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Nationwide Prevalence of Hepatocellular Carcinoma in Saudi Arabia: A Population-Based Analysis for 2021

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Purpose: Liver cancer, predominantly hepatocellular carcinoma (HCC), represents a significant health burden in Saudi Arabia, ranking as the 8th most common cancer in males and 14th in females. Accurate prevalence estimation is essential for healthcare planning, resource allocation, and understanding disease burden. Challenges in prevalence assessment include incomplete capture of historical cases by the Saudi Cancer Registry (SCR) before its full operational capacity, as well as the absence of dedicated prevalence surveys. This study estimates the point prevalence of HCC in Saudi Arabia for the year 2021 using population-based incidence data, survival estimates, and census information.

Patients and Methods: A population-based prevalence estimation study was conducted using incident HCC cases reported to the SCR (2005–2017), population census data (2005–2020), and published national survival data. The study population comprised all newly diagnosed HCC cases reported during the study period. Prevalence was calculated by multiplying incident cases from each diagnosis cohort by their corresponding age- and gender-specific survival probabilities to estimate the number of HCC survivors alive in 2021, divided by the population at risk. Monte Carlo simulation with binomial distribution (n = incident cases; p = survival probability) was performed 1000 times to generate a distribution of prevalent cases, with 2.5th and 97.5th percentiles defining 95% confidence intervals. Age- and gender-specific prevalence rates were standardized to the WHO 2000–2025 World Standard Population using direct standardization for international comparability.

Results: Between 2005 and 2020, 6743 HCC cases were newly diagnosed and reported to the SCR, comprising 4685 males (69.5%) and 2058 females (30.5%). By the end of 2020, the estimated number of male HCC survivors was 637.3 (95% CI: 612.8–663.2), while females numbered 496.9 (95% CI: 474.1–521.8). In 2021, the age-standardized prevalence rate of HCC was 8.62 per 100,000 population for males (95% CI: 8.28–8.98) and 6.36 per 100,000 for females (95% CI: 6.08–6.67), with an overall combined age-standardized rate of 7.49 per 100,000 (95% CI: 7.25–7.76). HCC prevalence increased progressively with age, with the highest proportion of diagnosed cases occurring in individuals aged 75 years and above (males: n=1315; females: n=420). Younger cohorts diagnosed after 2015 showed markedly improved survival rates compared to those diagnosed in 2005, reflecting advances in treatment modalities.

Conclusion: This study provides a comprehensive population-based estimate of HCC prevalence in Saudi Arabia, demonstrating substantial gender and age disparities in disease burden. The predominance of HCC in males and elderly populations underscores the need for targeted epidemiological research to identify modifiable risk factors, particularly given the markedly lower prevalence of alcohol-related liver disease compared to global HCC endemic regions. The methodological framework utilizing integration of incidence, population-based survival data, and WHO standardization provides a replicable model for disease burden estimation in countries with limited prevalence survey infrastructure. Future research should focus on disease etiology, including the role of chronic hepatitis B, chronic hepatitis C, metabolic-associated steatotic liver disease, and the evolving patterns of liver disease in Saudi Arabia.

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Introduction

Liver cancer represents a major global health burden and ranks as the fourth leading cause of cancer-related mortality worldwide.[1] In 2022, approximately 865,269 new cases and 757,948 deaths due to liver cancer were reported globally.[2] Within the Arabian Gulf region, Saudi Arabia accounts for the largest proportion of liver cancer cases at 83.4% of regional cases, followed by Oman (6.6%), Kuwait (4.3%), Bahrain (2.4%), the United Arab Emirates (1.8%), and Qatar (1.6%).[3] In Saudi Arabia specifically, hepatocellular carcinoma (HCC) ranks eighth among all cancers in males and fourteenth in females,[4] with peak incidence in males aged 45–74 years and females aged 60–74 years.[5] According to the Saudi Cancer Registry, 376 HCC cases were reported in 2015,[5] increasing to 450 cases in 2020, representing 3.2% of all newly diagnosed malignancies in the Kingdom.[6]

The epidemiology of HCC in Saudi Arabia differs markedly from global patterns, primarily due to the region's unique profile of chronic liver disease etiologies. In most HCC endemic regions worldwide (particularly Southeast Asia and sub-Saharan Africa), hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection account for approximately 80% of HCC cases globally.[7] However, Saudi Arabia exhibits a distinctive epidemiological pattern characterized by a very low prevalence of alcohol-related liver disease,[8] and evolving patterns of viral hepatitis and metabolic liver disease.

Historically, HBV was the leading cause of HCC in Saudi Arabia,[9] but a nationwide neonatal vaccination program since 1989 has significantly reduced HBV prevalence (now about 1–2%) and related HCC cases,[10,11] with lower rates among younger cohorts. Despite this success, HCV remains a major health issue, currently estimated at 0.3% prevalence and projected to decrease further due to improved treatments,[10,12] though it now surpasses HBV as a cause of cirrhosis and HCC in recent studies.[13] The rise of metabolic-associated steatotic liver disease (MASLD)[14,15] – driven by high rates of diabetes and obesity (over 20% and 35–40%, respectively, among adults)[16] – is reshaping HCC epidemiology in Saudi Arabia, with MASLD-related HCC expected to increase substantially as the population burden grows.[17,18]

