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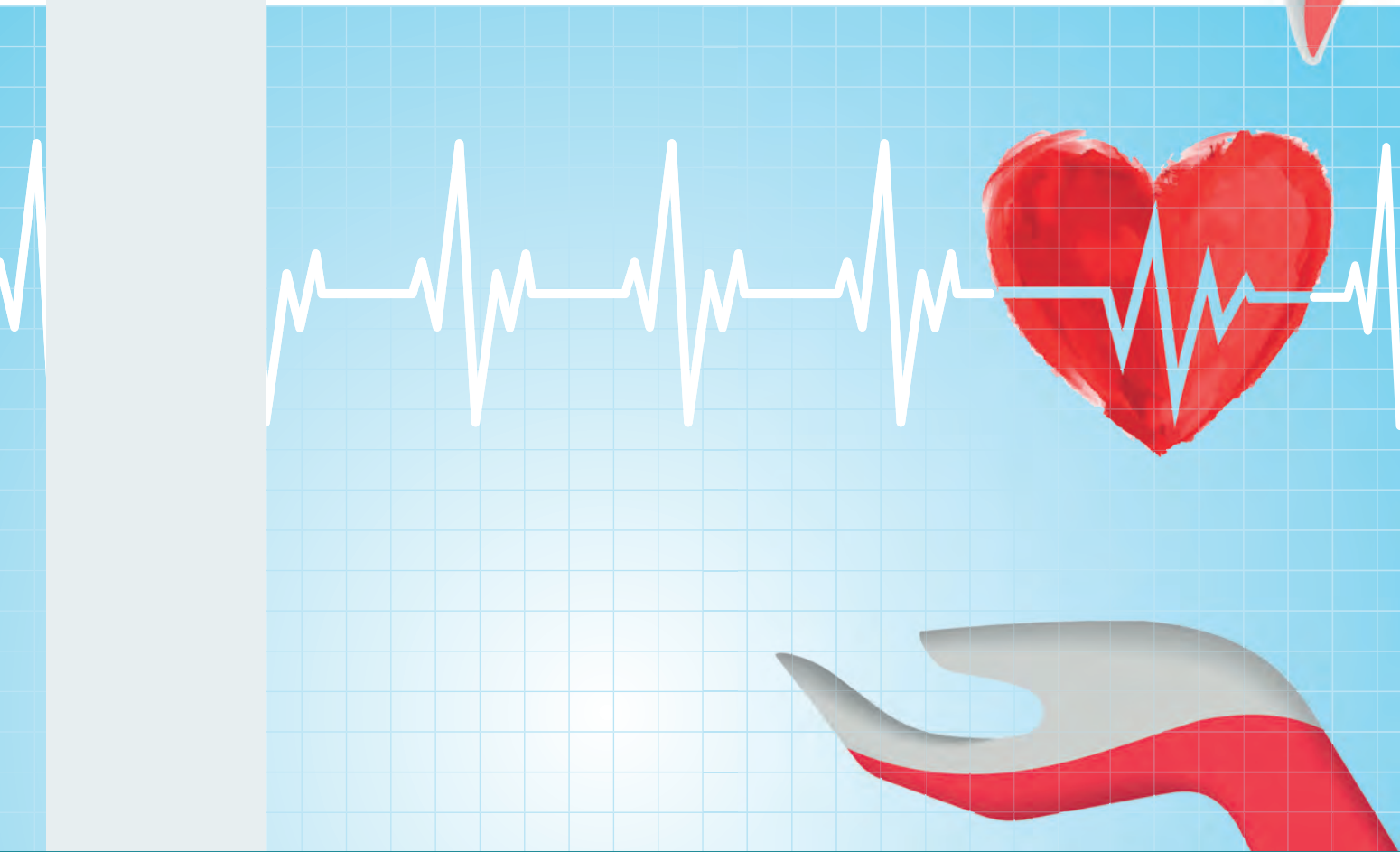

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Brugada syndrome: variability of clinical and genetic characteristics

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ABSTRACT

AIM: To evaluate the clinical characteristics of patients with diverse genetic variants of Brugada syndrome.

MATERIALS AND METHODS: 24 patients (17 male and 7 female) aged 18 to 55 years (median age 32.5 [20; 42] years) with a pattern of Brugada syndrome on electrocardiogram were observed for 3 years. From their ECGs, a type 1 pattern was found in 9 (37.5%) of these patients, type 2 pattern in 14 (58.3%) and type 3 pattern only in 1 patient. The clinical and instrumental study included 12-lead electrocardiogram, 24-hour Holter electrocardiogram monitoring, provocative drug testing with intravenous administration of sodium channel blockers (novocainamide), electrophysiologic study according to indications, genealogical history collection and family history of sudden cardiac death, transthoracic echocardiography and cardiac magnetic resonance imaging to detect structural myocardial changes. High-throughput sequencing was utilized to search for mutations in genes linked to the onset of channelopathies and other inherited rhythm disorders.

RESULTS: In 15 (62.5%) of the 24 probands included in the study, variants of the nucleotide sequence of pathogenicity classes III–V according to The American College of Medical Genetics and Genomics criteria (2015) were found in genes encoding sodium (*SCN5A*, *SCN10A*) and potassium (*KCNE3*, *KCNJ2*, *KCNJ8*, *KCNA5*) channels, as well as in *HCN4* and *SNTA1* genes linked with these channels. Moreover, 3 variants were identified in *ANK2* gene associated with ankyrinopathies, and 3 variants in *DSP* and *DES* genes connected with arrhythmogenic right ventricular cardiomyopathy. Four genetic variants in *SCN5A* gene were of pathogenicity classes IV and V, the rest were variants of uncertain clinical significance (class III). Six (40.0%) of the 15 genotype-positive patients had several genetic variants. The most severe form of the disease, manifested by the development of ventricular fibrillation with successful resuscitation and subsequent cardioverter-defibrillator implantation, was observed in patients with mutations in *SCN5A*, *SCN10A* genes. Recurrent syncope, polymorphic ventricular tachycardia induced by programmed ventricular stimulation during electrophysiologic study, followed by cardioverter-defibrillator implantation were observed in patients with variants *KCNJ8* and *HCN4*, *DES* and *MYH11*. In 2 patients with clinical manifestations, no mutations were identified. 13 (54.2%) patients were asymptomatic, while 3 of them had pathogenic and likely pathogenic mutations in *SCN5A* gene, as well as variants of uncertain clinical significance.

CONCLUSION: Thus, this study examined various genetic variants in patients with Brugada syndrome based on their clinical manifestation. The impact of the genotype on the Brugada syndrome phenotype is not unambiguous. The most severe form of the disease with the development of ventricular fibrillation and successful resuscitation with subsequent cardioverter-defibrillator implantation was observed mainly in patients with variants in several genes (*SCN5A* and *JUP*, *KCNJ8* and *HCN4*, *DES* and *MYH11*). This substantiate the idea that Brugada syndrome, along with monogenic, may also have a polygenic nature of the disease, in which the clinical phenotype is determined by variants in respective genes linked to the onset of cardiovascular disorders.

Keywords: Brugada pattern; genotypic and phenotypic diversity; provocative drug tests.

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Синдром Бругада: вариабельность клинических и генетических характеристик

С.М. Комиссарова[1], Н.Н. Чакова[2], Н.М. Ринейская[1], С.С. Ниязова[2], Т.В. Долматович[2], В.Ч. Барсукевич[1], Л.И. Плащинская[1]

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АННОТАЦИЯ

Цель исследования — оценить клиническую характеристику у пациентов с различными генетическими вариантами синдрома Бругада.

Материалы и методы. Обследовано 24 пациента (17 мужского и 7 женского пола) в возрасте от 18 до 55 лет (медиана возраста 32,5 [20; 42] года) с паттерном синдрома Бругада на электрокардиограмме, наблюдаемых в течение 3 лет. У 9 (37,5 %) пациентов зарегистрирован спонтанный паттерн электрокардиограммы 1 типа, у 14 (58,3 %) — паттерн электрокардиограммы 2 типа, у 1 — паттерн электрокардиограммы 3 типа. Клинико-инструментальное исследование включало регистрацию электрокардиограммы в 12 отведениях, суточное мониторирование электрокардиограммы, проведение провоцирующего теста с блокатором натриевых каналов новокаинамидом, выполнение эндокардиального электрофизиологического исследования по показаниям, сбор генеалогического анамнеза с оценкой электрокардиограмм всех членов семьи с выявлением случаев внезапной сердечной смерти в семье или наличия семейной формы заболевания, эхокардиограммы и магнитно-резонансной томографии сердца для исключения структурных изменений миокарда. Поиск мутаций в кодирующих последовательностях генов, ассоциированных с развитием каналопатий и других наследственных нарушений ритма, проводили методом высокопроизводительного секвенирования.

Результаты. У 15 (62,5 %) из 24 включенных в исследование пробандов выявлены варианты нуклеотидной последовательности III–V классов патогенности согласно критериям Американского общества медицинской генетики (2015) в генах, кодирующих натриевые (*SCN5A*, *SCN10A*) и калиевые (*KCNE3*, *KCNJ2*, *KCNJ8*, *KCNA5*) каналы, а также в генах *HCN4* и *SNTA1*, ассоциированных с этими каналами. Кроме того, выявлено 3 варианта в гене *ANK2*, ассоциированном с анкиринопатиями, и 3 варианта в генах *DSP* и *DES*, ассоциированных с аритмогенной кардиомиопатией правого желудочка. Четыре генетических варианта в гене *SCN5A* были IV и V классов патогенности, остальные являлись вариантами с неопределенной значимостью (VUS, III класс). Шесть (40,0 %) из 15 генотип-положительных пациентов имели несколько генетических вариантов. Наиболее тяжелая форма заболевания, манифестирующая развитием фибрилляции желудочков с успешным проведением реанимационных мероприятий и последующей имплантацией кардиовертера-дефибриллятора, наблюдались у пациентов с мутациями в генах *SCN5A*, *SCN10A*. Рецидивирующие синкопальные состояния, полиморфная желудочковая тахиаритмия/фибрилляция желудочков, индуцированная программируемой стимуляцией желудочков при эндокардиальном электрофизиологическом исследовании, с последующей имплантацией кардиовертера-дефибриллятора наблюдались у пациентов с вариантами *KCNJ8* и *HCN4*, *DES* и *MYH11*. У 2 пациентов с клиническими проявлениями мутаций не выявлено. 13 (54,2 %) пациентов были бессимптомными, при этом у 3 из них обнаружены патогенные и вероятно патогенные мутации в гене *SCN5A*, а также вариант VUS в этом же гене.

Заключение. Изучены клинические проявления у пациентов с различными генетическими вариантами синдрома Бругада. Влияние генотипа на фенотип синдрома Бругада не однозначно. Наиболее тяжелая форма заболевания с развитием фибрилляции желудочков и успешным проведением реанимационных мероприятий с последующей имплантацией кардиовертера-дефибриллятора наблюдалась преимущественно у пациентов с вариантами в нескольких генах (*SCN5A* и *JUP*, *KCNJ8* и *HCN4*, *DES* и *MYH11*). Полученные данные подтверждают идею о том, что синдром Бругада наряду с моногенным может иметь и полигенный характер заболевания, при котором клинический фенотип обусловлен вариантами в нескольких генах, ассоциированных с сердечно-сосудистой патологией.

Ключевые слова: паттерн синдрома Бругада; генотипическое и фенотипическое разнообразие; провокационные пробы.

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ЭКО•ВЕКТОР

BACKGROUND

Brugada syndrome (BrS), an inherited cardiac channelopathy first diagnosed in 1992, is still considered a complex disorder in terms of diagnostics, arrhythmia risk prediction, pathophysiology, and treatment. It is electrophysiologically characterized by the typical electrocardiogram (ECG) pattern of BrS type 1, demonstrating *ST*-segment elevation by 2 mm, followed by a negative *T*-wave in at least one or two right precordial leads, and a high incidence of life-threatening arrhythmic events in the absence of structural heart diseases [1]. BrS may be the cause of 4%–12% of all sudden cardiac death (SCD) cases and up to 20% of SCD cases due to polymorphic ventricular tachyarrhythmias (VTs) or ventricular fibrillation (VF) [2]. The prevalence of BrS ranges from 1:5000 to 1:2000, with the highest incidence in Asians [3].

The onset of symptoms often occurs at a young age, and SCD or SCD with successful resuscitation may be the first clinical manifestation of BrS. Although BrS appears to occur equally in men and women, most patients with clinically significant BrS are men [4]. Patients more often experience fever or conditions that increase vagal tone, including sleep. The diagnosis is made by identifying the BrS type 1 ECG pattern, which can be noted either spontaneously or over the course of provocative testing with a sodium channel blocker such as ajmaline, flecainide, pilsicainide, or novocainamide [5]. These antiarrhythmic drugs, by inhibiting the fast sodium current (INa), increase the imbalance between inward and outward currents during the early phases of the action potential (AP), thereby eliciting the phenotypic expression of BrS. However, the disease is asymptomatic in most patients. Owing to the fact that the inducibility of VT/VF during the endocardial electrophysiological study (EEPS) is associated with the high risk of future ventricular arrhythmias, patients with BrS and induced VT/VF in the course of EEPS, consequently, have an implantable cardioverter defibrillator (ICD) inserted [6].

Clinical variability in BrS may be primarily due to genetic heterogeneity. BrS is most commonly caused by changes in *SCN5A* gene, which is responsible for the synthesis of the alpha subunit of the myocardial sodium channel Nav1.5. It accounts for 15%–30% of confirmed BrS cases. Genes encoding subunits of other sodium channels, as well as potassium and calcium channels, including *SCN10A*, *SCN1B-3B*, *GPD1L*, *RANGRF*, *SLMAP*, *ABCC9, KCNH2*, *KCNE3*, *KCNJ8*, *KCNE5*, *KCND3*, *HCN4*, *CACNA1C*, *CACNB2B*, *CACNA2D1*, *TRPM4*, and *PKP2,* are also associated with this syndrome. A plethora of identified variants in these genes are registered in individual families and cause < 5% of BrS cases.

Polymorphic variants of other genes, as well as nongenetic factors such as fever and intake of certain drugs, contribute to the phenotypic implementation of the main mutations. Therefore, the same genetic variant can lead to different phenotypes even among members of the same family [7]. BrS may represent a group of diseases with common ECG changes that are characterized by different clinical manifestations and inheritance patterns [8]. The reason is that the BrS phenotype may be due to variants in genes associated with other diseases. Thus, the so-called overlap syndrome of BrS with other heart diseases, such as arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, and long *QT* syndrome (LQTS), was noted. Desmosomal proteins, including plakophilin-2, encoded by *PKP2*, and desmoglein-2, encoded by *DGC2*, have been implicated in arrhythmogenic right ventricular cardiomyopathy (ARVC) and BrS by interacting with the NaV1.5 sodium channel [9]. However, the role of desmosomal proteins in the etiology of BrS is still debated.

These issues emphasize the need for a better understanding of the molecular genetic causes of BrS and more accurate genotype–phenotype correlations.

This study evaluated the clinical characteristics of patients with different BrS genetic variants.

MATERIALS AND METHODS

The study included 24 patients (17 men and 7 women) aged 18–55 years (median age, 32.5 [20; 42] years) with an ECG pattern of BrS. The median follow-up period was 3 years.

The clinical and instrumental study included recording a standard 12-lead electrocardiogram (ECG-12), 24-h ECG monitoring (24H ECG), provocative testing with the sodium channel blocker novocainamide, EEPS according to indications, and gathering a complete and accurate medical history with ECG assessment of all family members with identified SCD, or the family history of the disease.

According to ECG-12, the following parameters were assessed: heart rate (HR), corrected *QT* interval (*QT*c), *T*-wave morphology and alternans (negative, positive, or biphasic), *J*-point elevation, configuration (coved or saddle-shaped), and terminal part (smooth descending or elevation) of the ST-segment in the right precordial leads, presence of right bundle branch block, and intermittent prolongation of the *PR* interval.

In intensive care unit at the Republican Scientific and Practical Center "Cardiology", patients underwent a diagnostic testing with novocainamide (10 mg/kg for 10 min) under constant monitoring of ECG and blood pressure (BP). BrS was diagnosed if the patient had ECG changes in the right precordial leads (V1 and/or V2), characterized by *ST*-segment elevation from the *J*-point of >2 mm in a "coved" configuration along with a negative *T*-wave. For patients with BrS type 1 pattern, provocative testing was not performed due to no additional diagnostic value.

To rule out structural myocardial disorders, an echocardiographic study (EchoCG) was performed using an IE-33 device Philips (USA), as well as magnetic resonance imaging (MRI) using a Magnetom Aera 1.5 T tomograph (Siemens, Germany) according to relevant recommendations.

ECG was performed on the Intecard-3 hardware and software complex (Republic of Belarus). 24H ECG was performed using an Oxford Medilog AR12 recorder (UK). EEPS was performed on Siemens (Germany) and Bard (USA) systems.

During the 24H ECG, the average HR per day, QRS fragmentation, early repolarization pattern, prominent *S*-wave in lead *I*, diverse ventricular arrhythmias and sustained VT and VF), BrS ECG pattern (intermittent or permanent), and *ST*-segment and *T*-wave alterations were assessed. The ventricular genesis of the arrhythmia was confirmed by 24H ECG data, ECG registration during the arrhythmia episode and EEPS in some cases. Eleven patients underwent EEPS to screen for arrhythmic risk by examining the area and size of the arrhythmogenic substrate causing the arrhythmia burden. This method corresponded to an internationally recognized protocol using stimulation of two segments, namely, the region of the right ventricular apex and the right ventricular outflow tract, with a cycle length of 600, 430, and 330 ms, application of 1, 2, or 3 extrastimuli, and a progressive decrease in the coupling interval to minimum values (200 ms) [10]. Programed electrical stimulation was performed in accordance with a standard protocol. If sustained VT or VF lasting > 30 s was induced or cardioversion was required, patients were classified as having an inducible arrhythmia.

Mutations in the coding sequences of genes associated with the development of channelopathies and other inherited heart rhythm disorders were identified using high-throughput sequencing on a MiSeq genetic analyzer (Illumina, USA). Sample preparation was performed using the TruSight Cardio Sequencing Kit (Illumina, USA). Annotation of the sequencing results was performed using ANNOVAR software [11]. The pathogenicity of the new and previously described genetic variants was interpreted according to the recommendations of the American College of Medical Genetics and Genomics (ACMG, 2015) [12]. Pathogenic (class V) and likely pathogenic (class IV) genetic variants were considered diagnostically significant. The analysis also included variants of uncertain clinical significance (VUS, class III), pathogenic according to in silico predictors, whose incidence in population databases (GnomaD) did not exceed 0.01%.

This study was approved by the ethics committee of the Institute of Genetics and Cytology of the National Academy of Sciences of Belarus (Minutes No. 2 of the meeting of the Bioethics Committee dated 06/08/2021). All patients provided informed voluntary consent to participate in the study.

RESULTS

Twenty-four probands from unrelated families in whom the BrS pattern was recorded on ECG were examined (Table 1). The majority of patients were men (n = 17; 70.8%), with a median age of 32.5 (20; 42) years. Nine (37.5%) patients had a spontaneous type 1 ECG pattern, 14 (58.3%) represented with type 2, and 1 patient with type 3. Four (16.7%) patients had a family history of SCD among their close relatives. Seven (29.2%) patients had clinical manifestations of BrS (syncope, spontaneous or induced polymorphic VT/VF, with resuscitation after SCD). Of these patients, 4 probands (16.7%) had VF with successful resuscitation and subsequent ICD implantation, and 3 (12.5%) had recurrent syncope, polymorphic VT/VF induced by programed ventricular stimulation during EEPS, followed by ICD implantation. EEPS revealed sick sinus syndrome (SSS) that required pacemaker implantation in one patient, sinus node dysfunction in two patients, and loop recorder implantation in one patient. Supraventricular paroxysmal tachycardia was recorded in two patients. In one patient, premature ventricular contractions (PVCs) and episodes of second-degree atrioventricular (AV) block, type I, were registered. A loop recorder was implanted in a patient with a single syncope episode and a BrS type 3 ECG pattern. The remaining 13 (54.2%) patients were asymptomatic.

To determine the risks of arrhythmic events, 11 (45.8%) patients underwent EEPS with programed ventricular stimulation. In 3 (12.5%) patients, VT was induced, and an ICD was implanted. However, in 8 (33.3%) patients, VTs were not triggered. The clinical characteristics of the patients are presented in Table 1.

While genotyping, in 15 (62.5%) out of 24 probands included in the study, nucleotide sequence variants of pathogenicity classes III–V were identified according to the criteria of the ACMG (2015) in the genes encoding sodium (*SCN5A* and *SCN10A*) and potassium (*KCNE3, KCNJ2, KCNJ8,* and *KCNA5*) channels, as well as in *HCN4* and *SNTA1* genes associated with these channels (Table 1). In addition, three variants in *ANK2*, which are associated with ankyrinopathies, and variants in *DSP* and *DES*, which are mutations that lead to ARVC, were determined. Only four variants belonged to pathogenicity classes IV and V, two of which were new, and the rest were VUS, class III). All pathogenic and likely pathogenic variants were defined in *SCN5A*. Six (40.0%) out of 15 genotype-positive patients had several genetic variants, and predominantly they affected genes linked to cardiomyopathies.

In seven patients, variants were identified in the genes encoding sodium channels and associated proteins (Table 2). Five patients carried *SCN5A* variants.

The most severe clinical manifestations of the disease were registered in proband 799 (41 years old), in whom the disease manifested with VF with resuscitation measures, which required ICD implantation. His father died suddenly at the age of 28 years. The proband experienced syncope during the day, which clearly has not been related to exercise, and eventually cardiac arrest occurred at night. ECG showed a spontaneous BrS type 1 pattern. Upon further monitoring, the BrS pattern was not registered on the ECG; sinus rhythm was recorded with an HR of 68 beats/min, the *PQ* interval duration was 110 ms, the *QT*c interval was 380 ms, and

Table 1. Clinical and genetic characteristics of patients with Brugada syndrome
Таблица 1. Клинико-генетическая характеристика пациентов с синдромом Бругада

Patient code	Age	Sex	History of SCD	Syncope	Brugada pattern	EEPS	Test with novocainamide	Gene mutation	Pathogenicity class	Events/outcomes
611	26	F	+	+	Type 1	Not performed	Not performed	*SCN5A*	P	Refusal of ICD therapy
799	41	M	+	+	Type 1	Not performed	Not performed	*SCN5A* *JUP*	P VUS	VF and ICD
717	20	M	–	–	Type 1	Not performed	Not performed	*SCN5A*	LP	Transient SA block deg. 2 type 1
716	18	M	–	–	Type 2	Not performed	+	*SCN5A* *TPM1*	LP VUS	–
668	31	M	–	–	Type 1	Not performed	Not performed	*SCN5A*	VUS	–
732	55	F	–	+	Type 1	Not performed	Not performed	*SCN10A*	VUS	VF and ICD
641	38	M	–	–	Type 2	VT not induced	+	*SNTA1*	VUS	PVCs, AV block deg. 2 type I
638	37	F	+ #	+	Type 2	Induced polymorphic VT	+	*KCNJ8* *HCN4*	VUS VUS	ICD, PVT, and SVT
606	44	M	–	–	Type 2	VT not induced	+	*KCNJ2*	VUS	SVT
580c	36	M	+ *	+	Type 2	Induced VT	+	*DES* *MYH11*	VUS VUS	PVT/ICD
598	29	M	–	–	Type 1	VT not induced	Not performed	*DSP* *MYOZ2*	VUS VUS	–
788	26	M	–	–	Type 2	Not performed	Not performed	*DSP* *RBM20*	VUS VUS	–
796	25	M	–	–	Type 2	VT not induced	+	*ANK2*	VUS	SSS and PM
756c	19	M	_	+	Type 3	Not performed	+	*ANK2*	VUS	ILR
12м	19	M	–	–	Type 2	Not performed	+	*ANK2*	VUS	–
626	46	F	–	+	Type 1	Not performed	Not performed	Not detected	–	VF and ICD
789	34	F	–	+	Type 2	Induced PVT	+	Not detected	–	PVT/VF and ICD
667	47	F	–	–	Type 1	Not performed	Not performed	Not detected	–	–
605	55	M	–	–	Type 1	VT not induced	Not performed	Not detected	–	–
806	20	M	–	–	Type 2	VT not induced	+	Not detected	–	SND and ILR
792	18	M	–	–	Type 2	VT not induced	+	Not detected	–	SND
730	40	M	–	–	Type 2	VT not induced	+	Not detected	–	–
779	48	F	–	–	Type 2	Not performed	+	Not detected	–	–
2м	20	M	–	–	Type 2	Not performed	+	Not detected	–	–

Note: SCD — sudden cardiac death; SND — sinus node dysfunction; VT — ventricular tachycardia; ICD — implantable cardioverter defibrillator; PVT — polymorphic ventricular tachycardia; SVT— supraventricular tachycardia; SA — sinoatril; PVCs — premature ventricular contractions; SSS — sick sinus syndrome; VF — ventricular fibrillation; PM — pacemaker; EEPS — endocardial electrophysiological study; # — in 4 relatives; * — in 2 relatives.

