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EARLY ACTIVATION PATHWAYS IN PATIENTS UNDERGOING OPEN HEART SURGERY WITH MULTICOMPONENT GENERAL ANESTHESIA COMBINED WITH HIGH THORACIC EPIDURAL ANESTHESIA

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Anesthesia. Fast-Track, ERAS

Abstract

Background: Early mobilization of patients in the postoperative period after open heart surgeries, significantly decreases the risk of complications, accelerates the restoration of functional capacity, shortens the length of hospital stay, and reduces treatment costs

Materials and methods: Open heart surgeries were performed on 60 patients at Ankara "Bayındır" Hospital, Central Clinical Hospital, and Baku Health Center were included in the study. Patients were divided into two groups. 30 of them underwent the procedure with the use of multi-component balanced general anesthesia and intravenous fentanyl analgesia in the postoperative period. The other group of 30 patients underwent catheterization under high thoracic epidural anesthesia, with the administration of ropivacaine prior to induction and, in the postoperative period, ropivacaine and fentanyl. We conducted a study on central hemodynamic parameters and analgesic effects.

Results: Thirty of them underwent the procedure with the use of multi-component general anesthesia and intravenous fentanyl analgesia in the postoperative period. The other group of 30 patients underwent catheterization of the high epidural space with the administration of ropivacaine before induction and, in the postoperative period, ropivacaine and fentanyl. We conducted a study on central hemodynamic parameters and analgesic effects.

Conclusion: It has been established that for patients in the second group according to the Enhanced Recovery After Surgery strategy, hemodynamic support and effective pain management can contribute to early patient mobilization after surgery. Early mobilization, in turn, can expedite recovery and reduce the length of hospital stay, ultimately leading to potential cost savings.

Жоғары кеуделік эпидуральды анестезиямен ұштасатын көпкомпонентті жалпы анестезиямен ашық жүрекке хирургиялық операцияны бастан өткеретін науқастардың ерте белсену жолдары

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Тұжырым

Өзектілігі: Ашық жүрекке жасалған операциялардан кейінгі операциядан кейінгі кезеңде науқастарды ерте мобилизациялау, асқыну қаупін айтарлықтай төмендетеді, функционалдық мүмкіндіктерінің қалпына келуін тездетеді, ауруханада болу ұзақтығын қысқартады және емдеу шығындарын азайтады.

Материал және әдістер: Анкара «Байындыр» ауруханасында, Орталық клиникалық ауруханада және Баку денсаулық орталығында 60 науқасқа ашық жүрекке операция жасалды.Пациенттер екі топқа бөлінді.Олардың 30-ы операциядан кейінгі кезеңде көпкомпонентті теңдестірілген жалпы анестезияны және көктамырішілік фентанилді анальгезияны қолдану арқылы процедурадан өтті. 30 пациенттен тұратын басқа топ индукцияға дейін ропивакаинді, ал операциядан кейінгі кезеңде ропивакаин мен фентанилді енгізе отырып, жоғары кеуде эпидуральды анестезиясы астында катетеризациядан өтті. Біз орталық гемодинамикалық параметрлерге және анальгетикалық әсерге зерттеу жүргіздік.

Нәтижелер: Операциядан кейінгі кезеңде олардың 30-ы көп компонентті жалпы жансыздандыру және көктамырішілік фентанилді анальгезия қолдану арқылы процедурадан өтті. 30 пациенттің басқа тобына индукцияға дейін ропивакаинді, ал операциядан кейінгі кезеңде ропивакаин мен фентанилді енгізу арқылы жоғары эпидуральды кеңістікті катетеризациялау жүргізілді. Біз орталық гемодинамикалық параметрлерге және анальгетикалық әсерге зерттеу жүргіздік.

Қорытынды: Операциядан кейін жақсартылған қалпына келтіру стратегиясы бойынша екінші топтағы науқастар үшін гемодинамикалық қолдау және ауырсынуды тиімді басқару операциядан кейін пациенттің ерте мобилизациясына ықпал ете алатыны анықталды. Ерте жұмылдыру, өз кезегінде, қалпына келтіруді тездетеді және ауруханада болу ұзақтығын қысқартады, сайып келгенде, әлеуетті шығындарды үнемдеуге әкеледі.

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Кардиоанестезия, Эпидуральды Анестезия. Fast-Track, ERAS

Пути ранней активации пациентов, прошедших операцию на открытом сердце с применением многокомпонентной общей анестезии в сочетании с высокой грудной эпидуральной анестезией

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Абстракт

Актуальность: Ранняя мобилизация больных в послеоперационном периоде после операций на открытом сердце существенно снижает риск осложнений, ускоряет восстановление функциональных возможностей, сокращает сроки пребывания в стационаре и снижает затраты на лечение.

Материалы и методы: В исследование были включены операции на открытом сердце 60 пациентам в больнице «Байындыр» Анкары, Центральной клинической больнице и Бакинском центре здоровья.Пациенты были разделены на 2 группы. 30 прошли процедуру с применением многокомпонентной сбалансированной общей анестезии и внутривенной анальгезии фентанилом в послеоперационном периоде. Другой группе 30 больным была проведена катетеризация при высокой торакальной эпидурального анестезии, с введением ропивакаина до индукции и, в послеоперационном периоде, ропивакаина и фентанила. Мы провели исследование показателей центральной гемодинамики и анальгетических эффектов.

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Ключевые слова:
Кардиоанестезия, эпидуральная анестезия. Ускореннаяпроцедура, ERAS

Результаты: 30 из них прошли процедуру с применением многокомпонентной общей анестезии и внутривенной фентаниловой анальгезии в послеоперационном периоде. Другой группе из 30 пациентов перед индукцией проводилась катетеризация верхнего эпидурального пространства с введением ропивакаина, а в послеоперационном периоде — ропивакаина и фентанила. Мы провели исследование параметров центральной гемодинамики и анальгетического эффекта.

Заключение: Установлено, что у пациентов второй группы по стратегии Ускоренного восстановления после операциигемодинамическая поддержка и эффективное обезболивание могут способствовать ранней мобилизации пациентов после операции. Ранняя мобилизация, в свою очередь, может ускорить выздоровление и сократить продолжительность пребывания в больнице, что в конечном итоге приведет к потенциальной экономии затрат.

Introduction

Early mobilization of patients in the postoperative period after open heart surgeries (such as aortic coronary bypass grafting (CABG), aortic valve replacement or repair, mitral valve replacement or repair, closure of atrial septal defect (ASD), closure of ventricular septal defect (VSD), aortic aneurysm repair, removal of myxoma, implantation of a cardioverter-defibrillator and cardiac pacemaker, ablation procedure) performed for arrhythmias, ischemic heart disease, heart failure, valve stenosis or regurgitation, aortic aneurysm, congenital intracardiac and extracardiac defects, significantly decreases the risk of complications, accelerates the restoration of functional capacity, shortens the length of hospital stay, and reduces treatment costs.[1,2,3]

The solution to the problem of reducing hospitalization duration due to the increasing number of cardiac surgery patients has once again become one of the main issues of the modern era.[4]

At the end of the last century, the method of Enhanced Recovery After Surgery (ERAS) - accelerated rehabilitation protocol after surgery or Fast-Track, became widely spread, which is currently being widely reintroduced in surgery.[5] This strategy represents a new approach to patient management at the pre-, intra-, and postoperative stages and is aimed at reducing pain, complications, stress reactions, and organ dysfunctions in the postoperative period.[5] The ERAS program is divided into 3 stages, each of which is a multi-component system.[6]

1. Preoperative Phase: Patient education and instruction, bowel preparation, reduction of fasting period (no food intake for 6 hours and no liquids (tea, coffee, milk, juice) for 2 hours), provision of carbohydrate loading, prophylaxis against thromboembolic complications;

2. Intraoperative Phase: Antibiotic prophylaxis, use of regional (epidural) analgesia, avoidance of long-acting anesthetics, maintenance of perioperative therapy with minimal use of infection treatment, complete removal from continuous nasogastric intubation, normothermia, preservation of drainage tubes, minimal invasive surgery;

3. Postoperative Recovery: Effective wound healing, oral non-opioid analgesics, prophylaxis against vomiting and postoperative nausea, early mobilization, early enteral feeding.

Early mobilization prevents muscle weakness and pulmonary embolism by improving early activity of skeletal muscles, respiratory function, and oxygenation of tissues, while reducing the risk of deep vein thrombosis.[7]

The application of new "fast-track cardiac anesthesia" methods has resulted in early extubation, reduced stay in the intensive care unit and hospital, and prevention of complications.[8]

Cardiovascular diseases first came into focus in the literature in the middle of the last century, when high thoracic epidural anesthesia (HTEA) associated with cardiovascular surgery was noted.[9] In modern times, information about the use of HTEA began to be re-described in the literature by Jakobsen CJ, leading to extensive discussions about the placement of the catheter in the thoracic epidural space, anesthesia and analgesia during and after surgery, as well as the regulation of arterial hypertension.[9]

By the end of the last century, the technique of using HTEA began to be applied to patients before surgery, after which this technique became widely used. This method provides reliable analgesia during surgery and in the postoperative period, allowing for early extubation and attracting attention with its advantages over others.[9]

It should also be noted that during open-heart surgeries, A.D. Volkovet al. conducted a comparative study between patients who underwent anesthesia using a balanced method with propofol and fentanyl via the endotracheal route and analgesia with fentanyl in the postoperative period, and patients who underwent endotracheal and high thoracic epidural anesthesia (ropivacaine 0.75% - 10-12 ml and fentanyl 2-3 mcg/kg) with ropivacaine 0.2% and fentanyl 2 mcg/ml introduced into the thoracic epidural space at a rate of 3-10 ml/hour in the postoperative period. It was found that during epidural anesthesia, arterial hypertension and myocardial depression undergo insignificant changes. With the use of HTEA with 0.75% ropivacaine, a reduction in propofol consumption was 15%, and fentanyl was 50%.[1]

E.A. Korniyenko et al. note that after placing the catheter in the epidural space, injection of naropin in a dose of 2 mg/ml leads only to the use of a sensory block, while in a dose of 7.5 mg/ml, it leads to a motor block and intraoperative use (analgesic, high-quality analgesia) yielding more positive results. Additionally, the use of morphine by the epidural method enhances its analgesic effect. The duration of morphine action at a volume of 2-4 mg is 20 minutes, with a maximum starting from 30-60 minutes and lasting 8-12 hours, and at a volume of 5-10 mg, it lasts up to 16-30 hours.[10]

However, some authors consider the presence of analgesia in patients with a high risk of cardiovascular decompensation (injury to the left coronary artery) to be dangerous and recommend the use of general anesthesia. This type of anesthesia provides stable hemodynamics and coronary perfusion.[11]

The aim of the study is to determine the optimal anesthesia method based on central hemodynamic parameters by comparing patients who underwent open heart surgery with endotracheal balanced propofol-fentanyl anesthesia or multi-component general anesthesia (MGA) with postoperative fentanyl analgesia, to those who received MGA combined with high thoracic epidural anesthesia (ropivacaine 0.75% - 10-12 ml and fentanyl 2-3 mcg/kg) and postoperative epidural administration of ropivacaine 0.2% and fentanyl 2 mcg/ml at a rate of 3-10 ml/hour. Additionally, the study aims to implement and prepare for early activation according to the Enhanced Recovery After Surgery program in the postoperative period.

Material and Methods

A total of 60 patients (41 males, 19 females; mean age 52.18±6.38 years) who underwent open heart surgery at Ankara "Bayındır" Hospital, Central Clinical Hospital, and Baku Health Center were included in the study.

The study included patients undergoing aortic coronary bypass, aortic valve replacement or repair, mitral valve replacement or repair, closure of atrial septal defect, closure of ventricular septal defect (VSD), aortic aneurysm repair, removal of myxoma, implantation of cardioverter-defibrillator and pacemaker, and patients randomized to multi-component general anesthesia (MGA) with ablation procedure. The primary criterion for operated patients was the absence of contraindications to regional anesthesia. Additionally, patients not included in the research were those undergoing emergency surgery, those with ejection fraction below 30%, severe valve dysfunction, severe peripheral vascular injuries, decompensated stages of diseases, simultaneous interventions (carotid endarterectomy, etc.), and those connected to the artificial blood circulation device during surgery.

The initial condition of the patients was assessed through comprehensive laboratory and instrumental examinations, including Doppler echocardiography (EchoCG), ECG, X-ray, angiography. From the central hemodynamic parameters, the following parameters were determined using Doppler echocardiography: cardiac index, dPmax (maximum pressure gradient of the left ventricle), global ejection fraction (GEF), cardiac function index. Other parameters such

as heart rate (HR), maximum arterial pressure (MAP), minimum arterial pressure, mean arterial pressure (MAP), central venous pressure (CVP) were also evaluated.

Postoperative pain relief effect was assessed using the Visual Analog Scale (VAS) and the Efficacy-Safety Scale (ESS) or the Efficacy Safety Score (ESS).[12]

Central hemodynamic parameters were evaluated in 7 stages: the 1st stage before the start of anesthesia induction, the 2nd stage immediately after anesthesia, the 3rd stage during sternotomy, the 4th stage after the completion of the surgery, the 5th stage 6 hours after surgery, the 6th stage 12 hours after surgery, and the 7th stage 18 hours after surgery.

Depending on the type of anesthesia administered, the patients were divided into two groups.

The first group consisted of patients (n=30) who received endotracheal balanced propofol-fentanyl anesthesia or multi-component general anesthesia with postoperative intravenous fentanyl analgesia at a concentration of 10 mcg/ml at a rate of 1-5 ml/hour. The second group included patients (n=30) who underwent high epidural catheterization at the Th1-Th4 level together with MGA before induction (with ropivacaine 0.75% - 10-12 ml and fentanyl 2-3 mcg/kg) and received postoperative epidural ropivacaine 0.2% and fentanyl 2 mcg/ml at a rate of 3-10 ml/hour.

Premedication and general anesthesia were conducted according to general principles in both groups.

In the postoperative period, pain relief efforts were assessed using the Visual Analog Scale (VAS), where a score of <3 indicated mild pain at rest and <4 during coughing, while a score of 4 and above indicated inadequate pain control. According to this scale, pain levels were categorized as follows: 0-1 no pain, 1-3 mild pain, 3-5 occasional mild pain, 5-7 persistent mild pain, 7-9 severe pain, and 10 unbearable pain. According to the Efficacy-Safety Scale (ESS), agitation was noted in patients with scores of 10 and above.

Two methods were used during open heart surgeries: "Pump" method, where an artificial blood circulation device is connected to the heart to maintain cardiac and pulmonary function for a certain period. The other method is without artificial blood circulation, where the heart maintains its activity, which can only be achieved during coronary-artery-bypass.

During emergency and elective open heart surgeries, consent for the procedure was personally obtained from the patients themselves.

Statistical analysis was performed using non-parametric Mann-Whitney U test and Kruskal-Wallis test.

This study was a retrospective and observational single-center study. It was approved by the local institutional ethics committee. From January 1, 2019, to November 31, 2023, 60 open-heart surgeries using artificial circulation were performed at the "Bayındır" Clinic in Ankara, the Central Clinical Hospital, and the Health Center in Baku. Before the examination, each patient provided written informed consent, and contact was maintained after the operation. Patients came for routine check-ups to our department. All patients provided written informed consent to participate in the study.

Results

The results of the hemodynamic parameters measurements from the study are reflected in Table 1.

In both groups, bradycardia, a decrease in cardiac index, cardiac function index, and dPmax were noted before the start of the operation reflecting the dysfunction of the left ventricle function, along with an increase in CVP during intraoperative period. After performing sternotomy and openheart surgery, a slight increase was observed in MAP, CVP, CFI, and MVT. Similar changes have been reported by other authors as well. The explanation for this phenomenon is the compensatory elimination of peripheral vasospasm as a response to myocardial dysfunction, consequently, after resolving the defects, stability in central hemodynamic parameters is achieved.

Parameters	Groups	Hemodynamic parameters in different stages					
		Intraopertive phase				Postoperative phase	
		Induction	After Anesthesia	Sternotomy	Postoperative	6 hours	12 hours	18 hours
MAPmmHg	MGA	79.9±13.5	76.9±15.6	81.6±12.2	80.2±10.4	82.5±14.8	80.1±13.1	80.3±1.9
	MGA with HTEA	72.8±8.37*	67.8±13.5*	73.4±9.5*	74.2±12.6*	72.0±12.4*	76.1±12.4*	76.2±12.6*
HR min[1]	MGA	50.0 (42.3-59.8)	59.5 (51.3-64.8)	62.5 (50.5-70.5)	61.0 (55.3-74.5)	87.0 (80.3-99.0)	82.5 (75.0-96.6)	81.2 (74.0-95.5)
	MGA with HTEA	52.0 (43.3-59.8)*	51.5 (44.3-63.8)*	54.5 (48.3-62.8)*	56.0 (48.3-66.0)*	79.5 (75.3-92.0)*	81.0 (73.0-89.8)*	81.0 (73.0-89.8)*
CVPmmHg	MGA	11.3±3.6	14.0±4.0	11.8±3.7	12.7±3.5	5.0±4.0	5.8±4.6	5.9±4.7
	MGA with HTEA	12.5±3.1*	11.8±3.2*	9.4±2.5*	11.9±2.3*	6.3±4.2*	4.9±3.3*	5.1±3.1*
CI l/min/m²	MGA	2.20±0.42	2.43±0.59	2.96±1.23	2.70±0.80	3.69±0.78	3.39±0.38	3.46±0.42
	MGA with HTEA	2.20±0.44*	1.97±0.51*	2.55±0.33*	2.57±0.55*	3.39±0.38*	3.34±0.50*	3.32±0.44*
dP_{max}mmHg/s	MGA	697±116	537±169	567±142	565±145	770±255	744±412	915±339
	MGA with HTEA	542±136*	479±150*	552±141	567±201	880±293	1015±421	997±353
GEF %	MGA	24.6±6.1	21.0±6.6	22.2±7.0	22.0±5.6	24.0±6.3	22.0±5.4	21.7±5.3
	MGA with HTEA	26.2±7.30*	23.5±5.4*	26.1±6.3*	26.0±7.0*	24.2±6.1*	24.0±5.7*	22.9±5.5*
CFI	MGA	3.47±1.18	3.14±1.04	3.88±1.42	3.79±1.24	5.56±1.92	4.96±1.19	4.98±1.11
	MGA with HTEA	3.42±0.77*	3.03±0.65*	3.69±0.69*	3.65±0.87*	5.23±1.22*	5.13±1.14*	4.95±1.29*

*-p<0,05 compared with MGA group

Table 1.
Central hemodynamic parameters during the conducted research

Discussion

It should be noted that during sternotomy and open-heart surgery, patients who underwent MGA in combination with HTEA exhibited a 10% ($p<0.05$) decrease in MAP and a 11% decrease in HR compared to patients who received MGA alone. During the examination, it has been determined that the application of HTEA initially results in a decrease in MAP and HR, this is associated with sympathetic and motor blockade (due to vasodilation of arteries resulting in an increase in vascular volume). Also, a 25% ($p<0.001$) decrease in CVP was observed compared to initial measurements. During epidural anesthesia, the Bainbridge reflex is noted due to sympathetic blockage in the spinal cord, and this reflex is formed due to the superior and inferior venae cava and pulmonary veins. The stimulation is transmitted to the central sympathetic nucleus of the brainstem, resulting in an activation of the sympathetic autonomic nervous system, leading to tachycardia.[13]

Looking at the postoperative period, it can also be observed that arterial hypertension and tachycardia are less prominent in patients who received MGA in combination with HTEA. In fact, when comparing preoperative indicators to the first 24 hours postoperatively, no significant difference is observed. Additionally, after the operation, patients receiving ropivacaine and fentanyl epidurally showed an increase in dPmax, indicating an improvement in the function of the left ventricle. The stability of indicators such as CI, GEF and CFI during epidural analgesia has also been confirmed by other authors.[14]

Vasodilation effect of ropivacaine-induced epidural analgesia also improve the pulmonary system and systemic circulations. Additionally, HTEA exerts a positive effect on the respiratory system, further enhancing the quality of postoperative pain relief and preventing atelectasis.[15]

In general, HTEA results in pulmonary vasodilation, thereby preventing the accumulation of fluid in the lungs and improving respiratory mechanics and oxygenation.

None of the patients examined in the study experienced epidural hematoma related to perioperative hypocoagulation or other complications. Although literature reports mention arrhythmias associated with sympatholytic effects during epidural anesthesia, such cases were not observed in our study.[16]

In the postoperative period of cardiac surgery, the main etiopathogenesis of pain syndrome consists of the activation of dermal receptors and pleural nociceptors due to the effect of drainage tubes resulting from sternotomy, chondropathic pain in the joints of the sternum and rib-chest area,[17] as well as the formation of chronic neuropathic syndrome due to damage to the intercostal nerves from the thoracotomy retractor.[18] In such pains, simultaneous application of 5% medical lidocaine plaster and epidural analgesia significantly reduces postoperative pain.[18]

Epidural anesthesia is considered the "gold standard" of regional anesthesia, blocking the transmission of nociceptive impulses by afferent fibers, which can also be applicable to cardiac surgery. Additionally, it should be noted that epidural anesthesia at the Th_1-Th_4 level creates a sympathetic block in the heart and also has an additional cardioprotective effect.[19]

In foreign countries, "fast-track cardiac surgery" (perioperative anesthetic management aimed at facilitating extubation of patients from mechanical ventilation within 1-6 hours after cardiac surgery with the goal of reducing length of stay in the hospital, conducting intensive therapy, and reducing treatment costs) is based on the strategy of rapid discharge of patients from the intensive care unit after cardiopulmonary bypass and extubation, which is associated with restoring physical activity in the postoperative period.[20] The concept of "fast-track cardiac surgery," proposed by Lloyd-Donald P. and colleagues, showed that 4 out of 16 patients undergoing surgery according to the protocol were successfully extubated in less than 4 hours and transferred to the intensive care unit.[21]

In former Soviet Union countries, such an approach was called early mobilization and was associated with discharging patients from the intensive care unit, extubation, and restoration of postoperative physical activity.[22]

Maintaining the function of the cardiopulmonary apparatus for a prolonged period in patients with artificial circulation was considered the "gold standard" in previous years. However, modern research shows that using a low-opioid anesthesia protocol reduces the increase in IL-6 levels and brings the volume of the heart closer to normal.[23]

Starting from the 2000s, many countries began to advocate for early mobilization. Numerous authors have noted that the use of such strategy leads to significant reductions in complications of both blood circulation and respiratory systems, as well as inflammation-associated problems. In this regard, according to modern concepts, skeletal muscles are immunocompetent endocrine organs. During increased muscle activity, specific anti-inflammatory cytokines (myokines) are actively produced. Myokines participate in various clinical conditions, including the modulation of the inflammatory response in postoperative complications, systemic inflammatory reactions, endothelial dysfunction, and other pathophysiological mechanisms.[24]

Certainly, as HTEA has the analgesic effect within the first 6 hours after weaning off the mechanical ventilation, it contributes to cut down the expenses incurred in patients undergoing open-heart surgery until discharge from the hospital.[25]

The main components of early mobilization of patients undergoing open-heart surgery are as follows:

1. Patient admission to the hospital one day before or on the day of surgery;
2. Use of short-acting hypnotics or inhalation anesthetics, small doses of opioids, or ultra-short-acting drugs for anesthesia, with the use of HTEA;
3. Early separation of the patient from the mechanical ventilation, and use of HTEA after tracheal extubation;
4. Avoidance of high doses of opioids in the postoperative period, and use of HTEA;
5. Accelerated rehabilitation - early mobilization and feeding;
6. Stay in the intensive care unit for up to 6 hours and discharge from the stationary ward within 1-4 days;
7. Outpatient follow-up for 30 days.

Such accelerated early activation is referred to as "early extubation" or "early tracheal extubation" in English literature, which constitutes a fundamental stage in the patient's mobilization.[26]

In American sources, the term "fast track" is sometimes expressed with another specific term, such as "early discharge" or "ultra-fast track hospital discharge," which primarily entails the monitoring of patients in the hospital for 1-4 days after surgery.[16]

Literature refers to extubation within 30-40 minutes as "ultra-early extubation",[27] and extubation within 1 hour is termed as "ultra-early activation".[28]

During the postoperative period, among patients who received MGA in combination with HTEA, one patient had a score of 4 or higher on the Visual Analog Scale, whereas in the group of patients who underwent MGA alone, two patients had a VAS score of 4 or higher. Regarding to the efficacy-safety scale, among patients who received MGA in combination with HTEA, one patient had a score of 10 or higher, the same result also observed in patients who received only MGA.

Limitations: During the research, no limitations arose (in collecting data on patients and refusals, financial problems, etc.).

What's known? According to the concept of the ERAS strategy, patients who underwent open-heart surgery, should be mobilized early, monitored in the intensive care unit for up to 6 hours, and after 1-4 days, can be discharged from the hospital under outpatient follow-up

The application of "fast-track cardiac anesthesia" methods in cardio-anesthesia has resulted in early extubation, decreased duration of stay in the intensive care unit and hospital, prevention of complications, accelerated the treatment process, and significantly reduced treatment costs.

What's new? VAS and ESS scales play an effective role in predicting the intensity of pain syndrome in the early postoperative period of patients undergoing open-heart surgery regardless of the type anesthesia administered. However, the advantage of efficacy-safety scale is that, apart from VAS, this scale predicts the negative course of the postoperative phase and the development of postoperative complications

Conclusion

When comparing patients who underwent open heart surgery with endotracheal balanced propofol-fentanyl anesthesia or MGA with postoperative fentanyl analgesia, to those who received MGA combined with HTEA (ropivacaine 0.75% - 10-12 ml and fentanyl 2-3 mcg/kg) and postoperative epidural administration of ropivacaine 0.2% and fentanyl 2 mcg/ml at a rate of 3-10 ml/hour, it is observed that administration of the latter results in hypodynamic hemodynamic changes, making it an optimal anesthesia method for patients undergoing open-heart surgery.

