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Национальный научный центр хирургии им. А.Н. Сызганова
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Баспаның мекен-жайы:
050004, Алматы қ., Желтоқсан көш. 62,
тел. +7(727) 2795306
http://vhk.kz, e-mail: dr.gismailova@gmail.com
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Адрес редакции:
050004, г. Алматы, ул. Желтоксан, 62,
тел. +7 (727) 2795306
http://vhk.kz, e-mail: dr.gismailova@gmail.com
Дизайн и верстка:
ИП «Старков С.А.»
г. Кокшетау, ул. Ауельбекова,98

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SURGERY

ACUTE LIVER FAILURE ON THE BACKGROUND OF CHRONIC LIVER DISEASE DUE TO HEPATITIS VIRUS REACTIVATION

Bolatbek Baimakhanov[1], Shokan Kaniyev[1], Maxat Doskhanov[1], Almagul Jumabaeva[2], Zhambyl Ospan[1], Milliyenium Maulen[2], Ainur Aftandilkyzy[2], Magzhan Tursynbay[1]

1 - Syzganov National Scientific Center of Surgery, Almaty, Kazakhstan
2 - "Research Institute of Cardiology and Internal Diseases", Almaty, Kazakhstan

DOI: 10.35805/BSK2025III001
Baimakhanov B.
https://orcid.org/0000-0003-0049-5886
Kaniyev A.
https://orcid.org/0000-0002-1288-0987
Doskhanov M.
https://orcid.org/0000-0003-0167-9863
Jumabaeva A.
https://orcid.org/0000-0002-8899-944X
Maulen M.
https://orcid.org/0009-0007-5531-4372
Aftandilkyzy A.
https://orcid.org/0009-0002-1323-5055
Ospan Z.
https://orcid.org/0000-0001-6803-5806
Tursynbay M.
https://orcid.org/0009-0000-2261-7181

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Author for correspondence
Ainur Aftandilkyzy, Almaty, Aytekebi St. 120, Kazakhstan. Phone: +77781184801. Email: ainura_03.03@mail.ru.

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Keywords:
acute-on-chronic liver failure, liver transplantation, viralre activation, decompensated cirrhosis.

Abstract

Today, hepatitis B virus-associated acute liver failure remains the leading cause of liver failure (44% mortality in Asia and 41% in the United States). Studies show that among patients with hepatitis B-associated cirrhosis, acute liver failure develops in 10-20% of cases. Acute liver failure on chronic liver disease is a potentially reversible syndrome that occurs in patients with cirrhosis or chronic liver disease and is characterized by acute decompensation, organ failure, and high short-term mortality. Chronic hepatitis B virus infection is a leading cause of liver morbidity and mortality worldwide. When we talk about hepatitis B, there is a high risk of developing super infection hepatitis D, since hepatitis D remains infectious and can reactivate at very low titers that are not detected using modern analysis methods if HBsAg remains in the blood serum. The interaction of these viruses leads to accelerated progression of fibrosis and cirrhosis of the liver, which significantly increases the risk of developing acute liver failure against the background of chronic.

In our case, a patient diagnosed with liver cirrhosis as a result of viral hepatitis B with delta agent, class C according to Child–Pugh–Turcotte, MELD-36 points, the patient developed a severe form of acute renal failure, which required emergency intervention, so he was not included in the waiting list for a transplant from a cadaveric donor. His wife became the donor, which is an example of living donation, which provides higher chances of successful recovery due to a shorter waiting time and a lower risk of graft rejection. Timely examination of the donor and recipient, as well as prompt liver transplantation, contributed to a favorable outcome of the disease.

Introduction

In recent years, particular attention has been paid to the problem of viral reactivation, where an increase in viral activity in patients with chronic hepatitis may lead to disease exacerbation and liver injury.[1] Chronic hepatitis D (CHD) is a severe liver disease caused by the hepatitis D virus (HDV), which is prevalent globally.[2] The interaction between these viruses leads to accelerated progression of fibrosis and liver cirrhosis, significantly increasing the risk of acute-on-chronic liver failure (ACLF) development.[2] Relapses of hepatitis D after therapy are common and substantially reduce treatment efficacy.[3]

The prevalence and outcomes of ACLF vary depending on geographic region and disease etiology. According to a systematic review and meta-analysis, the global prevalence of ACLF among patients with decompensated cirrhosis is 35%.[4] In Asian countries, where HBV is highly endemic, viral activation frequently leads to the development of ACLF. Mortality among ACLF patients can reach up to 44%.[5] In the United States, patients with HBV-related decompensated cirrhosis who develop ACLF have a

30-day mortality rate of 41%, compared to 7% among patients without ACLF.[5] In Europe, where alcohol-related etiology predominates, the incidence of ACLF among cirrhotic patients ranges from 20% to 35%, with ACLF-related mortality between 30% and 50%.[6]

Classification of ACLF According to the EASL-CLIF Consensus

The classification of acute-on-chronic liver failure according to the EASL-CLIF (European Association for the Study of the Liver-Chronic Liver Failure) consensus is one of the most frequently cited classifications, proposed by the European Association for the Study of the Liver (EASL) and the CLIF research group. It classifies ACLF based on clinical criteria and the degree of damage to various organs (e.g., liver, kidneys, heart).[7] There are three types of ACLF related to organ failure, derived from the CLIF-SOFA score, which have been associated with high 28-day mortality rates: A (mild), B (moderate), and C (severe).

Type A: Liver failure with minimal dysfunction in other organs.[7] In a study conducted in Europe, the 28-day mortality rate among patients with Stage 1 ACLF was 23.3%, and the 90-day mortality rate was 55.2%.[8]

Type B: Manifest liver failure with progressive dysfunction of the organs. The 28-day mortality rate is 31.3%, and the 90-day mortality rate is 55.2%.

Type C: Severe liver failure with rapid progression of multi-organ failure requiring intensive treatment. The 28-day mortality rate is 74.5%, and the 90-day mortality rate is 78.4%.[7]

Thus, depending on the region and severity of the disease, the 28-day mortality rate in ACLF can range from 18% to 25%, and the 90-day mortality rate can range from 30% to 40%.[9]

The aim of this paper is to discuss a clinical case of a patient who underwent emergency liver transplantation due to acute liver failure on the background of chronic liver disease from aliving related donor.

Case presentation

A 35-year-old male patient was diagnosed with: Cirrhosis of the liver as a result of chronic hepatitis B with the delta agent, Class C by the Child-Pugh Score (CPS). MELD score: 36. Acute hepatic cell failure on the background of chronic liver failure (ACLF). Portal hypertension syndrome. Esophageal varices of grade 3. Ascites of grade 2 according to the International Ascites Club (IAC).

According to the patient, he considered himself ill starting from July 2023, when he noticed a moderate increase in abdominal size. He was examined at a private medical center, where a Fibroscan revealed liver fibrosis at stage F4. Subsequently, the patient underwent further examination at the A.N. Syzganov National Scientific Center of Surgery (NSC). PCR for hepatitis D on October 4, 2023, was positive, while PCR for hepatitis B was negative. Due to worsening of his condition, on January 8, 2024, the patient was hospitalized at the NSC for further examination and preparation for liver transplantation from a living donor.

Upon examination, ascites (biochemical analysis shown below in Table 1), esophageal varices grade 3 (E varix F3, Lm, CB, RCS (+)), and mild portal hypertensive gastropathy were found. Ultrasound on January 9, 2024, showed splenomegaly and bilateral hydrothorax (370 ml). CT from March 10, 2023 (1 a, b, c) revealed liver cirrhosis, splenomegaly, splenorenal and splenomesenteric shunts, recanalization of the umbilical vein, esophageal and gastric varices, and ascites. Based on these findings, the following diagnosis was made: Cirrhosis of the liver due to chronic hepatitis B with the delta agent, Class C by CPS. MELD score: 36. Acute hepatic cell failure on the background of chronic liver failure (ACLF). Portal hypertension syndrome. Esophageal varices grade 3. Ascites grade 2 according to IAC.

The patient was diagnosed with hepatitis D reactivation on the background of liver cirrhosis resulting from chronic hepatitis B with the delta agent, which led to decompensation of liver function and acute metabolic disorders. Due to a high total bilirubin level in the blood, plasma exchange sessions were initiated. However, due to the severity of

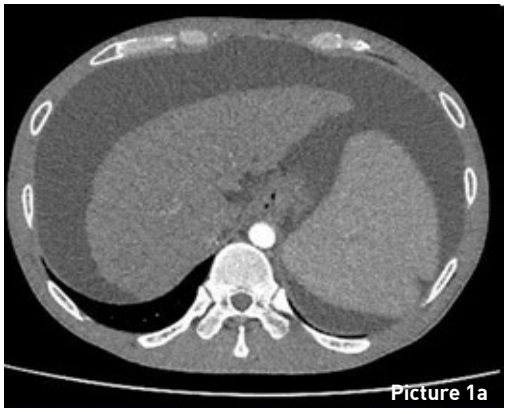
the patient's condition and progression of liver failure, it was recommended to proceed with liver transplantation from a living related donor. On January 18, 2024, an emergency liver transplantation surgery was performed from a living donor, with the donor being the patient's wife (K, 27 years old).

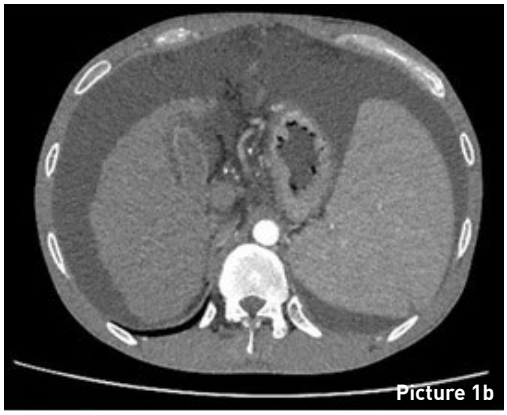
CT findings from October 9, 2023, showed: Liver volume–1345 cm³ (6,140 cm³). Volume of the left lobe of the liver +segment I–446.9 cm³ (33.2%).

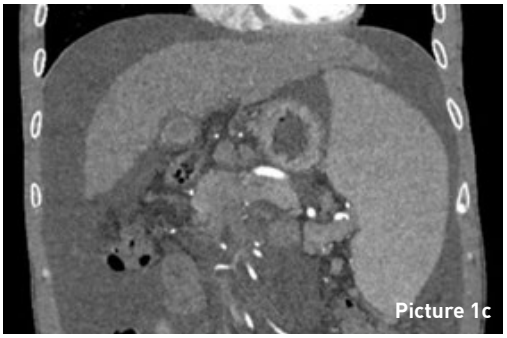
Table1.
Biochemical Indicators of the Patient Before Liver Transplantation

	January, 2024							
	08/01	**10/01**	**11/01**	**12/01**	**14/01**	**15/01**	**16/01**	**17/01**
ALT	60.40	46,60	41.70	33.70	32.70	35.30	46,0	51.80
AST	117.60	92,60	82.0	68.20	63.30	69.40	89.20	103.80
Total bilirubin	727.0	789	797	760	737.70	746.4	757.4	871.0
PTI	24.10	29.10	32.70	30.30	23.20	27.20	24.00	26.00
INR	2.83	2.39	2.16	2.30	2.94	2.53	2.70	2.63

Picture 1 (a, b, c).
CT from March 10, 2023: Liver cirrhosis, splenomegaly, portal hypertension, splenomesenteric and splenorenal shunts, recanalization of the umbilical vein, esophageal and gastric varices, ascites.

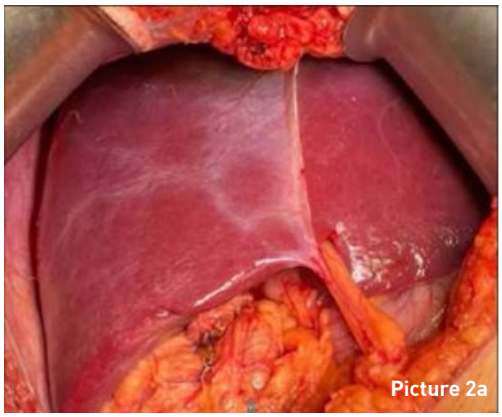

Picture 1a

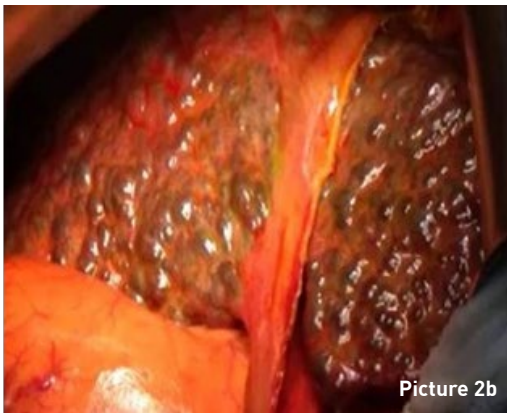

Picture 1b

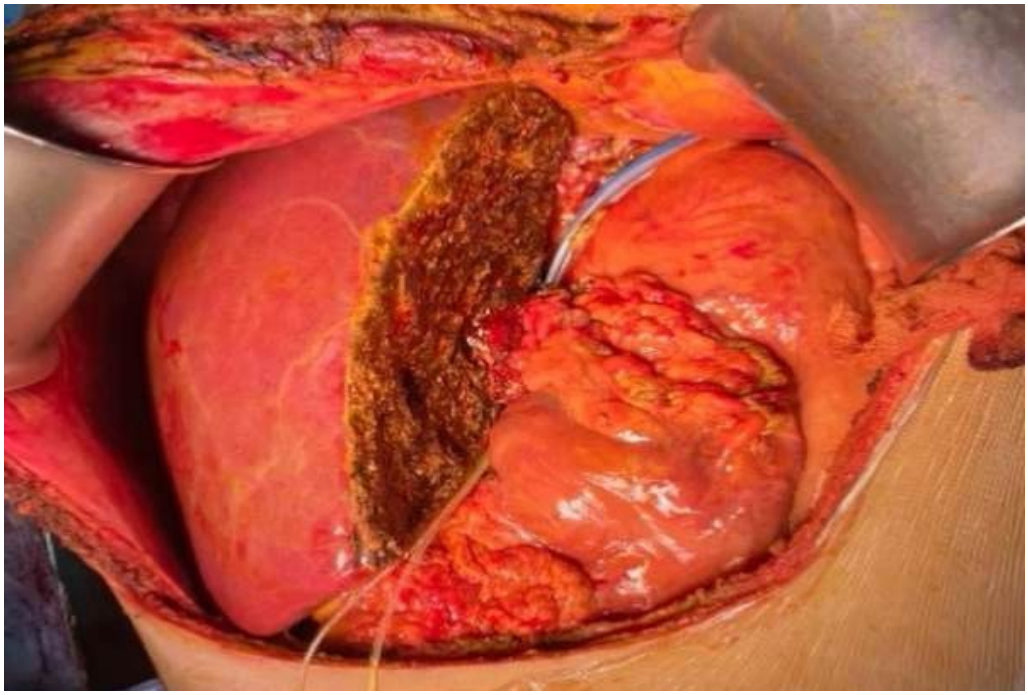

Picture 1c

Picture 2a.
ntraoperative Period Donor Liver

Picture 2b.
Cirrhotic Liver of the Recipient


Picture 2a


Picture 2b



Picture 2 c.
Final Appearance of the Transplanted Liver

	January 2024 year							
	19/01	**20/01**	**22/01**	**25/01**	**29/01**	**03/02**	**07/02**	**16/02**
ALT	93.60	92.50	58.30	66.80	52.40	52.20	68.20	31.50
AST	152.20	77.70	26.60	39.00	15.20	33.30	31.30	36.7
Total bilirubin	478.40	187.60	221.60	301.10	183.10	114.0	107.20	19.90
PTI	50.60	44.30	48.30	82.00	79.60	84.90	86.30	105.50
INR	1.49	1.66	1.55	1.11	1.13	1.09	1.08	0,97

Table 1.
Postoperative Period: A Decrease in Biochemical Parameters Was Observed

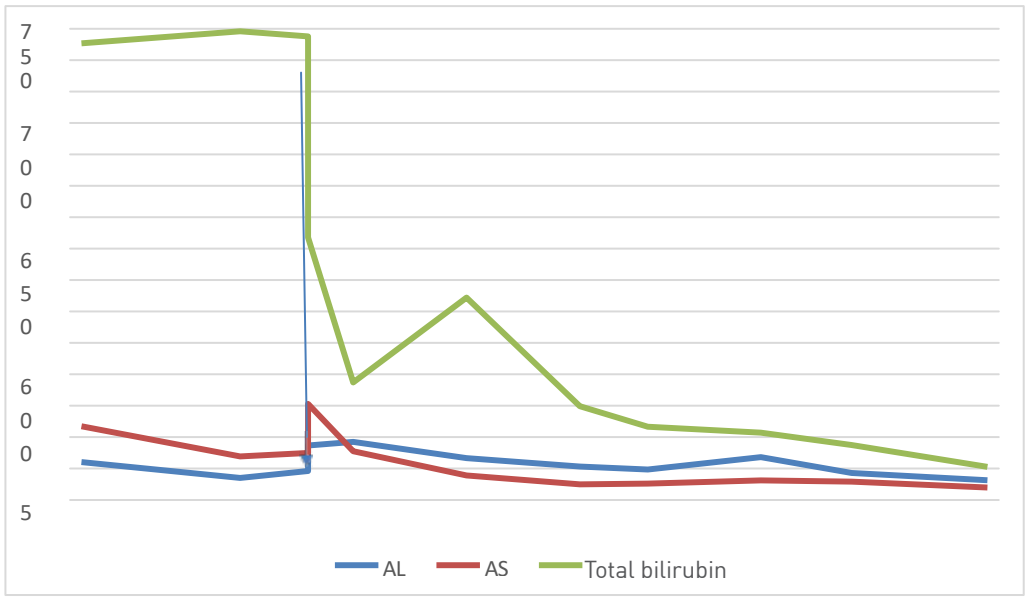
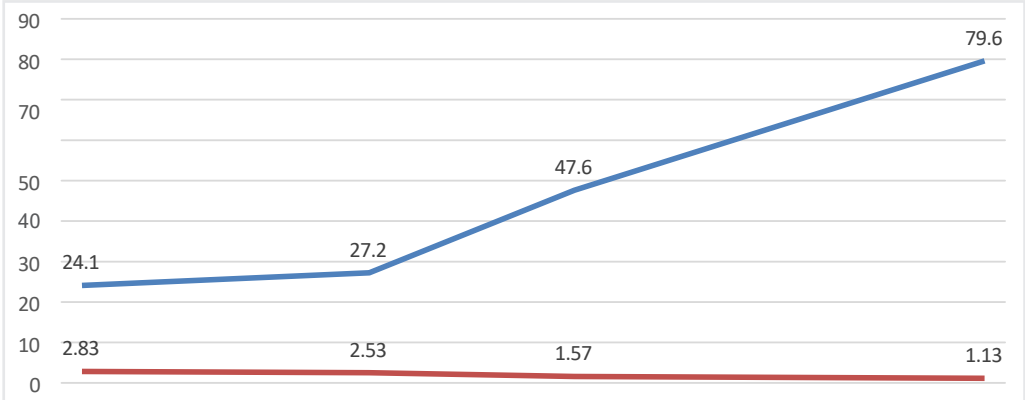


Figure 1.
Dynamic Changes in Biochemical Parameters

Figure 2.
Coagulation Profile in Dynamics



	08/01/2024	15/01/2024	20/01/2024	30/01/2024
PTI	24.1	27.2	47.6	79.6
INR	2.83	2.53	1.57	1.13

Discussion

Orthotopic liver transplantation (OLT) remains the only curative intervention capable of significantly improving outcomes in acute-on-chronic liver failure (ACLF), particularly at advanced stages where supportive therapy fails to ensure survival.[10] In the CANONIC study, 4.9% and 15% of ACLF patients underwent transplantation within 28 and 90 days of admission, respectively, with post-transplant survival for grades 2–3 reaching ~80% versus ~20% with conservative management.[11] Subsequent studies confirm one-year survival above 70%.[8]

This case is notable for both etiology and its rapid progression. Chronic HBV with HDV superinfection is known to accelerate fibrosis, cause earlier cirrhosis, and increase acute decompensation risk.[2] HDV reactivation—even at low, undetectable levels—poses diagnostic challenges and can delay treatment. In our patient, swift deterioration led to multiorgan failure, including severe acute kidney injury—a poor prognostic factor in ACLF.

Given the patient's critical state and ineligibility for deceased donor listing, living donor liver transplantation (LDLT) was performed. LDLT offers distinct advantages in emergencies: immediate graft availability, minimal cold ischemia, and in some reports, superior short- and medium-term graft survival.[9] In this case, using the patient's spouse as donor reduced immunologic risk and expedited surgery.

Postoperative labs (Table 2) showed steady improvement in liver and synthetic function, consistent with literature indicating optimal outcomes when transplantation occurs before irreversible extrahepatic organ failure.[12]

This case emphasizes the need for vigilant HDV monitoring in HBV-related cirrhosis, especially in endemic areas, and illustrates LDLT's role as a viable alternative in organ shortage settings. While limited by its single-case design, the scenario demonstrates that early ACLF recognition, rapid donor–recipient assessment, and timely transplantation can yield favorable short-term results even in severe HBV/HDV-associated disease.

Limitations. This is a single case report, which limits the generalizability of the results. In addition, long-term follow-up data are not yet available, as the patient received a liver transplant only 1 year ago. The level of maintenance of graft function to date has been assessed as satisfactory. In the future, monitoring of organ function indicators will be carried out on an ongoing basis.

What's Known? OLT remains the only curative treatment for ACLF. HBV/HDV coinfection is associated with accelerated progression of fibrosis, earlier cirrhosis, and increased risk of acute decompensation. Multiorgan failure, particularly acute kidney injury, is recognized as a poor prognostic factor in ACLF.

What's New? This report highlights

the successful use of LDLT as a life-saving option in HBV/HDV-related ACLF with multiorgan failure. It emphasizes that timely LDLT, even in patients with severe extrahepatic complications, can result in meaningful short-term recovery when deceased donor grafts are unavailable.

Conclusion

The presented clinical case demonstrates the critical importance of liver transplantation as the only radical method for treating patients with severe liver failure. Emergency transplantation significantly reduces waiting time and lowers the risk of organ rejection, which greatly improves the patient's prognosis. This case highlights the importance of early intervention and the use of living donor liver transplantation as a key aspect in the treatment of severe forms of liver failure.

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A RARE CASE OF CONGENITAL PORTOSYSTEMIC SHUNT (ABERNETHY MALFORMATION TYPE II) IN A CHILD: DIAGNOSIS, ENDOVASCULAR INTERVENTIONAL STRATEGY, AND CLINICAL FOLLOW-UP

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Kozhamkul A.
https://orcid.org/0009-0005-1458-8700
Bolatkan A.
https://orcid.org/0009-0001-6341-9322
Abilkhanov Y.
https://orcid.org/0000-0002-3730-6164
Onlasynov A.
https://orcid.org/0009-0006-6978-7886
Sapunov A
https://orcid.org/0000-0002-7125-8178
Pazilov S.
https://orcid.org/0000-0002-2677-3445
Saduakas A.
https://orcid.org/0000-0002-1640-8014
Manat Z.
https://orcid.org/0000-0002-0376-3172
Askar M.
https://orcid.org/0000-0001-8492-2958
Oraqbai E.
https://orcid.org/0009-0007-5523-2887

Kozhamkul Alisher[1], Bolatkan Arlan[1], Abilkhanov Yerzhan[1], Onlasynov Aziz[2], Sapunov Alexander[1], Pazilov Sabit[1], Saduakas Almas[1], Zhakubayev Manat[1], Matkerimov Askar[1], Oraqbai Ernur[1]

1 – Syzganov National Scientific Center of Surgery, Almaty, Kazakhstan
2- JSC «Scientific Center of Pediatrics and Children's Surgery», Almaty, Kazakhstan

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Author for correspondence:
Alisher Kozhamkul, 3rd-year resident at the NJSC «Syzganov National Scientific Center of Surgery», Almaty, Republic of Kazakhstan, E-mail: a.kozhamkul@mail.ru, ORCID: https://orcid.org/0009-0005-1458-8700; Tel.: +7 747 049 70 97;

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Abernethy malformation, hepatopulmonary syndrome, congenital portosystemic shunt (CPSS), pulmonary arteriovenous fistula (PAVF), transcatheter shunt closure.

Abstract

Congenital portosystemic shunt, also known as Abernethy malformation, is a rare vascular anomaly in which portal venous blood partially or completely bypasses the liver and enters the systemic circulation. This condition can lead to severe complications such as hepatopulmonary syndrome, hepatic encephalopathy, hypoxemia, and hyperammonemia. This article presents the first clinically confirmed and successfully treated case of Abernethy type II malformation in a child in Kazakhstan, who developed severe hepatopulmonary syndrome. A detailed description is provided of the diagnostic algorithm, angiographic evaluation, the endovascular intervention technique, and the patient's clinical course over a five-year follow-up period. Shunt closure resulted in marked clinical improvement, including normalization of oxygen saturation (from 60% to 98%), reduction in blood ammonia levels, increased exercise tolerance, and enhanced quality of life.The findings support the effectiveness of an individualized, stepwise approach in the management of type II CPSS. The importance of early recognition of this condition is emphasized, particularly in pediatric patients presenting with unexplained cyanosis, hypoxemia, or signs of hepatic dysfunction. Endovascular techniques, due to their minimally invasive nature and high clinical efficacy, represent an optimal therapeutic strategy in pediatric practice.

Introduction

Abernethy malformation, or congenital portosystemic shunt (CPSS), is a rare vascular anomaly in which blood from the portal circulation partially or completely bypasses the liver and drains directly into the systemic venous system. This condition disrupts hepatic metabolic function and may result in severe complications, including hepatopulmonary syndrome (HPS), hepatic encephalopathy, hypoxemia, hyperinsulinemia, and, in some cases, sudden death.[1,2]

The formation of the portal venous system occurs early in embryogenesis—between the 4th and 10th weeks of gestation. Aberrant vascular development during this period may lead to the forma-

tion of extra- or intrahepatic portocaval shunts. The congenital absence of the portal vein was first described by John Abernethy in 1793 during the autopsy of a child. A modern classification system for CPSS was proposed by *Morgan and Superina* in 1994, dividing the condition into two types: Type I — complete absence of the intrahepatic portal venous system; and Type II — presence of hypoplastic intrahepatic portal branches with partial shunting.[3]

Later, *Lautz et al.* refined the classification of Type II shunts into subtypes IIa, IIb, and IIc based on the anatomical origin of the shunt. *Kanazawa et al.* further introduced a classification based on the degree of hypoplasia of intrahepatic branches (mild, moderate, or severe), which is crucial for determining the optimal treatment strategy.[4,5]

The estimated prevalence of CPSS is approximately 1 in 30,000–50,000 live births.[6] However, due to the nonspecific nature of its clinical manifestations, diagnosis is often delayed. The most characteristic features include arterial hypoxemia, cyanosis, exertional dyspnea, platypnea, mucocutaneoustelangiectasias, and digital clubbing. These symptoms are typical of hepatopulmonary syndrome, which develops in more than 50% of patients with CPSS and is associated with severe oxygenation disorders.[7,8]

Other commonly observed findings include nodular regenerative hyperplasia of the liver (up to 50%), hyperammonemia, hyperinsulinemia with hypoglycemic episodes, and neurological disturbances related to manganese deposition in the basal ganglia. Hepatic encephalopathy often manifests at later stages, particularly in preschool-aged children.[4,6]

Despite the availability of modern imaging modalities such as ultrasonography, CT, MRI, and angiography, CPSS is frequently diagnosed late. This delay is due in part to the lack of awareness among clinicians to whom such patients typically present (e.g., gastroenterologists, neurologists, endocrinologists, and surgeons).[9] A diagnostically relevant laboratory marker is elevated blood ammonia; in one study, the mean ammonia level in children with CPSS was 123 ± 37 μg/dL, compared to a normal upper limit of 66 μg/dL.[5]

The cornerstone of treatment is shunt closure—either surgically (ligation) or via endovascular techniques (e.g., occluder placement). The choice of intervention depends on the results of an occlusion test: if portal pressure remains below 25 mmHg during temporary shunt closure, one-stage closure is feasible; otherwise, a staged approach is recommended to prevent portal hypertension.[4,7]

Endovascular techniques such as Amplatzer device placement offer high clinical efficacy with lower invasiveness compared to open surgery. However, complex vascular anatomy may necessitate surgical ligation.[7,10] Following intervention, ammonia levels typically normalize, and imaging (ultrasound, MRI, CT, angiography) is used for post-treatment monitoring.

Thus, early identification of CPSS and an individualized treatment strategy can prevent severe complications and significantly improve outcomes in pediatric patients. The present study reports the first documented case in the Republic of Kazakhstan of successful treatment of Abernethy type II malformation in a child with severe hepatopulmonary syndrome.

To assess the effectiveness of endovascular treatment for congenital portosystemic shunt (Abernethy malformation type II) in a child with hepatopulmonary syndrome, based on clinical outcomes and long-term follow-up.

Clinical case presentation

For the first time in clinical practice in the Republic of Kazakhstan, we identified and successfully treated a case of a congenital portosystemic shunt (CPSS) type II, also known as Abernethy malformation. The patient, S., a 7-year-old boy, was urgently transported by air ambulance and admitted to the Department of Cardiac and Interventional Pediatric Surgery at the National Center for Pediatric Pathology and Surgery. His presenting complaints included progressive dyspnea, marked fatigue, reduced tolerance to even minimal physical and emotional

exertion, intermittent leg pain, numbness in the fingers, and central cyanosis in the perioral area.

The medical history was notable for multiple hospitalizations dating back to 2018. The patient had been diagnosed twice with brain abscesses (in 2018 and 2019), which were complicated by right-sided hemiparesis, facial nerve neuritis, and toxic myocarditis. Additionally, neuroimaging revealed cerebral and arachnoid cysts, subcortical abnormalities, and hydrocephalus. Abdominal ultrasound (2020) identified hypoechoic liver lesions in the right lobe, and in 2021, an abnormality of the portal venous system was first suspected. Despite extensive evaluations, the diagnosis of CPSS was not established until March 2021 (Table 1).

Table 1.
Prior Medical History and Interventions

Date	Prior Medical History and Interventions
July 2018	Inpatient treatment. Diagnosis: Right cerebral hemisphere abscess. Conservative therapy administered. Discharged in improved condition.
April 2019	Inpatient treatment. Diagnosis: Left cerebral hemisphere abscess. Complicated by right-sided hemiparesis and right-sided facial nerve neuritis. Mild iron-deficiency anemia. Toxic myocarditis. Conservative treatment. Discharged in improved condition.
December 2020 – January 2021 – February 2021 March 2021	Chest CT (29.12.2020): No organic pathology. Abdominal ultrasound (29.12.2020): Diffuse parenchymal liver changes, gallbladder deformation, hypoechoic lesions in segments 7–8. Brain MRI (04.01.2021): Encephalopathy, cerebral cysts. Neurology consultation (08.01.2021): Multiple cerebral cysts and sequelae of brain abscesses. Referred to neurology department. Echocardiography (04.02.2021): Normal cardiac anatomy, LVEF 64%. Abdominal CT (26.02.2021): No significant pathology.
	Hospitalization at the National Center for Pediatric Pathology and Surgery for angiopulmonography and cardiac catheterization to confirm diagnosis and determine treatment strategy.
June 2021	Rehospitalization at the same center. A one-stage endovascular occlusion of the abnormal portosystemic shunt was successfully performed.

Patient Status and Interventions At the time of admission to the National Center for Pediatric Pathology and Surgery, the patient's condition was assessed as severe, with marked respiratory insufficiency (SpO_2 60–70%), cachexia (body weight 21 kg, height 126 cm), and a forced squatting posture with knees drawn to the chest. Pulmonary angiography, right and left heart catheterization, aortography, and retrograde mesenterico-splenoportography confirmed the diagnosis of congenital portosystemic shunt (CPSS) type II. The measured mean portal pressure was 22 mmHg, which allowed for a one-stage endovascular closure of the shunt.

On July 14, 2021, the patient underwent percutaneous transcatheter occlusion of the portosystemic shunt. The early postoperative course was complicated by persistent hypoxemia. However, after 12 days, follow-up angiopulmonography and embolization of pathological pulmonary arteriovenous communications were performed, resulting in significant clinical improvement.

Follow-up assessments over the subsequent three years demonstrated sustained recovery: weight gain, normalization of oxygen saturation (up to 98%), improved laboratory parameters (a decrease in blood ammonia from 95.1 to 72.3 μmol/L), and a marked increase in exercise tolerance—walking distance extended to 1500–2000 meters (Table 2).

Table 2.
Timeline of Interventions and Clinical Outcomes in a Patient with Abernethy Syndrome Type II

Date	ClinicalPresentation	DiagnosticEvaluation	Interventions
March 2021	Tachypnea, cyanosis, forced posture, SpO_2 60–70%, weight 21 kg, height 126 cm	Right/left heart catheterization, aortography, mesenterico-splenoportography, occlusion test. Portal pressure: 22 mmHg. Diagnosis: CPSS type II (Abernethy syndrome)	Diagnostic catheterization with angiography and occlusion testing
July 2021	Minimal weight gain, persistent cyanosis, SpO_2 60–65%	Abdominal ultrasound: portocaval anastomosis; Brain CT: hydrocephalus, cystic lesions; ALT: 786 U/L, AST: >913 U/L	Transcatheter closure of the portosystemic shunt (July 14, 2021)
July 26, 2021	Severe condition, respiratory failure, SpO_2 with oxygen: 60–65%, weight 18 kg	ALT: 7.0 U/L, AST: 14.0 U/L; BP: 106/72 mmHg; RV pressure: 115/8 mmHg; PA pressure: 110/54 mmHg. Conclusion: Abernethy syndrome, postshuntclosure status	Endovascular occlusion of distal pulmonary arteries bilaterally
August 6, 2021	Clinical improvement, SpO_2 85–90%, walking tolerance up to 100 m	—	—
September 2021	Weight gain, SpO_2 92–95%, walking distance up to 500 m	—	—
October 2021	+5 kg weight gain, SpO_2 95%, walking distance up to 1000 m	—	—
January 2022	Weight: 25.7 kg, height: 131 cm, SpO_2 98%, walking distance up to 1500 m; blood ammonia decreased from 95.1 to 72.3 μmol/L	—	—
October 2023	Further weight gain, SpO_2 92–95%, walking distance up to 1500 m; planned hospitalization	—	—
January 2024	Weight gain, SpO_2 92–96%, walking distance up to 1500–2000 m; planned hospitalization	—	—

This report presents a rare clinical case of Abernethy malformation type II successfully diagnosed and treated in Kazakhstan. Timely intervention during childhood prevented the progression of irreversible hepatic encephalopathy and severe hypoxemia, resulting in excellent long-term clinical outcomes and preserved quality of life (Figures 1 and 2).

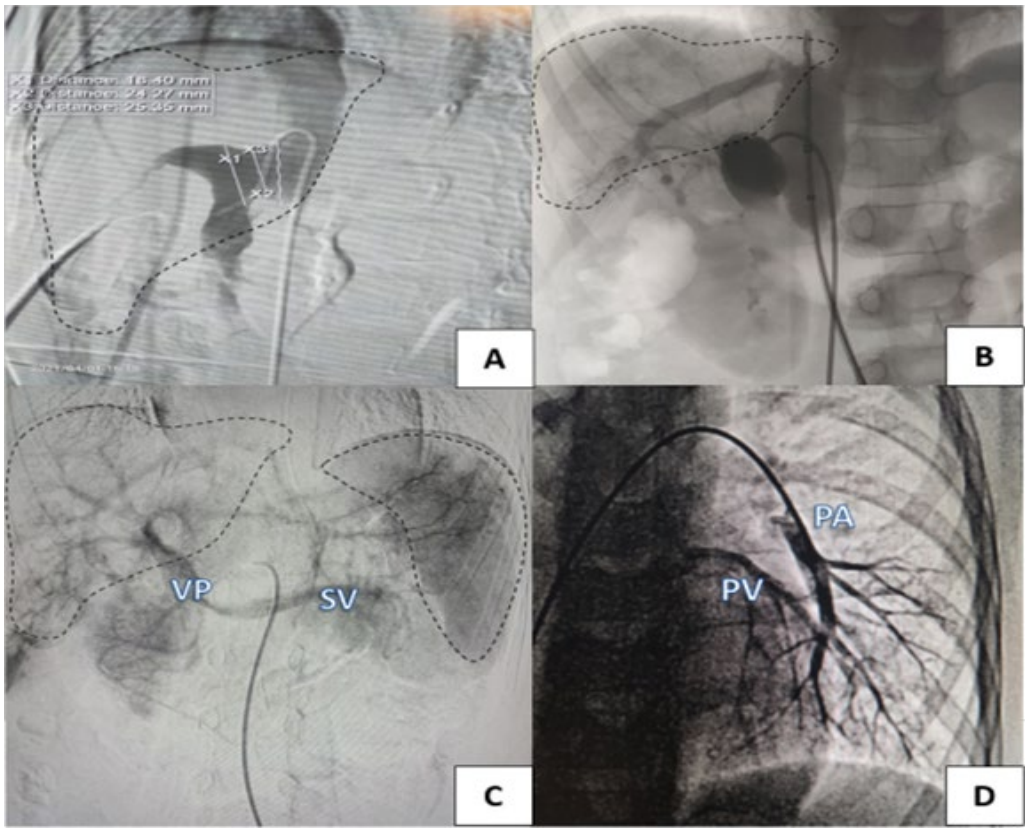

Figure 1
A – Direct cavaportography demonstrating a hypoplastic intrahepatic segment of the portal vein;B – Occlusion test with simultaneous portal venous manometry. The mean portal pressure measured at 22 mmHg;C – Retrograde celiaco-splenoportography showing angiographic visualization of the intrahepatic portal venous system following surgical disconnection of the congenital portosystemic shunt (CPSS);D – Selective segmental pulmonary angiography revealing simultaneous opacification of segmental pulmonary arteries and veins without parenchymal phase, indicative of pathological arteriovenous shunting.

