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LONG-TERM RESULTS OF SURGICAL TREATMENT IN PATIENTS WITH TOXIC GOITER AND SEVERE THYROTOXICOSIS

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ABSTRACT

Introduction. The surgical treatment of goiter with severe thyrotoxicosis may lead to an improvement of the general condition of the patient, and amelioration of the clinical manifestations of thyrotoxic cardiomyopathy.

The aim of the study was to evaluate the long-term results of surgical treatment in patients with toxic goiter and severe thyrotoxicosis, including the study of changes in cardiac activity and the level of physical activity.

Materials and methods. The study was conducted in 123 patients with toxic goiter and severe thyrotoxicosis treated surgically. The duration of thyrotoxicosis ranged from 18 to 74 months. Before the surgical treatment and one year after it, structural and functional changes of the heart were studied by echocardiography and electrocardiogram, and physical activity according to the six-minute walk test. The long-term effects of

RÉSUMÉ

Résultats à long terme du traitement chirurgical des patients atteints d'une goitre toxique et d'une thyrotoxicose grave

Introduction. Le résultat du traitement chirurgical du goitre atteint d'une thyrotoxicose sévère peut être une amélioration de l'état général et de l'activité physique, une diminution ou l'élimination des manifestations cliniques de la cardiomyopathie thyréotoxique.

Le but de l'étude. Étudier les résultats à long terme du traitement chirurgical des patients atteints de goitre toxique avec une thyréotoxicose sévère, et aussi des changements de l'activité cardiaque et de l'activité physique.

Matériaux et méthodes. L'étude a été menée chez 123 patients atteints de goitre toxique avec une thyréotoxicose sévère traités chirurgicalement. La durée de la thyrotoxicose variait de 18 à 74 mois. Avant le

treatment were considered good, satisfactory, unsatisfactory and ineffective.

Results. The results of surgical treatment depend on the severity of the manifestations of thyrotoxic cardiomyopathy. Good and satisfactory results were obtained in 44.7% cases, unsatisfactory results in 32.5% and ineffective treatment was found in 22.8% cases.

Conclusions. The surgical treatment of patients with toxic goiter and severe thyrotoxicosis allows eliminating thyrotoxicosis and in some patients the rhythm disorders, reducing the intensity of clinical manifestations of thyrotoxic cardiomyopathy and improving the capacity of physical activity.

Keywords: toxic goiter, severe thyrotoxicosis, surgical treatment, long-term results.

List of abbreviations: TG - toxic goiter; BGD -Basedow-Graves' disease; NTG - nodular toxic goiter; MTG - mixed toxic goiter; TT - thyrotoxicosis; HF heart failure; AF -atrial fibrillation; ECG - electrocardiography, 6 MWT - six-minute walk test.

Introduction

Long-term results of surgical treatment in patients with toxic goiter (TG) are evaluated by general surgical complications (postoperative bleeding, infiltration, suppuration), specific complications (laryngeal nerve injuries, phonation disorders and postoperative hypoparathyroidism), thyroid residual function, relapses of goiter and thyrotoxicosis (TT)¹⁻⁵.

The result of surgical treatment (thyroidectomy) in TT, with full compensation of postoperative hypothyroidism with thyroxine preparations, can be an improvement of the general condition and physical activity capacity (effective treatment) or improvement may not occur, it remains at the level before surgery and/or worsens (ineffective treatment).

Because of ineffective treatment, life prognosis is impeded⁶, secondary to complications of TG, including atrial fibrillation (AF)7, heart failure (HF)8, structural and functional changes in the heart muscle⁹⁻¹¹.

After medical or surgical treatment of TT and the achievement of euthyroidism, sinus rhythm is restored in 19-66% of the patients who had AF¹². Functional and structural changes of the heart in case of thyrotoxicosis, in particular AF, are the cause of the increase in mortality from embolism in these patients, 1.2-1.4 times compared to the general population¹³⁻¹⁶.

traitement chirurgical et un an après, les modifications structurelles et fonctionnelles du cœur ont été étudiées selon les indicateurs de l'échocardiographie et de l'ECG, l'activité physique selon le test de marche de six minutes. Les effets à long terme du traitement ont été évalués par les gradations développées: bons résultats, satisfaisants, insatisfaisants et traitement inefficace.

