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## CLINICAL FEATURES OF HEPATOCELLULAR CARCINOMA

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### Abstract

**Background.** Hepatocellular carcinoma (HCC) is the most common primary malignant neoplasm of the liver. HCC is the fifth most common cancer among men worldwide and seventh among women, and is the second leading cause of cancer deaths in the world. In Kazakhstan HCC consistently ranks 10th in the structure of oncological diseases.

The aim of the research is to study the organizational and clinical features of providing care to patients with HCC at National Scientific Center of Surgery named after A.N. Syzganov.

**Materials and methods.** Retrospective study. We studied inpatient records of patients diagnosed with HCC at National Scientific Center of Surgery named after A.N. Syzganov from 2012 to 2020. It was processed in the statistical package IBM SPSS Statistics 20. The following variables were used for the analysis: qualitative (history of diseases, stage of fibrosis) and quantitative (age, duration of hospital stay, bilirubin level, body mass index).

Pearson's chi-square test was applied to test for the difference. Chi-squared test was used to compare the categorical or nominal variables. Differences were considered statistically significant when  $P \leq 0.05$ . We assessed association between continuous variables total bilirubin and BMI in patients with HCC using Correlation Analysis.

**Results.** According to the results of the study, 183 patients were treated at National Scientific Center of Surgery named after A.N. Syzganov from 2012 to 2020 (ICD-10-C22.0). The average length of hospital stay was 12 bed-days. The average age of patients with HCC was  $61.67 \pm 8.928$  (95% CI: 59.84- 63.50). Among patients, the main reason for the development of HCC was a history of hepatitis B, C, B with a delta agent. Patients with elevated bilirubin levels have a low body mass index. Basically, in recent years, transarterial chemoembolization (TACE) is used in HCC at National Scientific Center of Surgery named after A.N. Syzganov.

**Conclusions.** The average bed-days for the clinical-cost groups diagnosed with HCC for 2012-2020 was 12 bed-days at National Scientific Center of Surgery named after A.N. Syzganov. The study revealed a correlation between BMI and the level of bilirubin associated with the development of HCC and subsequent cell necrosis.

**Key words:** Hepatocellular carcinoma, bilirubin, TACE.

### Резюме

## КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЫ

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**Актуальность:** Гепатоцеллюлярная карцинома (ГЦК) - наиболее частое первичное злокачественное новообразование печени. ГЦК занимает пятое место по распространенности рака среди мужчин во всем мире и седьмое место среди женщин и является второй ведущей причиной смертности от рака в мире. В Казахстане ГЦК стабильно занимает 10-е место в структуре онкологических заболеваний.

**Цель исследования:** изучить организационные и клинические особенности оказания помощи пациентам с печеночноклеточным раком в условиях АО «Национальный научный центр хирургии им.Сызганова».

**Материалы и методы исследования:** Ретроспективное исследование. Для обработки и анализа были использованы стационарные карты пациентов с диагнозом “Печеночноклеточный рак” в АО «Национальный научный центр хирургии им. А.Н.Сызганова». Данные с 2012 по 2020 годы были обработаны в статистической программе IBM SPSS Statistics 20. Для анализа были использованы следующие переменные: качественные (наличие заболеваний в анамнезе, стадия фиброза) и количественные (возраст, длительность пребывания пациентов в стационаре, уровень билирубина, индекс массы тела).

Для проверки разницы применялся критерий хи-квадрат Пирсона. Критерий хи-квадрат использовался для сравнения категориальных или номинальных переменных. Различия считались статистически значимыми при  $P \leq 0,05$ . Мы оценили связь между непрерывными переменными общего билирубина и ИМТ у пациентов с ГЦК с помощью корреляционного анализа.

**Результаты исследования:** Согласно результатам исследования 183 пациента проходили стационарное лечение с диагнозом по МКБ-10 “С22.0 Печеночноклеточный рак” в условиях АО «Национальный научный центр хирургии им. А.Н. Сызганова» с 2012 года по 2020 год. Средняя длительность пребывания больного в стационаре составила 12 койко-дней. Средний возраст пациентов с ГЦК составил  $61,67 \pm 8,928$  (ДИ 95%: 59.84- 63.50). Среди пациентов основной причиной развития ГЦК являлось наличие в анамнезе гепатита В,С, В с дельта-агентом. У пациентов с повышенным уровнем билирубина наблюдается низкий индекс массы тела. В основном в последние годы в АО «ННЦХ им. А.Н. Сызганова» при ГЦК применяется трансартериальное химиоэмболизация (ТАХЭ).

