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EPIDEMIOLOGICAL ASPECTS OF IN-STENT THROMBOSIS AND RESTENOSIS OF CORONARY ARTERIES IN PATIENTS WITH PREVIOUS REVASCULARIZATION AFTER CORONAVIRUS INFECTION

Gulnara B. Batenova¹, <https://orcid.org/0000-0003-3198-1860>

Lyudmila M. Pivina¹, <https://orcid.org/0000-0002-8035-4866>

Evgeny I. Dedov³, <https://orcid.org/0000-0002-9118-3708>

Diana G. Ygiyeva¹, <https://orcid.org/0000-0001-8391-8842>

Galiya A. Alibayeva², <https://orcid.org/0000-0002-1503-4663>

Zhansaya T. Aukenova¹, <https://orcid.org/0009-0001-3591-8175>

Andrey Yu. Orekhov¹, <https://orcid.org/0000-0001-7201-1399>

Assylzhan M. Messova¹, <https://orcid.org/0000-0001-5373-0523>

Maksim R. Pivin¹, <https://orcid.org/0000-0001-7206-8029>

Zhanar M. Urazalina¹, <https://orcid.org/0000-0002-4494-6565>

¹ NCJSC "Semey Medical University", Semey, Republic of Kazakhstan;

² Emergency Hospital, Semey, Republic of Kazakhstan;

³ Russian National Research Medical University named after. N.I. Pirogov, Moscow, Russian Federation.

Abstract

Introduction. Understanding the risk factors for thrombosis and in-stent restenosis is of particular importance for the people at risk for adverse outcomes, especially in older patients with previously revascularized myocardium and comorbid conditions including coronavirus infection.

The purpose of the study was to assess the risk factors for restenosis and in-stent thrombosis of the coronary artery in patients with previously revascularized myocardium who had suffered coronavirus infection.

Materials and methods. We conducted a retrospective epidemiological study of the prevalence of in-stent thrombosis and restenosis, calculating the odds ratio for each risk factor in a continuous sample of individuals who underwent coronary angiography followed by myocardial revascularization with stenting for the period from May 2020 to May 2023. During the entire study period, 7,738 people underwent coronary angiography, of which 4,619 patients received coronary artery stenting according to indications. Statistical analysis was performed using SPSS version 20.0 software (IBM Ireland Product Distribution Limited, Ireland). To assess the contribution of each risk factor to the development of late postoperative complications, odds ratios were calculated.

Results. The presence of diabetes mellitus more than doubles the chances of developing restenosis and coronary artery stent thrombosis; for arterial hypertension, this rate was 1.5. Male gender is associated with a 2.9-fold increased chance of in-stent restenosis. For D-dimer, troponin, ALT, AST, creatinine, C-reactive protein and CPK, the odds of coronary artery restenosis increased more than twice ($p < 0.001$). Age and left ventricular ejection fraction did not play a role in the development of the pathology under study. The maximum increase in the odds of coronary artery restenosis was observed in patients who had coronavirus infection – 3.176 ($p < 0.001$).

Conclusion. Maximum efforts should be made to prevent restenosis, taking into account modifiable risk factors and the possibility of an individualized approach to treatment.

Keywords: acute coronary syndrome, in-stent thrombosis, in-stent restenosis, coronavirus infection, odds ratio.

Резюме

ЭПИДЕМИОЛОГИЧЕСКИЕ АСПЕКТЫ РЕСТЕНОЗА КОРОНАРНЫХ АРТЕРИЙ У ПАЦИЕНТОВ С ПРЕДШЕСТВОВАВШЕЙ РЕВАСКУЛЯРИЗАЦИЕЙ, ПЕРЕНЕСШИХ КОРОНАВИРУСНУЮ ИНФЕКЦИЮ

Гульнара Б. Батенова¹, <https://orcid.org/0000-0003-3198-1860>

Людмила М. Пивина¹, <https://orcid.org/0000-0002-8035-4866>

Евгений И. Дедов³, <https://orcid.org/0000-0002-9118-3708>

Диана Г. Ыгиева¹, <https://orcid.org/0000-0001-8391-8842>

Галия А. Алибаева², <https://orcid.org/0000-0002-1503-4663>

Жансая Т. Әукенова¹, <https://orcid.org/0009-0001-3591-8175>

Андрей Ю. Орехов¹, <https://orcid.org/0000-0001-7201-1399>

Асылжан М. Месова¹, <https://orcid.org/0000-0001-5373-0523>

Максим Р. Пивин¹, <https://orcid.org/0000-0001-7206-8029>

Жанар М. Уразалина¹, <https://orcid.org/0000-0002-4494-6565>

¹ НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;

² Больница скорой медицинской помощи, г. Семей, Республика Казахстан;

³ Российский национальный исследовательский медицинский университет им. Н.И. Пирогова, г. Москва, Российская Федерация.

