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Risk-Based Screening of Hepatocellular Cancer in the Krasnoyarsk Region: The First Results

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Aim: to assess the prevalence of hepatocellular carcinoma in patients at moderate and high risk in the Krasnoyarsk Territory during screening activities carried out by the oncology service.
Materials and methods. To implement a risk-based approach, the study included men and women aged 40–70 years with F3–F4 fibrosis or cirrhosis of the liver, regardless of etiology, who signed an informed consent to participate in the study and those with a previously diagnosed hepatocellular carcinoma. The development program and routing algorithms were developed by the Interdisciplinary Society of Liver Tumor Specialists and approved by the Ministry of Health of the Krasnoyarsk Territory. The screening was conducted at the Krasnoyarsk Regional Oncology Dispensary. Methods used: a questionnaire to collect information about risk factors (the presence of cirrhosis, its causes, concomitant diseases, bad habits); blood sampling to determine the level of AFP (alpha-fetoprotein) + PIVKA-II (protein induced by vitamin K absence or antagonist-II) (Cobas, Roche, Switzerland); the use of the GAAD algorithm, combining gender, age, AFP and PIVKA-II levels with further risk stratification for differentiation of risk groups; instrumental diagnosis — MRI with hepatospecific contrast (gadoxetic acid). The data was processed using Statistica and StatTech statistical packages. The normal distribution was evaluated using the Shapiro — Wilk and Kolmogorov — Smirnov criteria. The results are described by averages, standard deviations, median, and quartiles.
Results. A total of 746 patients took part in the risk-oriented early diagnosis program; hepatocellular cancer was detected in 14 patients, with 50 % of cases occurring at early stages (I–II), indicating the high sensitivity of the chosen approach. The detection rate of malignant tumors during the conducted measures was 1.88 %. The pilot screening project influenced the unification of specialists into a multidisciplinary team, which in turn contributed to an increase in the number of surgical methods for treating hepatocellular carcinoma by 16.5 % and the number of liver biopsies by 33.2 %.
Conclusions. The introduction of a risk-based approach for a high-risk group using more sensitive diagnostic methods helps to increase the proportion of early stages and timely initiation of specialized treatment. The GAAD calculator is an effective method for identifying a high-risk group for hepatocellular carcinoma, where the use of MRI is justified as a sensitive method for early diagnosis of liver cancer.
Keywords: hepatocellular cancer, HCC, liver cancer, screening, early diagnosis, GAAD calculator
Conflict of interests: the authors declare no conflict of interest.

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Риск-ориентированный скрининг гепатоцеллюлярного рака в Красноярском крае: первые результаты

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Цель: оценить распространенность гепатоцеллюлярного рака у пациентов группы умеренного и высокого риска на территории Красноярского края в ходе проведения скрининговых мероприятий, проводимых онкологической службой.

Материалы и методы. Для реализации риск-ориентированного подхода в исследование включены мужчины и женщины в возрасте 40–70 лет с фиброзом F3–F4 или циррозом печени независимо от этиологии, подписавшие информированное согласие на участие в исследовании, и лица с ранее установленным диагнозом гепатоцеллюлярного рака. Программа разработки и алгоритмы маршрутизации разработаны Междисциплинарным обществом специалистов по опухолям печени и одобрены Министерством здравоохранения Красноярского края. Скрининг проводился в Красноярском краевом онкодиспансере. Используемые методы: анкетирование для сбора сведений о факторах риска (наличии цирроза, его причинах, сопутствующих заболеваниях, вредных привычках); забор крови для определения уровня АФП (альфа-фетопротеина) + PIVKA-II (белка, индуцированного отсутствием витамина K или его антагонистом-II) (Cobas, Roche, Швейцария); применение алгоритма GAAD, сочетающего в себе пол, возраст, уровень АФП и PIVKA-II, с дальнейшей стратификацией риска для дифференциации групп риска; инструментальная диагностика — МРТ с гепатоспецифичным контрастом (гадоксетовая кислота). Данные обрабатывали статистическими пакетами Statistica и StatTech. Оценивали нормальное распределение с помощью критериев Шапиро — Уилка и Колмогорова — Смирнова. Результаты описаны средними величинами, стандартными отклонениями, медианой и квартилями.
Результаты. В риск-ориентированной программе ранней диагностики приняли участие 746 пациентов, гепатоцеллюлярный рак был выявлен у 14 пациентов, причем в 50 % случаев — на ранних стадиях (I–II), что говорит о высокой чувствительности выбранного подхода. Частота выявляемости злокачественных опухолей при проведенных мероприятиях составила 1,88 %. Пилотный проект по скринингу повлиял на объединение специалистов в мультидисциплинарную команду, что в свою очередь способствовало увеличению количества хирургических методов лечения гепатоцеллюлярного рака на 16,5 %, количества биопсий печени — на 33,2 %.
Выводы. Внедрение риск-ориентированного подхода для высокой группы риска с применением более чувствительных методов диагностики способствует увеличению доли ранних стадий и своевременному началу специализированного лечения. Калькулятор GAAD является эффективным методом выявления группы высокого риска развития гепатоцеллюлярного рака, где оправдано использование МРТ как чувствительного метода ранней диагностики рака печени.
Ключевые слова: гепатоцеллюлярный рак, ГЦР, рак печени, скрининг, ранняя диагностика, калькулятор GAAD
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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor (80–85 % of all cases). According to the International Agency for Research on Cancer, in 2022, malignant neoplasms of the liver and intrahepatic bile ducts ranked sixth in prevalence and third in mortality among all malignant neoplasms. In 2022, over 850,000 new cases and more than 750,000 deaths associated with this pathology were recorded worldwide [1]. In the Russian Federation, a steady increase in the incidence of malignant liver neoplasms is observed. Thus, from 2014 to 2023, the absolute number of newly detected cases increased by 43.6 % (from 7,252 to 10,412 cases), the incidence rate increased by 43.5 % (from 4.96 to 7.12 per 100,000 population), while the proportion of cases detected at stages III–IV decreased by only 4.6 % (from 82.0 to 78.2 %), and first-year mortality after diagnosis decreased by 15.4 % (from 41.5 to 35.1 %) [2–6].