**Выводы:** В АО «ННЦХ им.А.Н. Сызганова» средний показатель койко-дней по клинико-затратным группам с диагнозом ГЦК за 2012-2020 годы составил 12 койко-дней. В ходе исследования выявлена корреляция между индексом массы тела и уровнем билирубина, связанного с развитием печеночноклеточной недостаточности и последующим некрозом клеток.

*Ключевые слова:* Гепатоцеллюлярный рак, билирубин, ТАХЭ.

Түйіндеме

## ГЕПАТОЦЕЛЛЮЛЯРЛЫҚ КАРЦИНОМАНЫҢ КЛИНИКАЛЫҚ ЕРЕКШЕЛІКТЕРІ

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**Өзектілігі:** Гепатоцеллюлярлық карцинома (ГЦК) - бауырдың ең жиі кездесетін бастапқы қатерлі ісігі. ГЦК бүкіл әлемде ерлер арасында обырдың таралуы бойынша бесінші және әйелдер арасында жетінші орында және әлемде обырдан өлімнің екінші жетекші себебі болып табылады. Қазақстанда ГЦК онкологиялық аурулар құрылымында 10-шы орынға ие.

**Зерттеу мақсаты:** «А.Н. Сызғанов атындағы Ұлттық ғылыми хирургия орталығы» АҚ жағдайында бауыр қатерлі ісігі бар науқастарға көмек көрсетудің ұйымдастырушылық және клиникалық ерекшеліктерін зерттеу.

**Зерттеу материалдары мен әдістері:** Ретроспективті зерттеу. "А.Н. Сызғанов атындағы Ұлттық ғылыми хирургия орталығы" АҚ-да «Бауыр қатерлі ісігі» диагнозы қойылған науқастардың стационарлық карталары. 2012 жылдан 2020 жылға дейінгі деректер IBM SPSS Statistics 20 статистикалық бағдарламасында өңделген. Талдау үшін келесі айнымалылар қолданылды: сапалық (аурулар тарихы, фиброз кезеңі) және сандық (жас, ауруханада болу ұзақтығы, билирубин деңгейі, дене салмағының индексі).

Айырмашылықтарды тексеру үшін Пирсонның хи-квадрат сынағы қолданылды. Категориялық немесе номиналды айнымалыларды салыстыру үшін хи-квадрат тесті қолданылды.  $P \leq 0,05$  кезінде айырмашылықтар статистикалық маңызды деп саналды. Біз корреляциялық талдауды пайдалана отырып, ГЦК бар науқастарда жалпы билирубиннің үздіксіз айнымалылары мен BMI арасындағы байланысты бағаладық.

**Зерттеу нәтижелері:** 2012 жылдан 2020 жылға дейінгі зерттеу нәтижелеріне сәйкес "А.Н. Сызғанов атындағы Ұлттық ғылыми хирургия орталығы" АҚ жағдайында АХЖ-10 "C22.0 Бауыр қатерлі ісік" диагнозымен 183 науқас стационарлық ем алған. Стационарда болудың орташа ұзақтығы 12 төсек-күнін құрады. ГЦК - мен ауыратын науқастардың орташа жасы  $61,67 \pm 8,928$  (ДИ 95%: 59.84-63.50) құрады. Науқастардың арасында ГЦК дамуының негізгі себебі анамнезінде В,С және дельта-агенті бар В гепатитінің болуы байқалады. Билирубин деңгейі жоғары науқастарда дене салмағының төмен индексі байқалады. Негізінен соңғы жылдары "А.Н. Сызғанов атындағы Ұлттық ғылыми хирургия орталығы" АҚ-да ГЦК-мен ауыратын науқастарға трансартериалдық химиоэмболизация (ТАХЭ) қолданылады.

**Қорытындылар:** "А.Н. Сызғанов атындағы Ұлттық ғылыми хирургия орталығы" АҚ-да 2012-2020 жылдары ГЦК диагнозымен клиникалық-шығынды топтар бойынша төсек-күндердің орташа көрсеткіші 12 төсек-күнін құрады. Зерттеу барысында бауыр-жасушалық жетіспеушілігінің дамуымен және кейінгі жасуша некрозымен байланысты дене салмағының индексі мен билирубин деңгейі арасындағы байланыс анықталды.