Résultats. Les résultats du traitement chirurgical dépendent de la gravité des manifestations de la cardiomyopathie thyréotoxique. De bons et satisfaisants résultats ont été obtenus dans 44,7% des cas, un résultat insatisfaisant dans 32,5% et un traitement inefficace a été trouvé dans 22,8% des cas.

Conclusions. Il est établi que le traitement chirurgical des patients atteints de goitre toxique avec une thyréotoxicose sévère permet d'éliminer la thyréotoxicose et chez certains patients - les troubles de l'activité cardiaque rythmique, réduisant l'intensité des manifestations cliniques de la cardiomyopathie thyréotoxique, améliorant l'activité physique et l'activité générale.

Mots-clés: goitre toxique, thyrotoxicose sévère, traitement chirurgical, résultats à long terme.

THE OBJECTIVE OF THE STUDY was to evaluate the long-term results of surgical treatment in patients with toxic goiter and severe thyrotoxicosis, including changes in cardiac activity and physical activity capacity.

MATERIALS AND METHODS

The study was conducted in 123 surgically treated patients with severe TG, admitted in the surgical department of Ternopil City Municipal Hospital N°1, Ukraine, from May 5, 2003 to August 17, 2018. The age of the patients ranged from 21 to 74 years. The duration of TT ranged from 18 to 74 months. Indications for surgical treatment were frequent relapses of TT, progression of thyrotoxic cardiomyopathy on the background of thyro-static therapy, with the development of heart rhythm disorders and heart failure. Thyrotoxicosis was caused by Basedow-Graves' disease (BGD) (82 cases), nodular toxic goiter (NTG) (29 cases), and mixed toxic goiter (MTG) (12 cases) (Table 1).

All the patients underwent general clinical examination, ultrasonography, determination of the level of thyroid-stimulating hormone (TSH), free thyroxine (T₄₁), antibodies to TSH receptors and thyroperoxidase anti-body (AbTPO), electrocardiogram (ECG), daily Holter ECG. Ultrasonography was performed in the mode 2D; the results were evaluated in comparison

Age of _		Total							
patients (years)	BC (n=0			ГG :29)	M′ (n=		(n=123)		
	female	male	female	male	female	male	female	male	
Under 30	19	1					19	1	
31-40	29	3					29	3	
41-50	16	3	5		1		22	3	
51-60	8	1	10	2	3	1	21	4	
61-70	2		7	1	6		15	1	
>70			4		1		5		
Total	74	8	26	3	11	1	111	12	

Table 1. Distribution of patients by age, sex and causes of thyrotoxicosis.

with the average standards presented in the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Research¹⁷. Changes in the severity and functional class of HF were evaluated according to the criteria of the 6MWT¹⁸⁻²². At the same time, the changes in heart rate and respiratory movements per minute were calculated not in absolute terms, but as a percentage of increase: 100% indicators were taken before the test.

Criteria for inclusion in the study: patients with BGD, nodular and mixed toxic goiter with severe thyrotoxicosis with recurrent course and ineffective drug treatment, heart failure NYHA class II, III.

Exclusion criteria – patients with BGD, nodular and mixed toxic goiter with severe thyrotoxicosis, recurrent course and ineffective medical treatment, NYHA class $IV^{23,\,24}$.

The patients were evaluated upon admission, after achieving medical euthyroidism, and one year after the surgical treatment. To analyze the long-term results of surgical treatment, the data obtained one year after surgery were compared with preoperative data.

Drug treatment before surgery consisted in antithyroid drugs, in doses that ensured the achievement of euthyroidism, and β -blockers. In individual cases, symptomatic therapy was also used. Treatment of patients with AF was carried out according to the algorithmic approach of the treatment of AF in hyperthyroidism of the European Society of Cardiology (ESC) 2016²⁰.

According to recommendations²²⁻²⁴ and 6MWT test results, patients were divided into two groups: with HF NYHA class II (95 patients) and HF NYHA class III (28 patients). The group of patients with HF NYHA class II included 61 patients (74.4%) with BGD, 24 patients (82.8%) with NTG and 10 patients (83.3%) with MTG. Correspondingly, HF NYHA class III and BGD was encountered in 21 patients

(25.6%), NTG in 5 patients (17.2%), MTG in 2 patients (16.7%).