In Krasnoyarsk region, over the same period, the absolute number of newly detected cases of liver and intrahepatic bile duct malignancies increased by 130.1 % (from 150 cases in 2014 to 346 cases in 2023), the incidence rate increased by 131.6 % (from 5.25 to 12.16), the proportion of cases detected at stages III–IV increased by 3.2 % (from 77.2 to 79.7 %), and first-year mortality increased by 61.5 % (from 30.7 to 49.6 %) [2–6]. The presented epidemiological data characterize an unfavorable situation regarding hepatocellular carcinoma in the region.

The most significant etiological risk factor for HCC development is liver cirrhosis and preceding advanced-stage liver fibrosis (F3–F4), which most commonly develop against the background of chronic viral infections such as hepatitis B and C [7]. The presence of liver cancer in close relatives also remains significant. However, in recent years, a transformation of the etiological structure of HCC development has been observed, and these changes are increasing each year [8, 9]. According to the authors' observations, the role of hepatitis C is substantially decreasing, and conversely, the influence of alcohol and metabolic dysfunction-associated fatty liver disease

is increasing in both men and women. This may lead to an increase in the number of patients undergoing HCC screening over the next 10–20 years due to a rising proportion of patients with hepatic steatosis and diabetes mellitus progressing to metabolic steatohepatitis and cirrhosis. In this context, a transition from universal screening to a risk-oriented approach is necessary. In such a screening model, the proportion of clinically significant diagnoses increases, the percentage of detected cases increases, and a positive economic effect is observed [10].

The risk-oriented approach begins with patient stratification based on HCC development risk (low, moderate, high). The GAAD model has proven to be an effective tool for dividing patients into groups, which includes the parameters: sex, age, alpha-fetoprotein (AFP) level, and level of protein induced by vitamin K absence/deficiency-II (PIVKA-II) [11]. After stratification, the choice of screening method and frequency of investigations is determined. For patients in low and moderate risk groups, ultrasound (US) examination of abdominal organs and serum AFP level determination remain the preferred methods. The list and frequency of these investigations in the Russian Federation are established in Order No. 168n of the Ministry of Health of the Russian Federation dated March 15, 2022, "On approval of the procedure for dispensary observation of adults" (hereinafter — Order No. 168n) [12]. For patients at high risk for HCC development and, likely, more aggressive disease progression, more sensitive and specific diagnostic methods capable of detecting tumor process at the preclinical stage are necessary. One of these is magnetic resonance imaging (MRI) with hepatospecific contrast agent [13, 14].

An equally important goal of screening, in addition to reducing mortality rates, is the detection of malignant neoplasms at early stages, which increases treatment efficacy and improves patient prognosis. It should be noted that currently, resection and liver transplantation for HCC patients with cirrhosis remain the only methods capable of curing patients or providing the longest possible survival extension [15]. Properly organized screening in high-risk groups and adherence to timelines for patient care will help increase the proportion of patients eligible for radical surgical treatment of HCC.

Aim of the study

To assess the prevalence of hepatocellular carcinoma in moderate- and high-risk patients in Krasnoyarsk Territory during screening activities.

Materials and methods

Inclusion criteria for screening: age 40–70 years, fibrosis (F3–4) / liver cirrhosis (duration more than 5 years) of viral and non-viral etiology. Exclusion criterion: lack of signed voluntary informed consent to participate in screening.

