

Original Article

Gender-based differences in the effectiveness of antihypertensive therapy with losartan compared with enalapril

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Abstract

Objective: Today there is a limited number of gender-based characteristics of the enalapril and losartan administration in order to correct blood pressure in patients with arterial hypertension. The aim of the study was to compare the effectiveness of enalapril and losartan for blood pressure correcting in patients with arterial hypertension (AH), depending on gender. **Materials and methods:** The study was carried out in 2019 at Military Hospital 175 in Ho Chi Minh city, Vietnam. To achieve this goal, 100 people were included in the study (50 females in the menopause and 50 males) with grade I-II arterial hypertension aged 50 to 60 years. Patients with hypertension were divided into the following groups: group 1A – 25 males, who received enalapril 20 mg/d and 12.5 mg/d hydrochlorothiazide once per day as antihypertensive therapy; group 1B – 25 males, who received losartan 50 mg/d and hydrochlorothiazide 12.5 mg/d once per day; group 2A – 25 females, who received enalapril 20 mg/d and hydrochlorothiazide 12.5 mg/d once per day; group 2B – 25 females, who received losartan 50 mg/d and hydrochlorothiazide 12.5 mg/d once per day. The follow-up was 12 weeks. **Results and discussion:** The study showed that antihypertensive therapy with losartan is more effective in females compared with enalapril, as evidenced by a significant SBP decrease by 21.1% ($p < 0.05$) at the end of treatment with losartan in females versus 18.6% ($p < 0.05$) when using enalapril with the presence of a statistically significant intergroup difference in the indicator ($p < 0.05$). **Conclusion:** Our results indicate the presence of a gender difference in the antihypertensive effect of losartan and enalapril.

Keywords: comparison of losartan and enalapril in females; differences in the functioning of cytochrome P450; drug metabolism in females; gender features of the pathogenesis of hypertension.

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Introduction

Despite the achievements of modern medical science, arterial hypertension (AH) is still the most common chronic disease in the world¹⁻⁵. In particular, in 2015, the global prevalence of hypertension amounted to about 1.13 billion people^{1,2}, in central and eastern Europe – 150 million¹, in the USA – 51.2 million⁴.

Among the adult population, the total prevalence of hypertension is about 30-45% and does not depend on social status or income level^{3,6,7}. The prevalence of hypertension is higher in people aged 60+ and makes up more than 60%, which is 1.5-2 times more than in younger age groups^{1,6,7}. The number of people with hypertension is estimated to continue to increase,

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reaching about 1.5 billion people by 2025¹.

In recent years, gender characteristics of the prevalence, pathogenesis, and treatment of hypertension have attracted more and more interest⁶⁻⁸. In males AH occurs 10 years earlier than in females, who have AH debut with the onset of menopause in the vast majority of cases^{8,9}. An interesting fact is that the prevalence of hypertension in people aged under 50 is higher among males and in older age groups among females⁹. In particular, in a large-scale study conducted in Korea (n=27887, of which 12089 were males, 15798 were females over the age of 30), the prevalence of hypertension in males was higher (34.6%) compared with females (30.8%). In the group of people over 60 years old, AH was more common in females. At the same time, AH control was better in females (51.3%) than in males (44.8%), but in the age category over 60 this tendency changes exactly the opposite¹⁰.

In another large study (n=14497) with young people (aged 24-34 years), there were gender differences in hypertension found starting from 24 years, in particular, according to this study, the prevalence of hypertension among females of this age category was 12%, and among males – 27%¹¹.

In contrast, another large-scale cross-sectional study (n=17856), conducted in France between 2000-2015, showed that the prevalence of AH among females and males was the same – 50% and 50%. But according to the data of this investigation the resistant hypertension prevalence did not significantly change over 15 years of observation (in females from 14% to 13% (p=0.25), in males from 20.8% to 18.8% (p=0.058)) and was higher among males¹².