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PANCREATIC CANCER DIAGNOSIS OVERCOMING BIAS AND ERRORS (CASE SERIES)

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Abstract

Diagnosing malignant pancreatic neoplasms presents a challenging task fraught with the possibility of diagnostic errors due to similarities with other pathologies such as pancreatitis, neuroendocrine tumors, and cystic formations. The key diagnostic method is contrast-enhanced multi-detector computed tomography, yet even this method has certain limitations that may affect diagnostic accuracy.Through the analysis of clinical cases, typical errors accompanied by visual characteristics that can be misleading in differential diagnosis have been identified. Hypodensity and tissue structure alterations, changes in ducts, or mass effect may be common features of both cancer and pancreatitis. Comparing visual signs with the clinical picture and employing additional methods aids in reaching a more precise diagnosis.It is important to note that rare pathologies such as serous oligocystic adenoma and intraductal papillary mucinous neoplasm may also pose additional challenges for accurate diagnosis due to their unusual characteristics on computed tomography scans.The conclusions of the study underscore the importance of a multimodal approach to diagnosing malignant pancreatic neoplasms, including the use of various imaging methods to ensure an accurate diagnosis and the selection of the most appropriate treatment strategy

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Ұйқы безінің қатерлі ісігінің диагностикасы біржақтылық пен қателерді жеңу (жағдайлар сериясы)

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Тұжырым

Ұйқы безінің қатерлі ісіктерін диагностикалау күрделі, ол панкреатит, нейроэндокринді ісіктер және кистоздық түзілімдер сияқты басқа патологиялармен ұқсас болғандықтан диагностикалық қателер жиі кездеседі. Негізгі диагностикалық әдіс - көп кесінділі контрастты компьютерлік томография, бірақ бұл әдіс диагноздың дәлдігіне әсер ететін шектеулерге ие.Клиникалық жағдайларды талдау кезінде, дифференциалды диагностикада көрнекі сипаттамалармен қатар жүретін типтік қателер анықталды. Гиподенсивтілік және тін құрылымының өзгеруі, түтіктердің өзгеруі немесе масс- әсер ісіктің де, панкреатиттің де ортақ белгілері болуы мүмкін. Визуалды белгілерді клиникалық көрініспен және қосымша әдістермен салыстыру дәлірек

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Түйінді сөздер:
Ұйқы Безі Түтікшелік Аденокарциномасы, Түтікішілік Инвазивты Папилярлы Муцинозды Обыр, Нейроэндокринді Обыр, Компьютерлік Томография, Ұйқы Безі.

диагноз қоюға көмектеседі.Серозды олигоцисталық аденома және интрадукталды шырышты-папиллярлы ісік сияқты сирек патологиялар компьютерлік томография сканерлеуіндегі ерекше сипаттамаларына байланысты дұрыс диагноз қоюға қосымша қиындықтар тудыруы мүмкін екенін атап өткен жөн.Зерттеу нәтижелері дәл диагнозды қамтамасыз ету және ең қолайлы емдеу стратегиясын таңдау үшін әртүрлі бейнелеу әдістерін қолданумен қоса, ұйқы безінің қатерлі ісіктер диагностикасында мультимодальды тәсілдің маңыздылығын көрсетеді.

Диагностика рака поджелудочной железы: преодоление погрешностей и ошибок (серия случаев)

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Протоковая Аденокарцинома Поджелудочной Железы, Инвазивный Внутрипротоковый Папиллярный Муцинозный Рак, Нейроэндокринная Опухоль, Компьютерная Томография, Поджелудочная Железа

Аннотация

Диагностика злокачественных новообразований поджелудочной железы представляет собой сложную задачу, обремененную возможностью диагностических ошибок из-за сходства с другими патологиями, такими как панкреатит, нейроэндокринные опухоли и кистозные образования. Ключевым методом диагностики является мультиспиральная компьютерная томография с контрастным усиление, однако и этот метод имеет определенные ограничения, которые могут сказаться на точности диагностики.В ходе анализа клинических случаев были выявлены типичные ошибки, сопровождающиеся визуальными характеристиками, которые могут ввести в заблуждение при дифференциальной диагностике. Гиподенсивность и изменение структуры ткани, изменения в протоках или масс-эффект могут быть общими признаками как рака, так и панкреатита. Сопоставление визуальных признаков с клинической картиной и дополнительными методами помогает поставить более точный диагноз. Редкие патологии, такие как серозно-олигокистозная аденома и внутрипротоковая слизисто-папиллярная опухоль, могут также представлять собой дополнительные сложности для правильной диагностики из-за их необычных характеристик на сканах компьютерной томографии.Выводы исследования подчеркивают важность мультимодального подхода к диагностике злокачественных новообразований поджелудочной железы, включая использование различных визуализационных методов для обеспечения точного диагноза и выбора наиболее подходящей тактики лечения.

Introduction

Every year, over 1100 new cases of pancreatic cancer are registered in Kazakhstan, leading to the death of approximately 800 patients. The disease affects elderly men and women equally; however, the high mortality rate is due to late diagnosis at stages when surgical intervention is no longer possible. Surgical resection is the primary treatment method that can improve the five-year survival rate up to 30% if the disease is detected early. Nevertheless, most cases are discovered at an inoperable stage, highlighting the critical importance of timely diagnosis. Multislice computed tomography (MSCT) is a key diagnostic method, providing high accuracy and sensitivity in determining the stage of the disease. This not only facilitates precise staging and prediction of tumor resectabilitybut is also crucial for planning treatment strategies.1

The aim of this study is to analyze common diagnostic errors in pancreatic cancer (MSCT) and to differentiate it from other pathologies such as pancreatitis, neuroendocrine tumors, and cystic formations. The work focuses on identifying and thoroughly examining these errors to improve diagnostic approaches. Modern imaging methods combined with histological analysis offer opportunities for accurate differentiation of pancreatic cancer from other diseases, which is critical for selecting the optimal treatment strategy.

Materials and Methods

In this retrospective study, clinical and histological data from 301 patients diagnosed with pancreatic cancer between 2018 and 2022 were analyzed. Among these, 4 cases with the most challenging diagnostic scenarios were selected. The diagnostic evaluation was conducted in the Department of Radiology at the National Scientific Center of Surgery named after A.N. Syzganov, using multislice computed tomography (MSCT-160 Canon Aquilion). The studies were performed with slice thicknesses of 0.8 cm and the administration of the contrast agent Iopromide 370, with the dosage calculated based on the patient's body weight at a ratio of 1 kg x 1.22 ml of contrast agent.

Histological verification of diagnoses was based on materials obtained through cytobiopsies or surgical interventions. The processing of histological samples was carried out in the pathology department of the same center.

The study was approved by the ethics committee of the National Scientific Center of Surgery named after A.N. Syzganov. All participants provided informed consent for the processing and use of their medical data within the framework of this research project.

Case presentation

Patient 1, 32 years old

Complaints upon admission: Jaundice of the sclera and skin, abdominal pain and heaviness, and general weakness. Biochemical blood analysis: ALT - 36.90 U/L; AST - 33.50 U/L; Total Bilirubin - 40.20 μmol/L.

Ultrasound examination of the abdominal organs (US AB): Ultrasound findings suggest biliary hypertension. An irregular area in the projection of the major duodenal papilla (MDP) may correspond to a neoplasm.

CT of the abdomen with bolus contrast enhancement (CT AB with CE): The Wirsung duct is visualized throughout its entire length and is dilated up to 3 mm. In the MDP projection, circular thickening of the duodenal mucosa is noted, with an area of mucosal thickening adjacent to the head of the pancreas and the common bile duct (CBD), approximately 3.9 x 2.6 cm in size. Lymph nodes in the portahepatis, peripancreatic, and para-aortic regions are enlarged up to 3.0 cm. Conclusion of CT AB with CE: The CT findings are more consistent with an MDP neoplasm. Para-aortic adenopathy. Resident physicians' description: No differences from the primary conclusion.

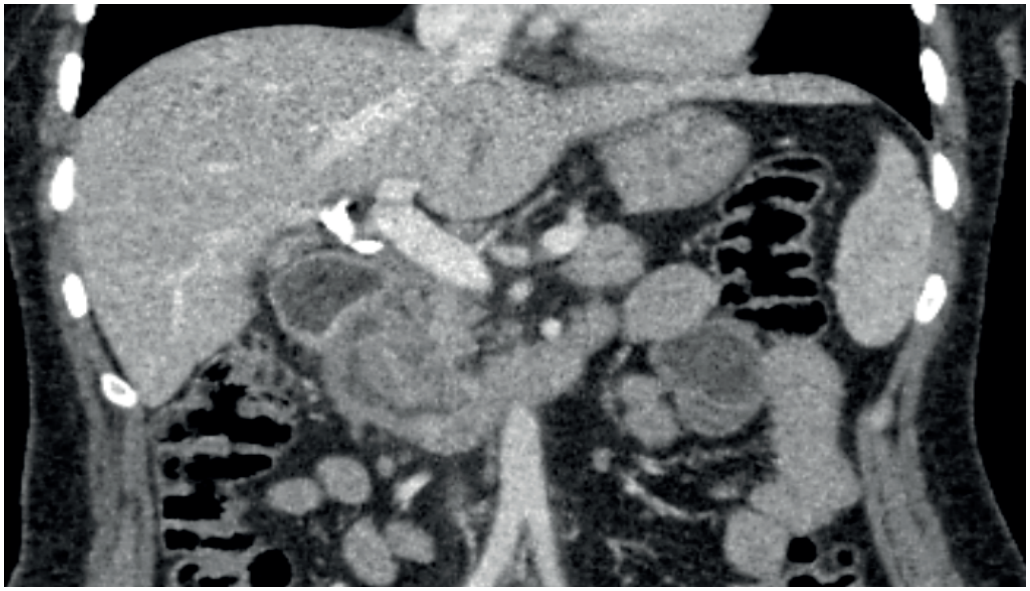


Figure 1.
Circular thickening of the duodenal mucosa in the MDP projection.

Figure 2.
Affected area adjacent to the head of the pancreas.

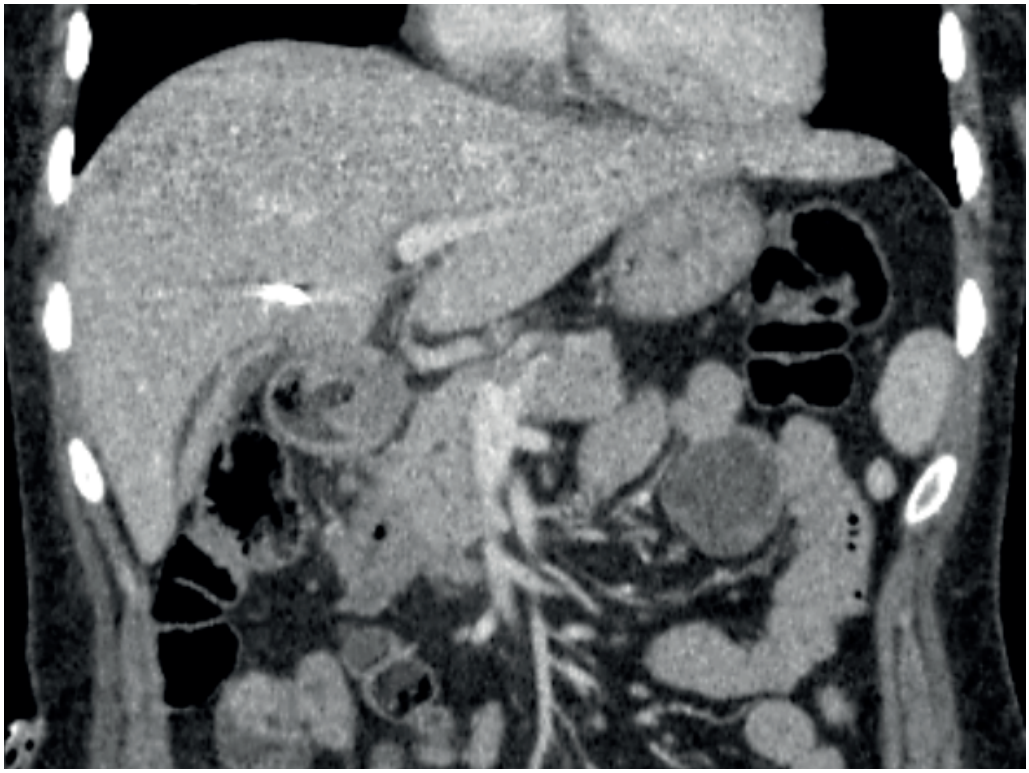
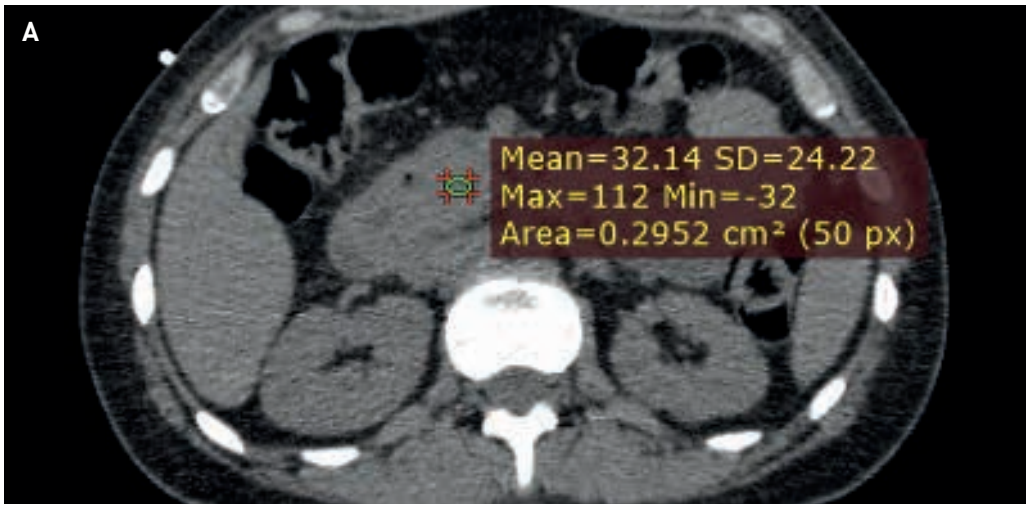
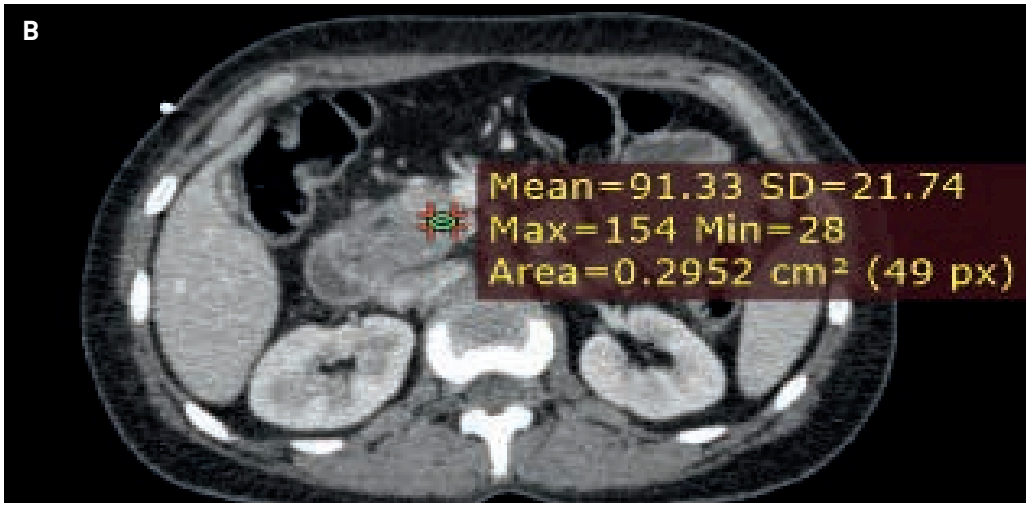
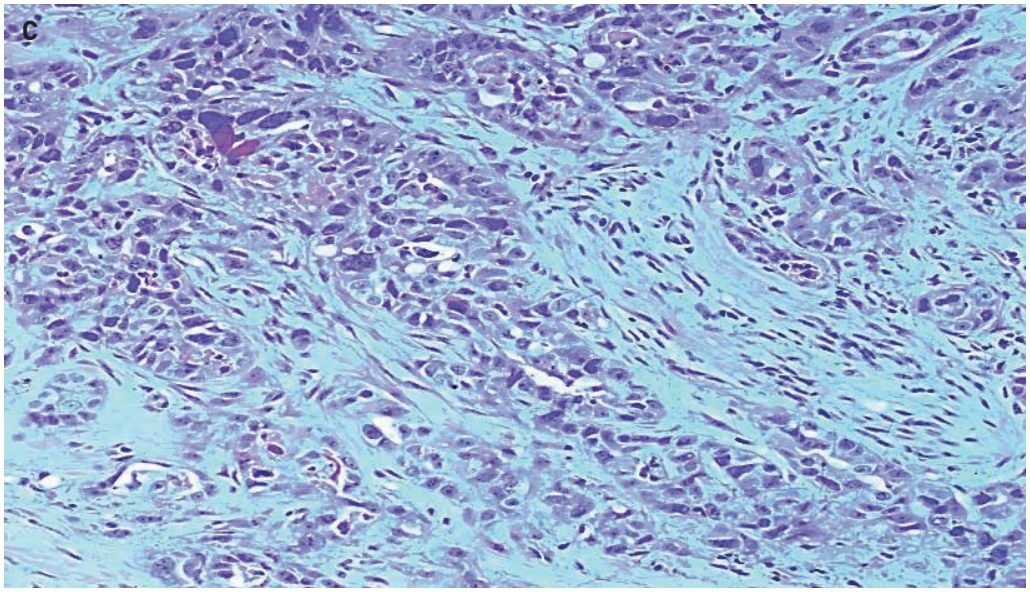


Figure 3 A, B.
Does not show signs of delayed contrast accumulation







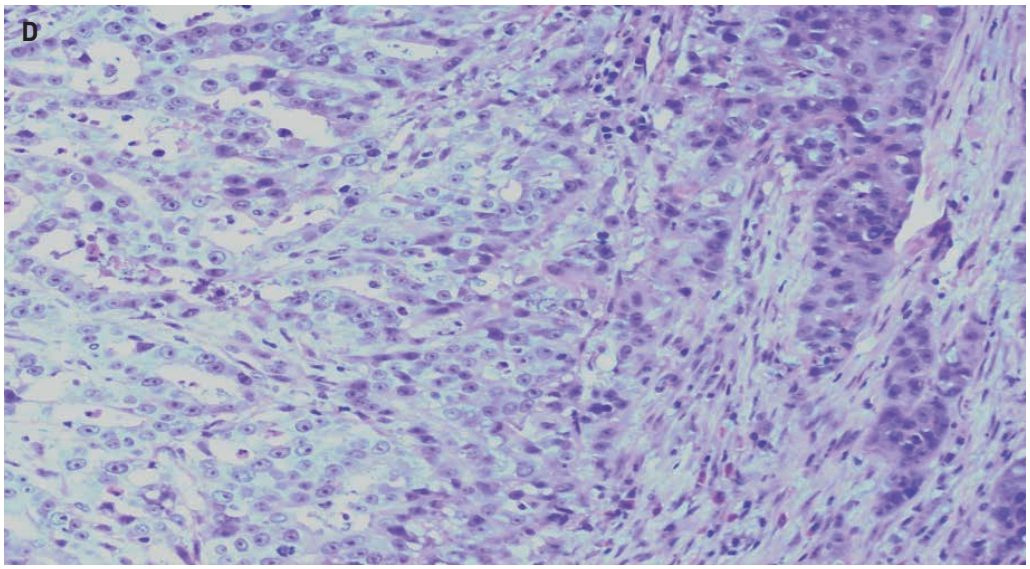


Figure 3 C, D.
The preparations contain fragments of a tumor of the head of the pancreas with a tumor of solid-tubular structure, made up of rounded cells with eosinophilic cytoplasm, high nuclear-cytoplasmic ratio, polymorphic vesicular nuclei with large nucleoli. Proliferative activity is up to 8 mitotic figures (including atypical mitoses) per 10 fields of vision at a magnification of x400.
Tumor complexes are immersed in desmoplasticstroma, infiltrated with neutrophils and lymphocytes.
Stained with HE. UV x200

Patient 2, 57 years old

Complaints upon admission: Episodes of pain in the right hypochondrium and epigastrium of a girdling nature, general weakness, fatigue, and a weight loss of 14 kg over the past year. Biochemical blood analysis: ALT - 15.40 U/L; AST - 22.50 U/L; Total Bilirubin - 8.40 μmol/L.

CT of the abdomen with bolus contrast enhancement (CT AB with CE): In the projection of the pancreas body, a mass with well-defined, irregular contours and heterogeneous structure is noted, intensely and heterogeneously accumulating contrast medium, measuring 8.4 x 8.1 cm, with vessels within its structure. The pancreatic duct is slightly dilated. Enlarged peripancreatic and para-aortic lymph nodes up to 1.6 cm are observed (Figure 4).

endocrine tumor of the pancreas body with secondary adrenal involvement. Para-aortic and peripancreaticadenopathy.

Resident physicians' description: No differences from the primary conclusion. Histological conclusion: Serous oligocystic adenoma of the pancreas.

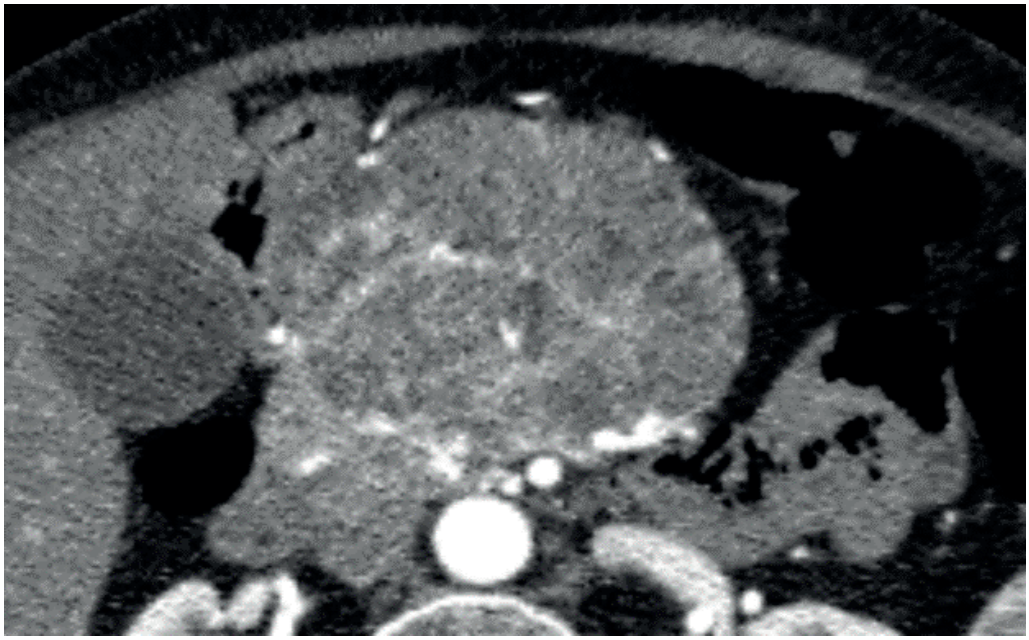


Figure 4.
In the projection of the pancreas body, a mass with well-defined, irregular contours and heterogeneous structure, intensely and heterogeneously accumulating contrast.

Conclusion of CT AB with CE: The CT findings may correspond to a neuroendocrine tumor of the pancreas body with secondary adrenal involvement. Para-aortic and peripancreaticadenopathy.

Resident physicians' description: No differences from the primary conclusion. Histological conclusion: Serous oligocystic adenoma of the pancreas.

Patient 3, 66 years old

Complaints upon admission: Pain in the epigastric region and retrosternal area, vomiting, weight loss of 10 kg over 2 weeks, general weakness. Biochemical blood analysis: ALT - 17.3 U/L; AST - 100.80 U/L; Total Bilirubin - 51.5 μmol/L.

Conclusion of abdominal ultrasound (US AB): Diffuse changes in liver tissue consistent with hepatitis. Calcification in the right lobe of the liver. Splenomegaly.

CT of the abdomen with bolus contrast enhancement (CT AB with CE): In the projection of the pancreas head, a mass with indistinct contours and tissue density is noted, measuring 4.0 x 3.8 cm, with slight contrast enhancement after administration. The mass involves the duodenum (DU), gastroduodenal artery (GDA), and the wall of the portal vein (PV) (about 30%). The superior mesenteric vein (SMV) is not involved. The pancreatic duct is dilated up to 5 mm. Enlarged lymph nodes in the peripancreatic and para-aortic regions up to 1.7 cm (Figure 5,6).

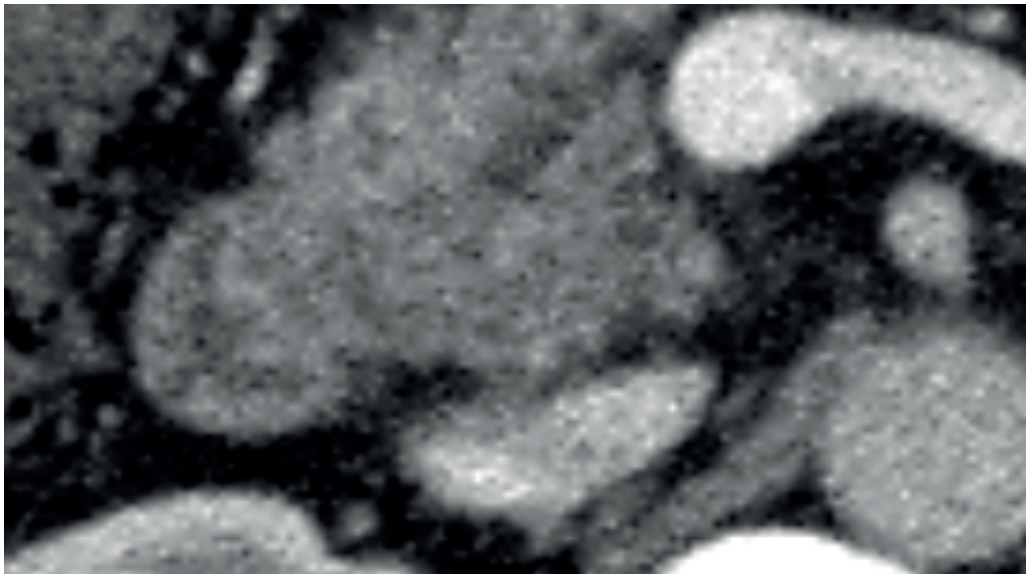


Figure 5.
In the projection of the pancreas head, a mass with indistinct contours and tissue density, with slight contrast enhancement after administration.