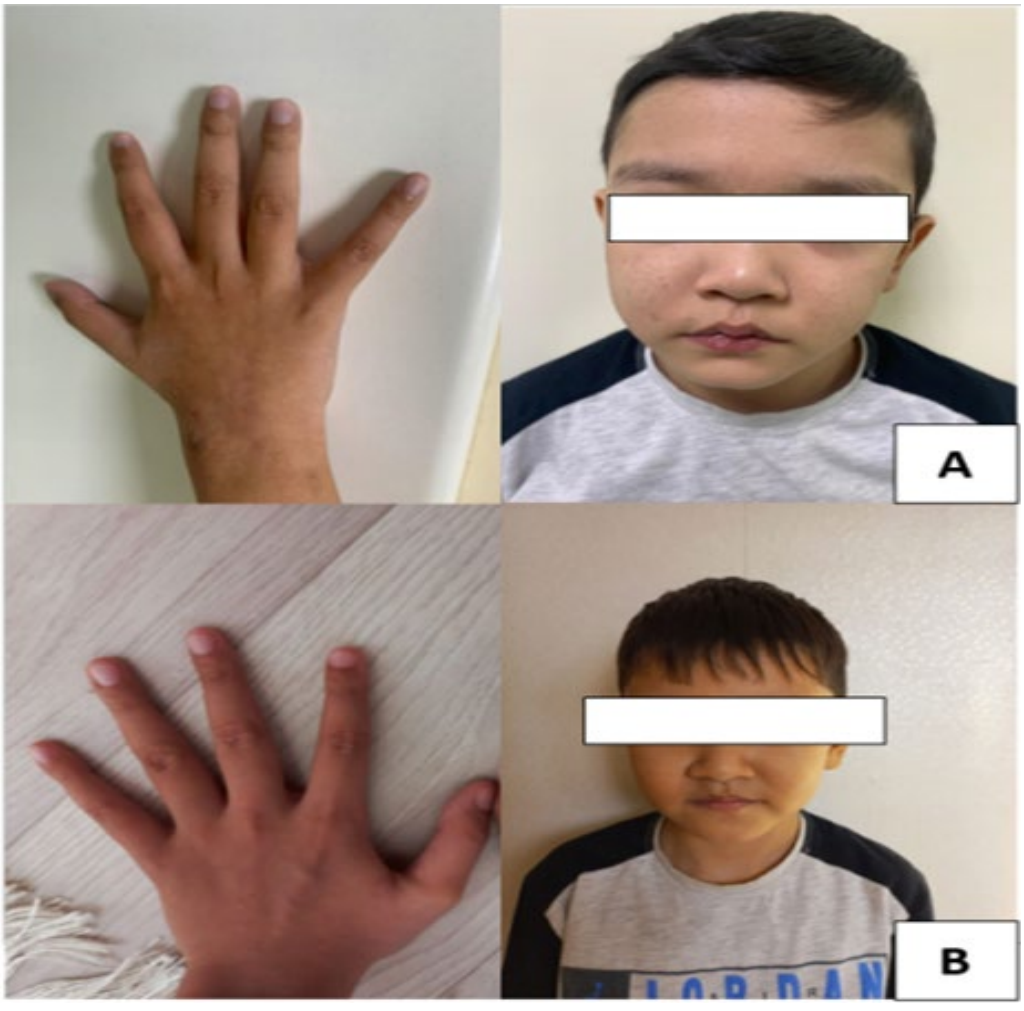

Figure 2.
A – External appearance of the patient with congenital portosystemic shunt (CPSS);B – External appearance of the patient 5 months after surgical disconnection of the CPSS.

Discussion

Congenital portosystemic shunts (CPSS), including Abernethy malformations, are rare vascular anomalies in which blood from the portal venous system partially or completely bypasses the liver and drains directly into the systemic circulation.[1,2] The Morgan and Superina classification categorizes CPSS into two types: type I is characterized by complete absence of intrahepatic portal venous branches, whereas type II retains partial intrahepatic portal perfusion.[3]

Abernethy malformation type II, as presented in this case, is a potentially correctable condition. According to current guidelines and clinical practice, the most informative preoperative assessment includes catheter-based evaluation with an occlusion test and direct measurement of portal venous pressure to assess the risk of portal hypertension following shunt closure.[4] In our case, the mean portal pressure was 22 mmHg, which was considered acceptable for endovascular intervention.

Modern treatment strategies for CPSS include both open surgical correction and minimally invasive transcatheter embolization, with the latter being particularly suitable for patients with type II anomalies.[6,7] In our patient, a staged hybrid approach was employed: initial shunt occlusion followed by selective pulmonary artery intervention due to severe hepatopulmonary syndrome. This strategy enabled the restoration of physiological portal flow and regression of clinical manifestations including hypoxemia and developmental delay.[8]

Early diagnosis of CPSS remains challenging due to the heterogeneity of clinical presentations. Cyanosis, hypoxemia, growth retardation, neurocognitive symptoms, and hyperammonemia may be the initial manifestations.[9] Therefore, CPSS should be included in the differential diagnosis of pediatric patients with unexplained oxygen desaturation and neurologic symptoms.

High-resolution imaging modalities such as multiphase CT, MRI, Doppler ultrasonography, and angiography, combined with interventional diagnostic procedures, provide accurate visualization of the shunt anatomy and aid in treatment planning.[10] In our case, the patient demonstrated sustained clinical improvement over a 5-year follow-up, including normalized oxygen saturation (95–98%), weight gain, reduction in neurological symptoms, and stabilization of hepatic biochemical markers.

This case underscores the importance of early detection and a staged interventional approach in the management of Abernethy type II malformations. It represents the first documented case in the Republic of Kazakhstan of successful endovascular and surgical treatment for this rare condition.

Limitations. This study is limited by its single-case design, reflecting the rarity of CPSS, particularly type Ia and Ib, which are frequently underdiagnosed or associated with early mortality before surgical intervention is feasible. The statistical power is therefore restricted, limiting extrapolation to a broader population. Furthermore, the study was conducted in a single specialized center, introducing potential selection bias. The absence of a control group precludes direct comparison with conservative or alternative therapeutic modalities.

What's known? CPSS is a rare congenital vascular anomaly with a broad clinical spectrum, ranging from asymptomatic forms to severe complications such as hepatic encephalopathy and hepatopulmonary syndrome. The Morgan and Superina classification, supplemented by Kanazawa's grading of intrahepatic portal hypoplasia, facilitates individualized therapeutic planning. Shunt closure, when indicated, can result in reversal of clinical symptoms and improvement in laboratory indices. Delayed diagnosis remains common due to the non-specific nature of symptoms and limited awareness among clinicians.

What's new? This is the first reported and documented case in Kazakhstan of successful treatment of Abernethy malformation type II in a child with severe hepatopulmonary syndrome. The efficacy of a staged approach—occlusion testing and portal pressure monitoring

using Kanazawa's protocol, followed by transcatheter shunt closure—was confirmed. Long-term remission was achieved, including normalization of oxygen saturation, weight gain, reduced ammonia levels, and resolution of respiratory symptoms. This case highlights the importance of including CPSS in the differential diagnosis of children with unexplained neurocognitive and hepatogastrointestinal symptoms, as well as nodular hepatic hyperplasia.

Conclusion

Congenital portosystemic shunting is a rare but potentially curable vascular anomaly requiring high clinical vigilance and a multidisciplinary approach. This case illustrates a successful diagnostic and therapeutic pathway for type II CPSS in a child with advanced hepatopulmonary syndrome. The use of an occlusion test with portal pressure measurement enabled a safe, staged treatment plan. Transcatheter intervention was effective and minimally invasive, making it highly suitable in pediatric settings. Restoration of physiological portal venous flow led to significant improvement in metabolic parameters and overall clinical status. Early diagnosis and timely intervention are crucial to improving outcomes and preventing irreversible complications.

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CLINICAL AND PROGNOSTIC SIGNIFICANCE OF INTRA-ABDOMINAL PRESSURE IN CHOOSING A SURGICAL STRATEGY FOR GASTROSCHISIS IN NEWBORNS

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Bissaliyev Bauyrzhan N.[1], Tsap Natalya A.[2], Sarsenova Valentina V.[1], Tussupkaliev Assylbek B.[1], Baubekov Zhenysbek T.[1], Abdullayeva Gulzhamal Z.[3], Li Dmitriy V.[1], Zhaksybayeva Nurbakyt Zh.[1]

1 - West Kazakhstan Marat Ospanov State Medical University, Aktobe, Kazakhstan.
2 - Ural State Medical University, Yekaterinburg, Russian Federation.
3 - Multidisciplinary Regional Children's Hospital, Aktobe, Kazakhstan.

Bissaliyev B.
https://orcid.org/0000-0002-4875-1140
Tsap N.
https://orcid.org/0000-0001-9050-3629
Sarsenova V.
https://orcid.org/0000-0003-2904-8959
Tussupkaliev A.
https://orcid.org/0000-0003-2386-2984
Baubekov Z.
https://orcid.org/0000-0001-7274-7478
Abdullayeva G.,
https://orcid.org/0000-0002-9018-5891
Li D.
https://orcid.org/0009-0006-8836-1944
Zhaksybayeva N.
https://orcid.org/0009-0005-2224-0261

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Corresponding author:
Bissaliyev Bauyrzhan N. West Kazakhstan named after Marat Ospanov State Medical University, Aktobe, Kazakhstan, 68 Maresyev Street, Aktobe 030019, Republic of Kazakhstan. Phone: +7 775 179 3525 E-mail: baurjan.79@mail.ru

Keywords:
gastroschisis; intra-abdominal pressure; infant, newborn; surgical wound closure; abdominal compartment syndrome.

Abstract

Background. Gastroschisis is a congenital defect of the anterior abdominal wall in newborns, characterized by the evisceration of bowel loops without a protective sac. Timely and appropriate abdominal wall closure is essential for favorable outcomes. Objective: To evaluate the clinical and prognostic significance of intra-abdominal pressure monitoring for determining the optimal surgical strategy in newborns with gastroschisis.

Materials and Methods. A retrospective cohort study was conducted on 32 newborns with gastroschisis treated in two tertiary centers in Kazakhstan and Russia from 2015 to 2025. Patients were allocated into two groups based on intraoperative intra-abdominal pressure values: Group 1 (n=21) underwent primary fascial closure using the Elective Delayed Midgut Reduction technique; Group 2 (n=11) received staged silo-assisted closure. intra-abdominal pressure was measured intravesically, and a threshold of 22–24 cm H_2O was used to guide the surgical decision. Clinical outcomes included duration of mechanical ventilation, total parenteral nutrition, ICU stay, hospital stay, complication rate, and mortality. Statistical analysis was performed using the Mann–Whitney U test ($p < 0.05$).

Results. Group 1 had significantly better outcomes, including shorter durations of mechanical ventilation (6 vs. 13 days, $p = 0.01$), ICU stay (12 vs. 20 days, $p = 0.01$), parenteral nutrition (14 vs. 22 days, $p = 0.04$), and lower mortality (4.8% vs. 27.3%, $p = 0.03$). Group 2 showed a higher complication rate, especially adhesive obstruction and sepsis.

Conclusion. Intraoperative intra-abdominal pressure measurement is a valuable tool for guiding surgical strategy in gastroschisis. An individualized approach based on physiological parameters improves safety and outcomes in neonatal surgical care.

Introduction

Gastroschisis is one of the most common congenital anomalies of the anterior abdominal wall in newborns. This defect is characterized by evisceration of the bowel loops through a paraumbilical defect without a covering sac, which distinguishes it from omphalocele. The extra-abdominal location of the intestines and their prolonged exposure to amniot-

ic fluid in utero lead to serosal inflammation, bowel wall edema, and impaired peristalsis.[1-3]

According to contemporary population-based data, the incidence of gastroschisis reaches 4.5–5 per 10,000 live births, particularly among young women of reproductive age, and shows an increasing trend, particularly in low- and middle-income countries.[4,5]

A key challenge in the management of gastroschisis remains the choice of optimal abdominal wall closure technique. The two main surgical approaches are primary fascial closure and staged silo-assisted closure using a temporary silo bag (silo).[6] Primary closure is preferred when the bowel appears viable and there is no significant viscero-abdominal disproportion. However, in the presence of bowel dilation or elevated intra-abdominal pressure (IAP), placement of a silo becomes the safer strategy.[7,8]

The major limiting factor for primary closure is the risk of developing intra-abdominal hypertension and abdominal compartment syndrome, resulting from diaphragmatic compression, decreased pulmonary compliance, impaired venous return, and reduced organ perfusion.[9,10]

To objectively assess the level of IAP, a method of intraoperativeintravesical pressure measurement has been adapted for neonatal practice. This approach allows for timely detection of critical elevations in IAP and supports an evidence-based decision for staged abdominal wall closure.[11]

Therefore, there is a pressing need to develop an objective, physiologically sound algorithm for surgical decision-making in neonates with gastroschisis, based on intraoperative intra-abdominal pressure monitoring.

Materials and Methods

Study design and setting. This was a retrospective, two-center cohort study conducted between 2015 and 2025at the Multidisciplinary Regional Children's Hospital in Aktobe (Republic of Kazakhstan) and the Regional Children's Clinical Hospital in Yekaterinburg (Russian Federation).

Participants. A total of 32 newborns with confirmed antenatal or postnatal diagnosis of gastroschisis were included in the study. All patients were admitted within the first 24 hours of life.

Inclusion criteria:

- Confirmed diagnosis of gastroschisis.
- Admission during the first 24 hours after birth.

Exclusion criteria:

- Severe congenital heart or lung defects.
- Associated gastrointestinal anomalies requiring stoma formation at the initial stage of treatment.

Measurement of intra-abdominal pressure. IAP was measured intraoperatively using the intravesical method. A sterile 0.9% sodium chloride solution (0.5 mL/kg; Kelun-Kazpharm LLP, Republic of Kazakhstan) was instilled into the bladder through a CH 6 urinary catheter (outer diameter 2.0 mm, inner diameter 1.1 mm; JULDYS KENAN Co., Ltd, Republic of Kazakhstan; ISO 13485:2016–certified). The height of the fluid column was measured in the supine position using a sterile transparent medical-grade ruler. An IAP level of 22–24 cm H_2O was considered critical (Figure 6).

Primary outcomes:

- Duration of mechanical ventilation.
- Time to initiation of enteral feeding.
- Duration of total parenteral nutrition.
- Length of intensive care unit stay.
- Total duration of hospitalization.
- Postoperative complications (adhesive intestinal obstruction, sepsis, necrotizing enterocolitis).
- Mortality.

Ethical approval. The study was approved by the local ethics committees of both participating institutions (Protocol No.7-2025-09/HC, approved 03 July 2025). All patient data were anonymized, and no personally identifiable information was included. The study complied with the principles of the Declaration of Helsinki (2013 revision).

Statistical analysis. Statistical analysis was conducted using IBM SPSS Statistics software, version 20.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were compared using the Mann–Whitney

U test. A p-value of < 0.05 was considered statistically significant.

Results

Perinatal characteristics. The two groups were comparable in terms of gestational age and birth weight. However, the median 5-minute Apgar score was significantly higher in Group 2 compared with Group 1 (8 vs7; p = 0.03), which may indicate more stable neonatal condition at birth (Table 1).

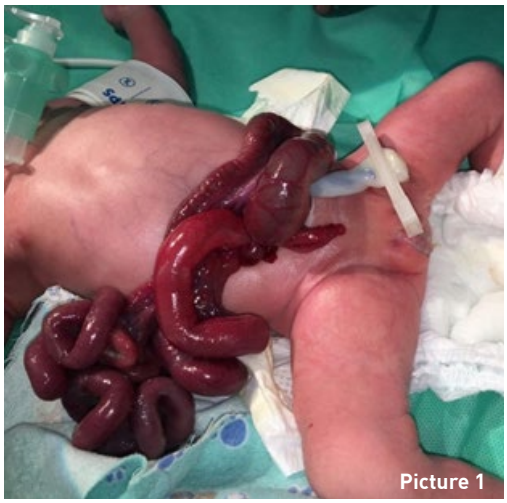
Table1. Perinatal characteristics of newborns with gastroschisis

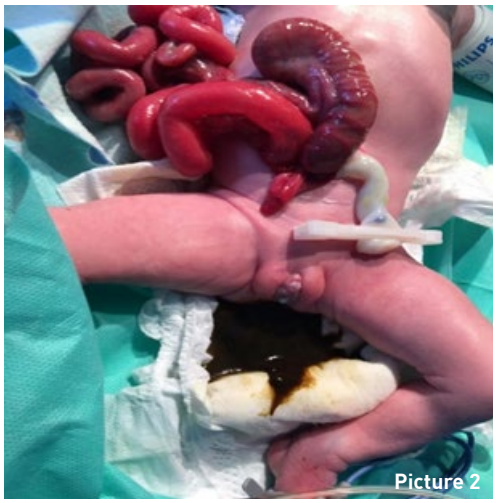
Variable	Group 1 (n = 21)	Group 2 (n = 11)	p-value
Gestationalage, weeks	37 (36–38)	38 (36–39)	0.21
Birthweight, grams	2350 (1990–2425)	2480 (2260–2770)	0.18
5-minute Apgarscore, points	7 (6–7)	8 (7–8)	0.03

Intervention

Preoperative care. In most patients, bowel loops were visibly edematous, inflamed, and covered with fibrin (Figure 1). Immediately after birth, all newborns received cleansing siphon enemas to reduce the visceral component of the viscero-abdominal disproportion. Passage of meconium was considered a positive prognostic sign indicating intestinal patency (Figure 2).

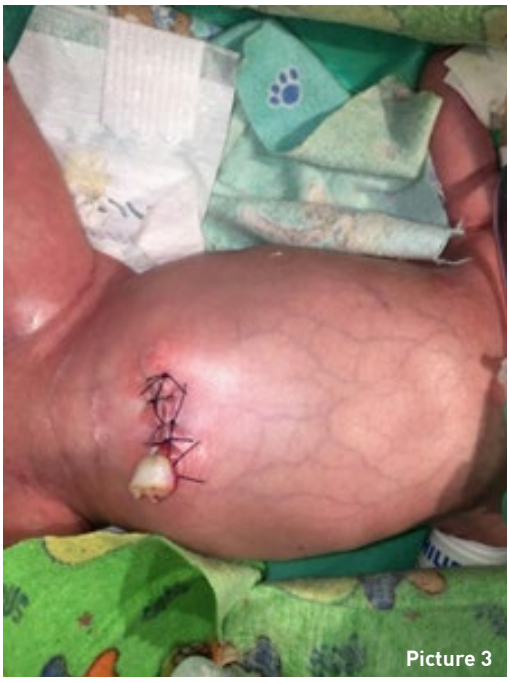
Picture 1. Clinical appearance at birth: subtotal evisceration of edematous, inflamed bowel loops covered with fibrin.


Picture 1

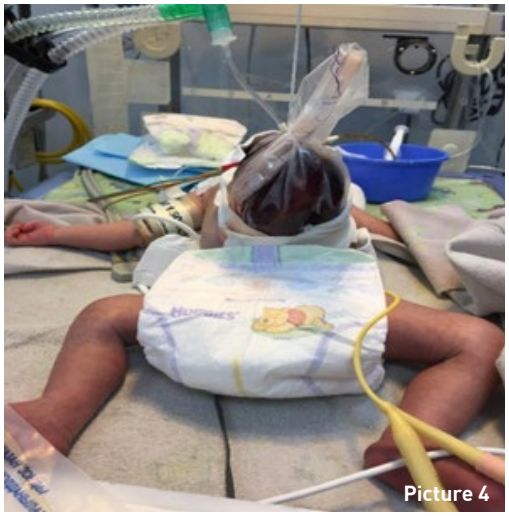

Picture 2

Picture 2. Reduced viscero-abdominal disproportion after siphon enema; passage of meconium observed – a favorable prognostic sign.

Picture 3. Complete primary fascial closure using the Elective Delayed Midgut Reduction (EDMR) method by *A. Bianchi.*


Picture 3

Group 2 (n = 11): Staged silo closure using an improvised sterile polyethylene bag when the IAP threshold was exceeded (Figure 4–6).



Picture 4. Staged silo-assisted reduction using an improvised sterile polyethylene bag in case of severe viscero-abdominal disproportion.

Picture 5. Intermediate stage of silo reduction: bowel loops fully reduced into the abdominal cavity on postoperative day 5, prior to definitive closure.

Picture 6. Intra-abdominal pressure measurement via urinary bladder using a CH6 catheter and sterile ruler prior to surgical decision.

Postoperative course. Group 1 (primary fascial closure) demonstrated significantly better outcomes in the early postoperative period. These included shorter durations of mechanical ventilation (6 vs 13 days; p = 0.01), intensive care unit stay (12 vs 20 days; p = 0.01), and total parenteral nutrition (14 vs 22 days; p = 0.04). The total length of hospitalization was also shorter (30 vs 41 days; p = 0.04). Notably, mortality in Group 1 was significantly lower than in Group 2 (4.8% vs 27.3%; p = 0.03) (Table 2).

Parameter	Group 1 (n = 21)	Group 2 (n = 11)	p-value
Duration of mechanical ventilation, days	6 (3–11)	13 (7–20)	0.01
Length of intensive care unit stay, days	12 (7–18)	20 (16–28)	0.01
Duration of total parenteral nutrition, days	14 (8.5–18)	22 (18–28.5)	0.04
Total hospitalization, days	30 (25–42)	41 (34–47)	0.04
Mortality, number (%)	1 (4.8%)	3 (27.3%)	0.03

Table 2. Early postoperative parameters

Postoperative complications. The overall rate of postoperative complications was significantly higher in Group 2 (64%) compared to Group 1 (24%; p=0.03). Specifically, adhesive intestinal obstruction occurred more frequently in Group 2 (55% vs 19%; p = 0.04), and sepsis was observed only in Group 2 (27% vs 0%; p = 0.02). The incidence of necrotizing enterocolitis was identical in both groups (Table 3).

Table 3.
Frequency of postoperative complications

Complication	Group 1 (n = 21)	Group 2 (n = 11)	p-value
Adhesive intestinal obstruction	4 (19%)	6 (55%)	0.04
Neonatal sepsis	0	3 (27%)	0.02
Necrotizing enterocolitis	1 (4.8%)	1 (9.1%)	1.00
Total complications	5 (24%)	7 (64%)	0.03

Causes of mortality. There was one death in Group 1, which occurred due to delayed diagnosis of adhesive intestinal obstruction. In Group 2, three deaths were recorded-two due to adhesive obstruction and one due to neonatal sepsis. Necrotizing enterocolitis did not result in mortality in either group (Table 4).

Table 4.
Causes of mortality

Cause of death	Group 1 (n = 21)	Group 2 (n = 11)
Adhesive intestinal obstruction	1	2
Neonatal sepsis	0	1
Necrotizing enterocolitis	0	0
Total deaths	1	3

Discussion

The choice of optimal surgical strategy for abdominal wall closure in newborns with gastroschisis remains a subject of ongoing clinical debate. The primary dilemma lies in selecting between immediate fascial closure and staged silo-assisted reduction, with the overarching goal of minimizing the risk of intra-abdominal hypertension and its associated complications.

In recent years, intraoperative measurement of intra-abdominal pressure has gained recognition as an objective and physiologically grounded criterion to guide surgical decision-making. According to published literature, IAP values exceeding 22–24 cm H_2O are strongly associated with thoracoabdominal organ compression, reduced venous return, impaired pulmonary function, and compromised tissue perfusion[12,13]. In this study, adherence to the aforementioned threshold enabled timely identification of patients at risk and guided the appropriate choice of surgical strategy.

The Elective Delayed Midgut Reduction (EDMR) technique, as described by A. Bianchi, yielded superior clinical outcomes. Patients in this group experienced shorter durations of mechanical ventilation, total parenteral nutrition, and intensive care unit stay, along with significantly lower mortality rates. These findings align with international meta-analyses that support primary closure in the absence of elevated IAP.[7]

For patients with pronounced viscero-abdominal disproportion and elevated IAP, staged silo-assisted reduction was implemented using improvised sterile polyethylene bags. While commercial silicone silos with circumferential rings (e.g., Schuster silo) are considered ideal,[14] their high cost and limited availability necessitated the use of resource-appropriate alternatives. The safety and effectiveness of such improvised solutions have also been validated in prior clinical reports.[10,11]

The higher rates of adhesive intestinal obstruction and sepsis observed in the staged treatment group may be attributed to prolonged extra-abdominal exposure of inflamed bowel loops and delayed restoration of intestinal motility. This underscores the importance of achieving early closure whenever physiologically feasible. Moreover, histological data suggest that earlier fascial clo-

sure reduces the extent of inflammatory and degenerative changes in the bowel wall, potentially improving long-term functional outcomes.

In summary, the findings of this study highlight the clinical and prognostic utility of intraoperative IAP monitoring in selecting a safe and effective surgical approach for gastroschisis. An individualized strategy, grounded in objective physiological indicators, contributes to improved perioperative outcomes and reduced complication rates in neonatal surgical practice.

Limitations. This study has several limitations. First, its retrospective design inherently carries the risk of selection and information bias. Second, the sample size was relatively small, particularly in the staged treatment group, which may limit the generalizability of the findings. Third, long-term outcomes, such as bowel function and quality of life, were not assessed. Finally, the use of improvised silos may introduce variability in technique and postoperative care, potentially affecting complication rates. Prospective multicenter studies with larger cohorts are needed to validate these results and further refine surgical decision-making algorithms.

What's known? Primary fascial closure is preferred in gastroschisis when feasible, yet the decision often relies on subjective judgment. Elevated intra-abdominal pressure is linked to adverse outcomes, and its intraoperative measurement is recognized as a valuable tool to guide surgical strategy.

What's new? This study validates a defined intra-abdominal pressure threshold (22–24 cm H_2O) as an objective criterion for selecting between primary closure and staged silo repair, demonstrating improved early postoperative outcomes and reduced mortality in newborns with gastroschisis.

Conclusion

The results of this study confirm the clinical effectiveness of intraoperative intra-abdominal pressure monitoring in determining the optimal surgical strategy for newborns with gastroschisis. Applying a critical threshold value of 22–24 cm H_2O enables objective assessment of the feasibility of safe primary fascial closure and supports timely transition to staged silo-assisted repair when required. The Elective Delayed Midgut Reduction (EDMR) technique demonstrated superior early postoperative outcomes, including shorter duration of mechanical ventilation, parenteral nutrition, and intensive care stay, as well as lower mortality rates. Conversely, staged management was crucial in patients with marked viscero-abdominal disproportion to prevent life-threatening complications associated with elevated IAP. Personalized surgical strategies based on IAP monitoring should be regarded as an essential component of gastroschisis management algorithms in neonatal practice, enhancing safety, reducing complications, and improving overall outcomes.

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authors read and approved the final version of the manuscript and agree to be responsible for all aspects of the work.

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IMPROVING THE ORGANIZATION OF EARLY DIAGNOSIS OF MANIFESTATIONS OF MICROANGIOPATHY TO PREVENT THE RISK OF COMPLICATIONS

Sandybek Alibek B., Akhmetov Ualikhan I., Popova Tatyana B.

Kazakhstan Medical University "KDSM", Almaty, Republic of Kazakhstan.

DOI: 10.35805/BSK2025III004
Sandybek A.
https://orcid.org/0000-0002-5005-8695
Akhmetov U.
https://orcid.org/0000-0003-4462-4504
Popova T.
https://orcid.org/0000-0003-3073-3881

recived: 21.07.2025
accepted: 16.08.2025

Corresponding author:
Sandybek Alibek Berikuly,
master of Medical Sciences,
sandyalibek@gmail.com

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Abstract

Background. Microangiopathy is a heterogeneous group of pathological conditions characterized by damage to small-caliber blood vessels, leading to impaired microcirculation and subsequent disruption of trophic, gas exchange, detoxification, and immune functions. It frequently develops in diabetes mellitus, arterial hypertension, systemic autoimmune, infectious, and neurodegenerative diseases. Untimely detection of microangiopathic changes significantly increases the risk of severe complications such as diabetic retinopathy, nephropathy, neuropathy, cognitive impairment, stroke, and dementia.

Material and methods. A retrospective analysis was conducted using brain magnetic resonance imaging data obtained on a 1.5 Tesla General Electric scanner at Clinical Hospital No. 5 in Almaty from 2022 to 2024. Patient records were evaluated for the presence and severity of microangiopathic changes according to the Fazekas scale.

Results. Among 1,814 patients who underwent brain magnetic resonance, pathological changes were detected in 58% of cases, of which 79% were of a microangiopathic nature. Early-stage changes (Fazekas 1) accounted for 57% of cases, suggesting that detection often occurs before severe structural damage develops. Advanced microangiopathy (Fazekas 2–3) was observed in the remaining cases, indicating the need for closer clinical monitoring and targeted intervention.

Conclusion. The findings demonstrate the high prevalence of microangiopathy among patients undergoing brain magnetic resonance in Almaty. Early detection through neuroimaging provides an opportunity for timely preventive and therapeutic measures, potentially reducing the risk of severe neurological complications and improving patient outcomes.

Introduction

Microangiopathy is a group of heterogeneous pathological conditions characterized by damage to small-caliber blood vessels. This condition leads to a violation of microcirculation in the body and causes a violation of trophic, gas exchange, detoxifying and immunological functions of tissues and organs.[1] Microangiopathy most often develops against the background of diabetes mellitus, arterial hypertension, systemic autoimmune diseases (for example, systemic lupus erythematosus), infectious processes and neurodegenerative diseases.[2,3] The role of microangiopathic changes in the stage of complications of these pathologies is of decisive importance. For example, diabetic retinopathy, nephropathy and neuropathy are microangiopathic complications that are common in patients with diabetes mellitus and lead to disability.[4]

According to international data, 17.9 million people die annually in the world from diseases of the cardiovascular system, which ranks first in the structure of human mortality.[5] One of the main factors contributing to the high level of this indicator is the untimely detection

and insufficient assessment of microangiopathic changes.[6] In addition, in the data of the American Heart Association (2022), even in acute conditions such as stroke and myocardial infarction, the pathology of the microcirculatory channel is considered as one of the leading pathogenetic links.[7]

About 40% of patients with diabetes mellitus experience microangiopathic complications.[8] These pathologies not only reduce the quality of life of patients, but also lead to economic losses, disability and disruption of social adaptation.[9] In this regard, the development of modern approaches to the early detection and effective management of these diseases is one of the urgent tasks of medical science, including Public Health.[10]

At the same time, the problem of dementia is becoming more and more relevant at the global level. According to data from the World Health Organization, today more than 55 million people in the world live with dementia, and every year this number is replenished with 10 million new cases.[11] This means that one person receives a dementia diagnosis every three seconds. Microangiopathy and damage to small vessels in the brain lead to the development of subcortical infarction, periventricular leukoareosis and other structural changes, creating conditions for the appearance of cognitive disorders, including vascular dementia.[12] These data indicate the close relationship of pathology of small vessels with neurodegenerative processes and the need for timely investigation of this problem.

In the national project for the development of the healthcare sector of the Republic of Kazakhstan for 2021-2025 "healthy nation", early detection of complications of cardiovascular diseases and diabetes mellitus and the introduction of high-quality diagnostic methods are identified as priority areas (*Report on the implementation of the "Almaty Development Program - 2025" for 2021*). At the same time, identifying microangiopathy at the initial stage, assessing risk factors and combining Visualization, Laboratory and clinical data in clinical decision-making is one of the strategically important tasks for the domestic healthcare system.

However, today in Kazakhstan at the level of primary health care (PHC), this issue has not been sufficiently resolved. For example, limited availability of visualization methods (MRI, CT, ultrasound), insufficient human resources, as well as incomplete implementation of diagnostic standards prevent early detection of microangiopathy. In megacities, where there is a high rate of urbanization, this problem is clearly manifested.

For example, according to expert data conducted from 2021 to 2025 using a GE MRI machine with a capacity of 1.5 Tesla in Almaty, pathological changes were detected in 58% of patients with MRI of the brain, of which more than 79% were microangiopathic.[13] This indicator clearly proves the prevalence of microcirculatory disorders and the importance of early diagnosis.

In modern clinical practice, the combination of visualization methods (MRI, CT) with laboratory biomarker indicators (HbA1c, creatinine, microalbuminuria, C-reactive protein, etc.) makes it possible to improve diagnosis and prognosis.[14] This integrative approach contributes to making a clear and evidence-based clinical decision, improving the quality of treatment, and reducing the risk of complications.

In addition, large-scale research is being carried out in the international scientific community in the direction of assessing risk factors for microangiopathy, early diagnosis and building prognostic models. However, in Kazakhstan, the number of comprehensive scientific works on this topic is limited, and there is no close connection with domestic clinical practice. In order to fill these gaps, our research will focus on providing solutions to current problems.

As a result of survey studies conducted by the author, 100% of medical workers noted the need to improve their knowledge of early detection of microangiopathy. At the same time, the polarity of opinions on clinical protocols (50% – effective, 50% – ineffective) and the fact

that most of the proposed solutions (40% – strengthening training programs, 30% – information measures, 20% – state support, 10% – other recommendations) are focused on knowledge and practice – further increase the relevance of the study.

Thus, the scientific and practical significance of the dissertation work is directly related to the need to identify manifestations of microangiopathy at the initial stage, systematically assess risk factors, improve the diagnostic process at the level of the domestic PHC and improve the quality of clinical decision – making. The results of this study can not only characterize the features of the spread of microangiopathic pathologies in Kazakhstan, but also make a significant contribution to the development of the public health system through specific recommendations and solutions.

Purpose of the study. Evaluation and optimization of the organization of early diagnosis of manifestations of microangiopathy in order to prevent the risk of complications.

Materials and methods

This retrospective study was conducted at Clinical Hospital No. 5 in Almaty, Kazakhstan, and included analysis of brain magnetic resonance imaging (MRI) data obtained between January 2022 and December 2024. Imaging was performed using a 1.5 Tesla GE Signa Explorer scanner with standard brain MRI protocols, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences. Microangiopathic changes were assessed on FLAIR images using the Fazekas scale (grades 0–3).

Sample size and study groups A total of 1,814 patients were included in the analysis. Patients were stratified into groups according to the severity of white matter changes (Fazekas 0, 1, 2, or 3).

Inclusion criteria:

Patients aged ⩾18 years;

Underwent complete brain MRI examination on a 1.5 T GE scanner;

Availability of complete MRI images and clinical records;

No significant artifacts in MRI scans.

Exclusion criteria:

History of acute traumatic brain injury within the past 6 months;

Presence of brain tumors or demyelinating diseases;

Severe motion artifacts on MRI preventing accurate evaluation;

Incomplete MRI or missing clinical data.

Methods of analysis. All MRI studies were reviewed independently by two experienced radiologists. Discrepancies in Fazekas scoring were resolved by consensus. Demographic data (age, sex) and comorbid conditions (diabetes mellitus, hypertension, cerebrovascular disease) were extracted from electronic medical records.

Ethical approval. The study protocol was approved by the Local Ethics Committee of Clinical Hospital No. 5, Almaty. All patient data were anonymized in accordance with the Declaration of Helsinki (2013). Extract from Protocol No. 7 dated 29.01.2025 y.

Statistical analysis. Statistical processing was performed using IBM SPSS Statistics, version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the data distribution. Categorical variables were presented as absolute numbers and percentages. Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics of the study population The analysis included 1,814 patients (57.2% women, 42.8% men) with a mean age of 58.4 ± 12.7 years (range: 19–88). Hypertension was present in 63.1% of patients, diabetes mellitus in 21.4%, and both conditions in 15.8%.

Distribution of microangiopathy severity:

Fazekas 0 (no lesions): 765 patients (42.2%);

Fazekas 1 (mild lesions): 1,033 patients (56.9%);

Fazekas 2 (moderate lesions): 258 patients (14.2%);

Fazekas 3 (severe lesions): 98 patients (5.4%).

Among patients with any microangiopathic changes (Fazekas 1–3), 79% had isolated mild white matter hyperintensities, while 21% had moderate-to-severe lesions requiring follow-up and targeted management.

Correlation with comorbidities. The prevalence of microangiopathy (Fazekas ⩾ 1) was significantly higher in patients with hypertension ($p < 0.001$) and diabetes mellitus ($p = 0.004$) compared to those without these conditions.

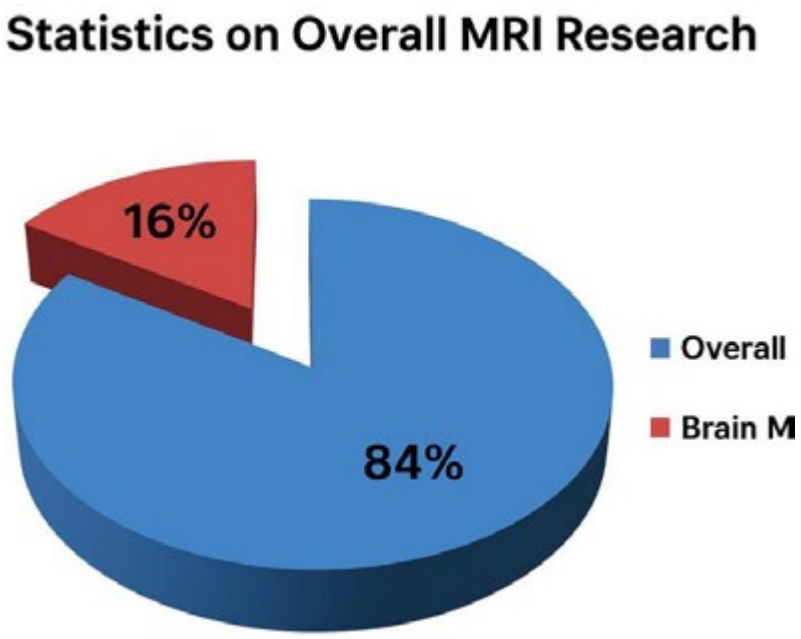

Figure 1. The indicator of general studies conducted in Clinical Hospital No. 5 of Almaty in 1.5 Tesla GE magnetic resonance imaging, (%).

A total of 11,342 patients underwent MRI studies during the said period. 84% of these studies (9,518 patients) were conducted on various organs and systems, and 16% (1,814 patients) were focused on magnetic resonance imaging of the actual brain. That is, on average, every sixth patient was referred for an MRI with headaches or other neurological complaints. This indicator testifies to the fact that neurological symptoms are often recorded in modern medical practice and its diagnostic significance.

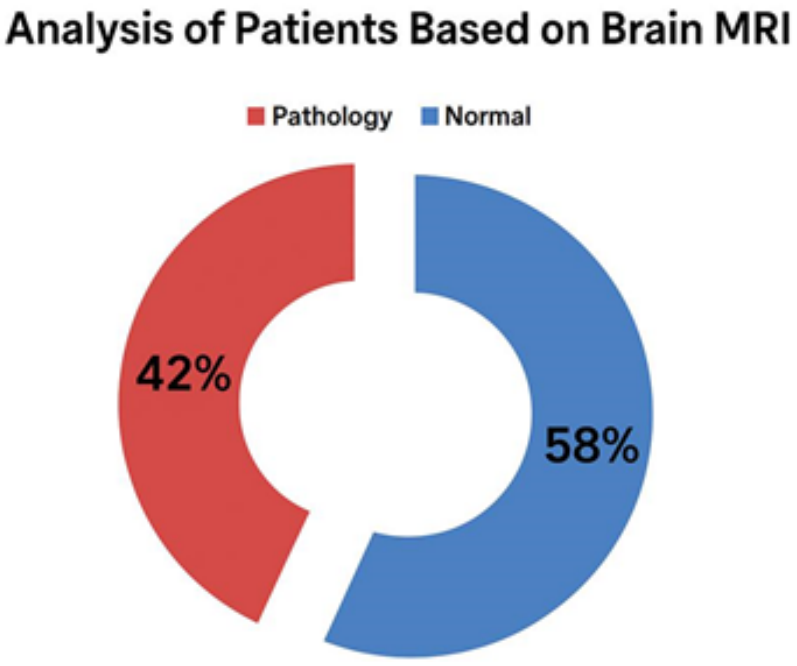

Figure 2. Brain studies conducted in Clinical Hospital No. 5 of Almaty at 1.5 Tesla GE magnetic resonance imaging, %.

Of the 1,814 patients who underwent an MRI examination of the brain:

✓ In 761 patients (42%), no pathological changes in the structure of the brain were detected, that is, the result of the study was within the norm.

✓ In the remaining 1053 patients (58%), various pathologies were recorded.