While HCC is characterized by relatively short overall survival compared to some other malignancies, prevalence remains an epidemiologically meaningful and clinically important metric. Prevalence estimation serves several critical functions in cancer epidemiology as it provides a snapshot of the current disease burden in a population at a specific point in time, essential for healthcare planning and resource allocation; it reflects the cumulative impact of both incidence and survival, providing a comprehensive picture of active disease burden; it enables tracking of changes in disease burden over time, which can reflect either declining incidence (due to improved prevention or screening detection of early lesions) or improving survival (due to therapeutic advances); and it identifies populations living with HCC who require ongoing clinical management, surveillance, or palliative care. Furthermore, a small but meaningful subset of HCC patients achieve long-term survival through liver transplantation or aggressive multimodal therapy,[19] creating a subpopulation of long-term survivors whose care needs differ substantially from newly diagnosed patients. Point prevalence estimates capture these surviving patients and their associated healthcare needs.

Accurate estimation of HCC prevalence in Saudi Arabia faces substantial methodological challenges. Traditional prevalence estimation approaches, such as cross-sectional surveys or linkage between cancer registries and national vital statistics databases, are limited by high costs, incomplete population coverage, and data gaps.[20,21] The Saudi Cancer Registry has captured HCC cases increasingly comprehensively over time since its establishment in 1994, yet historical data completeness and case ascertainment have evolved. Additionally, point-in-time prevalence surveys are not routinely conducted in Saudi Arabia. This study addresses these methodological gaps by employing established epidemiological techniques that integrate cancer registry incidence data, published national survival estimates, and population census data to derive robust prevalence estimates and confidence intervals.

Patients and Methods

Study Design and Population

This is a population-based prevalence estimation study conducted in the Kingdom of Saudi Arabia, a country with a population of approximately 34 million inhabitants (2021 census). The study population comprised all individuals newly diagnosed with HCC who were reported to the Saudi Cancer Registry between 2005 and 2020, stratified by gender, age-group (16 categories: 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75+ years), and year of diagnosis.

Data Sources

Cancer incidence data were obtained from the Saudi Cancer Registry (SCR), which operates under the governance of the Ministry of Health and represents the national cancer surveillance system for the Kingdom of Saudi Arabia. The SCR collects incidence data from cancer diagnostic and treatment facilities nationwide and is supported by mandatory reporting requirements for all newly diagnosed malignancies to health authorities.[22] For this analysis, HCC incidence data were extracted for the period 2005–2017. The SCR data collection for 2018–2020 was not yet finalized at the time of analysis; therefore, 2018–2020 incidence rates were projected using validated cubic polynomial modeling of 2005–2017 trends. Data were available through 2017 at the time of analysis due to standard data validation and quality control procedures, which require a processing lag of approximately 2–3 years.

Population Census Data: Age- and gender-specific population data for the years 2005–2020 were obtained from the Saudi General Authority for Statistics (GASTAT),[23] the official source of national demographic data. For years with missing population estimates (2018–2020), estimates from the Ministry of Economy and Planning population projections were incorporated.[24] These projections are based on the 2016 national census and applied standard demographic methodology incorporating vital statistics. Total population figures were missing for 2011, 2013, and 2014 in certain stratifications; these were interpolated from adjacent years using linear interpolation methodology. All population figures refer to the Saudi Arabian population that includes Saudi nationals only.

Survival Data: Published survival estimates were obtained from the most recent Saudi Arabia-specific source available at the time of analysis. Age- and gender-specific one-year, three-year, and five-year survival probabilities for HCC were extracted from the most recent published report,[25] which analyzed HCC survival outcomes in the Saudi population using the cohort method with follow-up conducted through vital statistics linkage and medical record review. These published estimates reflect cause-specific survival adjusted for competing causes of mortality and were stratified by age-group and gender, enabling robust estimation of expected survivors.

Definition of Hepatocellular Carcinoma

For this analysis, HCC was defined according to the 10th revision of the International Classification of Diseases (ICD-10) histology code C22.0, which is used by SCR.[26] The analysis focused exclusively on HCC and excluded other histological types of primary liver cancer.

Prevalence Calculation Methodology

It is critical to distinguish the prevalence estimation methodology employed in this study from survival analysis, as these represent fundamentally different epidemiological concepts. Survival analysis measures the probability that an individual diagnosed with a disease remains alive for a defined period of follow-up; it requires individual-level time-to-event data and is typically estimated using the Kaplan-Meier method or Cox proportional hazards models.[27] In contrast, point prevalence estimation measures the number of individuals in a population who have a given disease (in this case, HCC) at a specific point in time (January 1, 2021). This study performs prevalence estimation, NOT survival analysis. The prevalence calculation integrates published survival proportions with incidence data to estimate how many individuals diagnosed in prior years remain alive in 2021—this is an arithmetic application of population epidemiological principles, not a statistical survival analysis.[28]

Mathematical Framework

Point prevalence of HCC was calculated using the following formula:

$$\mathrm{P}_{age,\ gender}(2021) = \frac{\sum_{y=2005}^{2020} I_{age,\ gender}(y) \times\ S_{age,\ gender}(y \rightarrow 2021)}{N_{age,\ gender}(2021)} \times 100{,}000$$

Where:

$P_{age,gender}(2021)$ = age- and gender-specific point prevalence rate per 100,000 population in 2021

$I_{age,gender}(y)$ = number of incident HCC cases diagnosed in year y in the specific age-gender stratum

$S_{age,gender}(y \rightarrow 2021)$ = probability of survival from year of diagnosis y to 2021 in the specific age-gender stratum

$N_{age,gender}(2021)$ = population size of the specific age-gender stratum in Saudi Arabia in 2021.

