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ISOLATED ABERRANT RIGHT SUBCLAVIAN ARTERY: SHOULD INVASIVE INTERVENTION BE RECOMMENDED IN THE ERA OF NONINVASIVE PRENATAL TESTS?

İZOLE ABERAN SAĞ SUBKLAVYAN ARTER: NONİNVAZİV PRENATAL TESTLERİN VARLIĞINDA PRENATAL TANI İÇİN İNVAZİV GİRİŞİM ÖNERİLMELİ Mİ?

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ABSTRACT

Objective: An aberrant right subclavian artery (ARSA) is an aortic arch anomaly isolated or associated with other ultrasound markers and/or congenital anomalies. This study aimed to evaluate the necessity of invasive prenatal tests (PIT) in cases with isolated ARSA (iARSA) in prenatal sonography.

Materials and Methods: The presence of ARSA was evaluated retrospectively in 7690 fetuses who underwent a second-trimester ultrasonography evaluation between March 2015 and February 2021. PIT was recommended for patients with non-iARSA. cfDNA test (including 22q11.2 microdeletion/duplication syndrome (MMS) or PIT was suggested for patients with iARSA.

Results: The mean week of gestation was 20.26±3.93 in 95 fetuses diagnosed with ARSA. Of the fetuses, fourty-two (44%) had iARSA, and 53 (56%) had additional findings. No chromosomal abnormality was found in any of the isolated cases. Trisomy 21 in 14, Trisomy 18 in one, 47,XX,+i(9)(p10) in one of 53 were found in non-isolated cases. Additional abnormalities and/or soft ultrasound markers were accompanied in all fetuses with chromosomal abnormalities.

Conclusion: When iARSA is detected in prenatal ultrasonography, cfDNA testing may be sufficient, including 22q11.2 MMS. However, PIT should be recommended in the presence of struc-

ÖZET

Amaç: Aberan sağ subklavyen arter (ASSA), izole veya diğer ultrason belirteçleri ve/veya konjenital anomalilere eşlik eden bir aortik ark anomalisidir. Bu çalışmada, prenatal sonografide izole ASSA saptanan olgularda prenatal invaziv test (PIT) gerekliliğinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Mart 2015 ile Şubat 2021 arasında ikinci üçay ultrasonografi değerlendirilmesi yapılan 7690 fetüsten oluşan popülasyonda, ASSA varlığı retrospektif olarak değerlendirildi. ASSA ile birlikte ek konjenital anomalisi olan hastalara PIT önerilirken, ASSA'nın izole olduğu olgularda 22q11.2 mikrodelesyon/dublikasyon (MMS) dahil hücre dışı DNA (cfDNA) testi veya PIT önerilmiştir.

Bulgular: ASSA bulunan 95 fetüste ortalama gebelik haftası 20,26±3,93 olarak saptanmıştır. Bunlardan 42'sinde izole ASSA, 53'ünde ise ASSA dışı ek bulgular mevcuttu. İzole olguların hiçbirinde kromozom anomalisi saptanmazken, izole olmayan 53 olgudan, 14'ünde Trizomi 21, birinde Trizomi 18, birinde ise 47, XX,+i(9)(p10) saptanmıştır. Kromozom anomalisi saptanan fetüslerin tamamında ek anomali ve/veya minor belirteçler eşlik etmekteydi.

Sonuç: Prenatal ultrasonografide izole ASSA saptanan olgularda, 22q11.2 MMS da dahil olmak üzere noninvaziv cfDNA testinin

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tural abnormalities, soft ultrasound markers, or increased risk in the antenatal screening test.

Keywords: Aberrant right subclavian artery, Cell-Free DNA, Down syndrome, 22q11.2 microdeletion, prenatal diagnosis, ultrasound

yapılması yeterli olabilir. Ancak, ek majör anomali, minör belirteç veya tarama testinde risk artışı varlığında PIT önerilmelidir.

