Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: March 31, 2024

Citation: Ivanikov, I., O., et al., 2024. Trends and insights in liver cancer from a single institution study from Main Medical Directorate of the Russian Presidential Administration over 35 years (1981-2015). Medical Research Archives, [online] 12(3). https://doi.org/10.18103/mra.v12i3.5238

DOI: https://doi.org/10.18103/mra.v12i3.5238

ISSN: 2375-1924

RESEARCH ARTICLE

Trends and insights in liver cancer from a single institution study from Main Medical Directorate of the Russian Presidential Administration over 35 years (1981-2015)

Igor Olegovich Ivanikov[1], Mariia Evgenevna Zharova[2*], Natalya Nikolaevna Vinogradova[3], Julia Vasilevna Grigoreva[4], Dmitry Pavlovich Ananyev[5], Oksana Valentinovna Kryuchkova[6], Natalya Vladimirovna Efremova[7], Elena Vladimirovna Myasnikova[8], Evgeniy Leonidovich Nikonov[9]

[1]Leading Specialist in Gastroenterology Central Clinical Hospital of Russian Federation Presidential Administration (Moscow, Russia) Professor at Pirogov Russian National Research Medical University (Moscow, Russia)
[2]Technician at Pirogov Russian National Research Medical University (Moscow, Russia) – Corresponding Author
[3]MD at Cancer Registry Central Clinical Hospital of Russian Federation Presidential Administration (Moscow, Russia)
[4]Head of the Gastroenterology Department Central Clinical Hospital of Russian Federation Presidential Administration (Moscow, Russia) Assistant Professor at Pirogov Russian National Research Medical University (Moscow, Russia)
[5]Deputy Chief Physician of Surgery Central Clinical Hospital of Russian Federation Presidential Administration (Moscow, Russia)
[6]Head of Diagnostic Radiology Central Clinical Hospital of Russian Federation Presidential Administration (Moscow, Russia)
[7]Head of the 3rd Internal Medicine Department Central Clinical Hospital of Russian Federation Presidential Administration (Moscow, Russia)
[8]Head of the 2nd Internal Medicine Department Central Clinical Hospital of Russian Federation Presidential Administration (Moscow, Russia)
[9]Head of the Gastroenterology Department Pirogov Russian National Research Medical University (Moscow, Russia)

*zharowa.mariya@yandex.ru

ABSTRACT

Background: This study aims to analyze liver and bile duct tumors over 35 years in the population of the Main Medical Directorate of the Russian Presidential Administration with a view to identifying epidemiological trends and their possible causes.

Objective: to assess incidence and mortality rates, examine gender-specific patterns, describe histological picture, and evaluate the effectiveness of routine screenings on patient outcomes.

Methods: Retrospective data from the cancer registry of the Main Medical Directorate of the Russian Presidential Administration for 1981-2015 were analyzed. Incidence and mortality rates were assessed with regard to gender distribution, histological confirmation, and survival rates. Standardized indicators were compared with national and international benchmarks.

Results: For a period of 35 years, 227 cases of primary liver and bile duct tumors (ICD-C22) were identified. Of these, males made up 66% (149 cases), whereas for females it was 34% (78 cases). The average age of patients was 71.6 ± 11.4 years. The study reveals a consistent decrease in morbidity and mortality rates for both men and women within the studied population, contrasting with national trends. Study showed 20% increase in the 3-year survival rate for patients diagnosed during routine screenings compared to those presenting with symptoms (p=0.0001). Hepatocellular carcinoma was the most common type of liver cancer in the population. Surgical intervention was utilized in 16% of cases, while chemotherapy was used in 25%. Symptomatic treatment constituted a significant proportion of the treatment modalities.

Conclusion: Our study provides insights into promising epidemiological trends in liver and bile duct tumors. Factors contributing to favorable outcomes include immunization, antiviral treatments, and lower alcohol consumption. Gender-specific patterns highlight the necessity for tailored screening. This study supports the adoption of regular screening efforts to boost early detection rates and enhance patient outcomes. These findings provide significant clinical implications and pave the way for future research.

Keywords: liver neoplasms; bile duct neoplasms; incidence; survival rate; registries.

Introduction

Liver cancer is malignant neoplasms with high lethality and low median survival rates in the majority of countries worldwide[1].

Liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020. The rates of both incidence and mortality are 2 to 3 times higher among men than among women in most countries. Liver cancer ranks fifth in terms of global incidence and second in terms of mortality for men. Incidence rates among men are 2.4-fold greater in transitioned countries with the disease being the most common cancer in 11 geographically diverse countries in Eastern Asia, South-Eastern Asia, and Northern and Western Africa[1].