This means that more than one in every two brain studies reveals abnormalities to a certain extent. This result indicates the effectiveness of neuroimaging in diagnostics and the ability to identify pathological changes at an early stage with its help.

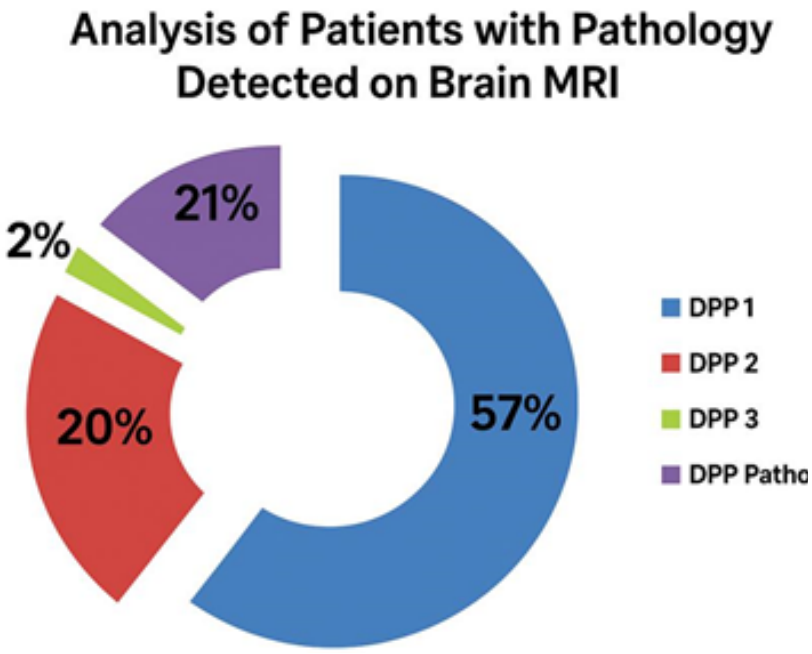

Figure 3.
Brain studies conducted in Clinical Hospital No. 5 of Almaty at 1.5 Tesla GE magnetic resonance imaging, %.

Among the 1053 patients with pathology, special attention is paid to microangiopathic changes. Of these patients, the following diagnoses are made:

✓ 599 patients (57%) were diagnosed with Phasecas Level 1 microangiopathy Diffusion/Perfusion Project (DPP 1). In this case, small hyperintensive foci are usually observed in the subcortical white matter of the Cerebral Hemispheres. Such changes are often seen as a sign of primary-stage chronic circulatory disorders.

✓ 210 patients (20%) had phasecas Level 2 microangiopathy (DPP 2). In this stage pathology, many hyperintensive foci are detected in the subcortical and deep white matter, among which there may be fused foci.

✓ 21 patients (2%) were diagnosed with Phasecas Level 3 microangiopathy (DPP 3). At this stage, changes are very clearly observed, and the involvement of many large foci and drainage zones is recorded in the subcortical and deep white matter. Such a manifestation usually develops as a result of prolonged cerebral circulation disorders.

✓ In the remaining 220 patients (21%), other pathological changes were detected, which were not microangiopathic in nature. In this category of patients, the brain has different etiologies (from birth, * inflammatory, tumor-like, etc.) other pathologies may be registered.

The statistical data obtained by MRI examination of the brain prove that microangiopathic changes are more common among patients. The fact that changes in the early stage (Fazecas 1) are often recorded indicates that this condition is being diagnosed at an early stage and there is a possibility of timely application of preventive or therapeutic measures.

The results of the study will help doctors classify patients and develop personalized treatment and control strategies for them. In addition, these data are an important basis for predicting the

prevalence and severity of neurological diseases in the public health field.

Discussion

The present study demonstrated a high prevalence of microangiopathic changes in patients undergoing brain MRI in Almaty, with pathological findings in 58% of cases, 79% of which were consistent with microangiopathy. Early-stage lesions (Fazekas 1) predominated, accounting for 57% of cases, which is consistent with data indicating that white matter hyperintensities are common in middle-aged and elderly populations and are often detected incidentally through neuroimaging.[1,12]

Our findings align with international reports emphasizing the role of small vessel pathology in the development of stroke, vascular dementia, and cognitive decline.[4,6] For example, WHO estimates that 17.9 million people die annually from cardiovascular diseases, in which microvascular pathology contributes significantly to adverse outcomes.[4] In diabetes mellitus, up to 40% of patients develop microangiopathic complications such as retinopathy, nephropathy, and neuropathy,[2,8] while microangiopathy is also a key link in the pathogenesis of neurodegenerative disorders.[1]

In our cohort, hypertension and diabetes mellitus were strongly associated with higher Fazekas scores, which is consistent with previous studies identifying these conditions as major risk factors for cerebral small vessel disease.[9,14] Importantly, the high proportion of Fazekas 1 lesions suggests that opportunities for preventive measures exist before irreversible damage occurs, which is in line with recommendations from the American Heart Association (2022) for early identification and management of microvascular disease.[15]

The public health implications of our findings are substantial. *The "Healthy Nation" national project in Kazakhstan (2021–2025)* prioritizes early detection of chronic diseases, including vascular complications. The integration of MRI-based Fazekas scoring into primary health care could improve risk stratification, guide timely interventions, and reduce the burden of disability associated with stroke and dementia.

To summarize the above, we recommend:

- Incorporate early MRI-based screening for microangiopathy into clinical protocols;
- Use the Fazekas scale for standardized reporting and risk stratification;
- Enhance preventive programs targeting vascular risk factors;
- Strengthen collaboration between neurologists, radiologists, and primary care physicians for timely intervention.

Limitations. This study was conducted at a single center, which may limit the generalizability of the findings. The retrospective design relied on existing MRI and medical records, which could introduce selection bias. Clinical follow-up data on patient outcomes were not available, limiting correlation between imaging findings and long-term prognosis. Additionally, the absence of advanced MRI techniques (e.g., diffusion tensor imaging, perfusion studies) restricted assessment to conventional structural markers.

What's Known? Microangiopathy is a key factor in the development of cognitive impairment, stroke, and diabetic complications, and MRI is an effective tool for its detection.

What's New? This study provides quantitative data on the prevalence and severity of microangiopathy using the Fazekas scale in a Kazakh cohort.

Conclusion

The study revealed a high prevalence of microangiopathy in patients undergoing brain MRI in Almaty. Pathological changes were detected in 58% of cases, with 79% being microangiopathic in nature and 57% at the early Fazekas 1 stage. These findings support the need for integrating early MRI-based diagnosis into national screening and preventive programs. Routine application of the Fazekas scale in clinical practice, coupled with targeted management of hypertension and diabetes, could significantly reduce the burden of stroke,

dementia, and related complications in Kazakhstan.

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Author Contributions: U.I. – study conception and design, data analysis, manuscript drafting; S.A. – MRI data review, interpretation of imaging findings; T.P.– statistical analysis, literature review. All authors approved the final manuscript.

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THE RADICALITY OF PITUITARY ADENOMA REMOVAL IN THE REPUBLIC OF KAZAKHSTAN

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Mustafin Halit, Doskaliyev Aidos, Yelyubayev Alimkhan, Teltayev Alimkhan

National Centre for Neurosurgery, Astana, Kazakhstan

Mustafin H.
https://orcid.org/0000-0003-3984-9565
Doskaliyev A.
https://orcid.org/0000-0001-8727-567X
Yelyubayev A.
https://orcid.org/0000-0002-0862-1747
Teltayev A.
https://orcid.org/0000-0002-4990-8410

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Author for correspondence:
Yelyubayev A.Z., resident-neurosurgeon, National Centre for Neurosurgery, Astana, Kazakhstan. 8(775)9541496.
E-mail: yelubaev.96@gmail.com

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pituitary adenoma, transnasal endoscopic surgery, Kazakhstan, neurosurgery.

Abstract

Background. Pituitary adenoma is a common tumor of the chiasmosellar region. By hormonal activity, pituitary adenoma's are classified as somatotropinomas, non-functioning, prolactinomas, corticotropinomas, and mixed types. Treatment tactics vary by type. Objective:To assess radicality of removal of different pituitary adenoma types in patients operated.

Materials and methods. Retrospective analysis of 929 patients (721 – endoscopic transnasal approach) treated at JSC "National Centre for Neurosurgery" between 2010–2022. Clinical data and magnetic resonance imaging findings were evaluated.

Results. Significant differences in "Extent of Resection" were found among pituitary adenoma types. The highest rate of total resection occurred in mixed tumors compared to prolactinomas (76.5% vs 50%). Subtotal removal was seen in 23.5% of mixed tumors, none had partial resection. Prolactinomas showed total removal in 50%, subtotal in 41.9%, partial in 8.1%. Conservative resection of prolactinomas is linked to their high sensitivity to medical therapy, enabling full recovery with dopamine agonists postoperatively. More radical removal of mixed pituitary adenoma's is justified by their aggressive behavior and relative drug resistance.

Conclusion. Extent of resection correlates with pituitary adenoma type. Lower radicality in prolactinomas reflects their benign course and responsiveness to drugs, whereas mixed pituitary adenoma's require aggressive surgery due to severe hormonal disturbances. Greater radicality should be pursued when possible while preserving quality of life. The transnasal endoscopic approach remains the safest and most effective surgical method for pituitary adenoma's in Kazakhstan, as confirmed by high total resection rates and low postoperative complications.

Introduction

Pituitary adenomas (PAs) are benign neoplasms originating from the anterior lobe of the pituitary gland and account for a significant proportion of all intracranial tumors. According to large meta-analyses, the prevalence of PAs in the general population ranges from 78 to 116 cases per 100,000 people.[1,2] Despite their widespread occurrence, late diagnosis of PAs remains common, particularly in developing countries. This may be attributed to the nonspecific nature of clinical manifestations and limited patient access to neuroimaging techniques.[3,4]

Depending on their hormonal activity, pituitary adenomas (PAs) are classified into somatotropinomas, non-functioning adenomas, prolactinomas, corticotropinomas, and mixed types. The treatment approach for each type has its own specific features. Mixed forms of PAs are less common than other types but are characterized by complex clinical manifestations, as these tumors secrete two types of hormones into the bloodstream rather than one.[5] As a result, more severe hormonal imbalances occur in the body.

There are three morphological types of mixed adenomas: mixed GH-cell/PRL-cell adenoma, mammosomatotroph adenoma, and acidophilic stem cell adenoma.[5] *Kreutzer et al.* state that mixed PAs behave more aggressively than other GH-secreting types and have a lower

success rate of surgical treatment.[6,7]

This is why greater attention should be given to this type of PA, as mixed adenomas cause significant hormonal disturbances in patients with pituitary adenomas.

Material and methods

Study Design: Retrospective analysis was performed at JSC National Center for Neurosurgery, Astana, Kazakhstan, between 2010 and 2022.

Inclusion Criteria of patients: with a confirmed diagnosis of pituitary adenoma, who underwent transnasal endoscopic surgical treatment.

Data collection performed: Clinical characteristics: age, gender, symptoms, as well as hormonal profile: levels of prolactin, ACTH, TSH, etc.

Neuroimaging using magnetic resonance imaging (MRI) of the brain. Analysis of surgical data: resection volume, complications.

Ethical approval: Ethical commission protocol №4 10th July 2025.

Statistical Analysis. Descriptive statistics were used to summarize the demographic, clinical, radiological, and histopathological characteristics of the patients. Quantitative variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. Categorical variables were expressed as absolute numbers and percentages. Comparisons between groups (based on histological type of pituitary adenoma) were performed using the Chi-square test exact test for categorical variables and the Student's t-test test for continuous variables, as appropriate. The extent of tumor resection was compared among groups using contingency tables and significance testing. The level of statistical significance was set at $p < 0.05$. All analyses were conducted using SPSS Statistics (IBM).

Results

790 patients (85.06%) had complete data on all required clinical, radiological, and histopathological parameters for statistical analysis, which supports the reliability of the results. The patients were distributed according to their hormonal activity as follows: non-functioning adenomas (NFA) – 549 (59.09%), somatotropinomas – 172 (18.51%), prolactinomas – 154 (16.57%), corticotropinomas – 34 (3.66%), and mixed adenomas – 20 (2.15%). See Table 1

The primary treatment method was endoscopic transnasaladenomectomy, performed in 721 cases (90.1%). The rate of gross total resection in mixed adenomas reached 76.5%. Subtotal resection was mainly performed in cases involving cavernous sinus invasion or other complicating factors. These data are consistent with international experience, demonstrating comparable efficacy rates.[8,9] The comparison was statistically significant ($p < 0.05$).

Type of Pituitary Adenoma and resection	**Somato tropinomas, (N=143)**	**Non-functioning Adenomas (NFA), (N=404)**	**Prolac tinomas,**	**25/01**	**29/01**	**03/02**
(N=124)	Cortico tropinomas (N=25)	Mixed Adenomas (N=17)	Level P, (df=8)	66.80	52.40	52.20
Partial	7 (4.9%)	39 (9.7%)	10 (8.1%)	(0.0%)	-	0.005
Subtotal	32 (22.4%)	150 (37.1%)	52 (41.9%)	6 (24.0%)	4 (23.5%)	
Total	104 (72.7%)	215 (53.2%)	62 (50.0%)	19 (76.0%)	13 (76.5)	

Table 1. Distribution of Different Types of Pituitary Adenomas According to the Extent of Tumor Resection. Different degrees of resection were compared across various histological groups

Total resection was performed in 413 (52.3%) cases, compared to subtotal 244 (30.8%), Chi-squared 28.688, 95% CI [13.7;28.7], P< 0.0001. With Somatotropinomas 104 (72.7%) more often than Non-functioning Adenomas 215 (53.2%), Chi-squared 11.03, 95% CI [8.2; 11.6], P = 0.0009. The frequency of total resection in Non-functioning Adenomas and in Prolactinomas 62 (50.0%) did not have a statistically significant difference, Chi-squared 0.197, 95% CI [10.5; 16.9], P = 0.6572

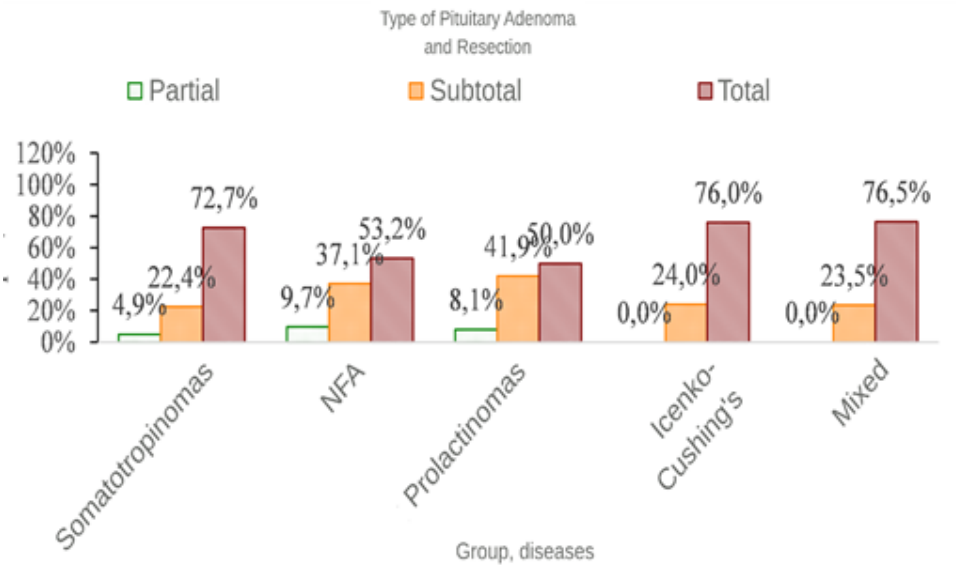

Figure 1. Percentage Distribution of the "Resection, Type" Indicators Across All Levels of the "Group, Disease" Variable.

Discussion

Our study analyzed 929 patients with various types of pituitary adenomas treated at the JSC "National Centre for Neurosurgery" over a 12-year period, focusing on the relationship between tumor type and the extent of surgical resection. The results demonstrate that tumor biology, hormonal activity, and morphometric features significantly influence surgical strategy and radicality.

Previous studies have reported high rates of gross total resection (GTR) with the endoscopic endonasal approach. For example, *Chao Tao et al.* achieved GTR in 74.7% of cases, with cerebrospinal fluid (CSF) leakage occurring in 2.7%.[10] In our series, GTR was achieved in 65% of patients, which is within the range of international reports, particularly given our higher proportion of complex and hormonally active tumors.[11,12]

Mixed adenomas, although relatively rare (2.1% of our cohort), exhibited more aggressive behavior and were associated with severe hormonal disturbances. Statistical analysis revealed significant intergroup differences in "Extent of Resection" ($p < 0.0001$), with total removal achieved in 76.5% of mixed adenomas compared to 50% of prolactinomas. The high total resection rate in mixed adenomas can be explained by their relative resistance to pharmacological therapy, necessitating maximal cytoreduction. By contrast, prolactinomas showed a more conservative surgical profile (subtotal resection in 41.9%, partial in 8.1%), reflecting their excellent response to dopamine agonists, consistent with the literature.[13,14]

Beyond resection patterns, our extended statistical analysis of 30 parameters across five histological groups identified significant differences in 9 of 14 general clinical variables, 1 of 16 hematological parameters, and 11 of 19 binary characteristics. IGF1 levels in mixed adenomas were markedly higher than in non-functioning adenomas (difference of 1624.5 ng/mL; $p < 0.0001$), and GH levels in corticotropinomas exceeded those in prolactinomas by 1636.8 ng/mL ($p < 0.0001$). These hormonal patterns likely influence tumor invasiveness and surgical difficulty.

Risk factor modeling for pituitary apoplexy highlighted three key predictors: treatment period 2010–2011, diagnosis before 2013, and presence of chiasmal syndrome. Each of these factors more than doubled the risk of hemorrhage into the pituitary, consistent with earlier findings that tumor size, vascular compromise, and delayed diagnosis predispose to apoplexy. Similarly, predictors of poor outcomes included disease duration ⩾ 24 months, hypopituitarism, and prior cranial surgery, each tripling the risk of adverse prognosis.[10]

Our findings align with other large series, which emphasize that surgical

radicality should be individualized, balancing the goal of complete tumor removal against the risk of hypopituitarism and other complications. The transnasal endoscopic approach proved to be effective and safe, with low complication rates and outcomes comparable to leading neurosurgical centers worldwide.[12]

In conclusion, the extent of pituitary adenoma resection is closely linked to tumor type, hormonal profile, and specific clinical factors. Aggressive resection is justified for mixed and hormonally active tumors, while a conservative strategy is preferable for prolactinomas due to their responsiveness to medical therapy. Incorporating risk factor analysis into preoperative planning can further optimize outcomes and reduce the likelihood of recurrence or complications.

Limitations. This study has several limitations. First, its retrospective design carries an inherent risk of selection and information bias, as the data were collected from existing medical records. Second, although our sample size was large, the distribution of patients across tumor subtypes was uneven, with a relatively small number of cases in the mixed adenoma and corticotropinoma groups. This imbalance may limit the statistical power for subgroup analyses. Third, the follow-up period was not uniform for all patients, making it difficult to assess long-term recurrence rates and endocrine outcomes consistently.

Another limitation is the reliance on MRI and intraoperative assessments for determining the extent of resection; histopathological confirmation of residual tumor was not performed in all cases. Additionally, variations in surgical techniques and surgeon experience over the 12-year study period could have influenced the results. Finally, some clinical and laboratory parameters had incomplete data, which, although not critical for the main statistical analysis, may have introduced minor inaccuracies.

Future prospective studies with standardized follow-up protocols, balanced representation of tumor subtypes, and integration of advanced imaging modalities are needed to validate our findings and refine surgical decision-making strategies.

What's Known? Pituitary adenomas vary in hormonal activity and aggressiveness, influencing surgical radicality. Endoscopic transnasal approaches are widely used, with reported gross total resection rates of 60–75% internationally.

What's New? This study links adenoma type to resection extent using large-scale of Kazakhstan data, identifying key clinical and hormonal predictors influencing surgical strategy.

Conclusion

Our observations confirm a correlation between the extent of pituitary adenoma (PA) resection and the tumor type: a high rate of gross total resection in mixed adenomas, and a lower rate in prolactinomas within the studied group. This may be explained by the fact that mixed PAs cause more severe hormonal imbalances in patients, necessitating a more radical surgical approach. In contrast, prolactinomas typically follow a more benign and favorable course and can often be effectively managed with medical therapy, thus not requiring the same level of surgical radicality. Additionally, mixed adenomas tend to behave more aggressively than other hormone-secreting types, such as GH-secreting tumors, and have a lower surgical success rate. The findings of our study clearly demonstrate a link between the extent of resection and the type of PA. We believe that regardless of adenoma type, the surgical goal should be maximal tumor removal while preserving the patient's quality of life. The transnasal endoscopic approach remains the most effective and safest treatment method for pituitary adenomas in Kazakhstan. This is supported by the high rate of total resections and the low rate of postoperative complications observed at the JSC "National Centre for Neurosurgery."

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Authors 'Contributions: M.H., D.A.: Conceptualization and design of the study; M.H.: Methodology, formal analysis; M.H., T.D.: Validation of the results; M.H., Y.A.: Writing of the original draft (introduction, methods, results); Y.A., M.H.: Review and editing of the manuscript (discussion, conclusion). All authors reviewed, edited, and approved the final version of the manuscript.

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AN OPTIMIZED APPROACH TO THE FORMATION OF THE UPPER EYELID AMONG EUROASIANS

Muradov Mismil, Abdukarimova Aidana, Zagainova Maria, Dzhamaldinov Timur

Syzganov National Scientific Surgery Center, Almaty, Kazakhstan.

DOI: 10.35805/BSK2025III006
Muradov M.
https://orcid.org/0000-0002-9168-8618
Abdukarimova A.
https://orcid.org/0000-0001-8083-4571
Zagainova M.
https://orcid.org/0009-0001-3559-5708
Dzhamaldinov T.
https://orcid.org/0009-0006-2427-0891

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Author for corresponds:
Abdukarimova A.T. -MD, resident of plastic-reconstructive microsurgery department of NSSC Syzganov National Scientific Center of Surgery, Almaty, Kazakhstan.
https://orcid.org/0000-0001-8083-4571
E-mail: talgatovnaa06@gmail.com

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Oriental blepharoplasty, upper eyelid, epicanthus.

Abstract

Background. Blepharoplasty of the Asian eyelid is a variant of operation in which a fold of the eyelid is created. The Asian upper eyelid is characterized by a low, absent, or variable skin fold, a fuller eyelid with a smaller orbit, and a medial epicanthal fold.The presence of this fold is explained by a different attachment of the muscle that raises the upper eyelid.

Material and methods. In the conditions of the NSCS named after Syzganov, between 2020-2024, we operated on 127 patients. In 101 cases, blepharoplasty was performed separately, in 26 cases in combination with other operations.

Results. In the postoperative period, no general surgical complications were observed in patients, in 2 cases there was an inconsistency of the formed fold.

Conclusions. Our method is a proven choice for the Europeanization of Asian eyelids, in which the postoperative scar does not extend beyond the cutout of the eyes. Low injury rate of the operation. Indirect epicanthoplasty is the method of choice for oriental blepharoplasty, since this method does not require additional incisions, therefore, the duration of rehabilitation, the number of possible complications, and the time of surgery are reduced. Only 2% of patients had an unsatisfactory result. The economic validity of this methodology: no need to stay in the hospital for a long time. This minimizes the costs of the medical facility and reduces the burden on medical staff.

Introduction

Blepharoplasty of the Asian eyelid is a variant of blepharoplasty of the upper eyelids, in which a fold of the eyelid is created, often absent or poorly expressed in representatives of the Asian eyelids. The Asian upper eyelid is characterized by a low, absent, or variable skin fold, a fuller eyelid with a smaller orbit, and a medial epicanthal fold.[1,2] The upper eyelid looks a little "swollen" due to ethnically conditioned, innate subcutaneous fat and retrobulbar fiber, the fold on it is absent or poorly visualized. In addition, Asian eyelids have a skin fold that connects the upper eyelid with the lower one, passing through the bridge of the nose (the so-called epicanthus). The presence of this fold is explained by a different attachment of the muscle that raises the upper eyelid. Therefore, the main focus of blepharoplasty of Asian eyelids is to form the eyelid fold of varying degrees of severity and depth, according to the anatomical features and desires of the patient.

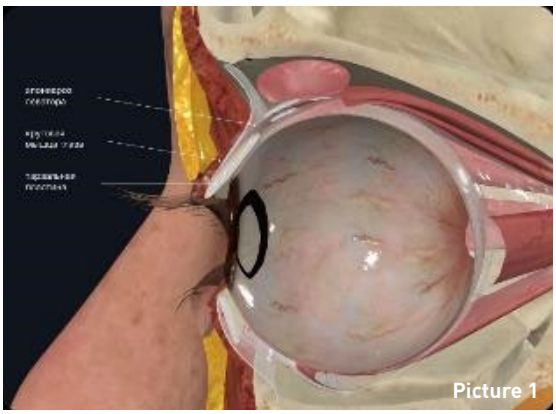
The eyelids can be divided into the following 7 structural layers: • skin and subcutaneous connective tissue • muscles of protraction • orbital septum • orbital fat • muscles of retraction • tarsus • conjunctiva.[3]

The fold of the upper eyelid is an anatomical invagination of the eyelid skin along the upper border of the tarsal plate and is formed due to the attachment of the aponeurosis of the levator to the skin of the tarsal plate and the m.orbicularis oculi.[2] The absence of a crease in the upper eyelid gives a smooth eyelid from the eyebrows to the lash line.

The crease of the upper eyelid should not be surgically formed "above" one-third of the distance between the pupil and the eyebrow. Approximately 50% of Southeast Asians have natural (albeit

small) folds, while a distinctive feature of Asian blepharoplasty is a change in this fold and the often associated epicanthus.[3]

The anatomical structure of the Asian upper eyelid has its own characteristics that significantly affect the surgical technique duringsurgery.[4]



Picture 1.
Features of the anatomical structure of the Asian century: low or variable skin fold of the upper eyelid (supratarsal fold); the presence of a medial epicanthic fold; fuller eyelid with pronounced anterior orbital fat packs; a smaller orbit; a shorter tarsal plate; almond-shaped shape with varying degrees of inclination; lowered eyelashes.

The epicanthus (epicanthal fold) is a skin flap in the medial part of the upper eyelid that runs down the side of the nose and may hide the medial part of the eyeball, making the pupils appear closer to the midline.

There have been many theories of the formation of wrinkles on the eyelids, but none of them has been scientifically proven, as several factors may be involved.

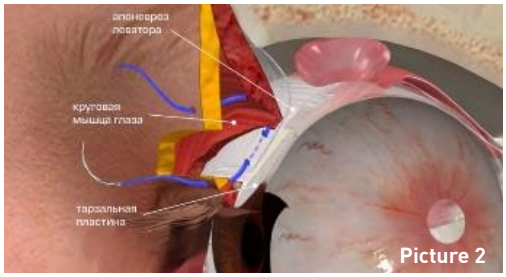
The above anatomical features, combined with classical external characteristics, create the so-called Asian eyelid.

Materials and methods

In the conditions of the NSCS named after Syzganov, between 2020-2024, we operated on 127 patients, 124 of them women and 3 men. In 101 cases, blepharoplasty was performed separately, in 26 cases in combination with other operations.

Patients are selected based on their availability for an appointment with a plastic surgeon.

After conducting a general medical examination and passing all tests, patients are admitted to the hospital. Photo documentation and marking of the surgical field is carried out.



Picture 2.
Technique of operation.

Picture 3.
Preoperative marking

The selection of the height of the fold is 7 mm; Drawing a semi-oval line along the future fold, repeating the shape of the eye; Drawing an oblique longitudinal line at the outer corner of the eye towards the tip of the eyebrow; Drawing an oblique longitudinal line crossing the epicanthus at the inner corner; According to the 3:2:1 rule, the distance from the upper incision line to the eyebrow was 14 mm; Drawing lines connecting the lower and upper borders of the sections.

The operations were performed under both local anesthesia and general anesthesia. The infiltration was carried out with a solution of Klein Sol. Sodium chloride 0.9% 20ml + Sol. Lidocaini 2% 10ml + Sol. Adrenalini 0.18% 0.3ml. After the expiration of the exposure time of 15 minutes, incisions were made on the skin of the upper eyelids according to the previously applied markings. After excision of the skin flaps, excision of the subcutaneous part of the circular muscle of the eye is performed on average from 1 to 2 mm. Fat bags are removed and coagulated. The aponeurosis of the upper eyelid lifting muscle is sutured to the skin with external nodular sutures, threaded Prolene 5.0, according to the preoperative marking. Epicanthoplasty is performed directly. An intradermal Halsted suture is applied to the length of the wound of the upper eyelid with a Prolene 6.0 thread. The eyelid sutures are removed on the 7th day after surgery.

In the period from 2020 to 2024, 127 surgical interventions were performed.

Total number of operations	127
Isolated blepharoplasty with the formation of an upper eyelid fold	101 (79.5%)
Blepharoplasty with the formation of an upper eyelid fold in combination with other operations	26 (20.5%)

Table 1.
Patients groups according to surgeries.

Age	female	male
18-25 y.o.	17 (13.4%)	-
26-33 y.o.	81 (63.8%)	2 (1.6%)
34-41 y.o.	22 (17.3%)	1 (0.8%)
42-49 y.o.	4 (3.1%)	-

Table 2.
Age and gender characterictics.

The subjective satisfaction of patients with the results after blepharoplasty was assessed using the FACE-Q questionnaire: FACE-QTM - ADVERSE EFFECTS: EYES.[6]

FACE-Q™ - ADVERSE EFFECTS: EYES

For each question, circle only one answer. These questions ask about problems you may be experiencing. With your eyes in mind, in the past week, how much have you been bothered by:

	Not at all	A little	Moderately	Extremely
a. How your eyelid scars look (obvious, noticeable, uneven)?	1	2	3	4
b. Dry eyes?	1	2	3	4
c. Eye irritation (e.g. redness, itching)?	1	2	3	4
d. Excessive tearing?	1	2	3	4
e. Your eyes looking hollowed out?	1	2	3	4
f. Difficulty closing your eyes?	1	2	3	4

Figure 1.
FACE-QTM - ADVERSE EFFECTS: EYES.[6]

The results of the assessment of patients' subjective satisfaction with the results of the operation are described in Figure 3.

Ethical approval. The study protocol was approved by the local Ethics Committee of JSC NSCS named after A.N. Syzganov" (approval No. dated 06.05.2025).

Statistical analysis. The statistical analysis included descriptive and analytical statistics where for variables with a normal distribution, parametric statistical methods were used and presented as means ± standard deviation. Numerical variables of non-normally distributed data were presented as mean values ± standard deviation. Statistically significant difference P≤0.05

Results

In the postoperative period, no general surgical complications were observed in patients, in 2 cases there was an inconsistency of the formed fold. In 1 case, 8 months after the operation, in 2 cases after 1 year.

Postoperative photographs of patients in the intermediate and long-term rehabilitation period:


Picture 4a


Picture 4b

Picture 4(a,b).
Before and after 7 days from the moment of surgery

Picture 5(a,b). Before and after 1month from the moment of surgery


Picture 5a


Picture 5b

Picture 6(a,b). Before and after 3 month from the moment of surgery


Picture 6a


Picture 6b

Picture 7(a,b). Before and after 6 month from the moment of surgery


Picture 7a


Picture 7b

The results of the assessment of patients' subjective satisfaction with the results of the operation are described in Table 3.

Table 3. Results of the assessment of subjective satisfaction of patients with the results of surgery

Total number of patients (n = 127)	Not at all	A little	Moderately	Extremely
a. How your eyelid scars look (obvious, noticeable, uneven)?	89 (70.08%)	87 (68.50%)	1 (0.79%)	-
b. Dry eyes?	104 (81.89%)	23 (18.11%)	-	-
c. Eye irritation (e.g. redness, itching)?	111 (87.40%)	14 (11.02%)	2 (1.57%)	-
d. Excessive tearing?	101 (79.53%)	26 (20.47%)	-	-
e. Your eyes looking hollowed out?	125 (98.43%)	1 (0.79%)	1 (0.79%)	-
f. Difficulty closing your eyes?	119 (93.70%)	5 (3.94%)	3 (2.36%)	-

To the question - How your eyelid scars look (obvious, noticeable, uneven)? - there is no statistically significant difference, P = 0.9092

Not at all complaints of the nature: dry eyes, eye irritation (eg, redness, itching), excessive tearing, eyes looking hollowed out, difficulty closing eyes - statistically significant was not observed, P < 0.0001.

Discussion

There are many different techniques for forming the palpebral groove. Globally, they can be divided into surgical and non-surgical.

Table 4. Comparative characteristics of methods of forming the eye fold

Surgical		Non-surgical
Full-layer (end-to-end) methods	**Minimal-incision method**	**Thread techniques**
Park Method (Dermal-Levator Aponeurosis Fixation) – fixation of the skin to the levator of the upper eyelid without removing the muscle, which gives a more natural result.[7]	Formation of the eyelid fold by fixation of the dermis to the aponeurosis through small incisions with or without excision of fat and muscle. Fixation of the dermis to the aponeurosis.[8]	A fold is formed using surgical suture material. The effect is short-term (1-3 years).
The essence of the method An incision is made along the intended line of the	Several pinpoint cuts (2–4 mm) along the line of the future fold (instead of a	

future fold (usually 6–8 mm from the eyelash line). Removal of a strip of skin underlying the orbicularis oculi muscle (orbicularis oculi) and sometimes parts of the preaponeurotic fat. Fixation of the skin to the aponeurosis of the muscle that lifts the upper eyelid (levator) using sutures.	continuous cut). Partial removal/ redistribution of fat through micro-accesses. Fixation of the skin to the levator or tarsal plate with absorbable or non-absorbable sutures.	

Table 5.
Distinctive characteristics with other methods

Method	Invasiveness	Durability	Fat/skin correction
Park (Dermal-Levator Fixation	High (full layer)	Constant	Yes
Thread method	Minimum	1-3 years	No
minimal-incision method	Moderate	Long lasting	Partially

Conclusion

Based on our experience of oriental blepharoplasty, we came to the following conclusions. Our Asian eyelid blepharoplasty method is a proven choice for the Europeanization of Asian eyelids, in which the postoperative scar does not extend beyond the cutout of the eyes. Low injury rate of the operation. Indirect epicanthoplasty is the method of choice for oriental blepharoplasty, since this method does not require additional incisions, therefore, the duration of rehabilitation, the number of possible complications, and the time of surgery are reduced. According to our statistics, only 2% of patients had an unsatisfactory result – the absence of a palpebral fold in one eye. The economic validity of this methodology. In view of all of the above, the patient does not need to stay in the hospital for a long time. This minimizes the costs of the medical facility and reduces the burden on medical staff.

Limitations. One of the key limitations of this study is that it was conducted at a single center, namely the Syzganov National Scientific Surgical Center. This may limit the generalizability of the findings, as the patient populations at other institutions could differ in terms of demographics, comorbidities, or surgical protocols. Many patients refused to give permission for their photographs to be used.

What is Known? Chosen method of oriental blepharoplasty is the most optimized technique of the formation of the upper fold among euroasians.

What is New? According to our surgery technique, we don't use absorbable threads into the wound. The aponeurosis of the upper eyelid lifting muscle is sutured to the skin with external nodular sutures, threaded Prolene 5.0, according to the preoperative marking. An intra dermal Halsted suture is applied to the length of the wound of the upper eyelid with a Prolene 6.0 thread. This ensures less inflammation and swelling.

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FEATURES OF RISK FACTORS FOR THE DEVELOPMENT OF ATHEROSCLEROSIS-ASSOCIATED CARDIOVASCULAR DISEASES IN THE KAZAKHSTANI POPULATION: ETHNONATIONAL ASPECT

Makhabbat Bekbossynova, Tatyana Ivanova-Razumova, Aliya Sailybayeva, Sadyk Khamitov, Kamila Akzholova

"University Medical Center" Corporate Fund, Astana, Kazakhstan.

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Bekbossynova M.
https://orcid.org/0000-0003-2834-617X
Ivanova-Razumova T.
https://orcid.org/0000-0002-6471-1587
Sailybayeva A.
https://orcid.org/0000-0002-1489-3837
Sadyk K.
https://orcid.org/0000-0001-6296-0507
Akzholova K.
https://orcid.org/0009-0000-2527-8947

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Corresponding Author:
Makhabbat Bekbossynova,Associated Professor, Deputy Chairman of the Management Board, cardiologist, "University Medical Center" Corporate Fund, Astana, Kazakhstan Republic of Kazakhstan, 010000, Astana, Kazakhstan.
E-mail: cardiacsurgeryres@gmail.com

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atherosclerosis, cardiovascular risk factors, Kazakhstan, urban-rural disparities, lipid metabolism, preventive cardiology

Abstract

Background. Atherosclerosis-associated cardiovascular diseases exhibit significant ethnic and regional variability in risk factors. Kazakhstan's high cardiovascular disease mortality rates necessitate population-specific profiling, particularly given urban-rural disparities and lifestyle differences unique to Central Asia.

Methods. This cross-sectional study (2023–2024) analyzed 368 Kazakhstani adults stratified by European Atherosclerosis Society risk tiers: low (n=67), high (n=127), and very high risk (very high-risk group, n=174). Assessments included lipid profiles (low density lipoprotein, high density lipoprotein, and apolipoprotein B to apolipoprotein A ratio), lifestyle factors (smoking, diet, physical activity), and residence (urban/rural). Statistical analyses employed multiclass logistic regression (MNLogit) with FDR-adjusted p-values.

Results. Age (OR=8.01, 95% CI:4.40–14.58, p<0.001), male sex (OR=3.27, CI:1.82–5.88), and smoking (OR=7.19, CI:1.52–34.15) were strongly associated with very high-risk group. Rural residents faced 2.6-fold higher very high-risk group odds (CI:1.52–5.68, p=0.002) versus urban counterparts. Protective effects emerged for physical activity (OR=0.03, CI:0.004–0.32) and female sex (High-Density Lipoprotein: +8.1 mg/dL vs. males, p<0.001). No alcohol association was observed (p=0.836).

Conclusion. A thorough study of the gender aspect of the development of atherosclerotic pathology is required. Physical activity has a strong protective effect. It is interesting that, according to the comparative analysis of binary variables, rural residents have a higher risk of developing atherosclerosis.

Introduction

Atherosclerosis and its complications remain a global health problem and a leading cause of cardiovascular disease. However, the prevalence of atherosclerosis-associated cardiovascular disease (ASCVD) and the structure of risk factors vary significantly across geographic regions, ethnicities, socioeconomic conditions, and cultural traditions. According to the Global Burden of Disease Study (2021), the highest cardiovascular disease (CVD) mortality is observed in Eastern European and Central Asian countries, including Kazakhstan and Russia, where rates of hypertension, smoking, and dyslipidemia are high. In particular, CVD mortality among men aged 55-59 in the Commonwealth of Independent States (CIS) countries of Belarus, Kazakhstan, Kyrgyzstan, Russia, and Ukraine is higher than among the male population of France in the age group 75-79. Statistics for the female population are approximately at the same level.[1,2,3] At the same time, in Western European and North American countries, thanks to effective prevention, there has been a decrease in the incidence of the disease.