Примечание: ВСС — внезапная сердечная смерть; ДСУ — дисфункция синусового узла; ЖТ — желудочковая тахикардия; ИКД — имплантируемый кардиовертер-дефибриллятор; ПЖТ — полиморфная желудочковая тахикардия; СВТ — суправентрикулярная тахикардия; СА — синоатриальная; ЖЭС — желудочковая экстрасистолия; СССУ — синдром слабости синусового узла; ФЖ — фибрилляция желудочков; ЭКС — электрокардиостимулятор; ЭЭФИ — эндокардиальное электрофизиологическое исследование; # — у 4 родственников; * — у 2 родственников.

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Table 2. Genetic characteristics of patients with variants in genes encoding sodium channels and associated proteins
Таблица 2. Генетическая характеристика пациентов с вариантами в генах, кодирующих натриевые каналы и ассоциированные с ними белки

Patient code	Gene	Nucleotide substitution/Rs	Amino acid substitution	Variant class	MAF (GnomaD)
799	*SCN5A*	c.142G > A, rs199473048	p.Glu48Lys	P	0.000039
	JUP	c.427G > A, rs375788626	p.Ala143Thr	VUS	0.000098
611	*SCN5A*	c.3840 + 1G > A rs1366120635	–	P	0.0000048
716	*SCN5A*	c.4055G > A	p.Gly1352Asp	LP*	–
	TPM1	c.76G > C	p.Glu26Gln	VUS	–
717	*SCN5A*	c.2572dupA	p.Met858Asnfs*73	LP*	–
668	*SCN5A*	c.5360G > A, rs199473316	p.Ser1787Asn	VUS	0.000495
732	*SCN10A*	c.5216 A > T, rs760863009	p.Asp1739Val	VUS	0.000014
641	*SNTA1*	c.787G > T, rs150576530	p.Ala263Ser	VUS	0.00026

Note: * — new variant; P — pathogenic variant; LP — likely pathogenic variant; VUS — variant with uncertain significance; MAF — minor allele frequency.
Примечание: * — новый вариант; P — патогенный вариант; LP — вероятно патогенный вариант; VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

the *QRS* was 120 ms. Genotyping revealed a p. Glu48Lys pathogenic variant in *SCN5A* and an additional substitution in *JUP* associated with ARVC. Cardiac MRI revealed no changes in myocardial structure and no evidence of ARVC.

In patient 611 (26 years old) with a family history of SCD in a relative (elder brother aged 30 years) and a spontaneous BrS type 1 pattern on ECG, no clinical manifestations of BrS were observed, and, ultimately, she refused further EEPS and ICD implantation. Genotyping revealed a pathogenic mutation, c.3840 + 1G > A, affecting a splice site in *SCN5A*.

Patients 668, 716, and 717 also had an asymptomatic disease course. ECG of proband 717 (20 years old) showed a BrS type 1 pattern. Genotyping revealed a new probably pathogenic duplication of one nucleotide c.2572dupA, leading to a reading frame shift and the appearance of a premature stop codon (p. Met858Asnfs*73) in *SCN5A*. The patient refused EEPS. Patient 716 (18 years old) had a BrS type 2 pattern on ECG, and the novocainamide test was positive. In this patient, a new variant was detected, which was pathogenic according to the in silico predictors, c.4055G > A (p. Gly1352Asp) in exon 23 of *SCN5A*. Patient 668 (31 years old) had a BrS type 1 pattern on ECG. Genotyping revealed a p. Ser1787Asn substitution of unknown clinical significance in *SCN5A*.

Proband 732 (female, 55 years old), who had no known risk factors for the development of coronary heart disease and no family history of SCD, was admitted to the intensive care unit by reason of cardiac arrest with documented VF and underwent ICD implantation; a BrS type 1 pattern was detected on serial ECG. Genotyping revealed p. Asp1739Val substitution in *SCN10A*, which encodes the neuronal sodium channel (Nav1.8) and is associated with BrS, which was proven in recent genome-wide association studies (GWAS) [13]. A study demonstrated similarities in phenotypes between patients with a *SCN10A* variant and those with *SCN5A* variants, including family history, presence of syncope, and spontaneous ECG patterns [14]. In our cohort, a *SCN10A* substitution was also associated with disease manifestation, VF development, and cardiac arrest, followed by ICD implantation. D. Hu et al. [15] identified *SCN10A* mutations in 25 of 150 probands (17%) with BrS, emphasizing the crucial role of this gene in this disease. Its significance was confirmed by studies on the influence of *SCN10A* on both cardiac conduction [16] and the autonomic nervous system [17]. In proband 641 (male, 38 years old), a BrS type 2 pattern was recorded for the time of a routine ECG (Fig. 1).

The novocainamide test was positive. In the course of EEPS, ventricular arrhythmias were not induced. Holter ECG monitoring recorded frequent PVCs and episodes of second-degree AV block, type 1. Antiarrhythmic drug treatment was prescribed. Genotyping revealed p. Ala263Ser substitution in *SNTA1*, which encodes syntrophin, a scaffold protein of the cytoplasmic peripheral membrane and a component of the dystrophin-associated protein complex. This gene is a member of the syntrophin gene family and encodes the most abundant syntrophin isoform detected in cardiac tissue. The N-terminal PDZ domain of this syntrophin protein interacts with the C-terminus of the pore-forming alpha subunit (*SCN5A*) of the cardiac sodium channel Nav1.5. This gene is associated with LQTS and sudden infant death syndrome (SIDS). This protein also binds to dystrophin and dystrophin-related proteins at neuromuscular junctions and alters intracellular calcium ion levels in muscles [18].

In two patients with BrS, variants were identified in the genes encoding potassium channels (Table 3), and their clinical manifestations were analyzed.

Patient 638 (female, 34 years old) had a family history of SCD via parental lineage in her closest relatives (a second cousin aged 24 years and three paternal uncles aged 36, 47, and 52 years), and a BrS type 2 pattern was registered on the ECG (Fig. 2). The proband has experienced rapid heart palpitation accompanied by shortness of breath and dizziness since the age of 16 years. Several months before

Table 3. Genetic characteristics of patients with variants in potassium channels
Таблица 3. Генетическая характеристика пациентов с вариантами в калиевых каналах

Patient code	Gene	Nucleotide substitution/Rs	Amino acid substitution	Mutation class	MAF (GnomaD)
638	*KCNJ8*	c.980T > C rs1940609307	p.Ile327Thr	VUS	0.0000034
	HCN4	c.415C > T	p.Pro139Ser	VUS*	–
606	*KCNJ2*	c.845T > G rs758092571	p.Leu282Trp	VUS	0.00001735

Note: * — new variant; VUS — variant with uncertain significance; MAF — minor allele frequency.
Примечание: * — новый вариант; VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

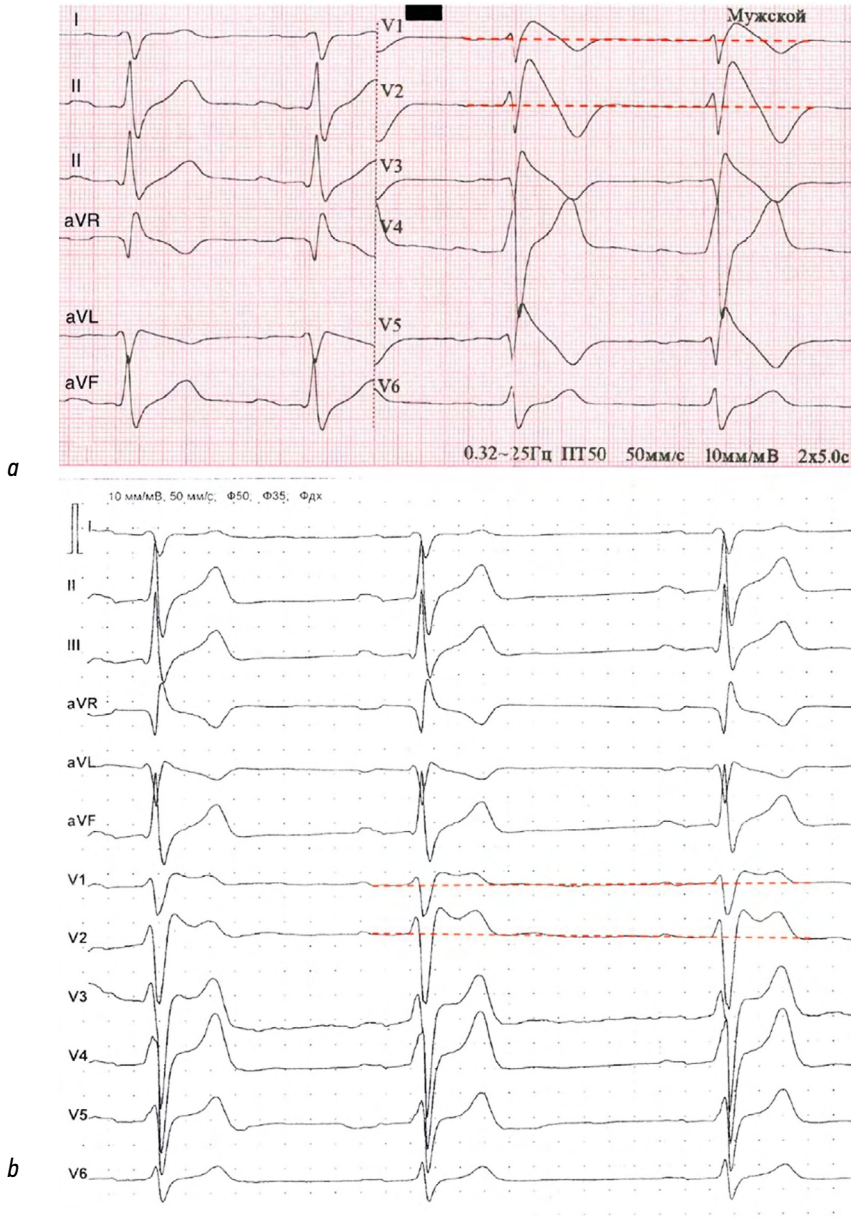

Fig. 1. 12-lead electrocardiogram of patients (598 and 641) with distinct Brugada patterns: *a* — Brugada pattern type 1 (coved), showing a "vaulted" elevation of the *ST* segment of more than 2 mm in more than one right precordial lead, followed by a negative *T*-wave; *b* — Brugada pattern type 2 (saddle-back), showing a "saddle-shaped" elevation of the *ST* segment of more than 2 mm in more than one right precordial lead, followed by a positive *T*-wave
Рис. 1. Электрокардиограмма в 12 отведениях пациентов № 598 и 641 с разными паттернами Бругада: *a* — паттерн Бругада тип 1 (coved), показывающий «сводчатый» подъем сегмента *ST* более 2 мм в более чем одном правом прекордиальном отведении, за которым следует отрицательный зубец *T*; *b* — паттерн Бругада типа 2 (saddle-back), показывающий «седловидный» подъем сегмента *ST* более 2 мм в более чем одном правом прекордиальном отведении, за которым следует положительный зубец *T*

hospitalization, the patient endured three episodes of syncope. Changes were recorded in the analysis of a series of ECGs, namely, abnormalities of intraventricular conduction (widening of the *QRS* complex up to 130 ms), or R-wave progressionin leads V1–V3, slowing of AV conduction with transient first-degree AV block, transient second-degree SA block type I, and pauses lasting 1495 ms.

During a novocainamide testing (10 mg/kg body weight intravenously for 10 min) at the tenth minute, changes were recorded in leads V1–V2, such as a coved-type ST-segment elevation (Fig. 3), characteristic of a BrS type 1 pattern (amplitude > 2 mm, width > 4 mm, Corrado index > 1).

During EEPS, programed stimulation of the ventricles with extrastimuli (coupling intervals of 220 and 230 ms) provoked a sustained paroxysm of polymorphic VT with a cycle of 224–176 ms, which was terminated spontaneously, and a characteristic BrS pattern with 2–3 mm *ST* elevation. Considering the presence of BrS, recurrent syncope, induced polymorphic ventricular tachycardia during EEPS, and a high SCD risk, a single-chamber ICD was implanted for urgent indications. During treatment (metoprolol 12.5 mg twice a day under HR and BP control), the patient's medical state improved, and she was discharged in a satisfactory condition. Genotyping

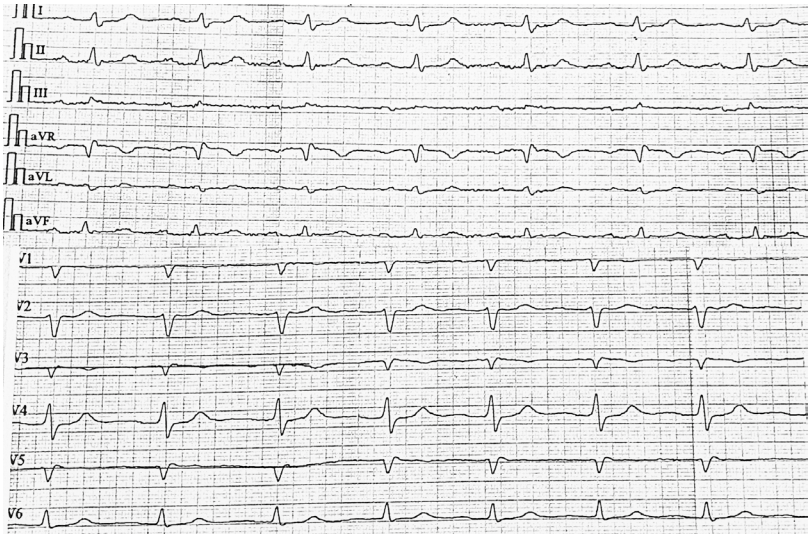

Fig. 2. 12-lead electrocardiogram of patient 638 at rest, 10 mm/mV, 50 mm/s
Рис. 2. Электрокардиограмма в 12 отведениях пациентки № 638 в покое, 10 мм/мВ, 50 мм/с

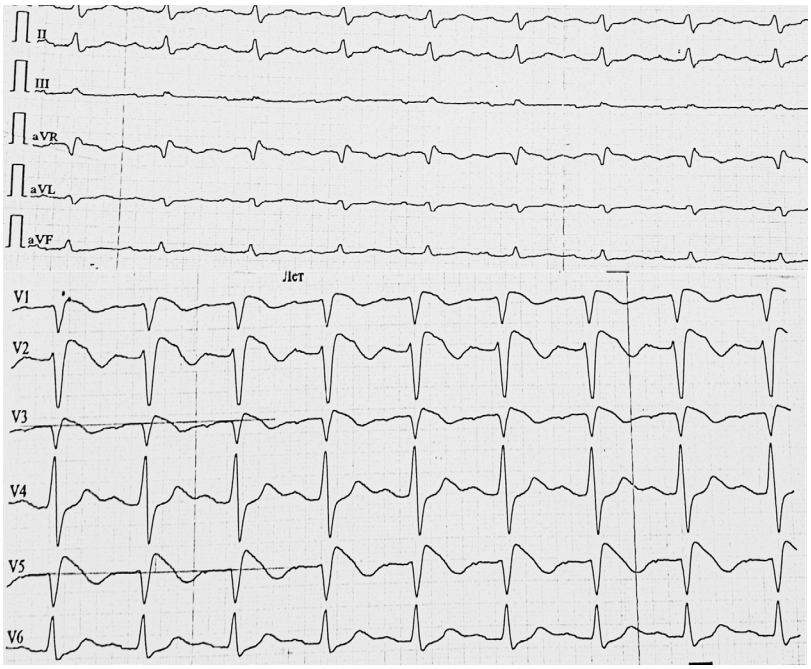

Fig. 3. 12-lead electrocardiogram of patient 638, 10 min of the novocainamide testing, 10 mm/mV, 50 mm/s
Рис. 3. Электрокардиограмма в 12 отведениях пациентки № 638 на 10-й минуте проведения новокаинамидовой пробы, 10 мм/мВ, 50 мм/с

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revealed two new allelic variants: the p. Ile327Thr mutation in *KCNJ8*, which encodes a subunit of the ATP-sensitive potassium channel Kir6.1, and the p. Pro139Ser mutation in *HCN4*, which is responsible for the synthesis of one of the family members controlled by cyclic nucleotides in hyperpolarization-activated potassium channels.

In patient 606 (44 years old) with a BrS type pattern on ECG and asymptomatic disease course, the novocainamide testing was positive. While conducting EEPS, VT was not induced. Antiarrhythmic drug therapy was prescribed. Genotyping revealed a variant of unknown clinical significance of p. Leu282Trp in *KCNJ2*, encoding the alpha subunit of the influent potassium current channel Kir2.1.

Genetic variants leading to BrS in one of the potassium channels usually result in increased channel function. Rare *KCNJ8* variants, by increasing the throughput of the ATP-sensitive potassium channel (IK-ATP), reduce the AP as well as plateau depression, causing the ECG changes registered in BrS [19]. The severe clinical presentation in proband 638 was conceivably due to the presence of another, also not previously described, mutation c.415C > T (p. Pro139Ser) in *HCN4*, which encodes the protein of hyperpolarization-activated cyclic nucleotide-dependent potassium channel 4.

KCNJ2 variants are associated with LQTS type 7 and short *QT* syndrome type 3. This gene is related to *KCNJ8*, which is associated with BrS type 8, and its variants presumably cause this syndrome.

In patients 598, 788, and 580c (male) with the BrS pattern on ECG were revealed desmosomal gene substitutions (Table 4).

Proband 580c (36 years old) with recurrent syncope and BrS type 2 ECG pattern and SCD in two family members (father and brother aged 32 years) underwent a novocainamide

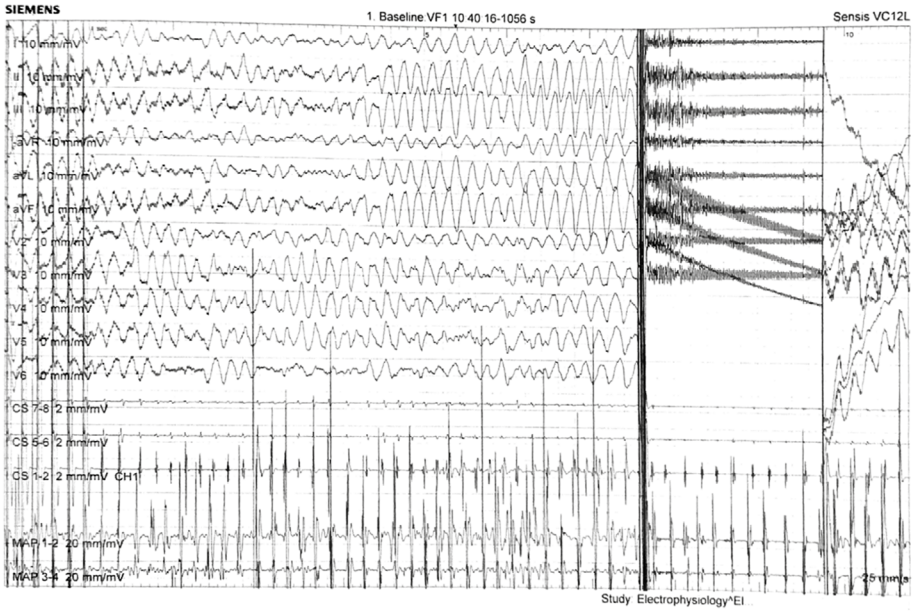

Fig. 4. Endoelectrogram of proband 580c, representing the paroxysm of ventricular fibrillation
Рис. 4. Эндоэлектрограмма пробанда № 580с, представляющая пароксизм фибрилляции желудочков

Table 4. Genotyping results of patients with Brugada syndrome (overlapping phenotypes with right ventricular arrhythmogenic cardiomyopathy)
Таблица 4. Результаты генотипирования пациентов с синдромом Бругада (перекрывающие фенотипы с аритмогенной кардиомиопатией правого желудочка)

Patient code	Gene	Nucleotide substitution/Rs	Amino acid substitution	Mutation class	MAF (GnomaD)
580c	*DES*	c.752A > C	p.Gln251Pro	VUS*	–
	MYH11	c.3925G > C	p.Asp1309His	VUS*	–
598	*DSP*	c.6188G > A rs142927608	p.Arg2063Gln	VUS	0.00001115
	MYOZ2	c.674C > T rs200428820	p.Pro225Leu	VUS	0.0001289
788	*DSP*	c.6014C > T rs749925817	p.Ala2005Val	VUS	0.000007
	RBM20	c.1244G > A rs748133931	p.Ser415Asn	VUS	0.000035

Note: * — new variant; VUS — variant with uncertain significance; MAF — frequency of the minor allele.
Примечание: * — новый вариант; VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

testing (positive) and EEPS. During EEPS, VF paroxysm was induced and was successfully terminated by cardioversion, and the arrhythmia substrate was ablated (Fig. 4). Considering the persistently high SCD risk, an ICD was implanted as a next step. Genotyping revealed two new variants that were pathogenic according to in silico predictors, precisely, p. Gln251Pro in *DES*, which encodes desmin and is associated with ARVC [20], and p. Asp1309His in *MYH11*, which is linked to SCD and familial aortic aneurysm.

In patient 598 (29 years old), without clinical disease manifestations and family history, a BrS type 1 pattern was recorded on ECG (Fig. 1). Throughout the EEPS, VT was not induced, and the patient was followed up. A VUS p. Arg2063Gln was identified in *DSP*, which encodes desmoplakin.

Patient 788 (26 years old) without clinical manifestations had a BrS type 2 pattern on ECG. Novocainamide testing and EEPS were not performed. The patient refused further examination. Cardiac MRI did not reveal any evidence of cardiac structural alterations. Genotyping revealed p. Ala2005Val substitution in *DSP.*

In patients 580c, 598, and 788, genetic testing revealed rare variants in *MYOZ2, RBM20*, and *MYH11* associated with changes in myocardial structure.

Genetic variants in desmosomal genes in patients with BrS ECG patterns specify an overlap between BrS and ARVC phenotypes. Genes encoding desmosomal proteins, known as ARVC susceptibility genes [21], have also been described in several patients with signs of BrS in the absence of evident structural disease manifestations. In vitro functional studies in HL-1 cells and human cardiomyocytes derived from induced pluripotent stem cells showed that desmosomal gene mutations can reduce sodium ion (INa) current by disrupting the interaction between desmosomal proteins and the Nav1.5 channel in the cardiac muscle [22]. These data enabled us to hypothesize that ARVC and BrS are not completely different conditions and could thereby be considered final stages of the same disease, i.e., cardiac connexome disease [9].

In patients 12m, 756c, and 796, genotyping revealed *ANK2* substitutions (Table 5).

Patients 12m and 756c (both male, 19 years old) with BrS type 2 and 3 ECG patterns that transformed into type 1 during the novocainamide testing were asymptomatic. In patient 796 (25 years old), VT was not induced during EEPS; however, SSS was detected, and an PM was implanted.