In addition, adverse cardiovascular events in females occur at a later age and with a lower frequency¹³. This was demonstrated in a study conducted by Boggia et al., which included 9357 people (average age 52.8 years, 47% of the examined were females) who underwent 24-hour blood pressure monitoring. Over the course of 11.2 years, 1245 participants died, including 472 due to cardiovascular causes. Females are characterized by a connection between the indicator of night blood pressure (BP) and the incidence of adverse cardiovascular events, coronary complications, cerebrovascular events, and mortality. The indicator of complications can be prevented was significantly higher in females compared with males: for all cardiovascular

complications it is 35.1% in females versus 24.3% in males, coronary complications – 35.1% against 19.4%, for cerebrovascular events – 38.3% and 25.9%, respectively, and for total mortality – 23.1% and 12.3%¹³.

The lower prevalence of hypertension in young females is explained by the protective effect of estrogens in the premenopausal period^{6,9,13-15}. Estrogens can cause vasodilation by the way of sympathetic nervous system inhibition, stimulating of nitric oxide synthesis, renin-angiotensin-aldosterone system (RAAS) inhibition due to for blocking angiotensin (AT1) receptors and angiotensin converting enzyme (ACE), which helps to reduce the level of angiotensin II (AT-II)^{9,13,14}. In addition, estrogens reduce the creation of endothelin, resulting in a decrease in renal vasoconstriction and reabsorption of Na⁺ ions. In males, androgens cause the angiotensinogen synthesis increasing, and, as a result, leads to increasing of the concentration of AT-II^{6,9,14}. Male sex hormones increase Na⁺ reabsorption in the proximal tubules of the renal glomeruli by acting on the androgen and AT1 receptors^{14,15}.

Despite a large number of studies and a rather rapid breakthrough in the development of new strategies for the treatment of hypertension, blood pressure control still stays unsatisfactory, and disability as a result of hypertension continues to increase sharply¹⁶. The reason for this is irrational hypertension pharmacotherapy, in particular. Researchers claim that about 80% of patients in Europe with hypertension are administered only one drug, instead of switching to two-component therapy^{1,16}. The appropriateness of starting two-component antihypertensive therapy is confirmed in the latest recommendations of the European Society of Cardiology (ESC) and the European Society for Arterial Hypertension (ESH) 2018¹. Besides, it is so important to investigate the gender characteristics of the pathogenesis of hypertension, pharmacodynamics and pharmacokinetics of antihypertensive drugs^{9,17,18}, which still remain insufficiently studied, because most such researches in this direction have been conducted mainly with the participation of males.

In accordance with the latest ESC/ESH recommendations for AH 2018, first-line drugs for the AH treatment are ACE inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) in combination with thiazide diuretics or calcium

channel blockers¹. As a result of a large number of studies, the efficacy of enalapril and losartan with the goal of stable and long-term control of blood pressure was proved^{1,6,19-22}. However, today there are not many studies that have studied the gender characteristics of the use of enalapril and losartan in order to correct blood pressure in patients with hypertension.

The study aimed to compare the effectiveness of enalapril and losartan for correcting blood pressure in patients with arterial hypertension, depending on gender.

Materials and methods:

The study was carried out in 2019 at Military Hospital 175 in Ho Chi Minh city, Vietnam.

To achieve this goal, 100 people were included in our study (50 of them were females in menopause and 50 males) with grade I-II arterial hypertension (AH) between the ages of 50 and 60, as well as 25 healthy individuals (HI). The disease duration in our patients was from 5 to 12 years. Patients with hypertension were divided into the following subgroups depending on the treatment received, randomized by age, duration of the disease, glomerular filtration rate (GFR), microalbuminuria level (MAU): group 1A – 25 males, who received a fixed combination of enalapril as antihypertensive therapy 20 mg/d and hydrochlorothiazide 12.5 mg/d once per day; group 1B – 25 males, who received a fixed combination of losartan 50 mg/d and hydrochlorothiazide 12.5 mg/d once per day; group 2A – 25 females in the menopause, who received a fixed combination of enalapril 20 mg/d and hydrochlorothiazide 12.5 mg/d once per day; group 2B – 25 females in menopause, who received a fixed combination of losartan 50 mg/d and 12.5 mg/d hydrochlorothiazide once per day. All patients were given recommendations on lifestyle modification and nutritional correction. 14 days before the start of the study, patients stopped preliminary antihypertensive therapy. The follow-up was 12 weeks. 4 weeks after the start of therapy, when the target blood pressure level was not achieved, a dose titration of enalapril and losartan was performed. Control examinations of patients to assess physical status, blood pressure measurement and compliance verification with the regimens of drugs were carried out every 2 weeks.