At the population level, 80% of all cases of atherosclerosis are caused by traditional risk factors. Global epide-

miological studies conducted in recent decades have identified new risk factors - systemic inflammation, high levels of lipoprotein (a) (Lp (a)), microalbuminuria, prothrombotic factors.[4] Different populations and ethnic groups have significant differences in the prevailing risk factors for the development of atherosclerosis, which is due to differences in the rate of lipid metabolism, the incidence of insulin resistance and diabetes mellitus, the level of urbanization of the country, the environmental situation, and ethnic characteristics of commitment to a healthy lifestyle. An important role is also played by state screening programs.

In Western European countries, the predominant risk factors for the development of atherosclerosis-associated diseases are obesity and physical inactivity.[5] At the same time, in Eastern Europe, smoking, alcohol abuse and uncontrolled arterial hypertension predominate.[3]. In Asian countries, the risk factor profile is fundamentally different. In China, the increase in atherosclerosis is associated with urbanization, air pollution and changes in diet.[6] In Japan, despite the low level of obesity, high salt intake plays a significant role. In South Asian countries, there is the so-called "Asian paradox" - a high prevalence of diabetes and low HDL levels.[7] In the Persian Gulf region (UAE, Saudi Arabia), up to 40% of the population suffers from metabolic syndrome.[8] The population of Latin America suffers from hypertension and a low level of medical control over dyslipidemia. In Brazil and Mexico, excess consumption of processed carbohydrates plays a significant role.[9] These data demonstrate that there are no universal solutions for preventing atherosclerosis, nor are there universal risk factors. Thus, strategies that take local conditions into account are needed.

According to national studies, the prevalence of dyslipidemia among the adult population of Kazakhstan reaches 40-45%, and arterial hypertension - 30-35% (*Ministry of Health of the Republic of Kazakhstan, 2022*). Of particular concern is the increase in metabolic syndrome and type 2 diabetes mellitus, which significantly accelerate the development of atherosclerotic lesions.[10] In addition, there are regional differences: in industrial cities (Karaganda, Temirtau, Ust-Kamenogorsk), the incidence is higher, which may be due to environmental factors and nutritional characteristics.[10]

Identification of country-specific risk factors in the population of the Republic of Kazakhstan will allow us to identify gaps in existing preventive and screening programs and develop algorithms for patient management taking into account national and ethnic characteristics. In addition, the results obtained will contribute to the development of targeted population programs to reduce the impact of risk factors prevailing in our country.

The aim of the study is to identify ethnospecific features of risk factors for the development of atherosclerosis in the Kazakhstani population, as well as to assess their contribution to the formation of cardiovascular risk.

Materials and methods

The study design included 3 groups. Group 1 - patients with high cardiovascular risk (HR) - 127 people. Group 2 - patients with very high risk (VHR) of developing cardiovascular diseases, according to the risk stratification of the European Atherosclerosis Society - 174 people. Control group - healthy - 67 people - low risk (LR). Inclusion criteria for the very high-risk group were the presence of one of the following factors: documented atherosclerotic cardiovascular disease either clinically or by imaging methods, including a history of acute coronary syndrome (ACS) (myocardial infarction, unstable angina), stable angina, coronary artery revascularization (percutaneous coronary intervention, coronary artery bypass grafting), stroke or transient ischemic attack, significant coronary artery stenosis (atherosclerotic plaques) according to coronary angiography or CT angiography, multivessel coronary artery disease, calculated 10-year risk of fatal cardiovascular events according to the SCORE scale ≥ 10%.

The criteria for including a patient in the high-risk group are a significant increase in one of the following risk factors: total cholesterol >8 mmol/l, LDL >4.9 mmol/l, BP> 180.110 mmHg, patients with diabetes without target organ damage, diabetes duration> 10 years or an additional risk factor, moderate Chronic Kidney Disease (CKD) (SCF 30-59 ml/min/1.73 m2), estimated SCORE> 5% and < 10% risk of developing cardiovascular diseases and adverse events.

Exclusion criteria for the study: patients with cancer, age over 65 years.

The studies were conducted at the National Scientific Cardiac Surgery Center in 2023-2024 and were cross-sectional. All study participants underwent a one-time questionnaire survey, anamnesis collection, and physical examination. Laboratory tests included determination of lipid and glycemic profiles. The lipid profile included: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipoprotein (a), Apo-B, Apo-A.

The presence of risk factors was determined based on anamnesis and physical examination data. The main risk factors included: gender, age, various dyslipidemias, arterial hypertension, smoking and alcohol consumption, excess body weight, the presence of metabolic syndrome, low physical activity, environmental factors (industrial regions of the Republic of Kazakhstan, the presence of hazardous industries in the region of residence, urbanization).

The anamnesis of patients revealed the presence of episodes of development of cardiovascular diseases both in the patient himself and in first-degree relatives. Eating habits were assessed: commitment to healthy eating, adherence to a special diet (comorbid conditions - diabetes mellitus, renal failure). The anamnesis regarding arterial hypertension was clarified. The presence of bad habits - smoking, alcohol consumption - was determined. Physical activity was assessed based on the number of minutes with physical activity during the week and its intensity. Lifestyle was assessed as sedentary (hypodynamia) - with almost complete absence of physical activity, < 150 minutes per week and low intensity of loads.

Ethical approval. Patients all signed informed consent and the study was approved by the local ethical committee (approval number № 2023/01-008 from 05.07.2024).

Statistical analysis. The Excel statistical software package was used for statistical data processing. Statistical processing included descriptive and analytical statistics. When analyzing variables with a normal type of data distribution in the population, parametric statistics methods were used for comparative analysis. Numerical variables were presented as the mean ± standard deviation. Correlation analysis with calculation of the correlation coefficient was used to determine the degree of relationship between the indicators. For all types of analysis, the Student criterion was determined to determine statistical significance; a value of $p < 0.05$ was considered significant. For variables that do not have a normal distribution, nonparametric research methods were used.

For quantitative variables, the Kruskal–Wallis test (H-test) was used to assess differences between risk groups (LR, HR, VHR) with p-value correction using the Benjamini–Hochberg method (FDR-BH, $p < 0.05$), the n^2 indicator for the effect size (<0.01 — insignificant, 0.01–0.06 — small, 0.06–0.14 — medium, >0.14 — large), and the Jonckheere–Terpstra test (JT-test) for monotonic trends ($p < 0.05$, FDR-BH). Pairwise comparisons were performed using the Dunn test with Holm correction (FWER-Holm) and effect size (r).

For binary and categorical variables, the omnibus chi-square (x^2) test with Benjamini–Hochberg p-value correction (FDR-BH, $p < 0.05$) and Cramér's V coefficient (<0.10 — very weak, 0.10–0.20 — weak, 0.20–0.30 — moderate, >0.30 — strong association) were used. Linear trends were assessed by the Cochran–Armitage test (CATT, $p < 0.05$, FDR). Pairwise comparisons were performed by the Fisher test with Holm correction (FWER-Holm), with calculation of the

odds ratio (OR) and 95% confidence interval.

Correlations were estimated by Spearman's rho (ρ) for quantitative, point biserial (r_pb) for binary, and Phi coefficient (φ) for categorical data, with Benjamini–Hochberg p-value correction (FDR, $p < 0.05$). The correlation matrix is visualized with a color scale.

Multiclass logistic regression (MNLogit) was used to model risk factors, estimating the probability of HR and VHR relative to LR. Results are presented as adjusted odds ratios (OR), 95% confidence intervals, and p-values. Model quality was assessed using pseudo-R^2.

Results

In previous studies conducted in Kazakhstan on the study of risk factors for the development of cardiovascular diseases, a number of features were identified. In the study by Kaliyev R.S., such risk factors as arterial hypertension, dyslipidemia, obesity, smoking, and physical inactivity were studied in two ethnic groups - Kazakhs and Russians.[10] It was found that ethnic Kazakhs have a higher prevalence of abdominal obesity and low HDL. However, neither this work nor the works of other domestic researchers included differentiation of study participants by risk groups for the development of atherosclerosis-associated CVD, and accordingly, the most significant risk factors at the level of the country population were not identified.

This study included 368 people, divided into 3 groups depending on the level of risk of developing cardiovascular diseases associated with atherosclerosis. The baseline characteristics of the study participants, including risk factors and lipid profile indicators, are presented in Table 1.

Table 1.
Comparative characteristics of methods of forming the eye fold

Parameter	Group I (LR) (n= 67)	Group II (HR) (n= 127)	Group III (VHR) (n= 174)	p-value
Age	43.31 ± 9.20	53.34 ± 7.67	56.36 ± 6.96	< 0.00001*
Floor				
Men	25(37.3%)	63(49.6%)	115(66.1%)	0.000184*
Women	42(62.7%)	64(50.4%)	59(33.9%)	>0.05
Bmi	27.51 ± 4.49	30.00 ± 5.77	29.74 ± 4.79	0.006931*
Early menopause (women)	6(14.3%)	9(14.1%)	17(28.8%)	0.078927
Heredity for cardiovascular diseases				
Burdened	33(49.3%)	85(66.9%)	109(62.6%)	0.076181
Not burdened	34(50.7%)	42(33.1%)	65(37.4%)	>0.05
Smoking	3(4.5%)	26(20.3%)	43(25.0%)	0.001966*
Alcohol consumption				
Does not use	39 (58.2%)	68 (53.5%)	98 (56.3%)	0.817624
Uses	28 (41.8%)	59 (46.5%)	76 (43.7%)	>0.05
Physical activity level				
Hypodynamia	7 (10.4%)	40 (31.5%)	32 (18.4%)	>0.05
Moderate physical activity	48 (71.6%)	83 (65.4%)	137 (78.7%)	>0.05
Active life style	12 (17.9%)	3 (2.4%)	5 (2.9%)	>0.05
Professional sports	0 (0%)	1 (0.8%)	0 (0%)	>0.05
Average activity level	1.07 ± 0.53	0.72 ± 0.54	0.84 ± 0.44	0.000144*
Eating habits				
Traditional food for the region (no diet)	59 (88.1%)	111 (87.4%)	126 (72.4%)	0.000124*
Low fat diet	4 (6.0%)	6 (4.7%)	11 (6.3%)	>0.05
Low carbohydrate diet	1 (1.5%)	3 (2.4%)	31 (17.8%)	>0.05

Low fat and low carbohydrate diet	3 (4.5%)	5 (3.9%)	5 (2.9%)	>0.05
Place of residence				
Country side	7(10.4%)	17(13.4%)	41(23.6%)	0.016272*
City	60(89.6%)	110(86.6%)	133(76.4%)	>0.05
Lipid profile				
Total cholesterol	190.69 ± 31.84	210.82 ± 40.10	197.91 ± 50.07	0.001189*
Triglycerides	114.22 ± 73.23	149.40 ± 147.29	161.37 ± 91.44	0.001248*
Ldl	126.12 ± 26.56	144.34 ± 33.41	134.47 ± 42.84	<0.00001*
Hdl	54.83 ± 12.47	53.52 ± 13.33	46.75 ± 11.75	0.000092*
Apo-A	1.44 ± 0.28	1.34 ± 0.36	1.12 ± 0.32	<0.00001*
Apo-B	0.94 ± 0.24	1.08 ± 0.25	1.04 ± 0.34	0.001785*
Lp(a)	38.57 ± 52.67	27.72 ± 38.02	37.74 ± 52.98	0.464560
*Statistically significant difference P≤0.05				

The baseline characteristics of the study cohort (*N*=368) revealed significant differences across cardiovascular risk groups (LR, HR, VHR). Participants in the VHR group were older (56.4±7.0 years) compared to the LR group (43.3±9.2 years; p<0.001) and had higher prevalence of male sex (66.1% vs. 37.3%; OR=3.27, 95% CI:1.82–5.88). Lipid profiles worsened with increasing risk: LDL was elevated in HR (144.3±33.4 mg/dL) and VHR (134.5±42.8 mg/dL) groups versus LR (126.1±26.6 mg/dL), while HDL was lowest in VHR (46.8±11.8 mg/dL vs. 54.8±12.5 mg/dL in LR; p<0.001). Smoking prevalence tripled from LR (4.5%) to VHR (25.0%; p=0.004), and rural residence was associated with higher risk (23.6% in VHR vs. 10.4% in LR; p=0.036). Notably, 72.4% of VHR patients adhered to no specific diet, versus 88.1% in LR (p=0.003).

To determine the relationship between the risk of developing atherosclerosis-associated diseases and individual risk factors, a correlation analysis was performed with the construction of a correlation matrix. Table 2 presents significant correlations between clinical and demographic variables, including the level of cardiovascular disease (CVD) risk according to the EAS scale (eas_risk_score), defined as the target variable. Correlations were calculated using Spearman's coefficients (ρ), point biserial (r_pb) and the Phi correlation coefficient (φ), with p-values adjusted by the Benjamini-Hochberg method (FDR). Significance was established at p < 0.05.

Table 2.
Correlations between clinical and demographic variables.

Variable 1	Variable 2	Corr_metric	Corr_val	Fdr adj. P-value
Cityorvillage	EAS risk	r_pb	0.142476777	0.041*
Diet 2	EAS risk	r_pb	0.243136878	p<0.01*
EAS risk	age	ρ	0.452501369	p<0.01*
EAS risk	Apo-A	ρ	-0.418333625	p<0.01*
EAS risk	HDL	ρ	-0.29413681	p<0.01*
EAS risk	triglycerides	ρ	0.24004479	p<0.01*
Levelofphysica-lactivity	EAS risk	r_pb	-0.203293998	0.001*
Floor	EAS risk	r_pb	-0.224108558	p<0.01*
Smoking	EAS risk	r_pb	0.181995757	0.005*
* Statistically significant difference P≤0.05				

Next, to determine the significance of each risk factor in the development of atherosclerosis, a comparison of risk groups by binary variables was performed. Table № is a comparative analysis of clinical, demographic, and laboratory characteristics between three groups of patients classified by the level of cardiovascular risk according to the EAS recommendations: low (LR), high (HR), and very high (VHR) risk. The table allows us to estimate which variables are statistically associated with belonging to a risk group and to determine the presence of directional trends. The first step was to estimate the x^2 p-value obtained as a result of the chi-square omnibus test. If significant differences were identified by the x^2 test, the strength of the relationship between the variable and the risk groups was further analyzed using the Cramér's V coefficient. This is a dimensionless metric, the values of which are interpreted as follows: less than 0.10 is a very weak relationship, from 0.10 to 0.20 is weak, from 0.20 to 0.30 is moderate, and more than 0.30 is a strong relationship. For variables where the presence of an ordering of risk levels was assumed, the Cochran-Armitage test (CATT) was used, which assesses the presence of a linear trend in the distribution of the feature. At CATT p-value < 0.05, the trend was assessed as statistically significant, and its positive or negative direction was also determined.

Table 3.
Comparison of risk groups by binary variables.

Variable	Group LR (n=67)	Group HR (n=127)	Group VHR (n=174)	x^2 p-value (FDR adj.)	Cramér's V	Significant Pairwise Comparisons (OR [95% CI], p-value)
Urbanvs. Rural	89.6% urban	86.6% urban	76.4% urban	0.036	0.149	VHR vs. LR: OR=0.38 [0.16–0.89], p=0.083
Gender (Male)	37.3%	49.6%	66.1%	<0.001*	0.225	VHR vs. LR: OR=3.27 [1.82–5.88], p<0.001*
Smoking	4.5%	20.3%	25.0%	0.004*	0.190	VHR vs. LR: OR=7.19 [1.52–34.15], p=0.013*
Alcohol Use	41.8%	46.5%	43.7%	0.836	0.034	Not significant
Family History (CVD)	49.3%	66.9%	62.6%	0.088	0.127	HR vs. LR: OR=3.33 [1.41–7.84], p=0.006*
Low-Carb-Diet	1.5%	2.4%	17.8%	<0.001*	0.268	VHR vs. LR: OR=0.07 [0.01–0.52], p<0.001*
Physical Inactivity	Highe ractivity	Moder-ate ac-tivity	Lower ac-tivity	<0.001*	—	VHR vs. LR: OR=33.3 [0.004–0.32], p=0.003*
*Statistically significant difference P≤0.05						

Table 3 compares key risk factors across cardiovascular risk groups (LR, HR, VHR). Significant differences were observed for urban/rural residence (p=0.036), sex (p<0.001), smoking (p=0.004), and low-carbohydrate diet adherence (p<0.001). Men exhibited higher odds of very high risk (VHR) compared to women (OR=3.27, 95% CI: 1.82–5.88), while smoking increased VHR likelihood by 7.19-fold (CI: 1.52–34.15). A protective effect was noted for physical activity (VHR vs. LR: OR=0.03, CI: 0.004–0.32). No association was found for alcohol use (p=0.836).

The correlation matrix is attached as Appendix 1. The most significant findings are described below:

Gender Analysis When comparing gender and the degree of risk of devel-

oping CVD, a moderate negative correlation was noted (r_pb = -0.224, p = 0.0002), indicating that women have a lower risk of developing CVD compared to men, which may be due to both hormonal and behavioral differences.[11,12] For women a significantly higher level was noted both very high density lipoproteins and Apo-A, correlation positive with HDL (r_pb = 0.411, p < 0.0001), and ApoA (r_pb = 0.290, p < 0.0003).

Comparison of the groups by binary variables revealed significant differences (x^2 p = 0.0005, Cramér's V = 0.225, moderate association). The proportion of women decreases from 62.7% in the LR group to 50.4% and 33.9% in the high and very high risk groups, respectively, with a pronounced negative trend (CATT p = 0.0001). Pairwise comparisons confirm that women are less common in the VHR compared to the LR (OR = 3.27, p = 0.0002) and in the VHR compared to the HR (OR = 1.98, p = 0.0090), indicating a higher probability of high risk in men. . We also analyzed the incidence of early menopause in women in the study groups. The proportion of patients with early menopause was highest in the very high-risk group (28.8%) and statistically significantly higher than in the other two groups (14.3 and 14.1%), p<0.05.

Age When analyzing this variable, a strong positive correlation was found (ρ = 0.453, p < 0.0001) indicating that the risk of CVD increases consistently with age. This highlights age as a key risk factor, which is in full agreement with international studies.[13,14]

Body mass index comparative analysis by binary variables showed significant differences between the study and control groups (H = 11.23, p = 0.004, n^2 = 0.025, small effect). The median BMI increased from 26.85 in the control group to 28.91 in the high-risk group and 29.37 in the very high-risk group, with a moderate increasing trend (JT Z = 2.69, p = 0.014).

Smoking according to international studies, it is one of the leading risk factors for atherosclerosis, included in the risk stratification tables. *(Global Adult Tobacco Survey in Kazakhstan, 2019).* In our study, the frequency of smoking statistically significantly differs between the groups (x^2 p = 0.011, Cramér's V = 0.187). The lowest proportion of smokers was noted in the HP group (4.5%), in the high and very high risk groups the percentage was 20.3% and 25.0%, respectively. There is a reliable positive trend (CATT p = 0.0036). At the same time, according to the Bureau of National Statistics of the Republic of Kazakhstan, as of July 2023, 19.4% of the population smoke tobacco (in 2022 - 20.4%) or 36% of men, 8.5% of women. In 2023, compared to 2022, the proportion of smokers in the 29-38 age group increased, while in other age groups there was a decrease in this indicator. (*World Health Organization & Ministry of Health of the Republic of Kazakhstan. (2023). National study of health behavior in school-aged children (11-15 years) in relation to health and mental well-being (HBSC).*

Alcohol consumption in order to systematize the data for the analysis of this risk factor, binary coding was used, where "0" means does not consume alcohol, "1" means does. By analogy with the analysis of the specified indicator in large meta-analyses,[13] the coding "consumes" included: drinking 1 drink per week, moderate consumption, excessive consumption. The percentage of patients who completely abstained from alcohol and those who consumed it in varying quantities was distributed in approximately equal proportions in all three groups, with a slight predominance of the former - 58.2%, 53.5% and 56.3% in the control, high and very high risk groups. Comparative analysis established the insignificance of differences between the groups (x^2 p = 0.8358, Cramér's V = 0.034, very weak association), without a trend (CATT p = 0.9330). Thus, in our patient cohort, no association was found between alcohol consumption and the risk of developing atherosclerosis.

Dietary habits (presence of a diet) one of the risk factors frequently mentioned in studies on the development of atherosclerosis is the nature of the diet. Unhealthy food can independently lead to the development of such controllable

risk factors as dyslipidemia (increased levels of LDL and triglycerides), diabetes and arterial hypertension and, accordingly, contribute to the development of atherosclerosis.[12] In our study, several variants of dietary habits were encountered in the cohort of patients. No diet - patients adhered to the dietary style typical for the region of residence, taking into account the peculiarities of the national cuisine, this type of diet was characterized by the consumption of large amounts of meat, flour products, high fat and preservatives.

The proportion of patients without a diet was 88.1% in the control group, 87.4% in the high-risk group, and 72.4% in high-risk patients, with a positive trend (CATT p = 0.0031). A total of 323 people in the study population did not follow any diet, that is, they had a traditional diet for the country. In the remaining patients, dietary compliance was due to the presence of comorbid pathology: a low-fat diet was observed in 22 people (5.5%), carbohydrate restriction was observed in 37 (9.3%) of the study subjects, and 13 people (3.2%) limited the consumption of both fats and carbohydrates. Pairwise comparisons show a higher probability of no diet in the VHR compared to the LR (OR = 2.81, p = 0.0208) and HR (OR = 2.64, p = 0.0050), which may indicate reverse causality, where high-risk patients are less likely to follow a diet. Significant differences were also found in adherence to a low-carbohydrate diet (x^2 p < 0.0001, Cramér's V = 0.268, moderate association). The proportion of patients on a low-carbohydrate diet in the control group was 1.5, in the high-risk group 2.4%, and significantly increased in the very high-risk group to 17.8%, a positive trend (CATT p < 0.0001). Pairwise comparisons confirm a lower probability of a diet in LR (OR = 0.07, p = 0.0005) and HR (OR = 0.11, p < 0.0001) compared to HR, which correlates with a higher prevalence of carbohydrate metabolism disorders (diabetes mellitus, insulin resistance) in patients with a very high risk of developing ASCVD.

Physical activity level the following gradation was used to assess the level of physical activity in our study: hypodynamia - no physical activity, moderate activity - walking or less than 150 minutes per week of low-intensity activity, active lifestyle - regular exercise (>150 minutes per week of moderate/high-intensity physical activity), professional athletes. Correlation analysis revealed only a weak negative correlation (r_pb = -0.203, p = 0.0011), i.e. a more active lifestyle (lifestyle_2) is associated with a lower risk of CVD. To be able to analyze the trend of activity by risk groups, the level of physical activity (lifestyle) was analyzed as a quantitative variable, since it has an ordinal structure. This type of analysis revealed significant differences (H = 21.44, p < 0.0001, n^2 = 0.053, small effect). Pairwise comparisons revealed differences between LR and HR (p = 0.0001, r = 0.249), LR and VHR (p = 0.0022, r = 0.155) and HR and VHR (p = 0.0166, r = 0.107), indicating a protective effect of an active lifestyle.

Place of residence (urban/rural) we analyzed the relationship between the risk of developing atherosclerosis-associated CVD and living in an urban or rural area. Comparative pairwise analysis demonstrated the presence of significant differences (x^2 p = 0.0359, Cramér's V = 0.149, weak relationship). The proportion of rural residents progressively increases from 10.4% among patients in the control group to 13.4% and 23.6% in the high-risk and very high-risk groups, respectively. The trend is assessed as positive (CATT p = 0.0140). Pairwise comparisons show a lower probability of rural residence in the control group compared to patients with very high risk (OR = 0.38, p = 0.0825) and in HR compared to VHR (OR = 0.50, p = 0.0825), although the significance is at the border of statistical reliability. The identified trend indicates a higher risk of developing ASCVD among the rural population, which may be due to several factors: cultural characteristics - lack of interest in their own health, eating habits, as well as the inaccessibility of highly specialized medical care in remote regions. Urban-rural disparities in cardiovascular risk factors align with global trends.

The results are consistent with WHO reports where rural populations in Eastern Europe/Central Asia face 23% greater CVD mortality due to healthcare access gaps. Conversely, urban populations globally exhibit higher rates of obesity (+19%) and physical inactivity (+15%), though our cohort showed stronger rural risks—likely reflecting Kazakhstan's unique challenges, such as limited rural screening programs and traditional diets high in processed meats.

The final step of the analysis aimed at identifying the most significant risk factors for the development of atherosclerosis-associated cardiovascular diseases for this cohort was the implementation of multiclass logistic regression (Multinomial Logistic Regression).

The results of the MNLogit analysis to estimate factors associated with the EAS cardiovascular disease (CVD) risk are presented in the accompanying table. The model estimates the probability of high risk (HR) and very high risk (VHR) compared with low risk (LR), with adjusted odds ratios (OR), 95% confidence intervals (CI), and p-values. Some variables are used to internally classify patients into EAS risk levels, which may influence the estimate of their effect.

Age significantly increased the odds of developing ASCVD by 4.14 times (95% CI: 2.38–7.19, p < 0.0001) in the high-risk group and by 8.01 times (95% CI: 4.40–14.58, p < 0.0001) in the very high-risk group.

The presence of a burdened family history of CVD increases the likelihood of developing atherosclerosis and related cardiovascular pathology by 3.33 times (95% CI: 1.41–7.84, p = 0.0059). This factor may indicate an important role of polygenic heredity, as well as indicate an environmental predisposition due to the preservation of dietary patterns and lifestyle characteristics within the framework of family traditions.

In the high and very high risk groups, the likelihood of developing atherosclerosis was higher in men than in women (OR = 0.18, 95% CI: 0.06–0.56, p = 0.0031), which may be associated with hormonal differences or with gender-related lifestyle characteristics (less tendency to smoke, drink alcohol, more attention to one's own health, other eating habits).

According to the results of multiclass logistic regression, smoking demonstrated its significance in the development of ASCVD; in the HR group, it increased the likelihood of atherosclerotic processes by 5.45 times (95% CI: 1.19–24.99, p = 0.0291), and in the VHR group by 7.19 times (95% CI: 1.52–34.15, p = 0.0130) compared with the general population.

Moderate physical activity reduces the risk of atherosclerosis-associated diseases by 4.3 times (OR = 0.23, 95% CI: 0.07–0.81, p = 0.0223), and an active lifestyle or sports - by 33.3 times (OR = 0.03, 95% CI: 0.004–0.32, p = 0.0029), which indicates the protective effect of physical activity.

Low-fat diet was associated with an 8.03-fold increased risk of VHR (95% CI: 1.26–51.09, p = 0.0273), which may reflect reverse causality, with patients with known high risk being more likely to adhere to the prescribed diet, and requires further study.

Discussion

Analyzing the obtained data, we can conclude that in the Kazakhstani population, using the example of the study cohort, age is one of the main risk factors for the development of atherosclerosis-associated CVD. Older age increases the risk of developing ASCVD by 4.14 times (95% CI: 2.38–7.19, p < 0.0001) in the high-risk group, and in the very high-risk group, the OR for age reaches 8.01 (95% CI: 4.40–14.58, p < 0.0001). These data are consistent with the results of a meta-analysis published in 2022 on ethnic differences in the relationship between risk factors and manifestations of atherosclerosis.[13] In particular, the authors found that age is the most important driver of the atherosclerotic process in the African, African American, European and Hispanic groups. The leading role of age in the development of atherosclerosis was previously identified by the results of the Framingham study.[14] The persistent association of age with the risk of developing ASCVD in almost

all ethnic groups emphasizes the role of screening studies and the need to manage other risk factors in patients of older age groups.

Gender analysis in our study demonstrated that men have a higher risk of developing atherosclerotic processes than women, which is possible both due to the protective effect of estrogen at a younger age and differences in behavioral patterns. The hormonal protective mechanism is also supported by the maximum number of patients with early menopause (28.8%) recorded in the very high risk group. According to the meta-analysis conducted by *Engelbert A. Nonterah et al.*, manifestations of atherosclerosis (thickening of the intima-media complex in the carotid artery) developed more often and were more pronounced in men than in women in all ethnic groups except Africans, where these indicators were approximately at the same level.[4] Given the presence of pronounced ethnic differences in the gender aspect according to international studies, it is necessary to study it more deeply in the population of the Republic of Kazakhstan, especially in the context of age-related dynamics of hormonal levels in women.

One of the most important risk factors for the development of atherosclerotic processes is smoking. This fact has been confirmed in several studies and in most ethnic groups. According to the results of our study, the proportion of smokers progressively increased from the control group to the subpopulation with very high risk of CVD from 4% to 25%, respectively. At the same time, smoking in the VHR group increased the risk of developing ASCVD by 7.19 times (95% CI: 1.52–34.15, p = 0.0130). In Kazakhstan, according to WHO and the Bureau of National Statistics, it has been at the level of 21% for several years, but there is an increase in the number of smoking respondents in the young age group. In addition, in recent years a new cohort has been formed - "consumers of smokeless tobacco and heated tobacco products", the number of which is steadily growing, currently a total of 2.4%.[15] The impact of this form of smoking on atherosclerotic processes has not been studied and requires in-depth research.

The relationship between alcohol consumption and the risk of developing atherosclerosis-associated cardiovascular diseases remains debatable. In our study, in all groups, the proportion of patients consuming alcohol in minimal/safe amounts was 53-58% without statistically significant differences between the groups. According to the Ministry of Health of the Republic of Kazakhstan, the majority of the population consumes alcohol in moderate amounts or does not consume it at all - 98.3%. Alcohol consumption in dangerous doses was recorded among men in 2.7%, among women in 0.7%**.** According to the National Center for Public Health, the number of adolescents with experience of alcohol consumption is growing in the country,[16] which does not allow us to completely ignore this risk factor. In the cohort of patients in our study, no association was found between the risk of ASCVD and alcohol consumption. At the same time, the world literature provides data on the multidirectional relationship between these indicators. In the African population, alcohol consumption was associated with a reduced risk of developing ASCVD, in men there was an improvement in the lipid profile and a decrease in the level of atherosclerosis-associated inflammatory markers.[17]

Regular physical activity reduces the severity of some risk factors, in particular arterial hypertension, lipid profile imbalance, glucose level, cardiac function. However, studies on the relationship between physical activity and the risk of developing ASCVD have given conflicting results.Some researchers have found no relationship[18] or even a positive relationship.[4] According to the results of the analysis using the multiclass logistic regression method, one can speak about the protective role of physical activity. In particular, in patients with moderate physical activity, the risk of atherosclerosis-associated diseases decreased by 4.3 times (OR = 0.23, 95% CI: 0.07–0.81, p = 0.0223), and an active

lifestyle or sports led to an even more pronounced reduction in risk - by 33.3 times (OR = 0.03, 95% CI: 0.004–0.32, p = 0.0029).

According to the binary comparative analysis, the proportion of patients living in rural areas increased progressively from the control group to the CVD risk group. In world practice, a national study conducted in Poland revealed a difference in the prevalence of risk factors depending on whether they lived in a city or a rural area.[19] Among the urban population of Poland, risk factors such as high fasting glucose and total cholesterol levels, and arterial hypertension were prevalent. Among the rural population, high BMI and a high TC/HDL ratio were more common. The higher risk of developing atherosclerotic processes in the rural population revealed in our study may be due to several factors - mental characteristics and lifestyle features (low attention to one's own health, dietary habits, high smoking habits. In addition, low availability of highly specialized care in rural areas may have a major impact. This issue requires in-depth large-scale country studies in order to subsequently create an optimal screening program and prevention of atherosclerotic diseases.

Limitations. The study has several limitations, including its cross-sectional design, which prevents establishing causality. The sample was limited to Kazakhstani adults, potentially reducing generalizability to other populations. Additionally, self-reported lifestyle factors like diet and physical activity may introduce recall bias.

What's Known? Previous research has identified age, smoking, and dyslipidemia as key risk factors for atherosclerosis globally, with regional variations in risk factor prevalence. Studies in Kazakhstan highlighted high rates of hypertension and metabolic disorders but lacked stratification by cardiovascular risk levels.

What's New? This study provides the first ethnonational analysis of atherosclerosis risk factors in Kazakhstan, revealing rural residence as a significant risk factor and emphasizing the protective role of physical activity. It also highlights gender differences and the impact of early menopause, offering insights for targeted preventive strategies.

Conclusion

Age, smoking and family history of CVD are the main risk factors for the development of ASCVD in the study cohort. Women demonstrate a lower risk of developing atherosclerotic processes compared to men, while the group of patients with early menopause had the highest percentage of women with early menopause. A thorough study of the gender aspect of the development of atherosclerotic pathology is required. Physical activity has a strong protective effect. It is interesting that, according to the comparative analysis of binary variables, rural residents have a higher risk of developing atherosclerosis. This result also requires a detailed and large-scale study, with the definition of the most significant risk factors among the urban and rural population, as well as the influence of the region of residence on the development of ASCVD. The data obtained in this study, as well as the results of future studies, will optimize country preventive strategies for managing risk factors and preventing the growth of ASCVD among the population of the Republic of Kazakhstan.

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PERIODONTITIS AS A POSSIBLE CAUSE OF CHRONIC HEART FAILURE

Dana Yessimgalikyzy, Baurzhan R. Aipov, Nurlan R. Kassiyet, Aldanysh Zhumazhan, Ainur T. Taukelova, Saltanat K. Jetybayeva, Islambek Laiskanov, Aliya Sailybayeva, Makhabbat S. Bekbosynova, Almagul R. Kushugulova

"University Medical Center" Corporate Fund, Astana, Republic of Kazakhstan

DOI: 10.35805/BSK2025III008
Aipov B.
https://orcid.org/0000-0003-2124-0065
Nurlan K.
https://orcid.org/0000-0007-7389-2811
Aldanysh Z.
https://orcid.org/0009-0000-9451-3867
Taukelova A.
https://orcid.org/0000-0002-4237-9835
Jetybayeva S.
https://orcid.org/0000-0003-3442-3223
Laiskanov I
https://orcid.org/0009-0001-6406-3209
Sailybayeva A.
https://orcid.org/0000-0002-1489-3837
Bekbosynova M.
https://orcid.org/0000-0003-2834-617X
Kushugulova A.
https://orcid.org/0000-0001-9479-0899

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Correspondent-author:
Yessimgalikyzy Dana – dentist ,
KF " University Medical Center ",
Astana, Kazakhstan
Postal address: Turan 38, 010000,
Astana, Republic of Kazakhstan
E-mail: yessimgalikyzydana@gmail.com
Phone :+7 708 009 99 09

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Abstract

Background. The objective of this study was to investigate the prevalence of periodontitis in patients with chronic heart failure, as well as to characterize the microbiological profile of periodontitis across different chronic heart failure phenotypes. The objective is to analyze the link between oral health and heart disease.

Materials and Methods. A cohort of 98 chronic heart failure patients (mean age 62.22 ± 8.62 years, 69 men) was assessed through comprehensive cardiological and periodontal examinations. Patients were categorized into heart failure with reduced ejection fraction, mildly reduced ejection fraction, and preserved ejection fraction. Periodontal parameters, including probing pocket depth, clinical attachment loss, and bleeding on probing were evaluated. Microbiological and statistical analyses were conducted.

Results. Severe periodontitis (Stage C) was identified in 30% of patients, while 48% had moderate periodontitis (Stage B). Patients with chronic heart failure with reduced ejection fraction exhibited the highest prevalence of severe periodontitis, with a significant correlation between increased probing pocket depth and reduced ejection fraction. Candida species abundance was associated with lower ejection fraction (p≤0.0Y) and advanced periodontitis (p≤0.0X). Elevated NT-proBNP levels (1121.00–7611.00 pg/mL) correlated with Streptococcus mitis prevalence, while C-reactive protein levels (up to 2.35 mg/dL) were highest in patients with Klebsiella pneumoniae.

Conclusion. The study highlights a strong association between periodontal disease, microbial dysbiosis, and CHF. Findings suggest that oral microbial imbalances, particularly involving Candida, Streptococcus mitis, and Klebsiella pneumoniae, contribute to systemic inflammation and cardiovascular complications.

Introduction

Chronic Heart Failure (CHF) is becoming a disease that is more common today.[1] As we look for surgical and preventive methods, this study analyzes the link between oral health and heart disease. Additional trials are needed to clarify further the causal relationship between the CHF and its cause. CHF is an inflammatory condition caused by bacteria in plaque, leading to the destruction of gum tissues and the bone of your jaws, and, if left untreated, can result in tooth loss.[2] Beyond the oral cavity, the inflammatory component of gum disease has been associated with an increased risk of heart disease.[2,3,4] Also we can assuredly say that periodontists can affect a human's immune system by weakening the inflammatory response of the body to trigger various inflammatory diseases such as heart diseases, diabetes, swelling in arteries and kidney failure.[5,6]

Significant associations between oral health status and a number of systemic diseases have been established, including, but not limited to, cardiovascular diseases, Alzheimer's disease and dementia, obesity, diabetes and metabolic disorders, rheumatoid arthritis, and several cancers.[7,8,9]

In order to understand the true cause of systemic diseases better we can also consider microbiological background. By studying bacteria and its morphology and pathogenicity we can understand how viruses, fungi and bacteria have an enormous impact on human body immune response and the role of microbiology in pathophysiology.

Material and methods

A cohort of 98 patients with chronic heart failure was examined, comprising 69 men, with a mean age of 62.22 ± 8.62 years. All participants underwent comprehensive cardiological evaluations. Patients with CHF were stratified into three groups according to their phenotype: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF).

All included patients underwent a complete periodontal and dental examination. The oral assessment encompassed periodontal parameters, including probing pocket depth (PPD), clinical attachment loss (CAL), bleeding on probing (BOP), percentage of current bone loss, and diagnosis (stage). The periodontal screening index was employed to quantify the severity of periodontal disease. Attachment loss was calculated using probing depths and gingival recession measurements.

For microbiological assessment, microorganisms were initially cultured on nutrient media Endo agar, salt egg yolk agar, blood agar 5%, Sabouraud Agar and subsequently identified using the MALDI-TOF MS method.

Ethical approval. This study is based on de-identified and anonymous, aggregated healthcare data and does not involve direct patient interactions or their personal information. Ethical approval (2023/01-009) was obtained from institutional review board and all the analyses were conducted in compliance with national data protection regulations.

Statistical analysis. The statistical analysis included descriptive and analytical statistics where for variables with a normal distribution, parametric statistical methods were used and presented as means ± standard deviation. Numerical variables of non-normally distributed data were presented as mean values ± standard deviation. For all types of analysis, statistical significance was determined using the Student's t-test, with a significance level set at $p < 0.05$. Statistical analysis was performed using Python v3.9.16 and R v4.2.2. The Mann-Whitney U test and logistic regression were employed, accounting for age, sex, and various oral health parameters in relation to overall survival and cardiac events/transmissions. Data visualization was conducted with Matplotlib and Seaborn libraries.

Results

In this cohort study, severe periodontitis (Stage C) was observed in 59 (30%) patients, while moderate periodontitis (Stage B) was present in 94 (48%) patients. A higher prevalence of severe periodontitis was noted among patients with chronic heart failure with reduced ejection fraction (HFrEF). The investigation revealed a direct correlation between the greatest probing pocket depth (PPD) and both heart failure with mildly reduced ejection fraction (HFmrEF) and reduced ejection fraction (HFrEF), as depicted in Figure 1-6.