**Түйінді сөздер:** Гепатоцеллюлярлық карцинома, билирубин, ТАХЭ.

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#### Background

Hepatocellular carcinoma (HCC) is a major health problem worldwide and the most common type of primary malignant neoplasm of the liver [22]. HCC is the fifth most common cancer in men worldwide and seventh among women and is the second leading cause of cancer deaths in the world. More than half a million new cases are diagnosed each year. In Kazakhstan, HCC has been ranked 10th in the structure of all type of cancer over the past 5 years. According to Isamatov et al. in terms of mortality from malignant neoplasms in 2017, HCC ranks 10th after malignant neoplasms of the lung, stomach, breast, esophagus, colon, pancreas, hemoblastosis, rectum, cervix. HCC accounts for 4.2% of all cancer mortality. Pilot liver cancer screening was implemented in some regions of the Republic of Kazakhstan from 2013 to 2017.

The major risk factors for HCC are liver cirrhosis, viral hepatitis B (HBV), C (HCV), alcohol, tobacco use, non-alcoholic fatty liver disease, diabetes [17]. The most common cause of HCC is chronic liver disease caused by hepatitis B virus (HBV) or hepatitis C virus (HCV). Thus,

prevention and treatment of chronic viral hepatitis are measures to prevent HCC [19]. HBV is the most common cause of HCC worldwide, accounting for 54% of all liver cancer cases [2]. Chronic HBV infection increases the relative risk of developing HCC in 15–20 times with a mortality rate of approximately 30%–50% among all cases of chronic HBV infection [15] [11]. In the USA, about 10–16% of HCC cases are HBV-related. In the USA, about 10–16% of HCC cases are HBV-related. Approximately 10% of HIV-infected people are co-infected with chronic hepatitis B and have a higher risk of developing HCC than patients with mono-infection of hepatitis B virus or HIV with a lower CD4 + [7] [13]. A unique variant of HBV infection is occult viral hepatitis B, which can also lead to liver cirrhosis and HCC [27] [4].

In 10–25% of all HCC cases, HCV is the second most common risk factor for HCC and is estimated to be associated with it worldwide [11] [8]. In developed countries, including Japan and the United States, HCV is the most common causative agent [20] [26]. Chronic infection HCV is associated with a 20–30-fold increased risk of developing

HCC compared with uninfected people. HCC develop in under 2.5% of patients with chronic HCV infection [3]. Even in the absence of an effective HCV vaccine, introduce a combination of laboratory measures such as screening of blood and blood products, public health initiatives such as identification and counseling, and treatment of infected individuals and high-risk individuals can reduce, and possibly even reduce, worldwide HCV infection rates[23].

Alcohol-related cirrhosis is considered the third most common cause of HCC [14]. Alcohol acts synergistically with hepatotropic viruses, increasing the likelihood of developing HCC [6]. This effect was more pronounced in those people who consumed more than 60 g of alcohol per day. Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the USA and is consistently thought to be the cause of HCC, which occurs primarily in the presence of cirrhosis [25]. The incidence is increasing in parallel with the rise in obesity, diabetes and metabolic syndrome. Interestingly, Nonalcoholic steatohepatitis (NASH) patients without cirrhosis do not have an increased risk of HCC [5].

The aim of the research is to study the organizational and clinical features of providing care to patients with HCC at National Research Center of Surgery after A.N. Syzganov and correlation between BMI (body mass index) and bilirubin level.

**Materials and methods.** Retrospective study. We studied inpatient medical records of patients with HCC at National Scientific Center of Surgery named after A.N. Syzganov from 2012 to 2020. It was processed in the statistical package IBM SPSS Statistics 20. To assess the severity of patients and staging, the CTP [21], MELD [1] and Barcelona and Milan criteria were used. [16]. The following variables were used for the analysis: qualitative (history of diseases, stage of fibrosis) and quantitative (age, duration of hospital stay, bilirubin level, body mass index).

Pearson's chi-square test was applied to test for the difference. Chi-squared test was used to compare the categorical or nominal variables. Differences were considered statistically significant when  $P \leq 0.05$ . We assessed association between continuous variables total bilirubin and BMI in patients with HCC using Correlation Analysis.