Ankyrin is a multifunctional protein involved in the functioning of ion channels and transporters in various tissues [23]. Despite their common basis, these proteins have different functions. The genes encode three different ankyrin proteins, namely, ankyrin-R (ANK-1), ankyrin-B (ANK-2), and ankyrin-G (ANK-3). ANK-2, like ANK-3, controls the functioning of the sodium channel Nav1.5 and is associated with BrS [24]. In case ANK-B is impaired, other arrhythmia phenotypes are distinguished, including SSS, atrial fibrillation, and life-threatening ventricular arrhythmias with SCD risk [25]. Hence, this phenotypic diversity of rhythm disorders was combined and presented as Ankirin B syndrome. In a Japanese cohort of 535 probands with inherited rhythm disorders, 12 (2.2%) had *ANK2* mutations, with 8 out of 12 probands having bradycardia, 2 having BrS phenotypes, and 7 having malignant VTs [26]. Thus, *ANK2* variants are potential candidates for BrS. Further functional and molecular studies of the detected variants should clarify the mechanisms associated with the *ANK2* variants underlying BrS.

DISCUSSION

In this paper, we characterized the clinical aspects, including adverse arrhythmic events, and analyzed the phenotypic manifestations depending on the genotype in patients with BrS ECG patterns. In the study cohort, the clinical diagnosis of BrS was confirmed by genetic testing in 7 (29.2%) patients; most patients (20.8%) were carriers of *SCN5A* variants, which is considered the most clinically significant in relation to this syndrome [27]. A patient with severe clinical presentation of BrS had a variant in *SCN10A*, which encodes another sodium channel, Nav1.8. Recent studies have highlighted that the Nav1.8 channel is a modulator of cardiac conduction and that *SCN10A* variants may be associated with atrial fibrillation and BrS [28]. *SCN10A* variants affect *PR* interval duration, *QRS*, HR, and arrhythmia risk [14].

In another female patient, two rare variants of *KCNJ8* and *HCN4*, which encode potassium channels and are

Table 5. Genotyping results of patients with Brugada syndrome associated with ankyrin
Таблица 5. Результаты генотипирования пациентов с синдромом Бругада, ассоциированные с анкирином

Patient code	Gene	Exon	Nucleotide substitution/Rs	Amino acid substitution	Mutation class	MAF (GnomaD)
12м	*ANK2*	38	c.6097A > G	p.Lys2033Glu rs756877862	VUS	0.0000032
756с	*ANK2*	38	c.9841C > G	p.Gln3281Glu rs372534074	VUS	0.00017
796	*ANK2*	26	c.2890A > G	p.Ile964Val rs750129234	VUS	0.00001055

Note: VUS — variant with uncertain significance; MAF — frequency of the minor allele.
Примечание: VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

associated with BrS, were identified. *KCNJ8* is responsible for the synthesis of the membrane protein of the inward rectifying potassium channel (Kir and IRK), through which positive ions easily pass into the cell. The flow of ions into the cell may play an important role in the regulation of neuronal activity, helping to stabilize the resting membrane potential of the cell. Defects in this gene may also cause *J*-wave syndrome and SIDS. *HCN4* encodes the hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 protein. This gene is expressed primarily in cardiac cells with high automaticity. Through the HCN4 channel, potassium and sodium ions enter the cells of the sinoatrial node, generating electrical impulses that trigger each heartbeat and maintain a regular heart rhythm. Moreover, the HCN4 protein is responsible for slow kinetic activation and inactivation and is essential in cardiac excitation and for the proper functioning of the cardiac conduction system [29]. Accordingly, mutations in this gene are also associated with SSS.

In 8 (33.3%) patients, rare substitutions were identified in *SNTA1, KCNJ2, ANK2, DSP,* and *DES*, which are associated primarily with LQTS and ARVC. Currently, growing evidence shows that some allelic variants of these genes may also cause BrS. Furthermore, this phenomenon is associated with the overlap syndrome of several diseases, namely, BrS and LQTS and BrS and ARVC.

Remarkably, 6 out of 15 patients with a positive genetic analysis had several nucleotide variants, which most often affected genes associated with changes in myocardial structure, specifically, *MYOZ2, RBM20, JUP, TPM1,* and *MYH11*. Although BrS was initially described as a monogenic autosomal dominant disorder with incomplete penetrance, it is increasingly evident that it may follow a more complex genetic model. Indeed, it can be considered an oligogenic or polygenic disease in which more than one causative gene contributes to the clinical phenotype [30].

On the other hand, no genetic changes were observed in 7 (29.2%) patients. No significant relationship was noted between the disease course and the patient's genotype. The most severe clinical course with cardiac arrest due to VF development at the age of 36–55 years was registered in patients 799, 732, and 580, who had *SCN5A* and *SCN10A* variants, and patient 789 who had no genetic changes. Polymorphic VT/VF induced by EEPS followed by ICD implantation was identified in patient 638 (female) with rare *KCNJ8* and *HCN4* variants, in patient 580s with *DES* and *MYH11* variants, and in a patient without mutations. Moreover, 13 (54.2%) patients were asymptomatic, whereas three of them (patients 611, 716, and 717) had pathogenic and likely pathogenic mutations in *SCN5A*, and a variant of uncertain clinical significance in the same gene was found in patient 668. However, BrS symptoms were more common in patients with mutations because out of 9 patients without genetic changes, 5 (55.6%) were asymptomatic, accounting for 33.3% (5 of 15) of those with rare genetic variants. SCD among close relatives with a family history was acclaimed in 50% of probands with pathogenic *SCN5A* mutations, implying a poor prognosis in carriers of pathogenic variants in this gene and the need for scrupulous examination of such patients.

The impact of genetic variants on the risk of developing cardiac arrhythmias and their prognosis is still debated. The extent to which different gene variants increase the risk of arrhythmic events and SCD remains unclear and is therefore not yet considered in risk stratification. However, genetic data can be another tool for risk stratification in genotype-positive patients, and if it does not result in an active treatment strategy, this could at least contribute to a lifestyle change (avoidance of drugs that may induce ST-segment elevation in right precordial leads and excessive alcohol intake).

CONCLUSION

This study substantiates the idea that BrS, along with monogenic inheritance, may also have a polygenic nature, in which the clinical phenotype is caused by variants in several genes associated with cardiovascular diseases. Mutations in patients with the BrS pattern have been associated with an increased likelihood of clinical manifestations of the disease. Nevertheless, the impact of genotype on the BrS phenotype is not entirely clear. The most severe form of the disease with VF development and successful resuscitation followed by ICD implantation was predominantly registered in patients with variants in several genes (*SCN5A* and *JUP; KCNJ8* and *HCN4; DES* and *MYH11*).

STUDY LIMITATIONS

The study limitations include the small number of patients with different genetic variants of BrS on grounds of its low prevalence. Nevertheless, the data presented are consistent with those described in the literature.

ADDITIONAL INFORMATION

Ethics approval. The protocol of the study was approved by Institute of Genetics and Cytology of Belarus National Academy of Sciences Ethics Committee, protocol No. 2, 08.06.2021.

Author contribution. All authors made significant contributions to the preparation of the article and read and approved the final version before publication.

Contribution of each author. S.M. Komissarova — concept and design of the study, writing — original draft, patient follow-up; N.N. Chakova — conducting and interpreting the results of genetic analysis, writing — original draft; N.M. Rineiska — data curation, diagnostic studies, writing — original draft, review and editing, literature review; S.S. Niyazova — conducting and interpreting the results of the genetic analysis; T.V. Dolmatovich — conducting and interpreting the results of the genetic analysis; V.Ch. Barsukevich — patient follow-up; L.I. Plaschinskaya — diagnostic studies.

Competing interests. The authors declare that they have no competing interests.

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REFERENCES

1. Brugada J, Campuzano O, Arbelo E, et al. present status of brugada syndrome: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(9):1046–1059. doi: 10.1016/j.jacc.2018.06.037

2. Garcia-Elias A, Benito B. Ion channel disorders and sudden cardiac death. *Int J Mol Sci*. 2018;19(3):692. doi: 10.3390/ijms19030692

3. Coppola G, Corrado E, Curnis A, et al. Update on brugada syndrome 2019. *Curr Probl Cardiol*. 2021;46(3):100454. doi: 10.1016/j.cpcardiol.2019.100454

4. Benito B, Sarkozy A, Mont L, et al. Gender differences in clinical manifestations of Brugada syndrome. *J Am Coll Cardiol*. 2008;52(19):1567–1573. doi: 10.1016/j.jacc.2008.07.052

5. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43(40):3997–4126. doi: 10.1093/eurheartj/ehac262

6. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol*. 2012;59(1):37–45. doi: 10.1016/j.jacc.2011.08.064

7. Monasky MM, Micaglio E, Giachino D, et al. Genotype-phenotype correlation in a family with brugada syndrome harboring the novel p.Gln371* nonsense variant in the scn5a gene. *Int J Mol Sci*. 2019;20(22):5522. doi: 10.3390/ijms20225522

8. Campuzano O, Sarquella-Brugada G, Cesar S, et al. Update on genetic basis of brugada syndrome: monogenic, polygenic or oligogenic? *Int J Mol Sci*. 2020;21(19):7155. doi: 10.3390/ijms21197155

9. Agullo-Pascual E, Cerrone M, Delmar M. Arrhythmogenic cardiomyopathy and Brugada syndrome: diseases of the connexome. *FEBS Lett*. 2014;588(8):1322–1330. doi: 10.1016/j.febslet.2014.02.008

10. Wilde AA, Antzelevitch C, Borggrefe M, et al. Study group on the molecular basis of arrhythmias of the european society of cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation*. 2002;106(19):2514–2519. doi: 10.1161/01.cir.0000034169.45752.4a

11. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res*. 2010;38(16):e164. doi: 10.1093/nar/gkq603

12. Richards S, Aziz N, Bale S, et al. ACMG Laboratory quality assurance committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genetics in Medicine*. 2015;17(5):405–424. doi: 10.1038/gim.2015.30

13. Andreasen L, Ghouse J, Skov MW, et al. Brugada syndrome-associated genetic loci are associated with j-point elevation and an increased risk of cardiac arrest. *Front Physiol*. 2018;9:894. doi: 10.3389/fphys.2018.00894

14. Monasky MM, Micaglio E, Vicedomini G, et al. Comparable clinical characteristics in Brugada syndrome patients harboring SCN5A or novel SCN10A variants. *Europace*. 2019;21(10):1550–1558. doi: 10.1093/europace/euz186

15. Hu D, Barajas-Martínez H, Pfeiffer R, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. *J Am Coll Cardiol*. 2014;64(1):66–79. doi: 10.1016/j.jacc.2014.04.032

16. Chambers JC, Zhao J, Terracciano CM, et al. Genetic variation in SCN10A influences cardiac conduction. *Nat Genet*. 2010;42(2): 149–152. doi: 10.1038/ng.516

17. Qi B, Wei Y, Chen S, et al. Nav1.8 channels in ganglionated plexi modulate atrial fibrillation inducibility. *Cardiovasc Res*. 2014;102(3):480–486. doi: 10.1093/cvr/cvu005

18. Jimenez-Vazquez EN, Arad M, Macías Á, et al. SNTA1 gene rescues ion channel function and is antiarrhythmic in cardiomyocytes derived from induced pluripotent stem cells from muscular dystrophy patients. *Elife*. 2022;11:e76576. doi: 10.7554/eLife.76576

19. Barajas-Martínez H, Hu D, Ferrer T, et al. Molecular genetic and functional association of Brugada and early repolarization syndromes with S422L missense mutation in KCNJ8. *Heart Rhythm*. 2012;9(4):548555. doi: 10.1016/j.hrthm.2011.10.035

20. James CA, Jongbloed JDH, Hershberger RE, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the Clinical Genome Resource Framework. *Circ Genom Precis Med*. 2021;14(3):e003273. doi: 10.1161/CIRCGEN.120.003273

21. Campuzano O, Fernández-Falgueras A, Iglesias A, Brugada R. Brugada Syndrome and PKP2: Evidences and uncertainties. *Int J Cardiol*. 2016;214:403–405. doi: 10.1016/j.ijcard.2016.03.194

22. Shy D, Gillet L, Abriel H. Cardiac sodium channel NaV1.5 distribution in myocytes via interacting proteins: the multiple pool model. *Biochim Biophys Acta*. 2013;1833(4):886–894. doi: 10.1016/j.bbamcr.2012.10.026

23. Musa H, Murphy NP, Curran J, et al. Common human ANK2 variant confers in vivo arrhythmia phenotypes. *Heart Rhythm*. 2016;13(9):1932–1940. doi: 10.1016/j.hrthm.2016.06.012

24. Mohler PJ, Rivolta I, Napolitano C, et al. Nav1.5 E1053K mutation causing Brugada syndrome blocks binding to ankyrin-G and expression of Nav1.5 on the surface of cardiomyocytes. *Proc Natl Acad Sci USA*. 2004;101(50):17533–17538. doi: 10.1073/pnas.0403711101

25. Sherman J, Tester DJ, Ackerman MJ. Targeted mutational analysis of ankyrin-B in 541 consecutive, unrelated patients referred for long QT syndrome genetic testing and 200 healthy subjects. *Heart Rhythm*. 2005;2(11):1218–1223. doi: 10.1016/j.hrthm.2005.07.026

26. Ichikawa M, Aiba T, Ohno S, et al. Phenotypic variability of ANK2 mutations in patients with inherited primary arrhythmia syndromes. *Circ J*. 2016;80(12):2435–2442. doi: 10.1253/circj.CJ-16-0486

27. Micaglio E, Monasky MM, Ciconte G, et al. Novel SCN5A Frameshift mutation in Brugada syndrome associated with complex arrhythmic phenotype. *Front Genet*. 2019;10:547. doi: 10.3389/fgene.2019.00547

28. Huang Y, Chen XM, Barajas-Martinez H, et al. Common variants in SCN10A gene associated with Brugada syndrome. *Hum Mol Genet*. 2021;31(2):157–165. doi: 10.1093/hmg/ddab217

29. Biel S, Aquila M, Hertel B, et al. Mutation in S6 domain of HCN4 channel in patient with suspected Brugada syndrome modifies channel function. *Pflugers Arch*. 2016;468(10):1663–1671. doi: 10.1007/s00424-016-1870-1

30. Marsman EMJ, Postema PG, Remme CA. Brugada syndrome: update and future perspectives. *Heart*. 2022;108(9):668–675. doi: 10.1136/heartjnl-2020-318258

СПИСОК ЛИТЕРАТУРЫ

1. Brugada J., Campuzano O., Arbelo E., et al. Present status of brugada syndrome: JACC state-of-the-art review // J Am Coll Cardiol. 2018. Vol. 72, N. 9. P. 1046–1059. doi: 10.1016/j.jacc.2018.06.037

2. Garcia-Elias A., Benito B. Ion channel disorders and sudden cardiac death // Int J Mol Sci. 2018. Vol. 19, N. 3. P. 692. doi: 10.3390/ijms19030692

3. Coppola G., Corrado E., Curnis A., et al. Update on brugada syndrome 2019 // Curr Probl Cardiol. 2021. Vol. 46, N. 3. P. 100454. doi: 10.1016/j.cpcardiol.2019.100454

4. Benito B., Sarkozy A., Mont L., et al. Gender differences in clinical manifestations of Brugada syndrome // J Am Coll Cardiol. 2008. Vol. 52, N. 19. P. 1567–1573. doi: 10.1016/j.jacc.2008.07.052

5. Zeppenfeld K., Tfelt-Hansen J., de Riva M., et al. ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death // Eur Heart J. 2022. Vol. 43, N. 40. P. 3997–4126. doi: 10.1093/eurheartj/ehac262

6. Priori S.G., Gasparini M., Napolitano C., et al. Risk stratification in brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry // J Am Coll Cardiol. 2012. Vol. 59, N. 1. P. 37–45. doi: 10.1016/j.jacc.2011.08.064

7. Monasky M.M., Micaglio E., Giachino D., et al. Genotype-phenotype correlation in a family with brugada syndrome harboring the novel p.Gln371* nonsense variant in the scn5a gene // Int J Mol Sci. 2019. Vol. 20, N. 22. P. 5522. doi: 10.3390/ijms20225522

8. Campuzano O., Sarquella-Brugada G., Cesar S, et al. Update on genetic basis of brugada syndrome: monogenic, polygenic or oligogenic? // Int J Mol Sci. 2020. Vol. 21, N. 19. P. 7155. doi: 10.3390/ijms21197155

9. Agullo-Pascual E., Cerrone M., Delmar M. Arrhythmogenic cardiomyopathy and Brugada syndrome: diseases of the connexome // FEBS Lett. 2014. Vol. 588, N. 8. P. 1322–1330. doi: 10.1016/j.febslet.2014.02.008

10. Wilde A.A., Antzelevitch C., Borggrefe M., et al. Study group on the molecular basis of arrhythmias of the European society of cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report // Circulation. 2002. Vol. 106, N. 19. P. 2514–2519. doi: 10.1161/01.cir.0000034169.45752.4a

11. Wang K., Li M., Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data // Nucleic Acids Res. 2010. Vol. 38, N. 16. P. e164. doi: 10.1093/nar/gkq603

12. Richards S., Aziz N., Bale S., et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology // Genetics in Medicine. 2015. Vol. 17, N. 5. P. 405–424. doi: 10.1038/gim.2015.30

13. Andreasen L., Ghouse J., Skov M.W., et al. Brugada Syndrome-Associated Genetic Loci Are Associated With J-Point Elevation and an Increased Risk of Cardiac Arrest // Front Physiol. 2018. Vol. 9. P. 894. doi: 10.3389/fphys.2018.00894

14. Monasky M.M., Micaglio E., Vicedomini G., et al. Comparable clinical characteristics in Brugada syndrome patients harboring SCN5A or novel SCN10A variants // Europace. 2019. Vol. 21, N. 10. P. 1550–1558. doi: 10.1093/europace/euz186

15. Hu D., Barajas-Martínez H., Pfeiffer R., et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome // J Am Coll Cardiol. 2014. Vol. 64, N. 1. P. 66–79. doi: 10.1016/j.jacc.2014.04.032

16. Chambers J.C., Zhao J., Terracciano C.M., et al. Genetic variation in SCN10A influences cardiac conduction // Nat Genet. 2010. Vol. 42, N. 2. P. 149–152. doi: 10.1038/ng.516

17. Qi B., Wei Y., Chen S., et al. Nav1.8 channels in ganglionated plexi modulate atrial fibrillation inducibility // Cardiovasc Res. 2014. Vol. 102, N. 3. P. 480–486. doi: 10.1093/cvr/cvu005

18. Jimenez-Vazquez E.N., Arad M., Macías Á., et al. SNTA1 gene rescues ion channel function and is antiarrhythmic in cardiomyocytes derived from induced pluripotent stem cells from muscular dystrophy patients // Elife. 2022. Vol. 11. P. e76576. doi: 10.7554/eLife.76576

19. Barajas-Martínez H., Hu D., Ferrer T., et al. Molecular genetic and functional association of Brugada and early repolarization syndromes with S422L missense mutation in KCNJ8 // Heart Rhythm. 2012. Vol. 9, N. 4. P. 548555. doi: 10.1016/j.hrthm.2011.10.035

20. James C.A., Jongbloed J.D.H., Hershberger R.E., et al. international evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the Clinical Genome Resource Framework // Circ Genom Precis Med. 2021. Vol. 14, N. 3. P. e003273. doi: 10.1161/CIRCGEN.120.003273

21. Campuzano O., Fernández-Falgueras A., Iglesias A., Brugada R. Brugada Syndrome and PKP2: Evidences and uncertainties // Int J Cardiol. 2016. Vol. 214. P. 403–405. doi: 10.1016/j.ijcard.2016.03.194

22. Shy D., Gillet L., Abriel H. Cardiac sodium channel NaV1.5 distribution in myocytes via interacting proteins: the multiple pool model // Biochim Biophys Acta. 2013. Vol. 1833, N. 4. P. 886–894. doi: 10.1016/j.bbamcr.2012.10.026

23. Musa H., Murphy N.P., Curran J., et al. Common human ANK2 variant confers in vivo arrhythmia phenotypes // Heart Rhythm. 2016. Vol. 13, N. 9. P. 1932–1940. doi: 10.1016/j.hrthm.2016.06.012

24. Mohler P.J., Rivolta I., Napolitano C., et al. Nav1.5 E1053K mutation causing Brugada syndrome blocks binding to ankyrin-G and expression of Nav1.5 on the surface of cardiomyocytes // Proc Natl Acad Sci USA. 2004. Vol. 101, N. 50. P. 17533–17538. doi: 10.1073/pnas.0403711101

25. Sherman J., Tester D.J., Ackerman M.J. Targeted mutational analysis of ankyrin-B in 541 consecutive, unrelated patients referred for long QT syndrome genetic testing and 200 healthy subjects // Heart Rhythm. 2005. Vol. 2, N. 11. P. 1218–1223. doi: 10.1016/j.hrthm.2005.07.026

26. Ichikawa M., Aiba T., Ohno S., et al. Phenotypic variability of ANK2 mutations in patients with inherited primary arrhythmia syndromes // Circ J. 2016. Vol. 80, N. 12. P. 2435–2442. doi: 10.1253/circj.CJ-16-0486

27. Micaglio E., Monasky M.M., Ciconte G., et al. Novel SCN5A frameshift mutation in Brugada syndrome associated with complex arrhythmic phenotype // Front Genet. 2019. Vol. 10 P. 547. doi: 10.3389/fgene.2019.00547

28. Huang Y., Chen X.M., Barajas-Martinez H., et al. Common variants in SCN10A gene associated with Brugada syndrome // Hum Mol Genet. 2021. Vol. 31, N. 2. P. 157–165. doi: 10.1093/hmg/ddab217

29. Biel S., Aquila M., Hertel B., et al. Mutation in S6 domain of HCN4 channel in patient with suspected Brugada syndrome modifies channel function // Pflugers Arch. 2016. Vol. 468, N. 10. P. 1663–1671. doi: 10.1007/s00424-016-1870-1

30. Marsman E.M.J., Postema P.G., Remme C.A. Brugada syndrome: update and future perspectives // Heart. 2022. Vol. 108, N. 9. P. 668–675. doi: 10.1136/heartjnl-2020-318258

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How to improve long-term results of patients with atrial fibrillation of non-valvular ethiology after embolism to main arteries of the limbs

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ABSTRACT

BACKGROUND: In patients with atrial fibrillation, systemic thromboembolic complications dramatically worsen the long-term prognosis. There is currently no generally accepted treatment tactics for patients with atrial fibrillation of non-valvular ethiology after embolism to main arteries of the limbs. Objective: evaluate the efficacy of our approach for patients with atrial fibrillationof non-valvular ethiology who survived an embolism to main arteries of the limbs and acute limb ischemia.

MATERIALS AND METHODS: For the period from 1991 to 2022, in the Department of Vascular Surgery of our institution, emergency care due to embolism and acute limb ischemia was provided to 1816 patients. In 1425 (78.5%) patients, the main disease that led to arterial embolism was non-valvular atrial fibrillation. In the long-term period after discharge from our clinic, it was possible to trace the fate of 216 patients and determine the cause of death for 106 patients. The main causes of death in the long-term period were the decompensation of chronic diseases of the cardiovascular system in 73,6% of patients and the recurrence of systemic thromboembolic complications in 21.7%. Since 2012, at our department an integrated approach has been developed and implemented. It included a set of measures aimed at compensating for chronic cardiovascular pathology and preventing the recurrence of systemic thromboembolic complications. The whole set of measures all patients underwent during their current hospitalization after the elimination of life-threatening complications associated with acute limb ischemia and the stabilization of their general condition. They formed the main group (n = 50). The control group (n = 166) consisted of patients after embolism and acute limb ischemia discharged before 2012. Their cardiac pathology was treated after discharge from our department on an outpatient basis in a polyclinic at their place of residence. The overall comparative survival rate was analyzed. The survival function was evaluated using the Kaplan – Meyer method.