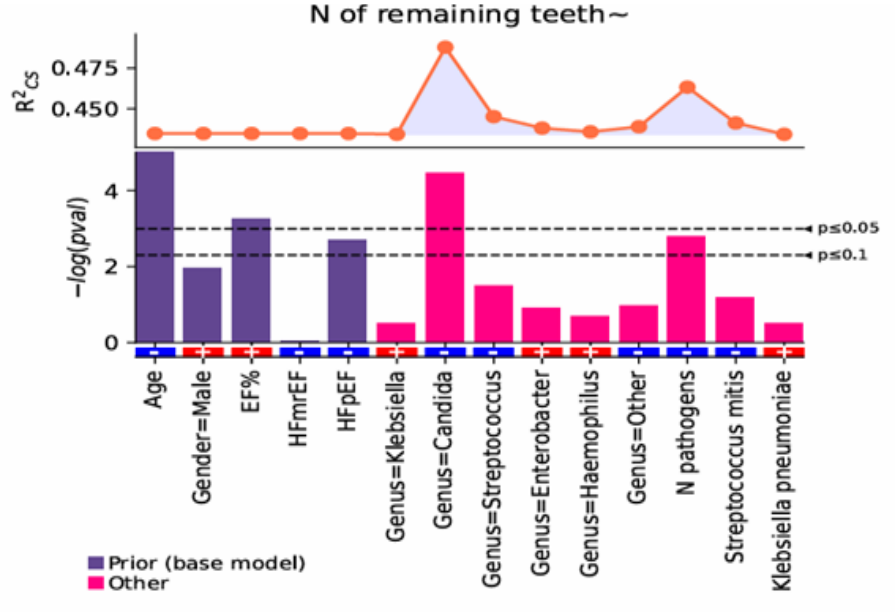

Figure 1. Number of Remaining Teeth and Pathogen Load. Inverse correlation between teeth count and pathogen abundance (Streptococcus mitis, Klebsiella pneumoniae), with adjustments for EF% and HF phenotypes ($p < 0.05$).

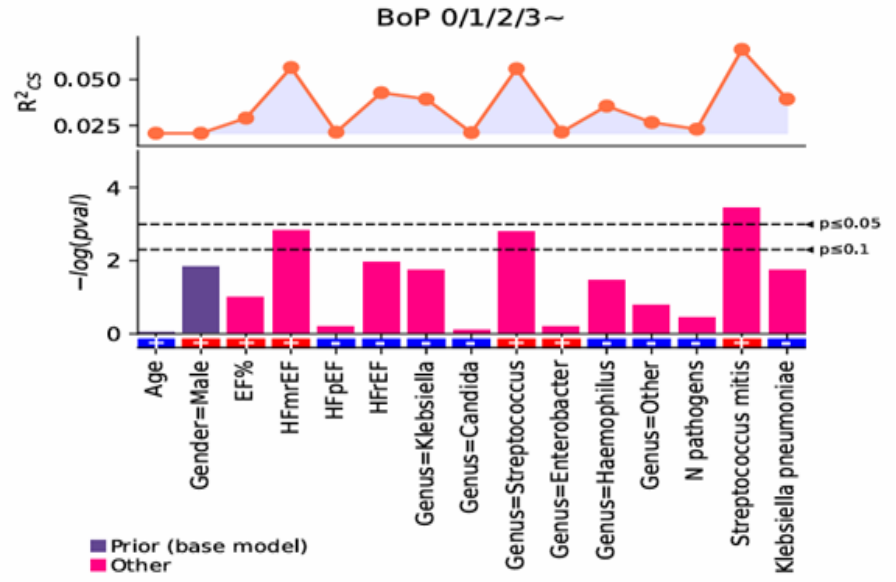

Figure 2. Bleeding on Probing (BoP) Scores and Microbial Factors. BoP scores (0–3) linked to specific genera (Candida, Streptococcus) and HF phenotypes. Significant associations ($p < 0.05$) highlighted.

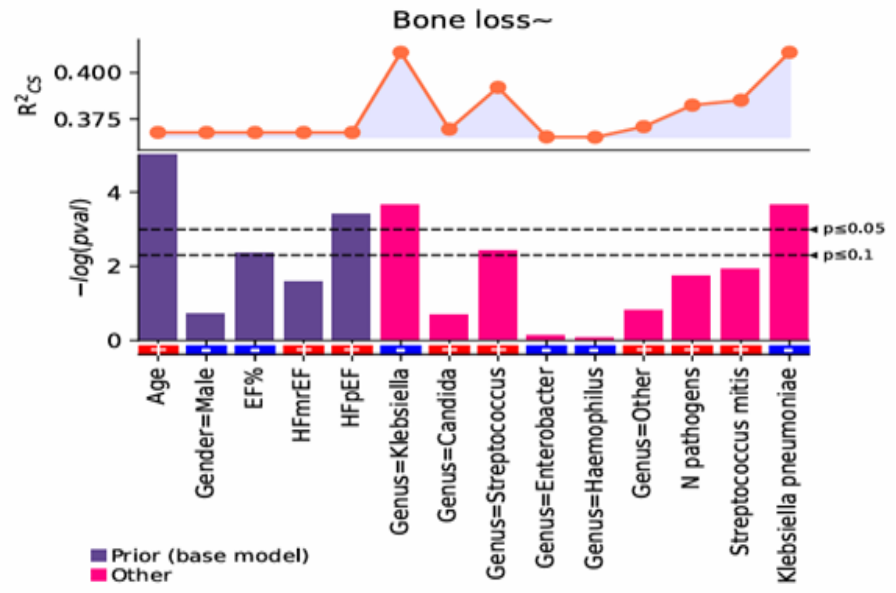

Figure 3. Alveolar Bone Loss and Cardiac-Microbial Interactions. Bone loss severity associated with Klebsiella and Streptococcus prevalence, stratified by HFmrEF/HFpEF. Polarization reflects effect size (log[p-value]).

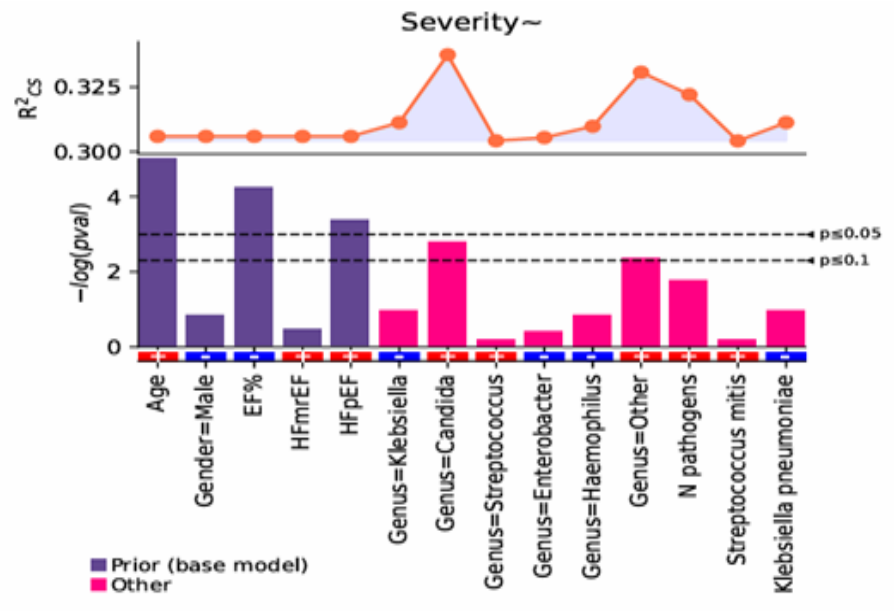

Figure 4. Periodontal Severity and Microbial Dysbiosis. Relationship between periodontal severity (R^2 = 0.325–0.300) and microbial genera (Klebsiella, Candida), adjusted for age, sex, and HF phenotypes.

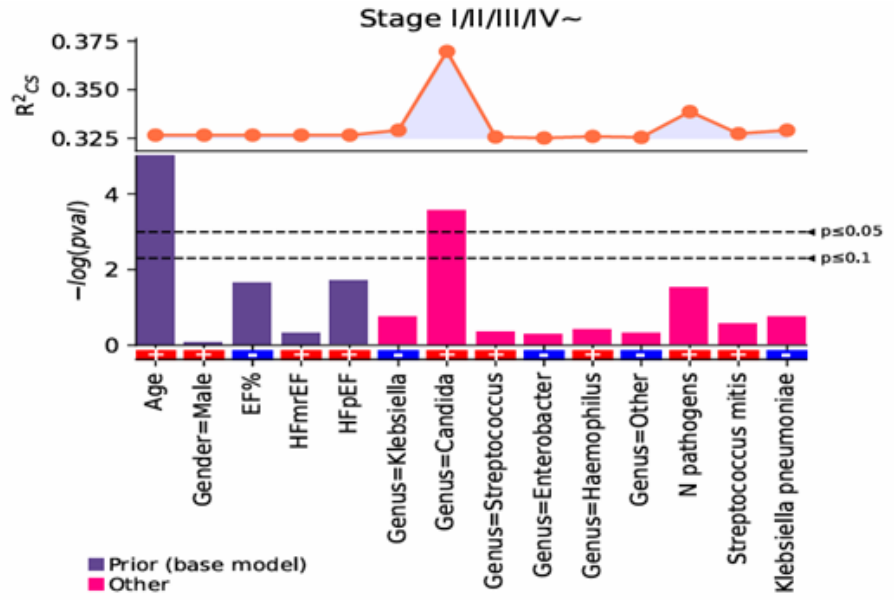

Figure 5. Periodontitis Stage (I–IV) and Systemic Predictors. Regression analysis of periodontitis stages (I–IV) against clinical variables (age, EF%, HF phenotypes) and microbial genera. Positive/Negative coefficients reflect directional associations (p ⩽ 0.1).

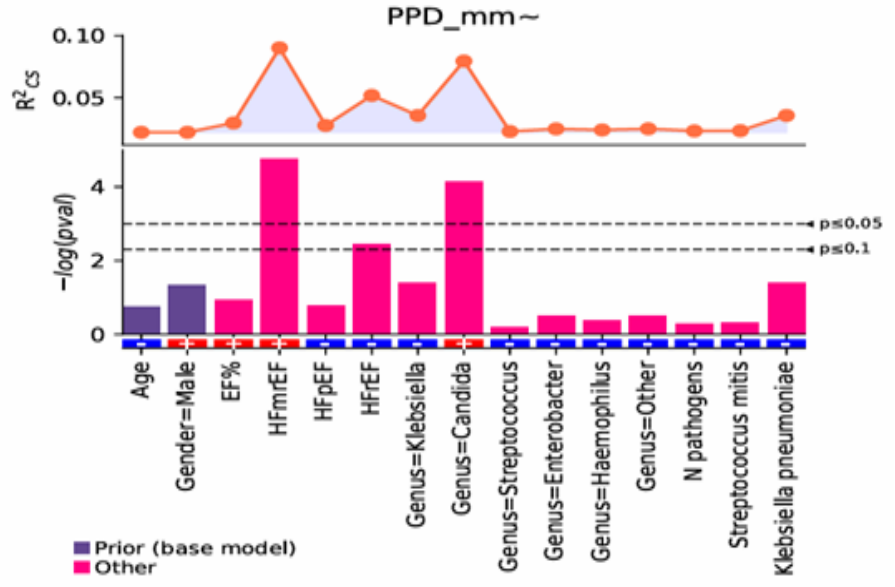

Figure 6. Probing Pocket Depth (PPD) by CHF Phenotype and Microbial Genera. Association between mean PPD (mm) and heart failure phenotypes (HFrEF, HFmrEF, HFpEF), stratified by dominant oral microbial genera (Klebsiella, Candida, Streptococcus). Dashed line indicates significance (p < 0.05).

Moreover, patients exhibiting a higher abundance of Candida species in their oral microbiome demonstrated significantly lower ejection fraction (EF) (p≤0.0Y), more advanced stages of periodontitis (p≤0.0X), and a reduced number of remaining teeth. It is postulated that Candida may exert direct influence on multiple factors potentially exacerbating heart failure progression. A significant association was observed between increased alveolar bone loss and extra-cardiac bacterial infections (p<0.05).

Elevated NT-proBNP levels, ranging from 1121.00 to 7611.00 pg/mL, were detected in patients with a predominance of Streptococcus mitis in their oral microbiota. C-reactive protein levels ranged from 1.32 mg/dL to 1.51 mg/dL, with the highest level of 2.35 mg/dL associated with the presence of Klebsiella pneumoniae in the microbiota [4]. Notably, Klebsiella species, particularly Klebsiella pneumoniae, exhibited the highest prevalence among the microbial factors examined. The most significant PPD was associated with HFmrEF (p<0.08).

As illustrated in Figures A, E, and F, a strong correlation was observed between Candida species and periodontal parameters, including the number of remaining teeth, probing pocket depth (PPD) (p<0.05), and the stage of periodontitis. These findings suggest a complex interplay between oral microbial ecology, periodontal health, and cardiac function in patients with chronic heart failure.

Discussion

This study investigated the association between periodontal status, systemic inflammation, and their impact on heart diseases. Our findings reveal a significant correlation between baseline periodontal status and microbial dysbiosis, particularly influenced by Candida species, Streptococcus mitis, and Klebsiella pneumoniae.[7-9]

We observed that severe periodontitis was more prevalent among patients with heart failure with reduced ejection fraction (HFrEF), with a direct correlation between the greatest probing pocket depth (PPD) and HFrEF. The most significant PPD was associated with heart failure with mildly reduced ejection fraction (HFmrEF).

Microbiological analysis revealed that a higher presence of Candida species was associated with significantly lower ejection fraction (EF), more advanced periodontitis stages, and fewer remaining teeth. Streptococcus mitis predominance correlated with elevated NT-proBNP levels, while Klebsiella pneumoniae presence was linked to the highest levels of C-reactive protein.

Our results align with previous research suggesting that improved oral hygiene may contribute to a reduction in heart failure incidence. *Youn Huh et al.* reported that daily tooth brushing is associated with decreased heart failure rates.[2] *Rebecca L. Molinsky et al.* noted that heart failure remains a significant health concern for over a decade and is directly related to periodontal status. U.S. national data samples further support the association between heart failure and periodontitis.[3]

Notably, *Syed Adeel Hassan et al.* reported that Klebsiella pneumoniae, accounting for 5% of cases, is responsible for mortality in aortic and mitral valve conditions in nearly all instances.[7]

While our study did not explicitly examine differences in microbiological characteristics for heart failure with preserved ejection fraction (HFpEF), the findings suggest variations across different heart failure phenotypes. These results underscore the complex relationship between oral health, microbial ecology, and cardiovascular outcomes, highlighting the potential importance of periodontal care in managing heart failure risk.

Data indicate that in patients with CHF, 48% of patients with chronic heart failure have moderate periodontitis and 30% have severe periodontitis. This is generally consistent with the published literature. For example, *Schulze-Späte et al.* found that 69% of patients with heart failure had moderate to severe periodontitis.[10] However, exact percent-

ages may vary between studies due to differences in classification criteria and patient populations.

The mention of Candida, Streptococcus mitis and Klebsiella pneumoniae contributing to systemic inflammation is consistent with current research. Review by *Liccardo et al.* discusses how oral pathogens may contribute to systemic inflammation and cardiovascular disease.[11] However, the specific bacteria mentioned may vary between studies because the oral microbiome is complex and diverse.

CRP is a widely accepted marker of systemic inflammation. Numerous studies have shown a positive correlation between periodontal disease and elevated CRP levels. Meta-analysis by *Shailly Luthra et al.* found that patients with periodontitis had significantly higher levels of CRP compared to controls.[12] *Gomez-Filho et al* reported that severe periodontitis was associated with higher CRP levels, even after adjusting for other cardiovascular risk factors.[13] Some studies have looked at multiple inflammatory markers simultaneously. *Madeline X F Kosho et al.* found that patients with generalized periodontitis had significantly higher levels of CRP, IL-6, and neutrophils compared with controls.[14] A study by *Neeraj Gugnani et al.* showed that intensive periodontal treatment resulted in improved endothelial function and decreased levels of several inflammatory markers, including CRP and IL-6.[15]

It is important to note that although these associations are consistently observed, the relationships are complex and likely bidirectional. Periodontal disease can contribute to systemic inflammation, but systemic inflammation can also affect periodontal health. Moreover, the precise mechanisms linking periodontal disease to elevated inflammatory markers are still being elucidated. We propose several pathways: translocation of oral bacteria into the bloodstream; systemic distribution of inflammatory mediators from periodontal tissues; and immune response to periodontal pathogens affecting distant sites.

Although the association between periodontal disease and inflammatory markers is well established, more research is needed to fully understand the cause-and-effect relationships and potential implications for cardiovascular health.

Limitations. The study examined 98 patients, which may limit the generalizability of the findings to larger populations. The study doesn't mention a control group of individuals without heart failure, which could have provided a baseline for comparison. While the study accounted for age and sex, there might be other unmeasured confounding factors influencing the relationship between periodontal disease and heart failure. Without follow-up data, the study cannot assess how changes in periodontal status might affect heart failure progression over time.

What's known? Periodontitis has been linked to various systemic diseases, including cardiovascular conditions such as CHF. Studies suggest that bacterial infections in the oral cavity can contribute to systemic inflammation, which may lead to heart disease. Research has identified inflammatory markers, such as CRP, as being elevated in patients with both periodontitis and cardiovascular disease. Additionally, previous studies indicate that poor oral hygiene and microbial dysbiosis play a role in increasing the risk of CHF by weakening the immune system and promoting inflammatory responses that contribute to endothelial dysfunction and cardiac stress.

What's new? This study highlights a direct association between periodontitis severity and CHF phenotypes, demonstrating that severe periodontitis is more prevalent among patients with heart failure with HFrEF. A significant correlation was found between advanced periodontal disease markers, such as PPD, and lower ejection fraction levels. The findings also introduce the role of specific microbial species, including *Candida*, *Streptococcus mitis*, and *Klebsiella pneumoniae*, in exacerbating CHF progression. The study suggests

that microbial dysbiosis in the oral cavity may contribute to systemic inflammation and CHF-related complications, emphasizing the need for periodontal care in CHF management.

Conclusion

This study reveals a significant association between periodontal disease, microbial dysbiosis, and chronic heart failure. The complex interplay between oral health and cardiac function underscores the potential importance of periodontal care in managing heart failure risk. Further research is warranted to elucidate causal relationships and develop targeted interventions.

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SIX-MINUTE WALK TEST AS A TOOL FOR ASSESSING PHYSICAL ACTIVITY IN PATIENTS WITH HEART FAILURE

Makhabbat S. Bekbossynova[1], Almagul R. Kushugulova[2], Saltanat K. Jetybayeva[1], Ainur T. Tauekelova[1], Zhadyra S. Duisenbina[1], Aida, Zholdybaeva[1]

1 -"University Medical Center" Corporate Fund, Astana, Kazakhstan
2 -Center for Life Sciences of the C.U. National Laboratory Astana, Kazakhstan

DOI: 10.35805/BSK2025III009
Bekbossynova M.
https://orcid.org/0000-0003-2834-617X
Kushugulova A.
https://orcid.org/0000-0001-9479-0899
Jetybayeva S.
https://orcid.org/0000-0003-3442-3223
Tauekelova A.
https://orcid.org/0000-0002-4237-9835
Duisenbina Z.
https://orcid.org/0009-0006-1801-009X
Zholdybaeva A.
https://orcid/org/0009-0007-0255-599X

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Corresponding author:
Aida Zholdybaeva , Nursing Specialist, Corporate Foundation "University Medical Center", Astana, Kazakhstan
Mail: nnkc.pl@mail.ru
Phone: +7 771 604 27 27

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Keywords:
heart failure, six-minute walk test (6MWT), physical activity, cardiac rehabilitation, functional status, quality of life.

Abstract

Background. Heart failure is one of the most significant medical problems of our time, which is associated with the increase in the prevalence of the disease over the past decade. The six-minute walk test is a simple, accessible, and informative tool for assessing the physical activity of patients with heart failure. The test results correlate with peak oxygen consumption and can be used to monitor the effectiveness of rehabilitation programs. The aim of the study is to evaluate the effectiveness of the six-minute walk test as a tool for measuring the level of physical activity and functional status in patients with heart failure, and to determine its correlation with clinical indicators and quality of life in this category of patients.

Materials and methods. In this study, conducted on the basis of the UMC "Heart Center" Astana, Kazakhstan, private institution "National Laboratory Astana ", data of patients with heart failure of class I-IV according to a special classification were analyzed. The main objective of the study was to evaluate the effectiveness of the test as a tool for monitoring physical activity and functional status of patients.

Results. The results showed that the test is a reliable method for assessing the dynamics of physical capabilities and can be used to individualize rehabilitation programs.

Conclusion. The 6MWT remains an important component of clinical practice, helping to optimize functional outcomes and improve the quality of life of patients with heart failure.

Introduction

Heart failure (HF) is recognized as one of the most pressing medical problems worldwide, which is explained by a significant increase in the number of cases of the disease over the past decade.[1] HF symptoms such as shortness of breath (dyspnea), chronic fatigue and edema negatively affect health-related quality of life (HRQOL), impair physical activity and limit the ability of patients to cope with physical activity.[2] In this regard, cardiac rehabilitation programs play a vital role in the recovery of patients and their adaptation to everyday life.

The growing number of elderly people in the population is directly related to the increasing incidence of chronic diseases that can significantly reduce the functional capacity of the body. In this regard, medical professionals increasingly use functional tests to objectively assess the physical performance of patients. The results of such tests allow us to assess the general health and level of mobility. Particular importance is given to the study of spatiotemporal gait parameters, including walking speed, distance, length and frequency of steps. These indicators are critical for predict-

ing the risk of falls, assessing motor activity in the elderly, and monitoring the dynamics of patients who have suffered a stroke or suffer from Parkinson's disease. Thus, the analysis of motor activity is becoming an integral part of the clinical assessment of the patient's functional capacity.[3]

The 6MWT was officially recognized by the American Thoracic Society (ATS) in 2002 as a reliable method for assessing motor function and fatigue levels, which directly affect a patient's functional mobility. The main test parameter is the distance the patient covers in six minutes, which allows for an objective assessment of the dynamics of his or her physical capabilities. During the test, the patient moves at a comfortable pace, taking breaks for rest if necessary.[4]

The length of the corridor used for testing plays an important role in ensuring the accuracy of the results. In a confined space (less than 33 meters), frequent turns may reduce walking speed, resulting in a decrease in the total distance covered and, as a result, underestimation of the results. This may hinder the correct clinical interpretation of the data in accordance with the ATS recommendations. The results of the 6MWT serve as an important indicator of functional activity, since most daily tasks are performed at submaximal levels of exertion. Therefore, compliance with standardized test conditions is necessary to obtain reliable and clinically meaningful results.[5].

One of the key parameters of 6MWT is the distance traveled by the patient in six minutes (6MWD). This indicator has high clinical and research significance, since it is closely related to peak oxygen consumption, which makes it an important tool for assessing the functional state. Interpretation of the test results can be done in two ways: either by comparing the actual distance with the predicted value calculated on the basis of reference equations, or by analyzing the absolute value of the distance traveled.[6,7]

Comparison of actual and predicted 6MWD provides valuable information for assessing the patient's physical performance helps to determine the optimal level of physical activity and is used to monitor the effectiveness of rehabilitation programs. In addition, the test allows assessing the patient's readiness to return to daily life and social activity.[8]

In healthy individuals, the normal distance covered in six minutes is usually between 400 and 700 meters. If the patient covers less than 350 meters, this may indicate significant functional impairment and is associated with an increased risk of mortality. Therefore, 6MWT serves as an important tool for assessing the patient's condition and planning further medical interventions.[8]

In clinical practice, the 6MWT is widely used due to its simplicity and availability. However, despite clear recommendations from the American Thoracic Society (ATS), the standard test protocol is often subject to modifications, especially in resource-limited settings.[8,9]

6MWT has found wide application in cardiac rehabilitation, especially in patients who have undergone heart surgery, myocardial infarction or suffer from chronic heart failure. In addition, the test is an important indicator of the functional state in these pathologies.[9]

The 6MWT is widely used in clinical practice as an effective method for assessing patients' physical capabilities. Its popularity is due to its ease of implementation, availability, and high reliability of results. In the perioperative period, this test is used to predict possible complications after surgical interventions and also serves as an important tool for preliminary assessment of functional risks. In addition, the 6MWT helps to assess the effectiveness of preventive measures, such as prehabilitation. It also plays a key role in the early detection of patients with limited physical activity who may experience difficulties in the recovery process and helps to determine the optimal place for further observation after discharge from a medical institution.[10]

Cardiopulmonary exercise testing (CPET) is recognized as the gold standard for objectively assessing a patient's

maximal functional capacity. However, despite its high accuracy, CPET requires significant resources, including specialized equipment and qualified personnel, which limits its availability in a number of clinical situations. In contrast to CPET, 6MWT is widely used in clinical practice due to its simplicity, availability, and minimal resource requirements. This test is universal for various patient groups, does not require complex equipment or special skills, and better reflects everyday physical activity.[11]

Despite the relative standardization of the 6MWT, in real practice, modifications to the ATS-approved protocol are often made. Such adaptations may include changing the length and configuration of the track, introducing a training run, modifying the instructions or the level of reinforcement for participants. These changes may significantly affect the 6MWD, for example by reducing the walking speed, changing the step strategy, or increasing the number of turns.[12]

Materials and methods

Study design

This study is a cross-sectional analysis of data collected from a randomized feasibility study conducted at the KF UMC "Heart Center" Astana, RK, Data were collected from October 2023 to the present by the same investigator.

Study population and sample

Total number of participants: 471 participants in the CHF group and 100 participants in the control group.

The study included adult patients (≥ 18 years) receiving treatment at the UMC Heart Center with a diagnosis of heart failure (HF) of NYHA class I–IV. Inclusion criteria

- Ability to move independently (using assistive devices such as a cane or walker if needed).
- Stable condition without contraindications to physical activity.

Exclusion criteria:

- The presence of acute conditions that prevent the test from being performed (eg, acute myocardial infarction, unstable angina).
- Pregnancy.
- Wheel chair bound.
- Six-minute Walk test (6MWT) protocol
- The test was performed according to the American Thoracic Society (ATS) guidelines and taking into account available resources.

Stages of implementation:

Preparation:

- Participants rested for at least 10 minutes before starting the test.
- Baseline parameters measured included blood pressure, heart rate (HR), oxygen saturation (SpO2), and fatigue and dyspnea levels using the modified Borg scale.

Conducting the test:

- Participants completed a six-minute walk along a "50-meter straight corridor."
- During the test, participants moved at a pace that was comfortable for them, taking breaks to rest when necessary.
- Medical staff recorded the distance traveled (6MWD), as well as changes in heart rate, SpO2, and subjective sensations of the patient.

Completion of the test:

- After completion of the test, blood pressure, heart rate, SpO2 and fatigue level were measured again.
- Any adverse events (chest pain, dizziness, shortness of breath, fatigue) were recorded.
- Data collection

For each participant, demographic characteristics (age, gender), clinical parameters (NYHA heart failure class, comorbidities), six-minute walk test (6MWT) results, including distance traveled, heart rate (HR) changes, oxygen saturation level (SpO_2) and subjective sensations, as well as additional parameters such as medications taken and hospitalization history were recorded. Data analysis was performed using the test results. Descriptive statistics (means, standard deviations), comparison of 6MWD values between patient groups (by NYHA classes), correlation analysis between distance traveled and clinical parameters (HR, SpO_2) and assessment of the minimal clinically important difference (MCID) for 6MWD were

used. All participants provided written informed consent. The main limitations of the study are the limited sample of patients from one medical institution, the possible influence of comorbidities on the test results and the lack of long-term follow-up to assess the dynamics of physical activity.

Ethical approval. Private Institution "National Laboratory Astana". This study was approved by the Local Ethics Committee #2023/01-009. All data were recorded digitally using an online platform. Each participant was assigned a unique identifier and the data were anonymized before analysis. Informed consent was obtained from all participants in Kazakh and Russian.

Statistical analysis. The statistical analysis included descriptive and analytical statistics where for variables with a normal distribution, parametric statistical methods were used and presented as means ± standard deviation. Numerical variables of non-normally distributed data were presented as mean values ± standard deviation. For all types of analysis, statistical significance was determined using the Student's t-test, with a significance level set at $p < 0.05$. Statistical analysis was performed using Python v3.9.16 and R v4.2.2. The Mann-Whitney U test and logistic regression were employed, accounting for age, sex, and various oral health parameters.

Results

The Table 1 presents the baseline characteristics of patients in control and case groups, including their age, BMI. The additional values are given for different group regarding the ejection fractions.

Table 1.
Baseline characteristics of control and experimental groups, with different ejection fractions.

Characteristics	Value	Control group	Experimental group	HFpEF	HFmrEF	HFrEF	p value
Age	Mean and SD	57.77 ± 11.23	51.23 ± 9.21	61.41 ± 10.56	58.45 ± 10.93	58.08 ± 10.93	<0.01
	Median and Q1-Q3	59.00 [51.00-65.00]	52.00 [44.00 - 58.00]	63.00 [56.00 - 69.00]	61.00 [53.25 - 65.75]	59.00 [52.50 - 65.00]	<0.01
	Min-Max	21.00 - 81.00	26.00 - 77.00	21.00 - 81.00	25.00 - 78.00	24.00 - 78.00	<0.01
BMI	Mean and SD	29.35 ± 5.08	27.36 ± 4.42	29.67 ± 5.02	29.71 ± 5.78	30.48 ± 4.85	<0.01
	Median and Q1-Q3	29.00 [25.57 - 32.24]	27.00 [24.00 - 30.27]	29.00 [25.78 - 32.80]	30.46 [25.62 - 33.10]	29.98 [27.43 - 32.83]	<0.01
	Min-Max	11.00 - 46.93	17.99 - 46.00	19.07 - 46.93	11.00 - 45.20	20.69 - 45.34	<0.01

HFpEF - Heart Failure With Preserved Ejection Fraction; HFmrEF - Heart Failure with mid-Range Ejection Fraction; HFrEF - Heart failure with Reduced Ejection Fraction; BMI - Body Mass Index.

The differences between the groups of patients with different ejection fraction (EF) of the left ventricle - the control group, HFpEF, HFmrEF and HFrEF - were analyzed according to a number of quantitative variables. The age and BMI variables are given as examples of interpretation of the general approach and structure of analysis.

To identify differences between groups, a non-parametric Kruskal-Walli's test was used, adequate for abnormal distributions and differences in dispersions. This test made it possible to determinewhether there are generally statistically significant differences between four independent groups. For example, for the age variable, the value $p < 0.000001$ indicates the existence of significant age differences between groups. Similarly, the BMI variable showed significant differences with $p = 0.0000002$.

In addition to the Kruskal-Walli's test, the size of the n^2 effect (eta-square) was calculated, which allows to quanti-

fy the variance fraction explained by the grouping factor. In the context of medical statistics, the following benchmarks are used to interpret n^2: values less than 0.01 are considered negligibly small, from 0.01 to 0.06 - small, from 0.06 to 0.14 - moderate, and above 0.14 - large. Thus, for the variable, n^2 was 0.132, which is interpreted as a moderate effect. This indicates that the differences between groups explain about 13.2% of the total age variance. For the BMI variable, $n^2 = 0.049$ corresponds to a small effect, which indicates the presence of differences, but less clinical significance.

Since Kruskal-Wallis only indicates the existence of differences in general, post-hock comparisons were made using the Dunn criterion with an amendment to multiple comparisons. For each pair of groups, the values of p and the size of the effect r based on z-statistics were calculated. The interpretation of r values is based on the same principles as for Spearman's correlation coefficient: r about 0.1 indicates a small effect, about 0.3 - a moderate one, and from 0.5 and above - a large effect. For example, the age comparison between the control group and HFpEF gave p = 0.0000 and r = 0.465, which corresponds to a medium-large effect. This indicates not only a statistically significant difference, but also its severity with potential clinical significance. Similarly, for BMI, when comparing the control group and HFpEF, the value r = 0.225 indicates a small but significant effect.

Figure 1.
Comparison of 6-minute walk test results between patients with CHF and the control group

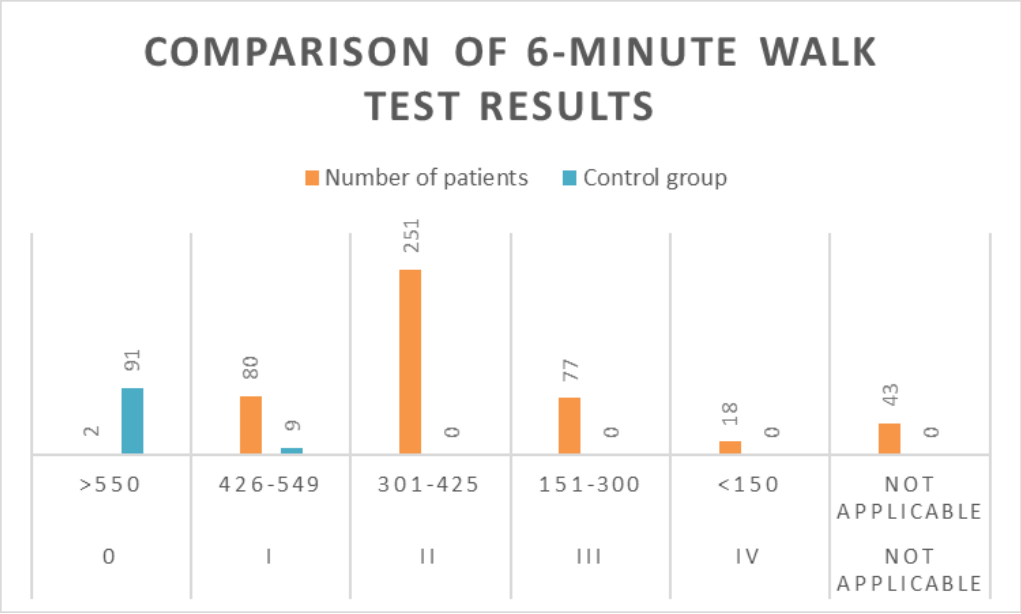

Figure 1 shows the distribution of patients with CHF and control group participants by categories of distance traveled in a 6-minute test corresponding to functional classes (FC).

Control group (healthy):

• 91% of participants covered more than 550 meters (FC 0), indicating excellent physical endurance, as shown in Figure 2.

• Only 9% fell into the 426–549 m (FC I) range, which may be due to individual characteristics or random factors.

• 0% of the control group participants did not show a decrease in physical activity to levels corresponding to FC II–IV. Also, no one refused the test.

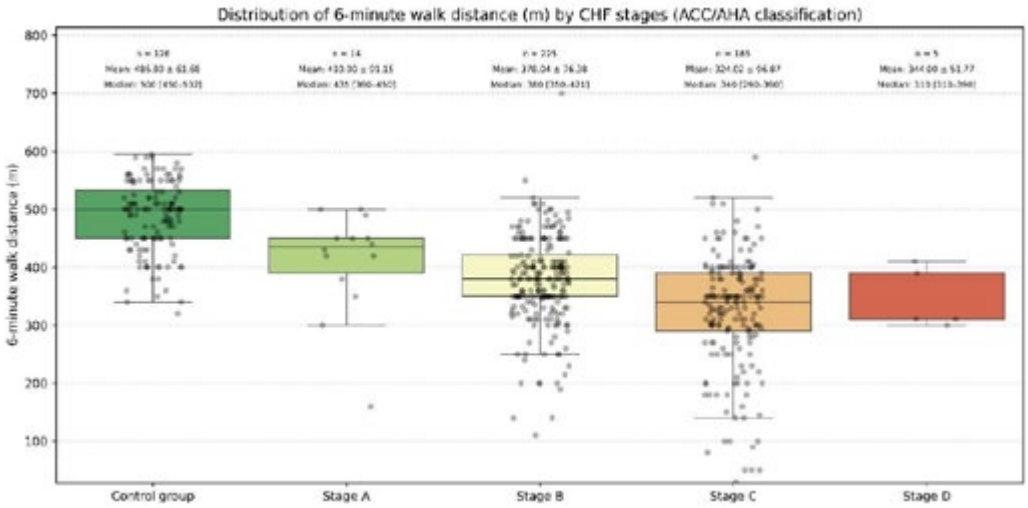

Figure 2.
Distribution of 6-minute walk distance by CHF stages

Patients with CHF:

•Only 0.4% covered more than 550 m, that is, they were comparable to absolutely healthy people.

•17% fell into the FC I category (426–549 m) – moderate decrease in physical activity.

•More than 53% demonstrated significant limitation (FC II, 301–425 m) – the largest group.

•16% showed severe intolerance to the load (FC III, 151–300 m).

•3.8% walked less than 150 m (FC IV), which indicates an extremely serious condition.

•In 9.1% the test was not performed due to severe physical condition; there were no such cases in the control group.

Table 2.
The correlation of 6MWT is compared with the named factors.

Values	6 MWT	Age	BMI	LV ejection fraction	Log (NT-proB-NP)	Global longitudinal deformation	SpO2	Chronic kidney disease
6 MWT	p= 1.00	p= -0.41	p= -0.17	p= 0.41	p= -0.47	p= -0.38	p= 0.39	p= -0.16
Age	p= -0.41	p= 1.00	p= -0.02	p= -0.11	p= 0.36	p= 0.13	p= -0.27	p= 0.15
BMI	p= -0.17	p= -0.02	p= 1.00	p= -0.14	p= 0.07	p= 0.23	p= -0.16	p= 0.15
LV ejection fraction	p= 0.41	p= -0.11	p= -0.14	p= 1.00	p= -0.57	p= -0.67	p= 0.20	p= -0.21
log(NT-proBNP)	p= -0.47	p= 0.36	p= 0.07	p= -0.57	p= 1.00	p= 0.54		
Global longitudinal deformation	p= -0.38	p= 0.13	p= 0.23	p= -0.67	p= 0.54	p= 1.00	p= -0.26	p= 0.21
SpO2								
p= 0.39	p= -0.27	p= -0.16	p= 0.20		p= -0.26	p= 1.00		
Chronic kidney disease	p= -0.16	p= 0.15	p= 0.15	p= -0.21		p= 0.21		p= 1.00

Considering the variable 6-minute walk distance as an integral indicator of the patient's functional state, the following statistically significant associations were identified in Table 2 ($p < 0.05$ after FDR correction):

- A moderately positive correlation with the left ventricular ejection fraction ($\rho = 0.41$, $p < 0.05$) was found, reflecting an improvement in functional endurance with preserved systolic function. An inverse relationship with age was observed

(ρ = –0.41, p <0.05), which corresponds to the expected decrease in physical performance in elderly patients. A negative correlation with the body mass index (ρ = –0.17, p <0.05) was also found, confirming the effect of excess weight on limiting physical activity.

- A strong negative association was observed between 6MWT and log NT-proBNP (ρ = –0.47, p < 0.05), highlighting the association of low functional capacity with higher cardiac overload. Similarly, 6MWT was negatively associated with myocardial global longitudinal strain (GLS) (ρ = –0.38, p < 0.05), consistent with worse longitudinal contractility in patients with limited exercise capacity.