The diagnosis of hypertension was verified according to the 2018 ESC/ESH Recommendations. Inclusion criteria: age 50-60 years; verified diagnosis of

hypertension I-II; for females – period of menopause; signed patient informed consent to participate in the study.

Criteria for exclusion from the study: resistant, malignant, secondary hypertension; coronary artery disease; acute cerebrovascular accident (less than 6 months before the start of the study); chronic heart failure III-IV FC according to NYHA classification; type 1 or type 2 diabetes, obesity; bilateral renal artery stenosis or artery stenosis of a single kidney; severe renal or hepatic insufficiency; presence of concomitant pathology in the acute stage; malignant neoplasm; mental illness; history of IAPR, ARB, diuretics intolerance; data on abuse of alcohol and drugs; pregnancy, lactation; lack of compliance.

Before inclusion in the study, as well as at the 4th, 6th and 12th week of treatment, all patients underwent a general clinical study, blood pressure measurement, 24-hour blood pressure monitoring, general clinical analysis of blood and urine, a study of blood biochemical parameters (blood glucose, lipid profile, coagulogram, blood levels of urea, creatinine, uric acid, potassium, sodium, activity of ALAT and AsAT), MAU determination, GFR calculation, ECG registration, echocardiography.

BMI was calculated using the Kettle formula: $BMI = m/h^2$, where m is the body weight in kg, h is the height in m².

GFR (ml/min) was calculated using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) using an online calculator: <https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr>.

The MAU level was determined by the immunoturbidimetric method using a Siemens Dimension Xpand plus biochemical analyzer (USA). The criterion for the presence of MAU was considered the rate of urinary albumin excretion from 20-30 to 300 mg/day.

ECG recording in 12 leads was performed using a Heaco 300G apparatus (United Kingdom). During the ECG, the presence of signs of left ventricular hypertrophy, hyperkalemia was assessed. Daily monitoring of blood pressure and ECG was performed on a Card (X) Plore apparatus (Meditech, Hungary) under the conditions of normal physical activity of the patient. In order to determine the left ventricle ejection fraction (LVEF), to stratify the risk and assess diastolic LV function, echocardiography was

Table 1. Clinical characteristics of the examined patients before treatment, M±m

Indicator	Groups of subjects				
	HI (n=25)	1A (n=25)	2A (n=25)	1B (n=25)	2B (n=25)
Age, years	38.62±1.41	39.52±1.45	41.04±1.30	40.22±1.18	40.86±1.34
BMI, kg/m ²	23.45±1.17	27.90±1.20	27.20±1.33	28.17±1.24	27.52±1.43
Duration of illness, years	-	8.40±0.80	8.16±1.03	8.05±0.99	7.98±0.96
HR, bpm	68.94±1.60	70.05±1.28	68.60±1.47	72.10±1.81	69.33±1.14
SBP, mmHg	119.30±2.28	157.7±4.36*	158.13±2.25*	158.84±3.47*	157.21±3.08*
DBP, mmHg	77.50±1.86	97.10±2.24*	97.48±2.01*	98.62±1.66*	97.14±1.23*
GFR, ml/min/1.73m ²	109.56±3.08	80.81±1.44*	81.20±2.10*	82.03±1.86*	81.54±2.02*
MAU, mg/day	2.1±0.74	28.03±0.95*	26.96±0.87*	27.46±1.01*	27.54±0.92*

Notes: * – the difference is statistically significant in comparison with the HI ($p<0.05$); 1A – males who received enalapril; 1B – males who received losartan; 2A – females who received enalapril; 2B – females who received losartan.

performed using a Siemens Acuson X150 apparatus (Germany).

Statistical processing of the obtained research results was carried out using parametric (Student's t-test, Fisher F-test) and non-parametric methods (Mann-Whitney U-test, Wilcoxon's T-test) of variation statistics. Quantitative indicators that had a normal distribution, presented as mean (M) ± standard deviation (m). Differences were considered statistically significant at $p\leq 0.05$. The frequency of the revealed indicators in the studied groups was compared by calculating the odds ratio (OR) using the Past 3 program. For statistical analysis of the research results, the SPSS 13.0 software and Microsoft Excel 2013 were used.