The geographical distribution of liver cancer incidence and mortality reveals significant variability, indicative of the complex interplay of genetic, environmental, and lifestyle factors contributing to its etiology. In particular, regions such as Eastern Asia, South-Eastern Asia, and parts of Africa exhibit high incidence rates, underscoring the influence of regional risk factors and healthcare infrastructure on disease prevalence and outcome[1–6].

In Russia in 2021, the incidence of liver cancer among men was 8.23 per 100,000 population, while among women it was 4.84 cases; the mortality rates were 9.42 and 5.80 respectively. It is noteworthy to highlight interregional variability in the incidence and mortality rates, with higher rates observed in the Republics of Sakha, Tuva, Kalmykia, Buryatia, Altai, the Chukotka Autonomous Okrug, as well as in the Tomsk Oblast [7]. Higher mortality rates compared to incidence rates suggest underreporting of new cases, which observed in Russia but also in other developing countries[8,9].

The etiological landscape of liver cancer is diverse, with chronic infections of hepatitis B (HBV) and hepatitis C (HCV) viruses, exposure to aflatoxins, excessive alcohol consumption, obesity, type 2 diabetes, and smoking being predominant risk factors[10–16]. The major risk factors vary from region to region, with chronic HBV infection and aflatoxin exposure being key determinants in high-risk areas such as China, the Republic of Korea, and sub-Saharan Africa[1].

Incidence and mortality rates of liver cancer have decreased in many high-risk countries in Eastern and South-Eastern Asia, including China, Taiwan, the Republic of Korea, and the Philippines, since the late 1970s and in Japan since the 1990s[1]. Rates in Italy have also declined since 1995, likely reflecting declines in the population seroprevalence of HBV and HCV as well as a reduction in aflatoxin exposure[1].

Vaccination against HBV has been a major public health success, dramatically reducing the prevalence of HBV infection and the incidence of hepatocellular carcinoma (HCC) in high-risk countries in Eastern Asia[1,17,18].

Viral hepatitis used to be the primary cause of chronic liver disease (CLD) for many years[19]. However, access to HBV vaccination and effective treatment with direct-acting antiviral therapies (DAAs) for HCV has led to improvements in CLD trends. This has resulted in a decrease in mortality from CLD over the past 30 years, dropping from 21 to 16.5 per 100,000 population between 1990 and 2017[20,21]. Despite these positive changes, mathematical modeling studies predict an increase in the burden of CLD over the next

decade, particularly noting a significant rise in decompensated cirrhosis and NAFLD-related deaths. Other factors contributing to development of CLD will include alcohol consumption and intravenous drug use (IVDU)[19]. That means that prevalence of liver cancer might rise due to these causes.

The decrease in incidence and mortality rates in certain high-risk countries signifies progress; however, the global burden of liver cancer continues to grow, accentuating the need for enhanced surveillance, early detection, and comprehensive management strategies. The interplay of genetic predispositions, environmental exposures, and lifestyle choices in liver cancer etiology necessitates a multifaceted approach to prevention, screening, and treatment, particularly in high-risk populations.

As we delve deeper into the multifactorial dimensions of liver cancer, it is imperative for the scientific and medical communities to foster a deeper understanding of the disease's epidemiology, risk factors, and evolving trends. This knowledge is crucial for developing effective public health strategies, optimizing clinical management, and ultimately, reducing the global impact of liver cancer.

Objective

To assess incidence and mortality rates, examine gender-specific patterns, describe histological picture, and evaluate the effectiveness of routine screenings on patient outcomes based on cancer registry of Main Medical Directorate of the Russian Presidential Administration from 1981 to 2015.

Material and methods

This is a retrospective cohort study of liver cancer cases from cancer registry of Main Medical Directorate of the Russian Presidential Administration.

Adult patients over the age of 18 years who were diagnosed with the biliary tract and primary liver tumors (ICD-C22) between 1981 and 2015 were included.

To facilitate a comprehensive longitudinal analysis, the study period was segmented into seven consecutive five-year intervals: 1981–1985, 1986–1990, 1991–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2015. This stratification allowed for the observation of trends over time and the evaluation of the impact of advancements in medical interventions and public health policies on the epidemiology of liver cancer.

The rationale for selecting this specific time frame was dictated by the completeness and reliability of the dataset, which contains all the essential variables required for an exhaustive analysis. Data from subsequent years were excluded due to the absence of critical information, necessitating a manual and therefore more time-consuming data retrieval process. Analysis of these later years is currently underway and will constitute the subject of a forthcoming article.

Exclusion criteria were applied to cases with incomplete data records, particularly those lacking information on cancer staging, treatment regimen, or outcome measures.

