ANNOTATION

Dissertation by Serikuly Yerbol, titled "Epidemiology of Hepatocellular Carcinoma in Kazakhstan" is submitted in the requirements for the degree of Doctor of Philosophy (PhD) in the specialty 8D10101 – "Public Health"

Relevance of the Research Topic

Hepatocellular carcinoma (HCC) is the most common form of primary malignant liver neoplasm [1]. It ranks sixth in frequency among all registered cancer cases and accounts for 95% of all hepatocellular, biliary, and mesodermal tumors in humans. HCC constitutes about 85% of all malignant liver tumors, whereas cholangiocarcinoma (CCA) occurs in 5–10% of cases [2].
HCC remains one of the most significant medical and social problems in the Republic of Kazakhstan. From 2013 to 2017, the incidence increased to 5.5 cases per 100,000 population, while mortality remained high—approximately 1,000 people die annually from this disease. In 2017, 82.3% of HCC patients died within the first year after diagnosis, with a five-year survival rate of only 23.7%.
On average, HCC mortality decreased by 0.84% per year over the past decade, and the absolute number of deaths decreased by 8% in 2017 compared to 2007. However, the five-year survival rate remains low, not exceeding 18%, with a postoperative recurrence rate of up to 50%.
Analyzing data on HCC incidence and mortality is crucial for assessing the epidemiological situation in Kazakhstan and developing effective measures for HCC prevention and diagnosis [6].
The main scientific directions of this dissertation include research aimed at improving the organization of medical care for HCC patients and developing effective diagnostic and treatment methods for this malignant neoplasm. A thorough study of HCC may contribute to improving prognosis and reducing mortality from this disease.

The aim of this dissertation research is to study the epidemiological characteristics of hepatocellular carcinoma in Kazakhstan and to develop measures for prevention, early detection, and reduction of HCC mortality.

Research Tasks:

1. To study the incidence, including gender and regional characteristics, and mortality from hepatocellular carcinoma in Kazakhstan for the period 2012–2021.
2. To assess the treatment outcomes of HCC patients, including survival rates, recurrence frequency, and the effectiveness of therapeutic approaches, as well as to establish the relationship of these outcomes with risk factors.
3. To evaluate the effectiveness of HCC diagnostic and treatment methods based on data from medical institutions in Kazakhstan and the results of surveys of medical professionals.
4. To forecast the incidence and mortality of HCC in Kazakhstan up to 2027, considering gender and regional differences.
5. To develop a prevention and mortality reduction model for hepatocellular carcinoma in Kazakhstan, considering regional risk factors and aimed at improving disease detection and diagnosis.

Research Objects: Patients with liver cirrhosis of various etiologies and HCC undergoing outpatient and inpatient treatment in Kazakhstan.
Research Subject: Patients with hepatocellular carcinoma.

Research Methodology
Study Design:

- Retrospective Analysis – Examination of outcomes from previous years.
- Sociological Analysis – Cross-sectional study of patients with hepatocellular carcinoma (HCC) using a descriptive assessment approach.

Research Methods:

1. Information-analytical method
2. Sociological survey
3. Statistical data processing

Various activities were conducted to achieve the research objectives, using specific methods for each segment (research program):

1. Literature Review on the topic of "Epidemiology of Hepatocellular Carcinoma" using databases such as Cochrane Library, PubMed, Medline Complete, Wiley Online Library, Springer Link, Google Scholar, and eLibrary.
2. Monitoring of primary incidence of hepatocellular carcinoma across the regions of the Republic of Kazakhstan from 2012 to 2021. During this period, 7,072 patients were registered.
3. Analysis of the distribution of official HCC incidence indicators by age, gender, and ethnicity across the regions of Kazakhstan from 2012 to 2021.
4. Analysis of treatment outcomes of 185 patients with hepatocellular carcinoma treated at the A.N. Syzganov National Scientific Center of Surgery.
5. Survey of specialists to identify challenges in the diagnosis, treatment, and rehabilitation of hepatocellular carcinoma patients. The number of respondents was 156.
6. Analysis of quality of life and physical activity levels in HCC patients using the International Physical Activity Questionnaire (IPAQ), with a sample size of 27 patients.
7. Predictive assessment of key hepatocellular carcinoma indicators in Kazakhstan up to 2027.