The following steps were undertaken to estimate the prevalence rate:

Step 1 – Incident case ascertainment: for each year from 2005–2017 with complete SCR data, the number of newly diagnosed HCC cases was extracted, stratified by 5-year age groups and gender. The resulting age-specific incidence rates were calculated as cases per 100,000 person-years at risk.

Step 2 – Incidence projection for 2018–2020: for years 2018–2020, when SCR data processing had not been completed, age- and gender-specific incidence rates from 2017 were projected forward using validated cubic polynomial modeling of incidence trends from 2005–2017 data. The cubic polynomial function fits a three-dimensional age-period surface to historical incidence data and provides stable rate projections for short periods (1–3 years) when recent trends are stable Statistical analysis of the fitted model demonstrated that incidence trends declined after 2010 but stabilized with minor variations after 2015 (Supplementary Figure S1), justifying the application of 2017 rates to the 2018–2020 period. These projected rates were applied to population projections for 2018–2020 to estimate incident cases.

Step 3 – Survival probability assignment: for each cohort of incident cases (defined by diagnosis year, age-group, and gender), the corresponding age- and gender-specific survival probability to 2021 was determined. Where survival probabilities were published for specific age groups matching registry age categories, published values were directly applied. For age groups where directly published estimates were unavailable, survival probabilities were interpolated from adjacent age groups using linear interpolation, assuming a monotonic change in survival probability with age. All survival estimates represented all-cause mortality estimates; in other words, they account for both deaths from HCC and deaths from other causes, reflecting the net probability of a patient diagnosed in a given year remaining alive in 2021.

Step 4 – Calculation of expected number of survivors: for each age-gender-year cohort, the expected number of survivors in 2021 was calculated as:

$$Expected\ Survivors_{age,\ gender,\ year} = I_{age,\ gender}\ (year) \times S_{age,\ gender}\ (year \rightarrow 2021)$$

This calculation produced age-gender-year-specific estimates of expected survivors, many of which were non-integer values. Non-integer values emerged from three aspects of the methodology: (1) age-standardization involving weighting factors applied to each age stratum; (2) application of survival probabilities as proportional multipliers; and (3) population interpolation procedures for years with missing census data. These values represent weighted, standardized, and estimated values rather than actual case counts.

Step 5 – Confidence interval estimation via Monte Carlo simulation: To appropriately represent uncertainty in the prevalence estimates, we employed Monte Carlo simulation methodology.[29] For each age-gender-year cohort, the number of survivors was modeled as a binomial random variable with parameters n (number of incident cases) and p (survival probability). This process was repeated 1000 times to generate a distribution of total prevalent HCC cases for each stratum. The 2.5th and 97.5th percentiles of this distribution defined the 95% confidence interval around the point estimate. This approach accounts for probabilistic uncertainty in survival without requiring normality assumptions and appropriately handles the discrete nature of count data.

Age Standardization

Age-standardized prevalence rates were calculated using the direct standardization method applied to the WHO 2000–2025 World Standard Population. The WHO standard was selected for this analysis to enable comparison with

recently published international HCC epidemiology data, as it has become the accepted reference for direct age standardization in contemporary cancer epidemiology.[30,31] The WHO 2000–2025 standard population differs from the previously used SEGI-Doll standard and European Standard populations by incorporating a higher proportion of older age groups (reflecting contemporary global age structures) and fewer young children, making it more appropriate for age-standardizing cancer incidence and prevalence rates in the current demographic era.

Age-standardized rates were calculated as:

$$ASR = \frac{\sum_i w_i \times r_i}{\sum_i w_i} \times 100{,}000$$

Where:

w_i = weight (population proportion) for age group i in the WHO 2000–2025 standard population

r_i = age-specific HCC prevalence rate (per 100,000) for age group i in the Saudi population

The denominator sums to 100,000. Additional detailed definitions, assumptions, and calculations for missing data are included in the Supplementary Files: Appendix A and Appendix B (Supplementary Tables 1–3).

Statistical Analysis

Prevalence rates are presented as point estimates with 95% confidence intervals. Age-specific and gender-specific rates are presented separately. Overall prevalence rates (combining all ages and genders) are presented as age-standardized rates. Proportional differences in HCC prevalence between males and females were compared using the ratio of age-standardized rates. Temporal trends in the number of survivors were examined using descriptive analysis by year of diagnosis, examining whether surviving numbers increased across more recent diagnostic cohorts (reflecting shorter follow-up time in addition to either higher incidence or improved survival in recent years).

Results

Incident Cases and Case Ascertainment

Between 2005 and 2020, the Saudi Cancer Registry reported 6743 newly diagnosed HCC cases, comprising 4685 males (69.5%) and 2058 females (30.5%), representing a male-to-female ratio of 2.28:1. The distribution of incident cases by age-group demonstrated marked age-related patterns, with peak incidence occurring in older age groups. Individuals aged 75 years and above accounted for the largest single age-group among newly diagnosed cases: 1315 males (28.0% of all male cases) and 420 females (20.4% of all female cases). The 70–74 age-group represented the second most affected age stratum, followed by the 65–69 age-group. Notably, incident cases occurred across all age groups, with smaller numbers diagnosed in younger age-groups (Figure 1A).