Demographic data encompassed gender and age at diagnosis, and these variables were cross tabulated with diagnostic methods employed, mortality rates, and morbidity outcomes. Diagnostic tests recorded in the

study ranged from imaging modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), to biopsy procedures and serological markers.

Data compilation and initial processing were conducted using Microsoft Excel, subsequent statistical analyses were carried out using Statistica 8 software.

Descriptive statistics were employed to characterize the study population, with categorical variables summarized as frequencies and percentages. Continuous variables were subjected to a normality test using the Shapiro-Wilk test, with results reported as mean values with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate to the data distribution.

Incidence and mortality rates were calculated per 100,000 population affiliated with the registry and were adjusted to the standardized population distribution for comparability with global rates as recommended by international epidemiological reporting standards.

Survival trends were evaluated using the Kaplan-Meier method, and survival curves were generated to provide a graphical representation of the survival probabilities over time. In this study, p-value of less than 0.05 was predetermined as the threshold for statistical significance. Comparative analyses were conducted only on complete case data; thus, records with missing data were excluded from these analyses to preserve the integrity of the statistical inferences.

Results

Over a 35-years in the cancer registry, 227 cases of primary liver and bile duct tumors (ICD-C22) were identified: 149 (66%) in males and 78 (34%) in females. The average age of the affected individuals was 71.6±11.4 years. The maximum age among those affected was 96 years, while the minimum was 41 years. This demographic information suggests that liver cancer predominantly affects older adults, a finding that has implications for healthcare resource allocation and screening strategies in aging populations.

Our study found that the postmortem morphological confirmation of liver cancer ranges from 64% to 75% during different periods. Autopsy data complements the study, bringing it to a total of 100%. HCC (hepatocellular carcinoma) is the primary and most frequently encountered form of liver cancer, while cholangiocarcinoma (CC), arising from intrahepatic bile duct cells, is less commonly diagnosed. Histological samples analysis showed a ratio of HCC to CC at 4:1. There has been a decrease in unspecified tumors and a notable increase in both HCC and CC proportions over time. Throughout this period, liver cancer accounts for approximately 1% among men and 0.6% among women within all neoplasm morbidity structure; within gastrointestinal tract neoplasms structure, it represents about 4.6% among men and 3% among women (Table 1,2).

Table 1. Percentage of Liver Cancer Cases among Newly Diagnosed Malignancies from Main Medical Directorate of the Russian Presidential Administration (1981—2015)

Year	Men		Women	
	Absolute number	%	Absolute number	%
1981—1985	2	0.2	1	0.1
1986—1990	21	1.7	6	0.5
1991—1995	36	2.1	16	1
1996—2000	21	1.1	14	0.7
2001—2005	21	1.0	14	0.7
2006—2010	32	1.1	18	0.7
2011—2015	16	0.5	9	0.3
1981—2015	149	1.1	78	0.6

Our investigation revealed the incidence and mortality rates of liver cancer per 100,000 population, with men consistently exhibiting higher rates than women throughout the 35 years. When comparing these figures to standardized rates based on world and Russian population data from 2016, our study found the incidence rates in our cohort to be slightly higher than the national average, while mortality rates were notably lower (Table 2).

Table 2. Incidence of Liver Cancer And Cancer-Related Mortality for The Period 1981—2015 from Main Medical Directorate of the Russian Presidential Administration (Per 100 000)

Period and Indicator	Incidence		Mortality	
	Men	Women	Men	Women
1981—1985	0.1	0.5	0.1	0
1986—1990	23.4	3.5	18.8	3.5
1991—1995	18.1	7.8	15.8	5.3
1996—2000	11.2	5.5	8.0	3.5
2001—2005	11.8	5.3	7.3	3.7
2006—2010	10.3	4.5	8.5	2.7
2011—2015	5.7	2.5	5.0	2.2
1981—2015	11.8	4.2	9.1	3.0
Standardized rate (World data)	6.2	2.8	3.7	1.2
Standardized rate (Russia), 2016	4.94	2.07	5.76	2.35

During two periods, from 1981 to 1985 and from 2011 to 2015, there was a high level of active liver cancer diagnostics during standard check-ups. These periods accounted for 67% and 49% respectively of all newly detected cases of liver cancer. Throughout the entire period, this indicator amounted to an overall average of 35% (Table 3).