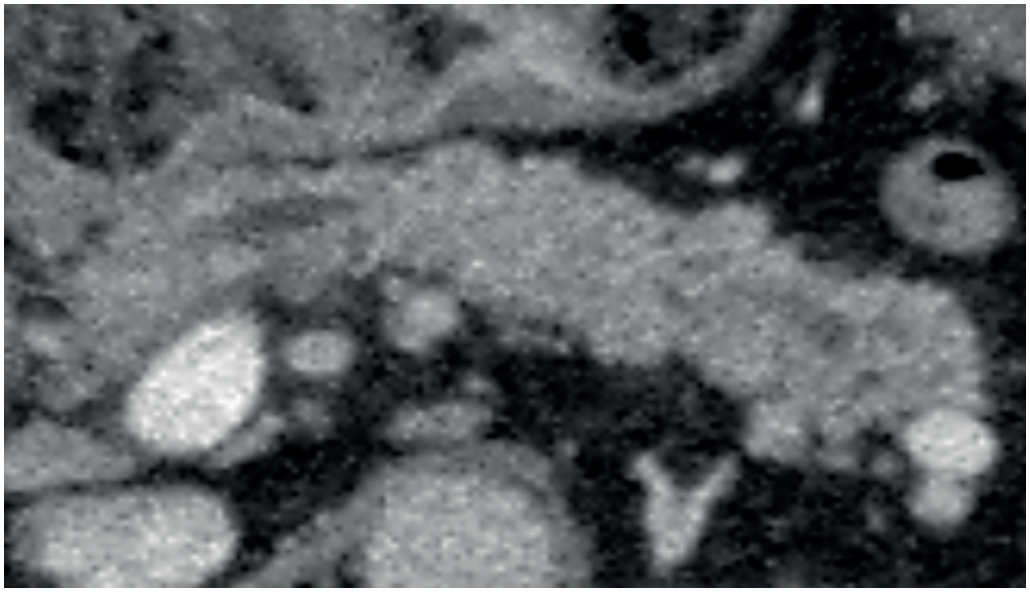


Figure 6.
The pancreatic duct is dilated up to 5 mm.

Conclusion of CT AB with CE: The mass in the projection of the pancreas head is more consistent with adenocarcinoma involving the DU, PV, and GDA. Pancreatic duct dilatation (Virungaectasia). Para-aortic and peripancreatic adenopathy.

Resident physicians' description: No differences from the primary conclusion. Histological conclusion: In durative calculous pancreatitis of the head with foci of inflammatory exacerbation.

Patient 4, 63 years old

Complaints upon admission: Pain in the epigastric region, general weakness. Biochemical blood analysis: ALT - 41 U/L; AST - 31 U/L; Total Bilirubin - 7.6 μmol/L.

Conclusion of abdominal ultrasound (US AB): Moderate choledochoectasia. A mass in the retroperitoneal space, likely originating from the uncinate process or head of the pancreas.

CT of the abdomen with bolus contrast enhancement (CT AB with CE): Hypodense mass along the posterior contour of the pancreas head, irregular in shape with unevenly thickened walls and parietal inclusions, measuring 5.8 x 4.7 x 3.8 cm. The mass shows intense contrast enhancement of the walls, displaces the pancreas head anteriorly, and intimately abuts and compresses the common bile duct and right adrenal gland (Figure 7).

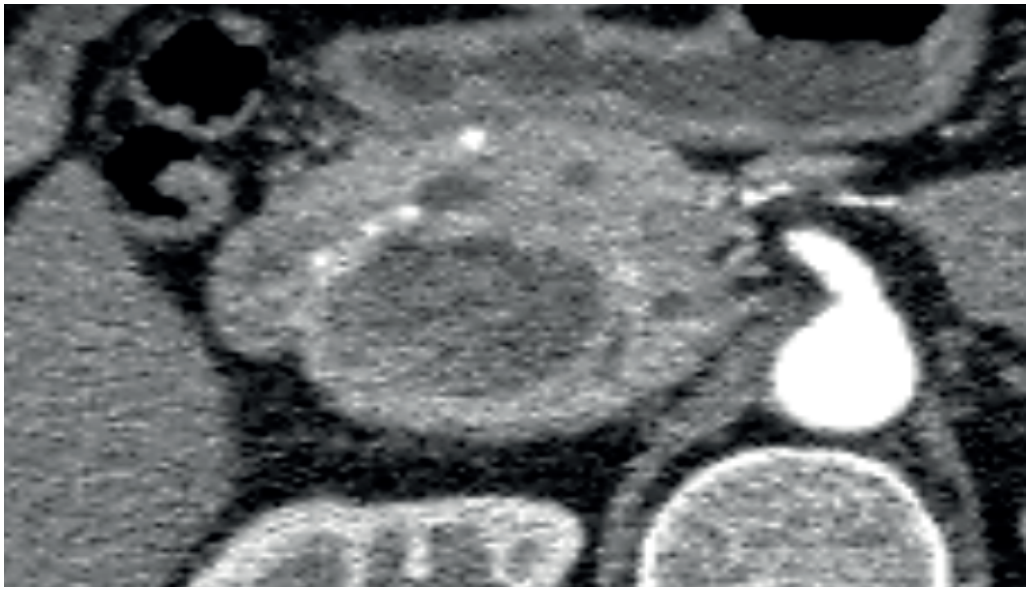


Figure 7.
Hypodense mass along the posterior contour of the pancreas head, irregular in shape with unevenly thickened walls and parietal inclusions.

Conclusion: A mass in the right retroperitoneal space, with a differential diagnosis of neuroendocrine tumor (NET) and gastrointestinal stromal tumor (GIST). Moderate biliary hypertension.

Resident physicians' description: No differences from the primary conclusion. Histological conclusion: Intraductal papillary mucinous neoplasm (IPMN) of the pancreas associated with invasive carcinoma.

Discussion

Patient 1, 32 years old

The clinical presentation of ampullary cancer often mimics that of pancreatic cancer. Definitive surgical intervention is crucial for accurate histological diagnosis.2 The Whipple procedure is the standard surgical treatment for both adenocarcinoma and ampullary cancer.2 Despite the misdiagnosis not altering the treatment strategy, it is important to identify the key features that might have been overlooked or misinterpreted, leading to diagnostic errors. In Figures 1 and 2, the thickening of the mucosa in the duodenum with an area of thickening in both the mucosal and submucosal layers, closely abutting the head of the pancreas and the common bile duct, is evident.

The location of the neoplasm in this case does not allow the radiologist to clearly differentiate the primary growth. Due to the predominant localization of most of the neoplasm in the area of the distal bile duct system (DBDS), preference was given to this etiology. This demonstrates the limitation of the CT imaging technique. Pancreatic adenocarcinoma can involve neighboring tissues without showing radiological signs in the primary zone, as observed in this case. This phenomenon indicates the limitations of the CT diagnostic method and the necessity of using a comprehensive approach in evaluating such cases.

Patient 2, 57 years old

Upon analysis of the CT scans of the patient in the projection of the pancreatic body, a large-sized formation with clear contours and heterogeneous structure was identified, which intensely and heterogeneously accumulated contrast material. Such characteristics often indicate the presence of a neuroendocrine tumor (NET), which typically manifests as a well-vascularized, hyperdense nodule with intense contrast enhancement in the arterial phase.3

However, histological examination revealed that the true pathology in this case was serous oligocystic adenoma (SOA) of the pancreas. Despite SOA being considered a rare pathology and traditionally not included in the main differential diagnosis, this does not exempt the radiologist from the responsibility of thorough consideration of all possible diagnoses.4 The rarity of the disease necessitates special attention to detail when analyzing diagnostic images to avoid missing key features that may indicate such unusual conditions. This case underscores the importance of a comprehensive approach to diagnostics, where every possible diagnosis should be carefully considered, even if rare, to ensure the best treatment plan and avoid potential diagnostic errors.

Patient 3, 66 years old

Ductal changes: Malignant neoplasms as well as chronic pancreatitis can induce alterations in pancreatic ducts. However, in pancreatitis, ductal changes are typicallyless uniform and may be accompanied by calcifications, which are not characteristic of cancerous tumors. In the examined scans, however, calcifications within the duct content were not identified.

Upon analysis of the CT scans of this patient, the physician and resident identified slight contrast material (CM) accumulation and washout in the region of the pancreatic head, which was interpreted as a possible adenocarcinoma.5 However, histological examination refuted this diagnosis, revealing patterns characteristic of focal indurated calcific pancreatitis with inflammatory foci.

Key visual features contributing to the diagnostic error:

1. Hypodensity and tissue structure alteration: Both adenocarcinoma and pancreatitis can lead to similar tissue density changes. In pancreatitis, this is often associated with fibrosis and calcifications, which may be mistakenly interpreted as tumorous alterations.

Localized thickening or mass effect: Chronic inflammation associated with pancreatitis can cause tissue thickening, mimicking the mass effect typical of ad-

enocarcinoma. This complicates differentiation based solely on CT data without histological confirmation.

This case underscores the complexity of diagnosing pancreatic diseases, particularly when similar visual signs are present on CT scans. Even with histological examination, differentiating indurativecalculous pancreatitis from adenocarcinoma remains one of the most challenging tasks in clinical practice. This case highlights the necessity of a comprehensive approach, involving not only imaging methods but also thorough examination for accurate diagnosis.

Patient 4, 63 years old

Upon analysis of the CT scans of the patient in the projection of the pancreatic head, a formation with clear, irregular contours and heterogeneous structure was identified, intensively and heterogeneously accumulating contrast material. These characteristics often indicate a neuroendocrine tumor (NET), which typically presents as a well-vascularized, hyperdense nodule with pronounced contrast enhancement in the arterial phase. However, histological examination revealed that the true pathology was an intraductal papillary mucinous neoplasm (IPMN) of the pancreas associated with invasive carcinoma.[6]

IPMN may resemble a cystic variant of NET, leading to a diagnostic error. Typically, IPMN presents as a round, single- or multi-cystic formation with septations, often with a larger cystic component and without a wide contrast-enhancing rim. In this case, these features were not clearly evident on the CT scans, complicating accurate diagnosis.[7]

This error underscores the importance of careful interpretation of CT data and consideration of all possible pathologies. The treatment approach for NET differs from that for IPMN and pancreatic adenocarcinoma: NET requires a specialized approach, while IPMN and adenocarcinoma necessitate resection and aggressive treatment.[8]

Thus, a comprehensive approach, involving various imaging studies, is necessary for accurate diagnosis and selection of the optimal treatment strategy.

Limitations: one-center conducted study

Conclusion

In conclusion, diagnosing pancreatic tumors remains challenging for physicians due to their similarity to other diseases, as well as the presence of rare pathologies that may appear similar to more common tumors on imaging studies. Histological examination remains a necessary step for accurate diagnosis.

It is important to note that even with the use of modern imaging methods, such as contrast-enhanced computed tomography, diagnostic errors are possible. A comprehensive approach is necessary, incorporating various imaging techniques as well as histological examinations, for precise diagnosis and selection of the optimal treatment strategy for patients with pancreatic tumors.

The conclusion highlights that diagnosing pancreatic tumor remains challenging. Therefore, diagnosing different pancreatic tumors remains complex, necessitating a comprehensive approach that integrates diverse imaging modalities and histological examinations for accurate diagnosis and treatment planning.

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Authors' Contributions. AS acquired the data and drafted the manuscript. DB supervised and coordinated study and revised the manuscript. DA, AM and DN were involved in the participants recruitment and screening, data collection. DN performed the statistical analysis. AM conceived and designed the study. All authors read, approved the final manuscript and agreed to publish the article.

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KIDNEY TRANSPLANTATION FROM LIVING DONOR WITH RENAL MASS: CLINICAL CASE

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Abstract

Introduction. Renal transplantation is the best treatment option for end-stage renal disease, but organ demand continues to overweight organ supply. The transplantation of kidneys from donors with small renal masses represent a potential avenue to expand the donor pool. We represent the clinical case of kidney transplantation from living related donor with small renal mass and performed literature review of results of these cases.

Methods. Case presentation of kidney transplantation from living related donor with incidental finding of small renal mass. Mass was excised and subsequently kidney was engrafted successfully. Up to date both patients are under follow up during 8 months and any signs of recurrence were seen.

Results. Donor kidney was procuredby laparosopic hand-assissted technique. Intraoperatively small renal mass was encountered whereas during preop evaluation renal cyst was diagnosed. Renal mass was excised fully and defect was closed with interruptive suture. Histological evaluation has revealed highly differentiated renal cell carcinoma. Postoperative period was uneventful. Patient was discharged with good graft function.

Conclusion. Careful use of kidneys from donors with single renal masses is feasible and safe, with an overall recurrence rate of less than 1.5%. The use of such kidneys could help alleviate the organ shortage crisis.

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Key words:
Renal Mass, Transplantation, Donor

Бүйрек ісігі бар тірі туысты донордан бүйрегі трансплантациялау

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Тұжырым

Өзектілігі. Бүйрек трансплантациясы соңғы сатыдағы бүйрек ауруын емдеудің ең жақсы нұсқасы болып табылады, бірақ органдарға қажеттілік әлі де жоғары. Кіші бүйрек ісіктері бар донорлардан бүйрек трансплантациясы донорлық қорды арттырудың әлеуетті әдісі болып табылады. Бүйректегі кіші түзілістер (2 смге дейін) бар тірі туысқан донордан бүйрек трансплантациясының клиникалық жағдайы ұсынылған және осы жағдайлардың нәтижелері бойынша әдебиеттерге шолу жасалады.

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Түйінді сөздер:
Бүйрек Түзілісі, Трансплантация, Донор

Материалдар мен әдістер. Бүйректегі кіші түзілістербар тірі туысқан донордан бүйрек трансплантациясының клиникалық жағдайы. Түзіліс алынып тасталды, содан кейін бүйрек сәтті имплантацияланды. Бүгінгі таңда екі науқаста 8 ай бойына қайталану белгілері байқалмаған. Біз сондай-ақ MEDLINE/PubMed және SCOPUS деректер қорын зерттеу нәтижелерін ұсынамыз.

Нәтижелер. Донордың бүйрегі лапароскопиялық қол әдісімен жойылды. Операция кезінде шағын бүйрек массасы анықталды, ал операция алдындағы бағалау кезінде бүйрек кистасы деп берілген. Бүйрек массасы толығымен кесіліп, дефекті үзіліс тігіспен жабылған. Гистологиялық зерттеуде жақсы дифференцияланған бүйрек жасушалы карциномасы анықталды. Операциядан кейінгі кезең асқынусыз өтті. Науқас трансплантаттың жақсы функциясымен жазылды.

Қорытынды. Бір бүйрек зақымдануы бар донорлардың бүйректерін мұқият пайдалану мүмкін және қауіпсіз, жалпы рецидив 1,5%-дан аз. Мұндай бүйректерді пайдалану орган жетіспеушілігі дағдарысын жеңілдетуге көмектеседі.

Пересадка почки от живого родственного донора с опухолью почки

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Введение. Трансплантация почки является лучшим вариантом лечения терминальной стадии почечной недостаточности, но потребность в органах по-прежнему остается высокой. Трансплантация почек от доноров с небольшой опухолью (менее 2 см) почки представляет собой потенциальный путь увеличения пула доноров. Представлен клинический случай трансплантации почки от живого родственного донора с небольшой опухолью почки и проведен обзор литературы по результатам этих случаев.

Материалы и методы. Клинический случай трансплантации почки от живого родственного донора со случайным обнаружением небольших почечных образований. Образование было удалено, и впоследствии почка успешно прижилась. На сегодняшний день оба пациента находятся под наблюдением в течение 8 месяцев, признаков рецидива не наблюдается. Также представляем результаты исследования баз данных MEDLINE/PubMed и SCOPUS.

Результаты. Донорскую почку извлекали лапароскопическим ручным методом. Интраоперационно было обнаружено небольшое образование почки, тогда как во время предоперационной оценки была диагностирована киста почки. Опухоль почки была полностью иссечено и дефект закрыт прерывистым швом. Гистологическое исследование выявило высокодифференцированную почечно-клеточную карциному. Послеоперационный период протекал без осложнений. Пациент выписан с хорошей функцией трансплантата.

Заключение. Забор почек от доноров с единичными образованиями почек возможно и безопасно, при этом общая частота рецидивов составляет менее 1,5%. Использование таких почек могло бы помочь увеличить пул доноров почки.

Introduction

Renal transplantation is the gold standard for end-stage renal disease (ESRD) and offers significant survivaland quality of life for patients and economic benefits for country itself.[1-3] Despite this, only a minority of patients with ESRD ultimately receive a transplant and organ

demand continues to overweight supply in most developed nations.[1,4,5]

Multiple strategies have been implemented to increase organ donation and utilization, including increasing living kidney donation, donations after cardiac death (DCD), the use of expanded criteria donor (ECD) kidneys, and national programs to facilitate kidney-paired donations and transplants for highly sensitized patients.[5,6] In the Republic of Kazakhstan the situation with deceased donations after brain death is critically undeveloped.

The oncological management of small renal masses (SRMs) continues to evolve; nephron-sparing surgery, in the form of partial nephrectomy, is considered to be the standard of care for T1a (≤4 cm, organ-confined) renal masses, when technically feasible.[4,7,8] A recent U.S. nationwide analysis assessing the uptake of partial nephrectomy for the treatment of SRMs between 2009 and 2012 demonstrated rates of 48% and 33% in teaching and non-teaching institutions, respectively.[9] In Canada, a survey of academic centers revealed a partial nephrectomy rate of 78% for T1a tumors from 1988–2014, with an increasing trend over time.[10] Some SRMs, therefore, continue to be treated with radical nephrectomy. Often, this may be due to technical factors related to the tumor itself, but a proportion of cases result from patient preference for radical nephrectomy. Such kidneys may represent potentially transplantable organs that would otherwise be discarded.

Case presentation

This is the clinical case of kidney transplantation to 33 years old male patient from living related donor with small renal masses that was an incidental intraoperative finding. Donor was his elder sister. During preoperative evaluation on CT scans small left renal cyst was identified, otherwise patient was healthy. Donor kidney was procured by laparoscopic hand-assisted method. Intraoperatively renal cyst appeared to be small renal mass. A piece of tissue from latter was send express biopsy.

Pathology revealed highly differentiated renal cell carcinoma. Laparoscopic donor nephrectomy was performed successfully. The neoplasm was fully excised on back-table (Figure 1-2). The parenchymal defect was closed by interrupted suture (Figure 3). Kidney was engrafted on right iliac region with arterial and venous anastomosis with external iliac arteria and vein, respectively (Figure 4).

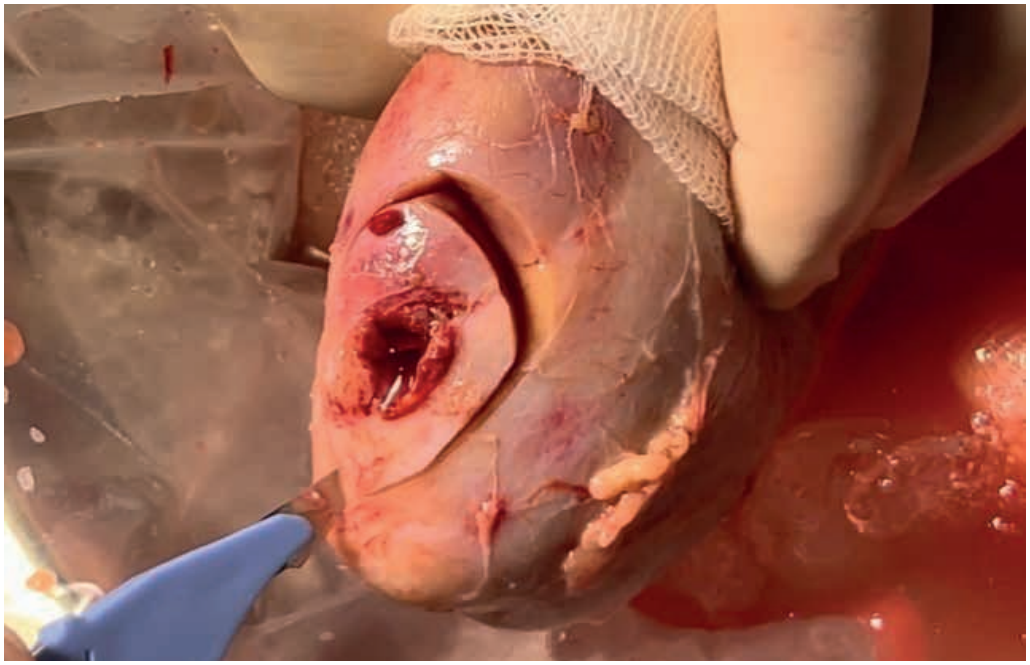


Figure 1.
Excision of renal mass on back table

Figure 2.
Post excision view of graft

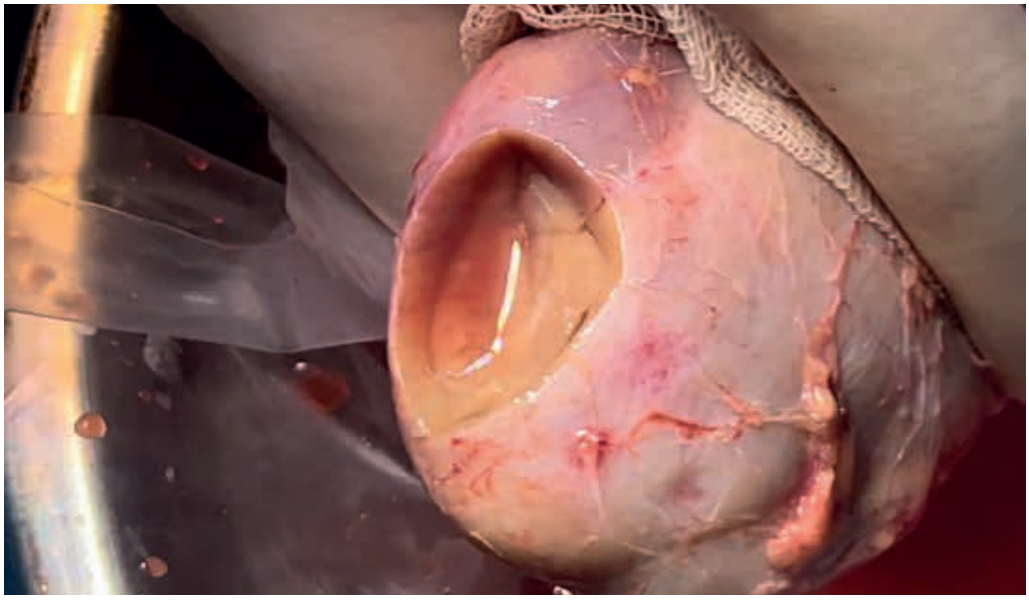


Figure 3.
The defect is closed by interrupted suture

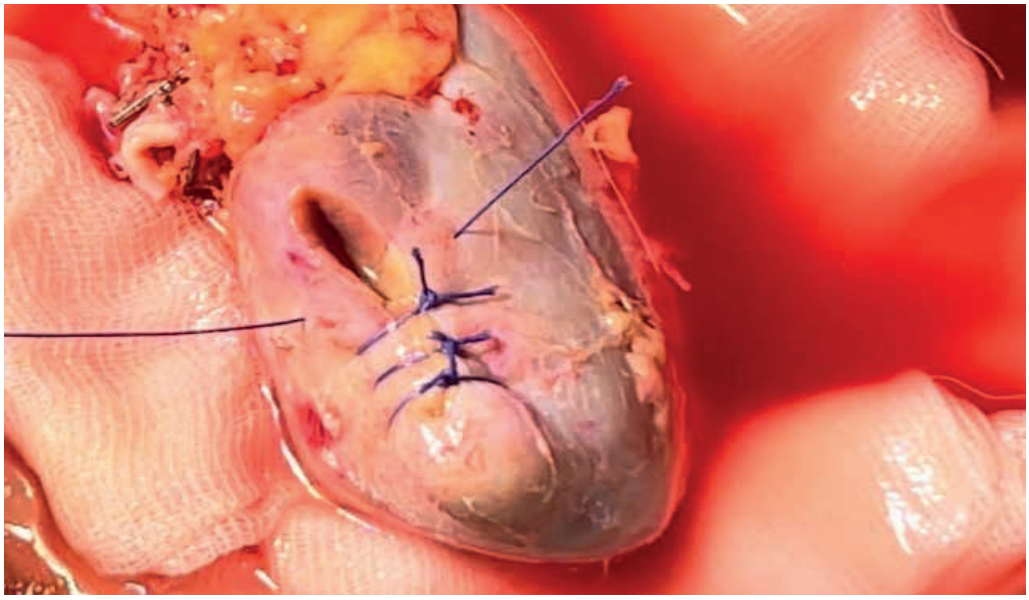
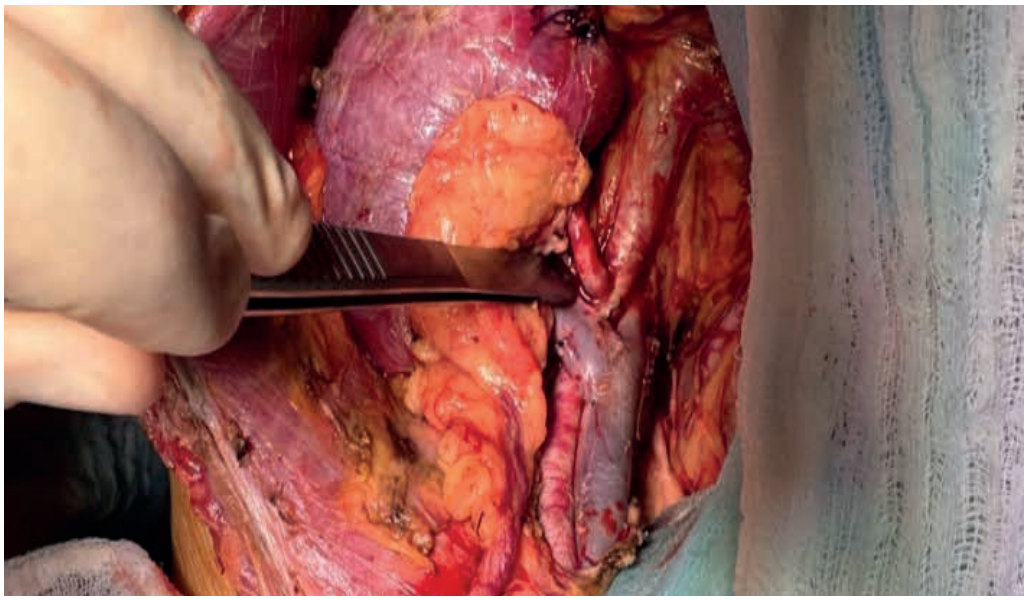


Figure 4.
Kidney after engraftment to iliac fossa



Discussion

It is well-known that solid organ transplantation increases the overall risk of malignancy in transplant recipients, most likely as a consequence of the post-transplant immunosuppressed state.[11,12] However, there is no evidence to suggest that immunosuppression has a negative impact on the natural history of localized RCC. Reflecting this, multiple existing clinical guidelines suggest that patients with small (<5 cm), incidentally discovered RCCs need not delay renal transplantation after undergoing surgical treatment, given the low risk of recurrence.[13,14]

The results of the aforementioned studies suggest that transplantation of tumorectomized kidneys is similarly safe and feasible, with only one suspected tumor recurrence demonstrated to date. The data supporting the transplantation of contralateral kidneys is more limited. However, the risk of concomitant metastatic disease for T1a renal masses is <2% and contralateral kidneys in this setting are, therefore, expected to be low risk for disease transmission with transplantation. To date, one case of recurrence has been described and occurred in a manner suggesting the presence of circulating cancer cells and/or micrometastases at the time of organ procurement. Taken together, the entire data set presented herein demonstrates a 1.4% recurrence rate among recipients of tumorectomized and contralateral kidneys from donors with confirmed small RCCs. This rate is comparable to that described in the literature for SRMs treated with partial nephrectomy.[15]

While not without risk, the small risk of RCC recurrence needs to be weighed against the risk of remaining on dialysis. In one analysis of 43 patients who received tumorectomized kidneys, Brook et al demonstrated an increased four-year survival rate over dialysis patients remaining on the waiting list; survival was comparable to recipients of living, unrelated kidneys matched for age, gender, and HLA mismatch.[16] Not all kidney transplant candidates would be willing to receive a kidney from a donor with a SRMS and, indeed, only a subset of patients would be suitable recipients. One survey of patients on a transplant list in northern England, however, revealed that 59% would support the use of such kidneys.[17]

The potential for safely transplanting kidneys with SRMs was recognized as early as 1982, when Stubenbord et al published a case report describing the transplantation of an allograft following removal of a small calcified renal mass, later confirmed to be an RCC.[13] A number of groups have since published multiple case series describing the transplantation of tumorectomized kidneys from living or deceased donors, as well as kidneys from donors with contralateral renal malignancies. Here, we review and summarize all known cases, to date, of kidneys transplanted from donors with SRMs complete with followup data. We conclude by outlining a framework for the implementation of a transplant protocol for kidneys recovered from donors with SRMs, and discuss the potential ethical and logistical pitfalls that may be encountered.