Anahtar Kelimeler: Aberran sağ subklavyen arter, hücre dışı DNA, Down sendromu, 22q11 mikrodelesyonu, prenatal tanı, ultrason

INTRODUCTION

An aberrant right subclavian artery (ARSA) is the most common aortic branching abnormality and occurs either in isolation or in association with other soft markers and congenital anomalies (1-4). Fetuses with ARSA are at risk of having chromosomal aberrations such as Trisomy 21 (Down syndrome; DS) and 22q11.2 microdeletion syndrome (DiGeorge Syndrome; DGS) (1). While the incidence of ARSA is about 1% to 2% in fetuses with normal karyotype, the incidence is reported to be about 28% to 37.5% in fetuses with DS diagnosed in the second trimester (2-4). In a recent systematic review covering 12 studies, ARSA established an important marker for DS, with a likelihood ratio (LR) of 26.9 (5). However, in a meta-analysis evaluating the performance of sonographic soft markers detected in the second trimester, it was suggested that the risk of aneuploidy in the prediction of Trisomy 21 risk was mainly derived from first trimester findings (6). Based on this data, in the absence of all other markers, the positive LR was found to be 3.94 in the presence of isolated ARSA (iARSA). Hence, according to local guidelines during the second trimester evaluation, some authors recommend that pregnant women be classified as low-intermediate and high-risk (6, 7). The published data has limited evidence to describe the value of microdeletion/duplication syndromes (MMSs) in fetuses with ARSA (8). In some countries, prenatal invasive testing, including chromosomal microarray, is recommended for fetal structural anomalies, including ARSA (1). Consequently, although an association between DS/DGS and ARSA has been reported in preliminary studies, this association still needs to be investigated, especially in isolated ARSA cases.

Cell-free DNA (cfDNA) in maternal circulation was first reported by Lo et al. in 1997, and this discovery brought up the development of a noninvasive prenatal approach as a screening test for fetal chromosomal abnormalities (9). Detection rates in a recent meta-analysis evaluating cfDNA screening were higher than 99% for trisomy 21, 98% for trisomy 18, and 99% for trisomy 13, with a combined false-positive rate of 0.13% (10). Conventional aneuploidy screening is not designed to detect MMSs, and fetal ultrasonographic assessment may be limited as prenatal findings associated with MMSs may not be obvious (11). Most of the MMSs associated with clinically significant copy number variations (CNVs) and the pathogenic CNVs are diagnosed by chromosomal microarray analysis (11, 12). It was reported that most cases of DGS, including both classical and nested deletions that are >500 kb, are identified with single-nucleotide polymorphism (SNP) based cfDNA screening (12). A more recent study presented that a targeted cfDNA test for DGS detects the common nested deletions with a low false-positive rate (12-14). Although there are long-held reservations about using prenatal cfDNA screening tests for microdeletion syndromes, recent studies have reported a sensitivity of 86.7% and a specificity higher than 99% for DGS, despite low positive predictive values (15). However, in more recent studies, the predictive values of cfDNA testing for DGS were higher (14). Hence, it is known that preventing unnecessary prenatal invasive testing by using cfDNA in border cases is still a controversial issue.

The study aimed to investigate whether there is a need for invasive intervention when cfDNA testing is used as a prenatal aneuploidy screening test for iARSA cases.

MATERIALS AND METHODS

This unselected population-based retrospective study was performed in a prenatal diagnosis clinic between March 2015 and February 2021. All data were obtained during detailed fetal midtrimester ultrasounds. Previous antenatal aneuploidy screening tests and cfDNA test results were evaluated and recorded in all patients who were admitted to our outpatient clinic for the routine mid-trimester fetal ultrasound scan. The records of the patients were kept in Medikbase's electronic medical record system, known as Gynobserve. After informing each patient about the success and limitations of the ultrasound to be performed and obtaining their consent, a detailed sonographic examination was performed using the checklists by the same operator. All fetal organ systems and soft markers were evaluated in detail with high-frequency transabdominal transducers (Voluson E8 Expert system, RAB6-D; GE Healthcare, Zipf, Austria). The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee of the Istanbul Faculty of Medicine (Date:21.10.2022, No:19).