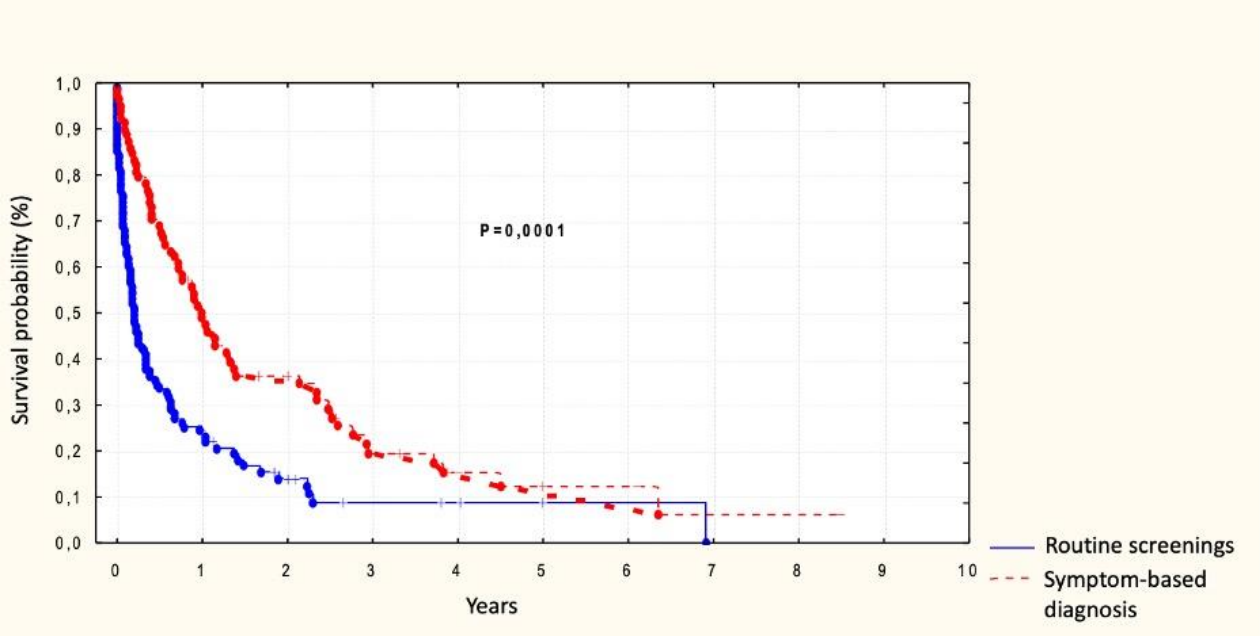
Table 3. Percentage of newly diagnosed patients with liver cancer for the period 1981—2015 during standard year check-ups (%)

Years	%
1981—1985	67
1986—1990	44
1991—1995	21
1996—2000	26
2001—2005	46
2006—2010	36
2011—2015	49
1981—2015	35

Note: In Russia, the share of active diagnostics was 7.0% (2017).

The importance of early detection was further reinforced by the survival analysis, which revealed that patients whose tumors were identified during routine check-ups had a 3-year survival rate of approximately 20%, a figure twice as high as those diagnosed following the presentation of symptoms, where the 3-year survival was around 10%. These statistically significant differences (p=0.0001) accentuate the life-saving potential of early diagnosis and screening programs (Figure 1).

Figure 1. Survival rates among liver cancer patients categorized by those diagnosed during routine screenings and those diagnosed based on symptoms.



Examining fatality rates within the first year of diagnosis, we found that mortality attributable to all causes and specifically to cancer progression varied across the different periods (Table 4). The overall fatality due to cancer progression stood at 61.5%, with a notable reduction to 51.6% in the last five-year period studied, compared to the national figure of 69.7% in 2017.

Table 4. Annual mortality from liver cancer in 1981—2015 (%)

Year	Cause of death (%)	
	All causes	Due to progression
1981—1985	100	50
1986—1990	73.7	73.7
1991—1995	83.0	83
1996—2000	74.4	74.4
2001—2005	59.9	57.9
2006—2010	71.7	71.7
2011—2015	51.6	51.6
1981—2015	69.9	61.5

As a treatment option surgical intervention used in 16% of cases, chemotherapy was utilized in 25% of cases, and symptomatic treatment constituted a larger proportion.

Finally, survival rates disaggregated by gender did not reveal a statistically significant difference (p=0.08), although women had a marginally higher 3-year survival rate of approximately 25% (Figure 2).

Figure 2. Survival rates among liver cancer patients categorized by gender.