RESULTS: In the control group, long-term survival was low, and the median life expectancy was 24 months after discharge. In the main group, long-term survival improved significantly, and the median survival period was not reached during the observation time set. The differences in overall survival estimated using the likelihood ratio test were statistically significant (p = 0.001). When evaluating the groups, the risk of death in the main group was 2.2 times lower than in the control group for each month of follow-up (p = 0.003).

CONCLUSION: the set of measures implemented in our clinic over the last decade for patients with atrial fibrillation of non-valvular ethiology hospitalized with arterial embolism and acute limb ischemia has proved its efficacy and significantly (p = 0.003) improved the survival rate of patients with long-term follow-up after discharge from our department.

Keywords: atrial fibrillation; embolism of the main arteries of the limbs; long-term survival rate.

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Пути улучшения отдаленных результатов лечения больных с фибрилляцией предсердий неклапанной этиологии, перенесших эмболию магистральных артерий конечностей

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АННОТАЦИЯ

Актуальность. У больных с фибрилляцией предсердий системные тромбоэмболические осложнения существенно ухудшают отдаленный прогноз. Общепринятой системы, определяющей дальнейшую тактику лечения больных с фибрилляцией предсердий неклапанной этиологии, перенесших эмбологенную артериальную непроходимость, в настоящее время нет.

Цель — оценить эффективность проводимого лечения пациентов с фибрилляцией предсердий неклапанной этиологии, перенесших эмболию магистральных артерий конечностей.

Материалы и методы. За период с 1991 по 2022 год в отделении сердечно-сосудистой хирургии № 1 (ангиохирургия) СЗГМУ им. И.И. Мечникова оказана экстренная помощь 1816 больным с эмболиями магистральных артерий конечностей. У 1425 больных (78,5 %) основным эмбологенным заболеванием была фибрилляция предсердий неклапанной этиологии. В отдаленном периоде после выписки из отделения удалось проследить судьбу 216 пациентов и установить причину смерти у 106 пациентов. Основными причинами смерти в отдаленные сроки стали декомпенсация хронических заболеваний сердечно-сосудистой системы у 73,6 % больных и рецидивы системных тромбоэмболических осложнений у 21,7%. С 2012 года в клинике внедрен комплекс мер, направленных на компенсацию хронической сердечно-сосудистой патологии и предупреждение рецидивов системных тромбоэмболических осложнений. Весь комплекс мер проводился в текущую госпитализацию после устранения угрожающих жизни осложнений, связанных с острой ишемией конечности, и стабилизации общего состояния пациентов. Они составили основную группу (n = 50). Контрольную группу (n = 166) составили пациенты с эмбологенной артериальной непроходимостью, выписанные до 2012 г. Лечение кардиальной патологии после перенесенной эмбологенной артериальной непроходимости они получали амбулаторно в поликлинике по месту жительства. Проведен сравнительный анализ показателей общей выживаемости. Оценка функции выживаемости проводилась по методу Каплана – Мейера.

Результаты. В контрольной группе отдаленная выживаемость была низкой, медиана средней продолжительности жизни составила 24 мес после выписки. В основной группе отдаленная выживаемость значительно улучшилась, медиана средней продолжительности жизни увеличилась и за период наблюдения достигнута не была. Различия общей выживаемости, оцененные с помощью теста отношения правдоподобия, были статистически значимы (p = 0,001). При оценке групп сравнения риск наступления летального исхода в основной группе был ниже в 2,2 раза по сравнению с контрольной группой на каждый месяц наблюдения (p = 0,003).

Заключение. Внедренный в отделении сердечно-сосудистой хирургии № 1 (ангиохирургии) СЗГМУ им. И.И. Мечникова за последнее десятилетие комплекс мер по лечению пациентов с фибрилляцией предсердий неклапанной этиологии, госпитализированных с эмбологенной артериальной непроходимостью, показал свою эффективность и достоверно (p = 0,003) улучшил выживаемость пациентов с отдаленные сроки после выписки из нашего стационара.

Ключевые слова: фибрилляция предсердий; эмболия магистральных артерий конечностей; отдаленная выживаемость.

Как цитировать

Сотников А.В., Мельников М.В., Пышный М.В., Семенюта В.В. Пути улучшения отдаленных результатов лечения больных с фибрилляцией предсердий неклапанной этиологии, перенесших эмболию магистральных артерий конечностей // Cardiac Arrhythmias. 2023. Т. 3, № 4. С. 21–31. DOI: https://doi.org/10.17816/cardar625527

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ЭКО•ВЕКТОР

Nonvalvular atrial fibrillation (AF) is common among elderly and senile people in Russia [1]. Moreover, systemic thromboembolic complications (STEC) significantly worsen the immediate and long-term prognoses of patients with AF. Embolism of the main arteries of the extremities ranks second in incidence following cardioembolic strokes among STEC [2]. The survival rate of patients with embologenic arterial obstruction (EAO) is extremely low [3]. The main causes of high mortality in the long term have not been sufficiently studied. Currently, there is no generally accepted system that determines further treatment approach for patients with nonvalvular AF with a history of EAO.

This study aimed to evaluate the efficiency of a set of treatment measures for patients with nonvalvular AF with a history of EAO.

MATERIALS AND METHODS

Overall, 1816 patients with EAO received treatment in the Department of Cardiovascular Surgery No. 1 of Peter the Great Clinic of Mechnikov North Western State Medical University between 1991 and 2022; in 1425 (78.5%) of the patients, acute limb ischemia (ALI) developed in presence of nonvalvular AF. The collection, accumulation, and computer processing of clinical material was performed using the original program "Doctor's Scientific Archive — DSM", which was developed at Mechnikov North Western State Medical University and registered in the "Register of Computer Programs" of the Federal Service for Intellectual Property, Patents, and Trademarks (certificate of official registration of the computer program no. 2004611296; May 26, 2004).

Table 1 presents the clinical characteristics of the patients.

Among patients hospitalized with EAO due to AF, women predominated (67.9%), and 88.3% of patients were elderly and senile. All patients were urgently admitted with a clinical presentation of ALI. The degree of ischemia was assessed according to the classification by Zatevakhin et al. The severity of ALI manifestations upon admission to the clinic varied. Moreover, 470 (33.0%) patients were hospitalized with nonthreatening limb ischemia (degree I). The clinical manifestations of ALI were pain and paresthesia

Table 1. Clinical characteristics of patients with AF of non-valvular etiology hospitalized at our clinic with acute limb ischemia due to embolism
Таблица 1. Клиническая характеристика больных с фибрилляцией предсердий неклапанной этиологии, госпитализированных в отделении сердечно-сосудистой хирургии №1 (ангиохирургии) СЗГМУ им. И. И. Мечникова с эмбологенной артериальной непроходимостью

Indicators	Categories	Number of cases (*n* = 1425)	Proportion, %	95% Confidence interval
Sex	Women	968	67.9	65.4–70.3
	Men	457	32.1	29.7–34.6
Age, years	30–39	3	0.2	0.0–0.6
	40–49 years old	36	2.5	1.8–3.5
	50–59 years old	128	9.0	7.5–10.6
	60–69 years old	314	22.0	19.9–24.3
	70–79 years old	518	36.4	33.8–38.9
	Over 80 years old	426	29.9	27.5–32.3
Degree of acute limb ischemia (according to Zatevakhin [4])	I	470	33.0	30.5–35.5
	IIa	480	33.7	31.2–36.2
	IIb	277	19.4	17.4–21.6
	IIc	99	6.9	5.7–8.4
	IIIa	9	0.6	0.3–1.2
	IIIb	90	6.3	5.1–7.7
Duration of limb ischemia before hospitalization	Up to 6 hours	447	31.4	29.0–33.8
	6–12 hours	563	39.5	37.0–42.1
	12–24 hours	150	10.5	9.0–12.2
	24–48 hours	73	5.1	4.0–6.4
	Over 48 hours	192	13.5	11.7–15.4
Atrial fibrillation	Paroxysmal or persistent form	470	33.0	30.5–35.5
	Permanent form	939	65.9	63.4–68.4
	Permanent form, PPM	16	1.1	0.6–1.6

End of the table 1

Indicators	Categories	Number of cases (*n* = 1425)	Proportion, %	95% Confidence interval
Ischemic heart disease	Chronic IHD without a history of myocardial infarction	669	46.9	44.8–49.1
	Postinfarction cardiosclerosis	205	14.4	12.6–16.3
	Acute period of myocardial infarction	43	3.0	2.2–4.0
Arterial hypertension	Degree I	77	5.4	4.3–6.7
	Degree II	1223	85.8	83.9–87.6
	Degree III	125	8.8	7.4–10.4
Chronic heart failure	Not expressed	59	4.1	3.2–5.3
	Stage 2	1291	90.6	89.0–92.1
	Stage 3	75	5.3	4.2–6.6
Concomitant disease	Atherosclerosis of peripheral arteries	256	18.0	16.0–20.1
	Diabetes mellitus	283	19.9	17.8–22.0
	Chronic nonspecific lung diseases	229	16.1	14.2–18.1
	Chronic kidney and/or liver diseases	63	4.4	3.4–5.6
	Others	23	1.6	1.0–2.4
History of acute disturbances in arterial blood supply	Acute cerebrovascular accident	179	12.6	10.9–14.4
	Embologenic arterial obstruction	126	8.8	7.5–10.4

Note: IHD — ischemic heart disease; PPM — permanent pacemaker; AF — atrial fibrillation.

Примечание: ИБС — ишемическая болезнь сердца; ПЭКС — постоянный электрокардиостимулятор; ФП — фибрилляция предсердий.

in the ischemic limb. Majority of the patients (856 cases; 60.1%) were hospitalized with manifestations of threatening ALI (degrees IIA–IIB). In addition to pain, the main clinical presentation was sensory and motor disorders in the ischemic limb, namely, paresis and paralysis. The most severe condition was noted in 99 (6.9%) patients hospitalized with irreversible acute ischemia (IIIa and IIIb), that is, distal or total contracture of the limb. Moreover, 588 (41.3%) patients had acute ischemia of the upper limb and 803 (56.3%) had the lower limbs affected, including 27 (1.9%) patients with acute ischemia of both lower limbs caused by embolism associated with aortic bifurcation. Multiple embolisms with simultaneous damage to two or three arterial territories of the extremities was diagnosed in 34 (2.4%) patients.

In all patients included in this study, AF was the major cause of EAO. Paroxysmal or persistent AF was detected in 470 (33.0%) patients, whereas the permanent form of AF was observed in 939 (65.9%) patients, and a permanent pacemaker had been previously implanted in 16 of these patients.

In most patients, AF-associated background cardiac pathology manifested as hypertension, ischemic heart disease (IHD), and atherosclerotic cardiosclerosis. Degree I arterial hypertension was detected in 77 (5.4%) patients, and degree II was found in 1223 (85.8%) patients. Arterial hypertension severity was correlated with chronic heart failure (CHF) severity. In most of the patients (1291 cases; 90.6%), clinical manifestations corresponded to stage IIa–b CHF. Other predisposing factors of AF included IHD such as stable effort angina without a history of acute myocardial infarction (AMI) in 669 (46.9%) patients, postinfarction cardiosclerosis in 205 (14.4%) patients, and an acute period of myocardial infarction in 43 (3.0%) patients. Concomitant noncardiac pathology was significant in the development of AF in several patients: diabetes mellitus in 283 (19.9%) patients and chronic nonspecific lung diseases in 229 (16.1%) hospitalized patients. In 256 (18.0%) patients, ALI coexisted with stage 2 chronic arterial insufficiency caused by peripheral atherosclerosis.

A crucial characteristic of the studied group of patients was their CHA2DS2-Vasc scale score [5]. More than 97% of the patients had a high or extremely high risk of STEC (Table 2).

The adherence to prescribed oral anticoagulant therapy during the prehospital stage of patients hospitalized in the past 10 years in the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University was approximately 12%. In earlier cases, systemic antithrombotic therapy in patients admitted with EAO was limited to acetylsalicylic acid.

In most cases, medical approach in relation to ALI in the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University included open surgical treatment aimed at restoring arterial blood supply to the limb. Moreover,

Table 2. Values of CHA2DS2-Vasc scores in patients hospitalized at our clinic with acute limb ischemia due to embolism
Таблица 2. Значения баллов по шкале CHA2DS2-Vasc у госпитализированных в отделение сердечно-сосудистой хирургии № 1 (ангиохирургии) СЗГМУ им. И.И. Мечникова пациентов с эмбологенной артериальной непроходимостью

Value on the CHA2DS2-Vasc scale	Number of cases (n = 1425)	Proportion, %	95% Confidence interval
2 points	5	0.4	0.1–0.8
3 points	31	2.2	1.5–3.1
4 points	151	10.6	9.0–12.3
5 points	290	20.4	18.3–22.5
6 points	385	27.0	24.7–29.4
7 points	380	26.7	24.4–29.0
8 points	158	11.1	9.5–12.8
9 points	25	1.8	1.1–2.6

Note: CHA2DS2-Vasc is a scale for assessing the risk of systemic thromboembolic complications in patients with atrial fibrillation [5].
Примечание: CHA2DS2-Vasc — шкала оценки риска системных тромбоэмболических осложнений у больных с фибрилляцией предсердий [5].

1241 (87.1%) patients underwent emergency surgery, and another 74 (5.2%) patients received surgical treatment within 24 h of admission. Operational activity was 92.3%. In 1239 (86.9%) patients, limb revascularization was performed using direct or indirect embolectomy with a balloon catheter. In 76 (5.8%) patients, because of irreversible ischemia, primary amputation of the limb was conducted within well-vascularized tissues.

Revascularization resulted in restoration of the main arterial blood supply in 892 (65.5%) patients, with complete ALI regression and peripheral pulse restoration. In 333 (25.3%) patients, the arterial blood supply to the limb was reestablished following surgery without restoring the pulsation of the distal limb arteries. The required limb perfusion was not achieved in 14 (1.0%) patients after the intervention. In 73 (5.1%) patients with nonthreatening ALI (grade I), arterial blood supply was restored through conservative treatment. Hospital mortality was 12.2%; 174 patients died. The main causes of in-hospital lethal outcomes were the initial terminal condition in 37 (2.6%) patients and postoperative complications, including ischemic intoxication, decompensation of the initial cardiac and other concomitant pathologies, and STEC relapses in 137 (9.6%) patients. Additionally, 1183 (83%) patients were discharged with a salvaged limb.

Furthermore, 216 patients were available for analysis of long-term treatment results. The follow-up period ranged from 1 to 12 years. The causes of lethal outcomes in long-term follow-up were established in 106 patients, that is, decompensation of CHF in 52 (49.1%) patients, AMI in 26 (24.5%), recurrent STEC in 23 (21.7%), and other causes in 5 (4.7%) (Fig. 1). Summarizing the causes of the high long-term mortality of patients discharged from the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University, after treatment for EAO, the most significant links in thanatogenesis in the long term were decompensation of chronic cardiovascular disease in 73.6% of the patients and relapse of systemic thromboembolic events in 21.7%.

Statistical analysis was performed using StatTech v. 4.0.4 (Stattech, Russia).

Until 2012, in the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University, after eliminating life-threatening complications associated with ALI and stabilizing the general condition, majority of the patients were discharged on days 5–7 for outpatient treatment under the supervision of a therapist at the primary healthcare facility. Patients available for contact in the long term after discharge (n = 166) formed the control group (CG) of follow-up.

The involvement of a cardiologist among the staff of our department in 2012 enabled the implementation of the main (cardiological) part of the rehabilitation. Since then, the cardiologist of the Department of Cardiovascular

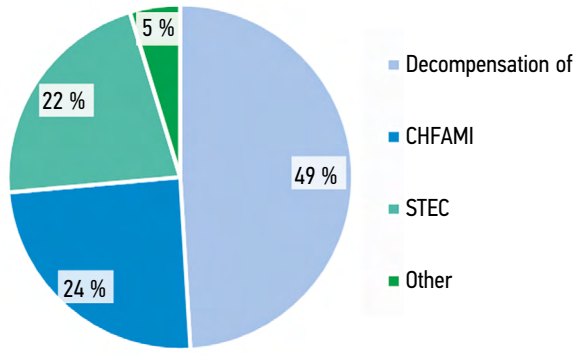


Fig. 1. The main causes of death of patients with AF in the long term follow-up discharged from our clinic after treatment for acute limb ischemia due to embolism. AMI — acute myocardial infarction; STEC — systemic thromboembolic events; AF — atrial fibrillation; CHF — chronic heart failure
Рис. 1. Основные причины смерти пациентов с ФП в отдаленные сроки, выписанных из отделения сердечно-сосудистой хирургии № 1 (ангиохирургии) СЗГМУ им. И. И. Мечникова после лечения по поводу эмбологенной артериальной непроходимости. ОИМ — острый инфаркт миокарда; СТЭО — системные тромбоэмболические осложнения; ФП — фибрилляция предсердий; ХСН — хроническая сердечная недостаточность

Surgery No. 1 (Angiosurgery) select directly and prescribe anticoagulants, antihypertensives, and cardiotropic therapy for patients of the main group (MG) according to current clinical recommendations, coordinate the treatment of concomitant noncardiac pathology, resolve the issue of further treatment strategies for AF ("rhythm control" or "rate control"), determine indications for consultation with an arrhythmologist, verify myocardial ischemia, identify indications for coronary angiography and the need and timing of myocardial revascularization, establish the significance of structural heart pathology and indications for consultation with a cardiac surgeon, and determine indications for alternative methods of preventing STEC such as implantation of an occluder of the left atrial appendage. Patients discharged after 2012 and who were available for contact in the long term after discharge were included in the MG (n = 50).

A cross-sectional and observational study was conducted in MG, whereas a retrospective analysis was performed in CG.

RESULTS

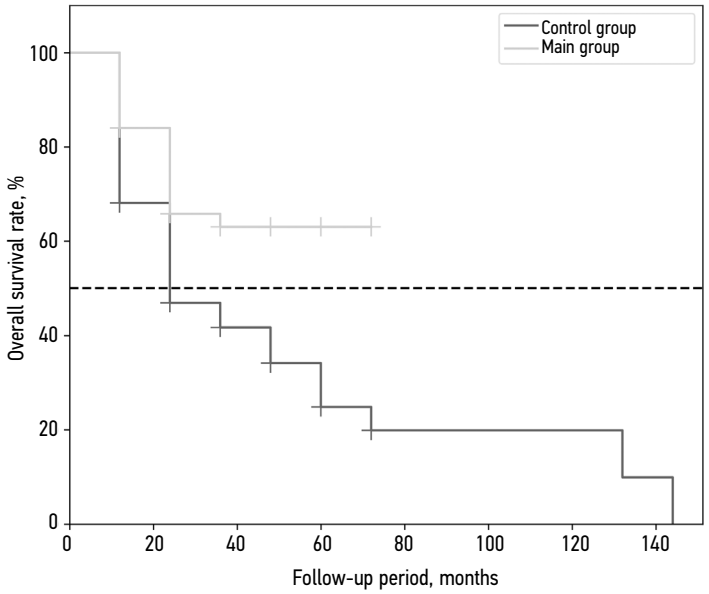
Analysis of the overall survival in the study participants was performed depending on the comparison groups. The survival function of patients was assessed using the Kaplan – Meier method (Fig. 2).

The analysis showed that the 75th percentile of life expectancy in CG was 12 (12–12) months from the start of monitoring, the median was 24 (24–48) months, and the 25th percentile was 60 (48–144) months. In the study group, the 75th percentile of life expectancy was 24 (12 – ∞) months, and the median and 25th percentiles for the entire follow-up period were not reached (Fig. 2). Differences in overall survival, which was assessed using the likelihood ratio test, were statistically significant (p = 0.001).

To determine the key factors that influenced the risk of lethal outcome, a multivariate Cox proportional hazards regression analysis was performed. Following multifactorial stepwise selection, only the factor of attitude toward the group was statistically significantly associated with the event occurrence. The final proportional hazards model was as follows:

$$h_i(t) = h_o(t) \times \exp(-0{,}801 \times X_{\text{Comparison groups : MG}})$$

where $h_i(t)$ is the predicted risk of the deceased for the i-th follow-up element (%), $h_o(t)$ is the basic risk of the deceased for a certain time period t (%), and $X_{\text{Comparison groups : MG}}$ — $X_{\text{Comparison groups : Main group}}$ (Table 3, Fig. 3).



Control group								
Cases	166	87	22	5	2	2	2	1
Censored	0	26	59	69	71	71	71	71
Events	0	53	85	92	93	93	93	94
Main group								
Cases	50	37	17	2	0	0	0	0
Censored	0	5	16	31	33	33	33	33
Events	0	8	17	17	17	17	17	17

Fig. 2. The overall survival curve depending on the comparison groups
Рис. 2. Кривая общей выживаемости в зависимости от групп сравнения

Table 3. Values of the basic risk of death for different periods for the general sample of the patients
Таблица 3. Значения базового риска смерти для разных временных периодов для общей выборки пациентов

Time periods, months	Base risk values $h_o(t)$, %
12	32.37
24	66.15
36	76.907
48	90.406
60	110.965
72	127.921
132	177.921
144	277.921

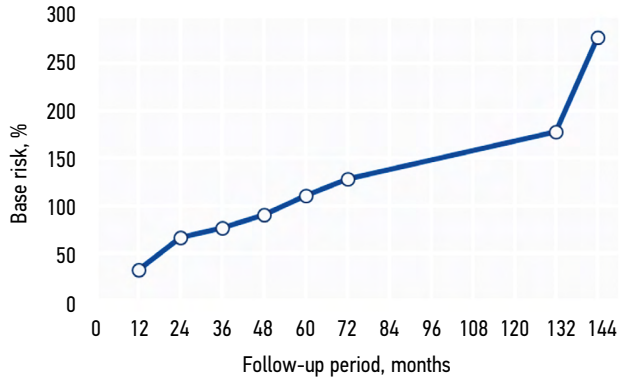


Fig. 3. The curve of the basic risk for the entire follow-up period for the general sample of the patients
Рис. 3. Кривая базового риска смерти на весь период наблюдения для общей выборки пациентов

The relative risk of MG was 0.449 (0.267–0.755; $p = 0.003$). Accordingly, the risk of lethal outcome in MG was 2.227 times lower than that in CG for each month of follow-up. This is equivalent to a 26.7-fold reduction in the risk of death for each year since the start of treatment.

DISCUSSION

The study results showed the advantages of developing a scheme for further conservative treatment of AF patients with a history of EAO during the current hospitalization compared with rehabilitation conducted at the outpatient stage.

The study was cross-sectional and observational in nature; therefore, full coverage of discharged patients was not expected. The study patients were mostly elderly and of low social status; thus, even at the end of year 1, contact with most of them was complicated. Data from the most compliant patients are presented, and the results showed a significantly increased survival rate of patients in long-term follow-up. The immediate causes of lethal outcomes of patients in the long-term period were mostly established according to information provided by relatives, since most of the patients died at home or in different hospitals in the city. More than two-thirds of the deaths were due to the decompensation of chronic cardiovascular diseases, and in a quarter of patients, sudden severe neurological symptoms indicated a relapse of STEC (Fig. 1).

Experience in the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University provided evidence on the extremely low adherence of hospitalized EAO patients to lifelong oral anticoagulant therapy, which should have been performed on an outpatient basis. Among EAO patients admitted to our hospital, the overall adherence to this type of treatment was approximately 12%. Moreover, this trend has not improved over the past decade. The lack of anticoagulant therapy was often associated with insufficient patient awareness of the risks associated with AF, or the arrhythmia was first identified during hospitalization. The lack of continuous anticoagulation therapy could be one of the main factors in the development of EAO. Low adherence to oral anticoagulant treatment among AF patients hospitalized for STEC has been noted among those admitted with embolism of the main arteries [6] and acute cerebrovascular accident (ACVA). Thus, 6.9%–17.5% of AF patients hospitalized for ACVA in 2014–2015 took anticoagulants regularly and in an adequate dose [7].

This type of treatment is critical for the study patients, considering their CHA2DS2-Vasc score (Table 2).