Estimated Number of HCC Survivors

Overall Survivor Numbers by Gender: By the end of 2020, based on applying published survival probabilities to incident cohorts from 2005–2020, the estimated number of male HCC survivors alive in Saudi Arabia was 637.3 individuals (95% CI: 612.8–663.2), while the corresponding number for females was 496.9 (95% CI: 474.1–521.8). These estimates represent cumulative survivors from all HCC diagnosis cohorts from 2005–2020, weighted by their respective age- and gender-specific survival probabilities to 2021.

Progressive Increase in Recent Survivors: The number of expected survivors increased substantially over time, reflecting shorter follow-up time in addition to possible improved outcomes in more recently diagnosed cohorts (Tables 1 and 2). Among males (Table 1), only 6.5 expected survivors remained from the 2005 diagnostic cohort (out of 211 diagnosed), representing a 3.1% survival to 2021. This low proportion reflects the extended follow-up time (16 years from 2005 to 2021) combined with the relatively short natural survival of HCC. In contrast, males diagnosed in 2015 had 40.8 expected survivors out of 274 diagnosed (14.9% survival to 2021), representing more than six-fold increase in absolute survivor numbers and approximately 5-fold increase in survival proportion compared to the 2005 cohort. By 2020, the year nearest to the prevalence assessment point, 104.4 males out of 264.3 diagnosed (39.5%) were

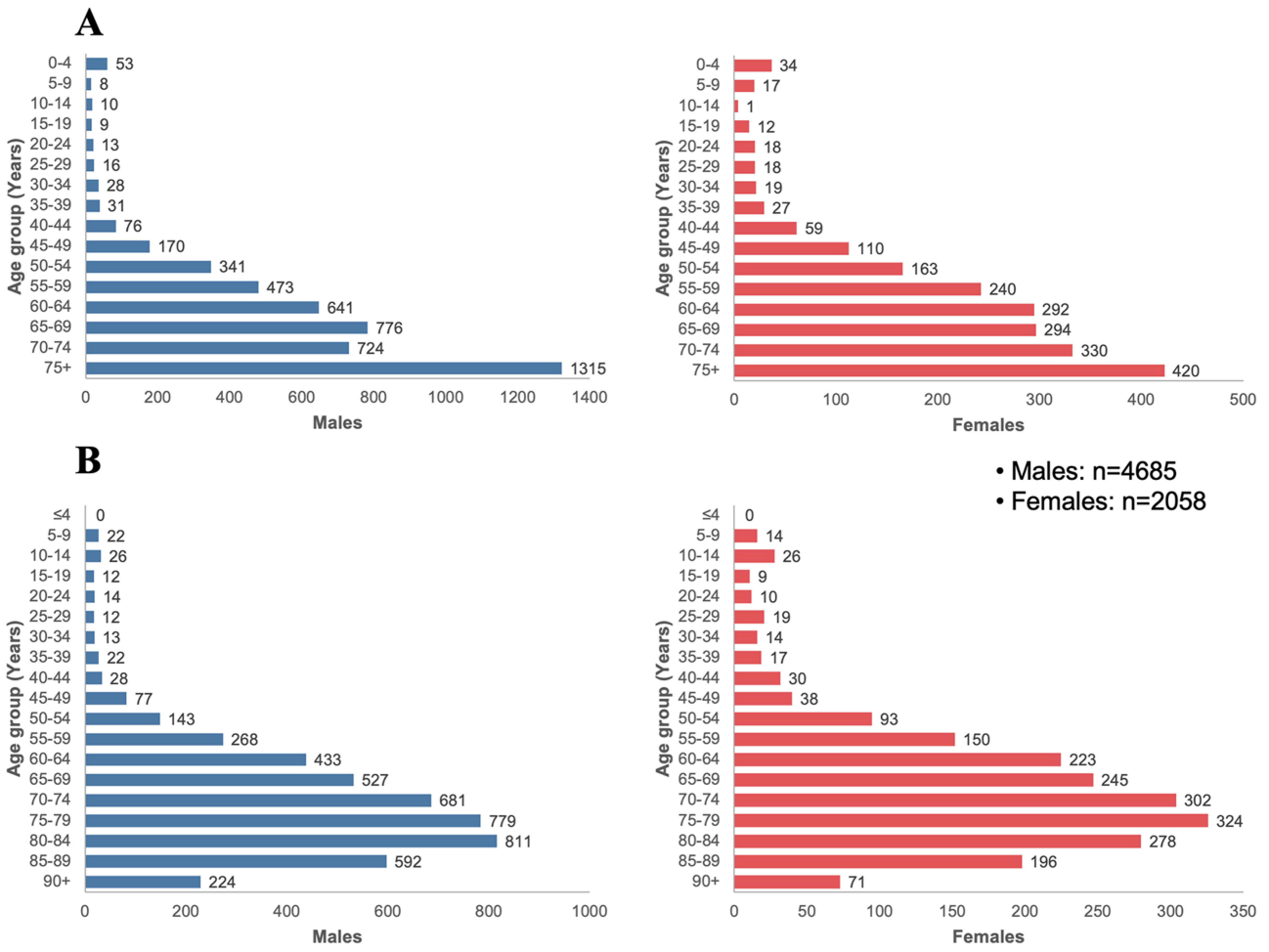

Figure 1 Diagnosed liver cancer cases. (**A**) Total number of cases by gender and age-group at the time of diagnoses (2005–2020), (**B**) Total number of cases between 2005 and 2020 by gender and estimated age-group in 2021.

expected to be alive in 2021, reflecting either once again a short follow-up with possible improved survival in recent years or a mix of improved survival and improved treatment outcomes.