During the study period, we followed by the “Rules of ethical principles for conducting scientific medical research with human participation”, approved by the Helsinki Declaration (1964-2013), ICH Principles GCP (1996), Council of Europe Convention on Human Rights and Biomedicine (from 04.04.1997), EU Council Directive No. 609 (24.11.1986), the International Ethics Guide for Biomedical Research involving people as subjects of the Council for International Organization of Medical Sciences (CIOMS).

Ethical clearance: The research was approved by ethical committee of I.M. Sechenov First Moscow State Medical University

Results

The clinical characteristics of the examined patients are shown in Table 1. The formed comparison groups did not significantly differ ($p>0.05$) by age, BMI, disease duration, heart rate, systolic and diastolic blood pressure (SBP, DBP), GFR and MAU.

The average SBP in males significantly decreased by 18.93% ($p<0.05$) by the end of the 12th week of hypertension therapy with enalapril, by 19.1% ($p<0.05$) with losartan without the presence of a statistically significant difference between the groups ($p>0.05$) (Table 2). But in females, the administration of losartan was more effective: at the end of the antihypertensive therapy, with the use of enalapril, SBP significantly decreased by 18.6% ($p<0.05$), while with losartan it decreased by 21.06% ($p<0.05$). There was a statistically significant difference in the decrease in SBP between the group of females receiving enalapril and losartan ($p<0.05$), as well as between the group of females and males receiving losartan ($p<0.05$).

With regard to DBP, it was possible to achieve a reliable decrease in all comparison groups by the end of treatment ($p<0.05$). In particular, the average DBP significantly decreased in males taking enalapril by 13.8% ($p<0.05$), in females – by 14.4% ($p<0.05$), in males taking losartan – by 14.3% ($p<0.05$), in females – by 15.48% ($p<0.05$) without the presence of a statistically significant intergroup difference in indicators ($p<0.05$).

When analyzing biochemical parameters in the dynamics of treatment in all groups, we didn't find statistically significant changes in the potassium blood content ($p>0.05$). However, against the background of antihypertensive therapy, the uric acid content in all the examined groups significantly decreased ($p<0.05$). The blood uric acid content decreased by 9.38% in males taking enalapril at the end of the 12th week of therapy ($p<0.05$), in males taking losartan – by 9.47% ($p<0, 05$) in females – by

Table 2. Dynamics of blood pressure, GFR, MAU and some biochemical parameters in the treatment process, M±m

Indicator	HI (n=25)	Group	Before treatment	After 12 weeks of treatment
SBP, mmHg	119.30±2.15	1A (n=25)	157.7±4.36*	127.85±2.07**/**
		2A (n=25)	158.13±2.25*	128.70±1.22**/**
		1B (n=25)	158.84±3.47*	128.52±1.16**/**
		2B (n=25)	157.21±3.08*	124.10±1.03**/**/**/#
DBP, mmHg	77.50±1.16	1A (n=25)	97.10±2.24*	83.72±1.27**/**
		2A (n=25)	97.48±2.01*	83.40±1.10**/**
		1B (n=25)	96.23±1.66*	82.47±1.16**
		2B (n=25)	97.14±1.23*	82.10±1.21**
Potassium in blood, mmol/l	4.17±0.31	1A (n=25)	4.61±0.20	4.58±0.32
		2A (n=25)	4.55±0.38	4.53±0.11
		1B (n=25)	4.47±0.16	4.49±0.26
		2B (n=25)	4.63±0.25	4.60±0.17
Uric acid, µmol/L	248.74±4.39	1A (n=25)	315.28±5.42*	285.72±4.78**/**
		2A (n=25)	297.3±4.61*	270.25±4.47**/**
		1B (n=25)	312.56±4.99*	282.94±5.23**/**
		2B (n=25)	298.10±5.05*	265.08±4.84**/**
GFR, ml/min/1.73m ²	109.56±3.08	1A (n=25)	80.81±1.44*	91.45±1.67**/**
		2A (n=25)	81.20±2.10*	91.70±1.89**/**
		1B (n=25)	82.03±1.86*	94.28±2.13**/**
		2B (n=25)	81.54±2.02*	95.30±1.85**/**
MAU, mg/day	1.85±0.74	1A (n=25)	28.03±0.95*	18.28±0.81**/**
		2A (n=25)	26.96±0.87*	18.35±0.73**/**
		1B (n=25)	27.46±1.01*	17.94±0.70**/**
		2B (n=25)	27.54±0.93*	16.12±0.62**/**