The selection and prescription of an oral anticoagulant for lifelong use should be performed during the current hospitalization, immediately after limb revascularization, and stabilization of the condition during inpatient treatment. Currently, the main oral medications for patients with AF are indirect anticoagulants (warfarin) and new oral anticoagulants (NOACs). According to current clinical guidelines, NOACs are the drugs of choice in patients with nonvalvular AF for the prevention of STEC; however, warfarin may also be considered [8]. In 2011–2016, the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University prescribed NOACs to MG patients in every third case; in the remaining cases, the warfarin dose was selected according to the international normalized ratio (INR). In recent years, NOACs have been prescribed to most patients, and the prescription of indirect anticoagulants has become an exception.

In this study, patient adherence to anticoagulant therapy in the long term after EAO and discharge from the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University was significantly higher than that before hospitalization, which was facilitated by regular follow-up of patients by an angiosurgeon and cardiologist. During the follow-up period, the average adherence of MG to this type of treatment prescribed upon discharge among patients available for contact was 52.0% (26 patients). The main drugs taken were NOACs. No relapses of hospitalizations were observed in MG patients with EAO in the Department of Cardiovascular Surgery No. 1 University over the past decade. Among newly admitted patients, a decrease in the frequency of EAO relapses during hospitalization was not noted (26 patients in MG (8.8%) versus 100 patients in CG (8.8%)).

Despite the convenience of using NOACs, warfarin may have advantages for treating some patients after EAO. First is the low cost (orders of magnitude less than NOAC drugs), which enables elderly patients, even those with low income, to provide themselves with this drug in case of difficulties with free provision of NOACs. Second is the constant availability of warfarin in pharmacies in various regions of Russia since it is produced in Russia. Finally, despite the safety of using NOACs, we believe that a drawback is the lack of an accessible method for monitoring the regularity of their intake. Upon detailed questioning of patients taking NOACs, evidence of errors in the regularity of administration was repeatedly revealed, which could affect the final efficiency. Over the years of monitoring, we identified only one patient in whom EAO occurred while taking warfarin in presence of target INR values. Thus, the choice of an anticoagulant drug for lifelong use in patients with AF who have undergone EAO requires a differentiated approach.

The next mandatory step for treating patients with AF who have undergone EAO is normalization of blood pressure. This component of therapy should be identified and implemented in the current hospitalization as soon as the patient's condition has stabilized. The data from our study indicate that all hospitalized patients had hypertensive disease (HD), with only 5.4% of patients having initial forms such as degree I arterial hypertension (AH). In the rest, degrees II and III AH were determined. The wide prevalence of HD among patients with nonvalvular AF in Russia is confirmed by literature data [1]. This emphasizes the leading role of chronic AH in the development of AF. Uncontrolled AH in patients with AF leads to increased CHF incidence, increased risk of STEC, and increased risk of hemorrhage during lifelong use of oral anticoagulants [9]. Therefore, the selection of effective antihypertensive therapy at the stage of inpatient rehabilitation after EAO, in addition to the selection of oral anticoagulants, is critical. Repeated studies have confirmed improved long-term survival of patients with AF when arterial normotension is achieved [10, 11].

Moreover, it is crucial to select cardiotropic therapy to compensate for the manifestations of CHF in accordance with current clinical recommendations. Optimization of this type of treatment during the current hospitalization, according to MG results, had advantages compared with delayed administration. The relevance of this type of treatment for patients was due to the high prevalence of high-grade CHF among hospitalized patients. Manifestations of chronic circulatory failure were at stage IIa–b in 90.6% of patients and at stage III in 5.3% of cases. In addition to significant limitations of physical activity and decreased quality of life, CHF decompensation was the leading cause of lethal outcomes in the long term after discharge in almost 50% of the patients. According to current clinical recommendations, the composition of drugs for optimal drug therapy for CHF should include angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and dapagliflozin [12]. Effective drug therapy improves long-term survival rates in patients with AF (CHARM 2006, ANTIPAF 2012, GISSI-AF 2009, EMPHASIS-HF 2012 studies). Furthermore, it aims to normalize coronary circulation in chronic forms of IHD. In the study group, 46.9% of patients had chronic IHD without a history of myocardial infarction, and another 14.4% of patients had postinfarction cardiosclerosis.

In addition to optimizing anticoagulant and cardiotropic therapy, patients with AF who underwent EAO during their current hospitalization required treatment for concomitant pathology, primarily diabetes mellitus (DM). The recommended composition of optimal drug therapy for the treatment of CHF includes the hypoglycemic drug dapagliflozin, even in the absence of DM, with recommendations class I and level of evidence A [12]. Notably, the prevalence of DM among hospitalized patients was 19.9%. The increased risk of thrombotic complications in DM is associated with an increase in the level of blood coagulation factors and inhibition of fibrinolysis, which is associated with chronic hyperglycemia [13]. Strict control of glucose levels and stable normoglycemia can reduce the risk of STEC in patients with AF [14].

When considering a treatment strategy for AF ("rhythm control" or "rate control") after EAO, most patients required a "rate control" strategy, i.e., achieving normosystole without attempting to restore the sinus pacemaker. This is due to the fact that most of the patients were elderly (66.3% of patients were over 70 years old) and that in 67.0% of cases, AF was permanent. The appropriateness of choosing the "rhythm control" strategy with this combination was controversial. In some cases of paroxysmal AF and high life expectancy, the "rhythm control" approach was chosen; however, these cases were rare. Therefore, conclusions about long-term efficiency require data accumulation.

A promising direction that can make a positive contribution to improving the long-term survival of patients with AF with a history of EAO in MG is endovascular implantation of an occluder of the left atrial appendage. This procedure is as effective as warfarin in preventing STEC in patients with contraindications to oral anticoagulants, as demonstrated in the PROTECT AF trial [15]. In the Department of Cardiovascular Surgery No. 1 (Angiosurgery) of Mechnikov North Western State Medical University, endovascular implantation of left atrial appendage occluders has been performed since 2019. The long-term results of this treatment type in patients with a history of EAO are currently being analyzed.

Optimization of conservative treatment during the current hospitalization in AF patients with a history of EAO improved long-term survival. We believe that the most significant difference was the normalization of anticoagulant therapy. However, the clinical role of the remaining links cannot be overestimated. The relatively small number of patients available for long-term follow-up did not enable to identify the most crucial among these links; therefore, continued research in this direction has been planned. This study primarily aimed to evaluate the influence of the optimization of cardiotropic therapy on long-term survival in EAO patients during the current hospitalization. We have not come across any publications in the available literature on the prospects for improving long-term results of treatment of patients with nonvalvular AF with a history of EAO.

CONCLUSION

The absence of a generally accepted system that determines further treatment approach for patients with nonvalvular AF with a history of EAO reduces long-term survival. Optimization of conservative treatment during rehabilitation after EAO during the current hospitalization led to a monthly reduction in the risk of lethal outcome by 2.2 times ($p = 0.003$).

ADDITIONAL INFORMATION

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REFERENCES

1. Shlyakhto EV, Ezhov AV, Zenin SA, et al. Clinical portrait of the atrial fibrillation patient in Russian Federation. Data from the global registry Gloria AF. *Russian Journal of Cardiology*. 2017;(9):21–27. EDN: ZIBDLB doi: 10.15829/1560-4071-2017-9-21-27

2. Menke J, Lüthje L, Kastrup A, Larsen J. Thromboembolism in atrial fibrillation. *Am J Cardiol*. 2010;105(4):502–510. doi: 10.1016/j.amjcard.2009.10.018

3. Melnikov MV, Sotnikov AV, Melnikov VM, Papava GD. Life expectancy of patients who underwent embolism of the aorta and main arteries of the extremities. *Angiology and Vascular Surgery*. 2018;24(3):26–31. (In Russ.) EDN: LYPVYT

4. Zatevakhin II, Tsitsiashvili MS, Zolkin VN. Acute arterial obstruction. Clinical classification and treatment tactics. *Angiology and Vascular Surgery*. 2002;8(2):74–77. (In Russ.)

5. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263–272. doi: 10.1378/chest.09-1584

6. Kempe K, Starr B, Stafford JM, et al. Results of surgical management of acute thromboembolic lower extremity ischemia. *J Vasc Surg*. 2014;60(3):702–707. doi: 10.1016/j.jvs.2014.03.273

7. Zolotovskaya IA, Davydkin IL, Duplyakov DV. Anticoagulation in atrial fibrillation patients after cardioembolic stroke: evaluation of treatment adherence in real practice (Cohort study "APOLLON"). *Russian Journal of Cardiology*. 2017;147(7):105–110. EDN: ZDEBWJ doi: 10.15829/1560-4071-2017-7-105-110

8. Arakelyan MG, Bockeria LA, Vasilieva EYu, et al. 2020 clinical guidelines for atrial fibrillation and atrial flutter. *Russian Journal of Cardiology*. 2021;26(7)190–260. (In Russ.) EDN: FUZAAD doi: 10.15829/1560-4071-2021-4594

9. Vemulapalli S, Inohara T, Kim S, et al. Blood pressure control and cardiovascular outcomes in patients with atrial fibrillation (from the ORBIT-AF Registry). *Am J Cardiol*. 2019;123(10):1628–1636. doi: 10.1016/j.amjcard.2019.02.010
10. Ishii M, Ogawa H, Unoki T, et al. Relationship of hypertension and systolic blood pressure with the risk of stroke or bleeding in patients with atrial fibrillation: the Fushimi AF Registry. *Am J Hypertens*. 2017;30(11):1073–1082. doi: 10.1093/ajh/hpx094
11. Proietti M, Romiti GF, Olshansky B, Lip GYH. Systolic blood pressure visit-to-visit variability and major adverse outcomes in atrial fibrillation: The AFFIRM Study (Atrial Fibrillation Follow-Up Investigation of Rhythm Management). *Hypertension*. 2017;70(5): 949–958 doi: 10.1161/HYPERTENSIONAHA.117.10106
12. McDonagh T, Metra M, Adamo N, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Russian Journal of Cardiology*. 2023;28(1):117–224. EDN: SJMIKK doi: 10.15829/1560-4071-2023-5168
13. O'Hara A, Pozin J, Darki A, et al. Glycemic control and plasma levels of pro-inflammatory and pro-thrombotic biomarkers in diabetic patients presenting with acute pulmonary embolism. *Clin Appl Thromb Hemost*. 2023;29:10760296231165058. doi: 10.1177/10760296231165058
14. Papazoglou AS, Kartas A, Moysidis DV, et al. Glycemic control and atrial fibrillation: an intricate relationship, yet under investigation. *Cardiovasc Diabetol*. 2022;21(1):39. doi: 10.1186/s12933-022-01473-0
15. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312(19):1988–1998. doi: 10.1001/jama.2014.15192

СПИСОК ЛИТЕРАТУРЫ

1. Шляхто Е.В., Ежов А.В., Зенин С.А., и др. Кинический портрет пациента с фибрилляцией предсердий в Российской Федерации. Данные глобального регистра GLORIA AF // Российский кардиологический журнал. 2017. Т. 22, № 9. С. 21–27. EDN: ZIBDLB doi: 10.15829/1560-4071-2017-9-21-27
2. Menke J., Lüthje L., Kastrup A., Larsen J. Thromboembolism in atrial fibrillation // Am J Cardiol. 2010. Vol. 105, N. 4. P. 502–510. doi: 10.1016/j.amjcard.2009.10.018
3. Мельников М.В., Сотников А.В., Мельников В.М., Папава Г.Д. Продолжительность жизни больных, перенесших эмболии аорты и магистральных артерий конечностей // Ангиология и сосудистая хирургия. 2018. Т. 24, № 3. С. 26–31 EDN: LYPVYT
4. Затевахин И.И., Цициашвили М.Ш., Золкин В.Н. Острая артериальная непроходимость. Клиническая классификация и тактика лечения // Ангиология и сосудистая хирургия. 2002. Т. 8, № 2. С. 74–77.
5. Lip G.Y., Nieuwlaat R., Pisters R., et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation // Chest. 2010. Vol. 137, N. 2. P. 263–272. doi: 10.1378/chest.09-1584
6. Kempe K., Starr B., Stafford J.M., et al. Results of surgical management of acute thromboembolic lower extremity ischemia // J Vasc Surg. 2014. Vol. 60, N. 3. P. 702–707. doi: 10.1016/j.jvs.2014.03.273
7. Золотовская И.А., Давыдкин И.Л., Дупляков Д.В. Антикоагулянтная терапия у пациентов с фибрилляцией предсердий, перенесших кардиоэмболический инсульт: оценка приверженности к антикоагулянтной терапии в реальной клинической практике (результаты когортного исследования «Аполлон») // Российский кардиологический журнал. 2017. Т. 147, № 7. С. 105–110. EDN: ZDEBWJ doi: 10.15829/1560-4071-2017-7-105-110
8. Аракелян М. Г., Бокерия Л. А., Васильева Е.Ю., и др. Фибрилляция и трепетание предсердий. Клинические рекомендации 2020 // Российский кардиологический журнал. 2021. Т. 26, № 7. С. 190–260. EDN: FUZAAD doi: 10.15829/1560-4071-2021-4594
9. Vemulapalli S., Inohara T., Kim S., et al. Blood pressure control and cardiovascular outcomes in patients with atrial fibrillation (from the ORBIT-AF Registry) // Am J Cardiol. 2019. Vol. 123, N. 10. P. 1628–1636. doi: 10.1016/j.amjcard.2019.02.010
10. Ishii M., Ogawa H., Unoki T., et al. Relationship of hypertension and systolic blood pressure with the risk of stroke or bleeding in patients with atrial fibrillation: the Fushimi AF Registry // Am J Hypertens. 2017. Vol. 30, N. 11. P. 1073–1082. doi: 10.1093/ajh/hpx094
11. Proietti M., Romiti G.F, Olshansky B., Lip G.Y.H. Systolic blood pressure visit-to-visit variability and major adverse outcomes in atrial fibrillation: The AFFIRM Study (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) // Hypertension. 2017. Vol. 70, N. 5. P. 949–958 doi: 10.1161/HYPERTENSIONAHA.117.10106
12. McDonagh T., Metra M., Adamo N., и др. 2021 Рекомендации ESC по диагностике и лечению острой и хронической сердечной недостаточности // Российский кардиологический журнал. 2023. Т. 28, № 1. 5168. EDN: SJMIKK doi: 10.15829/1560-4071-2023-5168
13. O'Hara A., Pozin J., Darki A., et al. Glycemic control and plasma levels of pro-inflammatory and pro-thrombotic biomarkers in diabetic patients presenting with acute pulmonary embolism // Clin Appl Thromb Hemost. 2023. Vol. 29. P. 10760296231165058. doi: 10.1177/10760296231165058
14. Papazoglou A.S., Kartas A., Moysidis D.V., et al. Glycemic control and atrial fibrillation: an intricate relationship, yet under investigation // Cardiovasc Diabetol. 2022. Vol. 21, N. 1. P. 39. doi: 10.1186/s12933-022-01473-0
15. Reddy V. Y., Sievert H., Halperin J., et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial // JAMA. 2014. Vol. 312, N. 19. P. 1988–1998. doi: 10.1001/jama.2014.15192

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Frequency and features of cardiovascular diseases in spondyloarthritis

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ABSTRACT

BACKGROUND: Group of spondyloarthritis include not only damage of musculoskeletal system, oftenly it's combination with a variety of comorbid pathologies, primarily involving the cardiovascular system, is characteristic. Given the high importance of early detection, assessment and further prediction of the risks of cardiovascular diseases in this cohort of patients, a competent interpretation of the risks of aggravating cardiovascular diseases and their prevention is one of the priority tasks not only for rheumatologists, but also for specialists in related fields.

AIM: To study the structure of comorbid pathology and assess the frequency of cardiovascular diseases in patients with ankylosing spondylitis, psoriatic arthritis and psoriatic spondyloarthritis, to conduct a comparative analysis of the incidence of cardiovascular comorbidities in different groups of spondyloarthritis.

MATERIALS AND METHODS: The study included 153 patients with a verified diagnosis of spondyloarthritis. Patients were divided into 3 groups depending on the nature of the lesion of the musculoskeletal system: ankylosing spondylitis meeting the modified New York criteria for ankylosing spondylitis (1984) ($n = 53$), psoriatic arthritis meeting the CASPAR criteria (Classification criteria of Psoriatic Arthritis, 2006) ($n = 40$) and psoriatic spondylitis simultaneously meeting the modified New York criteria for ankylosing spondylitis and the CASPAR criteria for psoriatic arthritis ($n = 60$). All patients taken with monoclonal antibodies (inhibitors TNF-alpha).

RESULTS: When studying cardiovascular comorbidity in patients with spondyloarthritis in three groups, arterial hypertension was most common in the ankylosing spondylitis group — 37.7%, in psoriatic arthritis — 62.5%, in the psoriatic spondyloarthritis group — 51.7%, conduction disturbance in ankylosing spondylitis — 28, 3%, in psoriatic arthritis — 17.5%, in the psoriatic spondyloarthritis group — 18.3%, dyslipidemia is significantly more common in the psoriatic arthritis and psoriatic spondyloarthritis groups — 47.5% and 51.7%, respectively, compared with the ankylosing spondylitis group — 18.9%. Along with cardiovascular diseases, endocrine disorders were detected with a high frequency of occurrence: overweight was more common in patients of the psoriatic arthritis and psoriatic spondyloarthritis groups — 35.0 and 38.3%, respectively, significant differences in the incidence of type 2 diabetes mellitus in the three groups has not been identified.

CONCLUSIONS: It is necessary to carry out medical examination in order to identify comorbidities in patients with various forms of spondyloarthritis, in order to determine further tactics of management and correction, depending not only on the activity of the disease, but also taking into account comorbidities.

Keywords: spondyloarthritis; comorbidities; ankylosing spondylitis; psoriatic arthritis; psoriatic spondylitis; cardio-vascular risk.

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Частота и особенности течения сердечно-сосудистых заболеваний при спондилоартритах

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АННОТАЦИЯ

Актуальность. Известно, что для спондилоартритов характерно сочетание с разнообразными коморбидными состояниями, в первую очередь заболеваниями сердечно-сосудистой системы. Учитывая высокую значимость раннего выявления рисков сердечно-сосудистых заболеваний у данной категории пациентов, необходима дальнейшая разработка дополнительных высокоинформативных маркеров их диагностики для проведения своевременной профилактики, что является одной из приоритетных задач для врачей многих терапевтических специальностей.

Цель — изучить структуру коморбидной патологии и оценить частоту сердечно-сосудистых заболеваний у пациентов с анкилозирующим спондилитом, псориатическим артритом и псориатическим спондилоартритом, а также провести сравнительный анализ встречаемости кардиоваскулярной патологии при различных формах спондилоартритов.

Материалы и методы. В исследование были включены 153 пациента с достоверным диагнозом спондилоартрит. Пациенты были разделены на 3 группы в зависимости от характера поражения опорно-двигательного аппарата: анкилозирующий спондилит (n = 53), псориатический артрит (n = 40) и псориатический спондилоартрит (n = 60). Все пациенты получали терапию ингибиторами ФНО-альфа. Структура коморбидной патологии оценивалась при помощи индексов Charlson и CIRS-G по Miller. Модифицированная шкала SCORE (Systematic COronary Risk Evaluation), шкала Рейнольдса (Reynolds Risk Score), модифицированная шкала QRISK3 использовались для оценки сердечно-сосудистых событий.

Результаты. Различные сопутствующие заболевания встречались у большинства обследованных пациентов со спондилоартритом (72 %), у более чем половины отмечалась полиморбидная патология. Среди коморбидных состояний преобладали заболевания сердечно-сосудистой системы (63 %), желудочно-кишечного тракта (53 %) и эндокринной системы (46 %). Артериальная гипертензия чаще встречалась у пациентов с псориатическим артритом и псориатическим спондилоартритом, а нарушение проводимости у пациентов с анкилозирующим спондилитом. Большинство пациентов имели 2 и 3 степень согласно шкалам SCORE и Рейнольдса. Более половины пациентов с псориатическим артритом и псориатическим спондилоартритом имели 3 и 4 степень риска, тогда как менее трети пациентов с анкилозирующим спондилитом имели 3 и 4 степень риска. Средние значения QRISK были достоверно выше у пациентов с псориатическим артритом и псориатическим спондилоартритом, чем у пациентов с анкилозирующим спондилитом. Ожирение и дислипидемия чаще встречались у пациентов с псориатическим артритом и псориатическим спондилоартритом. 10-летняя выживаемость была достоверно выше у пациентов с анкилозирующим спондилитом и псориатическим артритом, чем в группе больных с псориатическим спондилоартритом.

Заключение. При обследовании пациентов с псориатическим артритом целесообразно проводить не только оценку активности псориатического артрита и структурного прогрессирования в суставах, но и сопутствующих заболеваний с целью выбора наиболее оптимального лечения.

Ключевые слова: спондилоартриты; коморбидность; анкилозирующий спондилит; псориатический артрит; псориатический спондилит; сердечно-сосудистый риск.

Как цитировать

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INTRODUCTION

Spondyloarthritis (SpA) is a group of chronic inflammatory diseases affecting the spine, joints, and entheses that share clinical, radiographic, and genetic characteristics. SpA refers to ankylosing spondylitis (AS), which includes nonradiographic axial SpA, psoriatic arthritis (PsA), reactive arthritis, SpA associated with inflammatory bowel disease and uveitis, and undifferentiated SpA. These diseases are typically associated with the MHC class I molecule HLA-B27. They show several common clinical symptoms, including inflammatory back pain, peripheral arthritis, enthesitis, dactylitis, and extraarticular manifestations, such as anterior uveitis, psoriasis (PSO), and inflammatory bowel disease (IBD) [1]. Inflammation of the joints and enthuses causes gradual structural damage to the musculoskeletal system, leading to a reduced quality of life and a rapid onset of disability.

Spondyloarthritis, like many other rheumatic diseases, is treated with a treat-to-target approach to achieve remission or low disease activity. Rheumatologists might use various drugs depending on the form and stage of SpA. These drugs include nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), biological DMARDs (bDMARDs), and JAK inhibitors (small molecule inhibitors) [2].

Given that NSAIDs are the primary drugs used to treat axial SpA (axSpA) and must be used for a lengthy period of time, it is critical to closely monitor side effects related to gastrointestinal and cardiovascular damage [3, 4]. Furthermore, concomitant cardiovascular diseases (as signs of multimorbidity) are common in patients with SpA, affecting quality of life and life expectancy [5]. Long-term use of NSAIDs, even at low doses, may be contraindicated in patients with an increased risk of major adverse cardiovascular events (MACEs), upper gastrointestinal tract disorders, and IBD [6, 7]. Several studies have found a relationship between NSAID use and cardiovascular risk. However, recent studies examining the effect of long-term NSAID use on the risk of MACEs in AS patients (n = 22,929) during an 8-yr follow-up period found a modest correlation between cardiovascular events and NSAID use. Comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and upper extremity atherosclerosis increase the risk of MACE [8].

According to recent studies, SpA patients have a 5– to 7-yr lower life expectancy, 1.6–1.9 times higher total mortality, and 20%–40% higher cardiovascular mortality than the general population [9].

The most important standardized criteria for assessing cardiovascular risk in SpA patients and the characteristics of cardiovascular disease progression are currently under debate.

This study aimed to investigate comorbidities, analyze the incidence of cardiovascular diseases in patients with AS, PsA, and psoriatic SpA, and conduct a comparative analysis of cardiovascular comorbidities in various SpA groups.

MATERIALS AND METHODS

The study included 153 patients with confirmed SpA. Patients were divided into three groups based on the type of musculoskeletal damage: AS meeting the modified New York criteria for AS (1984; n = 53), PsA meeting the Classification Criteria of Psoriatic Arthritis (CASPAR, 2006; n = 40), and PsSpA meeting both the modified New York criteria for AS and the CASPAR for PsA (n = 60).