Provisions presented for defense

1. The regions of the Republic of Kazakhstan with the highest incidence of hepatocellular carcinoma among the adult population for the period 2012–2021 were identified, including the cities of Astana, Almaty and Shymkent, where stable growth trends were noted. It was found that the age peak in incidence occurs in men over 61 years of age and women over 76 years of age, while men are 2–3 times more likely to suffer from HCC. These data can serve as a basis for developing regional programs aimed at reducing morbidity by strengthening prevention and early diagnosis.
2. The analysis of inpatients diagnosed with HCC, conducted at the A.N. Syzganov National Research Center of Surgery, included an assessment of data on age, gender, alpha-fetoprotein level, and the treatment methods used. The approaches used included transarterial chemoembolization, radiofrequency ablation, liver resection and liver transplantation. The study results highlight the importance of a multidisciplinary approach to treatment, noting a significant improvement in survival and prognosis in patients who underwent liver transplantation, especially with long-term follow-up. An analysis of inpatients with RCC at the Syzganov National Research Center of Surgery revealed that patients who underwent liver transplantation demonstrate the most significant improvement in survival and long-term prognosis, especially with a multidisciplinary approach. It has also been noted that the use of treatment methods such as transarterial chemoembolization, radiofrequency ablation, and liver resection improves treatment outcomes in patients with localized HCC.
3. The analysis of key problems of diagnostics and treatment of RCC was conducted based on a survey of specialists. The need for unification of classifications used for diagnosis was

revealed, since the variety of methods affects the accuracy of diagnosis and the choice of adequate treatment. The data obtained made it possible to propose standardized approaches to diagnosis and treatment based on international recommendations.

4. A study of data on physical activity and quality of life in patients treated for RCC showed that the restoration of physical activity after therapy is directly associated with an improvement in quality of life. Factors influencing these indicators were also identified, including the patient's age, stage of the disease, type of treatment, and degree of rehabilitation. The results can be used to develop individual rehabilitation programs and monitor patients in the post-therapeutic period.

5. A forecast of the growth of morbidity and mortality from RCC in Kazakhstan until 2027 was compiled based on the epidemiological model of O. V. Baroyan and L. A. Rvachev. The forecast shows significant differences by gender, age and region. Those at greatest risk are men and those over 61 years of age, with an expected incidence rate of up to 260 cases per 100,000 men and 55 cases per 100,000 among those over 76 years of age. The cities of Astana, Almaty and Shymkent have the highest incidence and mortality rates, which highlights the need to strengthen prevention programs, early diagnosis, treatment and the development of regional strategies to control the disease.

Scientific novelty

For the first time in the Republic of Kazakhstan:

1. A comprehensive analysis of hepatocellular carcinoma (HCC) incidence and mortality in Kazakhstan from 2012 to 2021 has been conducted, allowing for the identification of key regional, gender, and age-related factors influencing the epidemiological profile of the disease. The study revealed a high incidence of HCC in major cities (Astana, Almaty, Shymkent), a significant predominance in men, and a high risk among individuals over the age of 60.

2. Diagnostic and therapeutic measures for HCC were analyzed through a survey of medical professionals, enabling the identification of key areas for improving medical care and addressing current challenges in diagnosis and treatment. The survey results highlighted the need for standardizing diagnostic algorithms, enhancing physician training, improving access to early screening, and optimizing patient referral pathways.

3. A forecast model for HCC incidence and mortality in Kazakhstan up to 2027 was developed**,** incorporating regional risk factors and demographic characteristics. This scientific projection provides a basis for targeted preventive strategies to reduce mortality rates and improve early detection.

4. A model of recommendations for optimizing preventive measures aimed at reducing HCC incidence and mortality in Kazakhstan was developed**,** offering a systematic and structured approach to improving prevention and treatment at the national healthcare system level. This model will contribute to more effective disease control and better patient outcomes.

Main Results

During the data analysis covering the period from January 2012 to December 2021, 7,072 cases of RCC were registered in the Republic of Kazakhstan based on data from the Unified National Statistical Database. The incidence rate of RCC was calculated for each region of Kazakhstan, as well as for the cities of Astana, Almaty, and Shymkent.

The overall incidence rate of RCC in Kazakhstan increased from 0.06 cases per 100,000 population to 7.53 cases per 100,000 population ($R^2 = 0.8261$, $P = 0.001$), with an average annual increase of 5.7%. A steady upward trend was observed from 2012 to 2021. In 2012, the incidence rate was 4.8 cases per 100,000 population, increasing to 5.7 cases in 2015, which corresponds to a growth of 5.56%. In 2017, the incidence rate reached 6.4 cases (+4.92%), rising to 6.8 cases in 2018 (+6.25%), 7.2 cases in 2019 (+5.88%), 7.4 cases in 2020 (+2.78%), and peaking at 7.53 cases per 100,000 population in 2021 (+1.76%). The highest incidence rates were recorded in the cities of national significance: Astana, Almaty, and Shymkent, while the lowest rates were observed in the Akmola region. These findings emphasize the need to strengthen preventive and diagnostic measures, considering regional characteristics. Notably, the highest incidence rates were recorded in three cities of national significance: Astana, Almaty, and Shymkent, while the lowest rates were

observed in the Akmola region. In terms of age, the highest incidence of RCC was found among the elderly, whereas the incidence rate was lower among individuals under 20 years of age. In terms of gender, it was also established that, in general, men have a higher incidence rate compared to women, which corresponds to international research data.