Введение. Понимание факторов риска для тромбоза и рестеноза стента имеет особую важность для в отношении лиц, подверженных риску неблагоприятных исходов, особенно у пациентов пожилого возраста с предварительно реваскуляризованным миокардом при наличии коморбидных заболеваний. К таким неблагоприятным ассоциированным заболеваниям относится коронавирусная инфекция.

Целью исследования явилась оценка факторов риска рестеноза и тромбоза стента коронарных артерий у лиц с ранее реваскуляризованным миокардом, перенесшим коронавирусную инфекцию.

Материалы и методы. Мы провели ретроспективное эпидемиологическое исследование распространенности тромбоза и рестеноза стента с расчетом отношения шансов для каждого из факторов риска на сплошной выборке из лиц, которым была проведена коронароангиография с последующей реваскуляризацией миокарда со стентированием за период с мая 2020 года по май 2023 года. За весь период исследования коронароангиографию прошли 7738 человек, из них 4619 пациентов получили стентирование коронарных артерий по показаниям. Статистические расчеты проводились с использованием программного обеспечения SPSS версии 20.0 (IBM Ireland Product Distribution Limited, Ireland). Для оценки вклада каждого из факторов риска в развитие поздних послеоперационных осложнений были рассчитаны отношения шансов.

Результаты. Наличие сахарного диабета более чем в два раза повышает шансы развития рестеноза и тромбоза стента коронарных артерий; для артериальной гипертензии этот показатель составил 1,5. Мужской пол связан с повышением шанса рестеноза стента в 2,9 раз. В отношении D-димера, тропонина, АЛТ, АСТ, креатинина, С-реактивного белка и КФК установлено повышение шансов рестеноза коронарных артерий более чем в два раза ($p < 0,001$). Возраст и фракция выброса левого желудочка не сыграли роли в развитии изучаемой патологии. Максимальное повышение шансов рестеноза коронарных артерий наблюдалось у больных, перенесших коронавирусную инфекцию – 3,176 ($p < 0,001$).

Заключение. Необходимо прилагать максимальные усилия по предотвращению рестеноза, принимая во внимание модифицируемые факторы риска и возможности индивидуального подхода к лечению

Ключевые слова: острый коронарный синдром, тромбоз внутри стента, рестеноз стента, коронавирусная инфекция, отношение шансов.

Түйіндеме

КОРОНАВИРУСТЫҚ ИНФЕКЦИЯНЫ ӨТКЕРГЕН, РЕВАСКУЛЯРИЗАЦИЯСЫ БАР НАУҚАСТАРДА КОРОНАРЛЫҚ АРТЕРИЯ РЕСТЕНОЗЫНЫҢ ЭПИДЕМИОЛОГИЯЛЫҚ АСПЕКТІЛЕРІ

Гульнара Б. Батенова¹, <https://orcid.org/0000-0003-3198-1860>

Людмила М. Пивина¹, <https://orcid.org/0000-0002-8035-4866>

Евгений И. Дедов³, <https://orcid.org/0000-0002-9118-3708>

Диана Г. Ыгиева¹, <https://orcid.org/0000-0001-8391-8842>

Галия А. Алибаева², <https://orcid.org/0000-0002-1503-4663>

Жансая Т. Әукенова¹, <https://orcid.org/0009-0001-3591-8175>

Андрей Ю. Орехов¹, <https://orcid.org/0000-0001-7201-1399>

Асылжан М. Месова¹, <https://orcid.org/0000-0001-5373-0523>

Максим Р. Пивин¹, <https://orcid.org/0000-0001-7206-8029>

Жанар М. Уразалина¹, <https://orcid.org/0000-0002-4494-6565>

¹ «Семей медицина университеті» КеАҚ, Семей қ., Қазақстан Республикасы;

² Жедел медициналық жәрдем ауруханасы, Семей қ., Қазақстан Республикасы;

³ Н.И. Пирогов атындағы Ресей ұлттық ғылыми-зерттеу медицина университеті, Мәскеу, Ресей Федерациясы.