- The 6MWT distance also positively correlated with the oxygen saturation level after the test (SpO_2 after 6MWT; ρ = 0.29, p = 0.019), which reflects preserved oxygenation in patients with good physical adaptation. Additionally, an inverse relationship was established with the presence of chronic kidney disease (φ = –0.26, p = 0.043), which may be a marker of systemic organ dysfunction limiting exercise tolerance.

6MWT has significant correlations with all CHF metrics used.

Discussion

Our results demonstrate that the six-minute walk test (6MWT) serves as a clinically meaningful measure of functional capacity in heart failure patients, with strong correlations to established disease markers. The significant inverse relationship between 6MWT distance and NT-proBNP levels (ρ = -0.47, p < 0.05) confirms previous findings that this simple test effectively reflects cardiac overload.[1,2,3] Importantly, the moderate positive association with left ventricular ejection fraction (ρ = 0.41) supports its utility in assessing systolic functio,[4] while the negative correlations with age and BMI align with known determinants of exercise tolerance.[7,12]

The clinical value of 6MWT is particularly evident in its ability to stratify patients by disease severity. Our finding that only 0.4% of HF patients achieved distances comparable to healthy controls (>550 m) reinforces its discriminative power. The test's practicality for routine clinical use represents a major advantage over more complex cardiopulmonary exercise testing,[5] especially in resource-limited settings. However, the inability of 9.1% of patients to complete the test suggests limitations in assessing the most severe cases, a finding consistent with other studies.[9]

These results build upon established guidelines[5] while providing new insights from a large patient cohort. The strong correlation with multiple clinical parameters supports the test's role in comprehensive patient assessment and rehabilitation planning.[6] However, our cross-sectional design limits conclusions about long-term prognostic value - an area requiring further investigation.[10]

Clinical Implications:

- Validates 6MWT as practical tool for functional assessment
- Supports use in monitoring disease progression
- Highlights need for standardized administration protocols
- Suggests value in rehabilitation program planning

While confirming the test's established utility, our findings emphasize its particular relevance for clinical practice in diverse healthcare settings. Future research should address longitudinal outcomes and protocol optimization to maximize clinical benefit.

Limitations. Limitations include its single-center, cross-sectional design, lack of long-term follow-up, possible confounding by comorbidities, and exclusion of the sickest patients who could not perform the test. Additionally, protocol adherence challenges in real-world settings may affect result reproducibility.

What's known? The six-minute walk test is a well-established, simple, and cost-effective method recommended by the American Thoracic Society for assessing functional capacity in patients with heart failure, correlating strongly with peak oxygen uptake and widely used in cardiac rehabilitation.

What's new? This study adds new evidence by analyzing a large cohort of 471 HF patients and 100 controls, demon-

strating a clear association between 6MWT distance and NYHA class, as well as significant correlations with key clinical indicators such as left ventricular ejection fraction, NT-proBNP, global longitudinal strain, oxygen saturation, and comorbidities. The findings reinforce the 6MWT as a practical tool for functional stratification and individualized rehabilitation planning in resource-limited settings.

Conclusion

The 6-minute walk test is an effective, affordable, and clinically relevant tool for assessing the functional status and physical activity level of patients with heart failure. The results of the study confirm its high diagnostic value for monitoring the dynamics of physical capabilities, as well as for developing personalized cardiac rehabilitation programs. However, to ensure the reliability and reproducibility of the results, strict adherence to standardized protocols recommended by the American Thoracic Society is necessary, especially in resource-limited settings. Thus, the 6MWT remains an important component of clinical practice, helping to optimize functional outcomes and improve the quality of life of patients with heart failure.

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COMPARATIVE ANALYSIS OF BISOPROLOL EFFICACY IN PATIENTS WITH NORMAL AND ALTERED CARDIAC ANATOMY IN THE POSTOPERATIVE PERIOD AFTER CATHETER ABLATION OF ATRIAL FIBRILLATION

Adil Baimbetov[1], Karlygash Kissikova[1], Madi Tokhtarov[1], Omirzhan Rysbayev[1], Ilinara Akhmetzhan[1], Moldir Seitbek[1], Alexander Sapunov[1], Rzaev Farkhad[2]

1 - Syzganov National Scientific Center of Surgery
2 - Davydovsky City Clinical Hospital, Russian Federation, Moscow

DOI: 10.35805/BSK2025III0010
Baimbetov A.
https://orcid.org/0000-0002-9971-1309
Kissikova K.
https://orcid.org/0009-0004-3763-4733
Tokhtarov M.
https://orcid.org/0009-0008-6951-484X
Akhmetzhan I.
https://orcid.org/0000-0002-2726-7296
Sapunov A.
https://orcid.org/0000-0002-7125-8178
Rzaev F.
https://orcid.org/0000-0002-4094-7771

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Author for correspondence:
Karlygash Kissikova - Cardiologist, JSC Syzganov National Scientific Center of Surgery, Almaty, Kazakhstan. +77059549639, karla95@mail.ru

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Keywords:
atrial fibrillation; catheter ablation; bisoprolol; β-adrenergic blockers; left atrial anatomy.

Abstract

Background. The aim of this study was to evaluate the effectiveness of the ß-adrenergic blocker bisoprolol in maintaining sinus rhythm in patients with atrial fibrillation following catheter ablation of the pulmonary vein ostia, considering the anatomical condition of the left atrium.

Material and methods. A total of 50 patients were enrolled and divided into two groups: those with normal left atrial anatomy (n = 25) and those with pathologically altered anatomy (n = 25). All patients received bisoprolol at a dose of 10 mg/day for 12 months post-ablation.

Results. Within the first 6 months of follow-up, no atrial fibrillation recurrences were observed in the group with normal left atrium anatomy (100%), whereas 92% of patients in the altered anatomy group experienced recurrences. In the second half of the follow-up period (months 6–12), differences between the groups were no longer statistically significant. Statistical analysis confirmed a highly significant difference in recurrence rates during the early postoperative period ($p < 0.001$) and no significant difference in the late period ($p > 0.3$).

Conclusion. The effectiveness of bisoprolol in maintaining sinus rhythm is highly dependent on the anatomical condition of the left atrium in the early period following ablation. The results highlight the importance of individualizing antiarrhythmic therapy based on morphofunctional characteristics.

Atrial fibrillation (AF) is one of the most common types of cardiac arrhythmias, significantly affecting patients' quality of life and associated with an increased risk of thromboembolic events and heart failure.[1] In recent years, catheter ablation of pulmonary vein has taken a key place in the treatment of both paroxysmal and persistent forms of AF, demonstrating high efficacy in eliminating arrhythmogenic substrates.[2] However, despite technical achievements and expansion of indications for ablation, the rate of arrhythmia recurrence in the early postoperative period, especially during the first three months, remains significant and reaches, according to several studies, up to 30–50% of cases.[3] The early postoperative period, often referred to as the "blanking period," is characterised by instability of atrial electrical activity due to ongoing inflammatory and remodeling processes.[3] This period is therefore critically important for maintaining sinus rhythm.

Pharmacological antiarrhythmic therapy during this phase aims to prevent early arrhythmia recurrence, stabilize electrophysiological parameters, and reduce the likelihood of repeated hospitalizations.[1] Among the medications used in post-ablation management, ß-adre-

genic blockers (Class II antiarrhythmic agents according to the *Vaughan Williams* classification), such as bisoprolol, hold a distinct position due to their antiarrhythmic, anti-ischemic, and antihypertensive properties, as well as their favorable safety profile.[4] However, the effectiveness of bisoprolol in maintaining sinus rhythm in post-CA may vary depending on the morphofunctional characteristics of the heart, in particular, the anatomical condition of the left atrium.[5] The extent to which the effectiveness of bisoprolol post-ablation is influenced by the presence or absence of structural alterations in cardiac anatomy remains insufficiently explored.[6]

Conducting a comparative analysis of bisoprolol's effectiveness in patients with normal versus pathologically altered left atrial anatomy represents a timely and clinically significant task in modern cardiology and interventional electrophysiology.[7,8] The findings may contribute to the individualization of antiarrhythmic therapy during the postoperative period, enhancing treatment efficacy and improving outcomes in this patient population.[2]

Object of the study. The object of the study was patients with paroxysmal and persistent forms of atrial fibrillation who underwent catheter ablation of pulmonary vein apertures.

Focus of the study. The focus of the study was the effectiveness of the ß-blocker bisoprolol in the postoperative period among patients with varying anatomical characteristics of the left atrium.

The aim of the study. The aim of this study was to assess the efficacy of bisoprolol in maintaining sinus rhythm over a 12-month period following catheter ablation in patients with either normal or altered anatomy of the left atrium.

Research hypothesis. It is hypothesized that bisoprolol is more effective in maintaining sinus rhythm after catheter ablation of atrial fibrillation in patients with normal left atrial anatomy compared to those with pathological anatomical changes.

Materials and methods

The study included 50 patients (both men and women) aged 47 ± 15 years with paroxysmal or persistent AF who underwent catheter ablation of the pulmonary vein. All patients were examined and treated at the clinical base of the Syzganov National Scientific Center of Surgery, in the Department of Interventional Arrhythmology.

The inclusion criteria were age between 18 and 75 years, documented AF confirmed by ECG or Holter monitoring, completion of CA of PV procedure, and absence of contraindications to the use of ß-blockers.

Exclusion criteria included: severe heart failure with left ventricular ejection fraction (LVEF) < 35%, significant sinus node dysfunction, second- or third-degree atrioventricular (AV) block without pacemaker, stage IV–V chronic kidney disease, decompensated chronic obstructive pulmonary disease, and hypersensitivity or individual intolerance to bisoprolol.

Patients were randomized in a 1:1 ratio using a random number generator into two equal groups of 25 individuals each, based on the anatomical condition of the LA. Cardiac anatomy was assessed using transthoracic echocardiography and computed tomography, with evaluation of LA volume, presence of dilatation, and structural abnormalities. Group 1 included patients with normal cardiac anatomy, while Group 2 consisted of patients with pathologically altered LA anatomy. All patients received bisoprolol at a fixed daily dose of 10 mg orally following CA of PV, which was continued for 12 months. Treatment was monitored based on clinical status, blood pressure, HR, and drug tolerability. No additional antiarrhythmic medications were administered during the study period. The effectiveness of therapy was evaluated by the recurrence rate of AF, recorded during scheduled visits at 1, 3, 6, and 12 months using ECG and Holter monitoring, as well as during outpatient visits triggered by arrhythmia-related symptoms. The primary endpoint of the study was the absence of a documented recurrence of AF within 12 months following catheter ablation. Secondary endpoints included time to first recurrence, the need for repeat ablation,

hospitalization rate due to arrhythmia, and bisoprolol tolerability.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of the JSC Syzganov National Scientific Center of Surgery with №4 protocol held on 10.11.2023. Prior to enrollment, all patients were informed about the aims, methods, and potential risks of the study. Each participant signed an informed consent to participate in the study and to process personal medical data. Anonymity and confidentiality of patient information were ensured at all stages of the work. Participation in the study did not affect the scope and nature of the medical care provided and was not accompanied by additional risks for patients.

Statistical analysis was performed using SPSS Statistics v.26. Continuous variables were presented as mean ± standard deviation, and categorical variables as absolute and relative frequencies (n, %). Between-group comparisons of continuous variables were conducted using Student's t-test or the nonparametric Mann–Whitney U test, depending on the data distribution. Kaplan–Meier analysis was used to assess time to recurrence. A p-value of <0.05 was considered statistically significant. The study received approval from the local ethics committee, and all participants provided written informed consent.

Results

The study included 50 patients with paroxysmal and persistent AF who underwent catheter ablation of the pulmonary vein ostia and received antiarrhythmic therapy with bisoprolol. Patients were evenly divided into two groups based on the anatomical condition of the LA: group 1 (n = 25) included patients with normal atrial anatomy, while group 2 (n = 25) included patients with pathological anatomical alterations of the LA. Follow-up results demonstrated a significant difference in the effectiveness of antiarrhythmic therapy between the groups. In group 1, bisoprolol monotherapy effectively maintained stable sinus rhythm throughout the entire 12-month observation period, with no recorded recurrences of AF or other clinically significant tachyarrhythmias. These findings indicate the high efficacy of ß-adrenergic blocker therapy in patients with anatomically intact atria. By the 6-month follow-up, 23 out of 25 patients (92%) in group 2 had experienced tachyarrhythmia recurrences, including 3 patients (12%) with atrial tachycardia episodes lasting more than 30 seconds, qualifying as reaching the primary endpoint. The remaining 20 patients (80%) had episodes of paroxysmal AF that required the initiation of additional therapy with amiodarone, a class III antiarrhythmic agent according to the Vaughan Williams classification. This distribution highlights the significantly lower efficacy of bisoprolol as monotherapy in patients with morphologically altered LA structure. Particular attention should be paid to the nature of arrhythmic activity in the early postoperative period. In both groups, episodes of supraventricular tachyarrhythmias lasting less than 30 seconds were observed during the first 3 months following ablation; these were considered manifestations of instability of electrical activity within the so-called "blanking period". The episodes were transient in nature and did not influence the therapeutic strategy. Between 6 and 12 months of follow-up, differences between the groups became more pronounced. In patients with normal LA anatomy, sinus rhythm was stably maintained with continued bisoprolol therapy, and no arrhythmia recurrences were observed. In contrast, at least one late episode of LA lasting more than 30 seconds was documented in the second group, confirming the trend toward reduced therapeutic efficacy in this patient category. It is also noteworthy that, regardless of the group, the overall use of antiarrhythmic drugs, especially in the first 3 months after ablation, was accompanied by a reduction in the number of hospitalizations throughout the follow-up period. This effect is presumably related to improved rhythm control and reduced symptom severity, but requires further clarification. The episodes were transient

and did not influence the therapy tactics. In the time interval from 6 to 12 months, the differences between the groups increased. In patients with normal LP anatomy, stable sinus rhythm retention was observed against the background of bisoprolol therapy continuation, without signs of arrhythmia recurrences. At the same time, the second group showed at least one late episode of atrial fibrillation lasting more than 30 seconds, which confirms the tendency to decrease the effectiveness of therapy in this category of patients. It should also be noted that, regardless of the group, the overall use of antiarrhythmic drugs, especially in the first 3 months after ablation, was accompanied by a reduction in the number of hospitalizations throughout the follow-up period. The effect is probably related to improved rhythm control and reduced symptom severity, but requires further clarification.

The stepwise analysis of AF recurrence rates in both groups is presented in Table 1. During the first 6 months following catheter ablation, all patients in the group with normal LA anatomy (n = 25) maintained stable sinus rhythm, corresponding to a 100% freedom from AF recurrence. In contrast, in the second group (with altered anatomy), recurrences were documented in 23 out of 25 patients (92%) during this early period, which underlines extremely low efficacy of bisoprolol monotherapy in conditions of morphological destruction of the LA.

Table 1.
Atrial fibrillation recurrence rates according to left atrial anatomy at different follow-up time points.

Follow-up period	Group	No recurrence, n (%)	With recurrence, n (%)	Total
0–6 months	Normal	25 (100%)	0 (0%)	25
	Altered	2 (8%)	23 (92%)	25
	Total	27 (54%)	23 (46%)	50
6–12 months	Normal	25 (100%)	0 (0%)	25
	Altered	24 (96%)	1 (4%)	25
	Total	49 (98%)	1 (2%)	50

Interestingly, during the 6- to 12-month follow-up period, rhythm stability was observed even among patients with LA pathology, 24 out of 25 patients (96%) remained free from AF recurrence, with only one patient (4%) experiencing a late episode of arrhythmia. This shift toward rhythm normalization may be attributed to atrial myocardial remodeling following ablation, as well as to progressive stabilization of atrial electrical activity. However, the potential impact of additional interventions and therapy adjustments in patients with early recurrences cannot be excluded. Overall, during the first 6 months post-ablation, AF recurrences were recorded in 46% of the total study group (23 out of 50 patients), with the vast majority of these cases (92%) occurring in the group with altered LA anatomy. These findings highlight that the most vulnerable period for this subgroup of patients is within the first six months following catheter ablation. By the 12th month, the number of new AF recurrences was 2%, however, the cumulative proportion of patients who experienced at least one episode of AF over the observation period remained at 46% (23 out of 50), which may indicate a general decline in arrhythmic activity in the late post-ablation period, especially with effective correction of pharmacological management. The results presented in Table 1 underscore high prognostic significance of the anatomical state of the LA in selecting the tactics of drug management after CA. In patients with structurally intact atria, bisoprolol provides stable rhythm control throughout the entire follow-up period. At the same time, in patients with morphological abnormalities of the left atrium, the drug demonstrates limited efficacy during the early postoperative period and may require either escalation of therapy or the initial implementation of a combined approach, taking into account both anatomical and electrophysiological parameters. The results highlight the importance of individualizing antiarrhythmic therapy after ablation, based on the structural condition of the atria. They also

indicate the advisability of more intensive monitoring and possible connection of class III antiarrhythmic agents in patients with altered LA anatomy during the initial months after intervention.

The Pearson's x^2 test was used to confirm the differences in AF recurrence rates between the groups with normal and altered LA anatomy. In analyses covering the first 6 months of follow-up,the results demonstrated a high level of statistical significance, Pearson's x^2 value was 42.593 with one degree of freedom, and asymptotic significance was less than 0.001 ($p < 0.001$). An additional continuity-corrected test yielded a similar result ($x^2 = 38.969$; $p < 0.001$), indicating that the differences between groups were extremely reliable. Likelihood ratios ($x^2 = 55.056$) and Fisher's exact test also confirmed statistically significant differences ($p < 0.001$ in both directions), indicating a dramatic difference in the efficacy of bisoprolol in patients with different LA anatomical status in the early postoperative period. However, during the follow-up period of 6 to 12 months, a similar x^2 analysis did not reveal statistically significant differences between the groups. The The Pearson's x^2 value was 1.020 with $p = 0.312$, and both the continuity correction and Fisher's exact test also indicated a lack of significance ($p = 1.000$). This may be attributed to the stabilization of myocardial electrical activity in the late post-ablation period, when anatomical differences lose their determining influence, and other factors, such as tissue remodeling and possible adjustment of therapy following early recurrences, begin to contribute to rhythm maintenance. The results of statistical analysis suggest that:

- during the first 6 months after ablation, LA anatomy has a pronounced effect on the efficacy of bisoprolol;

- In the period of 6-12 months, the differences between the groups become less apparent and lose statistical significance, which may indicate the completion of the phase of electrical instability and myocardial adaptation to postablation conditions.

The data emphasise the need for intensified monitoring and a more flexible therapeutic strategy in the first months after CA, especially in patients with altered atrial anatomy. A potential solution may involve the use of combination antiarrhythmic therapy or more frequent ECG monitoring in this group. Further studies may be aimed at identifying additional modifying factors such as the degree of fibrosis, LA size on CT, or the level of inflammatory biomarkers influencing the outcome of treatment. To gain a more precise understanding of the dynamics of differences in the time and severity of recurrence, additional comparative analyses were performed by time intervals. The results are summarised in Table 2.

Table 2.
Comparative analysis of AF recurrence rates between groups with normal and altered LA anatomy at different follow-up periods.

Follow-up period	Comparison group	Pearson's x^2 (p)	t-test (p)	Mean recurrence rate (M ± SD)	Effect size (Cohen's d)	Interpretation of the observed differences
0–6 months	Normal vs Altered	42.593 (p<0.001)	–16.61 (p<0.001)	0.00 ± 0.00 vs 0.92 ± 0.28	0.196 (smalleffect)	Statistically significant difference; bisoprolol efficacy is significantly lower in patients with altered atrial anatomy.
6–12 months	Normal vs Altered	1.020 (p=0.312)	–1.00 (p=0.322)	0,00 ± 0,00 vs 0.04 ± 0.20	0.141 (negligible effect)	No significant difference; bisoprolol is equally effective in maintaining sinus rhythm at the later stage

During the first 6 months after catheter ablation, a high rate of AF recurrence was observed in the group of patients with pathologically altered LA anatomy (92%), whereas in the group with normal anatomy, recurrences were completely absent. Pearson's χ^2-criterion confirmed statistically significant differences between the groups ($x^2 = 42.593$, $p < 0.001$). Also, Student's t-test revealed a highly significant difference in the mean values of recurrence rates ($t = -16.61$, $p < 0.001$). The mean recurrence rate was 0.92 ± 0.28 in the Altered group versus 0.00 in the Normal group. Although Cohen's d effect size is estimated to be small (0.196), the level of significance, confidence interval, and directionality of the effect support the practical significance of the differences. Thus, in the early postoperative period, the efficacy of bisoprolol is significantly lower in patients with atrial morphofunctional changes. In the period from 6 to 12 months, the differences between the groups practically disappear: in the Altered group, recurrences were registered in only one patient (4%), whereas they were still absent in the Normal group. Pearson's χ^2 (1.020; $p = 0.312$) and t-criterion ($t = -1.00$; $p = 0.322$) revealed no statistically significant differences. The mean recurrence rate in the Altered group decreased to 0.04 ± 0.20, and the effect size ($d = 0.141$) was below the threshold of clinical significance, which may indicate stabilisation of atrial electrical activity, tissue remodelling, and/or effectiveness of corrective therapy after early recurrences. These findings underscore the need for a personalised approach to the management of patients in the first months after ablation, taking into account the anatomical characteristics of the heart. At the same time, in the long-term period (6-12 months), bisoprolol may be effective in most patients, regardless of LA morphology, especially in the absence of early recurrences.

Further analysis of atrial fibrillation recurrence rate depending on left atrial anatomy is presented in Figure 1. Figure 1 shows the comparative frequency of AF recurrences and early arrhythmias at different periods after catheter ablation in patients with normal and pathologically altered left atrial anatomy. According to the presented data, the greatest differences between the groups were observed in the interval 0-6 months after the procedure. Thus, in the group of patients with altered anatomy (Altered), the recurrence of AF during this period was observed in 92 % of patients, whereas in the group with normal anatomy (Normal), the recurrences were completely absent (0 %). This difference is statistically significant ($\chi^2 = 42.593$, $p < 0.001$) and indicates a pronounced negative impact of morphological changes in the left atrium on the short-term efficacy of ablation therapy.

Figure 1.
Incidence of early arrhythmia and AF recurrence according to left atrial anatomy at different time points after catheter ablation.

Interestingly, during the early postoperative period (0–3 months), known as the "blanking period", the incidence of any arrhythmias (including paroxysmal AF and atrial flutter) was also higher among patients with altered atrial anatomy—60% compared to 40% in the group with normal anatomy. Although these episodes do not indicate a persistent recurrence, they may be considered predictors of adverse clinical outcomes, particularly in patients with morphological atrial changes such as increased volume, wall thickening, or areas of fibrosis. In the second half-year following ablation (6–12 months), the differences

between the groups were markedly reduced: atrial fibrillation recurrence was observed in only 4% of patients in the Altered group and remained absent in the Normal group. Statistical analysis for this interval did not reveal significant differences ($\chi^2 = 1.020$, $p = 0.312$), which may indicate stabilization of atrial electrical activity following the completion of the remodeling phase or greater effectiveness of antiarrhythmic therapy initiated in the higher-risk group. Overall, the presented data confirm that anatomical characteristics of the LA have a significant impact on early and mid-term outcomes after ablation. The high recurrence rate within the first 6 months among patients with altered anatomy highlights the need for closer follow-up in this group, potential prolongation of antiarrhythmic therapy, and the implementation of a personalized approach in the planning and performance of ablation procedures.

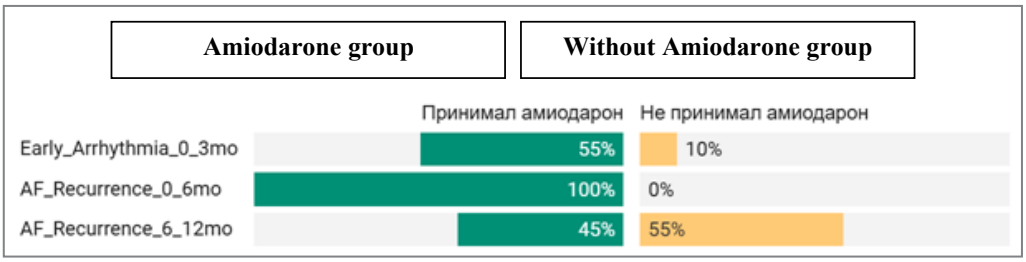

Figure 2.
Effect of amiodarone on the recurrence rate of atrial fibrillation and early arrhythmias after catheter ablation.

Figure 2 illustrates the differences in the incidence of early arrhythmias and AF recurrence between patients treated with amiodarone and those who did not receive the drug during the one-year follow-up after catheter ablation. The data demonstrate both temporal and clinical heterogeneity in the effect of antiarrhythmic therapy.

In the early postoperative period (0–3 months), known as the "blanking period," episodes of supraventricular tachyarrhythmias were recorded in 55% of patients receiving amiodarone, compared to only 10% in those who were not prescribed the drug. Although amiodarone has strong antiarrhythmic properties, this difference may be attributed to the fact that the drug is more often administered to patients at higher risk of recurrence or those who had already exhibited early arrhythmias. A statistically significant difference ($x^2 = 6.522$, $p = 0.011$) confirms an association between amiodarone use and the occurrence of early arrhythmias; however, it does not indicate a causal protective effect of the drug. The most pronounced differences were observed during the 0–6 month interval. All cases of AF recurrence in this cohort were observed exclusively among patients receiving amiodarone (100%), while no recurrences occurred in the group without the drug (0%). This situation may, on one hand, indicate the limited efficacy of pharmacological control in certain patient categories, and on the other hand, suggest that amiodarone was prescribed after the onset of recurrence in an attempt to prevent its reappearance. Given the high statistical significance ($x^2 = 50.000$, $p < 0.001$), it can be asserted that recurrence rates in this phase are closely associated with the fact of drug administration; however, the direction of this association requires clarification through prospective study designs. In the 6–12 month period following ablation, the differences in recurrence rates between the groups become less pronounced: 45% among those who continued taking amiodarone and 55% among those who did not. The results in this interval did not reach statistical significance ($x^2 = 1.198$, $p = 0.274$), which may reflect both the completion of atrial electrical remodeling and the stabilization of the clinical course following the active phase of intervention. The presented data indicate that amiodarone use is associated with a higher frequency of arrhythmia detection in the early post-ablation period. However, this association should be interpreted with caution, as the drug was

likely prescribed in response to already occurring AF episodes. This highlights the need for additional stratified analysis and prospective studies with a clear distinction between prophylactic and reactive use of antiarrhythmic therapy.

Discussion

The results of the study demonstrate that left atrial anatomy significantly affects the short-term effectiveness of bisoprolol in maintaining sinus rhythm after catheter ablation of AF. During the first six months, patients with normal LA anatomy had no AF recurrence, whereas in patients with pathological anatomical alterations, recurrences were observed in 92% of cases. These findings are consistent with earlier studies, which identified LA structural remodeling, such as dilatation and fibrosis, as key predictors of arrhythmia recurrence after CA.[3,5,9] Moreover, the results are consistent with current clinical guidelines, which emphasise the need to select a rate or rhythm control strategy based on the structural and functional characteristics of the heart.[1,2]

Bisoprolol, as a selective ß1-adrenergic blocker, has pronounced antiarrhythmic and rate-controlling properties, particularly in the early postoperative period, when atrial electrical instability is most pronounced.[4] Similar to the data from *Suzuki et al.,*[4] our study confirms the high efficacy of bisoprolol in patients without morphological alterations in the LA. However, in patients with pronounced atrial remodelling, the drug's effectiveness appears to be limited, which is probably due to the presence of stable arrhythmogenic substrates and changes in impulse conduction pathways.[6]

The observed trend toward equalization of results between groups in the 6–12 month interval may reflect the cumulative effect of reverse myocardial remodelling after ablation, adaptation of atrial electrical activity, and optimization of antiarrhythmic therapy, including the prescription of amiodarone in patients at high risk of recurrence.[6,7] This dynamic is consistent with data indicating that outcomes in the late postoperative period are less dependent on the initial anatomy of the LA, as the completion of fibrosis and scarring processes after ablation contributes to rhythm stabilisation.[9]

It should be noted that all early AF recurrences in the group with altered LA anatomy occurred during bisoprolol therapy, confirming the need for a personalized pharmacological approach in this cohort.[8] A possible option is the initial use of combined antiarrhythmic therapy including class III agents, as suggested in recent studies on rhythm control in patients with high anatomical risk.[6,7] Furthermore, the use of advanced imaging and left atrial reconstruction techniques based on artificial intelligence appears promising.[10]

Compared to previously published studies, the novelty of our work lies in demonstrating a pronounced dependence of bisoprolol efficacy in the early postoperative period on the morphological state of the LA. Although ß-adrenergic blockers are widely considered a key element of pharmacological management after CA,[1,4] few studies have directly stratified clinical outcomes by anatomical type of atria.[5,7] Thus, the results obtained contribute to the development of the concept of structurally oriented personalization of antiarrhythmic therapy.[2]

Atrial fibrillation (AF) remains one of the most prevalent types of arrhythmias, associated with an increased risk of cardiovascular complications and a decreased quality of life for patients.[1] Catheter ablation of the pulmonary vein is currently considered the gold standard for the treatment of paroxysmal and persistent AF.[2] Its success largely depends on the anatomical features of the left atrium, as well as on the choice of pharmacological support during the early postoperative period.[3,5] In this context, the use of ß-adrenergic blockers, in particular bisoprolol, has gained significant clinical relevance.[4]

Several studies confirm the effectiveness of bisoprolol in reducing AF recurrence rates after CA. Thus, *Marazzi et al. (*2011) and *Konishi et al.* (2010)

demonstrated that in patients with concomitant heart failure, bisoprolol exerted a pronounced antiarrhythmic effect, outperforming other ß-blockers such as carvedilol in several key parameters.[11,12] These findings are supported by more recent studies, which highlight the favorable tolerability and safety profile of bisoprolol, particularly in patients with preserved ejection fraction and normal LA volume.[6]

At the same time, the literature emphasizes that the morpho-functional condition of the LA is a key modifying factor influencing the effectiveness of both the ablation procedure and subsequent antiarrhythmic therapy.[3] Several authors demonstrated that LA dilation and the presence of fibrosis significantly increase the risk of AF recurrence within the first 12 months following the procedure.[3,13] Similar conclusions were reported by *Yamamoto et al.,* who emphasized that LA volume, degree of remodeling, and changes in its geometry are directly correlated with unfavorable clinical outcomes.[3]

Given the anatomical variability of the left atrium (LA), including rare pulmonary vein drainage patterns and the presence of accessory venous ostia, achieving complete electrical isolation can be challenging.[5] *Babic et al.* highlight the clinical implications of these structural anomalies, emphasizing the need for a personalized approach to catheter ablation.[5] In this context, novel imaging and mapping techniques are gaining relevance, enabling accurate anatomical reconstruction of the atrium.[10]

Of particular interest is the comparative analysis of bisoprolol formulations. In a study by *Suzuki et al.,* transdermal bisoprolol demonstrated superior efficacy in reducing the incidence of early AF recurrences following ablation compared to the oral form. These findings support the hypothesis that maintaining stable ß-blocker levels in the early postoperative period may be especially important in the context of unstable atrial electrical activity.[4]

Current guidelines[1,2] emphasize the importance of selecting a HR or rhythm control strategy based on the patient's anatomical and functional characteristics. Although a rhythm control strategy, including the use of antiarrhythmics and CA, is effective in maintaining sinus rhythm, it carries potential risks, especially in the presence of significant LA fibrosis or residual pulmonary vein (PV) activity.[3] In this context, ß-blockers serve as a versatile tool for HR control and rhythm stabilization during the "blanking" recovery phase.[4] The available literature supports the notion that bisoprolol remains a key component of post-ablation pharmacological management for AF, especially in patients with normal LA anatomy.[4] At the same time, anatomical features of the LA may significantly affect the effectiveness of antiarrhythmic therapy, underlining the need for comparative studies aimed at identifying tailored treatment approaches.[5] The present study, which analyzes the efficacy of bisoprolol in patients with normal versus altered LA anatomy, addresses this gap and represents a timely contribution to the field of personalized arrhythmology.[6,9]

Limitations. This study has a number of limitations that should be taken into account while interpreting the results. First, the sample size was relatively small (50 patients), which limits the statistical power and the ability to extrapolate the data obtained to a broader population. Second, the study was single-centered, which may reflect the organizational structure and clinical protocols of a specific institution. Third, in several cases, amiodarone was prescribed after the recurrence of arrhythmia had been detected, which could have affected the dynamics of the indicators in the subgroups and made it difficult to assess the preventive effect of the drug. Fourth, morphological assessment of the LA was performed using standard echocardiography and CT methods, without the use of additional tissue mapping parameters, which may have limited the accuracy of stratification. Finally, the follow-up period was 12 months, which does not allow for an assessment of the long-term effective-

ness of bisoprolol in maintaining sinus rhythm in different anatomical phenotypes.

What's Known? Bisoprolol, a selective ß-blocker, is commonly prescribed to control heart rate and maintain sinus rhythm after catheter ablation for atrial fibrillation. Its safety and effectiveness are well established, but previous research has rarely stratified outcomes according to left atrial morphology, despite evidence that structural remodeling significantly affects recurrence rates and long-term rhythm stability.

What's New? This study demonstrates that bisoprolol is highly effective in patients with normal left atrial anatomy, achieving complete prevention of early arrhythmia recurrences, whereas patients with structural alterations showed a 92% recurrence rate in the first six months. The findings highlight the importance of anatomical assessment for individualized pharmacological strategies in the early post-ablation period.

Conclusion

The aim of the present study was to evaluate the effectiveness of bisoprolol in maintaining sinus rhythm in patients with AF after catheter ablation, depending on the anatomical condition of the LA. The obtained results clearly demonstrated that the anatomical state of the left atrium significantly influences the efficacy of bisoprolol-based antiarrhythmic therapy in the early postoperative period. The study hypothesis that bisoprolol is more effective in patients with normal left atrial anatomy compared to those with morphological alterations was confirmed. During the first 6 months of follow-up, no AF recurrences were observed in patients with intact atrial structure (100%), whereas in the group with pathological anatomical changes, recurrences were recorded in 92% of patients, a difference that was statistically significant ($x^2 = 42.593$, $p < 0.001$). In the time interval between 6 and 12 months, the differences between the groups were no longer evident, which may be associated with the completion of the remodeling processes and myocardial adaptation, as well as with adjustments in therapy following early recurrences. Thus, the aim of the study was achieved, and the hypothesis was verified. The data obtained confirm that bisoprolol can be an effective agent for maintaining sinus rhythm in patients after catheter ablation, however, its efficacy in the early postoperative period is strongly dependent on the morphofunctional state of the left atrium. In patients with normal anatomy, bisoprolol demonstrated high clinical effectiveness and stability of outcomes, whereas in patients with anatomical alterations, therapy had to be revised and intensified. The scientific and practical significance of this study lies in its substantiation of the need for an individualized approach to pharmacological management of patients after ablation, taking into account the anatomical features of the heart. Stratifying patients according to the anatomical type of the atria prior to initiating therapy may enhance clinical treatment efficacy, reduce the incidence of recurrences and hospitalizations, and improve prognosis in patients with atrial fibrillation. Future research prospects include expanding the sample size, incorporating patients with varying degrees of left atrial fibrosis, utilizing additional imaging modalities, and developing algorithms for combined antiarrhythmic therapy based on the anatomical and electrophysiological characteristics of the atria.

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CARDIORESPIRATORY FITNESS AND ITS ROLE IN MANAGING ATRIAL FIBRILLATION: A LITERATURE REVIEW

Beisenbayeva Akmaral,[1]Bekbossynova Makhabbat,[1], Bekmetova Feruza[3], Aleushinova Uldana[1], Akhmetbek Dastan[1], Abdrakhmanov Ayan[2]

1 - Heart Center, "University Medical Center" Corporate Fund, Astana, Kazakhstan
2 - Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan
3 - Republican Specialized Scientific Practical-Medical Center of Cardiology, Tashkent, Republic of Uzbekistan

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Beisenbayeva A.
https://orcid.org/0009-0008-9182-2734
Bekbossynova M.
https://orcid.org/0000-0003-2834-617X
Bekmetova F.
https://orcid.org/0000-0002-0619-4729
Aleushinova U.
https://orcid.org/0009-0000-9614-8736
Abdrakhmanov A.
https://orcid.org/0000-0001-6315-5016

Corresponding author:
Beisenbayeva Akmaral – MD, MPH, PhD student, Cardiologist at the UMC "National Research Cardiac Surgery Center" Heart Center, "University Medical Center" Corporate Fund, Astana, Kazakhstan, https://orcid.org/0009-0008-9182-2734, doctor.akmaral.beisenbayeva@gmail.com;

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Keywords:
Atrial fibrillation; Cardiorespiratory fitness; Maximal oxygen consumption; Cardiovascular mortality; Ventilatory anaerobic threshold.

Abstract

Background. Atrial Fibrillation is a prevalent cardiac arrhythmia associated with irregular heartbeats, posing significant health risks. The purpose of the study is literature review seeks to explore the intricate relationship between cardiorespiratory endurance and Atrial Fibrillation, shedding light on how cardiorespiratory parameters can serve as essential markers for assessing physical activity levels.

Materials and methods. The search was conducted using electronic databases, particularly PubMed, Google Scholar, and Scopus. Titles and abstracts of identified studies were screened for relevance, and full-text articles were reviewed for eligibility. The following keywords were used in the search: atrial fibrillation, cardiorespiratory fitness, maximal oxygen consumption, cardiovascular mortality. The search depth is 25 years.

Results. Physical activity adherence lowers overall and cardiovascular mortality in Atrial Fibrillation patients. Tailored exercise regimens alleviate Atrial Fibrillation symptoms, improve heart rate control, and enhance well-being. Standardizing cardiorespiratory testing protocols is crucial for consistent comparisons. Various testing methods, including treadmill protocols and cycle ergometers, offer insights into Cardiorespiratory fitness. Differences between treadmill and cycle ergometer out-comes warrant careful interpretation. Normative values vary across populations, influenced by physical activity, geography, genetics, and testing modalities.

Conclusions. Integrating cardiorespiratory testing into AF management enhances diagnosis and personalized interventions, contributing to a nuanced approach in addressing this prevalent cardiac condition.

Introduction

Atrial Fibrillation (AF) is a prevalent cardiac arrhythmia characterized by rapid, irregular heartbeats originating in the atria – the upper chambers of the heart.[1] In a normal heart rhythm, the atria contract in a coordinated and rhythmic manner, allowing efficient blood flow into the ventricles resulting in an effective pump mechanism. However, in the case of AF, the electrical signals controlling the atrial contractions become chaotic, leading to disorganized and irregular heartbeats.[1,2] Atrial Fibrillation is strongly linked to various health conditions such as heart valve disease, diabetes mellitus,[2] hypertension, and obesity.[3] Additionally, it shares associations with sleep apnea and inflammation.[4]

Both genetic predispositions and modifiable lifestyle factors—such as

alcohol consumption and physical inactivity—contribute to its development. Due to its impact on cardiac function and blood flow, AF significantly elevates the risk of ischemic stroke (IS) and contributes to high morbidity, mortality, and economic burden worldwide.[5] According to the Global Burden of Disease (GBD) Study 2019, incident AF cases rose sharply to over 4.7 million in 2019, with a higher prevalence in males (60.82 per 100,000) compared to females (53.50 per 100,000).[6,7]

Age is the most significant risk factor for AF, with prevalence increasing sharply after the age of 50. Many individuals remain undiagnosed and at risk for serious health outcomes. The global burden of AF, measured in Disability-Adjusted Life Years (DALYs) or mortality, is highest in countries with high Socio-Demographic Index (SDI)[8] influenced by factors such as unfavorable metabolic profiles, heightened psychosocial stressors, neighborhood deprivation and socioeconomic disparities.