In the study, patients with AS or PsSpA received a bDMARD from the tumor necrosis factor-α (TNF-α) inhibitor group, alone or in combination with an NSAID. PsA patients were given TNF-α inhibitors and DMARDs (methotrexate, sulfasalazine, or leflunomide). The groups were sex- and age-matched. Patients with IBD were excluded from the study.

All patients had their clinical laboratory parameters, SpA activities (BASDAI, ASDAS-CRP, DAPSA, and DAS28-CRP), and SpA functional status (BASFI) examined.

All patients were evaluated at baseline for comorbidities and the severity and risk of severe adverse cardiovascular events (Charlson Comorbidity Index [CCI] and CIRS-G by Miller). Three approaches were used to determine the 10-yr risk of MACEs: the modified Systematic Coronary Risk Evaluation (SCORE) system, the Reynolds Risk Score (RRS), and the modified QRISK3. The SCORE, RRS, and QRISK3 values were interpreted in accordance with the European Society of Cardiology guidelines. The risk levels are classified as low (< 1%), moderate (⩾ 1% to 5%), high (⩾ 5% to 10%), and very high (⩾ 10%).

R 3.4.1 (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, R Core Team, 2017), with jamovi graphical user interface and jmv packages (Jmv: The "Jacobi" Analyses, version 0.9.5.0; Selker et al., 2018) was used to statistically analyze the study data.

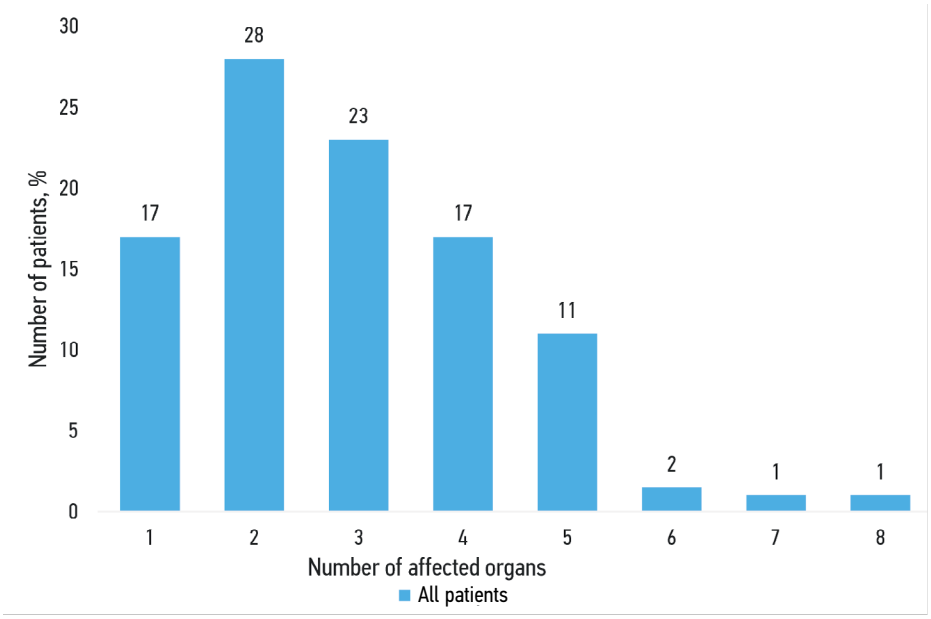
All patients signed an informed consent form. The patient data were anonymized. This study was approved by the Ethics Committee of the I.I. Mechnikov North-Western State Medical University.

RESULTS

The study had a low prevalence of men (55%) (Table 1). The mean age of patients was 46.7 ± 12.5 yr, and the disease

duration was 11.3 ± 8.1 yr. HLA-B27-associated disease was found in 73 patients (47.7%). Nonaxial SpA symptoms included enthesitis in 93 patients (60.8%), dactylitis in 57 patients (37.2%), and coxitis in 26 patients (17.0%). Extraskeletal symptoms (uveitis) were found in 20 patients (13.1%). BASDAI found that most patients (67%) had low-activity SpA at baseline. The study groups differed significantly in the presence of dactylitis, enthesitis, coxitis, and psoriatic onychodystrophy and the detection of HLA-B27 carriage ($p < 0.01$). When the results were compared between groups, it was observed that AS patients were more likely to have HLA-B27 carriage and sacroiliitis. PsSpA patients showed higher mean activity based on BASDAI than AS and PsA patients. According to ASDAS-CRP, baseline activity was very high (21.5%), increasing (29.6%), and moderate (28.5%), with 20.4% in clinical and laboratory remission. PsSpA patients had higher ASDAS scores. All patients received TNF inhibitors. Most AS patients had previously received one bDMARD, whereas one-third of PsA and PsSpA patients had previously received two or more bDMARDs.

Most patients (72%) had several comorbidities. The most common comorbidities were cardiovascular



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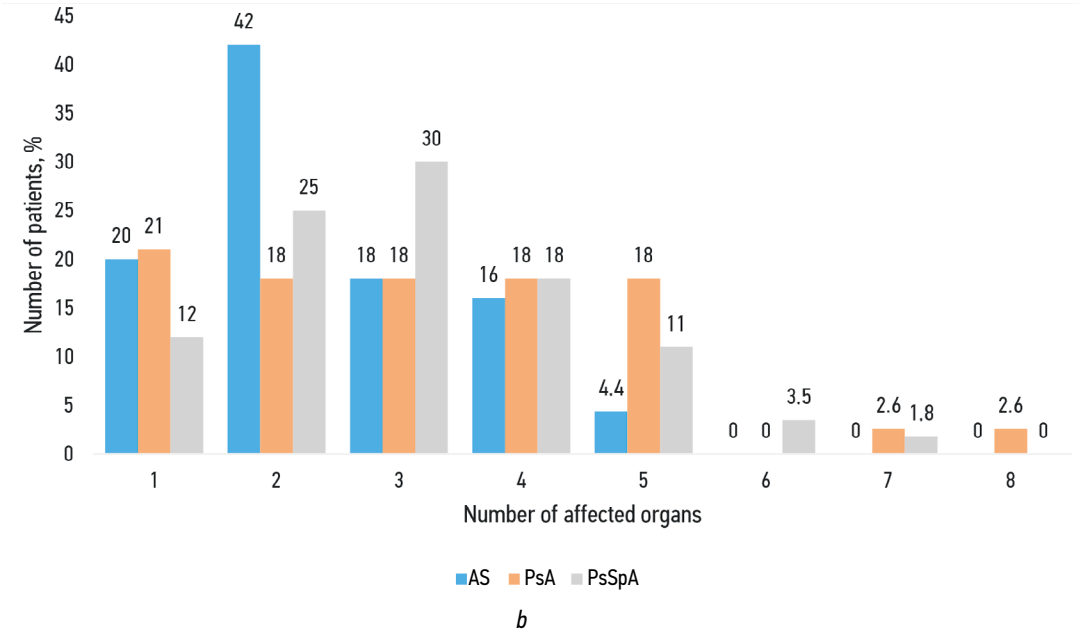

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Fig. 1. Affected organs and systems according to the CIRS-G by Miller in all patients (*a*) and by group (*b*). AS — ankylosing spondylitis; PsA — psoriatic arthritis; PSpA — psoriatic spondyloarthritis

Рис. 1. Количество пораженных органов и систем при оценке с помощью индекса CIRS-G по Miller у всех пациентов (*a*) и в зависимости от группы (*b*) АС — анкилозирующий спондилит; ПсА — псориатический артрит; ПсСпА — псориатический спондилоартрит

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(63%), gastrointestinal (53%), and endocrine (46%) disorders. Miller's CIRS-G revealed that most patients (56.5%) had several comorbidities. In total, 23.2% of PsA patients and 16.3% of PsSpA patients had five or more affected organs compared with only 4.6% of AS patients (Figure 1). The total CIRS-G score in AS patients was significantly lower than in PsA and PsSpA patients (4.22 vs. 5.5 vs. 5.67, $p = 0.013$).

Cardiovascular diseases were the primary focus of comorbidity analysis (Table 2). Hypertension was the most common cardiovascular disease, affecting 50% of the patients. Notably, hypertension was more prevalent in patients with PsA and PsSpA. Coronary artery disease (CAD) incidence was comparable in all groups. Eight patients experienced myocardial infarction. Only AS patients had a myocardial infarction while taking TNF inhibitors (1, 8, and

Table 1. Baseline clinical characteristics of patients ($n = 153$)
Таблица 1. Клиническая характеристика пациентов на момент включения в исследование, $n = 153$

Study parameters	AS ($n = 53$)	PsA ($n = 40$)	PsSpA ($n = 60$)
Male, *n* (%)	31(58.5)	21 (52.5)	32 (53.3)
Mean age at baseline, *M* ± *SD*	44.3 ± 11.9	48.8 ± 13.3	47.4 ± 12.4
Disease duration (yr), *M* ± *SD*	9.9 ± 8.3	13.2 ± 8.1	11.2 ± 7.9
Sacroiliitis, *n* (%)	52 (98)	26 (65)	50 (83)
Dactylitis, *n* (%)	5 (9.4)	21 (52.5)	31 (51.7)
Enthesitis, *n* (%)	20 (37.7)	25 (62.5)	48 (80.0)
Coxitis, *n* (%)	6 (11.3)	4 (10.0)	16 (26.7)
Uveitis, *n* (%)	11 (20.8)	4 (10.0)	5 (8.3)
HLA-B27 carriage, *n* (%)	42 (79.2)	10 (25.0)	21 (35.0)
BASDAI, points (*M* ± *SD*)	2.9 ± 1.9	3.0 ± 1.7	3.7 ± 2.0
ASDAS-CRP, points (*M* ± *SD*)	2.0 ± 0.9	2.0 ± 0.98	2.4 ± 1.1
Therapy duration and all bDMARDs	4.0 (1.0–6.0)	5.0 (2.0–8.2)	3.0 (2.0–5.0)
Therapy duration and the last bDMARD	3.0 (1.0–6.0)	2.8 (2.0–5.0)	2.0 (1.0–4.0)

Note: AS — ankylosing spondylitis; PsA — psoriatic arthritis; PSpA — psoriatic spondyloarthritis; GEBD — genetically engineered biological drugs; CRP — C-reactive protein; BASDAI — Bath Ankylosing Spondylitis Disease Activity Index; ASDAS — Ankylosing Spondylitis Disease Activity Score.

Примечание: АС — анкилозирующий спондилит; ПсА — псориатический артрит; ПсСпА — псориатический спондилоартрит; ГИБП — генно-инженерные биологические препараты; СРБ — С-реактивный белок; BASDAI — Bath Ankylosing Spondylitis Disease Activity Index; ASDAS — Ankylosing Spondylitis Disease Activity Score.

Table 2. Cardiovascular diseases in patients with AS, PsA, and PsSpA
Таблица 2. Структура сердечно-сосудистой патологии у пациентов исследуемых групп

Cardiovascular diseases	All patients ($n = 153$)	AS ($n = 53$)	PsA ($n = 40$)	PsSpA ($n = 60$)
Hypertension, *n* (%)	76 (49.7)	20 (37.7)	25 (62.5)	31 (51.7)
Grade 1	54 (35.2)	14 (26.4)	18 (45)	22 (36.7)
Grade 2	16 (10.5)	4 (7.6)	6 (15)	6 (10)
Grade 3	6 (3.9)	2 (3.8)	1 (0)	3 (5)
Coronary artery disease (CAD), *n* (%)	17 (11.1)	7 (13)	5 (12)	5 (8.3)
Stable angina, FC 1–2, *n* (%)	13 (8.5)	5 (9.4)	4 (10)	4 (6.8)
Acute myocardial infarction, *n* (%)	8 (5.2)	3 (2.0)	3 (7.5)	2 (3.3)
Atrial fibrillation, *n* (%)	4 (2.6)	2 (3.8)	1 (2.5)	1 (1.7)
Rhythm disorder, *n* (%)	16 (10.4)	6 (11)	5 (12.5)	5 (8.3)
Chronic heart failure (CHF), *n* (%)	14 (9.1)	3 (5.7)	6 (15)	5 (8.5)
CHF grade I, *n* (%)	3 (0.5)	1 (2)	2 (5)	0 (0)
CHF grade II, *n* (%)	11 (7.2)	2 (3.8)	5 (12.5)	4 (6.7)

Note: AS — ankylosing spondylitis; PsA — psoriatic arthritis; PSpA — psoriatic spondyloarthritis.

Примечание: АС — анкилозирующий спондилит; ПсА — псориатический артрит; ПсСпА — псориатический спондилоартрит.

10-yr after starting treatment), whereas other patients had a myocardial infarction before beginning treatment. Seven patients (4.6%) had coronary angiography and/or stenting, whereas one patient underwent coronary artery bypass surgery. Conduction disorders were 10% more prevalent in AS patients (28%) than in PsA patients (18%) and PsSpA patients (18%). The incidence of cardiac rhythm disorders was comparable in all groups. They were found in every 10th patient, with sinus tachycardia and extrasystole being the most common types. Chronic heart failure was more prevalent in patients with PsA. One PsA patient and three PsSpA patients had previously experienced an acute cerebrovascular accident.

Notably, 29% of the patients had dyslipidemia. Dyslipidemia was significantly more prevalent in PsA and PsSpA patients than in AS patients (Table 3). The lipid metabolism parameters of PsA and PsSpA patients were comparable. Mean cholesterol levels, low-density lipoprotein levels, and total cholesterol to high-density lipoprotein cholesterol ratio were significantly higher in PsA and PsSpA patients than in AS patients.

An intergroup comparative analysis was conducted based on obesity grades. The study found significant differences ($p < 0.001$) in obesity grades among AS, PsA, and PsSpA patients (Table 4). Obesity was more prevalent in patients with PsA and PsSpA with grade 1 or 2 in most cases.

The SCORE system, RRS, and modified QRISK3 were used to determine cardiovascular risk. The mean SCORE value was significantly higher in PsSpA patients (1.98 [0.75; 3.28] points) than in AS patients (1.59 [0.74; 3.61]) and PsA patients (1.73 [1.18; 4.36]). However, there were no significant differences after recalculating SCORE values for rheumatological diseases (× 1.5). Most patients had SCORE grades 2 and 3 (48% and 28%, respectively). There was no difference between the groups.

The mean RRS values were 2.0, 3.0, and 4.0 for AS, PsA, and PsSpA patients. Most patients had RRS grades 2 and 3.

QRISK found significant differences between the groups (Table 5). More than half of PsA and PsSpA patients had risk grades 3 and 4 compared with less than one-third of AS patients. The mean QRISK score was significantly higher in PsA and PsSpA patients than in AS patients (6.12 vs. 6.81 vs. 3.8, $p = 0.002$), indicating a higher cardiovascular risk.

The CCI was used to assess comorbidities and predict 10-yr survival rates (Figure 2). The CCI score was higher in PsA and PsSpA patients than in AS patients, affecting survival parameters. Thus, AS and PsA patients had significantly higher

Table 3. Lipid metabolism parameters in patients with AS, PsA, and PsSpA
Таблица 3. Показатели липидного обмена у пациентов исследуемых групп

Lipid metabolism parameters	AS (*n* = 53)	PsA (*n* = 40)	PsSpA (*n* = 60)	*p*
Dyslipidemia, *n* (%)	10 (19)	19 (48)	31 (52)	0,001
Cholesterol (mmol/L), *Me* (25%; 75%)	4.53 (4.13;5.23)	5.50 (5.00; 6.30)	5.80 (4.98; 6.33)	0.001
HDL (mmol/L), *Me* (25%; 75%)	1.70 (1.58; 1.85)	1.72 (1.52; 1.90)	1.70 (1.39; 1.90)	0.6
LDL (mmol/L), *Me* (25%; 75%)]	2.55 (2.00; 3.04)	2.89 (2.40; 3.62)	2.89 (2.10; 3.61)	0.023
Total cholesterol to HDL cholesterol ratio (mmol/L), *Me* (25%; 75%)	2.69 (2.47; 3.20)	3.33 (2.88; 3.71)	3.21 (2.87; 4.04)	0.001

Note: AS — ankylosing spondylitis; PsA — psoriatic arthritis; PSpA — psoriatic spondyloarthritis; LDL — low density lipoproteins; HDL — high density. lipoproteins.
Примечание: АС — анкилозирующий спондилит; ПсА — псориатический артрит; ПсСпА — псориатический спондилоартрит; ЛПНП — липопротеины низкой плотности; ЛПВП — липопротеины высокой плотности.

Table 4. Obesity grades in the study groups
Таблица 4. Распределение степени ожирения в исследуемых группах пациентов

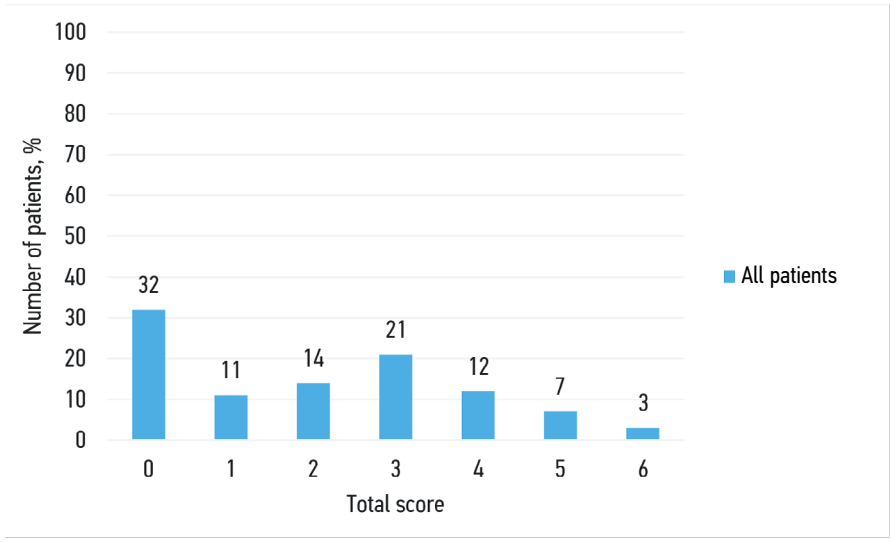
Obesity grade	AS, *n* (%)	PsA, *n* (%)	PsSpA, *n* (%)	*p*
0	34 (64)	8 (20)	14 (23)	< 0,001
1	13 (25)	15 (38)	23 (38)	
2	3 (5.7)	10 (25)	15 (25)	
3	2 (3.8)	5 (12)	5 (8.3)	
4	1 (1.9)	2 (5.0)	3 (5.0)	

Note: AS — ankylosing spondylitis; PsA — psoriatic arthritis; PSpA — psoriatic spondyloarthritis.
Примечание: АС — анкилозирующий спондилит; ПсА — псориатический артрит; ПсСпА — псориатический спондилоартрит.

Table 5. QRISK scores in patients with ankylosing spondylitis, psoriatic arthritis, and psoriatic spondyloarthritis
Таблица 5. Показатели шкалы QRISK у пациентов исследуемых групп

Patient group	Risk level				*p*
	1	2	3	4	
AS, *n* (%)	19 (51)	9 (24)	4 (15)	5 (14)	0.002
PsA, *n* (%)	4 (15)	6 (23)	13 (49,8)	3 (12)	
PsSpA, *n* (%)	7 (16)	15 (34)	13 (30)	9 (20)	

Note: AS — ankylosing spondylitis; PsA — psoriatic arthritis; PSpA — psoriatic spondyloarthritis.
Примечание: АС — анкилозирующий спондилит; ПсА — псориатический артрит; ПсСпА — псориатический спондилоартрит.



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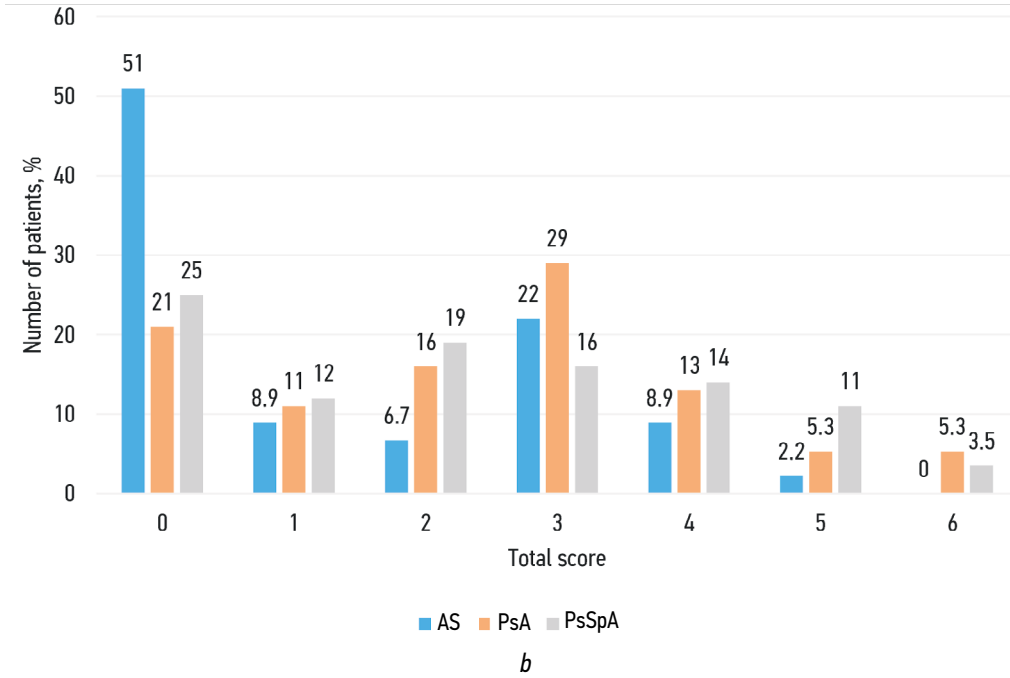

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Fig. 2. Distribution of AS patients depending on the incidence of comorbidities in all patients (*a*) and by group (*b*). AS — ankylosing spondylitis; PsA — psoriatic arthritis; PSpA — psoriatic spondyloarthritis
Рис. 2. Распределение пациентов с СпА в зависимости от распространенности сопутствующей патологии: *a* — для всех пациентов; *b* — по группам пациентов. АС — анкилозирующий спондилит; ПсА — псориатический артрит; ПсСпА — псориатический спондилоартрит

10-yr survival rates than PsSpA patients (78% vs. 78% vs. 54%, $p = 0.008$).

The findings indicate that PsSpA patients have more comorbidities than AS and PsA patients, affecting predicted 10-yr survival rates, which are significantly decreased in PsSpA patients.

DISCUSSION

A review of comorbidities in patients with various forms of SpA indicated that 72% of patients had at least one concomitant disease. Cardiovascular diseases were the most prevalent, affecting 63% of patients. Gastrointestinal diseases were the second most prevalent, affecting 53% of patients. The study cohort had a higher incidence of comorbidities than larger cohort studies.

In a study of 3,379 SpA patients, 51% reported at least one comorbidity, with 9% having three or more. The Rheumatic Disease Comorbidity Index was associated with higher BASFI scores, low quality of life (EuroQol), and lower employment rates. The most prevalent comorbidities were hypertension (33%), osteoporosis (13%), and gastrointestinal disorders (12%) [10].

In the British registry of axSpA patients ($n = 2,043$), 44% had at least one comorbidity. Comorbidities were more prevalent among older patients and those with lower levels of education. Smoking was more prevalent among patients with comorbidities (63% vs. 50%). Patients with comorbidities showed increased disease activity but no laboratory inflammatory markers. Each comorbidity increased the BASDAI score by 0.4 and the back pain score by 0.53. Depression, heart failure, and peptic ulcers were associated with increased disease activity [11].

The most common cardiovascular diseases in our cohort were hypertension (50%), CAD (11%), and conduction disorders (22%). The most common gastrointestinal diseases were *Helicobacter pylori*-associated chronic gastritis (37%), gastroesophageal reflux disease (21%), and peptic ulcer (10%).

When comparing the three groups, patients with PSO had more cardiovascular events and dyslipidemia, while patients with PsSpA had significantly higher incidences of hypertension, CAD, type 2 diabetes mellitus, dyslipidemia, and obesity.