In the group of patients with HF NYHA class II, the changes in the parameters of the past 6MWT distance were in the range from 324 to 425 m. The distance travelled by an individual depends on his physical activity capacity, which, in turn, is determined by the severity of functional and structural changes in the heart. Considering this, to study the effects of functional and structural changes in the heart on long-term results of surgical treatment of TG, according to the 6MWT distance, the first group of patients (with HF NYHA class II) was divided into three subgroups. The first subgroup included 12 patients who walked more than 395 m, the second one included 19 patients who walked a distance ranging from 381 to 390 m, and the third - 64 patients, who walked from 324 to 374 m. In patients of the second group, the distance travelled at 6MWT was less than 300 meters.

The long-term results were assessed by changes in the general condition of the patients, the severity and functional class of heart failure, structural and functional alterations of the heart, and the cardiac rhythm. According to the recommendations of the European Society of Cardiology²⁰, the long-term results of surgical treatment of patients with goiter and TT were considered as good, satisfactory, unsatisfactory results and ineffective treatment.

A good result was considered when patients noted a significant improvement in the general condition or felt healthy. The 6MWT distance travelled was at least 425 m. The functional class of heart failure improved, cardiac rhythm disorders were not determined and systolic and diastolic functions of the heart (by echocardiography) were normal.

When patients noted an improvement of the general condition, a satisfactory result was considered. At the same time, the severity and functional class of heart failure did not change, the 6MWT

distance increased and was at least 385 m. The severity of clinical manifestations has decreased.

If the result was unsatisfactory, the patients noted an improvement in their general condition, the 6MWT distance significantly increased in some cases by 5 to 19 meters and the severity of clinical manifestations of rhythm disturbances decreased in some patients. Structural and functional changes of the heart were unreliable, and the severity and functional class of heart failure remained unchanged.

Treatment was considered ineffective in patients who did not notice an improvement in their general condition, the severity and functional class of heart failure did not change, and there were no positive changes in thyrotoxic arrhythmias, 6MWT.

Statistical processing of the results was performed with Statsoft STATISTICA software package, using parametric and nonparametric methods. When assessing the difference in quantitative indicators between the groups, the Student's criterion was applied. The difference was considered significant at p<0.05.

After preoperative preparation, performed in order to achieve euthyroidism, the patients were surgically treated, under general anesthesia. Thyroidectomy was the method of choice. In the postoperative period, replacement therapy was prescribed with thyroxine in doses that ensured the state of euthyroidism, with the level of TSH within the reference values.

The study was performed according to the requirements of the Statute of Ukrainian Association for Bioethics and the GCP norms (1992), requirements and norms of ICH GLP (2002), typical ethics provisions of the Ministry of Public Health of Ukraine dated February 13, 2006.

RESULTS AND DISCUSSION

The study has shown that a decrease of the 6MWT distance was combined with an increase in the age of patients and the duration of TG disease. Thus, in the first subgroup, the age of patients and the duration of the disease were the lowest, and the average distance walked was the highest. In other subgroups, the age of patients and the duration of the disease increased and were the largest in the fourth subgroup (Table 2), and the distance walked, respectively, decreased.

Studies have shown that in response to exercise, compared to the physiological norms, in the selected subgroups of patients, the distance travelled by 6MWT decreased, and the values of oxygen consumption and tachycardia decreased. The rate of increase in heart rate also decreased, and tachypnea and Borg scores increased (see Tables 2, 3). A simultaneous

decrease in the increase in heart rate and aggravation of tachypnea are signs of poor exercise tolerance and progression of the severity of heart failure. In such cases, the heart muscle has no reserves to increase the heart rate and ensure adequate blood supply, and increasing hypoxia compensates for tachypnea.

In the study period, one year after the surgical treatment, the indices of 6MWT test compared with the previous data significantly increased in the first and second subgroups, which was reflected in the improvement of the general condition of the patients. Patients of the third subgroup and the second group did not present significant changes in the studied parameters (Tables 2, 3). The general condition of the patients of the third subgroup slightly improved, and in the patients of the second group, it remained unchanged.