Cardiorespiratory endurance plays a crucial role in cardiovascular health. Cardiorespiratory testing, specifically with physical stress, has become a widely used and objective method for evaluating fitness levels.[9] Low cardiorespiratory fitness – measured by parameters such as VO_2 max and ventilatory threshold (VT)–is a known predictor of cardiovascular and respiratory mortality.[10]

This literature review aims to explore the relationship between cardiorespiratory endurance and AF, shedding light on how cardiorespiratory parameters can serve as essential markers for assessing physical activity levels. Through this exploration, we endeavor to highlights the importance of physical fitness assessment in the management and prevention of AF, offering insights into improving outcomes for this prevalent cardiac condition.

Materials and methods

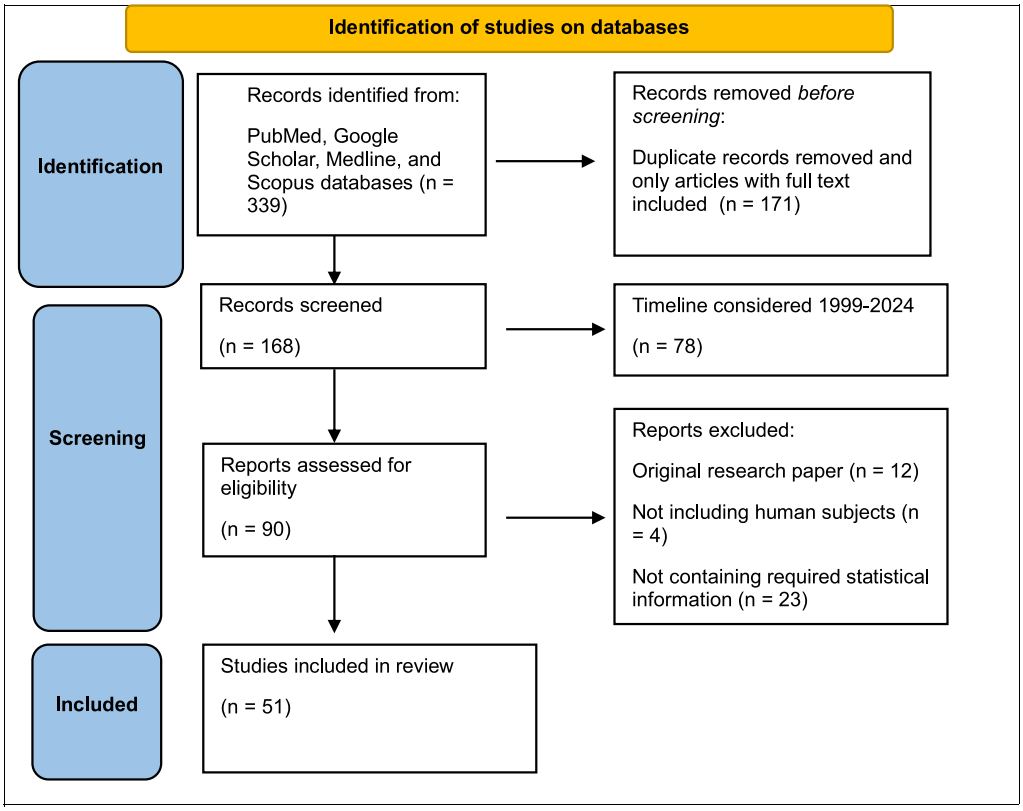
The search was conducted using electronic databases, particularly PubMed, Google Scholar, and Scopus. Titles and abstracts of identified studies were screened for relevance, and full-text articles were reviewed for eligibility. (Figure 1)

The inclusion criteria for this review encompassed literature reviews, meta-analyses, and comparative studies that related to atrial fibrillation management,role of cardiorespiratory fitness in the treatment of AF, cardiorespiratory endurance. Additionally, researches reporting on cardiorespiratory fitness testing methods was considered. Both published and unpublished studies were incorporated into the review.

The exclusion criteria eliminated studies that do not provide clear definitions or results for the management of atrial fibrillation and cardiorespiratory fitness, studies not available in English, animal studies, and in vitro studies are excluded.

The following keywords were used in the search: atrial fibrillation, cardiorespiratory fitness, maximal oxygen consumption, cardiovascular mortality, ventilatory anaerobic threshold. The search depth is 25 years. The selection of a 25-year search depth for the study was driven by the need to balance comprehensiveness with relevance. This time frame ensures inclusion of foundational studies that provide critical background information and contextual understanding. Simultaneously, it filters out information that may have become outdated, as statistical data.

Figure 1.
Flow chart showing selection of studies for literature review



Results

Cardiorespiratory Testing and its Role in Assessing Physical Fitness

Cardiorespiratory testing with physical stress is integral for assessing physical fitness because it provides a dynamic and real-world evaluation of the body's ability to efficiently transport oxygen to working muscles during activity.[11] Unlike resting measurements, which may not fully capture an individual's response to exertion, stress testing simulates the physiological demands of physical activity. This method allows for a comprehensive assessment of the cardiovascular and respiratory systems' performance under stress, mirroring the challenges encountered during various physical activities.[12] The inclusion of physical stress in testing is particularly crucial because it exposes potential limitations and abnormalities that may not manifest during rest. It enables a more accurate evaluation of an individual's capacity to endure exertion, making it an essential tool for tailoring personalized exercise prescriptions and interventions.

Cardiorespiratory fitness (CRF), as evaluated through parameters like maximal oxygen consumption and ventilatory anaerobic threshold, offers valuable insights into an individual's aerobic capacity and overall fitness. VO2 max represents the maximum amount of oxygen that an individual can utilize during intense exercise, and this value remains constant despite an increase in workload over a given time period.[13] It serves as a gold standard measure of aerobic fitness, reflecting the efficiency of oxygen transport and utilization. A higher VO2 max generally indicates better cardiovascular and respiratory fitness.[13] VT signifies the point during exercise at which the body transitions from aerobic to anaerobic metabolism. It reflects the threshold beyond which the body relies more on anaerobic pathways, indicating the limit of sustainable exercise intensity. Monitoring VT is crucial for optimizing training intensity and preventing premature fatigue during physical activities.[14]

A compelling body of evidence supports the association between low VO2 max and an elevated risk of mortality from cardiovascular diseases.[15] Individuals with lower aerobic capacity often exhibit reduced cardiovascular and

pulmonary health, making them more susceptible to conditions such as coronary artery disease, heart failure, and hypertension.[16] The link between low VO2 max and cardiovascular mortality underscores the importance of cardiorespiratory fitness as a prognostic marker. Regular assessment of VO2 max can serve as a powerful tool for identifying individuals at higher risk and implementing targeted interventions to enhance cardiovascular health and reduce mortality rates.[17]

Cardiorespiratory Fitness in the Context of AF

A significant volume of evidence, originating from epidemiological studies, shows the connection between CRF and diverse health outcomes. These outcomes include the risk of mortality from all causes, cardiovascular diseases (CVD),[18] cancer,[19] diabetes,[20] hypertension,[21] and obesity.[20] Cardio respiratory endurance emerges as a cornerstone in shaping both the prognosis and the effective management of AF, playing a pivotal role in various dimensions of the condition.[22]

A recent systematic review and meta-analysis examining the correlation between CRF and CVDs revealed noteworthy findings. In patients with CVD, those with high CRF exhibited a significant 58% reduction in the risk of all-cause mortality and a remarkable 73% lower risk of cardiovascular mortality compared to their less fit counterparts.[18] Additionally, for each 1 metabolic equivalent (1-MET) increase in CRF among CVD patients, there was a substantial 19% decrease in the risk of cardiovascular mortality. Individuals with higher cardiorespiratory endurance often show case better cardiovascular health. Further analysis within the subgroup of coronary artery disease patients highlighted a noteworthy 68% lower risk of all-cause mortality for those with high CRF, with each 1-MET increase correlating with a significant 17% reduction in the risk of all-cause mortality in this specific patient population.[18] Regular physical activity not only aids in weight management and blood pressure control but also cultivates a resilient cardiovascular system capable of coping with the challenges posed by CVDs.

Although the relationship between cardiovascular diseases and CRF seems straightforward, some re-search show that intense and prolonged exercise training is correlated with an increased incidence of atrial fibrillation.[23] This connection is likely attributable to modifications in atrial volume, left ventricular hypertrophy, and adjustments in autonomic nervous system activity. In addition, the Physicians' Health Study provided information on[9,16,21] individuals engaged in athletics, revealing that a higher frequency of intense exercise was linked to an elevated likelihood of developing AF in young men and joggers.[24] However, this risk diminished with age, offset by the recognized positive impacts of vigorous exercise on other factors associated with AF risk.[24] Despite these findings, a wealth of research data substantiates the link between low cardiorespiratory endurance and an elevated risk of developing and progressing AF. Sedentary lifestyles, often associated with poor physical fitness, contribute significantly to the initiation and advancement of AF.

A population-based study from Khan and colleagues showed that elevated CRF levels are linked to a decreased occurrence of AF.[25] Research indicates that heightened CRF levels correspond to lower levels of inflammatory markers, such as C-reactive protein.[26] Therefore, the diminished risk of AF at increased CRF levels may be influenced by a reduction in systemic inflammation. In the Norwegian study, re-searchers tracked 1117 AF patients to explore how self-reported physical activity and estimated cardiorespiratory fitness relate to outcomes. They found that AF patients who had followed physical activity guidelines had a lower risk of overall (HR = 0.55, 95%CI 0.41-0.75) and CVD mortality (HR = 0.54, 95%CI 0.34-0.86) compared to those who were inactive.[27] Additionally, for every 1 MET increase in CRF, there was a lower risk of overall (HR = 0.88, 95%CI 0.81-0.95) and CVD mortality (HR = 0.85, 95%CI 0.76-0.95) as well as

morbidity (HR = 0.88, 95%CI 0.82-0.95).[27] Recognizing and understanding this association forms the foundation for targeted interventions, underscoring the critical role of promoting physical activity as a preventive measure against AF development and progression.

The transformative impact of improving physical fitness on individuals with AF extends beyond the prevention of onset and progression. Tailored exercise regimens have emerged as a powerful tool in alleviating symptoms and enhancing the overall quality of life for AF patients. Regular exercise contributes to better heart rate control, optimized blood circulation, and enhanced cardiovascular function, all of which are essential components in managing the symptomatic aspects of AF.[28] Furthermore, increased cardiorespiratory endurance is intricately linked to a reduction in fatigue, an improvement in mood, and an overall enhancement in well-being.[29,30] Integrating physical fitness into the comprehensive management of AF not only addresses the immediate symptomatic challenges but also fosters a holistic approach that seeks to improve the overall health and resilience of individuals navigating the complexities of life with AF.

Cardiorespiratory Fitness Testing Methods

There are several methods to access cardiorespiratory endurance. Here the widely used ones will be discussed. The conventional approach for evaluating VO2 max involves utilizing specialized metabolic measuring equipment and follows a widely adopted treadmill-based protocol known as the Bruce protocol. The protocol entails stepping onto a treadmill and progressively elevating both speed and incline at three-minute intervals. The test concludes when you reach 85% of your maximum heart rate, your heart rate surpasses 115 beats per minute for two consecutive stages, or a determination is made that the test should be discontinued.[31]

The Balke Protocol, also treadmill-based, initiates with a constant speed of 3.3 miles per hour (mph), which is equal to 5.3 km per hour (kph) for men and 3.0 mph (4.8 kph) for women.[32] The test commences with a 0 percent incline, and for men, the incline rises by 2 percent after the first minute and then by 1 percent every subsequent minute. For women, the incline increases by 2.5 percent every 3 minutes.[33] Participants are expected to sustain this pattern for as long as possible, consistently pushing the pace and elevating the incline until reaching exhaustion. Notably, documenting the cessation time is crucial, as it is utilized in the calculations for determining VO2 max.

Another treadmill test follows Astrand protocol. The modified Astrand protocol starts with a 5-minute warm-up walk at 3.5 miles per hour [mph], which is equal to 5.6 kilometrres per hour (kph)< with a 2.5 percent grade.[34] Subsequently, participants run to exhaustion, where the running speed is adapted to tire each individual within a duration of 7 to 10 minutes.[34] This specific timeframe is considered adequate for the body to undergo optimal physiological adjustments.

In addition to treadmills, contemporary methodologies involving cycle ergometers, acknowledged as recently developed approaches, can be employed for the assessment of CRF. Cycle ergometry presents an attractive testing modality, distinct from treadmill procedures, due to several advantages: 1) it enables the precise selection of work rates, expressible in appropriate units of power [e.g., kgm•min-1]; 2) the non-weight-bearing nature of cycle ergometer exercise renders it well-tolerated by individuals with orthopedic or physical constraints; and 3) the facile collection of heart rate, blood pressure, and electro-cardiographic data during the testing protocol.[35] According to American Heart Association, two categories of stationary bicycles, namely mechanically braked and electronically braked, should be employed for testing purposes.[36] Mechanically braked ergometers necessitate the maintenance of a specified cycling rate to uphold a constant work rate. In contrast, electronically braked ergometers possess the capability to automatically

modify internal resistance, ensuring the maintenance of prescribed work rates corresponding to the cycling rate. Irrespective of the specific stationary bicycle type, it is imperative that the ergometer exhibits the capacity to adjust the work rate, either automatically or manually, in incremental measures.[36] In a Finnish study, a maximal incremental exercise test using a cycle ergometer was con-ducted by commencing the test at an initial workload of 60W, with subsequent increments of 20W applied each minute until the point of exhaustion.[37] In a Lithuanian study, the participants had 2 minutes of cycling without resistance, and the workload was increased for 15-30W each minute depending on the expected physical capacity, gender, age, and body mass.[38,39] The maximum duration of exercise was 8-12 minutes to induce maximal stress on the cardiopulmonary system.

Normative Values and Factors Influencing Exercise Tolerance

The evaluation of VO2 max should be adjusted to the corresponding age of individual and exercise modality. Considering the age-related decline in CRF, it is noteworthy that elevated values are typically observed in men[39] and there is a tendency for higher values on the treadmill as opposed to the cycle ergometer.[36] In addition, various investigations have demonstrated that the VO2 max recorded using a cycle ergometer is consistently 3% to 29% lower than the corresponding VO2 max values obtained through treadmill assessment.[40,41] The assessment of VO2 max exhibits notable variations across studies due to the diverse testing modalities employed. The utilization of different protocols, such as the Bruce protocol on treadmills, the Balke protocol, the modified Astrand protocol, and various cycle ergometer protocols, introduces considerable methodological diversity. These differences encompass factors like speed, incline, workload increments, and duration of the tests, making direct comparisons between study results challenging.

The treadmill engages a broader range of muscle groups, typically resulting in a higher VO2 max com-pared to the cycle ergometer.[42,43] Conversely, the cycle ergometer offers improved electrocardiographic (ECG) analysis due to fewer artifacts stemming from upper body motion.[34,44] This disparity in muscle involvement and ECG data quality between the two modalities can lead to inconsistent results in studies and assessments. Researchers should acknowledge and consider these inherent differences when interpreting and comparing VO2 max outcomes derived from treadmill and cycle ergometer testing. It is crucial to recognize that the choice of testing modality and protocol can significantly influence the obtained VO2 max values, as it was proven by previous research.[45,46] Researchers should be careful when comparing results from distinct studies, considering the distinct testing methodologies that contribute to the observed discrepancies in VO2 max outcomes.

In addition to the aforementioned differences, cardiorespiratory fitness within a specific population is intricately influenced by physical activity patterns, geographic location, body composition, genetic factors, and various other elements.[38,47] Consequently, reference values for cardiorespiratory fitness may exhibit significant divergence among different populations. Table 2 below illustrates age and sex-adjusted mean values of VO2 max in various countries, serving as reference benchmarks for the respective populations.

Table 1.
VO2 max (mLO2/kg/min)
Reference Values across
Countries

Sex	**Male**					
Agegroup (y.o.)	**18/20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**
USA [44]	N/A	43.0±9.9 (n = 963)	38.8±9.6 (n = 1327)	33.8±9.1 (n = 1078)	29.4±7.9 (n = 593)	25.8±7.1 (n = 137)
Norway[48]	N/A	49.1±7.5 (n = 324)	47.2±7.7 (n = 536)	42.6±7.4 (n = 466)	39.2±6.7 (n = 300)	35.3±6.5 (n = 76)
Norway	N/A	46.2±8.5 (n = 73)	42.7±9.3 (n = 91)	36.8±6.6 (n = 88)	32.4±6.4 (n = 81)	30.1±4.8 (n = 23)
Brazil[44]	45.0±7.5 (n = 1201)	43.5±7.9 (n = 4427)	41.6±7.8 (n = 4383)	38.6±7.9 (n = 1728)	33.7±7.1 (n = 362)	28.7±6.7 (n = 48)
Lithuania[49]	40.35±5.77 (n = 21)	36.65±8.16 (n = 24)	32.89±5.75 (n = 30)	29.54±5.48 (n = 16)		
Denmark[50]	43.4±6.6 (n = 343)	40.0±6.5 (n = 797)	38.9±6.4 (n = 1254)	36.4±6.2 (n = 1098)	33.2±5.2 (n = 921)	29.6±3.9 (n = 225)
Korea [51]	42.3±6.3 (n = 209)	42.0±5.0 (n = 170)	41.4±5.6 (n = 238)	38.0±5.7 (n = 274)	32.4±6.2 (n = 134)	27.2±5.6 (n = 83)
Sex	**Female**					
USA [52]	37.6±10.2 (n = 410)	30.9±8.0 (n = 608)	27.9±7.7 (n = 843)	24.2±6.1 (n = 805)	N/A	N/A
Norway$_1$[53]	43.0±7.7 (n = 215)	40.0±6.8 (n = 359)	38.4±6.9 (n = 493)	34.4±5.7 (n = 428)	N/A	N/A
Norway$_2$[54]	40.3±7.1 (n = 37)	37.6±7.5 (n = 63)	33.0±6.4 (n = 86)	30.4±5.1 (n = 79)	N/A	N/A
Brazil[44]	36.9±6.6 (n = 732)	36.0±7.0 (n = 2028)	34.7±7.1 (n = 1985)	31.4±6.5 (n = 624)	N/A	47.6±11.3 (n = 513)
Lithuania[49]	34.68±6.75 (n = 21)	27.37±4.11 (n = 18)	25.34±3.66 (n = 20)	24.98±4.52 (n = 18)	N/A	54.4±8.4 (n = 199)
Denmark[50]	35.6±5.5 (n = 592)	33.1±5.7 (n = 1158)	32.1±5.6 (n = 1782)	29.8±5.1 (n = 1543)	N/A	48.9±9.6 (n = 38)
Korea [46,51]	34.3±4.3 (n = 110)	32.2±4.5 (n = 211)	30.8±4.6 (n = 284)	28.3±4.6 (n = 367)	26.0±5.7 (n = 336)	23.9±4.4 (n = 195)

Note: *N/A = Not Applicable; this indicates that the specific data point does not apply to the study's design, methodology, or outcomes.*

Limitations. This literature review has several limitations. First, the included studies varied in design, population characteristics, and methodology, which may affect the consistency and comparability of the results. In particular, differences in cardiorespiratory fitness testing protocols (e.g., treadmill vs. cycle ergometer) and reporting standards may lead to heterogeneity in VO_2 max values. Second, not all studies stratified data by age and sex, which limited our ability to provide comprehensive normative comparisons across subgroups. Third, most data were derived from high-income countries, and therefore may not reflect population-specific differences in lower-income or underrepresented regions, including Central Asia. Finally, as this is a narrative literature review and not a systematic review or meta-analysis, there is a risk of selection bias and incomplete retrieval of all relevant evidence.

What' known? CRF has long been recognized as an important predictor of cardiovascular and all-cause mortality. Low VO_2 max levels are linked to poorer outcomes in patients with cardiovascular disease. Physical activity is known to support heart health, but its connection with AF has not been widely emphasized.

What's new? This review brings together recent findings that highlight the role of CRF in AF. It explores how improving physical fitness can reduce symptom burden, lower mortality risk, and enhance overall management. The review also discusses practical aspects of exercise testing and reference values across populations.

Conclusions

This literature review delves into the intricate connection between cardiorespiratory endurance and AF. Various testing protocols, such as the Bruce protocol, Balke protocol, modified Astrand protocol for treadmills, and cycle ergometer protocols, contribute to assessing CRF. However, differences in methodologies, like muscle group involvement and electrocardiographic data quality, necessitate careful interpretation and comparison of VO2 max outcomes. Promoting physical activity has proven beneficial in preventing and managing AF. Higher CRF levels are linked to a reduced AF risk and improved cardio-vascular health. Tailored exercise regimens enhance the well-being of individuals with AF. This comprehensive understanding contributes to a nuanced approach to addressing this prevalent cardiac condition. As research progresses, standardizing testing protocols and reference values will facilitate more consistent comparisons. Integrating cardiorespiratory testing into the clinical management of AF holds promise for improving outcomes and enhancing overall health.

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BILE DUCT ATRESIA. LITERATURE REVIEW

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Yerimova N.
https://orcid.org/0000-0002-0565-5327
Baimakhanov B.
https://orcid.org/0000-0003-0049-5886
Shirtayev B.
https://orcid.org/0000-0002-0773-3878
Kurbanov D.
https://orcid.org/0000-0002-0426-9387
Azadbekova Z.
https://orcid.org/0009-0000-5232-1939
Subhash G.
https://orcid.org/0000-0002-7782-2593

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accepted: 20.08.2025

Corresponding author:
Yerimova Nazira Zholdybaevna – pediatrician, pediatric hepatologist, JSC "National Scientific Center of Surgery named after A.N. Syzganov", Almaty, Kazakhstan., tel.: +77019525050, E-mail: nazier1611@gmail.com

Conflict of interest
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Biliary atresia, diagnosis, screening, cytomegalovirus, portoenterostomy, Kasai, liver, transplantation, immunology, immunosuppression.

Yerimova Nazira[1], Baimakhanov Bolatbek[1], Shirtayev Bakhytzhan[1], Kurbanov Doniyor[1], Azadbekova Zarnigora[1], Subhash Gupta[2]

1 - Syzganov National Scientific Center of Surgery
2 - Centre for Liver & Biliary Sciences Max Hospital, India, New Delhi

Abstract

Biliary atresia is a rare but severe congenital disease characterized by progressive obstruction of the extrahepatic and intrahepatic bile ducts and leading to cholestasis, fibrosis and cirrhosis of the liver in newborns. Epidemiological data demonstrate the variability of prevalence in different regions, which indicates the possible influence of genetic and environmental factors. The pathogenesis of the disease remains the subject of active study and includes the interaction of immune, viral and molecular mechanisms leading to damage to the bile ducts. Clinical diagnosis is difficult due to non-specific symptoms such as jaundice, light feces, and dark urine, which makes early detection critical to improve outcomes. Surgical intervention, known as Kasai surgery, remains the main treatment method and is aimed at restoring bile outflow, however, a significant proportion of patients eventually require liver transplantation. Current research focuses on the search for biomarkers for early diagnosis, the study of molecular targets, and the development of innovative therapeutic approaches, including immunomodulation and cellular technologies. The literature data emphasize the need for an integrated approach to disease management and further scientific research to improve clinical outcomes.

Introduction

In the structure of childhood diseases, an important place is occupied by congenital liver diseases, characterized by a variety of clinical forms, varying degrees of severity of liver damage, progressive course with a frequent outcome in cirrhosis of the liver (LC) and disability of patients. As a rule, the early stage of such diseases is asymptomatic. Liver diseases are one of the most difficult problems in modern hepatology. Liver damage in children is characterized by a high frequency of genetic disorders (both structural and metabolic) and a pronounced effect of the disease on the growth, mental and physical development of the child.[1]

The current stage of studying liver diseases in children is characterized not only by significant achievements, but also by the presence of many unresolved issues. One of them is the problem of early diagnosis of biliary atresia. In the Republic of Kazakhstan, there is no banal screening for the detection of biliary atresia (acholia / hypocholia of the stool). In this regard, early diagnosis was missed, and at the time of contacting our center, 82% of children with biliary atresia already have cirrhosis of the liver, which requires liver transplantation. More than 80% of patients with extrahepatic biliary atresia who undergo Kasai surgery before 60 days of life have jaundice, compared with 20-35% of patients who undergo portoenterostomy later. Age at the time of surgery remains an important predictor of the outcome of Kasai portoenterostomy. In cases with successful bile drainage, the 15-year survival rate is 87%. Kasai portoenterostomy is effective if the operation is performed within 45 days of the child's life. In world practice, the indication for Kasai portoenterostomyis clearly regulated. In the presence of cirrhosis of the liver, this operation is contraindicated. Timely diagnosis and treatment helps to avoid liver transplantation in children in 80% of cases. After 120 days, when cirrhosis of the liver has formed, the only way to save a child's life is liver transplantation.[2]

To date, the criteria for the differential diagnosis of congenital liver diseases have not been clearly defined. The issue of the frequency of formation and rate of progression of liver cirrhosis, as well as factors contributing to its development in other congenital liver diseases, chronic viral hepatitis, autoimmune hepatitis, and metabolic liver diseases in children, remains relevant.[3]

Issues related to the patient's route and the system and algorithm for monitoring patients with biliary atresia remain insufficiently studied, which indicates the need for an in-depth study of this important childhood problem.

The frequency of the disease occurs on average in 1 case per 20,000-30,000 births, accounting for about 8% of all internal organ defects in children, in Japan and China - 1 in 9600, in the USA 1 in 10,000 - 15,000, in Europe 1 in 16,000. About 15-25% of children have other congenital malformations.[4]

Materials and Methods

To prepare this literature review, a systematic search was conducted for publications on biliary atresia in international and national medical databases. Original articles, reviews, clinical recommendations, and case reports published in English and Russian were included.

The literature analysis was carried out in order to identify modern ideas about the pathophysiology of the disease, methods of early diagnosis, surgical and conservative treatment, as well as outcomes in patients of different ages. The articles were evaluated based on data quality, research methodology, and reliability of the information provided. The systematized information was grouped into thematic blocks: epidemiology, etiology, clinical picture, diagnostic approaches, surgical interventions and long-term treatment outcomes.

This approach allowed us to obtain a comprehensive understanding of the current state of knowledge about biliary atresia and identify promising areas for further research.

Ethical approval. This study is a review of published scientific evidence and did not include interventions involving humans or animals. In this regard, the approval of the ethics committee was not required. All the sources used were publicly available, and the work was carried out in accordance with the principles of scientific honesty and correct citation.

Results

Among diseases of the hepatobiliary system in infants of the first months of life, biliary atresia occupies a dominant position, occupying 45% of all cases.[4] Studies conducted by both domestic and foreign specialists confirm that asthma is the most common reason for the need for liver transplantation in children.[5,6] Kasai surgery, or portoenterostomy, is universally recognized as the optimal treatment for biliary atresia. During this operation, obliterated bile ducts are eliminated, restoring the normal outflow of bile through the bile ducts. The effectiveness of surgical intervention in biliary atresia (BA) is assessed according to the following criteria: the appearance of yellow stools, the disappearance of jaundice and a decrease in the concentration of total bilirubin to less than 34 mmol / l within 3-6 months after surgery.[7,8,9]

Diagnostics

1. Screening programs using fecal coloration assessment (acholia/hypocholia) are widely used in the early diagnosis of biliary atresia.

2. Biochemical blood analysis.

3. Ultrasound of the abdominal organs, MRCP.

However, in the conditions of the Republic of Kazakhstan, late diagnosis is noted due to non–compliance with diagnostic standards. In the world [5] and in our country, biliary atresia is the main indication for liver transplantation (Figure 1, 2, 3, 4).

Picture 1(a,b). The stool chart. Characteristic signs of biliary tract atresia, present from the first days of a child's life, are acidic (discolored) stools (1, 2, 3) and intense dark ("beer") colored urine. A stool chart is used to evaluate the feces of a newborn. The card includes directions to contact Perinatal Services British Columbia for follow up if their newborn's stool colour looks abnormal. (*http://bit.ly/biliary_atresia*).

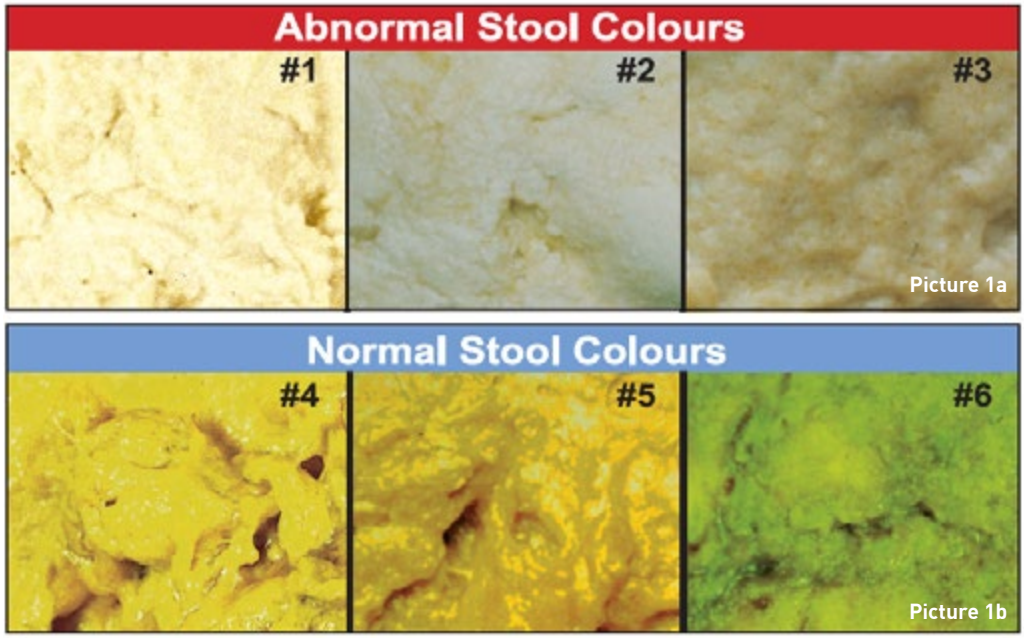


Figure 1. Evaluation of the Pediatric Patient for Liver Transplantation: 2014 Practice Guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Robert. (*Squireset al. Hepatology, Vol. 60, No. 1, 2014)*

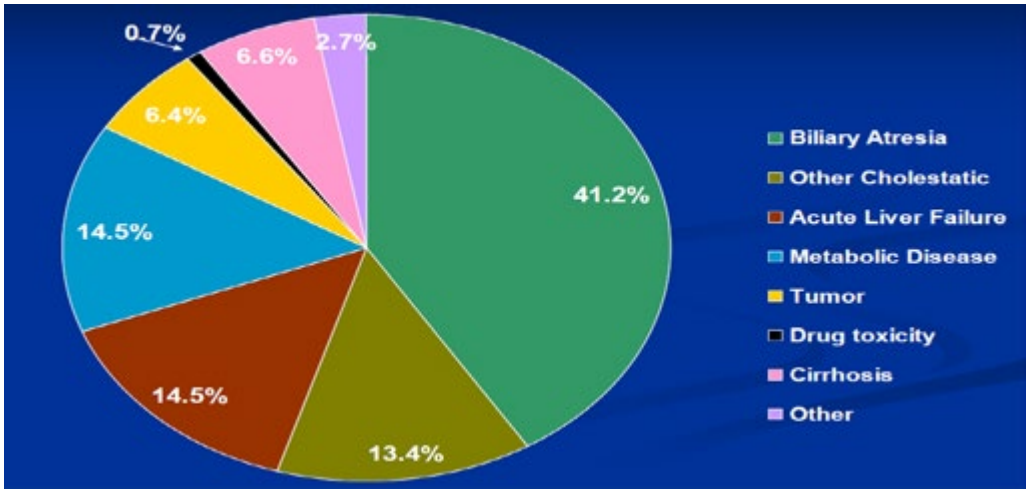
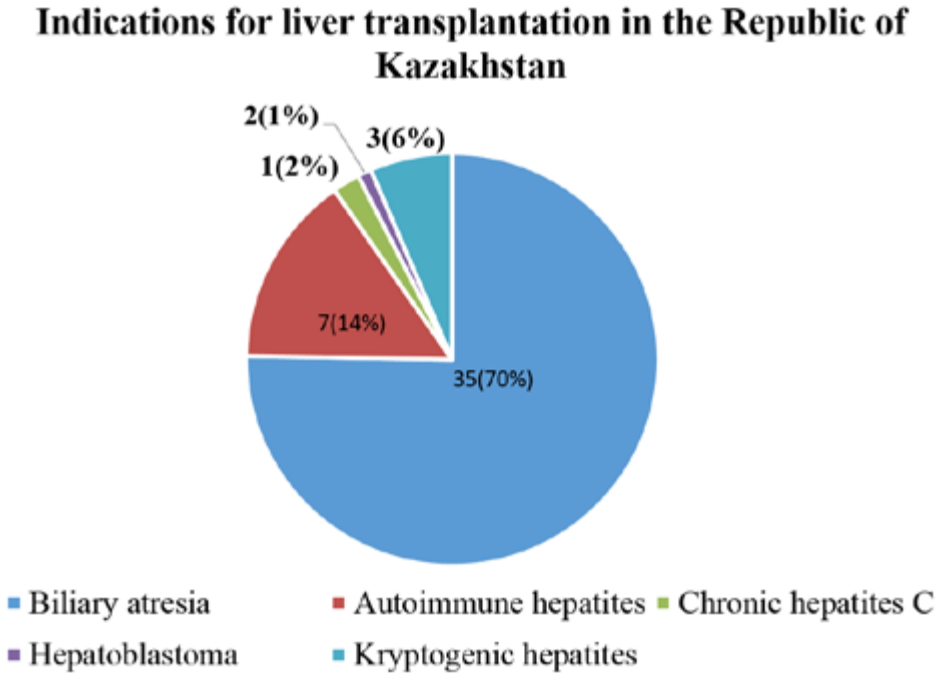


Figure 2. Indications for liver transplantation in children in the Republic of Kazakhstan (data from Syzganov National Scientific Center of Surgery).



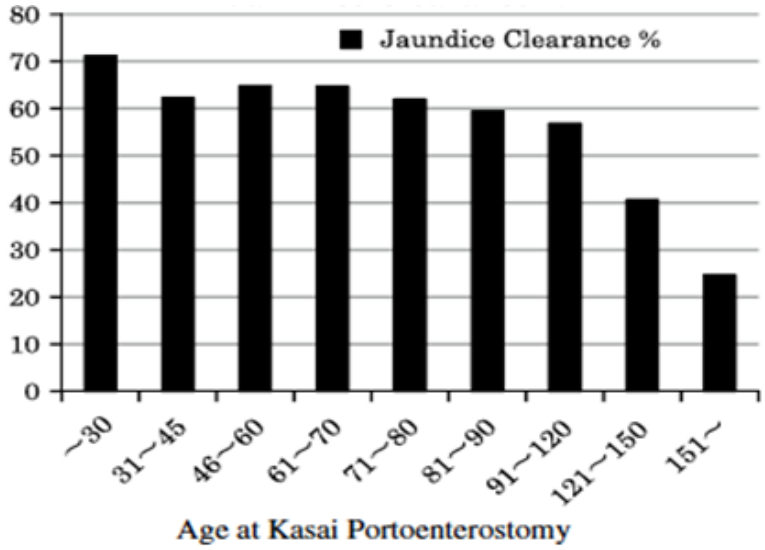


Figure 3.
The effectiveness of the Kasai procedure depending on the age of the child *(Japanese BA Registry) Nioetall. SurgeryToday 2015*

As can be seen in the figure, Kasai portoenterostomy is effective if the procedure is performed on time.[6] Thus, timely diagnosis and treatment helps to avoid liver transplantation in children in 50% of cases.

The success rate of surgical intervention ranges from 36% to 87.2%. In case of ineffectiveness of KPE (Kasai portoenterostomy), it is necessary to perform LT within 6-12 months after surgery, otherwise death is possible due to the development of liver failure.[10] To date, not all the determining factors affecting the effectiveness of surgical treatment have been fully identified.

Late diagnosis of diseases remains an urgent problem at the global level. Untimely detection of liver disease can not only negatively affect the prognosis, but also lead to an increased risk of complications. Hemorrhagic syndrome, which occurs in various locations, and intracranial hemorrhages are considered particularly dangerous, which, even with the restoration of liver function after transplantation, are irreversible.[5,11] Early diagnosis and administration of vitamin K preparation can prevent the development of hemorrhagic syndrome in children with congenital vitamin K deficiency.[12] Therefore, the study of clinical, laboratory and ultrasound signs of the disease in the early postpartum period is a primary task for the timely detection of BA.

The patient's age during Kasai surgery plays a significant role, but is not the only factor influencing the outcome of surgical treatment.[10,13] Several studies have been devoted to the study of both pre- and postoperative laboratory parameters, ultrasound data, and the results of morphological analysis of liver biopsy in order to identify factors predicting the effectiveness of surgical intervention. However, the results obtained are ambiguous and vary significantly.[14]

The development of molecular genetic research methods has significantly expanded our knowledge of the genetic mechanisms of biliary atresia. The scientific literature presents a wide range of studies, including the analysis of candidate genes, genome-wide association search (GWAS), the study of variations in the number of copies of genes (CNV), and exome sequencing (WES), aimed at identifying the causes of this disease.[1,15] Due to the phenotypic heterogeneity of Alzheimer's disease (AD), the genetic characteristics of each patient can significantly affect the severity of the disease and the success of surgical intervention. Despite this, the influence of genetic factors on the results of surgical treatment of BA has not yet been sufficiently studied.

Despite significant progress, the search for noninvasive markers capable of reliably diagnosing severe liver fibrosis and cirrhosis in children with Bauer's disease remains an urgent task. After

all, the progression of liver fibrosis after Kasai surgery and related complications have a significant impact on survival with native liver, and timely diagnosis of such changes makes it possible to determine the optimal time for transplantation.

Analyzing the presented information, it can be concluded that the research topic is highly relevant and consists in identifying factors predicting the effectiveness of Kasai surgery, based on a comprehensive analysis of clinical, ultrasound, and molecular genetic parameters.

Biliary atresia is a progressive disease of the bile ducts, both intrahepatic and extrahepatic. Without timely therapy, death occurs in the first two years of life. The causes of BA are still not fully understood. Kasai surgery is the main therapeutic approach, which, however, is palliative in nature and only prolongs life while preserving the native liver. If the Kasai operation is ineffective, the LT is performed.

The essence of the operation is to eliminate the obliterated bile ducts in order to ensure the outflow of bile into the intestine and thereby stop the development of the disease. However, the result of the operation is not always positive, and its effectiveness varies over a wide range – in about 32-59% of cases, it is possible to prolong life with a preserved liver up to 5-10 years. Recently, several studies have been conducted to identify the factors that influence the results of surgery. Among them, the age of the patient at the time of the operation, the qualification of the surgical surgeon,[16] the presence of other congenital anomalies in the child, the anatomical features of biliary atresia,[17] and the use of steroid drugs in the postoperative period[18] are particularly highlighted.

