been determined that the GPS and De Ritis ratio (Glasgow prognostic score and AST/ALT), which is mainly proposed to determine the prognosis of malignancies, is an indicator of cardiac mortality and morbidity in later periods. In patients in the pre-HT stage, simple laboratory parameters or scores that will predict HT progression, will be of great importance in daily life.

Since both laboratory parameters can determine inflammation and endothelial dysfunction, they may be markers for the progression of HT in prehypertensive patients [9-13]. In this study, we planned to investigate whether these two parameters differ in optimal BP and prehypertensive patients and whether De Ritis and GPS values in prehypertensive patients, at the time of the diagnosis of pre-HT, can help in the initiation of medical treatment in the follow-up.

METHODS

Four hundred and two patients who were followed for 24-hour ambulatory blood pressure monitoring (ABPM) with pre-diagnosis of HT in our clinic, between January and December 2018, were included in this retrospective study. The study flow diagram is presented in Figure 1.

The demographic and medical characteristics of the patients were obtained from patients' files and the digital system. Optimal blood pressure was defined as a systolic blood pressure (SBP) <120 mm Hg and, diastolic blood pressure (DBP) <80 mm Hg and pre-HT was defined as SBP 120-129 mm Hg and DBP<80 mm Hg and HT as ≥ 130/80 mm Hg[2]. Patients with known inflammatory disease, chronic liver disease, malignancy, those who were under 18 and over 85 years of age, those with coronary artery disease, diabetes mellitus, those who had any treatment that might increase liver function tests like statins and patients using medicines that lower arterial blood pressure for any reason, missing or insufficient ambulatory blood pressure patients and with missing laboratory parameters, were all excluded from the study.

Follow-up data of the patients until June 2020 were obtained from hospital record and phone interviews. The data of 278 were recorded during their check-up and the remaining 124 were reached by telephone. Those who started antihypertensive treatment due to high levels of arterial blood pressure during their follow-up were noted.

All blood samples were collected and the laboratory measurements of serum values of albumin, C-reactive protein (CRP), liver and kidney function tests, lipid parameters, other biochemical tests and complete blood count values were studied

in venous blood samples, taken at admittance. The De Ritis ratio was calculated as aspartate aminotransferase/ alanine aminotransferase (AST / ALT) and the GPS was defined based on the presence of hypoalbuminemia (<35 g/L) and elevated CRP (>10 mg/L): if both were abnormal, the score was 2; if either was abnormal, the score was 1; if neither was abnormal, the score was 0.

Statistical analysis: The Levene test was used to determine whether variables were homogeneously distributed. Continuous variables were expressed as mean ± standard deviation and compared using Student's t test and Kruskal-Wallis was used for variables without normal distribution. Categorical variables were presented as total number and percentages, and compared using the chi-square test. Correlations between variables was accomplished with the Pearson correlation if the variables distributed homogenously, and the Spearmen correlation if not. Multivariate analysis using logistic regression models tested variables with p ≤ 0.25 in univariate analysis. Receiver operating characteristics (ROC) curve analysis was performed to demonstrate the predictive values of the variables and the area under curve (AUC) of the scores were compared using the Delong method. A two-tailed p value of <0.05 was considered as statistically significant and 95% confidence interval (95 % CI) were presented for all odds ratios. All statistical analyses were performed using the SPSS Windows software (ver.15.0; IBM, NY, USA).

RESULTS

A total of 402 patients (mean age, 40.16 ± 13.01 years; 197 men [49%]) were included in this retrospective cohort study. Of these patients 226 were in prehypertension group with a mean SBP / DBP of 124.92 ± 2.52 / 73.20 ± 5.24 mm Hg and the remaining in optimal blood pressure group with 112.93 ± 4.55 / 68.63 ± 4.69 mm Hg (p<0.001 and p= 0.012, respectively).

There were no participants with GPS 3 in the study. Out of 176 individuals in the optimal blood pressure group, 163 (92.6%) of them had GPS 0 while this number was 202 (89.3%) in the prehypertension group. Table 1 shows the baseline demographic and laboratory results of the groups. The patients in pre-HT group were followed between January 2018 and June 2020 and antihypertensive treatment was initiated for 36 of them during their follow-up. Of these patients 14 (38.9) were male and the mean age was 47.22 ± 11.38. When the subgroups, according to initiation of antihypertensive treatment, were analyzed, they differed only in terms of age, De Ritis ratio and DBP levels, with p<0.001, 0.015 and 0.040, respectively (Table 2).