Several studies have found that patients with PsA are more likely to develop hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, and metabolic syndrome. Insulin resistance is associated with PsA.

Psoriasis is associated with lipid metabolism disorders and obesity; inhibiting TNF-α can promote adipogenesis, leading to weight gain [12].

According to Miller's CIRS-G, most patients had two to four affected organs and systems. The mean CCI score was 1.99 ± 1.77, and the mean 10-yr survival was 80.6% ± 24.0%.

Ballegaard et al. (2021) found that obesity, hypertension, and CCI ⩾ 1 were associated with low efficacy of PsA treatment [13].

This study focused on cardiovascular risk assessment. At present, no standardized techniques for assessing cardiovascular risk consider the presence of SpA.

Patients with PsSpA had the highest SCORE, QRISK3, and RRS values when assessing cardiovascular risk. QRISK3 was more helpful than SCORE and RRS.

Cardiovascular risk parameters in patients under the age of 40 yr were assessed using the only available instrument, QRISK3. Notably, 18% of patients had moderate to high risk of MACEs. PsA and PsSpA patients had significantly higher QRISK scores than AS patients (6.2 vs. 4.6 vs. 0.7, $p = 0.002$), indicating a higher cardiovascular risk.

The CCI score indicated that AS and PsA patients had the highest 10-yr survival rates (74%), whereas PsSpA patients had the lowest (54%).

Cardiovascular risks were assessed in a cohort study of 463 axSpA patients. During the 12 (7–19) yr of follow-up, 12 patients (2.6%) died, with five (1.1%) fatalities due to cardiovascular events. Nonfatal cardiovascular events occurred in 61 patients (13.2%), with CAD in 29.5%, myocardial infarction in 13.1%, transient ischemic attacks in 4.9%, stroke in 23%, and heart failure in 24.6%. Patients who experienced cardiovascular events were older, had more common risk factors, used statins, antihypertensive drugs, and acetylsalicylic acid more often, and had higher BASDAI scores, ESR, and CRP levels. FRS, SCORE, and QRISK3 identified 8.2%, 11.5%, and 1.8%, respectively, of 61 patients with cardiovascular events as being at high risk. High disease activity and BASDAI scores (⩾ 4) were associated with increased cardiovascular risk. No relationship was found between the study treatment and cardiovascular risk [14].

Within 10 yr of follow-up, 23 of 295 patients (7.8%) reported their first cardiovascular event, which was significantly associated with a high CRP level and high BASDAI scores (> 4) [15].

Cardiovascular events were associated with type 2 diabetes mellitus, hypertension, dyslipidemia, and atherosclerosis in a French cohort study of SpA patients; patients taking NSAIDs and TNF inhibitors had significantly lower cardiovascular risk than those taking IL-17 inhibitors [16].

Thus, previous studies have indicated a relationship between high disease activity and cardiovascular risk, underlining the importance of SpA treatment in a timely and appropriate manner.

In our study, three AS patients had myocardial infarction during treatment with TNF inhibitors. Although TNF inhibitors may be beneficial in reducing cardiovascular risk, an earlier study reported no TNF inhibitor-specific reduction in cardiovascular disease incidence in axSpA patients [17].

The study of Spanish colleagues, who developed a checklist for comorbidity assessment in axSpA patients for doctors and patients, is highly beneficial in practice. The checklist assesses comorbidities such as cardiovascular, gastrointestinal, renal, and pulmonary diseases, lifestyle, immunization status, and the risk of infectious diseases, affective disorders, osteoporosis, and fractures. "Practices to avoid" have been developed for physicians [18].

The ASAS-EULAR recommendations for axSpA management were released in 2022 [19], including two new and two revised recommendations since 2016 [20]. The two new recommendations consider comorbidities. To treat recurrent uveitis or IBD, anti-TNF-α monoclonal antibodies are recommended, whereas IL-17 inhibitors are preferred for psoriasis. If treatment does not yield results, comorbidities should be considered.

CONCLUSION

Screening patients with SpA for cardiovascular risk factors and diseases is recommended. Identifying risks and current diseases will aid in developing additional treatment and adjustment strategies depending on disease activity and comorbidities. A multidisciplinary approach to treating SpA patients will reduce the rheumatic disease burden while improving the prognosis and quality of life in chronic noncommunicable diseases.

ADDITIONAL INFORMATION

Author contribution. All authors made significant contributions to the preparation of the article and read and approved the final version before publication.

Contribution of each author. R.R. Samigullina — GC-MS, collection and preparation of samples, data analysis,writing the main part of the text, literature review, making final edits, V.I. Mazurov — experimental design, writing the main part of the text, making final edits, E.A. Vasilenko — collection and preparation of samples, data analysis,, E.A. Trofimov — literature review, data analysis.

Competing interests. The authors declare that they have no competing interests.

Disclosure of potential conflicts of interest. The authors declare that there are no potential conflicts of interest to disclose in this article.

Ethics approval. The protocol of the study was approved by the North-Western Medical State University named after I.I. Mechnikov Ethics Committee, protocol N 12, 06.12.2022.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Вклад каждого автора. Р.Р. Самигуллина — хроматографическое исследование, сбор и обработка материалов, анализ полученных данных, написание текста, обзор литературы, внесение окончательной правки, В.И. Мазуров — концепция и дизайн исследования, написание текста, обзор литературы, внесение окончательной правки, Е.А. Василенко — сбор и обработка материалов, анализ полученных данных, обзор литературы, Е.А. Трофимов — анализ полученных данных, обзор литературы.

Раскрытие потенциального конфликта интересов авторов. Авторы заявляют об отсутствии потенциального конфликта интересов, требующего раскрытия в данной статье.

Заключение этического комитета. Протокол исследования был одобрен локальным этическим комитетом ФГБОУ ВО СЗГМУ им. И.И. Мечникова Минздрава России (№ 12 от 06.12.2022).

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENSES

1. Mazurov VI, Vasilenko EA, et al. Treatment of patients with ankylosing spondilitis — real clinical practice. *RMJ*. 2019;27(12):37–40. EDN: AWVKEX

2. Liew JW, Dubreuil M. Treat to target in axial spondyloarthritis: pros, cons, and future directions. *Rheum Dis Clin North Am*. 2020;46(2):343–356. doi: 10.1016/j.rdc.2020.01.011

3. Karateev AE, Nasonov EL, Yakhno NN, et al. Clinical guidelines «Rational use of nonsteroidal anti-inflammatory drugs (NSAIDs) in clinical practice». *Modern Rheumatology Journal*. 2015;9(1):4–23. EDN: TLJUPZ doi: 10.14412/1996-7012-2015-1-4-23 3

4. Gaydukova IZ, Mazurov VI. Spondyloarthritis: approaches to terminology, classification, and diagnotics from

V.M. Bekhterev to our days. *Therapy*. 2019;(8):118–130. EDN: DGFNV doi: 10.18565/therapy.2019.8.118-130 4

5. Zhao SS, Robertson S, Reich T, et al. Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis. *Rheumatology (Oxford).* 2020;59(Suppl 4):iv47–iv57. doi: 10.1093/rheumatology/keaa246

6. Lanas A. Boers M, Nuevo J. Gastrointestinal events in at-risk patients starting non-steroidal anti- inflammatory drugs (NSAIDs) for rheumatic diseases: the EVIDENCE study of European routine practice. *Annals of the Rheumatic Diseases*. 2015;74(4):675–681. doi: 10.1136/annrheumdis-2013-204155

7. Lanza FL, Chan FK, Quigley EM. Practice parameters committee of the American College of gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol.* 2009;104(3):728–738. doi: 10.1038/ajg.2009.115

8. Fakih O, Desmarets M, Martin B, et al. Impact of NSAIDs on 8-year cumulative incidence of major cardiovascular events in patients with ankylosing spondylitis: a nationwide study. *Rheumatology (Oxford).* 2023;62(10):3317–3322. doi: 10.1093/rheumatology/kead072

9. Rebrov AP, Gaidukova IZ, Poddubnyy DA. Cardiovascular pathology in patients with ankylosing spondylitis. *Scientific and Practical Rheumatology*. 2012;51(2):100–105. (In Russ.) doi: 10.14412/1995-4484-2012-1281

10. Nikiphorou E, Ramiro S, van der Heijde D, et al. Association of comorbidities in spondyloarthritis with poor function, work disability, and quality of life: results from the assessment of spondyloarthritis international society comorbidities in spondyloarthritis study. *Arthritis Care Res (Hoboken).* 2018;70(8):1257–1262. doi:10.1002/acr.23468

11. Zhao SS, Jones GT, Macfarlane GJ, et al. Association between comorbidities and disease activity in axial spondyloarthritis: results from the BSRBR-AS. *Rheumatology (Oxford).* 2021;60(7):3189–3198. doi: 10.1093/rheumatology/keaa768

12. Mazhar F, Battini V, Pozzi M, et al. Changes in anthropometric parameters after anti-TNFα therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Bio Drugs*. 2020;34(5): 649–668. doi: 10.1007/s40259-020-00444-9

13. Ballegaard C, Skougaard M, Guldberg-Møller J, et al. Comorbidities, pain and fatigue in psoriatic arthritis, psoriasis and healthy controls: a clinical cohort study. *Rheumatology (Oxford).* 2021;60(7):3289–3300. doi: 10.1093/rheumatology/keaa780

14. Shi LH, Lam SH, So H, et al. High inflammatory burden predicts cardiovascular events in patients with axial spondyloarthritis: a long-term follow-up study. *Ther Adv Musculoskelet Dis*. 2022;14:1759720X221122401. doi: 10.1177/1759720X221122401

15. Navarini L, Currado D, Marino A, et al. Persistence of C-reactive protein increased levels and high disease activity are predictors of cardiovascular disease in patients with axial spondyloarthritis. *Sci Rep*. 2022;12(1):7498. doi: 10.1038/s41598-022-11640-8

16. Fakih O, Desmarets M, Martin B, et al. Impact of NSAIDs on 8-year cumulative incidence of major cardiovascular events in patients with ankylosing spondylitis: a nationwide study. *Rheumatology (Oxford*). 2023;62(10):3317–3322. doi: 10.1093/rheumatology/kead072

17. Kwon OC, Park MC. Effect of tumor necrosis factor inhibitors on risk of cardiovascular disease in patients with axial spondyloarthritis. *Arthritis Res Ther*. 2022;24(1):141. doi: 10.1186/s13075-022-02836-4

18. González C, Curbelo Rodríguez R, Torre-Alonso JC, et al. Recommendations for the management of comorbidity in patients with axial spondyloarthritis in clinical practice. *Reumatol Clin (Engl Ed).* 2018;14(6):346–359. doi: 10.1016/j.reuma.2017.03.011

19. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. 2023;82(1):19–34. doi: 10.1136/ard-2022-223296

20. Van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the asas-eular management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76(6):978–991. doi: 10.1136/annrheumdis-2016-210770

21. Verhoeven F, Prati C, Demougeot C, Wendling D. Cardiovascular risk in psoriatic arthritis, a narrative review. *Joint Bone Spine.* 2020;87(5):413–418. doi: 10.1016/j.jbspin.2019.12.004

22. Atzeni F, Gerratana E, Masala IF, et al. Psoriatic arthritis and metabolic syndrome: is there a role for disease modifying anti-rheumatic drugs? *Front Med (Lausanne).* 2021;8:735150. doi: 10.3389/fmed.2021.735150

СПИСОК ЛИТЕРАТУРЫ

1. Мазуров В.И., Василенко Е.А., Трофимов Е.А., и др. Лечение больных анкилозирующим спондилитом — данные реальной клинической практики // РМЖ. 2019. Т. 27, № 12. С. 37–40. EDN: AWVKEX

2. Liew J.W., Dubreuil M. Treat to target in axial spondyloarthritis: pros, cons, and future directions // Rheum Dis Clin North Am. 2020. Vol. 46, N. 2. P. 343–356. doi: 10.1016/j.rdc.2020.01.011

3. Каратеев А.Е, Насонов Е.Л., Яхно Н.Н., и др. Клинические рекомендации «Рациональное применение нестероидных противовоспалительных препаратов (НПВП) в клинической практике» // Современная ревматология. 2015. № 1. С. 4–23. EDN: TLJUPZ doi: 10.14412/1996-7012-2015-1-4-23 3

4. Гайдукова И.З., Мазуров В.И., Инамова О.В., и др. Спондилоартриты: изменения в терминологии, классификации и

диагностических подходах — от В.М. Бехтерева до наших дней // Терапия. 2019. Т. 5, № 8(34). С. 118–130. EDN: DGFNV doi: 10.18565/therapy.2019.8.118-130

5. Zhao S.S., Robertson S., Reich T., et al. Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis // Rheumatology (Oxford). 2020. Vol. 59, N. Suppl 4. P. iv47–iv57. doi: 10.1093/rheumatology/keaa246

6. Lanas A., Boers M., Nuevo J. Gastrointestinal events in at-risk patients starting non-steroidal anti- inflammatory drugs (NSAIDs) for rheumatic diseases: the EVIDENCE study of European routine practice // Annals of the Rheumatic Diseases. 2015. Vol. 74, N. 4. P. 675–681. doi: 10.1136/annrheumdis-2013-204155

7. Lanza F.L., Chan F.K., Quigley E.M. Practice parameters committee of the American College of gastroenterology. Guidelines for prevention of NSAID-related ulcer complications // Am J Gastroenterol. 2009. 104, N. 3. P. 728–738. doi: 10.1038/ajg.2009.115

8. Fakih O., Desmarets M., Martin B., et al. Impact of NSAIDs on 8-year cumulative incidence of major cardiovascular events in patients with ankylosing spondylitis: a nationwide study // Rheumatology (Oxford). 2023. Vol. 62, N. 10. P. 3317–3322. doi: 10.1093/rheumatology/kead072

9. Ребров А.П., Гайдукова И.З., Поддубный Д.А. Кардиоваскулярная патология у больных анкилозирующим спондилитом // Научно-практическая ревматология. 2012. Т. 51, № 2. С. 100–105. doi: 10.14412/1995-4484-2012-1281

10. Nikiphorou E., Ramiro S., van der Heijde D., et al. Association of comorbidities in spondyloarthritis with poor function, work disability, and quality of life: results from the assessment of spondyloarthritis international society comorbidities in spondyloarthritis study // Arthritis Care Res (Hoboken). 2018. Vol. 70, N. 8. P. 1257–1262. doi:10.1002/acr.23468

11. Zhao S.S., Jones G.T., Macfarlane G.J., et al. Association between comorbidities and disease activity in axial spondyloarthritis: results from the BSRBR-AS // Rheumatology (Oxford). 2021. Vol. 60, N. 7. P. 3189–3198. doi:10.1093/rheumatology/keaa768

12. Mazhar F., Battini V., Pozzi M., et al. Changes in anthropometric parameters after anti-TNFα therapy in inflammatory bowel disease: a systematic review and meta-analysis // Bio Drugs. 2020. Vol. 34, N. 5. P. 649–668. doi: 10.1007/s40259-020-00444-9

13. Ballegaard C., Skougaard M., Guldberg-Møller J., et al. Comorbidities, pain and fatigue in psoriatic arthritis, psoriasis and healthy controls: a clinical cohort study // Rheumatology (Oxford). 2021. Vol. 60, N. 7. P. 3289–3300. doi: 10.1093/rheumatology/keaa780

14. Shi L.H., Lam S.H., So H., et al. High inflammatory burden predicts cardiovascular events in patients with axial spondyloarthritis: a long-term follow-up study // Ther Adv Musculoskelet Dis. 2022. Vol. 14. P. 1759720X221122401. doi: 10.1177/1759720X221122401

15. Navarini L., Currado D., Marino A., et al. Persistence of C-reactive protein increased levels and high disease activity are predictors of cardiovascular disease in patients with axial spondyloarthritis // Sci Rep. 2022. Vol. 12, N. 1. P. 7498. doi: 10.1038/s41598-022-11640-8

16. Fakih O., Desmarets M., Martin B., et al. Impact of NSAIDs on 8-year cumulative incidence of major cardiovascular events in patients with ankylosing spondylitis: a nationwide study // Rheumatology (Oxford). 2023. Vol. 62, N. 10. P. 3317–3322. doi: 10.1093/rheumatology/kead072

17. Kwon O.C., Park M.C. Effect of tumor necrosis factor inhibitors on risk of cardiovascular disease in patients with axial spondyloarthritis // Arthritis Res Ther. 2022. Vol. 24, N. 1. P. 141. doi: 10.1186/s13075-022-02836-4

18. González C., Curbelo Rodríguez R., Torre-Alonso J.C., et al. Recommendations for the management of comorbidity in patients with axial spondyloarthritis in clinical practice // Reumatol Clin (Engl Ed). 2018. Vol. 14, N. 6. P. 346–359. doi: 10.1016/j.reuma.2017.03.011

19. Ramiro S., Nikiphorou E., Sepriano A., et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update // Ann Rheum Dis. 2023. Vol. 82, N. 1. P. 19–34. doi: 10.1136/ard-2022-223296

20. Van der Heijde D., Ramiro S., Landewé R., et al. 2016 Update of the ASAS-EULAR Management recommendations for axial spondyloarthritis // Ann Rheum Dis. 2017. Vol. 76, N. 6. P. 978–991. doi: 10.1136/annrheumdis-2016-210770

21. Verhoeven F., Prati C., Demougeot C., Wendling D. Cardiovascular risk in psoriatic arthritis, a narrative review // Joint Bone Spine. 2020. Vol. 87, N. 5. P. 413–418. doi: 10.1016/j.jbspin.2019.12.004

22. Atzeni F., Gerratana E., Masala I.F., et al. Psoriatic arthritis and metabolic syndrome: is there a role for disease modifying anti-rheumatic drugs? // Front Med (Lausanne). 2021. Vol. 8. P. 735150. doi: 10.3389/fmed.2021.735150

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Cardiac Implantable Electronic Device Induced Tricuspid Regurgitation: A Mini Review

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ABSTRACT

The continuing application of cardiac implantable electronic devices (CIED) has led to an increasing concern regarding disturbances in the tricuspid valve (TV). The most prevalent TV issue related to lead implantation is tricuspid regurgitation. CIED-induced tricuspid regurgitation is associated with emerging or worsening preexisting heart failure and increased mortality rate. Because discontinuing the implantation of these instruments is not feasible, further knowledge of their mechanical problems may lead to advancements. This review addresses the available data regarding CIED-induced tricuspid regurgitation, elucidating its plausible pathomechanisms, diagnostic methods, and prospective treatments.

Keywords: Cardiac implantable electronic device; tricuspid regurgitation; heart failure.

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Трикуспидальная регургитация, индуцированная сердечными имплантируемыми электронными устройствами (краткий обзор)

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АННОТАЦИЯ

Активное применение сердечных имплантируемых электронных устройств (СИЭУ) вызывает растущую обеспокоенность по поводу нарушений в работе трикуспидального клапана. Наиболее распространенной проблемой, связанной с имплантацией электродов, является трикуспидальная регургитация, которая приводит к возникновению или усугублению уже имеющейся сердечной недостаточности, а следовательно, к повышению уровня смертности. Поскольку отказ от имплантации этих устройств нецелесообразен, дальнейшее изучение механических проблем, связанных с их работой, может привести к улучшению ситуации. В данном обзоре систематизированы имеющиеся данные о трикуспидальной регургитации, вызванной имплантацией СИЭУ, описаны вероятные механизмы развития этой патологии, методы диагностики и перспективные направления в лечении.

Ключевые слова: сердечное имплантируемое электронное устройство; трикуспидальная регургитация; сердечная недостаточность.

Как цитировать

Аманда Р.З., Лаксно С. Трикуспидальная регургитация, индуцированная сердечными имплантируемыми электронными устройствами (краткий обзор) // 2023 Т. 3, № 4. DOI: 10.17816/cardar626186

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INTRODUCTION

Cardiac implantable electronic device (CIED) usage has become prevalent for cardiac rhythm detection and management. CIEDs typically involve inserting a lead through the tricuspid valve (TV) and fixing its end to the right ventricle (RV). Numerous publications have described the link connecting the device lead and the TV apparatus, leading to severe tricuspid regurgitation (TR). TV regurgitation is the most common TV malfunction associated with lead implantation. The interval between implantation and clinical appearance can range from a few weeks to up to 30 years [1–3].

TR progression is significantly noticeable in patients with a higher ejection fraction after progressing from no TV disease to mild TR. Nevertheless, TR progression is more crucial in individuals with advanced heart failure (HF) because it is associated with a considerably greater incidence of severe TV illness. HF therapies may not be effective in managing lead-induced TR, which could worsen the prognosis. Therefore, improved prevention and treatment are pivotal for identifying the patients most susceptible to the effects of TR [4, 5].

CIED-induced TR is becoming more widely acknowledged as a significant clinical disorder associated with an increased risk of HF and mortality. Poor clinical outcomes may result from the underestimation of TR severity or late diagnosis of worsening TR, regardless of the morphological varieties. This study aimed to review the information currently available on CIED-induced TR, describing its potential pathomechanisms, diagnostic methods, and therapeutic options [1, 2, 6].

METHODS

An extensive electronic search was conducted using search engines such as Google Scholar, ScienceDirect, and PubMed. The search was limited to English-language articles published between 2014 and 2023 using “cardiac implantable electronic device” AND “tricuspid regurgitation” as the keywords. The search results included reviews, original papers, and case reports. Articles with restricted access and those authored in languages other than English were excluded. The extracted articles were managed using the Mendeley software. After arranging the search results based on the titles and abstracts, the full texts of the publications were examined, and those that matched the exclusion criteria were eliminated. A total of 1.233 articles were retrieved through the search strategy, and 14 articles met the criteria. The literature search process is shown in Figure 1.

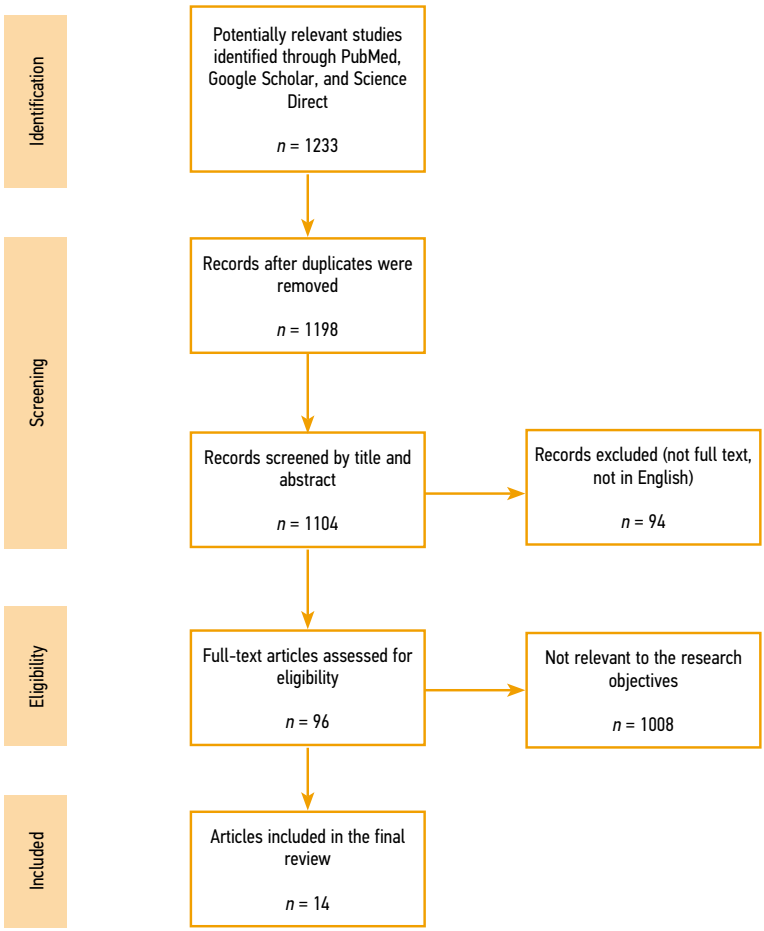

Fig. Diagram ilustrating study selection process
Рис. Диаграмма, иллюстрирующая процесс отбора исследований

RESULTS AND DISCUSSION

Definition

CIEDs, such as permanent pacemakers (PPMs), implantable cardiac defibrillators (ICDs), and cardiac resynchronization therapy devices, are increasingly being used in patients with severe cardiac disorders. The lead in CIEDs is usually placed extending across the TV and anchors in the ventricle, whereas leadless cardiac pacemakers (LCPM) are inserted right into the RV [7, 8].