*Notes: * – the difference is statistically significant in comparison with the HI (p<0.05); ** – the difference is statistically significant in comparison with such indicator before treatment (p<0.05); *** – the difference is statistically significant in comparison with group 2A at the end of treatment (p<0.05); # – the difference is statistically significant in comparison with group 1B in the end of treatment (p<0.05); 1A – males who received enalapril; 1B – males who received losartan; 2A – females who received enalapril; 2B – females who received losartan.*

9.1% (p<0.05) and 11.08% (p<0.05), respectively. Besides, we didn't find statistically significant differences in the blood content of uric acid in our study groups (p>0.05).

Against the background of antihypertensive therapy, a statistically significant (p<0.05) positive dynamic was observed for an increase in GFR in all groups of patients. In particular, at the end of the treatment (12th week), GFR significantly increased in males taking enalapril by 11.65% (p<0.05), and in males taking losartan – by 12.99% (p<0.05), in females – by 11.45% (p<0.05) and 14.48% (p<0.05), respectively, without the presence of a statistically significant intergroup difference in the indicator (p>0.05).

When analyzing MAU in the dynamics of treatment,

a significant decrease (p<0.05) of this indicator was found in all comparison groups: at the end of the treatment, MAU decreased in males taking enalapril by 1.53 times (p<0.05), in females – 1.46 times (p<0.05), MAU decreased in males taking losartan by 1.54 times (p<0.05) and in females – by 1.71 times (p<0.05) without a statistically significant difference in treatment dynamics between the studied groups (p>0.05).

Of the adverse reactions, only dry cough was observed in 4 females and 1 male (OR=4.571; 95% CI [0.473-44.172]), who received enalapril.

Discussion

The data obtained as a result of the study indicate that in males aged 50-60 years, antihypertensive therapy using enalapril has the same effectiveness as using losartan, as evidenced by the absence of a statistically significant (p>0.05) intergroup difference in the levels of lowering SBP and DBP in males at the end of 12 weeks of treatment. However, in females aged 50-60, the use of losartan was more effective,

since at the end of treatment a statistically significant difference (p<0.05) was found for a SBP decrease between the group of females taking enalapril and the group taking losartan. Losartan is more effective for controlling blood pressure in females than in males, which is confirmed by the presence of a statistically significant difference (p<0.05) in reducing the SBP level at the end of treatment with losartan between males and females. To reduce DBP level, gender differences in the effectiveness of the studied drugs were not found (p>0.05). The results indicate a more effective use of losartan to reduce SBP, which is very important because increased SPB has the negative impact on target organs in hypertension. In all

comparison groups the periods of sustained decrease in blood pressure were the same.

Nowadays, there is no convincing evidence base regarding gender differences in the effectiveness of certain antihypertensive drugs. According to the results of numerous studies, effectiveness of blood pressure control was the same both with the use of ACE inhibitors and with the use of ARBs²³. However, most large-scale studies did not conduct a comparative analysis of the effectiveness of antihypertensive therapy depending on the gender of patients.

In Sweden, a large-scale study, which included 292,428 individuals aged 20+ (average age was 63.0 ± 13.0 years, females' ratio in the study 53%), established that females with hypertension were more often treated with ARBs and diuretics, which were more effective for this gender in relation to the correction of blood pressure, and males with ACE inhibitors and calcium channel blockers (CCBs)²⁴. A systematic analysis of 13 studies on the effectiveness of ACE inhibitors for the hypertension treatment and 9 studies – ARBs, which included 74 105 patients (39.1% of females), showed that ACE inhibitors may be more effective in males, but the difference in rates most of the studies analyzed were small [25]. In a large-scale study (n=11312, of which the proportion of males was 57% (n=6456), females – 43% (n=4856)) conducted in China, the combination of ARB and BCC was more effective in females than in males²¹.