It should be noted that over the studied decade, the mortality rate from RCC remained relatively stable, ranking 10th among oncological diseases in Kazakhstan. An analysis of mortality trends showed that during the study period, mortality decreased by an average of 1.4% per year. In 2021, the absolute number of deaths from RCC decreased by 14.0% compared to 2012. However, despite the decline in mortality, the high incidence rate of RCC remains a significant public health issue, necessitating continued efforts for its control and prevention.

When studying the epidemiological aspects of RCC, comorbidities and risk factors play a crucial role, including metabolic syndrome, obesity, liver cirrhosis, diabetes mellitus, alcohol abuse, smoking, and viral hepatitis B and C. However, in Kazakhstan, data on such diseases are often recorded under different ICD codes, making their integration and comprehensive analysis challenging. The analysis of epidemiological data from 2012 to 2021 shows a decrease in the incidence of viral hepatitis B (HBV) by 44.8% and hepatitis C (HCV) by 35.8%. In 2012, the incidence of HBV was 88.7 per 100,000 population, and HCV was 77.9. The lowest values were recorded in 2020: HBV—47, HCV—42.7. However, in 2021, a slight increase was observed (HBV—49, HCV—50).

Between January 2017 and August 2023, the JSC "National Scientific Center of Surgery named after A.N. Syzganov" provided specialized treatment to 185 patients suffering from hepatocellular carcinoma. Among them, 14 patients received medical treatment, 14 patients underwent liver resection, 118 patients underwent transarterial chemoembolization, 14 patients received radiofrequency liver ablation, and 18 patients underwent liver transplantation. By analyzing this sample of 185 patients, we examined parameters such as age, gender, AFP levels, presence of liver cirrhosis, and outcomes, including mortality. Our goal was to gain a deeper understanding of the characteristics and factors influencing treatment outcomes in these patients.

Data analysis showed that overall patient survival after liver transplantation was high, reaching 72.9% over 3,000 days (approximately eight years). Among patients with RCC who underwent liver transplantation, survival reached 71.9% over the study period. The one-year survival rate after transplantation in this group was 83.3%, demonstrating the high effectiveness of this treatment method. For comparison, in patients who did not undergo transarterial chemoembolization (TACE), the one-year survival rate was significantly lower at 60.2%. The group of patients who did not undergo TACE showed a significant decline in survival, with only 21.5% surviving in the second and third years. Meanwhile, patients who received liver transplants had a much higher survival rate of approximately 59.5% over this period. Liver transplantation can significantly improve prognosis for this category of patients, especially in the long term. This analysis provides valuable information for clinicians and researchers evaluating the effectiveness of hepatocellular carcinoma treatment.

The data of 185 patients diagnosed with RCC who were treated at the A.N. Syzganov National Research Medical Center were analyzed. The most common conditions among patients were viral hepatitis B and C, with HBV detected in 51.4% of cases, HCV in 36.8%, and HBV-HCV coinfection in 8.1%, while 3.8% of cases had a non-viral etiology. Chronic alcoholism was recorded in 38.9% of patients, with 24.3% of them also having viral hepatitis, significantly increasing the risk of RCC progression. Additionally, 36.8% of patients were active smokers, and 27% had a combination of smoking, obesity, and alcohol consumption, which exacerbates the risk of developing cancer. Obesity (BMI >30) was identified in 22.7% of patients, while metabolic syndrome or NAFLD was reported in 16.2%. These conditions are associated with chronic inflammation and metabolic disorders, which in turn increase the risk of liver cancer. The combination of risk factors, such as obesity, alcoholism, smoking, and viral hepatitis B and C, plays a significant role in accelerating cirrhosis progression and the development of RCC.

The results of a sociological study conducted among medical professionals demonstrate a variety of approaches and practices in the diagnosis and treatment of hepatocellular carcinoma. Data analysis revealed the absence of a unified treatment standard for this disease across different regions of Kazakhstan, emphasizing the need to develop clear and scientifically grounded guidelines. This will improve the quality of medical care for RCC patients, enhance diagnostic accuracy, and optimize treatment strategies.