CIEDs can lead to TV malfunction, which includes regurgitation and, less typically, stenosis. TR provoked or intensified by a right ventricular lead after pacemaker placement is referred to as cardiac implantable electronic device-induced TR. Various mechanisms have been proposed to precipitate TR and right ventricular dysfunction after lead implantation [3, 4, 6].

For CIED implantation, three methods are most often used: prolapsing, direct crossing, and dropping down. Of the three main methods of right ventricular lead placement, the prolapsing technique may be less likely to result in leaflet perforation or rupture than other techniques because of less damage to the leaflets and subvalvular tissue. In addition, because leads are often inserted with some excess intraventricular lead loop length to allow movement of the arm, the lead loop may cause anterior leaflet entrapment [1, 9].

Epidemiology

The prevalence of CIED-associated TR varies from 7% to 45%, depending on the research methodology and population observed. The different standards used in the studies, such as wide variation in follow-up evaluation, imaging technique, availability of baseline echocardiograms, study design, and divergent interpretation for “significant” postprocedural TR, caused several prevalence [1, 10, 11].

No substantial disparity was noted between the implanted device type (ICD or PPM) and the likelihood of developing postimplantation TR. An increased risk of TR was associated with all devices. Patients’ TR severity increases by one or two grades from pre- to postpermanent lead implantation. Novel postimplant moderate or severe TR is associated with poor right ventricular function and long-term (>10 years) survival rates [12–14].

Hospitalizations for HF and all-cause mortality risk were related to CIED-associated TR. After CIED placement, there may be an increase in TR symptoms between 1 and 12 months, whereas hospitalization for HF only became relevant more than a year after CIED implantation [15, 16].

Identifying risk factors for TR development after CIED implantation has been the focus of numerous studies. Atrial fibrillation and right ventricular systolic pressures were linked to significant TR progression in a study by Van de Heyning et al. Atrial fibrillation remained the only independent predictor after adjusting for the baseline TR grade. Zhang et al. found no association between TR and baseline atrial fibrillation and mild TR, age, or left ventricular ejection fraction. In contrast, the time that passed since the implantation and lead interference were risk factors for worsening TR [6, 17].

Mechanism

Previously, the interaction between the device lead and TV leaflets was considered a primary cause of TR. Nonetheless, researchers have reclassified CIED-related TR as a distinct etiologic category because of the numerous causes of TR in the existence of a CIED. Mechanisms underlying CIED-related TR can be classified into implantation, pacing, and device-related [1, 8].

Conventional CIEDs require the implantation of a lead through the TV, which may contribute to TR generation. The most frequently mentioned mechanism among implantation-related TR is lead impingement, which is the mechanical interference of the ventricular lead with leaflet movement. Additional implantation mechanisms include leaflet perforation, impairment of the subvalvular apparatus, entangled or ruptured chordae tendinae, and perforated papillary muscles [1, 2, 4].

Frequently, TR is brought on by or made worse by typical functional causes. Pacing-induced TR is a pathological process triggered by electrical stimulation of the RV. In the absence of mechanical leaflet interference, dyssynchrony brought on by right ventricular stimulation appears to create geometric alterations in the RV that lead to insufficient mitral and TV coaptation. In this situation, nonapical right ventricular pacing — pacing of the interventricular septum or right ventricular outflow tract — may result in less dyssynchrony and more natural ventricular activity than apical pacing. It may also be linked to a decreased risk of TR worsening. The lead’s position in the RV — apical vs. nonapical — influences the lead–leaflet relationship during its crossing over the TV [1].

TR progresses at different rates depending on the mechanism after CIED implantation. Mechanical impingement/restriction of the leaflets or damage to the TV apparatus are possible causes of acute TR alterations. Significant changes in heart inflammation were also noted a few days after surgery. Furthermore, endocarditis or thrombus formation may be more likely to be caused by the device [8, 18].

For severe TR or lead-related infections, transvenous lead extraction (TLE) is a laborious treatment option. The fundamental problem with TLE is that because of considerable fibrous tissue growth along with lead attachment to the TV apparatus, there is a high likelihood of TV avulsion with increasing TR. The main risk associated with TLE operations is TV tissue avulsion throughout manual traction for lead expulsion, which can intensify TR severity [1].

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Leadless pacemakers potentially intensify or even develop TR because of their functional effects and mechanical disruption of the TV subvalvular apparatus. Because of the potential of leadless devices to become entangled in the chordae tendineae or to interact directly with leaflets, septal insertion of these devices has been demonstrated to have a fivefold increased risk of intensifying tendinopathy (TR) compared with apical implantation [11].

Because of lower left ventricular filling and elevated right ventricular pressure, CIED-induced TR may present as either left- or right-sided HF. Notable differences were observed in the responses to HF therapies between lead-induced and lead-nonrelated TR. If significant TR has occurred during follow-up, the underlying cause should be determined. HF therapies may not be effective in managing HF associated with lead-induced TR, which could worsen the prognosis [7, 15].

Diagnosis

The first imaging modalities for CIED implantation are chest X-ray or ultrasonography. Chest radiography is performed to verify the continuity of the leads and determine the dislocation of the leads and their position relative to each other. The gold standard for diagnosing and classifying TR severity is echocardiography along with associated imaging modalities. All available echocardiographic techniques must be employed for the correct diagnosis of lead-related TR and to distinguish the mechanism causing TR [1, 9].

Identifying a new or deteriorating TR after implantation can be arduous if a baseline echocardiogram (before implantation) is unavailable. In preparation for CIED implantation, candidates should optimally undergo a thorough baseline echocardiogram with the assessment of significance on TV and right ventricular performance. In addition, routine echocardiography after CIED implantation should be performed to establish the presence of TV remodeling and risky lead placement, both of which may result in lead-induced severe TR [5, 8].

Two-dimensional (2D) transthoracic echocardiography (TTE) has been the initial method for identifying and classifying TR and assessing its hemodynamic effects. 2D imaging is applicable to determine the cause of TR, grading of its severity, and evaluating how it affects right ventricular performance. Since only two TV leaflets may be seen at a time on the unusual parasternal view, conventional 2D TTE had limited ability to analyze the anatomy of the TV, all the more, figuring out how the leaflets and a CIED lead interact [1, 9].

The primary shortcomings of 2D echocardiography in evaluating lead-related TR have been resolved by three-dimensional echocardiography (3DE). All TV leaflets and the pacing lead position can be observed concurrently with 3D imaging. 3DE is critical for understanding the pathophysiological pathways that cause lead-related diseases. “En face” imagery from the ventricular and atrial viewpoints during TTE and 3DE can accomplish a thorough TV evaluation [1, 14].

The following steps are involved in diagnosing TR associated with lead: 1) Using a direct comparison of pre- and postimplant TTE studies, the presence of TR is determined; (2) TR is graded based on the most recommendations; (3) using 2D echocardiography and 3D imaging to show mechanical damage on the TV leaflets or apparatus; (4) assessing the hemodynamic effect on the RV if TR is greater than moderate; and (5) determining whether early TLE or surgical treatment is necessary and feasible [1].

When 3D TTE visualization of leaflets is insufficient, transgastric 2D or 3D transesophageal echocardiography (TEE) and cine cardiac CT can be used to provide short-axis TV imaging. On the condition that the lead position cannot be established with certainty, TEE should be considered an additional imaging modality. The use of cardiac magnetic resonance imaging (MRI) for diagnostic purposes is limited because notable local local artifacts in the vicinity of the CIED leads affect cardiovascular MRI and frequently obscure the view of the lead, valve, and related TR. Therefore, 3D echocardiography is the preferred imaging modality for diagnosing and planning interventional therapy for TR associated with CIED [9, 11, 19].

Management

Treatment options include medical therapy and percutaneous and surgical interventions. Medical therapy is aimed at alleviating TR symptoms and right heart dilatation, with diuretics as the primary treatment. Aldosterone antagonists are recommended as helpful supplemental medications, particularly for patients with hepatic congestion and secondary aldosterone rise, whereas loop diuretics are frequently used in severe TR and symptomatic right HF.[4]

The definitive therapy may require lead repositioning or removal, either surgically or percutaneously, depending on the expertise of each medical facility. Treating lead-related TR with TLE may be appealing. Given the lack of defined guidelines for the use of TLE in patients with pertinent TR, a comprehensive risk–benefit analysis is crucial. Although rare, significant damage to the TV apparatus may occur throughout TLE, with a reported incidence of 2.5% across over 2600 procedures. Furthermore, the clinical reason for stimulation or pacing when lead extraction is required must be reassessed, and alternative CIED techniques such as subcutaneous ICDs, leadless pacemakers, epicardial, His-bundle pacing, and coronary sinus lead positioning must be considered. Nonetheless, mechanical issues that result in substantial TR can still affect devices such as leadless pacemakers [1, 8, 20].

In addition to severity and irreversible TV leaflet impairment, risk for progressive tricuspid annular dilatation, right ventricular enlargement or malfunction, and right ventricular HF increased if CIED-related TR is not identified and treated quickly. Most often, these cases require surgical

valve replacement or repair. The current criteria for surgical valve repair or replacement when CIED-induced TR occurs consider the degree of regurgitation, presence of symptoms, and right ventricular functionality [20].

The 2021 ESC Guidelines for the Management of Valvular Heart Disease state that valve repair is preferred over valve replacement when there is neither substantial TV degradation nor annulus dilatation. No discernible difference in durability was observed between CIED-induced and CIED-associated TR, and TV repair was still feasible in 63% of the cases with satisfactory long-term results. In 30% of the cases, TV replacement was unavoidable. Several procedures have been employed to repair the valve in patients with CIED-induced TR. In some cases, a fibrotic reaction resulting in lead encapsulation in the TV leaflet was observed and removed. Typically, this process was adequate for the leaflet to move freely [10, 21].

Therapy including transcatheter TV replacement (TTVR) or percutaneous transcatheter edge-to-edge TV repair (T-TEER) for severe TR has recently become available as a nonsurgical option to reduce TR severity in high-risk patients. TTVR in patients with CIED achieves procedural performance and TR reduction similar to those in patients without CIED [22].

Limitation

The primary limitation to the generalization of these results is the heterogeneity of the research methodologies and populations observed in the studies. This article does not restrict the standards used in each investigation, such as study design, evaluation period, imaging technique, and availability of baseline echocardiography. Nonetheless, these findings must be interpreted with caution, and certain limitations should be considered.

CONCLUSION

Patients with CIED have a higher risk of TV disorders, particularly regurgitation. CIED-related TR is recognized as a particular etiologic group because of multiple causes, including implantation, pacing, and device-related. To facilitate the diagnosis of CIED-induced TR, candidates should undergo a comprehensive baseline echocardiogram in preparation for CIED installation and routine echocardiographic follow-ups. Medicinal treatments and percutaneous and surgical procedures are available for treating CIED-induced TR. A definitive treatment may necessitate lead repositioning or removal. Determining the precise mechanism of TR is basic for managing this illness, and determining whether corrective intervention is necessary and safe.

ADDITIONAL INFORMATION

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REFERENCES

1. Gelves-Meza J, Lang RM, Valderrama-Achury MD, et al. Tricuspid regurgitation related to cardiac implantable electronic devices: an integrative review. *J Am Soc Echocardiogr*. 2022;35(11):1107–1122. doi: 10.1016/j.echo.2022.08.004

2. Offen S, Strange G, Playford D, et al. Prevalence and prognostic impact of tricuspid regurgitation in patients with cardiac implantable electronic devices: From the national echocardiography database of Australia. *Int J Cardiol*. 2023;370:338–344. doi: 10.1016/j.ijcard.2022.10.160

3. Husain A, Raja FT, Fatallah A, et al. Tricuspid stenosis: An emerging disease in cardiac implantable electronic devices era. Case report and literature review. *J Cardiol Cases*. 2017;15(6):190–193. doi: 10.1016/j.jccase.2017.02.003

4. Addetia K, Harb SC, Hahn RT, et al. Cardiac implantable electronic device lead-induced tricuspid regurgitation. *JACC Cardiovasc Imaging*. 2019;12(4):622–636. doi: 10.1016/j.jcmg.2018.09.028

5. Nakajima H, Seo Y, Ishizu T, et al. Features of lead-induced tricuspid regurgitation in patients with heart failure events after

cardiac implantation of electronic devices – A three-dimensional echocardiographic study. *Circ J.* 2020;84(12):2302–2311. doi: 10.1253/circj.CJ-20-0620

6. Zhang XX, Wei M, Xiang R, et al. Incidence, risk factors, and prognosis of tricuspid regurgitation after cardiac implantable electronic device implantation: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth*. 2022;36(6):1741–1755. doi: 10.1053/j.jvca.2021.06.025

7. Seo Y, Nakajima H, Ishizu T, et al. Comparison of outcomes in patients with heart failure with versus without lead-induced tricuspid regurgitation after cardiac implantable electronic devices implantations. *Am J Cardiol*. 2020;130:85–93. doi: 10.1016/j.amjcard.2020.05.039

8. Andreas M, Burri H, Praz F, et al. Tricuspid valve disease and cardiac implantable electronic devices. *Eur Heart J*. 2024;45(5): 346–365. doi: 10.1093/eurheartj/ehad783

9. Chodór-Rozwadowska KE, Sawicka M, Morawski S, et al. Lead-related tricuspid regurgitation and ventricle dysfunction: Current management and future perspectives. *Adv Clin Exp Med*. 2023;32(9):1049–1061. doi: 10.17219/acem/159531

10. Carino D, Sala A, Zancanaro E, et al. Surgical treatment of tricuspid valve regurgitation in patients with cardiac implantable electronic devices: long-term results. *Eur J Cardiothoracic Surg*. 2022;62(3):ezac239. doi: 10.1093/ejcts/ezac239

11. Stankovic I, Voigt JU, Burri H, et al. Imaging in patients with cardiovascular implantable electronic devices: part 2—imaging after device implantation. A clinical consensus statement of the European Association of Cardiovascular Imaging (EACVI) and the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J Cardiovasc Imaging.* 2023.25(1).e33–e54. doi: 10.1093/ehjci/jead273

12. Javed N, Iqbal R, Malik J, et al. Tricuspid insufficiency after cardiac-implantable electronic device placement. *J Community Hosp Intern Med Perspect*. 2021;11(6):793–798. doi: 10.1080/20009666.2021.1967569

13. Alnaimat S, Doyle M, Krishnan K, Biederman RWW. Worsening tricuspid regurgitation associated with permanent pacemaker and implantable cardioverter-defibrillator implantation: A systematic review and meta-analysis of more than 66,000 subjects. *Heart Rhythm*. 2023.20(11):1491–1501. doi: 10.1016/j.hrthm.2023.07.064

14. Papageorgiou N, Falconer D, Wyeth N, et al. Effect of tricuspid regurgitation and right ventricular dysfunction on long-term mortality in patients undergoing cardiac devices implantation: >10-year follow-up study. *Int J Cardiol.* 2020;319:52–56. doi: 10.1016/j.ijcard.2020.05.062

15. Kanawati J, Ng ACC, Khan H, et al. Long-term follow-up of mortality and heart failure hospitalisation in patients with intracardiac device-related tricuspid regurgitation. *Heart Lung Circ*. 2021;30(5):692–697. doi: 10.1016/j.hlc.2020.08.028

16. Safiriyu I, Mehta A, Adefuye M, et al. Incidence and prognostic implications of cardiac-implantable device-associated tricuspid regurgitation: a meta-analysis and meta-regression analysis. *Am J Cardiol*. 2023;209:203–211. doi: 10.1016/j.amjcard.2023.09.064

17. Van De Heyning CM, Elbarasi E, Masiero S, et al. Prospective study of tricuspid regurgitation associated with permanent leads after cardiac rhythm device implantation. *Can J Cardiol*. 2019;35(4): 389–395. doi: 10.1016/j.cjca.2018.11.014

18. Arabi P, Özer N, Ateş AH, et al. Effects of pacemaker and implantable cardioverter defibrillator electrodes on tricuspid regurgitation and right sided heart functions. *Cardiol J.* 2015;22(6):637–644. doi: 10.5603/CJ.a2015.0060

19. Guigui S, Zedan A, LaPietra A, et al. Cardiovascular implantable electronic device-related tricuspid regurgitation: A multidisciplinary team approach. *J Thorac Dis.* 2020;12(5):2986–2989. doi: 10.21037/jtd.2020.01.64

20. Ehra A, Task A, Members F, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm. 2021;1–94. doi: https://academic.oup.com/eurheartj/article/42/35/3427/6358547?login=false

21. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Rev Esp Cardiol (Engl Ed).* 2022;75(6):524. doi: 10.1016/j.rec.2022.05.006

22. Lurz J, Rommel KP, Unterhuber M, et al. Safety and efficacy of transcatheter edge-to-edge repair of the tricuspid valve in patients with cardiac implantable electronic device leads. *JACC Cardiovasc Interv*. 2019;12(20):2114–2116. doi: 10.1016/j.jcin.2019.05.034

СПИСОК ЛИТЕРАТУРЫ

1. Gelves-Meza J., Lang R.M., Valderrama-Achury M.D., et al. Tricuspid regurgitation related to cardiac implantable electronic devices: an integrative review // J Am Soc Echocardiogr. 2022. Vol. 35, N. 11. P. 1107–1122. doi: 10.1016/j.echo.2022.08.004

2. Offen S., Strange G., Playford D., et al. Prevalence and prognostic impact of tricuspid regurgitation in patients with cardiac implantable electronic devices: From the national echocardiography database of Australia // Int J Cardiol. 2023. Vol. 370. P. 338–344. doi: 10.1016/j.ijcard.2022.10.160

3. Husain A., Raja F.T., Fatallah A., et al. Tricuspid stenosis: An emerging disease in cardiac implantable electronic devices era. Case report and literature review // J Cardiol Cases. 2017. Vol. 15, N. 6. P. 190–193. doi: 10.1016/j.jccase.2017.02.003

4. Addetia K., Harb S.C., Hahn R.T., et al. Cardiac implantable electronic device lead-induced tricuspid regurgitation // JACC Cardiovasc Imaging. 2019. Vol. 12, N. 4. P. 622–636. doi: 10.1016/j.jcmg.2018.09.028

5. Nakajima H., Seo Y., Ishizu T., et al. Features of lead-induced tricuspid regurgitation in patients with heart failure events after cardiac implantation of electronic devices - A three-dimensional echocardiographic study // Circ J. 2020. Vol. 84, N. 12. P. 2302–2311. doi: 10.1253/circj.CJ-20-0620

6. Zhang X.X., Wei M., Xiang R., et al. Incidence, risk factors, and prognosis of tricuspid regurgitation after cardiac implantable electronic device implantation: a systematic review and meta-analysis // J Cardiothorac Vasc Anesth. 2022. Vol. 36, N. 6. P.1741–1755. doi: 10.1053/j.jvca.2021.06.025

7. Seo Y., Nakajima H., Ishizu T., et al. Comparison of outcomes in patients with heart failure with versus without lead-induced tricuspid regurgitation after cardiac implantable electronic

devices implantations // Am J Cardiol. 2020. Vol. 130. P. 85–93. doi: 10.1016/j.amjcard.2020.05.039

8. Andreas M., Burri H., Praz F., et al. Tricuspid valve disease and cardiac implantable electronic devices // Eur Heart J. 2024. Vol. 45, N. 5. P. 346–365. doi: 10.1093/eurheartj/ehad783

9. Chodór-Rozwadowska K.E., Sawicka M., Morawski S., et al. Lead-related tricuspid regurgitation and ventricle dysfunction: Current management and future perspectives // Adv Clin Exp Med. 2023. Vol. 32, N. 9. P. 1049–1061. doi: 10.17219/acem/159531

10. Carino D., Sala A., Zancanaro E., et al. Surgical treatment of tricuspid valve regurgitation in patients with cardiac implantable electronic devices: long-term results // Eur J Cardiothorac Surg. 2022. Vol. 62, N. 3. P. ezac239. doi: 10.1093/ejcts/ezac239

11. Stankovic I., Voigt J.U., Burri H., et al. Imaging in patients with cardiovascular implantable electronic devices: part 2—imaging after device implantation. A clinical consensus statement of the European Association of Cardiovascular Imaging (EACVI) and the European Heart Rhythm Association (EHRA) of the ESC // Eur Heart J Cardiovasc Imaging. 2023. Vol. 25, N. 1. P. e33–e54. doi: 10.1093/ehjci/jead273

12. Javed N., Iqbal R., Malik J., et al. Tricuspid insufficiency after cardiac-implantable electronic device placement // J Community Hosp Intern Med Perspect. 2021. Vol. 11, N. 6. P. 793–798. doi: 10.1080/20009666.2021.1967569

13. Alnaimat S., Doyle M., Krishnan K., et al. Worsening tricuspid regurgitation associated with permanent pacemaker and implantable cardioverter-defibrillator implantation: A systematic review and meta-analysis of more than 66,000 subjects // Heart Rhythm. 2023. Vol. 20, N. 11. P. 1491–1501. doi: 10.1016/j.hrthm.2023.07.064

14. Papageorgiou N., Falconer D., Wyeth N., et al. Effect of tricuspid regurgitation and right ventricular dysfunction on long-term mortality in patients undergoing cardiac devices implantation: > 10-year follow-up study // Int J Cardiol. 2020. Vol. 319. P. 52–56. doi: 10.1016/j.ijcard.2020.05.062

15. Kanawati J., Ng A.C.C., Khan H., et al. Long-term follow-up of mortality and heart failure hospitalisation in patients with intracardiac device-related tricuspid regurgitation // Heart Lung Circ. 2021. Vol. 30, N. 5. P. 692–697. doi: 10.1016/j.hlc.2020.08.028

16. Safiriyu I., Mehta A., Adefuye M., et al. Incidence and prognostic implications of cardiac-implantable device-associated tricuspid regurgitation: a meta-analysis and meta-regression analysis // Am J Cardiol. 2023. Vol. 209. P. 203–211. doi: 10.1016/j.amjcard.2023.09.064

17. Van De Heyning C.M., Elbarasi E., Masiero S., et al. Prospective study of tricuspid regurgitation associated with permanent leads after cardiac rhythm device implantation // Can J Cardiol. 2019. Vol. 35, N. 4. P. 389–395. doi: 10.1016/j.cjca.2018.11.014

18. Arabi P., Özer N., Ateş A.H., et al. Effects of pacemaker and implantable cardioverter defibrillator electrodes on tricuspid regurgitation and right sided heart functions // Cardiol J. 2015. Vol. 22, N. 6. P. 637–644. doi: 10.5603/CJ.a2015.0060

19. Guigui S., Zedan A., LaPietra A., et al. Cardiovascular implantable electronic device-related tricuspid regurgitation: A multidisciplinary team approach // J Thorac Dis. 2020. Vol. 12, N. 5. P. 2986–2989. doi: 10.21037/jtd.2020.01.64

20. Ehra A., Task A., Members F., et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European // Heart Rhythm. 2021. P. 1–94. doi: https://academic.oup.com/eurheartj/article/42/35/3427/6358547?login=false

21. Vahanian A., Beyersdorf F., Praz F., et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) // Rev Esp Cardiol (Engl Ed). 2022. Vol. 75, N. 6. P. 524. doi: 10.1016/j.rec.2022.05.006

22. Lurz J., Rommel K.P., Unterhuber M., et al. Safety and efficacy of transcatheter edge-to-edge repair of the tricuspid valve in patients with cardiac implantable electronic device leads // JACC Cardiovasc Interv. 2019. Vol. 12, N. 20. P. 2114–2116. doi: 10.1016/j.jcin.2019.05.034

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