The clinical research program was developed by the Interdisciplinary Society of Specialists in Liver Tumors and approved by the Academic Council of National Medical Research Center of Oncology named after N.N. Blokhin. At a meeting of the working group of the Ministry of Health of Krasnoyarsk Territory, which included specialists in liver pathology, a patient routing algorithm through the "green corridor" to an oncologist was approved. Patients meeting moderate and high-risk criteria were referred by specialists in infectious diseases, internal medicine, and gastroenterology to Krasnoyarsk Regional Clinical Oncology Dispensary named after A.I. Kryzhanovsky (KRCOD). Since Krasnoyarsk region maintains a registry of patients with chronic viral hepatitis with data on liver fibrosis based on elastometry/elastography results, by decision of the working group, access to this registry was provided to KRCOD, whereupon the KRCOD contact center also engaged in active enrollment of patients in HCC screening.

Methods used: questionnaire survey to identify risk factors (questions regarding the presence of cirrhosis, its etiology, presence of viral hepatitis and its treatment, comorbidities including metabolic disorders, family oncology history, particularly liver malignancies, and harmful habits). The questionnaire also included data on recent laboratory tests (complete and biochemical blood analyses) and instrumental investigations (US and/or MRI and/or CT of abdominal organs); blood sampling to determine AFP + PIVKA-II levels (Cobas, Roche, Switzerland); MRI with hepatospecific contrast agent (gadoxetic acid).

To calculate the GAAD coefficient, depersonalized data (age, sex, AFP+PIVKA-II) were transmitted to Interdisciplinary Society of Specialists in Liver Tumors on a regular basis; using the online GAAD calculator, the risk coefficient was calculated. All data were collected in an internet-based database created by LLC Rosmedinfo according to the project of the Interdisciplinary Society of Specialists in Liver Tumors.

Data processing was performed using Statistica and StatTech software. Quantitative indicators were assessed for conformance to normal distribution using the Shapiro — Wilk test (for sample

size less than 50) or the Kolmogorov — Smirnov test (for sample size greater than 50). With normal distribution, data were described using arithmetic means (*M*) and standard deviations (*SD*); with non-normal distribution using median (*Me*) and lower and upper quartiles (Q_1–Q_3). Categorical data were described with absolute values and percentage proportions. For all values, 95 % confidence intervals (95% CI) are provided.

Comparison of patients with established diagnosis of hepatocellular carcinoma and without it by quantitative indicator with non-normal distribution was performed using the Mann — Whitney *U* test. Comparison of percentage proportions in analysis of 2 × 2 contingency tables was performed using Fisher's exact test (when expected values less than 10). As a quantitative measure of effect when comparing relative indicators, odds ratio (OR) with 95% CI was calculated. Comparison of percentage proportions in analysis of multi-cell contingency tables was performed using Pearson's chi-square test.

Results

Patients at risk for hepatocellular carcinoma (HCC) who were under routine observation by infectious disease specialists in the region were invited to participate in the screening program. A total of 3,416 patients were invited for clarification examinations. Between June and December 2024, 746 patients agreed to participate and attended the HCC screening pilot project. It should be noted that there was a high percentage of patient refusals to visit the dispensary for screening activities — 78.2 %. One patient met the exclusion criterion of previously established HCC. After completing the questionnaire, patients were routed to the procedure room for blood sampling to determine tumor marker