The ARSA assessment was carried out with the technique Chaoui et al. previously described (2). After the fetal three-vessel and tracheal views were obtained, Doppler velocity was reduced to 15 to 30 cm/s. An ARSA was diagnosed as a separate artery originating from the junction of the aortic and ductal arches and running between the trachea and vertebra. The thymus was also evaluated in all fetuses detected with ARSA. Cases with ARSA were considered isolated when there were no associated sys-

temic structural anomalies and/or soft markers during the midtrimester sonography. In the case of related abnormalities and/or soft markers, patients were categorized as non-isolated. Soft markers included increased nuchal translucency (NT)>95th percentile detected at first trimester ultrasonography, echogenic intracardiac focus, short femur <5th percentile, short humerus <5th percentile, choroid plexus cyst, thickened nuchal fold, pyelectasis, echogenic intestine, hypoplastic and/or absent nasal bone.

We offered either cfDNA testing or an invasive procedure to detect DS and DGS to the patients whose fetuses were found to have ARSA with no associated structural anomaly (for fetuses with isolated ARSA or fetuses with ARSA plus soft markers and/or screening test positivity). The invasive intervention was primarily recommended to pregnant women whose fetuses had concomitant cardiac or structural abnormalities other than ARSA. After counseling for prenatal invasive procedures, amniocentesis (AC) was performed by standard procedure. AC samples were investigated by cell-culture techniques with fluorescent in-situ hybridization (FISH). If the cfDNA test was positive for MMSs, microarray analysis was planned. Neonatal echocardiography was offered to all fetuses detected with ARSA after delivery to exclude other possible cardiac defects. Postnatal karyotyping was considered normal in newborns who did not undergo invasive prenatal testing. Postnatal karyotyping was offered if the newborn had any abnormal physical appearance or structural abnormality.

RESULTS

A detailed fetal systemic midtrimester ultrasound examination was performed on 7690 singleton pregnancies within the specified time period. Among them, ARSA was detected in 95 of them (1.23%) (Figure 1). In the study group, ARSA (isolated or non-isolated) was detected, the mean maternal age was 31.9±5.6, and the mean gestational age was 20.26±3.93 weeks at diagnosis. Hypoplasia or aplasia of the thymus was not detected in fetuses with ARSA.

Isolated ARSA as a sonographic finding was detected in 42 (44%) cases; antenatal screening tests were also positive in six cases. Prenatal invasive intervention or cfDNA testing was offered for all cases in the isolated ARSA group. Ten of the 42 cases had already undergone cfDNA testing. Five of the cases in this group chose the invasive procedure, and 10 chose the cfDNA testing. The remaining cases in this group accepted neither cfDNA testing nor an invasive procedure. No chromosomal abnormality was detected in this group.

The remaining cases (53/95; 56%) were categorized as non-isolated. Twenty-five cases (25/53; 47%) had at least one of the soft markers, 20 of the remaining cases (20/53; 38%) had cardiovascular abnormalities, and 8 (8/53; 15%) had extracardiac abnormalities (Table 1, 2). The prenatal invasive intervention was offered to all cases with any systemic structural abnormalities. In 25 fetuses with additional soft markers, four cases had cfDNA testing before ultrasonography, and the test results were negative. Six-