Кіріспе. Тромбоз және стент рестенозының қауіп факторлары жағымсыз нәтижелерге ұшырау қауіпі бар адамдарға, әсіресе коморбидті аурулары бар, алдын ала реваскуляризацияланған миокардпен ауыратын егде жастағы емделушілерге қатысты ерекше маңызды. Мұндай жайсыз ауруларға коронавирустық инфекция жатады.

Зерттеудің мақсаты: коронавирустық инфекцияны өткерген, бұрын ревазуляризацияланған миокарды болған адамдарда коронарлық артерия стентінің рестенозы мен тромбозының қауіп факторларын бағалау болды.

Материалдар мен әдістер. 2020 жылдың мамырынан 2023 жылдың мамырына дейінгі кезеңде жаппай таңдау арқылы коронарангиография жасалған, яғни оның ішінде миокард ревазуляризациясы мен стенттеуді өткерген адамдардың қауіп факторларының әрқайсысы үшін ықтималдық коэффициентін есептей отырып, тромбоз бен стент рестенозының таралуына ретроспективті эпидемиологиялық зерттеу жүргіздік. Зерттеудің барлық кезеңінде 7 738 адам коронарангиографиядан өтті, оның ішінде 4619 пациент көрсеткіштер бойынша коронарлық артерияларды стенттеуден өтті. Статистикалық есептеулер SPSS 20.0 бағдарламалық жасақтамасының көмегімен жүргізілді (IBM Ireland Product Distribution Limited, Ireland). Тәуекел факторларының әрқайсысының операциядан кейінгі асқынулардың дамуына қосқан үлесін бағалау үшін коэффициенттер есептелді.

Нәтижелер. Қант диабетінің болуы рестеноздың және коронарлық артерия стентінің тромбозының даму мүмкіндігін екі еседен астам арттырады; ал артериялық гипертензия үшін бұл көрсеткіш 1,5 құрады. Еркек жынысы стент рестенозының 2,9 есе жоғарылауымен байланысты. D-димерге, тропонинге, АЛТ, АСТ, креатининге, C-реактивті ақуызға және КФК-ға қатысты коронарлық артериялардың рестенозы ықтималдығының екі еседен астам жоғарылауы анықталды ($p < 0,001$). Зерттелетін патологияның дамуында сол жақ қарыншаның шығару фракциясы мен науқас жасы маңызды рөл атқармады. Коронарлық артериялардың рестенозы ықтималдығының максималды жоғарылауы коронавирустық инфекциямен ауыратын науқастарда байқалды – 3,176 ($p < 0,001$).

Қорытынды. Рестеноздың алдын алу үшін түрлендіруші қауіп факторларын және жеке емдеу мүмкіндіктерін ескере отырып, барынша күш салу қажет.

Түйін сөздер: Жедел коронарлық синдром, стент ішіндегі тромбоз, стент рестенозы, коронавирустық инфекция, шанстар қатынасы.

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Introduction

In recent decades due to progress in the field of interventional cardiology, there has been a significant growth in the number of cardiac surgeries for coronary artery stenosis and thrombosis, which has led to an increase in the life expectancy of patients with acute coronary syndrome and an improvement in their quality of life. Due to the development of new approaches to stenting and the emergence of new generations of drug-eluting stents, the number of complications of this intervention has significantly decreased; however, for numerous reasons, the risk of developing restenosis or thrombosis of the installed stent is preserved.

Restenosis is the process of repeated narrowing of the lumen of a previously implanted stent by more than 50% [10]. Stent endothelialization is usually completed within six months, but drug coating of stents, which protects against thrombus formation, can delay this process by up to two years [2]. The development of restenosis may be directly related to the presence of inflammation in a previously stented coronary vessel [4, 6].

According to international recommendations, after stent implantation, the patient is required to take antiplatelet therapy, which reduces the activity of the blood coagulation

system, since it is platelets that can make a decisive contribution to the development of vessel restenosis [2, 3].