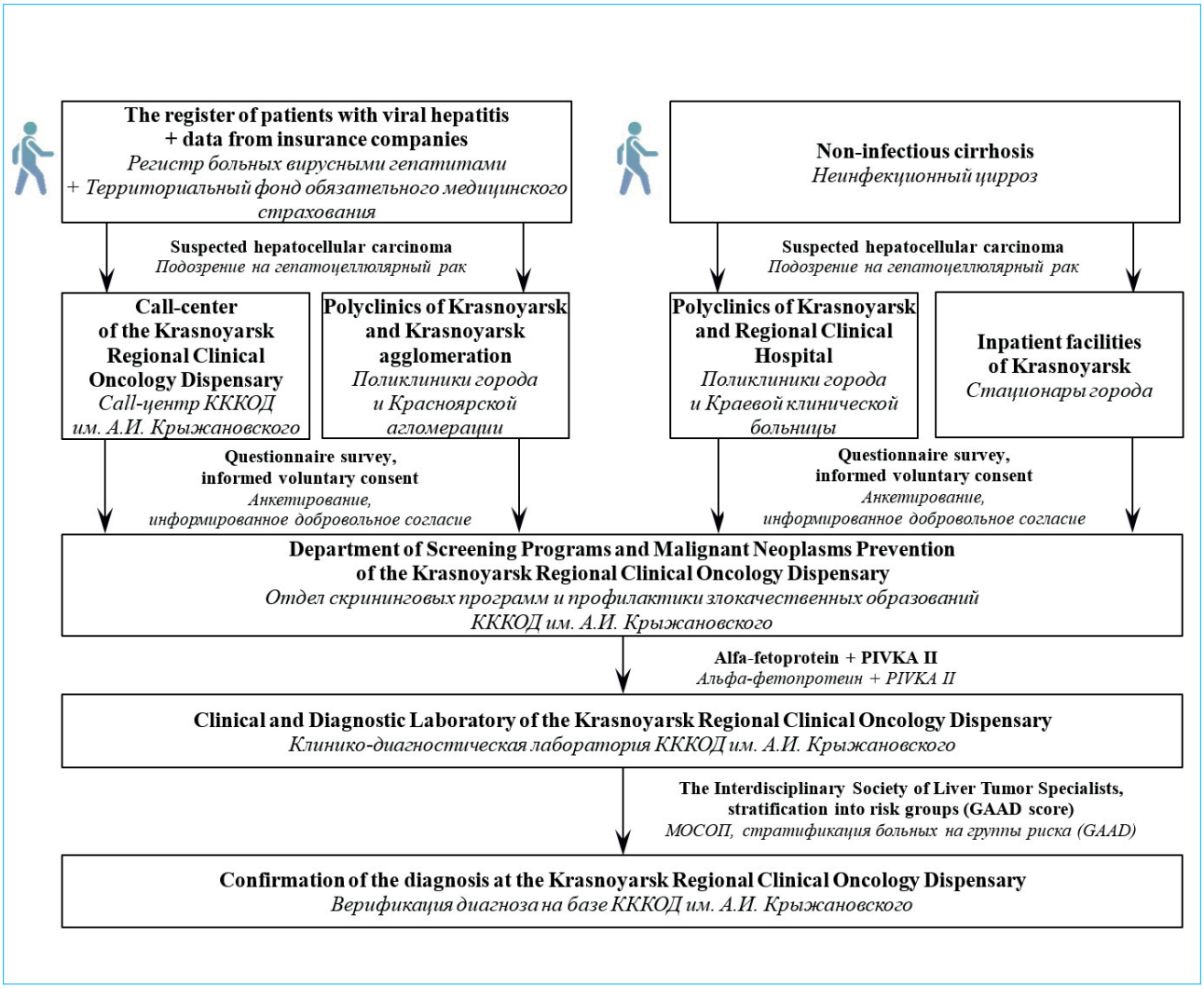

Figure. Screening model for hepatocellular carcinoma
Рисунок. Модель скрининга гепатоцеллюлярного рака

levels — AFP+PIVKA-II. The screening organization model is presented in Figure.

The mean age of patients who underwent screening examination was 56 years, ranging from 28 to 79 years. Female patients more often agreed to screening (54.85 %). The mean body weight of patients was 80 kg, height — 169 cm. Body mass index had a median value of 27.55, corresponding to overweight. Among harmful habits, smoking was most common: 34.5 % of patients were former or current smokers. Regular alcohol consumption was noted in only a small portion of patients (5.9 %) with a frequency of approximately four times a week. Liver fibrosis was observed in the vast majority of patients — 86.5 %, with most having severe stage F4 (74.6 %). Liver cirrhosis was diagnosed in half of the examined patients (56.9 %). The etiology of cirrhosis was predominantly viral — 86.4 %, with the majority attributed to chronic hepatitis C (HCV) at 77.5 %. Diabetes mellitus occurred in one-quarter of patients — 28.3 %, with type 2 predominating — 93.4 %. Hereditary predisposition to malignant neoplasms was identified in a significant

Table 1. Patient characteristics (quantitative variables)
Таблица 1. Характеристика пациентов (количественные переменные)