The survey was approved by the Ethical Committee of Kazakh National Medical University named after S.D. Asfendiyarov (№15 (121), 24.11.2021).

Inclusion criteria: All patients with HCC.

Informed consent of patients was not required for the study because retrospective data were processed using an information system.

Administration of clinic is aware of the study and does not object to the publication of the data in the open press.

**Results**

183 patients underwent inpatient treatment with a diagnosis of ICD-10 "C22.0 HCC" from 2012 to 2020 at National Scientific Center for Surgery named after A.N. Syzganov. 83 were females (45%) and 100 male patients (55%). The average age of the patients was  $61.67 \pm 8.928$  (95% CI: 59.84- 63.50), max = 84, min = 31. The average age of women was 60.75 years, men - 59.87 years ( $p = 0.524$ ). The average length of hospital stay was 12 bed-days.

Patients from the following regions applied for planned hospitalization with HCC: Almaty city - 76 (41.3%), Almaty region - 20 (10.9%), Zhambyl region - 18 (9.8%), Turkestan region - 15 (8.2%), Kyzylorda region - 14 (7.6%).

Among 183 patients, the main reason for the development of HCC was a history of hepatitis B, C, B with a delta agent. Hepatitis B was observed in 68 cases (37%), hepatitis C in 51 cases (27.9%) and hepatitis B with a delta-agent in 11 cases (6%), liver cirrhosis was observed in 108 patients (59%) and metastases were found in 20 (10.9%) (Table 1).

Table 1.

**The reasons for the development of HCC at National Scientific Center for Surgery named after A.N. Syzganov for 2012-2020.**

Risk factors (reasons), N=183	Yes Frequency (%)	No Frequency (%)	p-value
HBV	68 (37.2)	115 (62.8)	$\chi^2=12.071$ ; p=0,001
HBC	51 (27.9)	132 (72.1)	$\chi^2=35.852$ ; p<0,001
B+Delta	11 (6)	172 (94.0)	$\chi^2=141.645$ ; p<0,001
Autoimmune hepatitis	0	183	-
Primary biliary cirrhosis (PBC)	0	183	-
Alcoholic hepatitis	0	183	-
NAFLD	0	183	-
Liver cirrhosis	108 (59.0)	75 (41.0)	$\chi^2=5.951$ ; p=0,015
Metastases	20 (10.9)	163 (89.1)	$\chi^2=111.743$ ; p<0,001

Alpha-fetoprotein (AFP) is synthesized by a healthy liver in trace amounts quantities (normal level up to 20 ng / ml) and in higher concentration by HCC cells. This tumor marker has relative specificity and is found in increased concentration in 50-70% of patients with HCC. AFP is used as a tumor marker of HCC in the clinical protocols APASL, APPLE, EASL, ILTS, in the «Kazakhstan protocol for the diagnosis and treatment of HCC No. 14 dated 30.10.2015».

In international and other national clinical guidelines, PIVKA-II, AFP-L3 are used along with AFP [18].

The results of the analysis of our study, the biochemical parameters and the level of AFP upon admission of patients were: indirect bilirubin on average - 12.83  $\mu\text{mol} / \text{ml}$ , direct bilirubin - 29.31  $\mu\text{mol} / \text{ml}$ , ALT - 63.29 U/L, AST -77.73 U/L, AFP - 953.4.

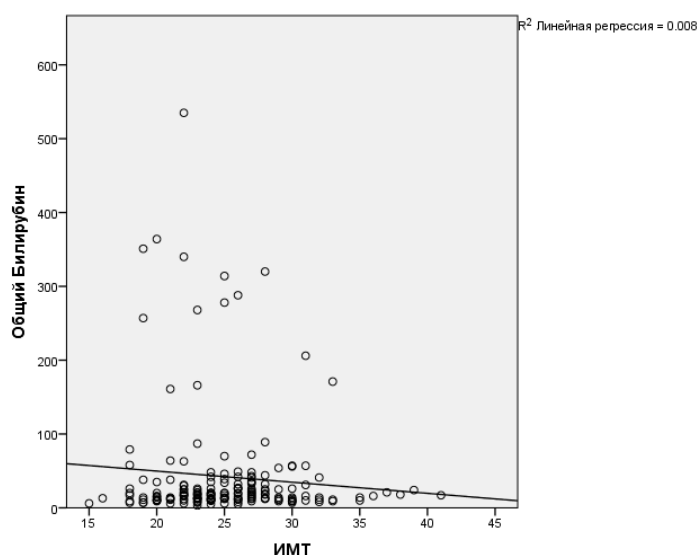


Fig. 1. Correlation between total bilirubin and BMI in patients with HCC.