Understanding the risk factors for thrombosis and in-stent restenosis is of particular importance in those at risk for adverse outcomes, especially in older patients with previously revascularized myocardium and comorbid conditions [5]. Such unfavorable associated diseases include coronavirus infection, which is accompanied by activation of the thrombus formation process and the development of hypercoagulation, thus acting as a trigger for the development of acute coronary syndrome and stent thrombosis even in the long-term period after COVID-19 [2,3].

The aim of our study is to assess risk factors for restenosis and coronary artery stent thrombosis in individuals with previously revascularized myocardium after coronavirus infection.

Materials and methods

Characteristics of the study group

In order to study the main risk factors for the development of coronary artery stent thrombosis and restenosis, we conducted a retrospective epidemiological study of the prevalence of stent thrombosis and restenosis with calculation of odds ratios for each of the risk factors in

a continuous sample of individuals who underwent coronary angiography followed by myocardial revascularization with stenting.

To determine the study group, we conducted a preliminary analysis of all cases of patients with signs of acute coronary syndrome who underwent coronary angiography for the period from May 2020 to May 2023 (the period of the officially declared coronavirus pandemic). All patients before and after percutaneous coronary intervention (PCI) received dual or triple antiplatelet therapy depending on the indications. The sample was complete; all patients meeting the inclusion criteria were included in the study.

Exclusion criteria: persons with autoimmune systemic diseases, cancer patients, patients who refused the study. All participants signed an informed consent form.

Methods of examination

All patients underwent coronary angiography, a specialized X-ray examination that provides detailed information about the patency of the coronary arteries and assesses blood flow. Based on the results of coronary angiography, PCI (balloon angioplasty or stenting) was performed. If a thrombus was present, the thrombus was aspirated.

Venous blood samples were collected from all patients within 10 minutes of admission. Laboratory tests included complete blood count (hemoglobin, neutrophils, platelets,

lymphocytes), high-sensitivity troponin I, D-dimer, creatine kinase (CK), creatine kinase-MB (CK-MB), serum creatinine and glucose, ESR, C-reactive protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and fibrinogen.

Statistical analysis methods

Descriptive statistics were performed. Statistical analysis was performed using SPSS version 20.0 software (IBM Ireland Product Distribution Limited, Ireland). To assess the contribution of each risk factor to the development of late postoperative complications, odds ratios were calculated, which are a characteristic for quantitatively describing the closeness of the relationship between signs in a certain statistical population.

Results and discussion

The results of the age and sex characteristics of the patients who underwent coronary angiography for the indicated period of time are presented in Table 1. Over the entire study period, 7,738 people underwent coronary angiography, of which 1,122 patients in 2020 (8 months), 2,556 people in 2021, 2786 people in 2022, 1274 patients in 2023 (4 months). Males were in the majority among the studied patients, on average their proportion was 66.04%. More than 60 percent of all patients were in the 50-70 age group, while only approximately 10 percent of patients were under 50 years of age.

Table 1.

Age and sex characteristics of persons who underwent coronary angiography in 2020-2023.

Year	N of coronary angiographies	Sex				Age					
		Female		Male		<50 years		50-70 years		>70 years	
		N	%	N	%	N	%	N	%	N	%
2020	1122	338	30.12	784	69.88	130	11.59	740	65.95	252	22.46
2021	2556	924	36.15	1632	63.85	256	10.02	1654	64.71	666	26.06
2022	2786	912	32.74	1874	67.26	344	12.35	1560	55.99	700	25.13
2023	1274	454	35.64	820	64.36	118	9.26	886	69.54	270	21.19
Total	7738	2628	33.96	5110	66.04	848	10.96	4840	62.55	1888	24.40

About 60% (4619) of patients received stenting of the coronary arteries according to indications (clinical characteristics, presence of complications, vessel stenosis of more than 70 percent, anatomical features of the vessels, presence of thrombosis or atherosclerotic plaques, study result on the GRACE scale). Of these, about a quarter received stenting of two or more coronary arteries. Acute coronary syndrome with ST elevation, including myocardial infarction, was diagnosed in an average of 12.23% of patients; acute coronary syndrome without ST elevation – in 38.5%; the most common diagnosis was angina pectoris -

about half of all patients. However, when analyzing the indicators over time, it is of interest that in 2020, during the first, most intense peak of the coronavirus infection pandemic, the rate of ACS with ST elevation reached 15.5%, while by 2023 it had halved (table 2). This fact may be due to the reluctance of patients in the midst of a pandemic to go to hospitals for help even if there are clear indications, a lack of resources aimed at combating the pandemic and the impossibility of conducting cardiac interventions for patients who were being treated for coronavirus infection at that time.