Parameters ***Показатели***	***Me / M* ± SD**	**95% CI / *95% ДИ*** Q_1–Q_3	***N***	**min**	**max**
Age, years *Возраст, лет*	56.00	49.00–63.00	745	28.00	79.00
Weight, kg *Масса тела, кг*	80.00	68.00–91.00	745	42.00	153.00
Height, cm *Рост, см*	169.00	163.00–176.00	745	143.00	194.00
Body mass index, kg/m^2 *Индекс массы тела, кг/м^2*	27.55	24.22–31.71	745	16.73	54.21
Regularity of alcohol consumption, times per week *Регулярность употребления алкоголя, раз в неделю*	4.00	3.00–6.00	25	1.00	7.00
Number of cigarettes per day *Количество сигарет в день*	10.00	10.00–20.00	257	1.00	60.00
Smoking experience, years *Стаж курения, лет*	30.00	20.00–35.00	257	1.00	55.00
Smoker's index, pack/years *Индекс курения, пачка/лет*	18.00	10.00–25.00	257	0.00	90.00
Albumin, g/L *Альбумин, г/л*	45.61	41.46–45.61	141	10.04	331.00
Total bilirubin, umol/L *Общий билирубин, мкмоль/л*	15.30	10.90–19.90	197	2.28	91.50
Platelets, 10^9/L *Тромбоциты, 10^9/л*	169.68	121.00–193.50	175	35.00	826.00
Creatinine, μmol/L *Креатинин, мкмоль/л*	74.60	64.00–90.50	171	4.60	790.00
Aspartate aminotransferase, U/L *Аспартатаминотрансфераза, Ед./л*	31.30	22.30–50.69	209	9.00	417.00
Alanine aminotransferase, U/L *Аланинаминотрансфераза, Ед./л*	27.00	19.20–43.13	205	5.00	279.00
Hemoglobin, g/L *Гемоглобин, г/л*	136.00	135.25–145.00	162	20.20	178.00
Leucocyte, 10^9/L *Лейкоциты, 10^9/л*	6.62 ± 2.55	6.02–7.23	71	2.22	12.90
Neutrophils, % *Нейтрофилы, %*	55.35 ± 10.05	52.63–58.06	55	33.70	76.00
Lymphocytes, % *Лимфоциты, %*	30.80	26.38–36.90	68	12.60	56.00
Alfa-fetoprotein, IU/mL *Альфа-фетопротеин, МЕ/мл*	2.24	1.49–3.46	739	0.75	689.60
PIVKA-II, ng/mL *PIVKA-II, нг/мл*	18.63	14.83–25.21	744	3.50	61 380.00

proportion of patients — 71.8 %, with 2.6 % specifically for HCC. Patients with esophageal varices constituted 16.6 % of the total sample (grade 1–2 — 77.4 %, grade 2–3 — 22.6 % of patients); variceal bleeding occurred in a small percentage of patients — 5.1 %. In most patients, moderate hepatic enzyme activity was observed for aspartate aminotransferase (median value — 31.3 U/L) and alanine aminotransferase (27 U/L). Total bilirubin level was also within normal range with a median value of 15.3 umol/L. White blood cell differential showed predominance of neutrophils (55.35 %) over lymphocytes (30.8 %). Median AFP value was 2.24 IU/mL, median PIVKA-II value was 18.63 ng/mL, with the upper interval limit reaching high levels — 25.21 ng/mL, approaching threshold risk indicators, with the maximum recorded level — 61,380 ng/mL.

Detailed description of risk factors in patients is presented in Tables 1 and 2.

Based on the results of blood sample assessment for two specific tumor markers, the following results were obtained: elevation of AFP only, with normal values 0.00–5.80 IU/mL, was observed in 43 patients; elevation of PIVKA-II only, with normal values 0.00–28.40 ng/mL, was observed in 120 patients; simultaneous elevation of both AFP and PIVKA-II — in 31 patients. In total, 194 patients demonstrated elevation of indicators above the normal level.

The GAAD calculator identified high risk for hepatocellular carcinoma (HCC) in 58 patients who had never previously been referred to the oncology dispensary with suspected HCC based on examinations included in Order No. 168n. All of them were referred to the second stage of screening — MRI with hepatospecific contrast agent, which was also performed at Krasnoyarsk Regional Clinical Oncology Dispensary; however, for two patients the examination was replaced with expert-level abdominal ultrasound due to contraindications for MRI — installed prostheses of mitral and aortic valves. Screening participants were scheduled for further examination. The average waiting time from receipt of test results to MRI was 3 days.

The GAAD calculator has a limitation in AFP values; if the calculated coefficient is less than 2.7, the calculator produces a “moderate” risk result regardless of other criteria values. Therefore, for patients with high PIVKA-II levels and AFP less than 2.7, a decision was made to refer the patient to the second stage — MRI with hepatospecific contrast agent. Based on the results of additional examinations, the most common findings in patients were: diffuse changes in liver parenchyma, manifesting predominantly as signs of cirrhosis (observed in virtually all reports); portal hypertension (noted almost universally when cirrhosis signs are present); less frequently but regularly observed were cirrhosis complications in the form of small ascites; hepatosplenomegaly and less frequently splenomegaly; liver cysts, signs of cholecystitis; diffuse changes in the pancreas. In 14 % of cases, small benign liver neoplasms were noted (hemangiomas, small regenerative nodules).