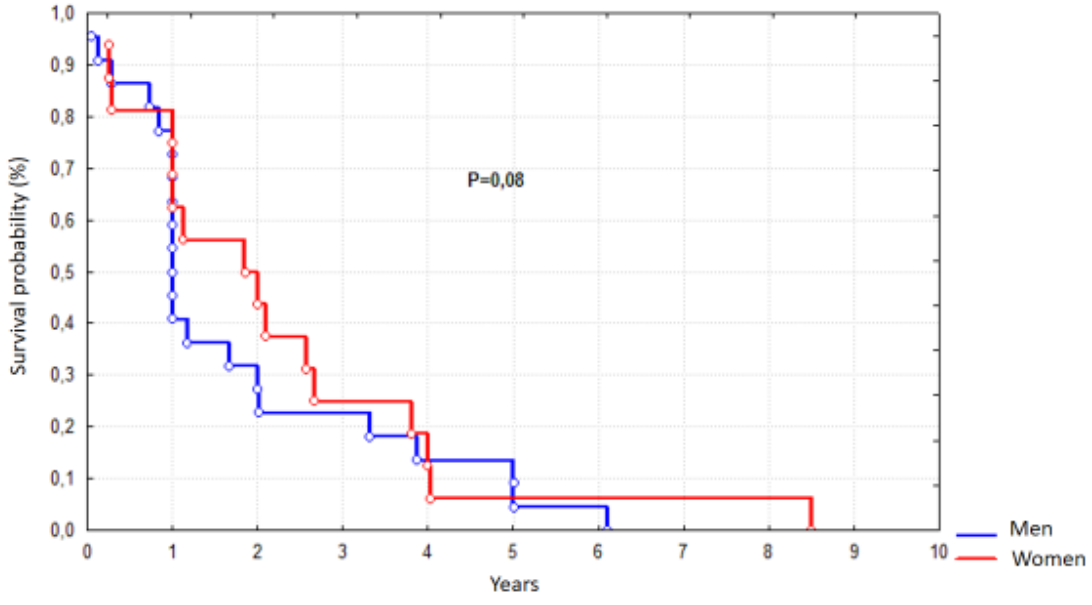


Fig.2

Discussion

Over the past 35 years, a thorough analysis has shown clear epidemiological patterns in liver and bile duct tumors.

Within the medical centers of Main Medical Directorate of the Russian Presidential Administration population, a downward trend in morbidity and mortality rates has been discerned for both men and women. It is noteworthy that the standardized indicators demonstrate a lower levels, comparable to European countries [1,11]. Increasing trends also were shown in studies from USA and Taiwan[22–24].

When compared to All-Russian trends incidence and mortality from liver cancer increasing over last two decades [7]. This contrast raises significant insights into potential factors contributing to these favorable outcomes. This discrepancy might be rooted in the particular sociopolitical dynamics of the region, including extensive hepatitis B vaccination efforts since 1998 and a robust antiviral treatment strategy for hepatitis C, which appear to have favorably impacted the epidemiology of liver cance[25–28]. These policies, alongside the global health priorities of the United Nations Sustainable Development Goals 2030[29].

Another factor that may contribute to lower levels of morbidity and mortality in our cohort is potentially lower alcohol consumption rates in our cohort compared to national averages. Decline in alcohol consumption since the 2000s, preceded by a peak in the early 1980s and a subsequent rise in the late 1980s and early 1990s, corresponds with shifts in CLD patterns in Russia. Given that alcohol abuse has been a leading cause of chronic liver disease in Russia, with the impact of alcohol-related liver diseases being most acute during the 1980s and 1990s, the observed epidemiological trends in liver cancer may, in part, reflect the subsequent public health responses and changing alcohol consumption patterns[30–33].

Beyond viral hepatitis and alcohol-induced liver disease, NAFLD has emerged as a significant contributor to the liver disease spectrum in Russia. With global prevalence rates of NAFLD reaching 59%[19], Russia has reported an alarming prevalence rate of over 27%[34] in certain adult cohorts. The interplay between NAFLD and metabolic syndrome components such as obesity and insulin resistance present a new frontier in the etiology of liver disease that warrants attention[35–37]. Considering the existing data and studies delineating the NAFLD progression to HCC[38,39], our cohort's lower morbidity and mortality rates may be influenced by the relatively recent emergence of NAFLD as a significant contributor to liver cancer etiology. It necessitates vigilance in monitoring, early diagnosis, and management strategies, considering its asymptomatic nature and potential to progress to advanced liver disease.

The evolution of the Russian healthcare system from the Semashko model, with a subsequent focus on primary care and modern healthcare reforms termed "optimization," underscores a period of transformation that may have influenced the management of liver cancer[40–42]. Such structural changes within the healthcare system could have had implications for the improved delivery of medical services and may reflect in the trends observed in our data.

There is a higher incidence among males, accounting for 66% of the identified cases,

this gender distribution was shown in other studies as well [1,7,43,44]. This gender disproportion highlights the necessity for customized screening and preventive measures, given the potential predisposition among males. Furthermore, the observed 34% incidence among females underscores the importance of gender-neutral awareness campaigns and comprehensive screening programs to ensure inclusive coverage. While gender-based differences in survival rates were observed, they were not statistically significant, suggesting a need for further exploration and understanding of nuanced factors influencing outcomes in both male and female patients.