Conclusion:

Transplantation of tenonectomies kidneys with SRMs is relatively safe against staying on dialysis considering the survival rates of patients. A forementioned data analysis shows low recurrence rates of cancer and nil effect of immunosuppression on this rate. In our clinical case transplantation went otherwise uneventful. Postoperative period also was uneventful. Both patients were under follow up for 10 months up to date and no signs of recurrence of cancer. Thus, kidney with SRM is thought to be potentially safe for transplantation with beneficial results.

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and interpretation, revising discussion section of the manuscript. E.B.: Data acquisition, analysis, and interpretation; surgeries, revising results section of the manuscript. E.S.: Data collection, drafting, revising results section. B.M: Data collection, medical diagnoses, surgical pathologic evaluations. N.T.: Study conception and design, overall responsibility of the study, data analysis and interpretation. All authors have approved the final version of the article.

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ASSOCIATION BETWEEN TOTAL BILIRUBIN LEVELS WITH INCIDENCE OF ATHEROSCLEROSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

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The authors declare no potential conflict of interest requiring disclosure in this article.

Keywords:
Total Bilirubin Level, Atherosclerosis, Meta-Analysis, Cardiovascular System

Abstract

Background. Bilirubin is a byproduct of the breakdown of erythrocytes. Bilirubin levels can potentially serve as a biomarker for cardiovascular risk assessment. In this study, we would be investigating most recent manuscripts, published in the last 5 years, that studied association of serum bilirubin level to atherosclerosis progression to elicit how strongly low level of total bilirubin can prognose the disease progression.

Methods. Using Pubmed search engine, all articles that included keywords "bilirubin" and "atherosclerosis" were retrieved. In total 67 search results emerged for the 2019-2023 timeline, the last 5 years.6 population-based studies that studied association between total bilirubin concentration and atherosclerosis development were used for the meta-analysis.

Results. Increasing blood total bilirubin level seems to decrease the odds of developing atherosclerosis, meaning that there is an inverse correlation between total bilirubin level and arterial plaque formation or stenosis. Pooled odds ratio was found to be 0.86 (95% CI 0.83-0.9), suggesting that there is 14% decreased chance of developing atherosclerosis for each mmol/L increase in bilirubin levels. Overall, higher total serum bilirubin levels were associated with a significantly decreased risk of progression to atherosclerosis.

Conclusion. The meta-analysis indicates a significant inverse association between low total bilirubin levels and the risk of developing atherosclerosis, suggesting that higher bilirubin levels may be protective against the progression of this disease.

Жалпы билирубин деңгейі мен атеросклероздың даму жиілігі арасындағы байланыс: жүйелі шолу және мета-талдау

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Тұжырым

Өзектілігі. Билирубин-эритроциттердің ыдырауының жанама өнімі. Билирубин деңгейі жүрек-қан тамырлары қаупін бағалау үшін биомаркер бола алады. Бұл зерттеуде біз сарысулық билирубин деңгейінің атеросклероздың прогрессиясымен байланысын зерттеген соңғы 5 жылда жарияланған ең соңғы қолжазбаларды зерттеп, жалпы билирубин деңгейінің аурудың дамуын қаншалықты төмен болжай алатынын анықтаймыз.

Әдістері. PubMed іздеу жүйесінің көмегімен "билирубин" және "атеросклероз"-кілттік сөздері бар барлық мақалалар табылды. 2019-2023 жылдар кезеңінде, соңғы 5 жылда барлығы 67 іздеу нәтижелері пайда болды. Мета-талдау үшін жалпы билирубин концентрациясы мен атеросклероздың дамуы арасындағы байланысты зерттейтін 6 популяциялық зерттеу қолданылды.

Нәтижелер. қандағы жалпы билирубин деңгейінің жоғарылауы атеросклероздың даму ықтималдығын төмендетеді, яғни жалпы билирубин деңгейі мен артериялық бляшкалардың пайда болуы немесе стеноз арасында кері байланыс бар. Біріктірілген коэффициент 0.86 (95% СИ 0.83–0.9) болды, бұл ммоль/л үшін билирубин деңгейінің әрбір жоғарылауымен атеросклероздың даму ықтималдығы 14% төмендейтінін көрсетеді. Жалпы, сарысудағы жалпы билирубиннің жоғары деңгейі атеросклероздың даму қаупінің айтарлықтай төмендеуімен байланысты болды.

Қорытынды. Мета-талдау жалпы билирубиннің төмен деңгейі мен атеросклероздың даму қаупі арасындағы айтарлықтай кері байланысты көрсетеді, бұл билирубиннің жоғары деңгейі аурудың дамуынан қорғай алады деп болжайды.

Мүдделер қақтығысы:
Авторлар мүдделер қақтығысының жоқтығын мәлімдейді

Түйінді сөздер:
Жалпы Билирубин Деңгейі, Атеросклероз, Мета-Анализ, Жүрек-Тамыр Жүйесі.

Связь между уровнем общего билирубина и частотой развития атеросклероза: систематический обзор и мета-анализ

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Абстракт

Введение. Билирубин является побочным продуктом распада эритроцитов. Уровни билирубина потенциально могут служить биомаркером для оценки сердечно-сосудистого риска. В этом исследовании мы будем исследовать самые последние рукописи, опубликованные за последние 5 лет, в которых изучалась связь уровня сывороточного билирубина с прогрессированием атеросклероза, чтобы выяснить, насколько сильно низкий уровень общего билирубина может прогнозировать прогрессирование заболевания.

Материалы и методы. С помощью поисковой системы Pubmed были найдены все статьи, содержащие ключевые слова «билирубин» и «атеросклероз». Всего появилось 67 результатов поиска за период 2019–2023 гг., за последние 5 лет. Для мета-анализа были использованы 6 популяционных исследований, изучавших связь между концентрацией общего билирубина и развитием атеросклероза.

Результаты. Повышение уровня общего билирубина в крови, по-видимому, снижает вероятность развития атеросклероза, а это означает, что существует обратная корреляция между уровня общего билирубина и образованием артериальных бляшек или стенозом. Было обнаружено, что объединенное отношение шансов составило 0.86 (95% ДИ 0.83–0.9), что позволяет предположить, что вероятность развития атеросклероза снижается на 14% при каждом увеличении уровня билирубина на ммоль/л. В целом, более высокие уровни общего билирубина в сыворотке были связаны со значительно сниженным риском прогрессирования атеросклероза.

Заключение. Мета-анализ указывает на значительную обратную связь между низким уровнем общего билирубина и риском развития атеросклероза, предполагая, что более высокие уровни билирубина могут защищать от прогрессирования этого заболевания.

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Introduction

Bilirubin is a byproduct of the breakdown of erythrocytes. It is generally recognized as a marker of liver function, however antioxidant and anti-inflammatory effects of bilirubin were extensively described in modern scientific literature. Naturally, bilirubin has been investigated for its role in different pathologic states. It was not until 1994, when the first clinical data showed that low bilirubin level can be an independent risk factor for atherosclerotic disease.

The relationship between bilirubin levels and atherosclerosis is complex and may involve different mechanisms. It has been widely described how total bilirubin (Tbil) level effect progression of atherosclerosis in patients with certain comorbidities. For instance, *Duman et al.* showed that low total bilirubin level and elevated high-sensitive C-reactive protein is associated with subclinical atherosclerosis. *Lee et al.* and *Hamur et al.* described that high total bilirubin level is associated with atherosclerosis in T2DM and prediabetes, respectively.[1-3]

Bilirubin levels can potentially serve as a biomarker for cardiovascular risk assessment. Protective role of total bilirubin was analyzed in meta-analysis by *Lan et al.*, higher total bilirubin was significantly negatively correlated with cardiovascular disease, pooled HR=0.83 (95% CI 0.73–0.94, P=.003). However, there is a lack of reviews that cover the research past 2019.[4,5]

In this study, we would be investigating most recent manuscripts, published in the last 5 years, that studied association of serum bilirubin level to atherosclerosis progression to elicit how strongly low level of Tbil can prognose the disease progression.

Methods

Using Pubmed search engine, all articles that included keywords "bilirubin" and "atherosclerosis" were retrieved. In total 67 search results emerged for the 2019-2023 timeline, the last 5 years (Figure 1). Inclusion criteria were: original studies on the adult population of patients that studied the effect of bilirubin level on atherosclerosis. Exclusion criteria were studies that did not report on association between bilirubin and atherosclerosis development; studies that did not include human subjects (animal studies); review articles, meta-analysis, letters, abstracts, and articles that did report statistical results on effect estimate of OR and 95%CI. Among the eligible studies, only the category of subjects with atherosclerotic disease was used for calculations.

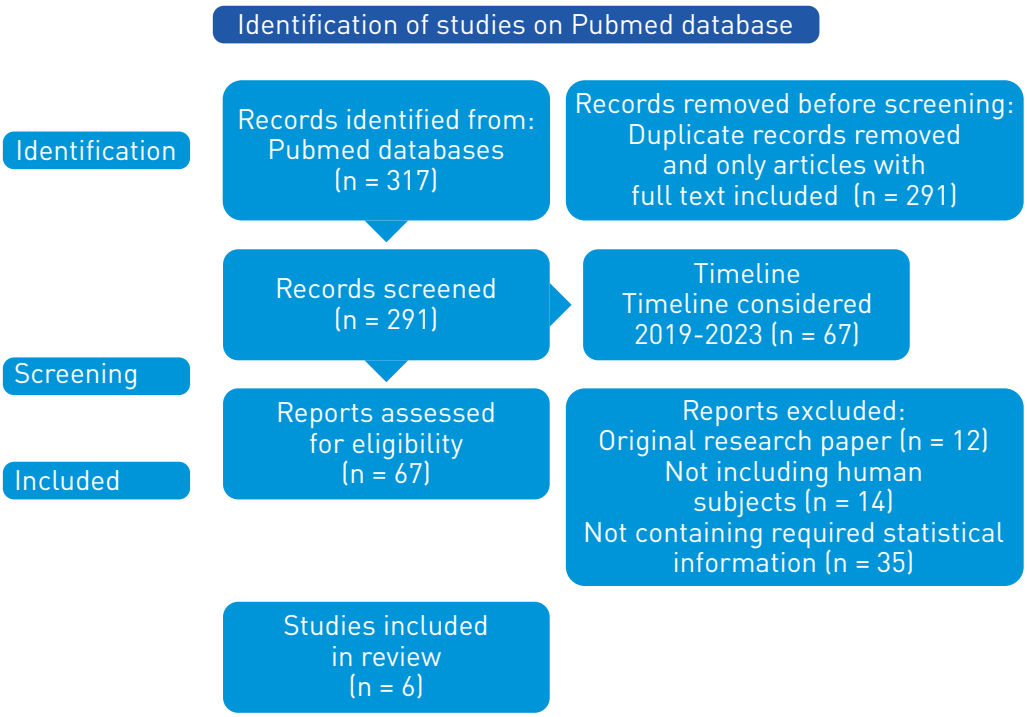

Figure 1.
Flow chart showing selection of studies for meta-analysis.

Furthermore, forest plot was calculated along with the pooled odds ratio for the extracted odds ratio and 95% CI intervals. All data were analyzed using the Excel and STATA 18.0 program. $P < 0.05$ was considered statistically significant.

Results

6 population-based studies that studied association between total bilirubin concentration and atherosclerosis development were used for the meta-analysis (Table 1). All odds ratios were found to be less than 1, and 95% confidence interval did not include 1, except for the *Su et al*. study, depicting no statistical difference.[6] (Figure 1) Increasing blood total bilirubin (Tbil) level seems to decrease the odds of developing atherosclerosis, meaning that there is an inverse correlation between Tbil and arterial plaque formation or stenosis. Pooled odds ratio was found to be 0.86 (95% CI 0.83-0.9), suggesting that there is 14% decreased chance of developing atherosclerosis for each mmol/L increase in bilirubin levels. Overall, higher total serum bilirubin levels were associated with a significantly decreased risk of progression to atherosclerosis.

Table 1.
Characteristics of studies included to meta-analysis

Authors (et al.)	Publication year	Sample size	Sex (M)	Median age	Study design	Events
Zhong et al.[7]	2020	NA	NA	57.59	Population-based study	Intracranial atherosclerosis
Lan et al.[5]	2020	78/543	287/543	NA	Retrospective	Peripheral arterial disease
Lee et al.[2]	2020	599/1381	277/599	59.6±9.2	Retrospective	Carotid atherosclerosis
Vitek et al.[8]	2022	69/466	35/69	62	Retrospective	Peripheral arterial disease
Su et al.[6]	2023	171/1274	NA	65	Cross sectional	Femoral and carotid atherosclerosis
Zhao et al.[7]	2023	5281/7284	3726/5281	60.2 ± 12	Cross sectional	Lower limb plaque

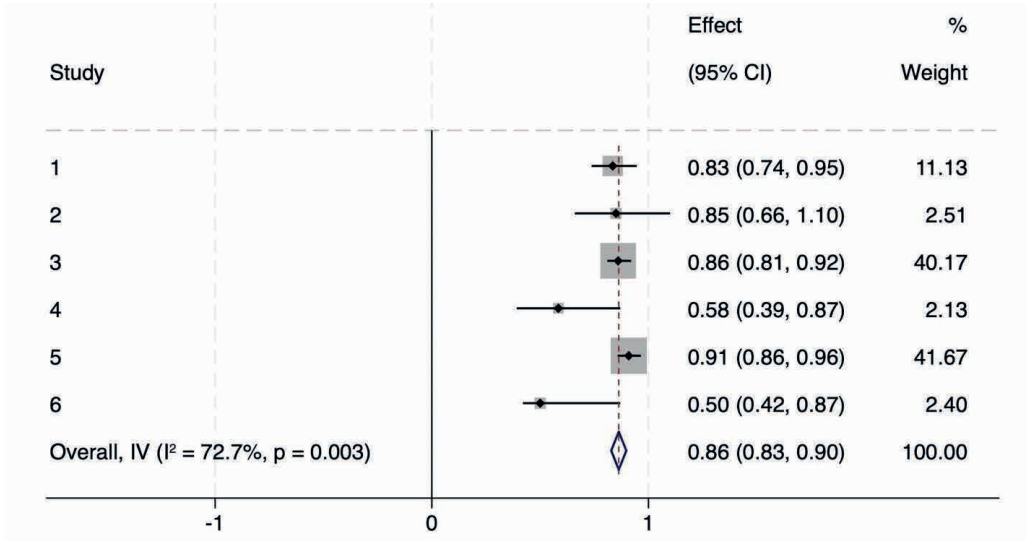

Figure 2.
Forest plot showing association between total bilirubin level and atherosclerosis

1 - Zhao et al.7, 2 - Su et al.6, 3 - Vitek et al.8, 4 - Lee et al.2, 5 - Lan et al.5, 6 - Zhong et al.7

Table 2.
Total bilirubin concentration values for patients with and without atherosclerosis

	With atherosclerosis			No atherosclerosis		
	Total bilirubin (mmol/L)	95%CI low	95% CI high	Total bilirubin (mmol/L)	95%CI low	95% CI high
Zhao et al.[9]	10.1	8.3	13.0	11.1	9.0	13.9
Su et al.[6]	15.6	12.4	19.9	15.7	12.5	19.8
Vitek et al.[8]	8.5	6.3	11,2	12.2	9.0	17.5
Lee et al.[2]	13.68±6.84	13.1	14.3	14.88±6.84	14.5	15.2
Lan et al.[5]	10.4±3.8	9.5	11.2	12.7±4.8	12.2	13.1

Total bilirubin level is lower in those patients that have atherosclerosis in comparison with patients that do not have (Table 2).

Discussion

In this meta-analysis, we tried to elicit the strength of inverse association between total bilirubin and atherosclerosis development. Our results align with previously described findings on this topic.

There are many proposed mechanisms of bilirubin's protective action in atherosclerotic patients. One of the possible mechanisms to target for reducing incidence of cardiovascular disease in patients with Gilbert's syndrome according to *Boon et al*. could be the facts that unconjugated bilirubin at physiologically normal level protects from protein and lipid induced MPO-generated hypochlorous acid, HOCL oxidation.[10] Bilirubin has been implicated in improving lipid profiles. Higher bilirubin levels were associated with lower values of total and LDL cholesterol, which are major risk factors for atherosclerosis.[11] Moreover, bilirubin seems to improve endothelial function by enhancing nitric oxide (NO) availability. Thus, it helps maintain vascular tone, reducing the risk of stenosis and atherosclerotic changes,[12] showed that bilirubin inhibits the proliferation of vascular smooth muscle cells, thus stabilizing the plaque. Most recently, showed that knockout of Bvra gene resulting in low bilirubin levels leads to proatherogenic changes in mice. Bilirubin deficient mice had increased systemic oxidative stress, endothelial dysfunction, thinning fibrous cap which led to plaque destabilization.[13]

A recent study in mouse animal models has revealed another possible mechanism of action of bilirubin on the development of atherosclerosis. *Wen et al.,* found that bilirubin can inhibit cholesterol synthesis by interfering with the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase, which is involved in endogenous synthesis of cholesterol, further contributing to the reduction of atherosclerosis. They also found that bilirubin can influence the number of immune cells such as myeloid-derived suppressor cells, natural killer cells and dendritic cells, which are associated with the formation of plaque, thereby improving atherosclerosis.[14]

Strength of the study is that it gives a glimpse on the association between bilirubin level and atherosclerosis development risk based on the past 5-year studies. It could be useful for making clinical decisions to increase the upper limit for total bilirubin, since mildly elevated bilirubin levels in the absence of underlying liver disease have a protective effect on the cardiovascular system. Limitation of the study is that there was a relatively small number of studies (six) for the meta-analysis. Small sample size may restrict the generalizability of the findings and increase the potential for bias. Moreover, the heterogeneity among the included studies in terms of population characteristics, study design, and measurement of bilirubin levels could introduce variability that impacts the robustness of the pooled results. Future research with a larger number of studies and more standardized methodologies would be beneficial to confirm and extend these findings.

What's known? The relationship between bilirubin levels and athero-

sclerosis is complex and may involve different mechanisms. Total bilirubin level effect progression of atherosclerosis in patients with certain comorbidities. Non-alcoholic fatty liver disease increases the risk of developing type 2 diabetes. Bilirubin levels can potentially serve as a biomarker for cardiovascular risk assessment.

What's new? Significant inverse association between low total bilirubin levels and the risk of developing atherosclerosis, suggesting that higher bilirubin levels may be protective against the progression of this disease.

Conclusion

The meta-analysis indicates a significant inverse association between low total bilirubin levels and the risk of developing atherosclerosis, suggesting that higher bilirubin levels may be protective against the progression of this disease.

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FEATURES OF THE COURSE OF NON-ALCOHOLIC FATTY LIVER DISEASE INTYPE 2 DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

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Abstract

Background. Non-alcoholic fatty liver disease and type 2 diabetes mellitus or impaired glucose tolerance are common diseases with a high risk of developing cardiovascular diseases, the leading cause of disability and death. Our aim is to develop new methods for screening, prevention, and treatment of cardiovascular diseases in patients with non-alcoholic fatty liver disease, type 2 diabetes mellitus, and impaired glucose tolerance.

Methods and methods. This study is single-center, open-label, uncontrolled, diagnostic study. Between 2023 and February 2024, 216 patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance were selected at Heart Center "University Medical Center" Corporate Fund.

Results. All examined patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease showed increased liver enzyme activity. Blood lipid profile indicators were significantly higher than optimal levels for patients with cardiovascular diseases. There was also a significant increase in liver enzymes, C-reactive protein, triglycerides, and lipoproteins in patients with cardiovascular diseases and non-alcoholic fatty liver disease combined with type 2 diabetes and impaired glucose tolerance.

Conclusion. Liver enzyme activity, C-reactive protein, glucose, and lipid profile analysis showed significant increases in these indicators in patients with cardiovascular diseases and non-alcoholic fatty liver disease, especially in the presence of type 2 diabetes and impaired glucose tolerance. All examined patients showed increased liver enzyme activity and lipid levels, indicating the impact of these diseases on the liver and metabolism.

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Conflict of interest:
The authors declare no potential conflict of interest requiring disclosure in this article.

Keywords:
Non-Alcoholic Fatty Liver Disease, Type 2 Diabetes, Glucose Tolerance, Cardiovascular Diseases, Metabolic Syndrome.

Бауырдың алкогольсіз майлы ауруларының үдерістерінің ерекшеліктері 2 типті қант диабеті және глюкозаға төзімділіктің бұзылуы

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Тұжырым

Өзектілігі. Бауырдың алкогольсіз майлы ауруы және 2 типті қант диабеті немесе глюкозаға төзімділіктің бұзылуы -бұл жүрек-қан тамырларыауруларының даму

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Бауырдың алкогольсіз майлы ауруы, 2 Типті қант диабеті, Глюкозаға төзімділігі, Жүрек-Қан тамырлары аурулары, метаболикалық синдром.

қаупі жоғары жалпы аурулар, мүгедектік пен өлімніңнегізгі себебі. Біздің мақсатымыз-жоғарыда аталған аурула диагнозы қойылған бар науқастарда жүрек қан тамыр ауруларының скринингінің, алдын алудың және емдеудің жаңа әдістерін әзірлеу.

Методология және әдістеме. Бұл зерттеу бір орталықты, ашық, бақыланбайтын, диагностикалық болып табылады. 2023-2024 жылғы ақпан аралығында "University Medical Center" корпоративтік қорының жүрек орталығында жүрек-қан тамырлары аурулары және бауырдың алкогольсіз майлы ауруы, 2 типті қант диабеті және глюкозаға төзімділік бұзылыстары бар 216 пациент іріктелді.

Нәтиже. Жүрек-қан тамырлары аурулары және бауырдың алкогольсіз майлы аурулары бар барлық тексерілген науқастарда бауыр ферменттерінің белсенділігі жоғарылаған. Қандағы липидті профиль көрсеткіштері жүрек-қан тамырлары аурулары бар науқастар үшін оңтайлы деңгейден едәуір жоғары болды. Сондай-ақ, 2 типті қант диабетімен және глюкозаға төзімділіктің бұзылуымен бірге жүрек-қан тамырлары аурулары мен алкогольсіз майлы бауыр аурулары бар науқастарда бауыр ферменттерінің, С-реактивті ақуыздың, триглицеридтердің және кіші липопротеин деңгейінің айтарлықтай жоғарылауы байқалды.

Қортынды. Зерттеу көрсеткендей, алкогольсіз майлы бауыр ауруы, 2 типті қант диабеті және глюкозаға төзімділігі бұзылған науқастарда стеатогепатит пен фиброздың жоғарылауы байқалады, бұл ерлерде де, әйелдерде де жүрек-қан тамырлары асқынуларының дамуын болжауы мүмкін. Бауыр ферменттерінің белсенділігі, С-реактивті ақуыз, глюкоза және липидті профильді талдау жүрек-қан тамырлары аурулары және алкогольсіз майлы бауыр аурулары бар емделушілерде, әсіресе 2 типті қант диабеті және глюкозаға төзімділіктің бұзылуы кезінде бұл көрсеткіштердің айтарлықтай жоғарылағанын көрсетті.. Барлық тексерілген емделушілерде бауыр ферменттерінің белсенділігі мен липидтер деңгейінің жоғарылауы байқалды, бұл осы аурулардың бауыр мен метаболизмге әсерін көрсетеді.

Особенности течения неалкогольной жировой болезни печени при сахарном диабете 2 типа и нарушении толерантности к глюкозе

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Анотация

Фон. Неалкогольная жировая болезнь печени и сахарный диабет 2 типа или нарушение толерантности к глюкозе являются распространёнными заболеваниями с высоким риском развития сердечно-сосудистых заболеваний, основной причиной инвалидности и смерти. Наша цель - разработать новые методы скрининга, профилактики и лечения сердечно-сосудистых заболеваний у пациентов с вышеуказанными заболеваниями.

Методы и методология. Данное исследование является одно-центровым, открытым, неконтролируемым, диагностическим. В период с 2023 по февраль 2024 года в Кардиологическом центре «Университетский медицинский центр» Корпоративного фонда отобрано 216 пациентов с сердечно-сосудистыми заболеваниями и сопутствующей неалкогольной жировой болезнью печени, сахарным диабетом 2 типа и нарушением толерантности к глюкозе.