Table 2.

Number of stentings and diagnoses as the reason for stenting for 2020-2023.

Year	Number of stenting				Acute coronary syndrome with ST elevation		Acute coronary syndrome without ST elevation		Unstable angina	
	1		2>		N	%	N	%	N	%
	N	%	N	%						
2020	504	83.72	98	16.28	174	15.51	316	28.16	632	56.33
2021	1214	83.90	233	16.10	366	14.32	802	31.38	1388	54.30
2022	1308	76.49	402	23.51	306	10.98	1286	46.16	1192	42.79
2023	672	78.14	188	21.86	100	7.85	572	44.90	602	47.25
Total	3698	80.06	921	19.94	946	12.23	2976	38.46	3814	49.29

Comparative characteristics of the number of coronary angiographic studies and the number of stentings over time from 2020 to 2023 is presented in Figure 1.

The number of stentings was more than half the number of coronary angiographic studies.

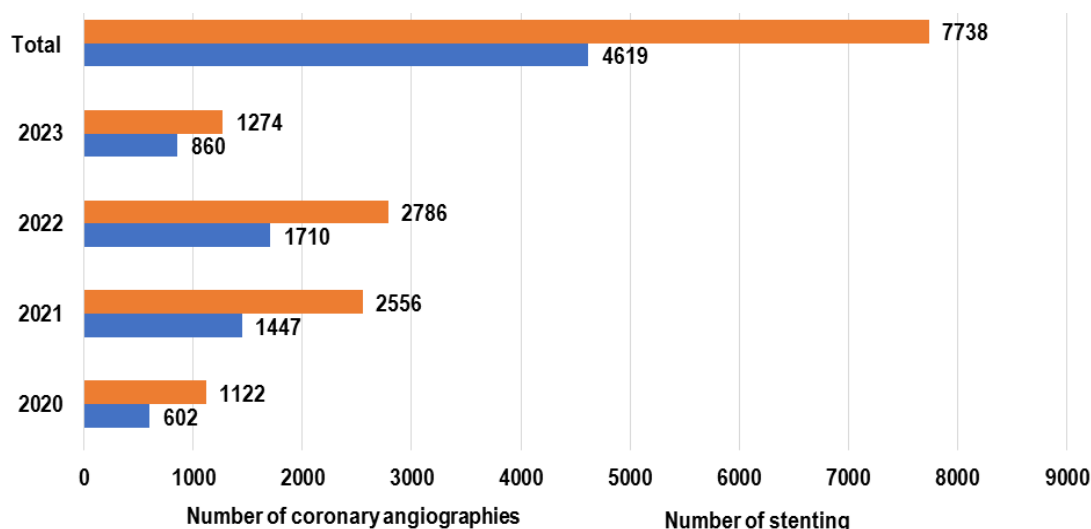


Figure 1. Comparative characteristics of the number of coronary angiographic studies and the number of stentings for the period from 2020 to 2023.

To achieve the purpose of the study, we selected from the specified database all patients with repeated revascularization for in-stent thrombosis and restenosis. There were 490 such patients, of which 47 patients had in-stent thrombosis, the remaining patients were diagnosed with stent restenosis according to coronary angiography.

It was of significant interest to us to clear the factors that determine the risk of developing in-stent restenosis and thrombosis of the coronary artery in this category of patients. It was found that a fifth of patients with such restenosis and thrombosis had comorbidity in the form of diabetes mellitus, the vast majority of patients had arterial hypertension, the majority of patients were in the age range from 50 to 70 years (more than 60%); only 8% of patients were in middle age up to 50 years; a quarter of the patients were female (Table 3).

Analyzing clinical and laboratory parameters in patients included in the epidemiological study, it can be noted that about half of the patients had a decrease in ejection fraction below 50%, according to echocardiography. About a third of patients had elevated levels of D-dimer, CPK and ALT, and more than a quarter had elevated levels of troponin and AST. In 13% of patients, a decrease in glomerular filtration rate was observed with an increase in creatinine levels above normal levels, and the level of C-reactive protein was elevated in more than 70%.