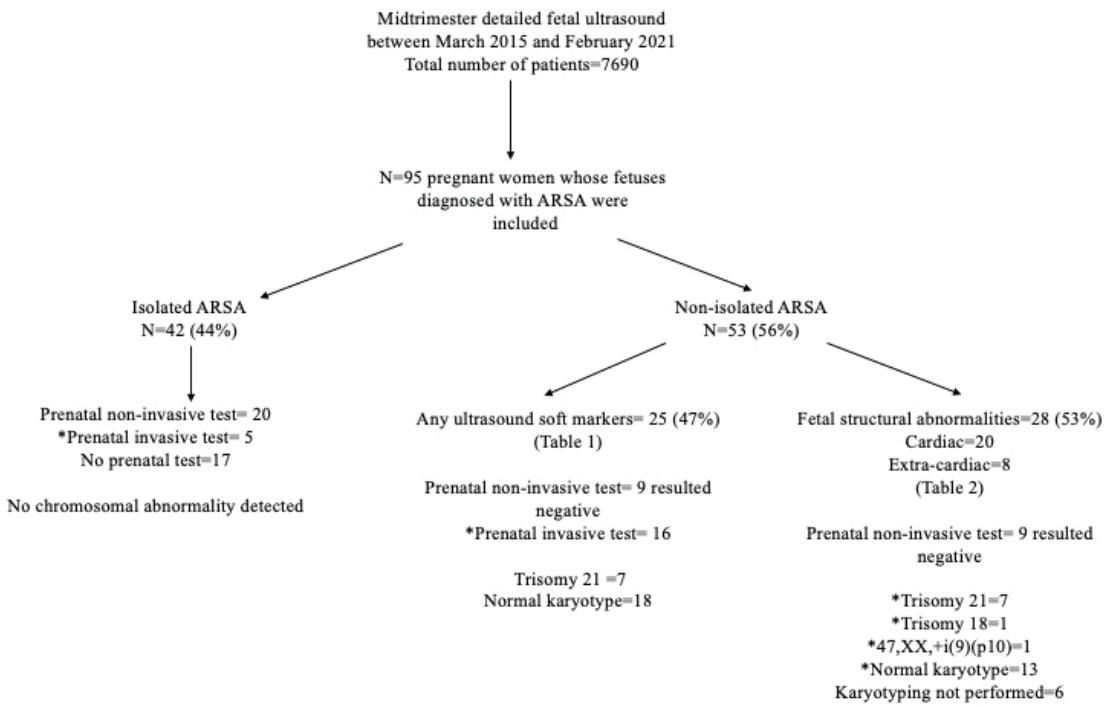

Figure 1: Diagnostic flow of all prenatal cases included in the current study (*Amniocentesis was performed in these prenatal cases)

Table 1: Prenatal ultrasonographic characteristics and outcomes in the cases of ARSA associated with soft markers

	Age	Screening test result	iNT	EIF	SH/SF	CPC	tNF	P	EI	NB	cfDNA testing	Fetal karyotype	Outcome
1	41	High risk	+	+								T21	TOP
2	32	High risk		+	+							T21	TOP
3	35	High risk		+				+				T21	Alive *
4	33	High risk		+							Low risk	Normal	Alive
5	39	Low risk		+		+						T21	TOP
6	30	Low risk					+					Normal	Alive
7	35	Low risk							+		Low risk	Normal	Alive
8	31	Low risk		+			+					Normal	Alive
9	34	Low risk						+			Low risk	Normal	Alive
10	37	Low risk					+					Normal	Alive
11	25	Low risk		+							Low risk	Normal	Alive
12	25	Low risk		+					+			T21	TOP
13	29	High risk	+									Normal	ID, CHARGE syndrome
14	28	Low risk		+		+			+		Low risk	Normal	Alive
15	33	Low risk						+			Low risk	Normal	Alive
16	33	Low risk					+	+				Normal	Alive
17	28	Low risk				+					Low risk	Normal	Alive
18	31	High risk	+							+		Normal	Alive
19	32	Low risk				+					Low risk	Normal	Alive
20	38	High risk	+									Normal	Alive
21	31	Low risk						+		+		T21	TOP
22	40	Low risk					+					Normal	Alive
23	27	Low risk		+				+				Normal	Alive
24	34	High risk	+	+								T21	TOP
25	23	Low risk		+							Low risk	Normal	Alive

cfDNA: cell free DNA, CPC: choroid plexus cyst, EI: echogenic intestine, EIF: echogenic intracardiac focus, NB: hypoplastic and/or absent nasal bone, iNT: increased nuchal translucency, tNF: thickened nuchal fold, SH: short humerus, SF: short femur, P: pyelectasis, T21: Trisomy 21, TOP: termination of pregnancy, ID: Infant death
**This case was diagnosed trisomy 21 postnatally.*

teen cases in this group chose the invasive procedure, and 5 chose the cfDNA testing. In this group, seven fetuses, one postnatal, were diagnosed with DS. A procedure-related abortion occurred in one case who had no chromosomal abnormality.

Prenatal invasive diagnostic testing was offered to all cases (28/53; 53%) which had an additional structural (cardiac or extracardiac) abnormality (Table 2). Although six denied prenatal invasive intervention, the remaining 22 cases opted to have karyotype. Pregnancies were terminated due to multiple anomalies in 2 of the 6 cases that underwent no invasive procedure. One case (case 9, table 2), which was associated with multiple abnormalities, including polyhydramnios, resulted in abortion after premature rupture of membranes. In the other case (case 12, table 2), the pregnancy was terminated due to maternal Mirror syndrome. The remaining 2 cases are currently alive and are under echocardiographic follow-up. The prenatal cardiac findings (case 10 and 14, table 2) were confirmed postnatally.