After preoperative preparation, patients in both groups revealed structural and functional changes in the heart. The ejection fraction was not changed in patients of the first subgroup, but in the second and third subgroups and in the cases of the second group it decreased (p<0.05). The final diastolic size of the left ventricle in patients of the second and third subgroups and the second group increased (p<0.05). The same pattern of changes also applied to the final systolic size of the left ventricle. The index of muscle mass of the left ventricle increased: in patients of the first subgroup, the changes were not significant and in the second and third subgroups the increase was significant (pp<0.05). In patients of the second group, this indicator was within or below the normal value. The diameter of the left atrium in patients of all subgroups was larger than normal: it increased significantly from 38.20 ± 0.16 to 45.70 ± 0.22 mm (p<0.05). Such dynamics of changes in echocardiography of the left heart indicate the severity and progression of heart failure against the background of thyrotoxic cardiomyopathy (Table 4).

One year after surgical treatment, the structural and functional indicators of cardiac activity in the patients of the first, second and third subgroups (p<0.05) improved compared to the previous data and did not change significantly in the patients of the second group. Similar changes in structural and functional indicators of cardiac activity in the treatment of thyrotoxicosis were revealed by Sviridenko et al²⁵ and Oliveros-Ruiz et al²⁶.

Thus, EF in patients of the first subgroup decreased, and in patients of the second and third subgroups increased (p<0.05) and did not change in patients of the second group. Indicators of the final diastolic and systolic dimensions of the left ventricle (p<0.05) significantly decreased (Table 4).

Table 2. Age of patients, duration of disease, 6MWT distance
and oxygen consumption in the subgroups of patients.

Patients groups and subgroups		ients groups and subgroups Age			ce travelled ters)	Test VO ₂ (ml/kg/min)		
		(years)	(months)	1	2	1	2	
First	First subgroup (n=12)	27.30± 2.53	23.10± 1.18	400.00± 4.18	449.00± 4.43 ²	16.80± 0.11	18.70± 0.13 ²	
group (n=95)	Second subgroup (n=19)	34.30± 2.75 ¹	27.90± 0.77¹	385.00± 2.12 ¹	403.00± 3.71 ^{1, 2}	15.90± 0.16¹	17.00± 0.19 ^{1, 2}	
	Third subgroup (n=64)	53.70± 0.67¹	45,90± 1.23 ¹	359.00± 4.23 ¹	373.00± 4.86 ^{1, 2}	15.40± 0.31	15.80± 0.48¹	
Second group (n=28)		66.30± 1.27¹	48.80± 2.35 ¹	285.00± 2.56 ¹	289.00± 2.04¹	13.60± 0.12¹	13.80± 0.14¹	

Legend (Tables 2-6): 1 – results of studies after preoperative preparation; 2 – results of studies one year after surgical treatment; ¹ – compared to the indicators of the previous subgroup; ² – compared to the indicators after preoperative preparation (significant changes are marked with symbols^{1, 2}, unreliable changes – without a mark).

Table 3. The increase in heart rate and respiration and the Borg score in the patient subgroups

Patie	ents groups and subgroups	Increase in	heart rate (%)		ase in y rate (%)	Borg scale (score)		
		1	2	1	2	1	2	
First	First subgroup	19.10±	16.40±	11.60±	8.70±	1.90±	0.90±	
	(n=12)	0.28	0.41²	0.26	0.28 ²	0.13	0.13 ²	
group	Second subgroup	15.70±	14.30±	13.70±	11.50±	2.10±	1.40±	
(n=95)	(n=19)	0.71 ¹	0.46 ¹	0.28 ¹	0.19 ^{1,2}	0.02	0.19 ²	
Third subgroup (n=64)		12.30±	11.90±	14.80±	13.70±	3.30±	2.90±	
		0.27 ¹	0.48¹	0.22¹	0.44¹	0.22¹	0.49¹	
S	Second group (n=28)	6.80± 0.30¹	7.30± 0.54 ¹	18.90± 1.75¹	18.60± 1.62¹	5.90± 0.23 ¹	5.80± 0.19¹	

Table 4. Structural and functional changes of the heart.