A history of coronavirus infection was found in 186 patients (38%) (Table 3). The vast majority of patients, taking into account their medical history, PCR diagnostic indicators and levels of IgG and IgM, suffered from COVID-19 before admission to the cardiology department for acute coronary syndrome. Only 33 patients had coronavirus infection at the time of treatment for ACS and were transferred to infectious diseases departments.

Table 4 presents the odds ratios for risk factors for restenosis and coronary artery stent thrombosis in individuals included in the epidemiological study. Analysis of data obtained using univariate regression analysis indicates that the presence of diabetes mellitus more than doubles the chances of developing restenosis and coronary artery stent thrombosis; for arterial hypertension this rate was 1.5. Male gender is associated with a 2.9-fold

increased chance of in-stent restenosis. With regard to such laboratory parameters as D-dimer, troponin, ALT, AST, creatinine, C-reactive protein and CPK, one can note an increase in the odds of coronary artery restenosis by more than two times ($p < 0.001$). Age and left ventricular ejection fraction did not play a role in the development of the pathology under study. The maximum increase in the odds of coronary artery restenosis was observed in patients who had coronavirus infection – 3.176 ($p < 0.001$).

Table 3.

Characteristics of risk factors for in-stent restenosis and thrombosis of the coronary artery.

Characteristics	N	%
Diabetes mellitus	Yes	100 20.4
	No	390 79.6
Hypertension	Yes	480 98
	No	10 2
COVID-19	Yes	186 38
	No	304 62
Age	< 50	40 8.2
	51-70	314 64.1
	71 >	136 27.8
Sex	male	369 75.3
	female	121 24.7
Left ventricular ejection fraction	< 50	224 45.7
	50 >	266 54.3
D-dimer	< 550	325 66.3
	550 >	165 33.7
Troponin	< 0,3	364 74.3
	0,3 >	126 25.7
ALT	< 32	331 67.6
	32 >	159 32.4
AST	< 34	359 73.3
	34 >	131 26.7
Creatinin	< 115	425 86.7
	115 >	65 13.3
C-reactive protein	< 5 mg/l	140 28.6
	5 > mg/l	350 71.4
Creatin kinase	< 294	364 74.3
	294 >	126 25.7

Table 4.

Odds ratios for risk factors for in-stent restenosis and thrombosis of the coronary artery.

Risk factors	B	OR	95% confidence interval for OR		p
			Lower limit	Upper limit	
Diabetes mellitus	0.847	2.33	0.522	1.327	<0.001
Hypertension	0.405	1.5	0.42	5.431	0.530
КВИ в анамнезе	1.156	3.176	0.287	0.631	<0.001
Age	-0.083	0.921	0.995	1.033	0.893
Male sex	1.023	2.781	0.477	1.196	<0.001
Left ventricular ejection fraction	-0.146	0.864	0.999	1.040	0.780
D-dimer	0.825	2.283	1.000	1.000	<0.001
Troponin	0.809	2.245	0.98	1.000	<0.001
ALT	0.791	2.205	0.999	1.002	<0.001
AST	0.816	2.261	0.999	1.001	<0.001
Creatinin	0.857	2.357	0.606	0.997	<0.001
C-реактивный белок	0.815	2.260	0.099	1.000	<0.001
C-reactive protein	0.952	2.590	0.999	1.000	<0.001

It is known that in-stent restenosis remains a problem for patients with coronary artery disease who have undergone myocardial revascularization using stents, and the risk factors for its occurrence are still not fully understood. It was of significant interest to us to conduct a comparative analysis of the results obtained with data from other epidemiological studies. Thus, a retrospective study conducted in southern China to evaluate the incidence and risk factors of coronary artery restenosis included 341 patients with acute coronary syndrome who had previously been implanted with at least one stent. Follow-up was carried out over 3 years. It turned out that in 18.2% of such patients, throughout the entire monitoring period, in-stent restenosis was established, which could form, on average, over a period of 32 months. The restenosis rates for the left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery were 6.7%, 20.9%, 19.4%, and 14.4%, respectively. Left ventricular ejection fraction (LVEF), number of stents, stent type, and antiplatelet therapy significantly contributed to the development of coronary artery restenosis. Multivariate logistic analysis showed that left ventricular ejection fraction and number of stents were significantly correlated with the incidence of coronary artery restenosis [7]. In our study, the number of patients with restenosis was about 10% of all cases of coronary artery stenting. The main risk factors for restenosis with high odds ratios were male gender, diabetes mellitus, increased laboratory parameters (creatinine, d-dimer, ALT, AST, troponin, CPK, C-reactive protein). However, for ejection fraction, there was no statistically significant association with restenosis (OR=0.78).