Among females (Table 2), only 19.4 expected survivors remained from the 2005 diagnostic cohort (out of 81 diagnosed), representing a 24.0% survival to 2021. This higher female survival proportion compared to males from

Table 1 Number of Males Diagnosed with Liver Cancer Per Year in Saudi Arabia and the Expected Number of Survivors

	Year	Diagnosed	Expected Alive[†]
Data from Registry	2005	211.0	6.5
	2006	291.0	11.4
	2007	314.0	18.3
	2008	303.0	23.5
	2009	295.0	25.2
	2010	329.0	31.2

(*Continued*)

Table 1 (Continued).

	Year	Diagnosed	Expected Alive[†]
	2011	330.0	37.1
	2012	344.0	39.0
	2013	339.0	41.2
	2014	310.0	40.0
	2015	274.0	40.8
	2016	290.0	45.0
	2017	264.0	44.9
Projection	2018	268.8	56.8
	2019	258.0	68.3
	2020	264.3	104.4
Total		4685.1	633.9

Note: [†]Expected alive = probability × total diagnosed.

Table 2 Number of Females Diagnosed with Liver Cancer Per Year in Saudi Arabia and the Expected Number of Survivors

	Year	Diagnosed	Expected Alive[†]
Data from Registry	2005	81.0	19.4
	2006	125.0	23.4
	2007	121.0	20.3
	2008	115.0	22.8
	2009	136.0	29.2
	2010	154.0	31.5
	2011	158.0	32.8
	2012	130.0	27.9
	2013	156.0	31.1
	2014	156.0	32.3
	2015	102.0	21.8
	2016	127.0	27.3
	2017	124.0	30.6
Projection	2018	126.2	36.9
	2019	122.2	43.3
	2020	124.6	67.9
Total		2058	498.6

Note: [†]Expected alive = probability × total diagnosed.

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the same 2005 cohort is notable (24.0% females vs 3.1% males). In the 2015 diagnostic cohort, females had 21.9 expected survivors out of 102 diagnosed (21.4% survival), indicating a relatively stable survival proportion compared to 2005. However, by 2020, females had 67.9 expected survivors out of 124.6 diagnosed (54.4% survival), representing a more than tripling of survivor numbers compared to 2015 and doubling compared to earlier cohorts.

Prevalence Rates – 2021

Age-Standardized Prevalence Rates: In 2021, the age-standardized HCC prevalence rate was 8.62 per 100,000 population for males (95% CI: 8.28–8.98) and 6.36 per 100,000 for females (95% CI: 6.08–6.67). The combined overall age-standardized prevalence rate across both genders was 7.49 per 100,000 population (95% CI: 7.25–7.76), calculated by combining the male and female estimates proportionally weighted by the Saudi population gender distribution.

The male-to-female ratio of age-standardized prevalence was 1.36:1, indicating substantially higher disease burden in males. This male predominance aligns with global HCC epidemiology and reflects both higher male incidence rates (male-to-female incidence ratio of 2.28:1) and more favorable female survival proportions in recent cohorts.

Age-Specific Prevalence Rates: Crude (non-standardized) age-specific prevalence rates demonstrated marked variation by age, with rates increasing progressively from the youngest age-groups to the oldest (Table 3). In males, crude prevalence rates were essentially zero (< 0.1 per 100,000) for age-groups 0–49 years, then increased to 0.45 per

Table 3 Prevalence of Liver Cancer Among Females and Males in the Saudi Arabian Population, 2020

Females					Males				ASR† (All)	Standard World Population
Age-Group (Years)	No. of Expected Alive	Person-Years at Risk	Crude Rate	Adjusted Rate	No. of Expected Alive	Person-Years at Risk	Crude Rate	Adjusted Rate		
0-4	0.0	1,118,772	0.0	0.0	0.00	1,156,740	0.0	0.0	0.0	12,000
5-9	12.87	1,094,213	1.18	0.12	16.50	1,131,036	1.5	0.15	0.13	10,000
10-14	22.60	983,142	2.30	0.21	22.35	1,009,509	2.2	0.20	0.20	9,000
15-19	7.98	923,703	0.86	0.08	7.50	955,017	0.8	0.07	0.07	9,000
20-24	6.97	1,009,686	0.69	0.06	7.33	1,105,616	0.7	0.05	0.05	8,000
25-29	8.74	1,007,650	0.87	0.07	6.40	1,027,552	0.6	0.05	0.06	8,000
30-34	6.11	911,036	0.67	0.04	6.61	924,990	0.7	0.04	0.04	6,000
35-39	6.77	794,568	0.85	0.05	3.43	811,980	0.4	0.03	0.04	6,000
40-44	11.90	662,067	1.80	0.11	4.29	686,927	0.6	0.04	0.07	6,000
45-49	11.16	546,749	2.04	0.12	16.11	577,297	2.8	0.17	0.14	6,000
50-54	27.96	435,625	6.42	0.32	41.12	460,430	8.9	0.45	0.38	5,000
55-59	48.82	330,131	14.79	0.59	75.27	359,440	20.9	0.84	0.71	4,000
60-64	58.47	243,614	24.00	0.96	99.77	260,327	38.3	1.53	1.25	4,000
65-69	46.34	168,598	27.49	0.82	88.42	158,369	55.8	1.67	1.25	3,000
70-74	58.89	118,941	49.51	0.99	77.96	115,620	67.4	1.35	1.17	2,000
75-79	62.25	77,381	80.45	0.80	85.68	76,360	112.2	1.12	0.96	1,000
≥80	99.04	96,684	102.44	1.02	78.58	90,358	87.0	0.87	0.95	1,000
All	496.9	10,522,560	4.72	6.36	637.3	10,907,568	5.84	8.62	7.49	100,000