Table 1: Baseline characteristics and laboratory results of groups and statistical analysis

	Prehypertension group(n=226)	Control group (n=176)	p
	mean ± sd	mean ± sd	
	39.85 ± 13.71	40.56 ± 12.07	0.589
Gender, m (%)	108 (47.7)	89 (50.5)	0.580
Systolic BP, mm Hg	124.92 ± 2.52	112.93 ± 4.55	<0.001*
Diastolic BP, mm Hg	73.20 ± 5.24	68.63 ± 4.69	0.012*
Glucose, mg/dL	97.28 ± 20.46	98.72 ± 24.02	0.375
Urea, mg/dL	25.71 ± 8.03	25.27 ± 8.06	0.644
Uric acid, mg/dL	5.50 ± 1.68	4.73 ± 1.94	0.004*
Creatinine, mg/dL	0.67 ± 0.16	0.64 ± 0.14	0.066
Na, mEq/L	146.89 ± 98.67	138.12 ± 11.58	0.311
K, mEq/L	4.42 ± 0.60	4.36 ± 0.58	0.328
AST, U/L	23.51 ± 7.70	21.81 ± 7.44	0.039*
ALT, U/L	23.66 ± 12.89	21.29 ± 10.18	0.068
LDL, mg/dL	141.67 ± 43.69	145.38 ± 35.28	0.505
HDL, mg/dL	48.52 ± 10.68	49.96 ± 13.72	0.394
Triglycerides, mg/dL	174.11± 110.41	174.08 ± 113.11	0.998
Albumin, mg/dL	42.81 ± 5.20	43.21 ± 4.13	0.672
CRP, mg/dL	6.42 ± 4.31	6.09 ± 4.77	0.232
WBC count, 103 /mL	7.77 ± 2.20	9.75 ± 15.24	0.077
Hgb, g/dL	13.65 ± 1.87	13.45 ± 1.66	0.224
Plt count, 103/mL	266.32 ± 68.34	271.64±73.60	0.498
GPS	0.10 ± 0.30	0.04 ± 0.20	0.035*
De Ritis ratio	1.28 ± 0.43	1.16 ± 0.36	0.023*

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BP: blood pressure, CRP: C-reactive protein, GPS: Glasgow prognostic score, HDL: high density lipoprotein cholesterol, Hgb: hemoglobin, K: potassium, LDL: low density lipoprotein cholesterol, Na: sodium, WBC: white blood cell, Plt : platelet

Multivariate logistic regression analysis showed that age and De Ritis ratio were independently predictors of initiation of antihypertensive treatment (Table 3). In ROC curve analysis, both age and De Ritis ratio were successful at predicting the initiation of antihypertensive treatment with an AUC:0.697 and p<0.001 and AUC:0.630 and p=0.018 respectively (Figure 2).

Table 2: Characteristics of prehypertension group

	No treatment group (n=190)	Antihypertensive drug group (n=36)	p
Gender, m(%)	94(49.4)	14(38.8)	0.244
Glucose, mg/dL	100 ± 27	101 ± 21	0.803
Age, years	38.45 ± 13.69	47.22 ± 11.38	<0.001*
Urea, mg/dL	25.5 ± 8	26.3 ± 8	0.635
Creatinine, mg/dL	0.67 ± 0.16	0.65 ± 0.13	0.449
Uric acid, mg/dL	5.42 ± 1.71	5.84 ± 1.52	0.324
AST, U/L	23.46 ± 7.76	23.77 ± 7.51	0.842
ALT, U/L	23.92 ± 3.28	22.33 ± 10.72	0.531
Na, mEq/L	139 ± 2,2	139 ± 1.4	0.855
K, mEq/L	4.40 ± 0.43	4.56 ± 1.10	0.192
CRP, mg/dL	6.46 ± 3.94	6.21 ± 3.89	0.988
Triglycerids, mg/dL	167.98 ± 104.93	205.64 ± 133.51	0.144
LDL-C, mg/dL	140 ± 45	148 ± 32	0.467
HDL-C, mg/dL	47.75 ± 8.95	52.34 ± 16.69	0.079
Systolic BP, mm Hg	125.01 ± 2.70	124.47 ± 1.72	0.747
Diastolic BP, mm Hg	72.09 ± 5.03	78.76 ± 0.90	0.040*
GPS	0.10 ± 0.30	0.085 ± 0.28	0.727
De Ritis ratio	1.25 ± 0.41	1.45 ± 0.46	0.015*

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BP: blood pressure, GPS: Glasgow prognostic score, HDL-C: high density lipoprotein cholesterol, K: potassium, LDL-C: low density lipoprotein cholesterol

Table 3: Univariate and Multivariate logistic regression of variables for antihypertensive treatment