Результаты. У всех обследованных больных с сердечно-сосудистыми заболеваниями и сопутствующей неалкогольной жировой болезнью печени выявлено повышение активности печеночных ферментов. Показатели липидного профиля крови достоверно превышали оптимальные уровни для пациентов с сердечно-сосудистыми заболеваниями. Также отмечено достоверное увеличение ферментов печени, С-реактивного белка, триглицеридов и малого липопротеина у пациентов с сердечно-сосудистыми заболеваниями и неалкогольной жировой болезнью печени в сочетании с сахарным диабетом 2 типа и нарушением толерантности к глюкозе.

Выводы. Анализ активности ферментов печени, С-реактивного белка, глюкозы и липидограммы показал достоверное увеличение этих показателей у пациентов с сердечно-сосудистыми заболеваниями и неалкогольной жировой болезнью печени, особенно при наличии сахарного диабета 2 типа и нарушения толерантности к глюкозе. У всех обследованных больных наблюдалось повышение активности ферментов печени и уровня липидов, что свидетельствует о влиянии этих заболеваний на печень и обмен веществ.

Introduction

Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT) are widespread diseases, each of which increases the risk of developing and progressing cardiovascular diseases (CVD), the main cause of premature disability and death in industrialized countries. Given the long asymptomatic course of both diseases and their impact on the patients' quality and longevity of life, screening for timely diagnosis and necessary therapy is essential.

Diabetes mellitus is one of the most pressing issues in modern medicine. According to the World Health Organization (WHO), this disease will rank 7th among all causes of mortality by 2030. In the absence of timely treatment, diabetes leads to damage to almost all organs and systems, with the development of macro- and micro vascular complications, causing disability and premature death.

Non-alcoholic fatty liver disease is recognized as a major component of metabolic syndrome and a primary risk factor for cardiovascular diseases, and in some studies, it even determines their outcome. The combination of type 2 diabetes mellitus and non-alcoholic fatty liver disease in a patient increases the risk of developing cardiovascular diseases by 53% and cirrhosis and hepatocellular carcinoma by 2–2.5 times.[1,2] Among patients with type 2 diabetes mellitus, the frequency of cardio- and cerebrovascular diseases, peripheral vascular lesions, as well as nephro- and retinopathy, is significantly higher when combined with non-alcoholic fatty liver disease.[3]

The goal of our study was to develop new methods for screening, prevention, and treatment of cardiovascular diseases in patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance.

Materials and Methods

This study is single-center, open-label, uncontrolled, diagnostic study.Between 2023 and February 2024, 216 patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance were selected at Heart Center "University Medical Center" Corporate Fund.

Inclusion criteria: patients from 18 to 65 years old, diagnosed with type 2 diabetes mellitus, impaired glucose tolerance, NAFLD and liver fibrosis.

Exclusion criteria: patients who did not sign informed consent, children and pregnant women.

Ethical approval

This study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Before commencing the research, approval was obtained from the Local Bioethics Committee of the Corporate Fund "University Medical Center" 2023/01-008 of 05.07.2023.

Statistical analysis

Data were analyzed using IBM SPSS Statistics software (IBM SPSS Inc.). Numerical variables were expressed as

mean ± SD and categorical variables as numbers and percentages. Nonparametric statistics were performed for dataset analysis. Between-group comparisons were assessed for numerical variables, and the Chi-square test was used for categorical variables and the corresponding causal relationship was evaluated by calculating the odds ratio (OR). P value ⩽0.05 was considered statistically significant.

Results

Study participants and diagnostic groups were divided according to Table 1.

Table 1.
Characteristics of patients with non-alcoholic fatty liver disease

Characteristics	Men (n=90)	Women (n=126)	Chi-squared	P value
Type 2 Diabetes	24 (11.1%)	14 (6.5%)	0,214	0,643
Impaired Glucose Tolerance	19 (8.8%)	7 (3.2%)	0.228	0.632
Non-alcoholic Fatty Liver Disease	110 (50.9%)	76 (35,2%)	4.462*	0.035*
Liver Fibrosis	99 (45,8%)	75 (34.7%)	2.161	0.142
*Chi-squared -test statistical significance; P⩽0.05 was considered statistically significant				

The definition of non-alcoholic fatty liver disease was adapted based on AASLD recommendations. We defined non-alcoholic fatty liver disease as the presence of steatosis - the absence of significant alcohol consumption (⩾2 portions per day for men, ⩾3 portions per day for women). The presence of steatosis in non-alcoholic fatty liver disease was quantified using either the Fatty Liver Index (FLI) or the US Fatty Liver Index (US-FLI) with threshold values ⩾60 and ⩾30,[4] respectively. Diabetes was defined as hemoglobin A1c (HbA1c) ⩾6.5%, fasting plasma glucose ⩾7 mmol/L, self-assessment of diabetes, or use of antidiabetic drugs. Impaired glucose tolerance was defined as HbA1c in the range of 5.7–6.5% or fasting plasma glucose in the range of 5.6–7 mmol/L. Non-invasive tests (NITs) for fibrosis included the Aspartate Aminotransferase to Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4) index, and NAFLD fibrosis score. These tests have an area under the curve (AUC) accuracy of 0.74 - 0.80 and 0.75–0.82, respectively, for diagnosing advanced fibrosis.[5,6,7] Lean patients were defined as having a body mass index (BMI) <23 kg/m^{2}for Asians and BMI <25 kg/m^2 for other races. Patients were considered overweight if their BMI was in the range of 23–27.5 kg/m^2 for Asians and 25–30 kg/m^2 for other races. Obese patients were defined as BMI >27.5 kg/m^2 for Asians and BMI >30 kg/m^2 for other races.[8,9]

Table 2.
Liver stiffness and fibrosis assessment

NAFLD / NASH	**CAP Assessment**	**Steatosis Degree**	**Liver area affected by fatty changes**
	≤238 dB/m	S 0	Normal
	238–260 dB/m	S 1	Lessthan ⅓ (from 11% to 33%)
	260–290 dB/m	S 2	From ⅓ to ⅔ (from 34% to 66%)
	290–400 dB/m	S 3	More than ⅔ (67%)
NAFLD / NASH	kPa Assessment	Fibrosis Degree	Liver area affected by scarring
	2–7 kPa	F0–F1	Normal, minimal
	7.5–10 kPa	F2	Moderates carring
	10–14 kPa	F3	Severes carring
	≥14 kPa	F4	Cirrosis

NAFLD - non-alcoholic fatty liver disease
NASH - non-alcoholic steatohepatitis

According to Table 1, the presence of non-alcoholic fatty liver disease shows a correlation with an increased risk of developing type 2 diabetes, as well as new convincing evidence that the risk varies with the severity of non-alcoholic fatty liver disease. However, it can be confirmed that patients without type 2 diabetes but with non-alcoholic fatty liver disease are also at increased risk of developing type 2 diabetes. The presence and severity of non-alcoholic fatty liver disease are independent risk factors for developing type 2 diabetes.

A fibroscan was performed on 186 patients (women - 76, men - 110), and the assessment of liver stiffness and fibrosis was conducted according to Table 2. The results of the patients are presented in Table 3.

Table 3.
Fibroscan test

Fibroscan	Men (n=110)	Women (n=76)	OR	95%CI	Z statistic	P value
Steatosis Degree						
S0	26 (14.0%)	16 (8.6%)	1.161[α]	[0.57;2.35]	0.414	0.679
S1	20 (10.8%)	12 (6.5%)	1.185[α]	[0.54;2.59]	0.425	0.671
S2	35 (18.8%)	22 (11.8%)	1.145[α]	[0.61;2.17]	0.417	0.676
S3	29 (15.6%)	26 (14.0%)	0.688[β]	[0.36;1.31]	1.150	0.250
Fibrosis Degree						
F0	47 (25.3%)	30 (16.1%)	1.143[α]	[0.63;2.07]	0.443	0.658
F1	39 (21.0%)	29 (15.6%)	0.890[β]	[0.48;1.63]	0.376	0.707
F2	20 (10.8%)	12 (6.5%)	1.189[α]	[0.54;2.59]	0.425	0.671
F3	4 (2.2%)	5 (2.7%)	0.536[β]	[0.14;2.06]	0.907	0.365
Odds ratio: α - OR=1 means that the odds are equal in both groups; β - OR<1 means that the event is directly related and has a chance of occurring in the second group z test statistical not significance P≥0.05						

The chance of developing severe forms of fibrosis stages F2 and F3 in men and women is almost equal, OR = 0.965, 95%CI [0.48;1.96], z = 0.09, p = 0.929. Women are more likely to develop severe forms of steatosis stages S2 and S3 than men, OR = 0.812, 95%CI [0.45;1.47], z = 0.68, p = 0.496.

From the data in Table 1 and Table 2, patients with type 2 diabetes and impaired glucose tolerance showed the following steatohepatitis results: S0 - absence of steatosis in 16 women (21.0%) and 26 men (23.6%). S1 - minimal steatosis in 12 women (15.7%) and 20 men (18.1%). S2 - moderate steatosis in 22 women (28.9%) and 35 men (31.8%). S3 - severe steatosis in 26 women (34.2%) and 29 men (26.3%).

Fibrosis: F0 - absence of fibrosis in 30 women (39.4%) and 47 men (42.7%). F1 - minimal fibrosis in 29 women (38.1%) and 34 men (30.9%). F2 - moderate fibrosis in 12 women (15.7%) and 14 men (12.7%). F3 - severe fibrosis in 4 women (5.2%) and 4 men (3.6%).

Analysis of patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance showed an exacerbation of the degree of steatohepatitis and fibrosis, which can be assessed as predictors of cardiovascular complications in both men and women.

Liver enzyme activity, C-reactive protein, glucose, and lipid profile analysis: ALT 25.20 (±17.8 U/L), AST 21.66 (±9.25 U/L), total bilirubin 3.41 (±23.20 mg/dL), direct bilirubin 0.18 (±0.12 mg/dL), CRP 057 (±2.82 mg/dL), glucose 112.35 (±39.17 mg/dL), glycated hemoglobin 5.82 (±1.61%), total cholesterol 196.2 (±43.93 mg/dL), LDL 132.71 (±3656 mg/dL), HDL 49.27 (±12.45 mg/dL), TG 143.30 (±89.58 mg/dL), apoA 1.29 (±0.63 g/L), apoB 1.09 (±1.27 g/L), LP (a) 37.01 (±49.95 mg/dL).

All examined patients with cardiovascular diseases and concomitant non-alcoholic fatty liver disease showed increased liver enzyme activity (ALT,

AST, total bilirubin). Blood lipid profile indicators were significantly higher than optimal levels for patients with cardiovascular diseases. There was also a significant increase in liver enzymes, C-reactive protein, triglycerides, and LP(a) in patients with cardiovascular diseases and non-alcoholic fatty liver disease combined with type 2 diabetes and impaired glucose tolerance. Therefore, overweight and obesity, non-alcoholic fatty liver disease can be considered predictors of type 2 diabetes and impaired glucose tolerance.

Discussion

Liver damage in this disease is characterized by fatty degeneration (steatosis) with inflammation and hepatocyte damage (non-alcoholic steatohepatitis, NASH) and fibrosis development. There is a risk of non-alcoholic fatty liver disease progressing to cirrhosis. In 75% of cases, non-alcoholic fatty liver disease is associated with obesity, dyslipidemia, arterial hypertension, type 2 diabetes mellitus, or impaired glucose tolerance.[3,10,11]These pathological processes are risk factors for the progression of atherosclerosis and the development of cardiovascular diseases. Patients with type 2 diabetes mellitus have a higher risk of severe liver disease compared to patients without diabetes.[3] In this case, we are talking about primary non-alcoholic fatty liver disease associated with obesity and carbohydrate and lipid metabolism disorders.

Studies of the frequency and structure of liver damage in patients with abdominal obesity and metabolic syndrome have shown that signs of non-alcoholic fatty liver disease at the steatosis stage are detected in 89% of cases in patients with abdominal obesity, and in 100% of cases in patients with early carbohydrate metabolism disorders and type 2 diabetes mellitus.[12]

Non-alcoholic fatty liver disease is characterized by the excessive accumulation of triglycerides and other cholesterol derivatives in hepatocytes due to an imbalance between the synthesis and utilization of these organic molecules. Non-alcoholic fatty liver disease includes non-alcoholic steatosis and non-alcoholic steatohepatitis (NASH); the latter encompasses a wide spectrum of diseases of varying severity, including fibrosis, cirrhosis, and hepatocellular carcinoma.[1,3]

There is no single proven mechanism for the development of non-alcoholic fatty liver disease. According to one model, the "two-hit" theory, the first "hit" is the excessive influx of free fatty acids (FFAs) into the liver, causing the "second hit" - oxidative stress, which in turn leads to the development of non-alcoholic steatohepatitis and fibrosis.[13] The "first hit" can be induced by tissue insulin resistance. Normally, postprandial insulin elevation leads to reduced lipolysis by inhibiting lipase, decreasing the content of free fatty acids in the blood plasma and liver. However, in the presence of insulin resistance (IR), the opposite process occurs: lipolysis is enhanced, releasing an increased amount of free fatty acids that induce oxidative stress development. Insufficient oxidation of free fatty acids leads to excessive triglyceride accumulation in the liver, secretion of increased amounts of very low-density lipoproteins, and hepatocyte death, resulting in elevated transaminase levels and subsequent fibrosis and cirrhosis.

Bile acids (BAs) are steroid monocarboxylic acids derived from cholanic acid. They are produced in the smooth endoplasmic reticulum of hepatocytes and secreted by liver epithelial cells. Bile acid biosynthesis is one of the important pathways for cholesterol elimination. The human bile acid pool is approximately equally represented by highly hydrophobic cholic, chenodeoxycholic, and deoxycholic acids. Primary bile acids are conjugated with glycine and taurine, increasing their hydrophilicity. They activate nuclear receptors regulating the expression of genes involved in the secretion, transport, and metabolism of primary bile acids, cholesterol, and triglycerides in hepatocytes and plasma.[1,12]In type 2 diabetes mellitus and insulin resistance, bile acid endocrine function is impaired, reducing their absorption, increasing liver fat in-

filtration, disrupting lipid metabolism in the liver and plasma, and accumulating triglycerides and low-density lipoproteins (LDLs). Biliary insufficiency develops, reducing the amount of bile and circulating bile acids, leading to fatty liver disease and cholelithiasis.[2,3]

According to the American Association for the Study of Liver Diseases (AASLD), the global prevalence of non-alcoholic fatty liver disease ranges from 6.3% to 33%, and non-alcoholic steatohepatitis from 3% to 5%, depending on the studied population and examination method.[3]

Non-alcoholic fatty liver disease increases the risk of developing type 2 diabetes by 1.5–5.5 times.[12] The prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes is 70–90%.[14] The prevalence of non-alcoholic fatty liver disease also increases with increasing body mass index (BMI): with morbid obesity, almost all patients have non-alcoholic fatty liver disease, with steatohepatitis in 25–70%. With the combination of obesity and type 2 diabetes, non-alcoholic fatty liver disease is found with a frequency of 5–20% to 75%, according to various authors.[13,15] Non-alcoholic fatty liver disease is not only associated with other components of metabolic syndrome - arterial hypertension, dyslipidemia, but is also its "unofficial" component. Non-alcoholic fatty liver disease, like type 2 diabetes, is a proven risk factor for cardiovascular diseases, increasing the occurrence of cardiovascular events and mortality by 1.2–6.2 times.[12,13,16,17]

Since there is no definitive answer as to whether insulin resistance and hyperglycemia (type 2 diabetes) are causes or complications of non-alcoholic fatty liver disease,[14] the overall relationship between non-alcoholic fatty liver disease and type 2 diabetes can be described as a "two-way street".[13] On one hand, non-alcoholic fatty liver disease precedes the development of type 2 diabetes, with its presence associated with an increased risk of the latter, the degree of risk being directly proportional to the severity of non-alcoholic fatty liver disease. The prevalence of type 2 diabetes is higher among those with non-alcoholic fatty liver disease than in the general population. On the other hand, in individuals with diabetes, the presence of non-alcoholic fatty liver disease worsens glycemic control and increases the already high risk of macrovascular complications.[18-20]

The pathogenesis of non-alcoholic fatty liver disease is represented by the two-hit hypothesis.[21,22] In the first stage, against the background of visceral obesity and impaired glucose tolerance, lipolysis increases, leading to elevated serum free fatty acid concentrations due to increased synthesis and inhibition of their oxidation in mitochondria, resulting in triglyceride accumulation and reduced fat excretion by hepatocytes. This creates conditions for the formation of liver fat degeneration - steatosis. Additionally, fatty hepatosis, regardless of its causes, can contribute to hyperinsulinemia due to decreased insulin clearance.[7,12,23,24]In the second stage of disease development, further accumulation of free fatty acids exerts direct lipotoxic effects on pancreatic beta cells and hepatocytes, stimulating glycogenolysis in the liver and predicting the increase of insulin resistance and hyperinsulinemia. Prolonged hypertriglyceridemia under insulin resistance conditions disrupts endothelial-dependent vasodilation, causing oxidative stress, resulting in lipid peroxidation products, reactive oxygen species, and cytokines, which are major risk factors for early atherosclerosis. Aldehydes, products of lipid peroxidation, are potent stimulators of stellate cells, leading to increased collagen synthesis (fibrogenesis) and neutrophil chemotaxis. As a result, with reduced hepatocyte membrane protective properties against lipotoxicity, direct or oxidative stress-mediated mitochondrial damage, tissue respiration uncoupling, hepatocyte apoptosis, and necrosis occur, activating fibrogenesis.

In the pathogenesis of non-alcoholic fatty liver disease, impaired adipose tissue function also plays a role. Adipocytes of visceral adipose tissue secrete

large amounts of free fatty acids directly into the portal vein, becoming not only a substrate for the formation of atherogenic lipoproteins but also inhibiting insulin binding to hepatocytes, leading to hyperinsulinemia and increasing insulin resistance. Secretion of adipokines and cytokines is also impaired, contributing to steatosis, inflammation, and fibrosis, and in the absence of adequate treatment, cirrhosis.[12,25,26] Elevated free fatty acid levels in the blood, even in healthy individuals, contribute to increased production of intercellular adhesion molecules, endothelial endothelin-1, E-selectin, and PAI-1, which are indicators of a procoagulant state, impaired vascular reactivity, and systemic inflammation. Non-alcoholic fatty liver disease increases the risk of thrombosis due to endothelial-leukocyte-platelet dysfunction.[27] Endothelial dysfunction occurs independently of insulin resistance and traditional risk factors. Non-alcoholic fatty liver disease promotes atherosclerosis progression, as evidenced by the relationship between the intima-media thickness of the carotid artery, brachiocephalic trunk arteries, coronary arteries, and the degree of liver histological changes. Research indicates that non-alcoholic fatty liver disease is characterized by specific cellular reactions inducing systemic endothelial dysfunction and unique cellular responses in fibrosis formation. Fibrosis in non-alcoholic fatty liver disease is characterized by sinusoidal capillarization, serving as a trigger for the cascade of systemic endothelial dysfunction.[26]

Thus, according to the European Association for the Study of the Liver (EASL) recommendations, screening for carbohydrate metabolism disorders in patients with non-alcoholic fatty liver disease is necessary, while screening for non-alcoholic fatty liver disease in patients with type 2 diabetes is recommended regardless of liver enzyme levels. Screening for other components of metabolic syndrome, representing a cluster of atherosclerosis risk factors, is also advisable.[13,28,29] The screening method for non-alcoholic fatty liver disease in patients with type 2 diabetes is liver ultrasound,[30] which detects moderate and severe steatosis and has advantages in diagnosing non-alcoholic fatty liver disease at the cirrhosis stage, especially in asymptomatic patients.[31] Non-invasive diagnostic methods include the FibroMax test (α-2-macroglobulin, haptoglobin, apolipoprotein A1, γ-glutamyl transpeptidase (GGT), and total bilirubin), the FibroMeter test (α-2-macroglobulin, γ-glutamyl transpeptidase, urea, prothrombin index (%), platelets) for differentiating fibrosis from cirrhosis, and elastometry to assess liver elastic properties changes based on reflected vibration impulses and their subsequent computer analysis at all fibrosis stages.[32]

Considering the increased risk of adverse outcomes, regular diabetes screening for non-alcoholic fatty liver disease and rapid lifestyle changes to slow disease progression are emphasized. Patients with impaired glucose tolerance and diabetic non-alcoholic fatty liver disease can benefit from early referral to cardiovascular specialists to reduce the risk of cardiovascular events and mortality.[27] Therefore, the pathogenic mechanisms of non-alcoholic fatty liver disease and type 2 diabetes are closely interconnected. Both diseases can mutually aggravate each other, increasing the risk of cardiovascular diseases and significantly raising the likelihood of liver fibrosis in patients.[33] Patients with non-alcoholic fatty liver disease will benefit from frequent monitoring, and rapid lifestyle changes should be initiated at early disease stages to prevent the progression of type 2 diabetes, which can significantly increase morbidity and mortality. Patients with impaired glucose tolerance and diabetic non-alcoholic fatty liver disease may also benefit from early cardiovascular risk assessment. Pharmacological agents should aim to improve glycemic control, reduce fibrosis, and protect the cardiovascular system.[27]

Limitations: It is important to take into account the many limitations of this study when evaluating the results. First,

the diagnostic standards and procedures applied in the included research vary significantly from one another. Second,the generalizability of the results is restricted by the absence of data from control group. This study is a diagnostic study without control groups and number of patients is not enough to generalize the study findings. All of the gaps in this review should be addressed in future research to provide more comprehensive information. Thus, the study results emphasize the importance of combating overweight, obesity, and non-alcoholic fatty liver disease as risk factors for type 2 diabetes and impaired glucose tolerance, and the need for further research to identify causative links between these conditions, as specific causes remain insufficiently studied. A deeper understanding of these connections will allow the development of more effective strategies for preventing and treating metabolic disorders.

What's known? Non-alcoholic fatty liver disease is associated with obesity, dyslipidemia, arterial hypertension, type 2 diabetes mellitus, or impaired glucose tolerance. Non-alcoholic fatty liver disease increases the risk of developing type 2 diabetes by 1.5–5.5 times.

What's new? Patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance have an increased degree of steatohepatitis and fibrosis, which may predict the development of cardiovascular complications in both men and women

Conclusion

Our task was to develop innovative approaches to screening, preventing, and treating cardiovascular diseases in patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance.

Non-alcoholic fatty liver disease can be considered an early indicator and key factor in the development of type 2 diabetes and other clinical manifestations of metabolic syndrome. The study showed that patients with non-alcoholic fatty liver disease, type 2 diabetes, and impaired glucose tolerance have an increased degree of steatohepatitis and fibrosis, which may predict the development of cardiovascular complications in both men and women. Liver enzyme activity, C-reactive protein, glucose, and lipid profile analysis showed significant increases in these indicators in patients with cardiovascular diseases and non-alcoholic fatty liver disease, especially in the presence of type 2 diabetes and impaired glucose tolerance. All examined patients showed increased liver enzyme activity and lipid levels, indicating the impact of these diseases on the liver and metabolism.

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FIRST EXPERIENCE OF LAPAROSCOPIC HEPATICOJEJUNOSTOMY FOR BILE DUCT STRICTURES

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Keywords:
Bile duct injury, cholecystectomy, laparoscopic hepaticoejunostomy, hepaticoejunoanastomosis.

Abstract

Background. Bile duct injury is a potentially life-threatening condition characterized by high morbidity and mortality, which occurs as a result of erroneous manipulation during surgical intervention, such as incorrect identification of the ducts, improper clipping, or thermal injury. The aim of the study is to investigate the effectiveness of laparoscopic hepaticojejunostomy in patients with post-cholecystectomy bile duct injuries and compare it with traditional open techniques.

Materials and Methods. A retrospective analysis of the results of laparoscopic and open hepaticojejunostomy in patients with bile duct injuries from 2017 to 2023 was conducted.

Results. Laparoscopic surgery was performed on 28 patients, while open surgery was performed on 57 patients. Statistically significant differences were noted in the presence of external biliary fistula, diameter of the anastomosis, duration of the operation, postoperative complications, and postoperative period. There were no significant differences in the frequency of intraoperative complications.

Conclusion. The laparoscopic approach in treating bile duct strictures classified as Strasberg E1 - E2 is safe and effective.

Өт жолдарының тарылуы кезіндегі лапароскопиялық гепатикоеюностомоздың алғашқы тәжірибесі

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Тұжырым

Өзектілігі. Өт жолдарының зақымдануы - хирургиялық ота кезінде түтіктерді дұрыс анықтамау, дұрыс емес кесу немесе термиялық әсер ету сияқты дұрыс емес

манипуляция нәтижесінде пайда болатын жоғары сырқаттанушылық пен өліммен сипатталатын өмірге қауіп төндіретін жағдай. Зерттеудің мақсаты-холецистэктомиядан кейінгі өт жолдарының зақымдануы бар науқастарда лапароскопиялық гепатикоеюноанастомозды қолданудың тиімділігін зерттеу және оны дәстүрлі ашық әдіспен салыстыру.

Материал және әдістер. 2017-2023 жж. өт жолдарының зақымдануы бар науқастарда лапароскопиялық және ашық салынған гепатикоеюанастомозының нәтижелеріне ретроспективті талдау жүргізілді.

Нәтижелер. 28 науқасқа лапароскопиялық ота жасалды, ашық әдіспен – 57 науқас. Сыртқы өт жыланкөзінің болуында, анастомоз диаметрінің мөлшерінде, операцияның ұзақтығында, операциядан кейінгі асқынуларда, операциядан кейінгі кезеңде статистикалық маңызды айырмашылықтар байқалды. Интраоперациялық асқынулардың жиілігінде елеулі айырмашылықтар болған жоқ.

Қорытынды. Страсберг E1 - E2 классификациясы бойынша өт жолдарының тарылуын емдеудегі лапароскопиялық тәсіл қауіпсіз және тиімді екенін айқын көрсетіп отыр.

Мүдделер қақтығысы:
авторлар мүдделер қақтығысының жоқтығын мәдімдейді

Түйінді сөздер:
Өт жолдарының зақымдануы, холецистэктомия, лапароскопиялық гепатикоеюностомия, гепатикоеюноанастомоз.