Note: †ASR, Age-standardized rate; Expected alive = probability × total diagnosed.

100,000 in the 50–54 age-group, 0.84 per 100,000 in the 55–59 age-group, and rose progressively to 1.53 per 100,000 in the 60–64 age-group. The oldest age-groups showed the highest crude rates, with 1.35 per 100,000 in 70–74 year-old males and 1.12 per 100,000 in 75–79 year-old males, declining slightly to 0.87 per 100,000 in males aged 80 years and above.

Female age-specific crude rates demonstrated a similar age-related pattern but with different magnitudes. Female crude rates were essentially zero for ages 0–49 years, then 0.32 per 100,000 in the 50–54 age-group, progressing to 0.96 per 100,000 in 60–64 year-old females, 0.82 per 100,000 in 65–69 year-old females, and showing slightly lower rates in the oldest age-groups (0.80 per 100,000 in 75–79 years) with 1.02 per 100,000 in females 80 years and above.

Distribution of Survivors by Age at Diagnosis: Analysis of the age-distribution of HCC patients alive in 2021 who were diagnosed between 2005–2020 revealed concentration in middle and older age-groups (Figure 1B). The largest proportions of living patients were those diagnosed in the 55–59 (representing the peak in historical diagnosis), 60–64, and 65–69 age-groups. However, individuals diagnosed at the oldest ages (80+ years) represented a notable subset of survivors despite lower absolute incidence in these age-groups, reflecting the competing effect of higher baseline non-HCC mortality in elderly populations.

Non-Integer Values in Tables

As noted in the methodology section, prevalence and survivor estimates contain non-integer values. These values are weighted, standardized expected values rather than actual case counts. The non-integer nature reflects: (1) the application of fractional age-standardization weights from the WHO standard population (eg, weights of 0.08857, 0.08687, for different age groups); (2) the multiplication of incident counts by survival probabilities (eg, 100×0.455 = 45.5); and (3) the interpolation of missing population data. While actual diagnosed cases are integers, prevalence estimates derived through standardized epidemiological methodology are properly expressed as non-integer weighted and standardized estimates.[32]

Discussion

The most striking epidemiological feature of HCC in Saudi Arabia is its concentration in elderly populations, particularly individuals aged 70 years and older. This study found that 58.4% of all HCC cases diagnosed during 2005–2020 occurred in individuals aged 70 years or older (approximately 80% threshold reported in some earlier analyses.[33] This strong age-related trend in HCC incidence reflects the biological reality that HCC develops after decades of chronic liver disease, requiring time for the accumulation of cirrhosis and malignant transformation. The median age at diagnosis for HCC globally ranges from 60–70 years, depending on geographic region and HCC etiology.[34] The concentration of HCC in older age-groups has important implications: it affects populations with higher baseline comorbidity burdens, potentially influencing treatment candidacy and prognosis; it requires age-appropriate screening and surveillance strategies in high-risk populations; and it raises questions about optimal clinical management balancing curative intent with quality-of-life considerations in elderly patients.

Our study confirms a pronounced male predominance in HCC epidemiology in Saudi Arabia, with males accounting for 69.5% of incident cases and demonstrating an age-standardized prevalence approximately 1.36 times higher than females. The male-to-female incidence ratio of 2.28:1 observed in this analysis aligns closely with global HCC epidemiology[35,36] and with HCC patterns reported in other Middle Eastern countries.[37] Multiple biological mechanisms have been proposed to explain gender-based HCC risk disparities: One prominent hypothesis implicates estrogen-mediated suppression of interleukin-6 (IL-6) production by Kupffer cells (hepatic macrophages), reducing hepatic inflammation and HCC risk in females.[38] IL-6 is a pro-inflammatory cytokine implicated in hepatocarcinogenesis, particularly in the context of chronic viral hepatitis and cirrhosis. Estrogen-responsive suppression of IL-6 production provides a potential biological explanation for lower HCC risk in premenopausal women and warrants investigation in Saudi populations. A second proposed mechanism involves gender differences in adiponectin production and metabolism. Lower adiponectin levels in males, independent of obesity status, have been associated with higher HCC risk through dysregulation of metabolic pathways, including AMP-activated protein kinase (AMPK) signaling.[39] Adiponectin has anti-inflammatory and anti-angiogenic properties; reduced levels promote hepatic