As a leading medical institution, the A.N. Syzganov National Research Center sees this information as a foundation for reviewing and improving the standards for diagnosing and treating RCC in the Republic of Kazakhstan. This is a critical area of work that could contribute to optimizing patient care and ensuring more effective treatment of this disease. A detailed study of the diverse medical practices used by physicians can serve as a basis for developing updated standards and recommendations in the field of diagnosis and treatment. This, in turn, will create more standardized and evidence-based approaches to treatment, improving the quality of healthcare and treatment outcomes for patients in Kazakhstan.

The results of a comparative analysis of physical activity in 27 patients who underwent various treatment methods using the EORTC QLQ-C30 questionnaire revealed significant differences in symptom intensity affecting patients' physical activity. Effective symptom management and physical activity support play a crucial role in improving patients' quality of life. Initially, the average level of physical activity declined due to treatment but increased after four weeks. Patients generally assessed their overall health and quality of life optimistically, despite experiencing some symptoms. Most responses fell in the middle of the scale, indicating relative stability and a moderate perception of their condition. This data can help guide patient adaptation and support during treatment and recovery.

In the chapter on predictive estimates of key indicators for hepatocellular carcinoma in Kazakhstan, an analysis and forecasting of morbidity and mortality from RCC in Kazakhstan until 2027 were performed based on the epidemiological model of Baroyan O.V. and Rvachev L.A. The forecast was developed considering demographic factors such as gender, age, and regional differences. Men remain at a higher risk of RCC, with a projected incidence rate of 60 cases per 100,000 population, compared to 40 cases per 100,000 among women. Mortality among men is also expected to be higher—35 cases per 100,000 compared to 20 cases per 100,000 among women. This is attributed to a higher prevalence of harmful habits (alcohol, smoking) and the greater prevalence of viral hepatitis among men. The most significant increase in morbidity is observed among individuals over the age of 61. In the group of people over 76 years old, the incidence rate is projected to reach 55 cases per 100,000, with a mortality rate of 50 cases per 100,000. In younger age groups, such as 18–30 years old, morbidity and mortality remain low—5 and 2 cases per 100,000 people, respectively. This is due to a lower prevalence of chronic liver diseases at a young age.

The highest risk of RCC incidence and mortality is projected in the regions of Almaty, Shymkent, and Astana. In these regions, the incidence rates are expected to be 55, 50, and 48 cases per 100,000 population, respectively, while the mortality rates are projected to be 30, 28, and 27 cases per 100,000 population. In the regions of Northern and Eastern Kazakhstan, lower incidence rates (ranging from 25 to 30 cases per 100,000 population) and mortality rates (ranging from 18 to 20 cases per 100,000 population) are anticipated. These regions are less affected by risk factors such as chronic viral infections and liver cirrhosis.

Thus, the projected data indicate significant differences in RCC incidence and mortality rates based on gender, age, and region of residence. Men and individuals over the age of 61 belong to the high-risk group, necessitating the development of targeted prevention and screening programs. It is essential to focus on implementing early liver disease detection measures, especially in regions with a high prevalence of viral hepatitis and cirrhosis.

Improving RCC prevention and reducing mortality in Kazakhstan requires a comprehensive approach, including the implementation of effective screening programs aimed at the early detection of risk factors and precursor diseases of RCC. An essential element is public

awareness of the importance of preventive measures and state support, which will not only improve access to modern medical technologies but also promote research in the field of liver cancer pathogenesis. The introduction of screening for chronic viral hepatitis B and C, liver cirrhosis, and other diseases predisposing to RCC will significantly enhance diagnostic results, enable early identification of patients at initial disease stages, and improve treatment effectiveness, ultimately reducing cancer-related mortality. The experience of countries with high RCC incidence rates, such as China, Japan, and the United States, confirms the importance of regular screening using ultrasound and alpha-fetoprotein measurement for patients with chronic hepatitis B and C and liver cirrhosis. The application of international recommendations and their adaptation to Kazakhstan's national conditions will allow for the development of an efficient screening model accessible at all levels of healthcare, including remote regions.

The early detection and management algorithm for patients at risk of RCC includes screening for risk factors, in-depth diagnostics, selection of treatment strategies, and dynamic follow-up, which will significantly improve disease diagnosis and treatment, prevent its progression, and reduce RCC-related mortality in the country.

The developed RCC diagnostic recommendations and algorithms represent a key step toward improving prevention and reducing mortality from RCC in Kazakhstan. These measures contribute to early detection and timely treatment, leading to lower mortality rates and improved quality of life for patients.