Our data revealed a high rate of morphological confirmation of liver cancer. According to national data, the diagnosis of liver cancer is morphologically confirmed in 66.3% of cases, making it the second lowest among all types of cancers, with pancreatic cancers having a slightly lower confirmation rate at 64.1% [7]. Morphological confirmation of liver cancer predominantly indicated HCC, surpassing cholangiocarcinoma in incidence. This trend is consistent with Russian and international data [1,7,43,44]. The predominance of HCC, along with a lower frequency of CC and changing proportions of unspecified tumors, highlights the evolving histological landscape. The observed 4:1 ratio of HCC to CC calls for a nuanced approach in diagnostic protocols and therapeutic strategies that recognizes the distinct pathophysiological profiles of these tumor types.

Our study's main results indicate a 20% increase in the survival rate of patients diagnosed with liver cancer during routine screenings compared to symptom-based diagnosis. Notably, there were elevated rates of detection during routine check-ups from 1981 to 1985 and 2011 to 2015, suggesting the pivotal role of standardized screenings in early identification. Other studies have also shown that active screening, particularly in high-risk groups, can improve detection and survival rates [9,45,46]. These findings advocate for the enhancement and promotion of routine screening programs to augment early detection rates and potentially improve patient outcomes.

Our analysis of different treatment methods for high-risk cancer patients supports the idea that a combination of preventive measures and carefully chosen therapies are essential for successful management of this serious condition. It is within these parameters that we can anticipate positive outcomes from the use of advanced, more effective liver cancer treatments.

The study provides valuable insights for clinical practice and future research, but it also has limitations. The retrospective study design relies on historical data, making it challenging to establish causal relationships and account for changes in diagnostic and treatment approaches over time. Additionally, the use of data from a single medical institution may limit its external validity, failing to fully capture the diversity of patient populations and treatment approaches seen in broader multi-center studies. Despite its illuminating insights, caution should be taken when generalizing findings due to the acknowledged limitations of its retrospective design and single-center focus. Nonetheless, this research sets the stage for future investigations aimed at improving preventive measures, treatment strategies, and screening protocols for liver and bile duct tumors.

Conclusions

The comprehensive analysis of cancer registry with focus on liver cancer over a 35-year period offers valuable insights into their epidemiology, diagnostic trends, treatment modalities, and patient outcomes. The predominance of HCC over cholangiocarcinoma underscores the need for tailored diagnostic and therapeutic strategies. The study revealed shifting trends in tumor identification, with higher detection rates during standard check-ups, emphasizing the significance of routine screenings in early diagnosis and potentially improved outcomes.

Conflict of Interest:

The authors have no conflicts of interest to declare.

Funding:

None

Acknowledgements

None

ORCID Id:

1. Igor Olegovich Ivanikov- 0000-0001-6691-8306
2. Mariia Evgenevna Zharova- 0000-0002-8325-5927
3. Julia Vasilevna Grigoreva- 0000-0001-5335-7933
4. Dmitry Pavlovich Ananyev- 0000-0002-0494-4098
5. Oksana Valentinovna Kryuchkova- 0000-0001-6483-2074
6. Evgeniy Leonidovich Nikonov - 0000-0002-5231-711X

References:

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660

2. Jemal A, Center MM, DeSantis C, Ward EM. Global Patterns of Cancer Incidence and Mortality Rates and Trends. *Cancer Epidemiol Biomarkers Prev*. 2010;19(8):1893-1907. doi:10.1158/1055-9965.EPI-10-0437

3. Sharma R. Descriptive epidemiology of incidence and mortality of primary liver cancer in 185 countries: evidence from GLOBOCAN 2018. *Jpn J Clin Oncol*. 2020;50(12):1370-1379. doi:10.1093/jjco/hyaa130

4. Lin L, Yan L, Liu Y, Qu C, Ni J, Li H. The Burden and Trends of Primary Liver Cancer Caused by Specific Etiologies from 1990 to 2017 at the Global, Regional, National, Age, and Sex Level Results from the Global Burden of Disease Study 2017. *Liver Cancer*. 2020;9(5):563-582. doi:10.1159/000508568

5. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):589-604. doi:10.1038/s41575-019-0186-y

6. Venook AP, Papandreou C, Furuse J, Ladrón de Guevara L. The Incidence and Epidemiology of Hepatocellular Carcinoma: A Global and Regional Perspective. *Oncologist*. 2010;15(S4):5-13. doi:10.1634/theoncologist.2010-S4-05

7. Kaprin AD, Starinsky VV, Shakhzadova AO. Malignant Neoplasms in Russia in 2021 (Morbidity and Mortality). MNIOI named after. P.A. Herzen - branch of the Federal State Budgetary Institution "National Medical Research Center of Radiology" of the Ministry of Health of Russia; 2022. (In Russ.)