inflammation and are associated with increased HCC susceptibility. This mechanism may be particularly relevant in Saudi Arabia, given the high prevalence of obesity and metabolic dysfunction. A third mechanism proposes that androgens have tumor-promoting effects, with androgens showing synergistic oncogenic effects with HBV in males but not females.[35] This mechanism may explain the particularly high HCC risk in males chronically infected with HBV and suggests that this pathway may be less active in HCV-related or MASLD-related HCC development. While alcohol-related liver disease is notably absent or extremely rare in Saudi Arabia due to Islamic religious practices proscribing alcohol consumption, smoking remains more prevalent in males than in females in Saudi Arabia. Tobacco smoke exposure has been associated with increased HCC risk through oxidative stress and impaired hepatic regeneration mechanisms.[40] Though likely a minor contributor compared to viral and metabolic pathways, smoking may contribute to gender differences in HCC risk.

An unexpected finding in this analysis was the apparent improvement in female survival in more recent diagnostic cohorts (2015–2020), with female survivors increasing from 21.8 expected survivors in 2015 to 67.9 in 2020, compared to male survivors increasing from 40.8 to 104.4 over the same period. This pattern warrants careful interpretation. One recent large cohort study of multi-ethnic Asian patients found that females diagnosed with HCC had superior overall survival compared to males, contrasting with some earlier analyses.[41] Potential explanations include: (1) stage at diagnosis—if females are diagnosed at earlier disease stages than males, stage-adjusted survival would appear superior; (2) performance status—females may present with better performance status at diagnosis; (3) treatment receipt—females may receive more aggressive treatment; and (4) comorbidity profiles—females may have fewer competing causes of mortality. A prior SEER database analysis found that women aged 55–65 years had superior survival compared to men of the same age, which the authors attributed to estrogenic protective effects.[35] These gender-based survival differences warrant further investigation in Saudi-specific cohorts with detailed clinical staging, treatment data, and comorbidity assessment.

The marked increase in absolute numbers of surviving HCC patients in more recent diagnostic cohorts (particularly 2015–2020) reflects one of the following: (1) increased HCC incidence in recent years, leading to more diagnosed patients overall; and (2) improved survival outcomes in recent years, resulting in higher survival proportions among diagnosed patients and (3) shorter follow-up time period. From a public health perspective, the increase in prevalent HCC cases has substantial implications for healthcare resource planning, oncology capacity, and supportive/palliative care needs. An increasingly prevalent population may reflect therapeutic progress (desirable), but also creates increased demand for long-term surveillance, management of treatment complications, and psychosocial support services.

The age-standardized HCC prevalence of 7.49 per 100,000 population observed in this study is lower than rates reported in HCC endemic regions (Southeast Asia, sub-Saharan Africa, where age-standardized incidence rates exceed 20–30 per 100,000 in some regions),[42] but represents a substantial disease burden for the Middle East. The 2020 GLOBOCAN estimates indicated global HCC age-standardized incidence of 9.2 per 100,000, with substantial geographic variation.[43] Saudi Arabia's observed prevalence is close to or slightly lower than global average incidence estimates, reflecting its intermediate position between HCC-endemic regions and HCC-non-endemic regions. However, relative to other countries in the Gulf Cooperation Council (GCC) region, Saudi Arabia bears the largest absolute burden of HCC cases, accounting for 83.4% of regional cases.[3]

The methodological approach employed in this study—integrating registry incidence data with published survival estimates and population census data to estimate point prevalence—represents a validated epidemiological technique.[20,28] Similar approaches have been employed in cancer registries worldwide to estimate prevalence when point-in-time surveys are unavailable. This methodological framework is replicable in other countries with similar data infrastructure limitations and could serve as a model for prevalence estimation in healthcare systems with established cancer registries but limited prevalence survey capacity.

This study possesses several important methodological strengths: (i) it is the first population-based prevalence estimate of HCC specifically for Saudi Arabia, filling an important epidemiological knowledge gap; (ii) it integrates multiple established data sources (cancer registry, population census, published survival data) using validated epidemiological techniques; (iii) it employs age- and gender-stratified analyses, enabling identification of high-risk subpopulations; (iv) it applies WHO 2000–2025 age standardization, enabling international comparisons and longitudinal tracking; (v) it incorporates Monte Carlo simulation methodology to derive 95% confidence intervals that appropriately account for

probabilistic uncertainty; and (vi) the results are presented transparently with detailed methodological description to enable external review and potential replication.