Practical Significance of the Obtained Results

1. Studying international experience has enabled the implementation of advanced diagnostic and treatment methods for RCC patients, which can significantly improve treatment outcomes and quality of life.
2. Analyzing the dynamics of morbidity and mortality has allowed for the identification of regional, gender, and age groups at the highest risk and has helped tailor medical strategies to current trends.
3. Forecasting RCC incidence and mortality will help assess future healthcare system burdens, ensuring timely resource allocation, development of preventive measures, and effective planning of medical services for disease control.
4. The newly obtained scientific data will provide practical recommendations for improving the healthcare system, including optimizing diagnostics, increasing accessibility to screening programs and early treatment, as well as reducing morbidity, mortality, and the economic burden associated with hepatocellular carcinoma (HCC) in Kazakhstan.

Personal contribution of a doctoral student

The doctoral candidate, with guidance from scientific consultants, independently conducted all stages of the research, including comprehensive data analysis, statistical processing, interpretation of the findings, and formulation of well-founded conclusions.

Conclusions

1. Between 2012 and 2021, a steady increase in RCC incidence was observed in Kazakhstan, rising from 0.06 to 7.53 cases per 100,000 population *($R^2 = 0.8261$, $P = 0.001$)*, indicating a significant spread of the disease. However, RCC mortality has decreased by an average of 1.4% per year, with a 14% reduction in 2021 compared to 2012, reflecting improved diagnostics and treatment.
2. RCC incidence is higher among men (65%) compared to women (35%). The highest incidence is recorded in the 40–59 age group (45%), with an average patient age of 61 years.
3. An analysis of treatment outcomes for 185 patients showed that liver transplantation demonstrates high survival rates (72.9% over 3,000 days, 83.3% in the first year). Among patients who did not undergo transarterial chemoembolization, the one-year survival rate was 60.2%, dropping to 21.5% in subsequent years.
4. Projections indicate that by 2027, RCC incidence may reach 60 cases per 100,000 among men and 40 cases per 100,000 among women, with the highest growth expected in regions with high prevalence of viral hepatitis and liver cirrhosis.

5. The developed RCC prevention model includes screening for high-risk groups (hepatitis B and C, cirrhosis, metabolic disorders), which will enhance early diagnosis and treatment effectiveness.

Presentation and Discussion of Results

The dissertation research materials were presented and discussed at the following international congresses, conferences, and forums:

- International Congress "Surgery: Yesterday, Today, Tomorrow" (Almaty, 2020)
- International Congress "Current Issues in Surgery and Transplantation" (Almaty, 2022)
- World Congress of the International Association of Surgeons, Gastroenterologists, and Oncologists (Ankara, Turkey, 2022)
- International Forum "Asfen Forum: New Generation – 2023" (Almaty, 2023)

Publications

Based on the dissertation research, 5 articles in scientific and practical journals recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Science and Higher Education. These include Oncology and Radiology of Kazakhstan (1 article), Science&Healthcare (2 articles). 2 articles were published in journals indexed by Scopus: 1 article in the «New Armenian Medical Journal» (Cite Score – 0.4 percentile 19), 1 article in the «Eurasian Journal of Medicine and Oncology» (Cite Score– 5,6, percentile medicine – 70, percentile oncology 64).

Implementation of Research Results

Act of implementation of the scientific research "The Role of PIVKA-II Tumor Marker in Hepatocellular Carcinoma" – JSC "National Scientific Center of Surgery named after A.N. Syzganov".

Practical Recommendations

1. At the level of the Ministry of Health: Develop regulatory and legal acts and targeted programs to improve RCC diagnosis, treatment, and prevention, as well as strengthen the technical and material base of medical institutions to ensure access to advanced technologies.
2. At the level of regional healthcare management: Establish specialized regional centers for RCC diagnosis and treatment, equip them with modern technology, organize additional professional training programs for medical specialists, and implement effective preventive programs, including morbidity monitoring.
3. At the level of specialized medical care: Develop and implement clinical protocols and treatment standards for RCC, incorporating new diagnostic and treatment technologies.
4. At the level of primary healthcare: Conduct screening programs for high-risk patients, including those with chronic liver diseases *(hepatitis B and C, cirrhosis, NAFLD)*, a family history of the disease, or alcohol abuse. These programs should include regular ultrasound examinations, AFP laboratory monitoring, the use of modern diagnostic methods *(elastography, CT, MRI)*, as well as public awareness campaigns on the importance of early RCC detection.

Volume and Structure of the Dissertation

The dissertation consists of 145 pages of text, 17 tables, and 39 figures, formatted according to established academic standards. The bibliography includes 246 sources *(95.48% in English, 4.07% in Russian, 0.45% in Kazakh)*.