Based on the results of risk-oriented HCC screening approach, 14 new cases of liver malignancies were identified among patients with GAAD coefficient > 2.7; notably, 7 (50.0 %) cases were verified at stages I–II according to TNM classification, indicating high sensitivity of the selected approach, confirmed by literature data [14]. Distribution by tumor stage was as follows: stage I — 2 (14.3 %) patients, stage II — 5 (35.7 %), stage III — 2 (14.3 %), stage IV — 5 (35.7 %). According to the Barcelona Clinic Liver Cancer classification (BCLC), distribution was as follows: BCLC A — 5 (35.7 %) patients, BCLC B — 7 (50.0 %) patients, BCLC C — 2 (14.3 %) patients. As a result, the proportion of clinically significant diagnoses when using the combination of AFP + PIVKA-II followed by MRI with hepatospecific contrast agent in patients at moderate and high risk for HCC development was 1.88 % (14 new cases in 745 examinations) (Table 3).

Among patients in whom the GAAD calculator determined high risk for HCC development (GAAD ≥ 2.7), males predominated (48 patients out of 58), median age (range) — 61.5 years (40–77 years). Median BMI was 27.58 kg/m^2, corresponding to overweight, with values ranging from 16.79 to 39.45 kg/m^2. Forty-seven patients (81.0 %) had chronic viral hepatitis in their history: HCV — 45 cases, HBV — 1 case, HCV + HBV — 1 case. Antiviral treatment for this disease was completed in only 31 (53.4 %) patients. Liver fibrosis in this subgroup was present in 42 (72.4 %) patients, predominantly F3–F4 according to METAVIR (41 patients). Liver cirrhosis was previously established in 40 (69.0 %) cases, of which of viral etiology — 32 cases, toxic etiology — 3 cases, combined (HCV + ethanol) — 1 case, other etiologies (including unknown) — 4 cases. Distribution of cirrhosis by Child — Pugh classification was as follows: class A — 26 patients, class B — 8, class C — 6. Esophageal varices were noted in 16 (27.6 %) patients, predominantly grade 1–2 (10 patients). Episodes of variceal bleeding occurred in 6 patients, 5 of whom had grade 2–3 disease. Harmful

Table 2. Patient characteristics (categorical variables)
Таблица 2. Характеристика пациентов (категориальные переменные)

Parameters ***Показатели***	**Category** ***Категория***	***N***	**%**	**95% CI** ***95% ДИ***
Gender *Пол*	female / *женский*	408	54.8	51.1–58.4
	male / *мужской*	337	45.2	41.6–48.9
Viral hepatitis *Вирусный гепатит*	no / *нет*	95	12.8	10.4–14.2
	yes / *да*	609	81.7	80.1–87.9
	no data / *нет данных*	41	5.5	3.2–7.2
Chronic hepatitis C infection *Хронический вирусный гепатит С*	yes / *да*	531	91.2	88.6–93.4
	no / *нет*	51	8.8	6.6–11.4
Chronic hepatitis B infection *Хронический вирусный гепатит В*	yes / *да*	96	12.9	10.6–15.5
	no / *нет*	649	87.1	84.5–89.4
Hepatic fibrosis *Фиброз печени*	no / *нет*	82	11.1	10.2–12.21
	yes / *да*	527	70.7	68.2–71.1
	no data / *нет данных*	136	18.2	16.6–20.4
Stage of fibrosis *Стадия фиброза*	F0	13	2.4	1.3–4.1
	F1	14	2.6	1.4–4.4
	F2	15	2.8	1.6–4.6
	F3	94	17.6	14.4–21.1
	F4	399	74.6	70.7–78.2
Hepatic cirrhosis *Цирроз печени*	no / *нет*	289	38.8	36.3–39.9
	yes / *да*	382	51.3	49.9–53.7
	no data / *нет данных*	74	9.9	8.7–11.1
Etiology of cirrhosis *Этиология цирроза*	viral / *вирусная*	330	86.4	82.5–89.7
	other / *другая*	35	9.2	6.5–12.5
	toxic / *токсическая*	9	2.3	0.7–5.7
	combined / *сочетанная*	8	2.1	0.9–4.1
Viral etiology of cirrhosis *Вирусная этиология цирроза*	HBV / *ХВГВ*	16	4.8	2.8–7.2
	HCV / *ХВГС*	296	89.7	75.2–92.2
	combined / *сочетанная*	18	5.5	4.5–8.8
Child – Pugh cirrhosis class *Класс цирроза по Чайлду – Пью*	C	22	5.8	3.6–8.6
	B	44	11.5	8.5–15.2
	A	316	82.7	78.6–86.4
Esophageal varices *Варикозное расширение вен пищевода*	no / *нет*	621	83.4	80.5–86.0
	yes / *да*	124	16.6	14.0–19.5
Stage of esophageal varices *Степень варикозного расширения вен пищевода*	1–2	96	77.4	69.0–84.4
	2–3	28	22.6	15.6–31.0
Bleeding from esophageal varices *Кровотечение из варикозно расширенных вен пищевода и желудка*	yes / *да*	38	5.1	3.6–6.9
	no / *нет*	707	94.9	93.1–96.4
Smoking (now or earlier) *Курение (сейчас или раньше)*	no / *нет*	488	65.5	62.0–68.9
	yes / *да*	257	34.5	31.1–38.0
Alcohol consumption *Употребление алкоголя*	yes / *да*	44	5.9	4.3–7.8
	no / *нет*	701	94.1	92.2–95.7
Complicated genetics (HCC) *Наследственность по ГЦР*	no / *нет*	726	97.4	96.0–98.5
	yes / *да*	19	2.6	1.5–4.0
Diabetes mellitus *Сахарный диабет*	yes / *да*	211	28.3	25.1–31.7
	no / *нет*	534	71.7	68.3–74.9
Type of diabetes mellitus (out of the total number of patients) *Тип сахарного диабета (из общего числа пациентов)*	2	197	26.4	21.7–31.2
	1	14	1.9	0.7–4.2