In another study of risk factors for in-stent restenosis in patients with unstable angina, the most significant ($p < 0.05$) risk factors for in-stent restenosis $\geq 50\%$ were stent diameter (OR 0.43), hypertension (OR 3.16), and neutrophil count (OR 2.22) [8]. In our study, one of the main risk factors for restenosis was the level of C-reactive protein, which, like the level of neutrophils, serves as an indicator of inflammation.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is capable of inducing a hypercoagulable state, which may complicate the management of patients with acute coronary syndrome. In the current literature,

there are insufficient studies to determine the contribution of coronavirus infection to the formation of restenosis of coronary artery stents; however, a number of studies have demonstrated the connection between these two conditions [9, 11]. In our study, COVID-19 was the most significant risk factor for the development of in-stent restenosis (OR = 3.176), indicating the role of inflammation in this process.

Conclusion

The results of our epidemiological study indicate that more than 10% of all patients admitted to the emergency department during the study period with signs of ACS and who underwent coronary angiography followed by stenting of the coronary vessels had signs of in-stent thrombosis or restenosis. The most significant risk factors for in-stent restenosis were diabetes mellitus, male gender D-dimer, troponin, ALT, AST, creatinine, C-reactive protein and CPK. The maximum increase in the chances of restenosis was observed in patients who had coronavirus infection.

Maximum efforts to prevent restenosis should be made, taking into account modifiable risk factors and individualized treatment options, as they are critical to prolonging the length and improving the quality of life of patients who have undergone previous myocardial revascularization.

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Information about the authors:

Gulnara B. Batenova – Assistant Professor, Department of Emergency Medicine named after Professor Dyussupov A.Z., Semey Medical University, Kazakhstan, +77751030602, gulnara_batenova@mail.ru

Lyudmila M. Pivina - Ph.D, Professor, Department of Emergency Medicine named after Professor Dyussupov A.Z., Semey Medical University, Kazakhstan, +77055227300, semskluda@rambler.ru

Diana G. Ygiyeva – PhD student, Semey Medical University, Kazakhstan, +77072808992, diana-dikosha@list.ru

Evgeny I. Dedov - Ph.D, Professor, Department of Hospital Therapy N2 named after N.I. academician Storozhakov G.I, MF, Pirogov Russian National Research Medical University, Moscow, Russian Federation, +79252479717, dedov-e-i@yandex.ru;

Galiya A. Alibayeva - Deputy director of Emergency Hospital, Semey, Kazakhstan, +77777463827, galiya.5@mail.ru

Zhansaya T. Aukenova, Assistant Professor, Department of Emergency Medicine named after Professor Dyussupov A.Z., Semey Medical University, Kazakhstan, +77076966772, a.zhansaya_95@mail.ru

Andrey Yu. Orekhov, PhD, Assistant Professor, Department of Therapy, Semey Medical University, Kazakhstan, +77774141476, orekhov-andrei@list.ru

Assylzhan M. Messova, Associate Professor, Department of Emergency Medicine named after Professor Dyussupov A.Z., Semey Medical University, Kazakhstan, +77772138307, assylzhan2006@mail.ru

Maksim R. Pivin, Resident, Semey Medical University, Kazakhstan, +77059058329, pivin97@mail.ru

Zhanar M. Urazalina, Associate Professor, Department of Emergency Medicine named after Professor Dyussupov A.Z., Semey Medical University, Kazakhstan, +77779372373, zhanar.urazalina@mail.ru

*Corresponding author:

Pivina Lyudmila, candidate of Medical Sciences, Professor of the Department of Emergency Medicine, NCJSC “Semey Medical University”, Semey, Kazakhstan.

Postal address: Kazakhstan, 071400, Semey, Abay st. 103.

Email: semskluda@rambler.ru

Phone: +7 (705) 522 73 00