Although gene variants have been identified in patients with BA and their correlation with the course of KPE has been established, the exact effect of genetic factors on the etiology and prognosis of treatment of patients remains unclear, given the polygenic nature of the disease. The data obtained in the studies are contradictory, and at the moment there is no single concept defining the predictors of the outcome of KPE.

The ineffectiveness of KPE in BA is often accompanied by rapid progression of the disease, resulting in cirrhosis of the liver (LC), which requires urgent liver transplantation (LT). The identification of factors predicting the effectiveness of KPE will make it possible to timely hospitalize a child in a transplant center, organize the selection and training of a donor, as well as optimize therapy, preventive measures, and conduct full-fledged counseling and education for parents. This statement formulates the purpose of this study and demonstrates the importance of the chosen topic for identifying factors affecting the effectiveness of KPE in children with BA.

Biliary atresia is characterized by an inflammatory process and subsequent fibrous obliteration of the extrahepatic bile ducts, which eventually spreads to the intrahepatic bile system, leading to the formation of biliary cirrhosis of the liver.[19] In the vast majority of cases (about 85%), BA occurs in an isolated form, not accompanied by other syndromes, that is, in the perinatal period. The embryonic (syndromic) form is diagnosed less frequently, accounting for 10-15% of all cases of the disease, while the cystic form of BA is detected in 5-8% of cases.[1]

The prevalence of biliary atresia in the population varies depending on the region, ranging from 1 in 8000 people in Asian and African countries to 1 in 18,000 in Europe. The prevalence of the disease is observed in girls.[20,21] Neonatal cholestasis is a characteristic clinical manifestation of asthma. In the first months of life, children need to be differentially diagnosed with a wide range of congenital and hereditary diseases that may disguise themselves as BA symptoms.[4,22] To confirm the diagnosis, a morphological examination of a liver and bile duct biopsy is required during surgery. Treatment of this pathology includes surgery and liver transplantation, which together increases the overall survival rate of children with this disease to 90%.[4,8,10,22] The exact causes of biliary

atresia and the factors influencing the effectiveness of its treatment remain the subject of active scientific research. Among the suggested etiopathogenetic mechanisms are genetic predisposition, immune disorders, and the influence of external influences, such as viral infections and toxins. Numerous studies have highlighted the significant role of immune dysregulation in the occurrence of this disease. Alzheimer's disease (AD) is characterized by a fibroinflammatory process, manifested by the infiltration of inflammatory cells, increased expression of cytokines and chemokines during microscopic analysis of liver biopsies of patients. The pathogenesis of asthma is based on an innate immune response that triggers the activation of NK cells and Th1-type cells, which are a subpopulation of adaptive immunity helper T cells. This mechanism attracts effector T cells, which eventually leads to inflammation and impaired patency. There is also a decrease in the number of Treg cells, which play a key role in suppressing inflammatory processes. After biliary tract obstruction occurs, the immune system continues to cause damage, even when bile outflow is restored. This situation is caused by the activation of T2 and T17 immune responses.[23] Unlike other immune diseases of the bile ducts, after liver transplantation, remissions of the disease are established and are not accompanied by relapses.[1,24]

Viral or toxic damage to the bile duct epithelium can provoke the appearance of new antigenic epitopes, which can cause or increase autoimmune inflammation.[25,26] Various viruses are considered as potential culprits for the development of the disease, including cytomegalovirus (CMV), human papillomavirus (HPV), herpes virus type 6, Epstein–Barr virus (EBV), reovirus and rotavirus.[27] Some studies using PCR to detect viral DNA/RNA or immunostaining for viral IgM+ or Mx protein have shown the presence of traces of a previous viral infection in liver tissues, but this fact has not been confirmed in all cases.[28] Currently, there is no convincing evidence to confirm a link between viral infection and the development of asthma. The results of research in this area are contradictory, due to the lack of control groups, methodological limitations, and ambiguous interpretation of the data obtained.[1,27,29] Despite the fact that a viral infection can worsen the course of BA and increase the risk of adverse consequences, it is interesting that adults infected with these viruses do not develop BA.[1,28,30]

In Australia, scientists have discovered the plant isoflavonoid, biliatreson, which can act as an exogenous toxin and provoke biliary tract atresia in various species. This substance is found in plants. The plant isoflavonoid, biliatreson has a devastating effect on the extrahepatic bile ducts of the larvae of the Danio rerio (Zebrafish) fish, which is a standard model system in biological research. Even without direct exposure to biliatreson, understanding the key mechanisms of bile duct damage can help identify toxins that may be associated with the development of biliary atresia in infants.[1]

Data on the genetic predisposition of patients to biliary atresia and its features are increasingly accumulating. However, the inheritance of this disease does not follow the usual Mendelian laws. Despite the fact that there are known examples of hereditary transmission of BA, the main cause of the disease does not have a direct genetic origin. The widespread occurrence of BA in some Asian regions may indicate a more frequent occurrence of genetic variants associated with asthma in these populations. However, it is impossible to exclude the influence of environmental factors such as nutrition, viral load, etc., as well as differences in diagnostic criteria used by Asian specialists.[1,31] When analyzing the genetic aspects of BA, it is necessary to take into account the results of studies performed with the participation of twins. In 2020, an international meta-analysis of clinical observations on the birth of twins, where one of them suffered from BA, analyzed 35 pairs of twins, including 19 monozygotic and 15 dizygotic pairs, as well as one pair with an unknown ge-

netic nature. The results showed that in only one dizygotic pair, BAwas diagnosed in both twins, whereas in the remaining 34 pairs, the disease was detected in only one of the twins (97.1% of discordant pairs). In a retrospective study conducted by Chinese scientists, 19 pairs of twins were identified, all of which had different BA status, including 8 monozygotic and 11 dizygotic pairs.[32] In the case when monozygotic twins have an identical genotype, but there is a discordance in the presence of a hereditary predisposition, this indicates that genetic factors are not the determining factors. The progression of the disease may vary between twins. On the other hand, if the disease is caused by an infectious or toxic factor, it is expected that it will affect both twins in the intrauterine period, which should lead to the same dynamics of the disease development, which does not correspond to what is observed in the case of discordance in twins.[1] In cases of toxic or infectious embryopathies, especially in monozygotic twins, there is a high frequency of concordance, reaching 80%. This indicates that in most cases both twins suffer from the same disease at the same time, which indicates a significant influence of genetic factors on the development of these pathologies.[1,30] In addition to genetic mutations, the phenotype can be influenced by epigenetic modifications that are transmitted according to non-classical laws of inheritance. Thus, even monozygotic twins with Alzheimer's disease (AD) may show differences in the manifestation of the disease, despite the same genotype, which indicates a possible role of epigenetic factors in the development of BA.

According to studies by various authors, the incidence of BA ranges from 5 to 32 cases per 100,000 newborns.[29,33] The disease is more often diagnosed in girls than in boys.[5] The first mention of this disease dates back to 1817 and belongs to *J. Burns*. He suggested that the appearance of jaundice and whitish stools in infants in the first months of life may be the result of an irreversible violation of the patency of the biliary tract, which poses a serious threat to the child's life. In 1852, *Ch. West* documented a case of the disease in a 13-week-old girl born on time from healthy parents. Despite the successful outcome of the birth, on the third day the child developed jaundice, which worsened every day, and his general condition worsened. *Zhou W.* emphasizes the importance of a comprehensive approach to the diagnosis of AF, combining traditional and modern ultrasound technologies with artificial intelligence to improve the accuracy and effectiveness of diagnosis.[23]

The etiology of BA is still not fully understood, and various hypotheses are being considered: viral, immune,[23] theory of congenital anomalies, genetic.[7,23] The question of the causes of BA is still debatable, and there are many works on its etiology in the world literature. Currently, international experts [33] distinguish two main anatomical types of biliary atresia: syndromic (approximately 10% of cases), which is accompanied by other congenital anomalies, such as polysplenia, asplenia, malformations of the abdominal cavity and heart (Situs inversus, pre-duodenal portal vein, gastrointestinal malformations), and non-syndromic (about 90% of cases), also known as isolated biliary atresia. There are two main classifications of this phenomenon: French, which includes 4 types, and Japanese / British, consisting of 3 types.[33-36] Within the framework of the French classification, type I is characterized by an isolated common bile duct and coincides with type 1 of the Japanese / British classification.[33] The French classification of type II is characterized by the presence of a cyst in the area of the liver gate and obstruction of the common bile duct, which coincides with type 2 in the Japanese / British classification.[33] In turn, type III according to the French classification is determined by obliteration of the left and right bile ducts, while maintaining the patency of the external bile ducts (gallbladder, cystic duct, hepatic duct and choledochus), which corresponds to type 3 in the Japanese / British classification system. Type IV BA is characterized by obstruc-

tion of all external bile ducts while maintaining the patency of the intrahepatic ducts. In the Japanese-British classification, this form is classified as type 3. The effectiveness of treatment in this case is determined by the type of BA.[33,35,36] To date, it is not possible to diagnose AD in the prenatal period with sufficient accuracy and information.[37,38] Diagnosis of biliary atresia is a difficult task, since a single conclusion about the presence of pathology cannot be made based on only one research method. In children with asthma, physical examination may reveal jaundice, acolic stools, and enlarged liver and spleen. However, the manifestation of specific symptoms varies depending on the age of the child. For the early diagnosis of BA, "stool color chart" were created in Japan, which are focused on the color of the stool and are widely used. To diagnose BA, a complex of studies is carried out: general and biochemical blood analysis, coagulogram, determine the spectrum of amino acids and acylcarnitines, the level of oxysterols, the spectrum of bile acids in urine, the concentration of lactate in the blood on an empty stomach and 20 minutes after eating, as well as the hormonal profile of the blood. A distinctive feature of cholestasis in the differential diagnosis of asthma from neonatal hepatitis is an increased level of gamma-glutamyltranspeptidase (GGTP). In children with asthma, the concentration of GGT is significantly higher (902.7 mmol/l) compared with children suffering from other cholestatic liver diseases (263/2 mmol/l). A study by *Tang et al* [39] showed that an increase in GGT levels above 300 mmol/L has a high specificity (98%) in the differential diagnosis of asthma from neonatal hepatitis, but its sensitivity is only 38%. Tan concludes that the ratio of GGT to AST above 2 indicates a high probability of biliary tract atresia and requires additional examination to confirm the diagnosis. An important diagnostic indicator is the relationship between GGT levels and age. The study by *Chen et al* notes that for the assessment of cholestasis by the level of GGT, the most optimal age is the period up to 120 days. In newborns aged 31 to 60 days, the diagnosis of asthma using GGT levels (more than 268 mmol/L) demonstrates high sensitivity (80.5%) and specificity (75.6%), which leads to a diagnostic accuracy of 79.1%. For older age groups (61-90 days), the recommended limit for GGT is 303 mmol/l, for 91-121 days – 298 mmol/l, and for children older than 121 days – 252 mmol/l. It is important to note that data from foreign studies may show a different picture of GGT levels for different age categories. In their study, *Lyu et al*[40] revealed a difference in optimal GGT levels in BA depending on age. For children younger than 4 weeks, the optimal GGT index is 150 mmol/l, at the age of 4 to 8 weeks this indicator rises to more than 250 mmol/l, and in children older than 8 weeks it reaches 300 mmol/l. Laboratory analysis data turn out to be an essential factor in the diagnosis of BA. Ultrasound diagnostics using expert-level devices has high information content and physiological safety in the study of the hepatobiliary system, without the need for preliminary patient training. A distinctive feature of this method is its non-invasiveness, painlessness, atraumatism and absence of contraindications to use.[41] During the newborn period, the diagnosis of biliary atresia is based on certain ultrasound features.[42] These include: the absence of a gallbladder or its unexpressed lumen, the size of the gallbladder not exceeding 19 mm, the absence of its contractile activity after eating, as well as the presence of a fibrous formation (fibrous triangle) in the area of the liver gate. In the case of BA, there is an increase in the ratio of the diameter of the portal vein to the diameter of the hepatic artery, and poly-splice, pre-duodenal portal vein, and situs inversusmay also occur. However, these ultrasound signs are rarely combined in one case. For example, in the third type, the gallbladder may be clearly visible, while in the second type, a cyst with anechoic filler may be found in the area of the hepatic gate. Studies have shown that the sensitivity of the ultrasound method varies from 83% to 100%, and the specificity ranges from

71% to 100%. The diagnostic arsenal also includes radioisotope testing and nuclear magnetic resonance imaging. However, none of these methods is absolutely accurate and cannot guarantee 100% effectiveness. Even with the use of all the listed diagnostic methods, it is not possible to exclude the need for laparoscopic revision of the liver gate and intraoperative cholangiography.[33] However, *Anouti et al*. believe that laparoscopy, unlike biopsy, does not provide information about the patency of the bile ducts and diagnosis of biliary atresia by laparoscopy is impossible. During hepatobiliary scintigraphy, in which technetium-labeled iminodiacetic acid derivatives are used,[23] the movement of bile with radiopharmaceutical (RFP) into the duodenum is analyzed. However, this method is difficult to interpret, as noted by *Wang et al.* and can only be effective in combination with other diagnostic procedures. The sensitivity of the method varies from 84% to 100%, and its specificity ranges from 34% to 93%. If noninvasive methods do not allow the diagnosis of BA, especially in the presence of a gallbladder and an acholic stool, intraoperative cholangiography is required. Pathomorphological analysis of liver biopsy is the most accurate and sensitive method for early diagnosis of biliary atresia, which is critically important for successful surgical intervention. Many researchers agree with this position.[35] Researchers *Liuet al.* 19 patients with biliary atresia (mean age 64 ± 18 years) were examinedusing various diagnostic techniques. The diagnostic accuracy of these methods was: liver biopsy – 96.9%; clinical examination – 70.8%, ultrasound scan – 69.2%, hepatobiliary scintigraphy – 58.5% and liver enzyme analysis – 50.8%. The authors of the study claim that percutaneous liver biopsy has a high diagnostic value not only in the diagnosis of biliary atresia, but also in the detection of other cholestatic liver diseases. Diagnosis with high accuracy is possible with sufficient quality of the liver biopsy. *Anouti et al*. It has been proven that percutaneous liver biopsy has diagnostic accuracy only if there are at least 5-7 portal tracts in the sample. In the case of asthma, the degree of morphological changes in the liver in children correlates with their age. At the age of one month, children showed mild manifestations of cholestasis, bile duct proliferation, and fibrosis in liver biopsies, but by the age of three months, these signs became more pronounced in all children. According to *Davenport M et al*., histological examination plays a key role in the diagnosis of BA, as in 87% (27 out of 31) patients, histological criteria reliably confirmed the diagnosis. The differential diagnosis of biliary atresia includes a distinction from other neonatal cholestases, such as Alagille syndrome, Byler's disease, Karoli syndrome, alpha-1-antitrypsin deficiency, tyrosinemia, Niemann-Pick type C disease, and others.[33,36] To accurately identify the etiology and exclude a wide range of metabolic and endocrine disorders manifested by cholestasis, panels of molecular genetic studies are conducted. Surgical treatment of biliary atresia was first undertaken by *J. B. Holmes* in 1916. It was he who proposed the classification of this disease into "correctable" and "uncorrectable" types. The first successful operations in the "correctable" type of asthma, which showed the effectiveness of surgical intervention, were presented by *W. E. Ladd* in 1928 in the prestigious edition of the American Medical Journal. The results of 11 successful operations led to the conclusion that the clinical and laboratory symptoms of the disease regressed during surgical treatment.[7,23] Despite numerous subsequent attempts at surgical intervention, according to *Zhou W.*, out of 147 operations, only 25 allowed to create a functionally complete portoduodenoanastomosis, which in 13 cases had a positive therapeutic effect. The patients had stool staining, decreased jaundice, and decreased bilirubin levels. However, the positive effect proved to be short-lived, and as a result, all children experienced a recurrence of cholestasis, which progressed to biliary cirrhosis, which ended in death.[23]

The variation in estimates of life expectancy in the presence of a native liver

varies among European and Asian authors. European researchers cite data on a 5-year survival rate ranging from 32 to 55%, while Asian authors show higher rates ranging from 60 to 78%. After the 5-year milestone, the survival rate of children with native liver is significantly reduced. In particular, the 10-year survival rate is estimated at 25-33%, and the 20-year survival rate is 10-20%. There is a known case in the medical literature of the longest catamnestic follow-up of a patient with biliary BA, conducted by *Professor Chardot* from France, which was 30 years.[33] There are many publications in the world and Russian scientific literature on the diagnosis and treatment of BA. BA is a multicomponent disease that requires highly specialized treatment, and centers with more experience in treating this pathology show better results. The study of foreign and Russian studies indicates that the life expectancy of children with congenital biliary atresia and preserved liver is determined by a number of factors: timely detection of pathology, the age of the patient at the time of surgery, the severity of liver fibrosis and obliteration of the intrahepatic bile ducts, the number of working ducts, the clinical form and type of asthma (syndromic or non-syndromic), the presence of episodes of ascending cholangitis and bleeding from the gastrointestinal tract after surgery, as well as the qualifications of the surgeon and the clinic's experience in treating children with this disease. Despite significant progress, a number of issues remain open. Scientists have not yet come to a unified theory about the occurrence of BA, and the optimal duration of surgery is still being debated. In addition, clear prognostic criteria based on biochemical blood parameters have not been developed.

The main symptoms of the BA are manifested in the form of jaundice, white stools and dark urine in newborns born on time and corresponding to their gestational age according to anthropometric indicators.[14,33,43] In the initial stage of the disease, hepatosplenomegaly is usually not observed, however, with the progression of BA and the development of portal hypertension (PH), it can occur. In infants with bilirubinemia, jaundice appears on the 2nd - 3rd day of life, after which its intensity decreases, and by the end of the first or second week of life, it increases. At the same time, about 60% of full-term and 80% of premature babies show symptoms of jaundice during the first week of life. In this regard, this manifestation of the disease is often interpreted as physiological jaundice or jaundice caused by breastfeeding. Acholia of the stool is usually a characteristic sign of congenital acholia, but its appearance does not always coincide with the birth of a child. Most often, it is noted after the discharge of meconium, when the baby is already at home. This circumstance creates difficulties for an accurate assessment of the stool condition by a neonatologist, since parents do not always manage to correctly determine the normal color of the newborn's stool. Screening programs using a newborn stool chart have already been implemented in a number of countries.[5] The main goal of these programs is to help parents correctly interpret the color of their child's stool and consult a doctor in a timely manner if necessary.[5,44] Stool chart contain information about normal shades and those that may indicate pathology.[5] The introduction of screening programs based on the analysis of the newborn's stool chart contributed to an increase in the percentage of early diagnosis.[43] Nevertheless, despite the successes achieved the problem of delayed diagnosis remains relevant at the global level. Vitamin K-deficient coagulopathy is a serious threat in asthma, and hemorrhagic syndrome, including intracranial hemorrhages, may be the first sign of the disease and a reason for examining a child. This complication is not only life-threatening when it occurs, but can also have long-term negative consequences for the child's health, even after transplantation. The development of hemorrhagic syndrome is caused by a violation of the outflow of bile into the intestine, which is characteristic of cholestatic liver diseases. It is important

to note that the absorption of fat-soluble vitamins, including vitamin K, occurs only in the presence of bile in the intestine. Vitamin K, in turn, plays a key role in the synthesis of blood clotting factors II, VII, IX and X produced by the liver.

Early and characteristic signs of cholestaticliver diseases, including BA, include an increase in the level of direct bilirubin fraction. At the same time, other biochemical parameters of cholestasis, for example, γ-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), cholesterol, bile acids and transaminases (ALT and AST), in newborns in the first months of life may not exceed the age norm. Markers of protein-synthetic liver function, such as albumin and fibrinogen, remain stable in the first months of life until liver failure develops. Currently, screening programs aimed at early diagnosis of liver diseases are based on the determination of both bilirubin fractions: total and direct, as well as on the analysis of their relationship to each other. Previously, the diagnosis of cholestasis was based on an analysis of the ratio of direct bilirubin to total, and if it exceeded 20%, cholestatic liver disease was diagnosed. However, modern studies show that cholestatic liver diseases, including neonatal jaundice, can be diagnosed with a high degree of confidence already in the first two weeks of life at a concentration of direct bilirubin above 17.1 mmol/l.[45] The study of ultrasound manifestations of Alzheimer's disease (AD) is of particular importance, since ultrasound is not only informative, but also a widely available imaging method. The key ultrasound signs of asthma include changes in the structure of the gallbladder (gall bladder), manifested in the form of its non-manifestation or visualization in the form of cords on ultrasound.

The absence of a reaction of the digestive tract to food intake and choleretics, as well as the presence of a "hyperechoic strain" are characteristic features of BA. One of the most striking ultrasound signs of the disease is the symptom of a "triangular scar", which is visualized as a hyperechoic seal located above the trunk of the portal vein. Some researchers also consider enlargement of the diameter of the hepatic artery as an ultrasound sign of asthma. In the early postnatal period, before the signs of portal hypertension appear, pathological changes in the liver and spleen, such as an increase in size and modification of the echostructure, are usually not observed. Magnetic resonance imaging and hepatobiliary scintigraphy, like other methods of imaging organs of the hepatobiliary system, are not widely used because they are invasive procedures, and their sensitivity and specificity remain extremely low.[46]

The diagnostic significance of liver biopsy is due to the fact that it allows to detect cholestasis, proliferation of bile ducts and giant cell transformation of hepatocytes. In addition, a liver biopsy makes it possible to determine the degree of fibrosis in this case. The diagnosis of BA is established on the basis of a morphological examination of a biopsy of the liver and external bile ducts, as well as upon detection of obliteration of the common bile duct.[7] Kasai surgery, or portoenterostomy, is considered the gold standard of BA treatment, it was developed by *Professor Morio Kasai* in the 1950s. The essence of surgery is to eliminate the blocked bile ducts and create a new connection between the duodenum and the bile ducts, which allows bile to flow freely through them again. Despite this, the effectiveness of the operation can vary significantly, and the factors influencing its success are still not fully understood. In the postoperative period, a number of complications may occur after Kasai surgery, such as bacterial cholangitis, dilation of the intrahepatic bile ducts, renal failure and hepatopulmonary syndrome, as well as progression of liver fibrosis. After surgery, 70% of children with biliary agenesis have increased liver fibrosis, which can later develop into cirrhosis of the liver. Cirrhosis of the liver, in turn, provokes portal hypertension and liver failure. The main motive for liver transplantation in children with BA is complications caused by cirrhosis. Liver biopsy is considered

the most reliable way to determine the degree of fibrosis. This procedure is invasive and carries the risk of complications, including pain, blood loss, and decreased blood pressure.[47]

Diagnosis of liver fibrosis by liver biopsy is difficult due to the need for general anesthesia, which precludes the possibility of repeated studies and dynamic monitoring of disease progression or regression.[7,48] Some studies have revealed certain disadvantages of liver biopsy, among which one can note the inaccuracy of the choice of biopsy material, as well as the subjectivity of interpretation and evaluation of histological data.[6,7] In the diagnosis of chronic liver diseases in adults, such as alcoholic liver disease, viral hepatitis B and C, and non-alcoholic fatty liver disease, doctors use non-invasive methods to determine the degree of fibrosis, as recommended by clinical guidelines.[7,49] To date, there are no such recommendations for determining the degree of liver fibrosis in children with chronic liver diseases.[7]

Liver fibrosis in adult patients with chronic liver diseases is often assessed using the APRI index (the ratio of aspartate aminotransferase activity to platelet count). This diagnostic method is considered simple and does not require invasive interventions.[7] Nevertheless, the use of the APRI index for the diagnosis of fibrosis in children with chronic viral hepatitis B, cystic fibrosis, and bronchial obstructive BA does not yet have clear recommendations.[19] Currently, visual diagnostic methods, including Doppler ultrasound, are being actively developed to determine the degree of liver damage by fibrosis and cirrhosis in chronic diseases.[7] Studies show that ultrasound signs, such as splenomegaly, a slight increase or decrease in the size of the liver lobes, an uneven contour, increased echogenicity of the parenchyma with an uneven structure, narrowing of the hepatic veins, dilation of the portal and splenic veins, as well as an increase in the index of resistance of the liver arteries, have high diagnostic value in predicting cirrhosis and portal hypertension in patients with chronic liver diseases.[7,10] However, the research was focused on adults and older children, which highlights the need to find non-invasive biomarkers of liver fibrosis and cirrhosis in toddlers, especially in patients with biliary atresia, for earlier diagnosis and intervention.

The success of Kasai's surgery is determined by such indicators as the appearance of stained stools, a decrease in jaundice, and a decrease in total bilirubin (T) to 34 micromol/L within 3-6 months after the intervention. In the long term, the criterion of success is survival with the preservation of a functional liver. However, data from different authors indicate a different effectiveness of the operation, which varies from 36% to 61% in European clinics, while according to *Masaki Nio*, the effectiveness of PE in Japan reaches 87.2%. Despite a significant amount of research conducted in recent decades, the mechanisms influencing the effectiveness of surgery and the prognosis of survival while preserving the native liver are still not fully elucidated.[25] Currently, the authors identify a number of factors affecting the outcome of treatment, which can be divided into modifiable and unmodifiable. The first group includes the patient's age at the time of KPE, the surgeon's professional experience,[17] and the use of steroid drugs in the postoperative period.[50] Unmodifiable factors include the type of biliary atresia, the presence of concomitant developmental abnormalities, indicators of biochemical markers, as well as histological examination data from a liver biopsy: the degree of fibrosis, inflammatory changes, and the diameter of the bile ducts.[14,50]

The genetic characteristics of each patient can significantly correlate with the severity of the disease, however, despite the variety of manifestations of the disease, research on the study of genetic factors affecting the results of surgical treatment, for example, Kasai portoenterostomy, is still limited.[1] Some scientists have suggested that genes such as A1AT, JAG1, and CFTR may influence the outcome of surgery.[21,48-50]

An inherited disease caused by alpha-1-antitrypsin deficiency manifests

itself as an autosomal recessive genetic disorder (genotype ZZ according to the A1AT gene) and is accompanied by pathological changes. In studies conducted with the participation of children,[1] it was revealed that the pathological alleles Z, S and others (in the heterozygous variant) are found more often in patients with chronic liver diseases, among which diseases such as Budd-Chiari disease (n = 67) are distinguished, compared with the data the general population. Children with asthma and the presence of these genotypes were more likely to require liver transplantation compared with children with asthma and having a normal MM genotype.[1] In Thailand, researchers conducted a WES analysis of DNA obtained from liver biopsy samples from 20 patients with intrahepatic jaundice after portoenterostomy.[1] As a result, seven patients had complete disappearance of jaundice after surgery, three had partial improvement, while ten patients had no improvement in portoenterostomy. 13 rare mutations in 9 genes associated with known hereditary diseases have been identified in patients with BA. Among them are cholestatic, although no clinical manifestations have been reported. The list includes: JAG1 (Alajille syndrome), MYO5B (congenital microvilli atrophy/progressive familial cholestasis type 6), ABCB11 (familial intrahepatic cholestasis type 2), ABCC2 (Dubin–Jones syndrome), ERCC4 (Fanconi anemia), KCNH1 (Zimmerman–Laband syndrome), MLL2 (Kabuki syndrome), RFX6 (Mitchell–Ray syndrome) and UG1A1 (Crigler–Najjar syndrome type I). Scientists believe that BA and other liver diseases may have the same causes and course. The detection of such links indicates the severity of the condition and an unfavorable prognosis for patients with asthma whose liver is healthy.[51]

9% of patients with BA, out of 102 examined, had a missense mutation in the JAG1 gene, but the classic signs of Alagille syndrome were not diagnosed. The researchers emphasize that children with this genetic variant have a less favorable prognosis and course of the disease. At the same time, recent studies indicate that Alagille syndrome (AGS) can manifest itself as clinical symptoms of BA: five children who were diagnosed with BA at an early age and pathogenic variants in the JAG1 gene were found to have developed a symptom complex characteristic of AGS by the age of three.[1,26]

Over the past decade, a lot of data has been accumulated on the compensatory mechanisms of the liver in cholestasis, which are associated with the regulation of hepatocyte transporters (BSEP, MDR1, MDR3, OSTb) and nuclear bile acid receptors (FXR, PXR, CAR).[1,52] The liver's high adaptivity to the accumulation of bile acids allows it to effectively cope with this condition. In children with normal development, a genetically determined deficiency of these receptors does not lead to clinical manifestations due to the presence of compensatory mechanisms.[1] However, in cholestatic diseases, including biliary atony, such changes can act as an additional factor contributing to the progression of pathology.[1] Normally, hepatocytes are protected from bile acid toxicity due to the work of hepatocyte transporters, which remove them through the BSEP transporter, and the biliary epithelium due to FIC1 and MDR3. Based on this, studies have been conducted to determine the expression level of genes encoding liver nuclear factors and hepatocellular transporters as potential predictors of liver failure in children with BA.

Studies have shown that in patients with an unfavorable course of liver failure, the expression of the PXR and CAR receptor genes in the liver is significantly lower than in patients with a favorable outcome.[1] In 5 out of 6 patients with decreased expression of both genes, liver transplantation was required before they reached one year of age (at the age of 7 to 11 months). Earlier studies on rats with the PXR gene turned off showed that they had significantly higher liver damage due to the accumulation of bile acids compared with the control group.[1] It is assumed that the decrease in CAR and PXR levels in humans may be due to both a genetic predisposition and in-

flammatory diseases.[1] It has been studied that the nuclear receptors of LC regulate the homeostasis of bile acids by interacting with them and penetrating into the cell nucleus. Inside the nucleus, they decrease the activity of genes responsible for the synthesis and reabsorption of LC, but at the same time enhance the expression of genes encoding transporters BSEP, MRP4 and OSTa-OSTb, which push LC out of the hepatocyte.[1,31,52]

The WES-analysis study was conducted to identify genetic mutations that are more common in children with biliary atony who require early liver transplantation due to the inefficiency of KPE, compared with children whose liver is functioning normally. As a result of the analysis of 98 children who needed early liver transplantation, it was found that the p.A934T variant in the ABCB4 gene was more common than in the group of 97 children with a normally functioning liver after portoenterostomy. A decrease in the activity of the ABCB4 gene responsible for the synthesis of MDR3 leads to a decrease in the content of phospholipids in bile, which can provoke damage to cholangiocytes due to the action of bile acids.

A study conducted in 2020 using full-transcriptome mRNA sequencing of 25 liver samples from patients with Alzheimer's disease (AD) identified two potential markers for predicting the progression of PE: MMP7 and PCK1. MMP7 is an enzyme that participates in the restructuring of the extracellular matrix during the development of liver fibrosis, and PCK1, despite its well-known role in gluconeogenesis, it has not yet been fully studied in the context of the development of BA. A significant increase in the expression of the MMP7 gene was observed in patients with incurable jaundice who underwent KPE and in patients with end-stage liver failure.[1] In contrast, patients with a favorable KPE outcome showed increased expression of the PCK1 gene, while patients with an unfavorable KPE prognosis showed a marked decrease.[1] Therefore, the study of gene expression models in liver and biliary tract tissues can become the basis for the creation of biomarkers predicting the outcome of KPE, which will pave the way for the development of new therapeutic approaches to BA.[1]

The pathogenesis of BA maybe caused by epigenetic changes, including DNA methylation, histone modifications, non-coding RNA expression, and other similar processes.[1] Studies have shown that in the cells of the bile ducts of patients with asthma, there is a significant decrease in the level of DNA methylation compared with patients suffering from other types of cholestatic liver diseases.[1,53] Such a decrease can lead to activation of the IFNy signaling pathway and, as a result, to the development of inflammatory processes.[1] Various epigenetic changes in peripheral leukocytes, such as CD4+ T cells, have already been noted in individual patients with bronchial asthma.[1,18,54] It was revealed that the platelet growth factor A gene underwent hypomethylation, and increased (over expressed) PDGFA production in liver biopsies of patients probably indicates its significant role in this process. The mechanism of BA development [1] is associated with the action of PDGF family proteins, which stimulate the processes of proliferation and fibrosis in various organs. In this context, the rs9690350 (G > C) variant in the PDGFA gene correlates with an increased probability of developing BA in 506 patients, which was revealed when compared with a group of 1,473 healthy people. In patients with Alzheimer's disease (AD), there are differences in the expression of certain microRNAs in the liver compared with healthy people. For example, mir-29b and mir-142-5p microRNAs show increased activity in the liver of patients with asthma, and their targets are the DNMT1 and DNMT3 genes encoding key enzymes involved in DNA methylation.[1] At the same time, the expression of mir-145-5p microRNA, which regulates the ADD3 gene, is reduced in the liver tissues of some patients with BA.[1,55]

The Kasai surgical procedure hepatoportoenterostomy, proposed in 1955, is a method of treating asthma aimed at preserving liver functionality and delay-

ing the need for transplantation in children. However, until now, little is known about the parameters that determine the effectiveness of this operation and the life expectancy of patients with preserved liver. The genetic characteristics of each patient, as well as the activity levels of various genes in liver and bile duct tissues, can serve as prognostic biomarkers, but further scientific research is required to confirm them.

Discussion

BA is a complex disease with a high risk of progression to fibrosis and cirrhosis of the liver, despite modern approaches to diagnosis and treatment. Current data confirm that an early Kasai procedure significantly increases the likelihood of restoring biliary outflow. However, a number of studies have shown significant variability in outcomes even during surgery in the first 30-45 days of life, which indicates the presence of additional prognostic factors, including the morphological features of the ducts and the degree of hepatic fibrosis at the time of the intervention.[1]

There are contradictions in the literature regarding the role of preoperative diagnosis. Some authors emphasize the high informative value of ultrasound and serial biochemical tests for early detection of BA, while others point to the low specificity of these methods and the need for invasive confirmation of the diagnosis (liver biopsy, cholangiography). This highlights the importance of developing standardized screening protocols and a multidisciplinary approach to patient assessment.[3,6]

Long-term outcomes remain problematic. Even after successful Kasai, a significant proportion of patients demonstrate the progression of fibrosis, cholestatic complications, and the need for liver transplantation. Literature data on the use of immunomodulatory therapy or anti-inflammatory strategies after surgery are still limited to small cohorts and different surveillance protocols, which makes it difficult to conclude the actual effectiveness of these approaches.

Thus, current data indicate the need for an integrated approach, including early diagnosis, individual choice of surgical tactics, and standardized postoperative follow-up schemes. To improve the prognosis, it is necessary to conduct multicenter studies with sufficient statistical power aimed at identifying predictors of a successful outcome and developing optimized algorithms for managing patients with BA.[15]

Limitations. The review is limited to retrospective and small cohort studies with different methodologies, which makes it difficult to compare data. Not all studies included long-term outcomes, and publications were reviewed only in English and Russian, which could exclude relevant studies.

What's Known? Biliary atresia is a rare neonatal disease causing progressive liver fibrosis and cirrhosis. Early diagnosis and Kasai portoenterostomy improve bile flow, but outcomes vary with age and liver damage. Standardized early detection and management protocols are lacking; many patients eventually require liver transplantation.

What's New? This review highlights current gaps in early diagnosis, heterogeneity of treatment outcomes, and long-term prognosis in biliary atresia. It emphasizes the need for standardized screening, unified management protocols, and further multicenter studies to improve patient outcomes.

Conclusion

Biliary atresia remains a serious neonatal liver disease with variable outcomes despite surgical intervention. Early diagnosis and timely Kasai portoenterostomy improve prognosis, but long-term complications and need for liver transplantation persist. Standardized diagnostic and management protocols, along with multicenter research, are essential to optimize care.

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К 90–ЛЕТИЮ ДОЦЕНТА УРАШЕВА С. Т.

Урашев Сапар Темирбаевич родился 2 июля 1933 года в поселке Чапаево Западно-Казахстанской области. После окончания Уральской фельдшерско-акушерской школы поступил в Алма-Атинский государственный медицинский институт. В 1958 году с отличием закончил АГМИ и был оставлен аспирантом кафедры госпитальной хирургии, возглавляемой профессором М.И. Брякиным. В 1961 году – по конкурсу на ученом Совете был избран на должность ассистента кафедры госпитальной хирургии.

Урашев С.Т. защитил кандидатскую диссертацию на тему: «Особенности изменения гемодинамики и оксигенации крови при право- и левосторонних чресплевральных операциях».

Будучи ассистентом кафедры госпитальной хирургии лечебного факультета АГМИ, с 1961 года по 1967 год заведовал общим хирургическим отделением больницы скорой медицинской помощи г.Алма-Аты, совмещая учебно-педагогическую деятельность с работой в системе практического здравоохранения.

Урашев С.Т в 1967 году по конкурсу избирается на должность доцента родной кафедры. Сапар Темирбаевич – автор 57 печатных трудов, 35 из них посвящены экспериментальным клиническим исследованиям по сравнительной оценке лечения терминальных состояний методом аутореинфузии с внутриартериальным нагнетанием и вспомогательным искусственным кровообращением аппаратами ИСЛ-2 и ИСЛ-3, остальные научные работы посвящены актуальным вопросам торакальной и абдоминальной неотложной и плановой хирургии.

Доцент Урашев С.Т. был хирургом широкого диапазона, владеющим оперативными вмешательствами на органах грудной и брюшной полости. Выполнял операции при сочетанной черепно-мозговой и спинальной травме, травмах магистральных сосудов, при переломах конечностей.

Несмотря на большую занятость клинической и учебно-педагогической работой, он выполнял изначимую общественно-политическую работу в институте.Благодаря природному орагнизаторскому таланту и высоким моральным качествам, гуманизму 11 лет избирался председателем профсоюзного комитета АГМИ. Урашев С.Т. в течение многих лет работал секретарем первичной партийной организации лечебного факультета.

При создании подготовительного отделения при АГМИ, для поступления в медицинский вуз, первым деканом был доцент – Урашев С.Т. Вместе со своим учителем профессором Брякиным М.И., участвовал в организации и проведении съездов хирургов Казахстана и Средней Азии, Пленумов правления Республиканского общества, где выступал с основными докладами, в прениях по программным докладам

Сапар Темирбаевич был высококвалифицированным педагогом, лекции и практические занятия проводил на высоком учебно-методическом уровне с демонстрацией больных по теме занятий.

С 1982 года доцент Урашев С.Т. работал на кафедре хирургических болезней лечебного, стоматологического

факультетов, возглавляемой профессором Ш.Н. Абдуллаевым. Параллельно с педагогической работой, клиническая работа занимала значительную часть его времени: консультировал службу экстренной хирургии ЦГКБ, являлся наставником молодых хирургов.

Доцент Урашев С.Т. заслуженно пользовался авторитетом и уважением среди студентов, сотрудников кафедры и больницы, любовью пациентов.

За заслуги в профессиональной и научно-педагогической деятельности С.Т.Урашев награжден медалью «За доблестный труд», государственным знаком «Отличник здравоохранения», почетными грамотами, имеет ряд благодарностей от правительства Республики, руководства медицинского университета.

Ушёл из жизни Сапар Темирбаевич 18 февраля 2004 года.

Дело его жизни продолжают дети и внуки. Память о благородном человеке, рыцаре медицины навсегда сохранится в сердцах его сподвижников, коллег и учеников.

Проф. Ибадильдин А.С.
Врач Аталыков Б.