The study must be interpreted in light of several important limitations: (i)The Saudi Cancer Registry captures the large majority of HCC cases diagnosed in Saudi Arabia but is subject to underascertainment due to incomplete case reporting, missed cases diagnosed outside the formal medical system, and potential geographical gaps in registry coverage. Registry data completion and case ascertainment have improved over the study period (2005–2020), introducing potential bias. This study likely underestimates true HCC prevalence. (ii) The analysis utilized published national survival estimates to estimate expected survivors. These published estimates, while from Saudi Arabian sources, may not perfectly capture the age- and gender-specific survival experiences for all HCC patients in the population. Variation in survival by stage at diagnosis, treatment received, comorbidity profile, and other factors is not captured in these summary survival estimates. This represents an important potential source of estimation error. (iii) For years 2018–2020, with incomplete registry data collection, incidence rates were projected using polynomial modeling of 2005–2017 trends. If actual incidence deviated substantially from projected trends, prevalence estimates for 2021 would be accordingly affected. However, statistical analysis demonstrated somewhat stability in incidence trends after 2015, supporting the validity of short-term projections. (iv) For years with missing census population data (2011, 2013, 2014, 2019–2020), linear interpolation was employed. This approach assumes linear population change between years with actual data, which may not reflect actual demographic dynamics (immigration, emigration, fertility changes). However, sensitivity analyses including and excluding these interpolated years were planned to assess the impact. (v) While this analysis discusses HCC etiology extensively, the SCR does not systematically capture underlying liver disease etiology (HBV, HCV, MASLD, autoimmune disease) for all HCC patients. Therefore, the study cannot provide etiology-specific prevalence estimates. Future epidemiological studies integrating HCC registry data with serology, imaging, and clinical assessment would enable etiology-specific disease burden estimation. (vi) The study presents prevalence estimates for a single point in time (beginning of 2021). Trends in prevalence over multiple years would enable assessment of whether disease burden is increasing or decreasing over time, which would have greater public health implications than a single-year snapshot. Longitudinal prevalence studies tracking disease burden across multiple years are needed. (vii) The findings of this study describe HCC epidemiology specifically in Saudi Arabia and may have limited generalizability to other Middle Eastern countries with different healthcare infrastructure, HCC etiology profiles, or disease surveillance systems.

The findings of this population-based prevalence estimation study have substantial implications for public health policy, clinical practice, and future research in Saudi Arabia: The estimated 1134 HCC survivors alive in Saudi Arabia in 2021 represent a distinct population requiring ongoing specialized oncological care, radiological surveillance, and management of treatment complications. This population size must be factored into healthcare system capacity planning, including oncology clinic staffing, imaging resources, transplantation capacity, and supportive care services. The substantial concentration of HCC in older age-groups reflects the long latency of HCC development from chronic liver disease. Current prevention efforts appropriately focus on: (i) continued HBV vaccination in children (achieving > 95% coverage for secondary prevention); (ii) scaling of HCV direct-acting antiviral therapy to reduce HCV-related cirrhosis and HCC; (iii) obesity prevention and management to reduce MASLD burden; and (iv) diabetes prevention and management, which addresses a key metabolic risk factor for MASLD and HCC. These prevention approaches, while not addressing current HCC patients, will reduce future HCC incidence as younger, vaccinated cohorts age.

The strong age-related trend in HCC incidence suggests that age-based screening strategies (targeting individuals 50–60 years and older with established cirrhosis or advanced fibrosis) are appropriate. However, etiological-specific screening is also important: individuals with chronic hepatitis B should undergo surveillance regardless of cirrhosis stage (as HCC can develop in non-cirrhotic HBV patients); those with advanced hepatitis C-related fibrosis should receive DAA therapy if not already treated; and those with MASLD-related cirrhosis require HCC surveillance.

Several important avenues for future research emerge from this study: (i) Etiology-specific prevalence estimates: Future research should integrate HCC registry data with serological (HBsAg, anti-HCV), imaging (ultrasound findings of cirrhosis), and clinical data (liver fibrosis assessments) to enable prevalence estimates stratified by HCC etiology (HBV, HCV, MASLD, and others). (ii) Longitudinal prevalence tracking: Repeating prevalence estimation at regular intervals (every 3–5 years) will enable tracking of disease burden changes over time and assessment of whether HCC burden is

increasing or decreasing. (iii) Analysis of HCC prevalence by geographic region within Saudi Arabia (Eastern Region, Central Region, Western Region, Northern Region, Southern Region) would illuminate regional variations in disease burden and enable targeted regional interventions. (iv) Stage-specific and outcomes data: Integration of tumor stage (TNM staging), treatment received, and clinical outcomes into prevalence analyses would enable more detailed characterization of the prevailing HCC population and could guide treatment and surveillance strategies, and (v) Detailed analysis of temporal trends in HCC incidence across 2005–2025 would clarify whether declining prevalence is occurring due to declining incidence (reflecting primary prevention success) or declining survival (reflecting potential therapeutic challenges).

Conclusion

This study presents the first population-based prevalence estimate of HCC in Saudi Arabia for 2021, demonstrating an age-standardized prevalence of 7.49 per 100,000 population, with males disproportionately affected (8.62 per 100,000) compared to females (6.36 per 100,000). HCC demonstrates marked concentration in older populations, with 58.4% of incident cases occurring in individuals aged 70 years and older. The male-to-female ratio of 2.28:1 for incidence and 1.36:1 for prevalence aligns with global patterns and reflects both biological factors and epidemiological factors.

Ethical Approval and Data Availability

This research was conducted in accordance with the Declaration of Helsinki and the ethical standards of the Kingdom of Saudi Arabia. Approval was granted by the Ethics Committee of King Faisal Specialist Hospital and Research Center (RAC 2240010). The study involved secondary analysis of de-identified cancer registry data; informed patient consent was waived due to the retrospective nature and use of de-identified data.

Individual-level patient data cannot be shared publicly due to Saudi healthcare data privacy regulations. Aggregated prevalence rates, age-specific rates, and population-level findings are provided in the paper and supplementary File. Requests for additional aggregated data analysis, not compromising individual privacy, may be directed to the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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