Note: *HCV – chronic hepatitis C infection, HCB – chronic hepatitis B infection, HCC – hepatocellular cancer.*
Примечание: *ХВГС – хронический вирусный гепатит С, ХВГС – хронический вирусный гепатит В, ГЦР – гепатоцеллюлярный рак.*

Table 3. The first results of risk-based hepatocellular cancer screening
Таблица 3. Первые результаты риск-ориентированного скрининга гепатоцеллюлярного рака

Parameters ***Показатели***	**Category** ***Категория***	***N***	**%**	**95% CI** ***95% ДИ***
Risk of HCC *Риск ГЦР*	high (GAAD ≥ 2.7) *высокий (GAAD ≥ 2,7)*	58	7.8	6.0–9.9
	moderate (GAAD < 2.7) *умеренный (GAAD < 2,7)*	687	92.2	90.1–94.0
MRI with gadoxetic acid *МРТ с гадоксетовой кислотой*	not performed *не проведено*	666	89.4	87.0–91.5
	performed *проведено*	79	10.6	8.5–13.0
Screening results *Результат скрининга*	HCC detected *ГЦР выявлен*	14	1.9	1.0–3.1
	HCC not detected *ГЦР не выявлен*	731	98.1	96.9–99.0
Stage of HCC (TNM) *Стадия ГЦР (TNM)*	III–IV	7	50.0	23.0–77.0
	I–II	7	50.0	23.0–77.0
Stage of HCC (BCLC) *Стадия ГЦР (BCLC)*	A	5	35.7	12.8–64.9
	B	7	50.0	23.00–77.0
	C	2	14.3	1.8–42.8

Note: *HCC — hepatocellular carcinoma, BCLC — Barcelona Clinic Liver Cancer staging system.*
Примечание: *ГЦР — гепатоцеллюлярный рак, BCLC (Barcelona Clinic Liver Cancer staging system) — Барселонская система стадирования гепатоцеллюлярной карциномы.*

habits were noted in 25 (43.1 %) patients, the majority of whom at the time of the study continued to actively smoke — 22 cases, median smoking index (pack/years) in these patients was 23.25 pack/years, number of cigarettes smoked daily ranged from 8 to 25 (median — 11 cigarettes/day), smoking duration ranged from 1 to 50 years (median — 39 years). Alcohol consumption/past consumption — 3 patients. Frequency of alcohol consumption varied from 3 to 7 times per week (median — 5 times). Malignant neoplasms of other sites were present in 4 patients: C61 — 2 patients, C18 — 1 patient, C67 — 1 patient. Concomitant type 2 diabetes mellitus was present in 20 (34.5 %) cases, type 1 diabetes mellitus/impaired glucose tolerance was not identified in any patient in this subgroup. Laboratory indicators in this subgroup were as follows: albumin — 27.30–58.00 g/L (median — 45.61 g/L), total bilirubin — 6.09–76.00 μmol/L (18.12 μmol/L), platelets — (36.00–281.00) × 10^9/L (169.68 × 10^9/L), creatinine — 52.00–126.00 μmol/L (80.00 μmol/L), alanine aminotransferase — 19.20–279.00 U/L (43.13 U/L), aspartate aminotransferase — 20.30–417.00 U/L (46.31 U/L), hemoglobin — 110.00–168.00 g/L (136.00 g/L), lymphocytes — 22.40–46.30 % (29.6 %). Leukocyte level was in the range (2.41–8.67) × 10^9/L (mean ± standard deviation — (5.48 ± 2.22) × 10^9/L), neutrophil percentage — (38.70–64.68) % (54.68 ± 9.84 %). Mean serum AFP level in this subgroup was 53.24 ± 128.20 IU/mL, PIVKA-II — 2842.34 ± 9572.98 ng/mL.