7. Petkau VV, Bessonova EN, Breder VV, Kartashov MV, Tarkhanov AA. Cause analysis of post-mortem diagnosis of hepatocellular carcinoma. *Dokazatel'naya Gastroenterol*. 2023;12(1):42. (In Russ.) doi:10.17116/dokgastro20231201142

9. Petkau VV, Bessonova EN, Breder VV, Anashkina MA. Preliminary findings of hepatocellular carcinoma screening in the at-risk population. *Dokazatel'naya Gastroenterol*. 2023;12(4):54. (In Russ.) doi:10.17116/dokgastro20231204154

10. Tsai WL, Chung RT. Viral hepatocarcinogenesis. *Oncogene*. 2010;29(16):2309-2324. doi:10.1038/onc.2010.36

11. Akinyemiju T, Abera S, Ahmed M, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level. *JAMA Oncol*. 2017;3(12):1683. doi:10.1001/jamaoncol.2017.3055

12. Hsu IC, Metcalf RA, Sun T, Welsh JA, Wang NJ, Harris CC. Mutational hot spot in the p53 gene in human hepatocellular carcinomas. *Nature*. 1991;350(6317):427-428. doi:10.1038/350427a0

13. Mancebo A, González–Diéguez ML, Cadahía V, et al. Annual Incidence of Hepatocellular Carcinoma Among Patients With Alcoholic Cirrhosis and Identification of Risk Groups. *Clin Gastroenterol Hepatol*. 2013;11(1):95-101. doi:10.1016/j.cgh.2012.09.007

14. Reddy KR, McLerran D, Marsh T, et al. Incidence and Risk Factors for Hepatocellular Carcinoma in Cirrhosis: The Multicenter

Hepatocellular Carcinoma Early Detection Strategy (HEDS) Study. *Gastroenterology*. 2023;165(4):1053-1063.e6. doi:10.1053/j.gastro.2023.06.027

15. Sohn W, Lee HW, Lee S, et al. Obesity and the risk of primary liver cancer: A systematic review and meta-analysis. *Clin Mol Hepatol*. 2021;27(1):157-174. doi:10.3350/cmh.2020.0176

16. Zhang H, Du X, Dong H, et al. Risk factors and predictive nomograms for early death of patients with advanced hepatocellular carcinoma: a large retrospective study based on the SEER database. *BMC Gastroenterol*. 2022;22(1):348. doi:10.1186/s12876-022-02424-5

17. Chang MH, You SL, Chen CJ, et al. Decreased Incidence of Hepatocellular Carcinoma in Hepatitis B Vaccinees: A 20-Year Follow-up Study. *JNCI J Natl Cancer Inst*. 2009;101(19):1348-1355. doi:10.1093/jnci/djp288

18. Chang MH, You SL, Chen CJ, et al. Long-term Effects of Hepatitis B Immunization of Infants in Preventing Liver Cancer. *Gastroenterology*. 2016;151(3):472-480.e1. doi:10.1053/j.gastro.2016.05.048

19. Cheemerla S, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. *Clin liver Dis*. 2021;17(5):365-370. doi:10.1002/cld.1061

20. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *lancet Gastroenterol Hepatol*. 2020;5(3):245-266. doi:10.1016/S2468-1253(19)30349-8

21. Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med*. 2014;12:145. doi:10.1186/s12916-014-0145-y

22. Su SY, Lee LT, Lee WC. Mortality trends in chronic liver disease and cirrhosis from 1981 to 2015 in Taiwan. *Popul Health Metr*. 2021;19(1):36. doi:10.1186/s12963-021-00269-w

23. Su S, Lee W. Mortality trends of liver diseases from 1981 to 2016 and the projection to 2035 in Taiwan: An age-period-cohort analysis. *Liver Int*. 2019;39(4):770-776. doi:10.1111/liv.14027

24. Yao Z, Dai C, Yang J, et al. Time-trends in liver cancer incidence and mortality rates in the U.S. from 1975 to 2017: a study based on the Surveillance, Epidemiology, and End Results database. *J Gastrointest Oncol*. 2023;14(1):312-324. doi:10.21037/jgo-23-25

25. Drepina AS, Belyakova V V., Appalup M V., Mayorova OA. Detactability of viral hepatitises in a donor contingent. *Dokazatel'naya Gastroenterol*. 2016;5(3):10. doi:10.17116/dokgastro20165310-17