DS was diagnosed in 7 of 28 fetuses. Trisomy 18 and 47,XX-,+i(9)(p10) were diagnosed in another 2 cases (case 19 and 20; table 2). All parents with fetal chromosomal abnormalities opted to terminate the pregnancy, except for one diagnosed with DS. The remaining 2 of the 13 cases died postnatally. One was diagnosed with Cornelia de Lange syndrome after birth, while the other died after cardiac surgery. Five of 6 live births are being followed up due to cardiac anomalies, and one case was operated on for a portosystemic shunt.

Table 2: Prenatal ultrasound findings and outcomes in ARSA cases with additional congenital anomalies

Case	Maternal age	CVS	CNS	Face/ Neck	GUS	GIS	Skeletal System	Number of associated soft markers	Karyotype	Outcome
1	38	AVSD			EK				T21	TOP
2	37	VSD	BBV		UDK	iGB		3	NP	TOP
3	30	VSD				DBS		2	T21	TOP
4	29	AVSD						3	T21	Alive
5	39	None	HC					1	Normal	TOP
6	41	VSD					Talipes	3	Normal	Alive
7	22	AVSD						2	T21	TOP
8	26	aDV						1	Normal	Alive (PSS surgery)
9	32	None	IHC, C			EA, poly-hydramniosis			NP	TOP
10	36	VSD							NP	Alive (surgery)
11	32	VSD						2	Normal	CdLS, ID
12	34	None		CH	BRA				NP	TOP (MMS)
13	31	RAA							Normal	Alive
14	29	PLSVC							NP	Alive
15	34	None				iGB			Normal (BA)	TOP
16	27	None		CH				1	Normal	TOP
17	23	VSD							Normal	Alive
18	34	None					SB		NP	TOP
19	34	AVSD			EK	Omphalocele		2	T18	TOP
20	31	DORV							47,XX,+i(9)(p10)	TOP
21	40	None	BBV	CLP					Normal	TOP
22	25	CoaAo				EA		1	Normal	Alive (surgery)
23	27	None				Omphalocele		2	T21	TOP
24	28	AVSD						1	T21	TOP
25	20	DORV						1	Normal	ID (perop)
26	42	RAA				DBS		1	T21	TOP
27	26	aDV	BBV				Talipes, DRD		Normal	TOP
28	29	AVSD		CLP	BRA		Talipes	1	Normal	TOP

aDV: Agenesis of Ductus venosus, AVSD: Atrioventricular septal defect, BBV: Bilateral borderline ventriculomegaly, BA: Biliary atresia, BRA: Bilateral renal agenesis, C: Cephalocele, CVS: Cardiovascular system, CNS: Central nervous system, CLP: Cleft lip-palate, CoaAo: Coarctation of aorta, CdLS: Cornelia de Lange syndrome, CH: Cystic hygroma, DRD: Distal reduction defect, DBS: Double-bubble sign, DORV: Double outlet right ventricle, EK: Echogenic kidneys, EA: Esophageal atresia, GIS: Gastrointestinal system, GUS: Genitourinary system, HC: Hydrocephaly, iGB: Invisible gall bladder, ID: Infant death, IHC: Interhemispheric cyst, MMS: Maternal Mirror syndrome, NP: not performed, PLSVC: Persistent left superior vena cava, perop: peroperative, PSS: Porto-systemic shunt, RAA: Right aortic arch, SB: Spina bifida, T21: Trisomy 21, T18: Trisomy 18, TOP: Termination of pregnancy, UDK: Unilateral dysplastic kidneys, VSD: Ventricular septal defect

DISCUSSION

ARSA is known to be a clinically useful prenatal ultrasound marker of DS. Regarding its association with DS, Paladini et al. demonstrated that ARSA was the third most important second trimester marker for Down syndrome after hypoplastic nasal bone and cardiac abnormalities (16). In our unselected population, the prevalence of ARSA was 1.23%, similar to the other studies. DS was not detected in any of the iARSA cases. Fourteen cases with ARSA were diagnosed with DS (14/53; 26%), and all were in the non-isolated ARSA group. Half of these DS fetuses had associated congenital anomalies, and the remaining seven had ultrasound soft markers. In the literature, some studies revealed ARSA as the only ultrasonographic marker in fetuses with Down syndrome (4,17,18). However, in these studies, study populations comprised mostly high-risk patients for chromosomal abnormalities (4,17,18). The meta-analysis by Agathokleous et al. demonstrated that ARSA is a significant marker for Down syndrome (positive likelihood ratio, LR+=21.48), whereas its normal course is a protective marker (negative likelihood ratio, LR−=0.7) (6).