Our results regarding the more effective use of losartan in females can be explained by gender differences in the pharmacokinetics of drugs, since the metabolism of the vast majority of antihypertensive drugs depends on the uptake of sex hormones, transporters, GFR, which is lower in females, the activity of metabolic enzymes, which is higher in females, features of the functioning of the cytochrome P450 system^{6,9,17, 26}. In particular, females are characterized by increased activity of CYP3A4, CYP2A6 and CYP2B6, while the activity of P-glycoprotein, CYP1A2, CYP2E1 is reduced, and in males – increased activity of CYP1A2, CYP2D6, CYP2E1⁹. In addition, females have a higher proportion of body fat with smaller sizes of internal organs, which also affects the distribution of drugs¹⁷.

According to our research, the frequency of ACE inhibitors side effects was higher for females: for

example, dry cough was observed in 4 females and 1 man (OR=4.571; 95% CI [0.473-44.172]), which is explained by lower GFR in females, higher metabolic enzyme activity, a smaller volume of distribution, and the hormonal background²⁷.

The higher efficiency of using losartan in females can be explained by the fact that females in menopause have an increased sensitivity of tissue RAAS due to increased renin levels and increased ACE expression on endothelial cells, excessive formation of AT-II, degradation of bradykinin, and a decrease in the synthesis of the main endothelium-relaxing and vasoprotective factor – nitrogen monoxide^{9,14,15,24,26}. Hypoestrogenemia that occurs during menopause contributes to the formation of an imbalance between AT-II and nitrogen monoxide, which caused to vasoconstriction and increasing of peripheral vascular resistance^{9,14,18}. The use of enalapril does not provide a complete blockade of RAAS activity, since it is not able to influence alternative ways of transforming angiotensin I (AT-I) into AT-II without the participation of ACE that occur in tissues^{9,14,15,18}. In contrast, ARBs (in our study, losartan) provide a more selective and complete blockade of the synthesis of AT-II, since they are inherently its antagonists and their blocking activity does not depend on the pathways of AT-II creation, and also does not affect the concentration of blood of bradykinin. Under conditions of estrogen deficiency during menopause, the intensity of the transformation of AT-I to AT-II increases, the sensitivity of receptors to AT-II increases significantly¹⁸, which suggests that antihypertensive therapy with ARB is more effective. In our study, we evaluated the treatment dynamics with losartan and enalapril by the MAU level, which is a prognostic factor of cardiovascular complications occurrence in patients with hypertension^{28,29}. In all comparison groups, at the end of treatment, a statistically significant decrease in the MAU level was observed ($p < 0.05$). In addition, at the end of treatment, patients with all the studied groups significantly increased GFR ($p < 0.05$). These data indicate the nephroprotective effect of therapy with these drugs. However, given that the study period was only 12 weeks, it is impossible to confidently state the organ-protective effect of enalapril and losartan.

A positive dynamic was also observed regarding the blood uric acid level. At the end of the antihypertensive

therapy, the uric acid level in the plasma significantly decreased in all comparison groups ($p < 0.05$). In this case, this is important, since all patients received hydrochlorothiazide as the second antihypertensive drug, prolonged use of which leads to increasing of uric acid level in the plasma, which was defined as an independent predictor of death from cardiovascular causes³⁰.

Conclusion:

The study found that antihypertensive therapy with losartan is more effective in females compared with enalapril, as evidenced by a significant decrease in SBP by 21.1% ($p < 0.05$) at the end of treatment with losartan in females versus 18.6% ($p < 0.05$) when using enalapril with the presence of a statistically significant intergroup difference in the indicator ($p < 0.05$). At the same time, antihypertensive therapy with enalapril and losartan was equally effective in males, as evidenced by SBP decrease in males by 18.9% ($p < 0.05$) and 19.1% ($p < 0.05$) without a statistically significant intergroup difference in the indicator ($p > 0.05$). In addition, a side effect in the

form of a dry cough when using enalapril was noted for 4 females and only 1 man (OR=4.571; 95% CI [0.473-44.172]). Our results should be taken into account when choosing the optimal regimens of antihypertensive therapy in the treatment of patients with arterial hypertension.

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Authors contribution:

T.D.C. recruited patients; collected samples and clinical data. T.D.C. and O.P. designed and supervised the study and carried out the statistical analyses, interpreted results, and wrote the article. A.B. and N.L. carried out the statistical analyses, participated in compiling and editing. All authors agreed with the results and conclusions.

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