Table 2. Division of patients on the MELD scale for assessing terminal stages of HCC at National Scientific Center of Surgery named after A.N. Syzganov.

CHILD	Frequency	%	p-value
A	122	66.7	P<0.001
B	53	29.0	
C	6	3.3	
Missed information	2	1.1	
Total	183	100.0	

The following surgical interventions were used at National Scientific Center of Surgery named after A.N. Syzganov: transarterial chemoembolization (TACE) in 81 cases (44.3%), radiofrequency ablation (RFA) in 6 cases (3.3%), embolization in 21 cases (11.5%), radical surgery was used in 23 cases (12.6%), conservative therapy without surgery was used in 52 cases (28.4%),  $\chi^2 = 12.07$ ;  $p < 0.001$ . Basically, RFA was used in patients with tumor sizes up to 3 cm and accessible localization. Since 2013 TACE have been used at National Scientific Center of Surgery named after A.N. Syzganov. The active use of this surgical intervention began in 2019.

Indications for TACE are the size of the tumor more than 3 cm in diameter, the absence of metastases to regional lymph nodes, distant metastases, portal invasion, and the patient's current state according to CTP (A-B class). Indications for RFA are a solitary nodule or several nodules not exceeding 3 cm in size, available localization and the patient's current state corresponding to the main class A according to CTP. Radical operations, such as liver resection, are the method of choice for patients with local resectable tumors; they were used mainly for solitary lesions not exceeding 2 cm in size and the patient's current state corresponding to CTP class A. Conservative treatment was used in patients with advanced stage C, D according to the BCLC classification, with invasion of the vessels or adjacent organs, and the presence of extrahepatic metastases. The criteria for determining the stage according to the Barcelona system are the prevalence of the tumor process, the functional state of the liver and the patient's current state according to the CTP.

The average BMI of women is 25.45 (5.390), men - 24.79 (3.453), ( $p = 0.321$ ). Patients with high total bilirubin levels had a lower body mass index (Fig. 1). The ratio of total bilirubin to BMI is associated with the development of HCC, leading to liver failure and cell necrosis.

The choice of treatment tactics for HCC depends on the size, location and number of lesions in the liver, indices for CTP, Milan criteria MELD, clinical guidelines for determining the stages of BCLC.

The patient's current state was assessed according to the CHILD-TURCOTTE-PUGH classifications and the MELD (NA) classification designed to assess the relative severity of the disease and the prognosis of life in patients with end-stage liver failure (awaiting liver transplantation) (Table 2-3).

Table 3. Division of patients on the CHILD-Pugh scale for measuring the severity of hepatocellular cancer at National Scientific Center of Surgery named after A.N. Syzganov.

MELD (NA)	Frequency	%	p-value
0-10	154	84.2	P<0.001
11-20	22	12.0	
21-30	7	3.8	
Total	183	100.0	

**Discussion.** According to our research, mainly HCC occurs in men, which is confirmed by statistical data from foreign sources with a male to female ratio of 2.4: 1 worldwide [9]. Due to the reasons for the development of HCC, hepatitis B, C was 65%, which is close to the data of foreign literature, where hepatitis B, C and liver cirrhosis were observed in 80% of cases [24].

TACE began to be used in 2013 at National Scientific Center of Surgery named after A.N. Syzganov, while in Japan the results of the effectiveness of TACE were published in the early 90s of the XX century [10] [12]. TACE is carried out for the first six months once every 2 months, for the second six months once every 3 months, then once every six months. According to the clinical protocol for the diagnosis and treatment of HCC, TACE is recommended for patients with stage B according to the Barcelona (hepatocellular) liver cancer (BCLC) staging system. Late treatment and detection of patients with HCC and the lack of technology in other regions leads to ineffectiveness of minimally invasive and radical surgeries.

**Conclusion.** The average bed-days for the clinical-cost groups diagnosed with HCC for 2012-2020 was 12 bed-days at National Scientific Center of Surgery named after A.N. Syzganov. The study revealed a correlation between BMI and the level of bilirubin associated with the development of HCC and subsequent cell necrosis.

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