Patients groups and subgroups		Ejection fraction (%)		Final diastolic size of the left ventricle (mm)		Final systolic size of the left ventricle (mm)		cle mas	cular mus- s index m²)	The diameter of the left atrium (mm)		
		1	2	1	2	1	2	1	2	1	2	
	First subgroup (n=12)	58.1± 0.34	54.7± 0.22 ²	49.2± 0.34	46.70± 0.21 ²	37.30± 0.25	31.40± 0.19 ²	106.90± 0.33	95.30± 0.22 ²	38.20± 0.16	33.80± 0.19 ²	
First group (n=95)	Second subgroup (n=19)	51.2± 0.33¹	53.1± 0.29 ^{1, 2}	50.5± 0.31	47.80± 0.27 ^{1, 2}	42.10± 0.25 ¹	32.50± 0.21 ^{1, 2}	118,20± 0.32¹	103.50± 0.21 ^{1, 2}	40.90± 0.19¹	35.20± 0,18 ^{1, 2}	
	Third subgroup (n=64)	41.4± 0.37 ¹	49.5± 0.48 ^{1, 2}	52.7± 0.37¹	51.10± 0.34 ^{1, 2}	46.70± 0.36 ¹	39.10± 0.31 ^{1, 2}	123.70± 0.33 ¹	117.90± 0.38 ^{1, 2}	43.80± 0.39¹	41.30± 0.57 ^{1, 2}	
	nd group n=28)	37.9± 0.23 ¹	38.6± 0.22¹	54.1± 0.19¹	53.70± 0.24 ¹	49.50± 0.39¹	47.70± 0.43 ¹	105.30± 0.23 ¹	105.10± 0.21¹	45.70± 0.22 ¹	45.30± 0.24 ¹	

After drug preparation for surgery, cardiac arrhythmias in patients of the first subgroup were represented by supraventricular (9) and ventricular extrasystoles (3), which were not detected one year after the surgical treatment. In patients of the second subgroup, supraventricular extrasystoles – in 10 cases and ventricular extrasystoles – in 5 patients, atrial

fibrillation in 4 patients: with normal heart rate (3) and rapid heart rate (1), after medical preparation. One year after surgery, 4 patients had no rhythm abnormalities, 4 patients had single extrasystoles, and 2 paired extrasystoles. Frequent (about 1000 extrasystoles per day) ventricular extrasystoles in 4 patients changed individually (less than 22 extrasystoles per

Table 5. Changes in supraventricular tachycardia, supraventricular and ventricular extrasystoles.

									Extras	systoles					
		- Tachycardia -		supraventricular							ventricular				
Patien	ts groups and subgroups			frequent		þai	ired	l group		frequent single		paired		gr	оир
•		1	2	1	2	1	2	1	2	1	2	1	2	1	2
	First subgroup (n=12)	0	0	6	0	2	0	1	0	2	0	1	0	0	0
First group (n=95)	Second subgroup (n=19)	0	0	7	3	3	1	0	0	5	1	0	0	0	0
(11)))	Third subgroup (n=64)	22	0	9	3	3	0	3	0	7					
Se	cond group (n=28)	28	28	0	0	0	0	0	0	0	0	0	0	0	0

Table 6. Changes in atrial fibrillation and flutter.

				Atrial flutter					
Patients groups and subgroups		Normal	heart rate	Brady	cardia	Rapid h	eart rate		
		1	2	1	2	1	2	1	2
First	First subgroup (n=12)	0	0	0	0	0	0	0	0
group	Second subgroup (n=19)	3	2	0	0	1	0	0	0
(n=95)	Third subgroup (n=64)	0	31	0	0	37	9	5	2
S	Second group (n=28)		1	0	0	19	21	9	6

Table 7. Long-term results of surgical treatment

Result of treatment	Number of cases and percentage; severity and FC of HF in patients
Good	n=12 (9.8%); HF NYHA class I
Satisfactory	n=43 (34.9%); HF NYHA class II
Unsatisfactory	n=40 (32.5%); HF NYHA class II
Ineffective treatment	n=28 (22.8%); HF NYHA class III

day). In 2 of 4 patients with atrial fibrillation, the sinus rhythm recovered, in one patient tachycardia changed to normo-cardia (Tables 5, 6), and in the other 2 patients it did not change.