26. Khantimirova LM, Kozlova TY, Postnova EL, Shevtsov VA, Rukavishnikov A V. Retrospective Analysis of Viral Hepatitis B Incidence in Russia from 2013 to 2017 in the Context of Preventive Vaccination. *Bioprep Prev Diagnosis, Treat*. 2018;18(4):225-235. doi:10.30895/2221-996X-2018-18-4-225-235

27. Mikhailova YuV, Gromov AV, Averyanova EL, Sterlikov SA. Dynamics of incidence of viral hepatitis in the population of the Russian Federation in 2015-2021. Modern problems of health care and medical statistics. 2022;(4):269-297. (In Russ.) doi:10.24412/2312-2935-2022-4-269-297

28. Kyuregyan KK, Kichatova VS, Isaeva O V., et al. Coverage with Timely Administered Vaccination against Hepatitis B Virus and Its

Influence on the Prevalence of HBV Infection in the Regions of Different Endemicity. *Vaccines*. 2021;9(2):82. doi:10.3390/vaccines 9020082

29. Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol*. 2019;4(2):135-184. doi :10.1016/S24 68-1253(18)30270-X

30. Public Chamber of the Russian Federation. Alcohol Abuse in the Russian Federation: Socio-Economic Consequences and Countermeasures; 2009.

31. Nemtsov AV. Mortality in Russia in light of the in alcohol consumption. *Demogr Obozr*. 2015;2(4):111-135.

32. Chen LC, Wittgenstein F, McKeon E. The Upsurge of Mortality in Russia: Causes and Policy Implications. *Popul Dev Rev*. 1996;22(3) :517. doi:10.2307/2137719

33. Zaridze D, Brennan P, Boreham J, et al. Alcohol and cause-specific mortality in Russia: a retrospective case–control study of 48 557 adult deaths. *Lancet*. 2009;373(9682):2201-2214. doi:10.1016/S0140-6736(09)61034-5

34. Maev I V., Andreev DN, Kucheryavyy YA. Prevalence of non-alcoholic fat disease liver in Russian Federation: meta-analysis. *Cons Medicum*. 2023;25(5):313-319. doi:10.26442/ 20751753.2023.5.202155

35. Aleksandrova YD, Kolosnitsyna MG. Overweight Population in Russia: Statistical Analysis. *Vopr Stat*. 2018;25(10):61-77.

36. Balanova YA, Shalnova SA, Deev AD, et al. Obesity in Russian population — prevalence and association with the non-communicable diseases risk factors. *Russ J Cardiol*. 2018;(6):1 23-130. doi:10.15829/1560-4071-2018-6-123-130

37. Kontsevaya A, Shalnova S, Deev A, et al. Overweight and Obesity in the Russian Population: Prevalence in Adults and Association with Socioeconomic Parameters and Cardiovascular Risk Factors. *Obes Facts*. 2019;12(1):103-114. doi:10.1159/000493885

38. Said A, Ghufran A. Epidemic of non-alcoholic fatty liver disease and hepatocellular carcinoma. *World J Clin Oncol*. 2017;8(6):429-436. doi:10.5306/wjco.v8.i6.429

39. Bellentani S. The epidemiology of non-alcoholic fatty liver disease. *Liver Int*. 2017;37 Suppl 1:81-84. doi:10.1111/liv.13299

40. Sheiman I, Shishkin S, Shevsky V. The evolving Semashko model of primary health care: the case of the Russian Federation. *Risk Manag Healthc Policy*. 2018;Volume 11:209-220. doi:10.2147/RMHP.S168399

41. Shishkin S, Sheiman I, Vlassov V, Potapchik E, Sazhina S. Structural changes in the Russian health care system: do they match European trends? *Health Econ Rev*. 2022;12(1):29. doi:10.1186/s13561-022-00373-z

42. Tagaeva T, Kazantseva L. Social impacts of health care reforms in Russia. Rudoy D, Olshevskaya A, Kankhva V, eds. *E3S Web Conf*. 2020;210:17011. doi:10.1051/e3sconf/ 202021017011

43. Yao Z, Dai C, Yang J, et al. Time-trends in liver cancer incidence and mortality rates in the U.S. from 1975 to 2017: a study based on the Surveillance, Epidemiology, and End Results database. *J Gastrointest Oncol*. 2023;14(1):312-324. doi:10.21037/jgo-23-25

44. Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by

histologic subtype, 1978–2007. *Int J Cancer*. 2016;139(7):1534-1545. doi:10.1002/ijc.30211

45. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2004;130(7). doi:10.1007/s00432-004-0552-0

46. Singal AG, Pillai A, Tiro J. Early Detection, Curative Treatment, and Survival Rates for Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis: A Meta-analysis. Klenerman P, ed. *PLoS Med*. 2014;11(4):e1001624. doi:10.1371/journal.pmed.1001624