However, in most recent studies, iARSA is found to be benign and not associated with Down syndrome or 22q11 microdeletion syndrome (19-21). Similarly, the meta-analysis by De León-Luis et al. showed no association between isolated ARSA and DS (22). They detected the LR+ as 0 in iARSA cases, whereas for non-isolated cases, it was 199 (23). They highlighted that the presence of high background risk, associated abnormalities, and/or soft markers should guide the management of karyotyping. In the current study, iARSA was not detected in any cases diagnosed with DS. Moreover, in a meta-analysis for DS, detection rate (DR) and false positive rates in singleton pregnancies were 99.2% (95% CI, 98.5 – 99.6%) and 0.09% (95% CI, 0.05 – 0.14%), respectively (23). From this point of view, it raises doubts that non-invasive prenatal tests should be included in the management steps in isolated ARSA cases.

In accordance with the recent literature, all fetuses with ARSA and genetic abnormalities had additional ultrasound findings in our cohort (6,20). Our previous study detected a weak association between ARSA and DS in an unselected population (24). With additional malformations, soft ultrasound markers, and high background risk, the risk of chromosomal abnormalities in a fetus with ARSA may be increased. As in the current study, 16 of the 53 fetuses (30.18%) in non- isolated ARSA group had chromosomal abnormalities. In this group, 14 fetuses were trisomy 21 (26%), one case was trisomy 18, and the other was 47,XX,+i(9)(p10). In a large case series in the Turkish population, it was reported that 18.9% of the cases with non-isolated ARSA were diagnosed with a chromosomal abnormality (25). It should be kept in mind that ARSA alone may not create a sufficient indication for invasive testing; instead, it may be managed with noninvasive prenatal testing.

Besides DS, the association between ARSA and DGS has also been reported in the literature (17). Although most guidelines do not recommend cfDNA testing as a routine screening test for microdeletions, recent studies report greater clinical performance of the test for DGS and suggest using cfDNA testing for pregnancies at risk for DGS to avoid maternal anxiety and unnecessary invasive procedures (14,15). Maya et al. demonstrated that ARSA was associated with DGS, especially in the presence of increased nuchal translucency (>4 mm), ventricular septal defect, clubfoot, right aortic arch, echogenic intracardiac focus, and increased risk for trisomy 21 at maternal serum screening (26). In the Sagi-Dain study, no 22q11.2 deletion was detected among 246 isolated ARSA cases (8). Although there are different results in the literature, no cases with DGS were detected in the current study, which was associated with ARSA with/without cardiac anomalies.

The main limitations of our study were its retrospective design and limited sample size of isolated cases. This may have affected the detection rate of chromosomal abnormalities in the current study, although several isolated cases were similar to those in other studies (22). Our study's strengths are that the same operator examined many fetuses, and all of these examinations were performed using the checklist. The number of patients in the current study was limited to generalize about both DS and DGS. Although no chromosomal/non-chromosomal abnormality was detected in isolated cases with ARSA, larger case series are needed to guide the literature. In addition, we think that the result of the current study may be noteworthy since it does not contradict the data published so far.

In summary, it has been shown that iARSA cases may not be associated with DS and DGS, as reported in the current study's results. The detection rate of cfDNA testing for DS has been reported as 99.7%, with a false positive rate of 0.04% (10). Hence, the current study is compatible with the literature about screening DS associated with soft ultrasound markers by non-invasive prenatal tests. Therefore, it is suggested that isolated cases of ARSA may be managed with non-invasive cfDNA testing, including analysis for 22q11 microdeletion. Moreover, karyotyping should be recommended in patients with additional major anomalies, associated soft markers, and/or high-risk results at screening tests.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 21.10.2022, No: 19).

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