	Univariate analysis			Multivariate analysis		
	OR	95 %CI	P	OR	95 % CI	p
Age	1.047	1.020-1.076	0.001	1.050	1.021-1.080	0.001
Gender, male	1.539	0.743-3.186	0.256			
DBP	1.053	0.975-1.138	0.186	1.062	0.976-1.156	0.165
SBP	0.913	0.545-1.529	0.729			
De Ritis Ratio	2.699	1.169-6.230	0.020	3.064	1.238-7.586	0.015
LDL	1.004	0.993-1.014	0.466			
GPS	0.797	0.224-2.840	0.726			
Na	1.018	0.841-1.232	0.854			
K	1.420	0.804-2.508	0.262			

DBP: diastolic blood pressure, SBP: systolic blood pressure, OR: Odds Ratio, CI: confidence interval, Na: Sodium, K: potassium, GPS: Glasgow prognostic score, LDL-C: low density lipoprotein cholesterol

DISCUSSION

This study showed that 1) in the 24-hour ambulatory blood pressure follow-up, 31.3% of the patients had pre-HT, 2) the mean systolic-diastolic blood pressure, mean GPS and De Ritis rate were higher in patients with pre-HT. 3) It was determined that pre-HT patients who started antihypertensive treatment were older, the rate of De Ritis ratio and mean diastolic blood pressure were higher, 4) Multivariate logistic regression analysis showed that De Ritis rate and age were independent predictors for initiation of antihypertensive therapy. These results are, to our knowledge, the first study in the literature to show the relationship between Pre-HT and De Ritis ratio and GPS.

Progression of pre-HT, which is determined according to the JNC 7 criteria and based on office blood pressure values, to HT is a frequently encountered health and social problem. Although there is no consensus on the necessity of treatment of pre-HT and the factors that cause it to progress to HT, many studies have expressed opinions on these issues [14]. In a large-scale study, PREVER-prevention, low dose chlortalidone and amiloride reduces the risk of HT and affects left ventricular mass in patients with pre-HT beneficially [15]. Furthermore, Lüders et al. found that angiotensin converting enzyme inhibitors reduced the risk of progression to manifest HT in patients with high-normal office blood pressure [16].

Multiple factors such as age, gender, increased BMI, high basal systolic/diastolic blood pressure and hyperuricemia, were evaluated in patients diagnosed with pre-HT, and there are studies showing that these increase the risk of developing HT [17]. The fact that hyperuricemia is a factor that increases both the risk of pre-HT and the progression to HT, has been supported by the studies of Liu and Kuwabara et al [18,19]. In our study, serum uric acid levels were higher in pre-HT group similar to these studies but we did not find any significant difference when the ones who received a antihypertensive treatment and who did not were compared.

Some studies indicate that the female gender increases the risk of developing HT whereas some indicate it's the male gender [20]. In our study,

we did not find any risk increase depending on gender. As the prevalence of HT increases with increasing age, the risk of progression of pre-HT to HT also increases, and this fact was also demonstrated in our study. Although there was no difference in age between patients with pre-HT and optimal blood pressure, the mean age of those diagnosed with HT and started on treatment in the pre-HT group was found to be significantly higher than the others. High basal systolic and diastolic blood pressure also affects the development of HT [21]. In our study, we were able to find that the group in need of antihypertensives only had higher diastolic blood pressure values, compared to the others.

Pre-HT patients are at risk of morbidity and mortality due to cardiovascular and cerebrovascular events because of endothelial dysfunction [22]. There is yet no scoring system or laboratory parameter that determines whose treatment should be started. The GPS and the De Ritis ratio are measurements that are used as indicators of endothelial dysfunction and consist of simple calculable laboratory parameters. In our study, which we planned based on this hypothesis, we found that the GPS and the De Ritis ratio in pre-HT patients were significantly higher than those with optimal blood pressure. In addition, it was observed that the De Ritis ratio in patients who progressed to HT was statistically significantly higher, than those who remained in the pre-HT period. The difference in GPS values was not observed in these subgroups. Moreover, the De Ritis ratio was successful in predicting the initiation of antihypertensive drugs in our study.

Our study had more than one limitation. The most important of these is that it was a small group of patients and it was single-centered. Groups were determined according to the mean values of ambulatory blood pressure monitoring, so the number of participants was low. If the office blood pressure levels were based on, the predictive power of starting antihypertensive treatment of variables may be changed. Furthermore, the design of the protocol was retrospective.

CONCLUSIONS

GPS and the De Ritis ratio were higher in prehypertensive patients than the ones with optimal blood pressure levels. Furthermore, the De Ritis ratio was found significantly higher in patients who were started on antihypertensive treatment, compared to those who did not use antihypertensives and it was also an independent predictor of initiation of treatment. However, there is a need for prospective studies with large participation, multi-center and long follow-up, for its use as a parameter that can predict the initiation of antihypertensive therapy.

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