Первый опыт лапароскопического гепатикоеюностомоза при стриктурах желчных протоков

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Ключевые слова:
Повреждение желчных протоков, холецистэктомия, лапароскопическая гепатикоеюностомия, гепатикоеюноанастомоз.

Аннотация

Фон. Повреждение желчных протоков - потенциально опасное для жизни состояние, характеризующееся высокой заболеваемостью и смертностью, которое происходит вследствие ошибочной манипуляции во время хирургического вмешательства, такого как неправильная идентификация протоков, неправильное клипирование или термическое воздействие. Целью исследования является изучение эффективности применения лапароскопического гепатикоеюноанастомоза у пациентов с постхолецистэктомическими повреждениями желчных протоков и сравнить его с традиционной открытой техникой.

Материал и методы. Проведен ретроспективный анализ результатов лапароскопического и открытого гепатикоеюноанастомоза у пациентов с повреждениями желчных протоков за 2017 - 2023 гг.

Результаты. Лапароскопически оперировано 28 пациентов, открытым способом – 57 пациентов. Отмечены статистически значимые различия в наличии наружного желчного свища, размерах диаметра анастомоза, в длительности операции, послеоперационных осложнений, послеоперационного периода. Отсутствовали значимые различия в частоте интраоперационных осложнений.

Заключение. Лапароскопический подход при лечении стриктур желчных протоков по классификации Страсберга E1 - E2 безопасен и эффективен.

Introduction

Bile duct injury (BDI) occurs as a result of erroneous manipulation during surgical intervention, such as incorrect identification of ducts, improper clipping, or thermal injury.[1] Cholecystectomy is the leading cause, and the frequency of bile duct injury varies from 0.1 to 0.2% after open cholecystectomy (OC) and 0.2-0.6% after laparoscopic cholecystectomy (LC).[2] This is a potentially life-threatening condition characterized by a high morbidity ranging from 2.3 to 23% and a mortality rate from 0.07 to 0.17%.[3] BDI has a significant impact on the physical and psychological quality of life of patients.[4,5] This is especially relevant for patients diagnosed with postoperative benign strictures of the bile ducts.[6] Surgical treatment of injuries to the extrahepatic bile ducts remains one of the most pressing issues in clinical surgery. Depending on clinical manifestations, surgical treatment methods include: percutaneous transhepatic cholangiostomy (PTBD), endoscopic retrograde cholangiopancreatography with placement of plastic stents (ERCP), and the definitive method of defect correction - reconstructive hepaticojejunostomy surgery with a Roux-en-Y loop.

Incorrect treatment can lead to serious complications, including recurrent cholangitis, secondary biliary cirrhosis, portal hypertension, and liver failure, significantly impacting the patient's quality of life.[7]

Bilioenteric anastomosis remains the gold standard for treating established strictures of the bile ducts, with excellent outcomes and a success rate exceeding 90% upon long-term follow-up.[8] According to reports from experienced centers, hepaticojejunostomy is performed when endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiostomy (PTC) are ineffective, and it can be done via open or laparoscopic approaches. Laparoscopic reconstruction is increasingly recognized in the treatment algorithm for bile duct injuries associated with cholecystectomy, offering an effective treatment option in specialized centers for selected patients.[9,10,11]

The aim of the study is to investigate the effectiveness of employing laparoscopic hepaticojejunostomy in patients with post-cholecystectomy bile duct injuries and to compare it with traditional open techniques.

Materials and methods

The aim of the study is to investigate the effectiveness of employing laparoscopic hepaticojejunostomy in patients with post-cholecystectomy bile duct injuries and to compare it with traditional open techniques.

Depending on the method of surgical treatment, patients (n=85) were retrospectively divided into 2 groups. The first group consisted of patients who underwent laparoscopic hepaticojejunostomy (n=28), and the second group consisted of patients who underwent traditional open hepaticojejunostomy (n=57). All patients had previously undergone laparoscopic or open cholecystectomy at external medical institutions and were referred to our center with bile duct injuries. The study was approved by the local ethics committee. Written informed consent was obtained from all patients preoperatively.

For the purpose of differential and topical diagnosis, a comprehensive examination was conducted, including general clinical and biochemical laboratory methods, ultrasonography, fistulography, and MR cholangiography. Bile duct lesions were classified according to the Strasberg-Bismuth classification. (Figure 1)

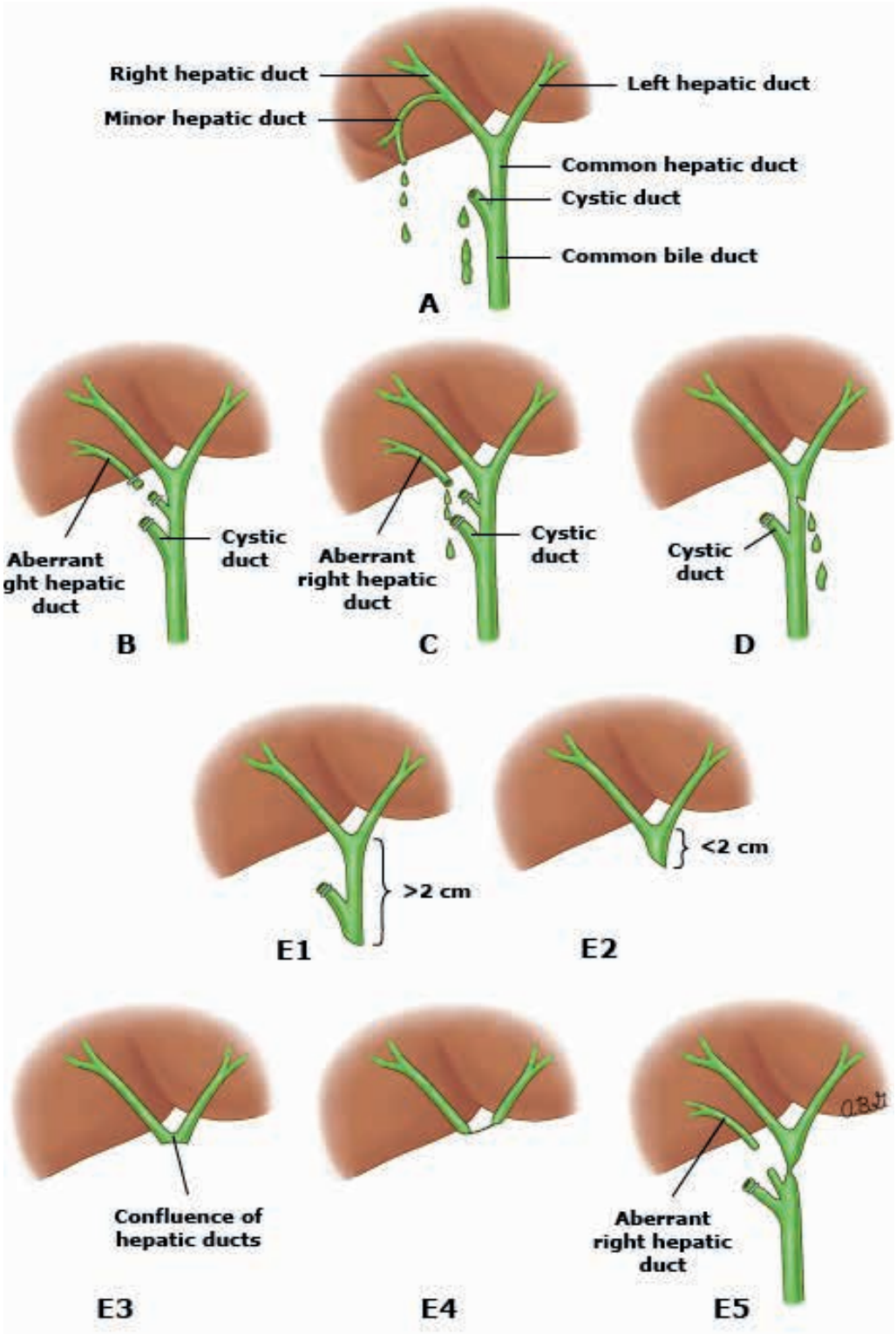


Figure 1.
Strasberg classification of bile duct injury 1995

The laparoscopic procedure was performed with the patient in the supine position with legs apart (French position). A five-port technique was used for laparoscopic access. After trocar placement, abdominal cavity organs were revised, and adhesiolysis was performed in the subhepatic space. Mobilization of the hepatoduodenal ligament (HDL) was carried out with the isolation of the common hepatic duct (CHD) and subsequent transection below the confluence to prepare the site for hepaticojejunostomy.

Then, the jejunum was isolated 40-60 cm from the Treitz angle and transected with a stapling device (Endo GIA

45mm). At a distance of 80 cm on the isolated Roux limb behind the ileocecal bowel, it was brought to the liver hilum. The anastomosis was created using atraumatic PDS 5/0 or 4/0 sutures, either continuous or interrupted. Subsequently, an interintestinal anastomosis was formed using a stapling device (Endo GIA 45mm) in a side-to-side fashion. For monitoring the integrity of the anastomosis, a drainage tube was left in the subhepatic space and in the pelvis.

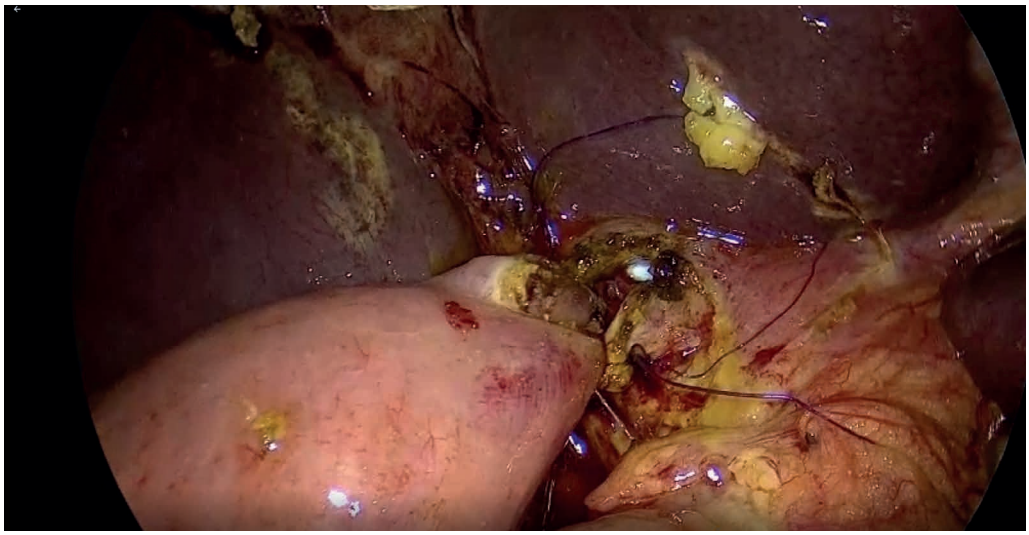
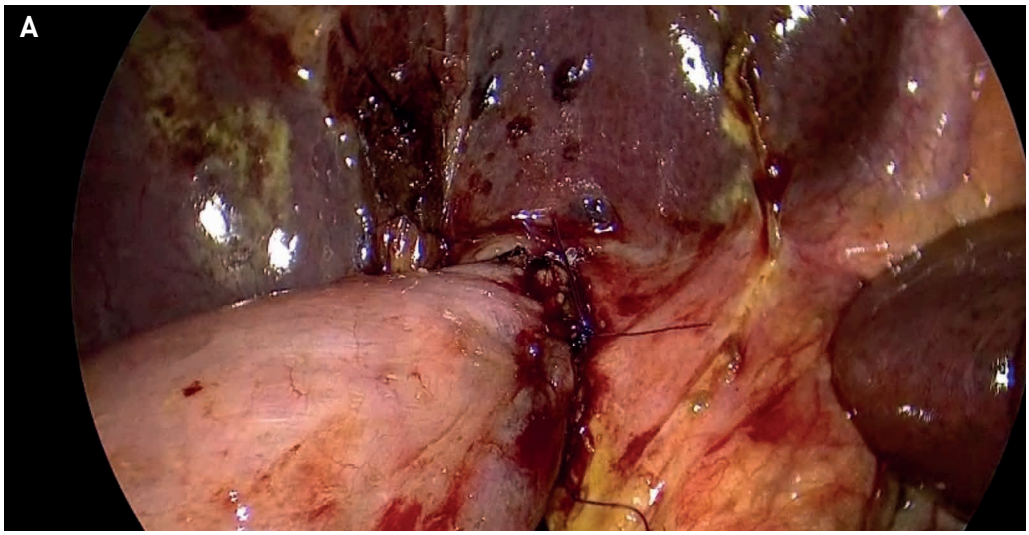


Figure 2.
Laparoscopic view of anastomosis between the posterior wall of the biliary ducts and the posterior wall of the intestine



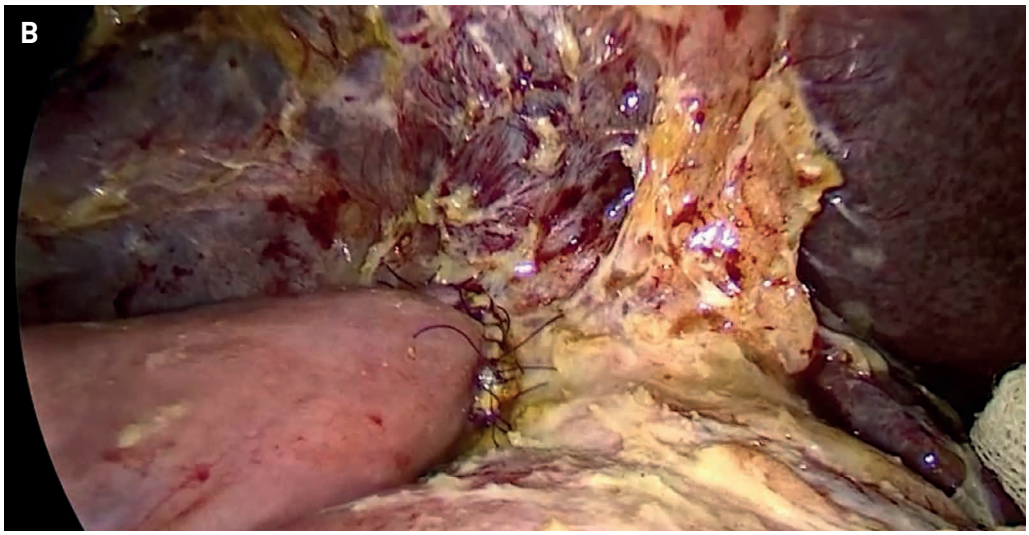


Figure 3.
Laparoscopic view of anastomosis between the anterior wall of the biliary ducts (A) and the posterior wall of the intestine (B).

Statistical analysis

Data were analyzed using IBMSPSS Statistics software (IBMSPSSInc.). Numerical variables were expressed as mean ± SD and categorical variables as numbers and percentages. Nonparametric statistics were performed for dataset analysis. Between-group comparisons were assessed for numerical variables, and the Chi-square test was used for categorical variables. P value ⩽0.05 was considered statistically significant.

Ethical approval

This study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Before commencing the research, approval was obtained from the Local Bioethics Committee of the«National Scientific Surgery Center named after A.N. Syzganov» JSC.

Results

The cause of iatrogenic injuries to the extrahepatic bile ducts was cholecystectomy - 28 patients. Among them, open cholecystectomy (OC) was performed in 14 (50%) cases, while laparoscopic cholecystectomy (LC) was performed in 14 (50%) cases.

During the postoperative period, all patients underwent scheduled follow-up examinations at 1, 3, 6, and 12 months.

In the first group, two-stage surgical treatment was performed in 10 (35.7%) cases. In the second group, it was performed in 41 (71.9%) cases. During the first stage, percutaneous transhepatic cholangiostomy was carried out under ultrasound and X-ray control.

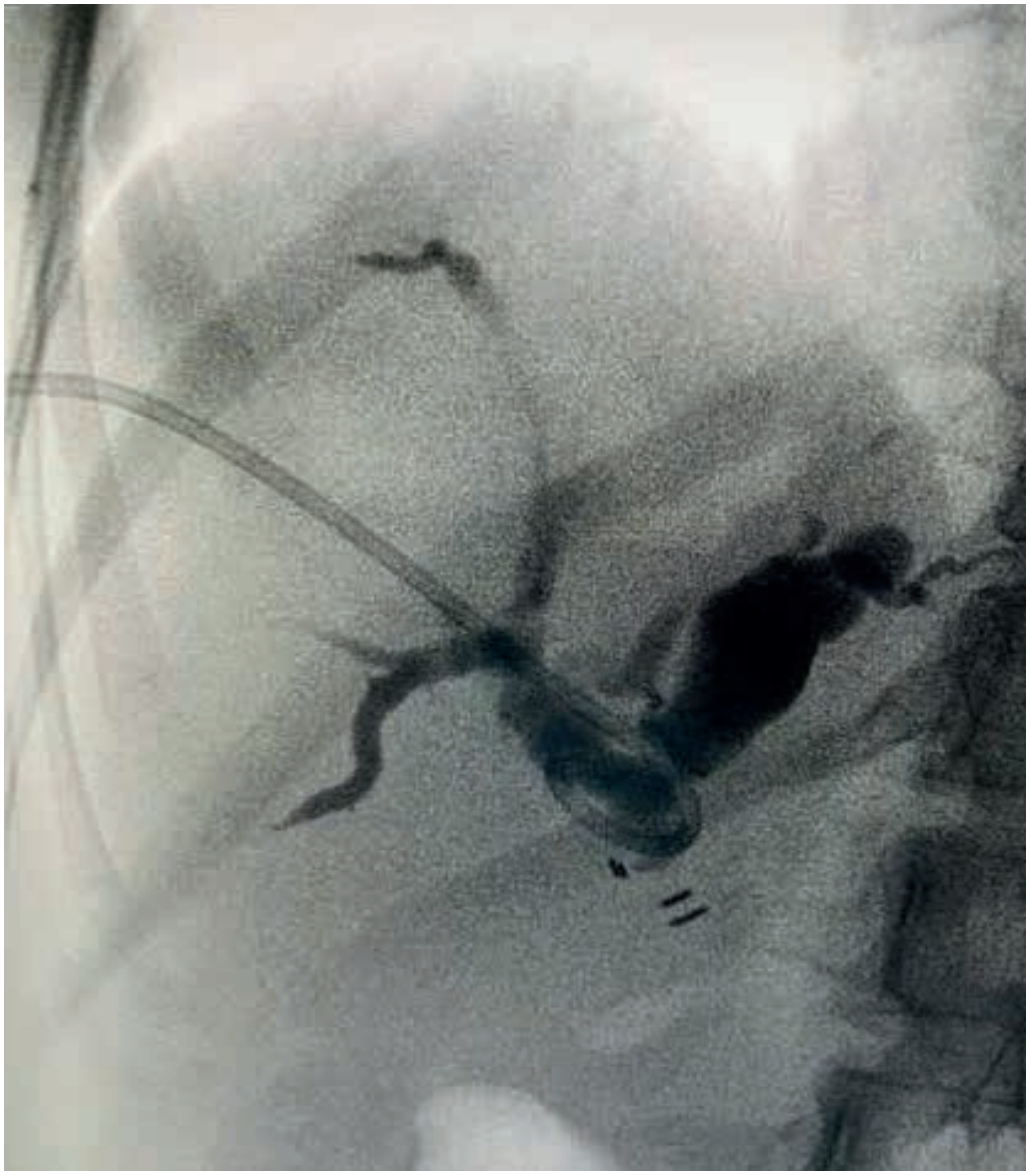


Figure 4.
Percutaneous transhepatic cholangiography. The orange arrow indicates the injury site of the common hepatic duct (Type E2 by Strasberg)

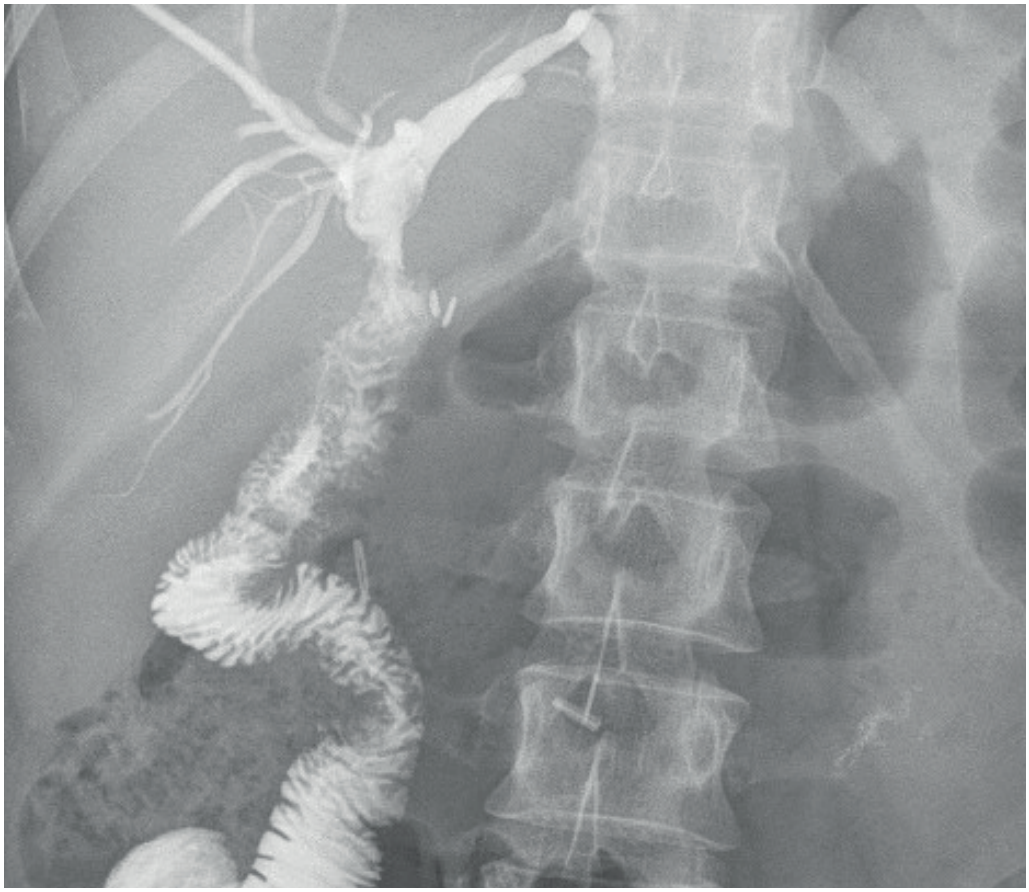


Figure 3.
Percutaneous transhepatic cholangiography performed 1 month after laparoscopic hepaticojejunostomy.

The first stage of the operation was completed with external drainage of the extrahepatic bile ducts to alleviate bile hypertension and stabilize the patients' general condition. The second stage involved laparoscopic or open hepaticojejunostomy on the Roux-en-Y limb. A statistical difference was found upon comparison, with the second group having more patients with external bile fistulae than the first group ($p<0.05$).

There were no intraoperative complications observed in either the first or second groups.

Table 1.
General clinical characteristics of patients with bile duct injury according to Strasberg classification E1-E2.

Characteristic	Hepaticoejunostomy		t-statistics	Chi-squared	P value
	Open	Laparoscopic			
Number of patients	57 (67.1%)	28 (32.9%)	-		-
Average age (yr)	45.6 ±10.5 (26-67)	47.3±11 (21 - 72)	0.691	-	0.491
Gender (male)	13(15.3%)	6(7.1%)	-	0.236	0.627
Strasberg classification E1	34(40.0%)	14(16.5%)	-	2.420	0.120
Strasberg classification E2	23(27.1%)	14(16.5%)	-	0.536	0.464
External biliary fistula	41(48.2%)	10(11.8%)	-	4.315	0.038*
Anastomosis size (cm)	1.08±0.18 (0.8 – 1.6)	1.24±0.19 (0.9 – 1.7)	3.782*	-	0.0002*
Duration of the operation (min)	269±61.06 (120-435)	372.3±106.7 (120 - 560)	5.675*	-	0.0001*

Intraoperative blood loss (ml)	93.6±70.1 (50-700)	69.2 ± 31.2 (20 - 150)	1.754	-	0.083
Postoperative bed days	11.1± 4.49 (6-31)	6.7 ± 1.7 (3 – 10)	4.989*	-	0.0001*
Laparoscopic chole-cystectomy	31(36.5%)	14 (16.5%)	-	1.787	0.181
Open cholecystectomy	28 (32.9%)	14 (16.5%)	-	1.231	0.267
*t -test statistical significance; P≤0.05 was considered statistically significant					

When comparing postoperative complications, a statistically significant difference was observed. Complications were more common in the second group than in the first group (p<0.05). In the postoperative period, one patient (1.7%) developed a stricture of the hepatico-enterostomy (HEA) two years after the open HEA procedure, and considering the HEA stricture, the patient underwent biliary stenting. Four patients (7.1%) were diagnosed with postoperative ventral hernia, which subsequently required reoperation for postoperative ventral hernia repair. Eight patients (14.1%) experienced wound infection in the postoperative period. There were no cases of mortality recorded.

The average postoperative hospital stay in the first group was 6.7 ± 1.7 days (range: 3 – 10), while in the second group, it was 11.1 ± 4.49 days (range: 6-31). A statistically significant difference was found when comparing the number of postoperative hospital days. Postoperative hospital days were higher in patients in the second group compared to those in the first group (p<0.05).