In conducting single-factor analysis of variance of intergroup differences (HCC not detected/HCC detected), the following significant factors were identified ($p < 0.05$): sex, presence/absence of liver cirrhosis, and GAAD coefficient (Table 4).

It should be noted that in one patient in the moderate risk group, during MRI performed to search for a possible focal lesion in the liver following detection of elevated oncemarker levels, a tumor of the pancreatic head was discovered, subsequently confirmed by morphological verification — the patient was diagnosed with pancreatic cancer stage IA.

Table 4. Univariate analysis results of the probability of detecting hepatocellular carcinoma
Таблица 4. Результаты однофакторного анализа вероятности выявления гепатоцеллюлярного рака

Parameters *Показатели*	Category *Категория*	Screening results Результат скрининга		OR (95% CI) *ОШ (95% ДИ)*	*p*
		HCC not detected *ГЦР не выявлен*	HCC detected *ГЦР выявлен*		
Gender *Пол*	male / *мужской*	326 (44.5 %)	12 (85.7 %)	0.134 (0.030–0.0604)	0.002
	female / *женский*	405 (55.5 %)	2 (14.3 %)		
Hepatic cirrhosis *Цирроз печени*	yes / *да*	369 (56.1 %)	13 (92.9 %)	0.099 (0.013–0.758)	0.005
	no / *нет*	288 (43.9 %)	1 (7.1 %)		
GAAD-score *Коэффициент GAAD*	< 2.7	44 (6.0 %)	14 (100.0 %)	–	< 0.001
	≥ 2.7	687 (94.0 %)	0 (0.0 %)		

Note: *HCC — hepatocellular carcinoma, OR — odds ratio.*
Примечание: *ГЦР — гепатоцеллюлярный рак, ОШ — отношение шансов.*

Discussion

The primary goal of screening aimed at detecting hepatocellular carcinoma, like any cancer screening, is to reduce mortality through early disease detection, since treatment initiated at an early disease stage provides chances for increasing patient survival [16]. It is too early to draw conclusions about long-term results of the pilot project for liver cancer screening. However, by the end of 2024, it was already possible to increase the number of newly detected HCC cases in the region from 346 cases in 2023 to 457 cases in 2024 — an increase of 32.1 %.

The difference in treatment efficacy and overall survival in patients with various hepatocellular carcinoma stages justifies screening activities. Similar clinical efficacy has been demonstrated in a number of foreign and Russian studies [17, 18]. Implementation of the tested screening model may contribute to achieving these results.

During the implementation of the pilot project for risk-oriented hepatocellular carcinoma screening, the detection rate reached 1.88 %, which exceeds the minimum threshold of annual risk (1.5 %), justifying screening activities not only from the perspective of clinical efficacy but also economic feasibility [19].

However, the question of the scope and frequency of examinations remains open for further implementation [20, 21]. In particular, this issue is especially acute for patients who were classified in the high-risk GAAD group but in whom hepatocellular carcinoma was not detected after contrast-enhanced MRI.

The study also evaluated the efficacy of risk-oriented screening for malignant tumors. Coordinated work at a major oncological institution with a screening programs department, equipped with all capabilities for early detection and treatment of HCC, undoubtedly leads to significant reduction in time from diagnosis to initiation of specialized treatment. The average duration of the period between establishment of confirmed HCC based on magnetic resonance imaging with hepatotropic contrast and subsequent comprehensive additional patient examination was 35 days.

The pilot HCC screening project at the oncological institution, motivated to detect tumors early, contributed to the unification of oncology specialists into a multidisciplinary team, which in turn increased the number of surgical treatment methods for HCC by 16.5 %, the number of liver biopsies by 33.2 %. The oncology service initiative is largely due to the absence (poor organization) of an HCC screening system in the general therapeutic and infectious disease network of the region, despite the existing order from the Ministry of Health of the Russian Federation.

The initial results demonstrated low public interest (fewer than 25 % of those invited agreed to participate) in active free screening, which underscores the importance of active health education work with patients at risk for HCC development.

To identify the high-risk group for HCC development, we used the GAAD calculator for the first time in the Russian Federation. This is a simple, effective, and validated tool using straightforward and accessible data, with which it is possible to identify a small group (approximately 8 % of the general population) of patients for whom MRI use, as a sensitive method for early liver cancer diagnosis, is justified.

Only the initial results from a brief six-month period of risk-oriented screening in a specific region of the Russian Federation are presented; further patient follow-up will continue.

Conclusion

Implementation of a risk-oriented approach for the high-risk group with application of more sensitive diagnostic methods will contribute to increasing the proportion of liver malignancies detected at early stages and timely initiation of specialized treatment.

Furthermore, the proven fact regarding hepatocellular carcinoma etiology associated with liver cirrhosis underscores the necessity of creating a registry of cirrhosis of both viral and non-viral etiology in the region.

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