Patients of the third subgroup, before surgery, had heart rhythm disorders in the form of extrasystoles, atrial fibrillation and atrial flutter. Extrasystoles were noted in 22 patients: supraventricular in 15 patients and frequent solitary ventricular extrabeats in 7 patients. From the supraventricular extrasystoles, 9 patients had frequent isolated extrasystoles, 3 patients paired extrasystoles, and 3 patients with bigeminy and trigeminy. Atrial fibrillation was diagnosed in 37 patients, and atrial flutter in 5 patients. One year after surgery, changes in cardiac rhythm disorders occurred over a wide range: frequent single supraventricular and ventricular extrasystoles disappeared; paired supraventricular extrasystoles in 2 patients disappeared, and one patient presented frequent single extrasystole; bigeminy in one patient disappeared, and in 2 patients switched to frequent single extrasystoles. The changes in the rhythm of patients with atrial fibrillation with rapid heart rate were as follows: in 31 cases it changed to normo-cardia, and in 6 cases it remained unchanged. Atrial flutter in 3 of 5 patients changed to atrial fibrillation, but did not change in two patients.

In patients of the second group, after the preoperative preparation, the most severe disorders of cardiac activity were registered (see Tables 5, 6). Atrial fibrillation with rapid heart rate was determined in 19 patients, and atrial flutter in 9 patients. One year after the surgical treatment, atrial fibrillation in one case changed from rapid heart rate to normal heart rate, and in 18 patients it remained unchanged. In 3 patients, atrial flutter changed to atrial fibrillation with rapid heart rate, and in 6 patients remained unchanged.

The results were used to assess the long-term results of treatment (Table 7). A good treatment result was obtained in patients of the first subgroup, in which the 6MWT distance before surgical treatment

ranged from 395 to 408 m, and after it to more than 425 m. Accordingly, the satisfactory result was in 19 patients of the second subgroup, in which the 6MWT distance travelled before surgical treatment was in the range from 381 to 390 m, and one year after it - to more than 398 m. A satisfactory result of treatment was found in 24 patients of the third subgroup, in which the 6MWT distance travelled before surgical treatment ranged from 361 to 374 m, and one year after it to at least 385 m. An unsatisfactory result of treatment was observed in 40 patients of the third subgroup, in which the 6MWT distance travelled before surgical treatment was 327-353 m, and one year after it increased in some cases by 15-19 meters. Ineffective treatment was found in patients of the second group (Table 7).

The study showed that the surgical treatment of TT had a positive effect (good and satisfactory results) only in 52 of 123 patients (44.7%). These results are alarming about the correctness of the therapeutic strategy and indications of the surgical treatment in patients with TG.

Fierro et al²⁷ consider that factors such as patient's age and duration of drug treatment have a significant impact on the long-term results of surgical treatment of toxic goiter, on the recovery of sinus rhythm especially. According to Biondi²⁸, the return to sinus rhythm occurs more often in successfully treated hyperthyroid patients under 50 years old with newly diagnosed heart rhythm disorders. Long-term treatment (more than 30 months) with thyro-static drugs in TG patients and thyrotoxicosis with cardiac disorders worsens the long-term results of surgical treatment²⁹⁻³¹.

Conclusions

The surgical treatment of patients with toxic goiter and severe thyrotoxicosis leads to positive results in 44.7% of cases: it eliminates thyrotoxicosis, reduces the intensity of clinical manifestations of thyrotoxic cardiomyopathy and improves cardiac activity, physical activity capacity and general condition of the patients. The long-term results of surgical treatment in patients with severe thyrotoxicosis depend on the duration of drug therapy for thyrotoxicosis and the age of the patients. The test for predicting the long-term results of surgical treatment in patients with toxic goiter is the length of the distance covered at the 6MWT. In patients with toxic goiter and signs of severe thyrotoxicosis, the main indication for surgical treatment is the presence of thyrotoxic cardiomyopathy with cardiac disorders.

Author contributions

Conceptualization, V.O.S. and M.I.S.; methodology, O.V.S.; software, I.M.P.; validation, G.S.K. and V.V.K.; formal analysis, O.V.S. and H.P.H.; investigation, V.V.M., V.V.T., and H.H.; resources, N.P.T.K.; data curation, A.A.P. and O.V.S.; writing – original draft preparation, O.V.S. and H.P.H.; writing – review and editing, V.O.S., O.V.S. and M.I.S.; visualization, V.V.K. and A.A.P.; supervision, G.S.K. and V.V.K.; project administration, N. P.T. All the authors read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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