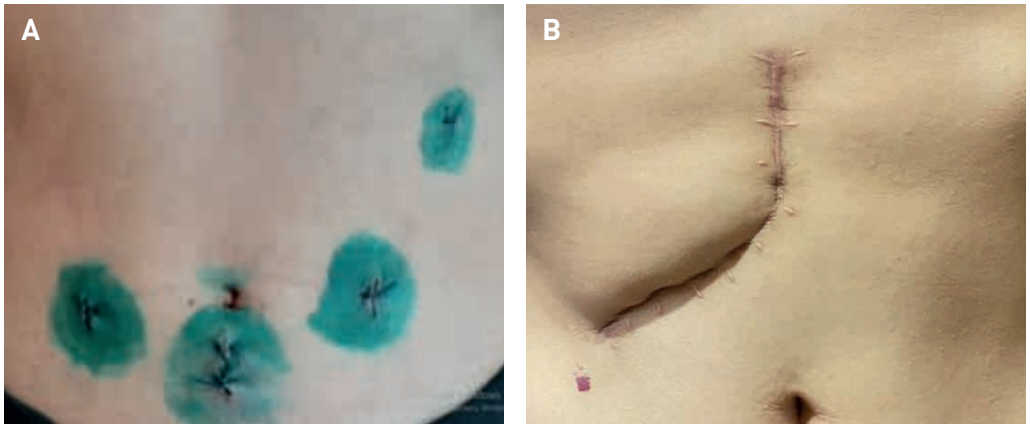


Figure 6.
Comparison between patient postoperative wounds after (A) laparoscopic and (B) open hepaticojejunostomy

Complications	Hepaticoejunostomy		OR	95 % CI	Z statistic	P value
	Open	Laparo-scopic				
Total complications	15(17.6%)	1 (1.2%)	9.64[a]	[1.2;77.3]	2.13*	0.03*
Bleeding	1 (1.2%)	0	1.51	[0.06;38.3]	0.251	0.802
Hepatic Subcapsular Biloma	1 (1.2%)	1 (1.2%)	0.48	[0.03;8.01]	0.509	0.611
Anastomosis stricture	1 (1.2%)	0	1.51	[0.06;38.3]	0.251	0.802
Wound Suppuration	8 (9.4%)	0	9.79[a]	[0.54;175.98]	1.547	0.122
Ventral hernia	4 (4.7)	0	4.79[a]	[0.25;92.24]	1.039	0.299
*z-test statistical significance; P≤0.05 was considered statistically significant; [a] OR>1 means that the event is directly related and has a chance of occurring in the first group.						

Table 2.
Postoperative complications

Discussion

Hepaticojejunostomy on an isolated Roux-en-Y loop is the most commonly performed surgical procedure in the treatment of BDI after multiple attempts to restore bile duct patency using endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiostomy. The majority of available literature on the surgical treatment and outcomes of post-cholecystectomy bile duct injuries involves open surgical intervention,[8] as BDI is typically associated with severe adhesion formation in the subhepatic space, posing technical challenges.[12,13] Currently, laparoscopic and robotic methods have become widely adopted in specialized centers equipped with appropriate medical equipment and experienced hepatobiliary surgeons. The outcomes of laparoscopic and robotic approaches for creating hepaticojejunostomy in patients with scar strictures can be comparable to those of open methods. Additionally, they offer several advantages such as better cosmetic results and faster recovery in the postoperative period.[7,10,14]

In our center, robotic technology is not available. However, the possibilities of using laparoscopic access in abdominal surgery, such as gastropancreaticoduodenal resections, liver resections, and intestinal anastomoses, have prompted us to propose laparoscopic repair of bile duct injuries after cholecystectomy. In our study, patients who underwent laparoscopic hepaticojejunostomy met the criteria for laparoscopic hepaticojejunostomy proposed by *Gupta et al.*: type E1-2 injuries according to the Strasberg classification, with a duct diameter of more than 3 mm.[15] Despite its technical complexity, the laparoscopic approach offers advantages over open access in terms of better intraoperative visualization, allowing for precise execution of a wide anastomosis.Literature also includes data on the application of the laparoscopic method of hepaticojejunostomy in patients with complex bile duct injuries classified as Strasberg E3-E4. However, for these injuries, we did not utilize the laparoscopic method due to the lack of conditions for precise technique execution. In cases of complex bile duct injuries, we recommend an open approach for creating hepaticojejunostomy to avoid a higher incidence of complications.[14]

The duration of volumetric laparoscopic surgeries is significantly longer compared to traditional open surgery.[16,17] The analysis of intraoperative parameters demonstrated that the duration of laparoscopic hepaticojejunostomy is statistically significantly longer than open hepaticojejunostomy ($p<0.05$). This could be associated with technical difficulties such as an unstable operative field, limited degree of freedom of movement, and challenges in complex suture placement.[2,10]

Complications of hepaticojejunostomy include bile leakage, anastomotic insufficiency, cholangitis, adhesive intestinal obstruction, postoperative ventral hernia, and surgical site infection. In our study, we found a significantly higher incidence of postoperative complications in the open hepaticojejunostomy group, which was 9 times greater than in the laparoscopic group ($p<0.05$). Analysis of postoperative complications in the open surgery group revealed a predominance of wound infection, attributed to repeated entries into the abdominal cavity via open methods within 3-6 months. The absence of large incisions in laparoscopic surgeries helped reduce complications related to the surgical wound (infection, hernias).

The results presented in the study confirm the benefits of minimally invasive approaches in the treatment of bile duct injuries. These benefits include excellent cosmetic outcomes due to the absence of a large incision, shorter postoperative recovery times, which are attributed to quicker removal of the safety drain and cessation of analgesic use.

It is important to emphasize that the performance of laparoscopic hepaticojejunostomy should be conducted in surgical centers equipped with the necessary experience and highly skilled specialists.[12] This requirement is due to the complexity of minimally invasive

surgeries. Expanding the practice of this technique contributes to improving the effectiveness of treatment for patients with scar strictures of the bile ducts after cholecystectomy.

Limitation: In our study, there are several limitations. Firstly, a small number of patients suitable for laparoscopic hepaticojejunostomy were included. Secondly, insufficient professional expertise of operating surgeons also limits the performance of this operation in other centers. Thirdly, the study was limited to data from only one center, which may have affected the reliability of the results. Nevertheless, based on our data, we believe that laparoscopic hepaticojejunostomy is safe and effective.

What's known? Given the prevalence of cholecystectomy worldwide, bile duct injury represents a significant potential burden on healthcare, as it can lead to disability.

What's new? The absence of a negative effect of the minimally invasive approach on the number of postoperative complications and on long-term treatment outcomes compared to traditional open surgery confirms the prospects for expanding the use of laparoscopic surgery in the treatment of bile duct injuries after cholecystectomy.

Conclusion

Thus, the application of the laparoscopic approach in selected patients with bile duct strictures (classified as Strasberg E1-E2) is safe and effective. It significantly reduces postoperative complications and shortens the length of hospital stay, providing better cosmetic outcomes for patients and enabling quicker rehabilitation.

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WHAT SCALES SHOULD THE CARDIOLOGIST USE IN PATIENTS WITH ATRIAL FIBRILLATION? WHAT IS NEW?

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Abstract

The current treatment algorithm for patients with non-valvular atrial fibrillation (AF) includes anticoagulation to prevent stroke and systemic embolism, improvement of AF symptom control by heart rate reduction or restoration and maintenance of sinus rhythm, and treatment of cardiovascular and other comorbidities. The evaluation of patients with AF should be structured and include assessment of stroke risk, symptom severity, severity of the AF burden (type of arrhythmia, number and duration of episodes, etc.) and predisposing condition. The use of the CHA2DS2-VASc (risk of stroke), HAS-BLED (risk of bleeding), EHRA (severity of AF symptoms), and 2MACE (risk of cardiovascular outcomes) scales is important to help assess the likelihood of adverse outcomes and select the optimal treatment to protect not only against stroke but also against cardiovascular events. It should be noted that the HAS-BLED scale is primarily necessary for identification of bleeding risk factors, the modification of which allows to increase the safety of anticoagulant therapy, and a high index value according to this scale can't serve as a reason to refuse anticoagulation in a patient with AF. New scales of stroke and hemorrhagic complications risk assessment in patients with AF on the basis of clinical parameters and laboratory biomarkers have been proposed, but their possible advantages over the existing indices need to be confirmed in special studies.

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Жүрекшелердің фибрилляциясы бар науқастарда кардиолог қандай таразыларды қолдануы керек? Не жаңалық?

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Тұжырым

Клапандық емес жүрекшелер фибрилляциясы (ЖФ) бар науқастарды емдеудің заманауи алгоритмі инсульт пен жүйелік эмболиялардың алдын алу, жүрек соғу жиілігін төмендету немесе синустық ырғақты қалпына келтіру және ұстап тұру арқылы ЖФ белгілерін бақылауды жақсарту және жүрек-қан тамырлары және басқа да қатар жүретін ауруларды емдеу мақсатында антикоагуляцияны қамтиды. ЖФ-мен ауыратын науқастарды тексеру құрылымды болуы керек және инсульт қаупін, симптомдардың ауырлығын, ЖФ жүктемесінің ауырлығын (аритмия түрі, эпизодтардың саны мен ұзақтығы және т.б.) және бейімділік жағдайын бағалауды қамтуы керек. Cha2ds2-vasc (инсульт қаупі), HAS-BLED (қан кету қаупі), EHRA (ЖФ симптомдарының ауырлығы) және 2MACE (жүрек-қан тамырлары қаупі) шкалаларын қолдану өте маңызды. Бұл қолайсыз нәтижелердің ықтималдығын бағалауға және инсульттан ғана емес, сонымен қатар оңтайлы емдеуді таңдауға көмектеседі. Айта кету керек, HAS-BLED шкаласы ең алдымен қан кету қаупінің факторларын анықтау үшін қажет, олардың модификациясы антикоагулянттық терапияның қауіпсіздігін жақсартуға мүмкіндік береді және осы шкала бойынша жоғары индекс мәні ЖФ бар науқаста антикоагуляциядан бас тартуға негіз бола алмайды. Клиникалық көрсеткіштер мен зертханалық биомаркерлер негізінде ЖФ бар науқастарда инсульт пен геморрагиялық асқынулардың қаупін бағалаудың жаңа шкалалары ұсынылды, бірақ олардың қолданыстағы индекстерден ықтимал артықшылықтары арнайы зерттеулерде растауды қажет етеді.

Какие шкалы должен использовать кардиолог у пациентов с фибрилляцией предсердий? Что нового?

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Аннотация

Современный алгоритм лечения больных с неклапанной фибрилляцией предсердий (ФП) предполагает антикоагуляцию с целью профилактики инсульта и системных эмболий, улучшение контроля симптомов ФП путем урежения частоты сердечных сокращений или восстановления и удержания синусового ритма и лечение сердечно-сосудистых и других сопутствующих заболеваний. Обследование пациентов с ФП должно быть структурированным и включать в себя оценку риска инсульта, выраженности симптомов, тяжести нагрузки ФП (тип аритмии, число и длительность эпизодов и т.п.) и предрасполагающего состояния. Важное значение имеет использование шкал CHA2DS2-VASc (риск инсульта), HAS-BLED (риск кровотече-

ния), шкалы EHRA (выраженность симптомов ФП) и 2MACE (риск сердечно-сосудистых исходов), которые помогают оценить вероятность неблагоприятных исходов и выбрать оптимальное лечение, обеспечивающее защиту не только от инсульта, но и от сердечно-сосудистых событий. Следует отметить, что шкала HAS-BLED в первую очередь необходима для идентификации факторов риска кровотечений, модификация которых позволяет повысить безопасность антикоагулянтной терапии, а высокое значение индекса по этой шкале не может служить основанием для отказа от антикоагуляции у пациента с ФП. Предложены новые шкалы оценки риска инсульта и геморрагических осложнений у больных с ФП на основе клинических показателей и лабораторных биомаркеров, однако их возможные преимущества перед существующими индексами нуждаются в подтверждении в специальных исследованиях.

Management of patients with atrial fibrillation (AF) includes anticoagulation for prevention of stroke and systemic embolism, improvement of AF-related symptoms by rate or rhythm control, and treatment for cardiovascular and other comorbidities. The structured characterization of AF should address four AF-related domains, that is, stroke risk, symptom severity, AF burden (type of AF, number and duration of episodes, etc.), and substrate severity. Various scores, i.e. EHRA (severity of AF-related symptoms), and 2MACE (risk of cardiovascular events), can be used to estimate the risk of outcomes and for treatment decisions. Noteworthy, bleeding risk assessment using HAS-BLED score focuses attention on modifiable risk factors. New clinical and biomarker-based risk scores were developed. However, their potential advantages over existing scores should be confirmed in clinical studies.

The incidence of atrial fibrillation (AF) in the adult population is 2-4% [1]. It increases with age, including due to various comorbidities and risk factors, such as arterial hypertension, diabetes mellitus, coronary heart disease, chronic kidney disease, obesity, alcohol consumption, smoking, etc. In the coming years, we can expect a further increase in the prevalence of AF not only due to increasing life expectancy and aging of the population, but also due to the introduction of new systems for screening of rhythm disorders using mobile technologies (smartphones) that allow registering low-symptomatic or asymptomatic rhythm disorders [2]. For example, in the REHEARSE-AF study, recording of single-lead ECG using a smartphone/tablet twice a week for 12 months in patients aged ≥65 years resulted in a 3.9-fold increase in the rate of AF diagnosis compared with conventional management [3]. The use of such devices for AF screening is most justified in the elderly and elderly, as well as in patients at high risk of stroke [4].

AF is associated with more than 3-fold increase in the risk of death [5] and is one of the main causes of stroke (20-30% and 10% of ischemic and cryptogenic stroke cases, respectively), which is characterized by a severe and recurrent course and often leads to death or disability [1]. AF is accompanied by cardiac dysfunction and the development of heart failure, both with reduced and preserved left ventricular ejection fraction, which is observed in 20-30% of such patients and causes additional deterioration of life prognosis [6]. Adverse effects of AF also include reduced quality of life, especially in women [7], cognitive impairment up to dementia [8], and frequent hospitalizations associated with increased costs to the health care system [9]. According to a meta-analysis of 35 studies, in a total of more than 300,000 patients with AF, the hospitalization rate averaged 43.7 per 100 patients per year, and older age was one of the main factors associated with an increased likelihood of hospitalization [10].

Management of patients with AF

Current approaches to the examination, management and treatment of patients with AF are described in detail in the relevant recommendations of the European Society of Cardiology, which were prepared jointly with the European Association of Cardiothoracic Surgery

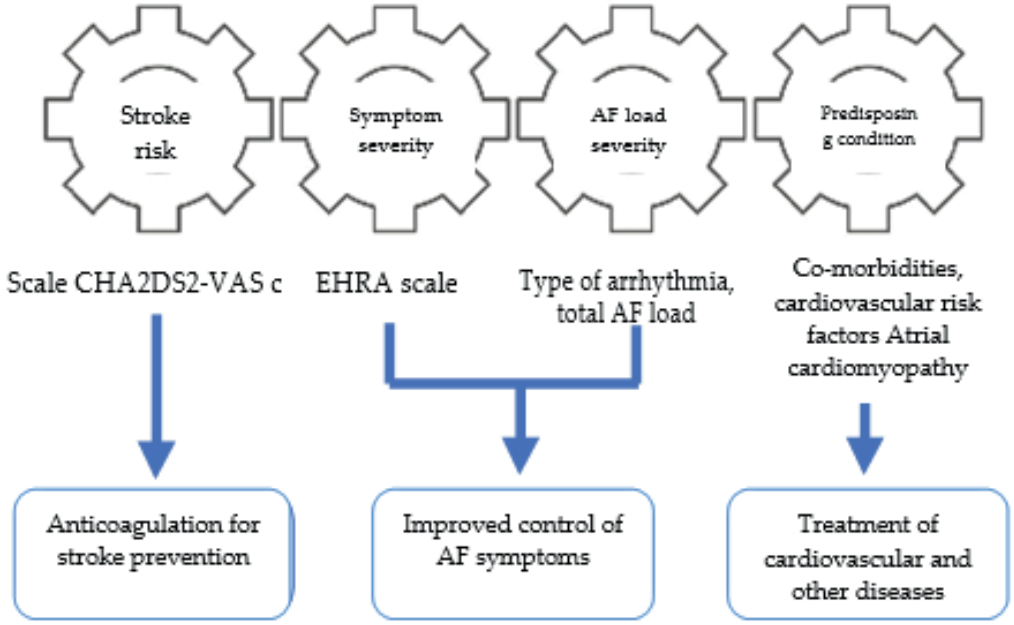

Figure 1.
Shematic of structured examination (4S-AF) and treatment algorithm (ABC) of patients with non-valvular FP

and published in 2020. [11]. These recommendations contain some important innovations, in particular, it was proposed to use a structured scheme of patient examination (4S-AF), involving the analysis of 4 domains (Fig. 1): stroke risk, symptom severity, severity of AF burden, and predisposing condition (AF substrate) [12]. Assessment of the above factors, including using special scales, such as CHA2DS2-VASc, HAS-BLED, EHRA scale, 2MACE, etc., has prognostic value and helps to choose the optimal treatment, which aims not only to provide adequate symptom control and improve quality of life, but also to prevent adverse clinical outcomes, including death. It should be taken into account that the type of AF (first diagnosed, paroxysmal, persistent, long-standing persistent or permanent) is not decisive for the choice of treatment tactics (excluding the question of the need to restore sinus rhythm), for example, to assess the feasibility of oral anticoagulants for the prevention of ischemic stroke.

In order to improve the results of treatment, experts of the European Society of Cardiology recommended using the ABC algorithm, where A - Anticoagulation/Avoid stroke, B - Better symptom management and C - Cardiovascular and Comorbidity optimization (Fig. 1) [13]. The results of clinical trials have shown that implementation of the above algorithm is associated with a reduced risk of death from any cause, cardiovascular events, a combined endpoint including stroke, major bleeding and cardiovascular death, and treatment costs [14-16]. D. Pastori et al. studied the effectiveness of treatment according to the ABC algorithm in preventing cardiovascular complications in a prospective study in 907 patients [17]. In the group of 198 patients who received optimal treatment for about 3 years there was a significant reduction in the risk of any cardiovascular events by 60% (p = 0.003) compared to that in patients in whom at least one component of treatment did not correspond to the optimal one.

Table 1.
CHA2DS2-VASC scale for stroke risk assessment in patients with non-valvular AF [18]

Risk factors	Definition	Score
C	Clinical symptoms of CHF, moderate and severe LV systolic dysfunction (including asymptomatic), hypertrophic cardiomyopathy	1
H	Arterial hypertension (SBP ⩾140 mm Hg, DBP ⩾90 mm Hg) or taking anti-hypertensive medications (target BP for AF 120-129/<80 mm Hg).	1
A	Over 75 years of age	2

D	Type 1 and 2 diabetes mellitus (fasting glycemia more than 7 mmol/l or taking sugar-lowering drugs or insulin therapy)	1
S	History of stroke/TIA/thromboembolism	2
V	History of cardiovascular disease (angiographically confirmed CID, myocardial infarction, clinically significant peripheral atherosclerosis, atherosclerotic plaque in the aorta)	1
A	Age 65-74	1
Sc	Female gender	1

Anticoagulant therapy

The CHA2DS2-VASc scale is used to assess the risk of stroke in patients with atrial fibrillation who require anticoagulant use (Table. 1) [18], which includes congestive heart failure, arterial hypertension, age 275 years, diabetes mellitus, stroke/transient ischemic disease attack/system. embolism in the anamnesis, cardiovascular diseases, including stenosing coronary atherosclerosis, confirmed by angiography, myocardial infarction, atherosclerosis of peripheral arteries or plaques in the aorta, age 65-74 years and women [18]. It should be noted that female gender changes the overall risk of stroke rather than being a risk factor in itself [19], since in the absence of additional risk factors, women have the same low probability of stroke as men, with the CHA2DS2-VASc index equal to 0. At the same time, if there is at least one additional risk factor, the probability of stroke increases in women to a greater extent than in men [20].

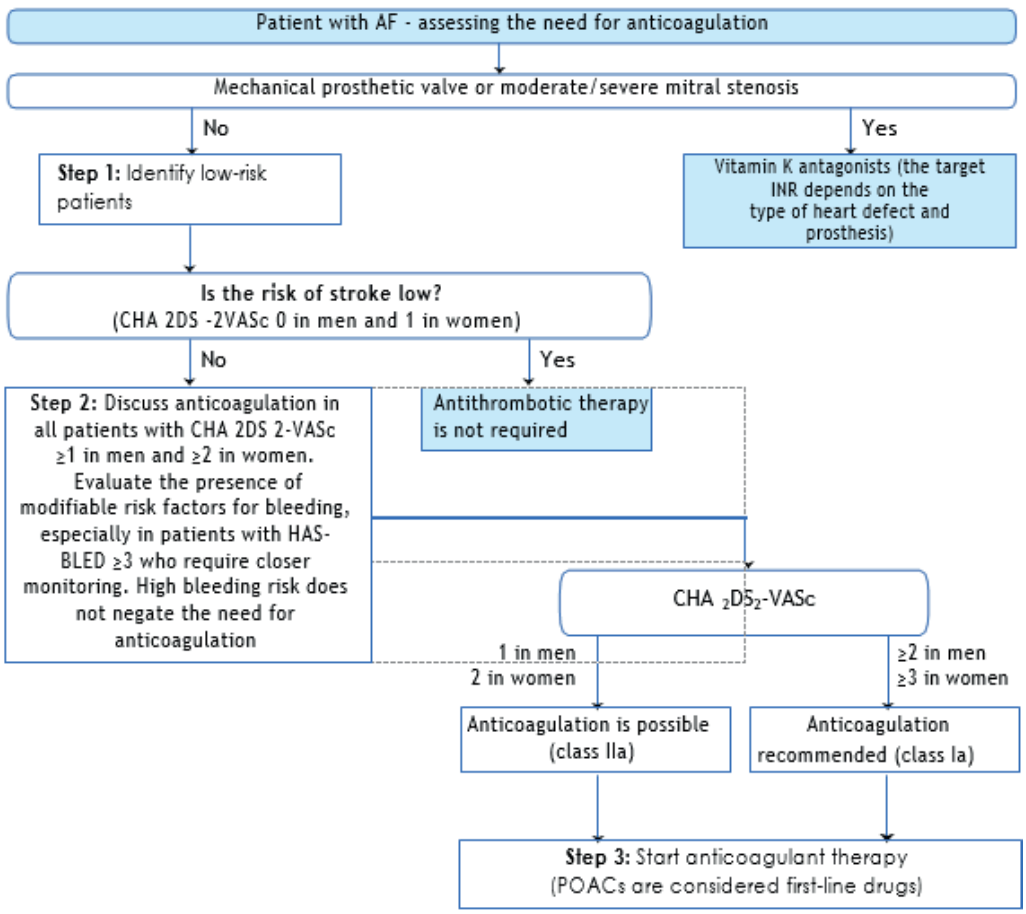

Figure 2.
Anticoagulant therapy in patients with non-valvular AF

In recent years, researchers have shown great interest in studying the role of various biomarkers, including those reflecting myocardial damage (troponin), cardiac dysfunction (natriuretic peptides), myocardial fibrosis (galectin-3),

impaired renal function (creatinine, cystatin C), inflammation (C-reactive protein, cytokines) and coagulant activity II (D-dimer), which may be associated with the pathogenesis of thrombosis, clinical outcomes and treatment effects [21]. The scales of stroke risk assessment in patients with AF are proposed, based not only on clinical risk factors, but also on some laboratory parameters, for example, the ABC scale takes into account the patient's age, the presence of stroke/transient ischemic attack (TIA) in the anamnesis and the levels of highly active sensitive troponin and NT-pro-BNP. The use of some new scales has increased the accuracy of predicting stroke risk in patients with atrial fibrillation, although the practical significance of their possible advantages over the generally accepted scale is small. CHA2DS2-VASc raises doubts, including due to the need for additional costs for the determination of biomarkers. However, it cannot be excluded that the latter they can be used to more accurately assess the likelihood of stroke in patients whose risk of stroke is regarded as low.

Table 2.
HAS-BLED scale for bleeding risk assessment in patients with non-valvular AF [22].

Risk factors	Definition	Score
H	Uncontrolled arterial hypertension (SBP>160 mmHg)	1
A	Renal and/or liver dysfunction (dialysis, kidney transplantation, serum creatinine >200 mmol/l, cirrhosis, bilirubin level more than 2 times the upper limit of normal, AST/ALT/alkaline phosphatase more than 3 times the upper limit of normal)	1*
S	Stroke (ischemic or hemorrhagic stroke)	1
B	Bleeding history or predisposition to bleeding (previous major bleeding, anemia, severe thrombocytopenia)	1
L	Labile INR in patients receiving vitamin K antagonists	1
E	Older age (age>65 years or "frail" patient)	1
D	Concomitant use of medications (antiaggregants and NSAIDs) and/or alcohol (heavy drinking or more than 14 units per week)	1*

Before prescribing oral anticoagulants to patients with AF, it is necessary to assess the risk of bleeding. For this, the HAS-BLED scale is usually used (Table 2). This school retains its importance despite the emergence of new indices, including those that take into account not only clinical and demographic indicators, but also the levels of laboratory biomarkers. For example, the ABC index is calculated taking into account age, a history of bleeding and laboratory biomarkers, including GDF-15, highly sensitive troponin and hemoglobin [22]. The recommendations of the European Society of Cardiology specifically emphasize that there is a high risk of bleeding in the absence of absolute contraindications cannot serve as a reason for refusing anticoagulation therapy, since the "pure" clinical benefit of anticoagulation is even higher in such patients. Risk assessment of hemorrhagic complications is primarily necessary to identify patients who need more careful monitoring (for example, every 4 weeks, not 4-6 months) and modification of risk factors.

Some risk factors for bleeding (age over 65, history of bleeding, renal replacement therapy, malignant tumors, genetic factors, etc.) are unmodified, but many others can be eliminated or reduced (arterial hypertension, concomitant administration of antithrombotic drugs alcohol abuse, anemia, thrombocytopenia, dangerous hobbies, etc.). It should also be taken into account that the change in the risk profile of bleeding in dynamics is of great importance for predicting more severe blood flow than its initial value. In a clinical study, a significant (3.5-fold) increase in the risk of major bleeding over the next 3 months was revealed in patients who had a change in the index on the HAS-BLED scale.

The tendency to fall by itself is not an independent risk factor for bleeding on the background of anticoagulant therapy, however, a fall injury in an elderly patient taking oral anticoagulants can lead to more severe bleeding, for example intracranial. Interesting data were obtained in one study that simulated the effects of falls in patients receiving oral anticoagulants. The authors showed that patients taking warfarin should fall about 295 times a year so that the threat of serious bleeding outweighs the benefit of reducing the risk of ischemic stroke. Nevertheless, these data do not negate the need to prevent falls with simple measures, such as the use of assistive devices when walking, wearing appropriate shoes, removing obstacles for an elderly person in an apartment (carpets, extra furniture).

Indications for the appointment of oral anticoagulants in the new recommendations of the European Society of Cardiology have not changed. Their use is necessary if the index value on the CHA2DS2 scale-VASc is at least 2 in males and 3 in females. This means that oral anticoagulants should be prescribed to all patients with AF (Atrial fibrillation) (regardless of gender) who have reached the age of 75 years, and patients aged 65-74 years in the presence of at least one additional risk factor for stroke, for example, arterial hypertension or diabetes mellitus, while at a younger age the basis for anticoagulation is the presence of at least two risk factors in both men and women (Fig. 2) . If the index on the CHA2DS2-VASc scale is 1 in men or 2 in women, then anticoagulant therapy is considered possible, although clear indications for its appointment in such cases are not given in the recommendations. AF (Atrial fibrillation) usually develops in elderly and senile people suffering from various diseases. Therefore, the index on the CHA2DS2-VASc scale in most patients with this arrhythmia exceeds these values, justifying the use of anticoagulants. In addition, the CHA2DS2-VASc index tends to increase both due to age and the addition of new diseases that increase the risk of stroke. It should be emphasized once again that the type of AF (Atrial fibrillation (paroxysmal/persistent or permanent) does not matter for solving the issue of anticoagulant therapy and is not taken into account when calculating the index on the CHA2DS2-VASc scale.

Vitamin K antagonists, primarily warfarin, or direct oral anticoagulants (OAC), including rivaroxaban, apixaban, dabigatran and edoxaban (the latter is not registered in the Russian Federation) are used to prevent stroke in patients with non-valvular AF. Combined therapy with acetylsalicylic acid and clopidogrel in such patients was inferior in effectiveness to warfarin and was accompanied by a comparable risk of bleeding [24], and monotherapy with acetylsalicylic acid was ineffective and associated with a higher risk of ischemic stroke in elderly people with AF [25]. Thus, antiplatelet drugs should not be considered as a safer alternative to oral anticoagulants in patients with AF who need effective stroke prevention.

Currently, oral anticoagulants (OAC) are considered first-line drugs in stroke prevention in patients with non-valvular AF [11]. In registration clinical trials, all drugs of this group were at least as effective as warfarin. However, a meta-analysis of clinical studies in patients receiving oral anticoagulants revealed a 19% reduction in the risk of stroke and systemic embolism compared to that with warfarin treatment, a 51% reduction in the risk of hemorrhagic stroke and a 10% reduction in the risk of death from any cause. In addition, when using oral anticoagulants (OAC), there was an unreliable decrease in the risk of major bleeding by 14% and a statistically significant decrease in the risk of intracranial bleeding by 52%, while the frequency of gastrointestinal bleeding increased by 25% [26]. These data allow us to consider oral anticoagulants (OAC) as a whole as a more effective and safer alternative to indirect anticoagulants.

Unlike oral anticoagulants (OAC), warfarin can interact with various medications that can enhance or, conversely, weaken its anticoagulant effect. When

treating with indirect anticoagulants, it is necessary to regularly monitor the international normalized ratio (INR) and, if necessary, adjust their doses. In general, vitamin K antagonists are considered effective and relatively safe drugs if the INR can be maintained in the therapeutic range for more than 70% of the time, although this is not always possible. A scale is proposed SAMe-TT2R2 (female, age less than 60 years, presence of at least two concomitant diseases, such as arterial hypertension, diabetes mellitus, coronary artery disease, atherosclerosis of peripheral arteries, heart failure, a history of stroke, lung disease and liver or kidney damage, treatment with certain drugs, smoking, non-European race), which makes it possible to identify patients with AF, in whom it is more difficult to ensure an adequate anticoagulant effect of warfarin [27]. The index value on this scale >2 serves as an additional argument in favor of choosing oral anticoagulants (POAC). If the patient still has to prescribe warfarin or another vitamin K antagonist (usually for economic reasons), then additional measures should be taken to increase the effectiveness and safety of therapy, for example, more frequent monitoring of INR, repeated consultations.

The efficacy profile of oral anticoagulants (OAC) in stroke prevention in patients with non-valvular AF was also confirmed in post-registration studies, the results of which corresponded to those of randomized controlled trials [28-30]. P. Kirchhof et al. the results of the use of rivaroxaban in 11121 patients with non-valvular AF (average age 70.5 ‡ 10.5 years) were summarized; 42.9% of women) included in studies conducted in routine clinical practice in 47 countries under the XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation) program [31]. Prospective research design increases the clinical value of the data obtained. Patients with AF who started taking rivaroxaban were monitored for 1 year. The frequency of major bleeding averaged 1.7 per 100 patient-years, death from any cause - 1.9 per 100 patient-years, stroke and systemic embolism - 1.0 per 100 patient-years. For comparison, the frequency of the primary endpoint, which included stroke and systemic embolism, in the randomized ROCKET AF study, confirmed the effectiveness of rivaroxaban in stroke prevention in patients with non-valvular AF, it was 1.7 per 100 patient-years [32]. The incidence of both bleeding and stroke was low in all countries participating in the XANTUS program, and the proportion of patients who continued taking rivaroxaban during the year was 77.4% (from 66.4% in East Asian countries to 84.4% in Western Europe). The high adherence to anticoagulant therapy reflects the convenience of using rivaroxaban, including the absence of the need for dose titration and regular monitoring of INR, the low risk of interaction with other drugs, the stability of the anticoagulant effect and the possibility of prescribing once a day.

All DOACs are partially eliminated by the kidneys, dabigatran to a greater extent and rivaroxaban and apixaban to a lesser extent, so renal function should be taken into account when choosing a drug and its dose. For example, the dose of rivaroxaban in patients with creatinine clearance15-49 ml/min should be reduced from 20 to 15 mg once daily. To ensure the safety of anticoagulant therapy in patients with atrial fibrillation, it is necessary to regularly monitor renal function using creatinine clearance calculated using the Cockcroft-Gold formula, since this is the indicator used in registration clinical studies. Renal function should be assessed at least once a year, or more frequently in patients at risk, such as those with baseline decreased renal function. In patients with impaired and/or deteriorating renal function, it is advisable to consider the use of oral anticoagulants, which are less excreted by the kidneys (rivaroxaban or apixaban).

The practice guideline of the European Association of Arrhythmology recommends measuring creatinine clearance every 6 months in patients aged >75 years (especially when treated with dabigatran) and "frail" patients. To estimate the minimum interval for determining

creatinine clearance in patients with initially reduced renal function, creatinine clearance should be divided by 10. For example, in patients with a value of 40 ml/min, creatinine clearance should be measured at least every 4 months. It must be taken into account that renal function can quickly deteriorate under the influence of various intercurrent diseases, for example, infections or acute heart failure. Accordingly, in such cases it is also necessary to measure creatinine clearance.

Atrial fibrillation in approximately a third of cases is combined with stage II-V chronic kidney disease (CKD), a decrease in the estimated glomerular filtration rate (GFR)<60 ml/min/1.73 m, which reflects the commonality of risk factors for the two conditions, such as old age, arterial hypertension, diabetes mellitus, etc. Moreover, approximately every fourth elderly patient with non-valvular atrial fibrillation can be expected to experience progression of CKD. For example, in the ORBIT-AF II study in 6682 patients with atrial fibrillation (median age 72 years) receiving DOACs or warfarin, the incidence of creatinine clearance decreases of more than 20% and 30% at 1 year of follow-up was 23.1 % and 10.6%, respectively. The combination of non-valvular AF with CKD is associated with an additional increase in the risk of ischemic stroke, bleeding and other adverse outcomes. In registration studies of DOACs, more than half of the patients had evidence of renal impairment. According to a meta-analysis of 4 randomized clinical trials ROCK-ET-AE, RE-LY, ARISTOTLE and ENGAGE AF-TIMI 48, which studied rivaroxaban, dabigatran, apixaban and edoxaban, accordingly, during the treatment of DOACs in patients with AF and impaired renal function, a significant reduction in the relative risk of stroke and systemic embolism was noted by 20% (p <0.01), major bleeding by 21% (p = 0.017) and death from any cause by 9% (p = 0.031) compared with that with warfarin.

Moreover, the "net" benefit of DOACs, which was assessed taking into account the risk of not only stroke/systemic embolism, but also bleeding, increased as renal function worsened and was highest in patients with creatinine clearance 30-50 ml/min. In the ROCKET AF study, progression of CKD, the criterion of which was a decrease in creatinine clearance by more than 20% compared to baseline, was detected in 26.3% of patients. Worsening renal function was associated with an increased risk of death from vascular causes, a composite endpoint of stroke, systemic embolism, cardiovascular death and myocardial infarction, and death from any cause compared with that in patients with stable renal function. Treatment with rivaroxaban compared with warfarin in patients with advanced CKD resulted in a reduced risk of stroke and systemic embolism and did not increase the risk of major and clinically significant minor bleeding.

Retrospective studies have shown that DOAC treatment in patients with non-valvular AF may be associated with improved renal outcomes compared with warfarin, including a reduction in the incidence of acute kidney injury (AKI) associated with nephropathy due to over-anticoagulation and glomerular hemorrhage. In a retrospective study, the incidence of warfarin-associated AKI was 33.0% in patients with CKD and 16.5% in patients with normal renal function. Treatment with DOACs can be expected to reduce the risk of AKI due to a more predictable anticoagulant effect compared to warfarin. C. Coleman et al. analyzed renal outcomes in a retrospective study of 72,000 patients with AF who started treatment with rivaroxaban or warfarin at for at least 12 months.

In another retrospective study, renal outcomes were assessed in 9769 patients with nonvalvular AF treated with various DOACs or warfarin. Treatment with DOACs for 2 years was associated with a significant reduction in the risk of developing or progressing CKD, in particular the likelihood of a reduction in GFR by at least 30% (odds ratio 0.77; 95% CI 0.66-0.89; p < 0.001) and doubling of serum creatinine (0.62; 0.40-0.95; p = 0.03) compared with that during treatment with warfarin. Improved renal

prognosis was found with rivaroxaban and dabigatran, but not with apixaban. This benefit of rivaroxaban may support its preferential use in patients with deteriorating renal function.

Improved symptom control

To assess the symptoms (palpitations, shortness of breath, fatigue, chest discomfort, etc.), AF uses a scale proposed by the European Association of Arrhythmologists (EHRA) and reflecting the effect of arrhythmia manifestations on the usual daily activity of patients (Table. 3) [46, 47]. It should be borne in mind that all these symptoms are nonspecific and may be the result of concomitant diseases, and it is sometimes possible to confirm their connection with AF only retrospectively. In the recommendations of the European Society of Cardiology, it is also proposed to assess the severity of the AF load, which reflects its type, the total duration of the rhythm disturbance during ECG monitoring, for example, for 24 hours, the number of arrhythmia episodes, their maximum duration, etc. [11]. It should be noted that the recommendations lack clear criteria for interpreting the data obtained. In some studies, an association was found between the parameters of the FTP load and adverse clinical outcomes. A. Ganesan et al. in a meta-analysis of 12 studies in approximately 100,000 patients with non-paroxysmal non-valvular AF revealed an increased risk of thromboembolism and death (relative risk 1.384; p <0.001, and 1.217, p <0.001, respectively) compared with that in patients with paroxysmal AF [39]. The load of AF may have a certain effect on the effectiveness of rhythm control in patients with VP [40]. Nevertheless, according to experts, the available data on the relationship of the load of AF with clinical outcomes are insufficient to give them decisive importance when choosing a treatment strategy.

The heart rate (HR) control strategy in patients with non-valvular AF was as effective in preventing adverse outcomes as the sinus rhythm control strategy and often proves to be sufficient to reduce symptoms, especially in elderly patients [11]. Research results RACE II showed that more "rigid" heart rate control, which assumed a decrease of <80 per minute at rest and <110 per minute with moderate physical activity, does not lead to a decrease in the overall risk of clinical outcomes [41]. In this regard, the target value of the resting heart rate when choosing a heart rate control strategy may be <110 per minute, although the goal of therapy may be revised if symptoms persist or left ventricular function worsens.

Table 3.
Scale for assessing the severity of AF symptoms (EHRA) [11]

EHRA Class	Symptoms	Description
1	absent	AF is not accompanied by any symptoms
2a	mild	AF symptoms do not affect normal daily activity
2b	moderate	Symptoms of AF do not affect normal daily activity, but cause anxiety in the patient
3	pronounced	Symptoms of AF disrupt normal daily activity
4	disabling	Normal daily activity is impossible

To control heart rate in patients with non-valvular AF, P-blockers are usually used, as well as digoxin, diltiazem and verapamil or a combination of these drugs, while antiarrhythmic agents such as amiodarone or sotalol are better prescribed to control sinus rhythm. Treatment usually begins with beta-blockers, although in the presence of chronic obstructive pulmonary disease or bronchial asthma, the advantages of non-dihydropyridine calcium antagonists are obvious. At the same time, the latter should not be prescribed to patients with a left ventricular ejection fraction < 40%. If combination therapy with drugs that reduce the heart rate is ineffective, atrioventricular node ablation can be performed in combination with implantation of an artificial pacemaker.

As mentioned above, a rhythm control strategy involving the restoration and retention of the blue rhythm does not improve clinical outcomes in patients with AF, therefore, its primary goal is to reduce symptoms and improve the quality of life of patients. The restoration of the sinus rhythm does not mean that there is no need to take medications that reduce heart rate, anticoagulation and correction of cardiovascular risk factors.

Control of the sinus rhythm can prevent the progression of AF, i.e. its transition to a more stable form, for example, the transformation of paroxysmal AF into persistent or permanent or persistent AF into a permanent form. In an American cohort study in 955 patients with newly diagnosed non-valvular AF, the rate of arrhythmia progression for 12 months against the background of sinus rhythm control was significantly lower than against the background of heart rate control (5.8% and 27.6%, respectively; p <0.001). The progression of AF was also associated with old age, the presence of persistent AF and stroke/TIA in anamnesis. The arguments in favor of choosing a sinus rhythm control strategy may be the following:

- younger age of the patient;
- the first episode of AF or a short history;
- cardiomyopathy caused by tachycardia;
- absence of pronounced dilatation of the left atrium;
- absence of heart disease or concomitant diseases;
- difficulties in heart rate control;
- transient cause of AF, for example, acute illness;
- the patient's desire.

Methods of monitoring the sinus rhythm after its restoration by electrical or medical cardioversion in patients with paroxysmal or persistent AF include the use of antiarrhythmic drugs and catheter ablation. The latter is considered an effective and safe method, although in the CABANA study catheter ablation did not significantly reduce the risk of a combined endpoint, which included death, disabling stroke, serious bleeding and cardiac arrest, compared with drug therapy, but was accompanied by a significant improvement in the quality of life. Catheter ablation is usually performed when at least one class I or III antiarrhythmic drug is ineffective or poorly tolerated, although it can also be considered as a first-line method in patients with paroxysmal AF or patients with persistent AF who lack the main factors of arrhythmia recurrence after intervention (such as age, left atrium dilation, duration of AF, impaired renal function, etc.) [11]. In addition, catheter ablation is recommended to restore the function of the left ventricle in patients with cardiomyopathy induced by tachycardia, and to increase survival and reduce the frequency of hospitalizations in patients with heart failure and reduced left ventricular function. At least one third of patients who have undergone catheter ablation have relapses of AF at various times after the intervention. Currently, various scales have been proposed to assess the risk of recurrence of arrhythmia after catheter ablation, including ALARMEc (type of arrhythmia, left atrium size, renal failure, metabolic syndrome and cardiomyopathy), BASE-AF2 (body mass index > 28 kg/m2, left atrium dilation >40 mm, early recurrence of AF after ablation, duration of AF >6 years and non-paroxysmal form of arrhythmia), APPLE (age ≥65 years, persistent AF, decreased glomerular filtration rate <60 ml/min/1.73 m", left atrium diameter 243 mm and left ventricular ejection fraction <50%), CAAP-AF (coronary heart disease, left atrium diameter, age, persistent or prolonged AF, ineffectiveness of antiarrhythmic drugs and female gender), ATLAS (age over 60 years, non-paroxysmal AF, left atrial dilatation, female sex and smoking), but none of them had significant advantages over the others [42]. Modification of various risk factors, including smoking, alcohol consumption, arterial hypertension, obesity, etc., may contribute to improving the results of catheter ablation in patients with non-valvular AF.

The recommendations of the European Society of Cardiology highlight

the following principles of antiarrhythmic therapy in patients with non-valvular AF:

• The purpose of antiarrhythmic therapy is to reduce the symptoms associated with AF.

• Antiarrhythmic therapy is characterized by moderate effectiveness in the prevention of AF relapses.

• Antiarrhythmic therapy reduces the number of recurrent arrhythmias rather than completely prevents them.

• If one antiarrhythmic drug is ineffective, then an acceptable clinical effect can be achieved with the help of another drug.

• Antiarrhythmic therapy is often accompanied by an arrhythmogenic effect and extracardial side effects.

• The choice of an antiarrhythmic drug is primarily dictated by safety, not effectiveness.

Amiodarone remains the most effective antiarrhythmic drug in patients with AF, including those with heart failure and low left ventricular ejection fraction. The recommendations indicate that, taking into account the extracardial toxicity of amiodarone, it is desirable to use other antiarrhythmic drugs, if possible, for longterm control of sinus rhythm in patients with AF [11]. However, as in previous versions of the recommendations, other antiarrhythmic agents, such as propafenone and sotalol, are recommended to be used only in the absence of signs of significant structural damage to the heart. Sotalol can be used in patients with coronary heart disease under careful monitoring of the QT interval, serum potassium levels, creatinine clearance and other risk factors for arrhythmogenic effects. The latter include old age, female gender, impaired kidney and/or liver function, coronary heart disease, hypokalemia, cases of sudden death in relatives. Antiarrhythmic therapy should not be prescribed to patients with a permanent form of AF who receive rhythm reducing drugs, as well as to patients with severe conduction disorders if they do not have a rhythm driver installed.

Table 4.
Scale 2 MASE, designed to assess the risk of cardiovascular events in patients with non-valvular AF [11]

Acronym	Risk factors	Score
2M	Myocardial infarction/coronary artery revascularization in anamnesis	1
	Metabolic syndrome	2
A	Age >75 years	2
C	Congestive heart failure (ejection fraction<40%)	1
E	Thromboembolism	1

Treatment of cardiovascular Vascular and other related diseases

Cardiovascular diseases and risk factors, on the one hand, contribute to the development and recurrence of atrial fibrillation, and, on the other hand, they themselves can cause adverse outcomes, including stroke, heart attack and death. A. Gómez-Outes et al. conducted a meta-analysis of 4 clinical trials in which direct, oral anticoagulants compared with warfarin in general in 71683 patients with non-valvular atrial fibrillation [33]. During the follow-up period, 9% of them died, and the adjusted mortality rate was 4.72% per year. The share of cardiac causes in the structure of total mortality was 46%. The main risk factors for death from any cause were heart failure, persistent/persistent atrial fibrillation, diabetes mellitus, male gender, old age and reduced creatinine clearance. Similar data were obtained in one of the studies included in the meta-analysis, ROCKET AF, in which rivaroxaban was studied [34]. These data indicate the importance of modifying cardiovascular risk factors to improve the prognosis in patients with non-valvular atrial fibrillation. Scales are proposed that allow stratifying patients with non-valvular atrial fibrillation by the risk of major cardiovascular events, including fatal and non-fatal myocardial infarction, coronary artery revascularization and death from cardiovascular causes. for example, based on a prospective cohort study in 1019 patients with atrial fibrillation,

a 2MASE index was developed, which is calculated taking into account age and the presence of metabolic syndrome, congestive heart failure and myocardial infarction/revascularization of the core-carotid arteries and thromboembolism in the anamnesis (Table. 4). The value of the 2MASE index varies from 0 to 7, and its value ⩾3 allowed predicting the development of unfavorable outcomes with high sensitivity and specificity in patients with non-valvular atrial fibrillation (risk ratio 3.92, 95% CI 2.41-6.40, p <0.001).

Treatment of concomitant diseases and modification of cardiovascular risk factors are considered as one of the key components of the modern management strategy for patients with atrial fibrillation [11]. In a randomized RACE trial 3 more "aggressive" treatment of concomitant cardiovascular diseases led to a significant increase in the frequency of sinus rhythm retention compared with conventional therapy (75% and 63%, respectively, p = 0.042) [11]. Some studies have studied the effect of modification of individual risk factors on the course of atrial fibrillation. In a randomized study in 184 patients with atrial fibrillation who underwent catheter ablation, more "aggressive" antihypertensive therapy did not cause a decrease in the risk of arrhythmia recurrence after the intervention, but was accompanied by an increase in the frequency of episodes of arterial hypotension. At the same time, optimal glycemic control for 12 months prior to catheter ablation was associated with a reduced risk of arrhythmia recurrence. In another randomized clinical trial, abstinence caused a decrease in the frequency of episodes of atrial fibrillation in patients who regularly consumed alcohol [35]. On the other hand, caffeine probably does not significantly affect the risk of atrial fibrillation, although coffee consumption may be accompanied by palpitations unrelated to arrhythmia [36]. Regular moderate physical activity can have a beneficial effect on the course of atrial fibrillation, while intense physical activity, on the contrary, is associated with an increased risk of its development [37]. Weight loss in obese patients and atrial fibrillation caused a decrease in symptoms and frequency of arrhythmia attacks [38]. In general, the results of modification of individual risk factors in clinical trials in patients with atrial fibrillation oca- became ambiguous. This is probably due to the fact that the development of atrial fibrillation is a consequence of the interaction of various cardiovascular and other risk factors and diseases.

Atrial fibrillation is often observed in patients with acute and chronic coronary syndrome, and approximately 10-15% of patients with atrial fibrillation have percutaneous interventions on the coronary arteries (Percutaneous coronary interventions) [39]. Medications that are used to treat coronary heart disease, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, statins, may interfere with the development of atrial fibrillation or have a beneficial effect on its course, while beta-blockers or non-dihydropyridine antagonists Calcium compounds are widely used in patients with atrial fibrillation to control heart rate. However, the possibility and feasibility of combination therapy with oral anticoagulants and antiplatelet drugs in patients with coronary heart disease and atrial fibrillation deserves a separate discussion, considering the significant increase in the risk of bleeding on the background of such treatment. The recommendations of the European Society of Cardiology indicate that when choosing antithrombotic drugs and the duration of antithrombotic therapy in patients with non-valvular atrial fibrillation who have undergone acute coronary syndrome (Acute coronary syndromes) and/or Percutaneous coronary interventions, it is necessary to carefully weigh the risk of ischemic stroke/systemic embolism, coronary ischemic complications and blood-currents associated with taking anti-thrombotic drugs [11]. In general, therapy with two antithrombotic drugs, including direct, oral anticoagulants and a P2U12 receptor inhibitor (preferably clopidogrel) was accompanied by a sig-

nificant reduction in the risk of bleeding compared with triple antithrombotic therapy. For example, the PIONEER AF-PCI study included 2124 patients with non-valvular atrial fibrillation who underwent coronary artery stenting (in half of cases for acute coronary syndromes), rivaroxaban therapy at a reduced dose of 15 mg once a day (in patients with impaired renal function, it was reduced to 10 mg/day) in combination with a P2Y12 receptor inhibitor (mainly clopidogrel) for 12 months according to its effectiveness in preventing unfavorable outcomes, including myocardial infarction, stroke, stent thrombosis and death from cardiovascular causes, It was not inferior to vitamin K antagonist therapy in combination with two antiplatelet drugs, but was accompanied by a significant reduction in the risk of clinically significant bleeding by 41% [40]. Nevertheless, experts of the European Society of Cardiology consider desirable a short course of triple antithrombotic therapy with oral anticoagulant, aspirin and clopidogrel (for example, for 51 weeks) in some patients with atrial Fibrillation who have undergone Acute coronary syndromes or Percutaneous coronary interventions, who have a high risk of ischemic complications [11]. The duration of triple therapy can be increased to < 1 month if the threat of stent thrombosis outweighs the risk of bleeding. Risk factors for thrombotic complications include diabetes mellitus, a history of acute coronary syndromes, damage to several coronary arteries, atherosclerosis of peripheral arteries, the development of coronary disease under the age of 45 or its rapid progression, chronic kidney disease of stage 3 [11].

Dual therapy with direct, oral anticoagulants and clopidogrel after uncomplicated coronary artery stenting in patients with acute coronary syndromes is usually continued for 1 year, and in patients with stable chronic coronary artery disease who have undergone percutaneous coronary interventions - for 6 months. If no ischemic complications were registered during the specified period, then in the future it is advisable to carry out monotherapy with an oral anticoagulant. Monotherapy is also recommended for patients with non-valvular atrial fibrillation and stable ischemic heart disease.

The arguments in favor of monotherapy with oral anticoagulants are, on the one hand, their supposed effectiveness in the prevention of cardiovascular events, and, on the other hand, a lower risk of bleeding, which inevitably increases with the addition of additional anti-thrombotic drugs. R. Kir et al. a meta-analysis of 28 randomized clinical trials was conducted, in which direct, oral anticoagulants were compared with vitamin K antagonists, antiplatelet drugs and/or placebo for various indications in a total of 196761 patients [43]. Treatment with rivaroxaban was associated with a reduction in the relative risk of myocardial infarction by 21% compared with placebo and by 31% compared with dabigatran. Similar data were previously obtained by other authors. For example, Y. Loke et al. a meta-analysis of 27 randomized controlled clinical trials revealed a reduction in the risk of coronary complications with the use of rivaroxaban compared with that with the treatment of dabigatran [44]. When interpreting the data obtained, it should be taken into account that direct, oral anticoagulants were not obtained in direct comparative studies, and indications for their use included not only non-valvular atrial fibrillation, but also other conditions.

Limitations

There were no significant limitations during research

Conclusion

The modern strategy for the treatment of patients with non-valvular AF, which is discussed in detail in the recommendations of the European Society of Cardiology 2020, involves anticoagulation for the prevention of stroke and systemic embolism, improving the control of AF symptoms by reducing heart rate or restoring and maintaining sinus rhythm and optimal treatment of cardiovascular and other concomitant diseases that are in the structure of mortality of patients with AF they occupy an even

more important place than ischemic stroke. Data are accumulating demonstrating additional advantages of POAC (Primary Options for Acute Care) over indirect anticoagulants. For example, meta-analyses of randomized clinical trials have shown a reduction in the risk of myocardial infarction/acute coronary syndrome when treated with rivaroxaban compared with controls. In retrospective studies, treatment with rivaroxaban improved renal outcomes in patients with non-valvular AF. Patients with AF should undergo a structured examination, including an assessment of the risk of stroke, the severity of symptoms, the severity of the load of AF (type of arrhythmia, number and duration of episodes, etc.) and predisposing condition. It is important to use various scales, including CHA2DS2-VASc (risk of stroke), HAS-BLED (risk of bleeding), EHRA scale (severity of AF symptoms) and 2MACE (risk of cardiovascular outcomes), which help to choose the optimal treatment. For a more accurate assessment of the risk of stroke and bleeding in patients with AF, new scales have been proposed based not only on clinical indicators, but also on laboratory markers, but their potential advantages over existing generally accepted indices need to be confirmed.

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