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The Analysis Study of Association of Type 2 Diabetes Mellitus and Hepatocellular Carcinoma : *A Comprehensive Systematic Review*

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer, and its incidence and mortality have been steadily increasing in recent decades. Numerous studies have shown that individuals with type 2 diabetes are more likely to develop HCC. This systematic review aims to evaluate the association regarding the role of diabetes in the development and progression of HCC based on literatures of the last decade. **Methods:** The study followed PRISMA 2020 guidelines, reviewing English-language publications from 2014 to 2024. Editorials, duplicate reviews from the same journal, and papers lacking a DOI were excluded. The literature search was conducted using PubMed, SagePub, SpringerLink, and Google Scholar. **Result:** A total of 2,172 articles were initially identified through online databases (PubMed, SagePub, SpringerLink, and Google Scholar). After three rounds of screening, eight relevant studies were selected for full-text analysis. **Conclusion:** T2DM is a significant risk factor for HCC, especially with metabolic comorbidities. GLP-1RAs show promise in reducing this risk. Public health interventions are needed to improve diabetes management, and further research is essential to validate and explore these findings.

Keyword: Hepatocellular carcinoma, Diabetes mellitus, Insulin resistance, Hyperinsulinemia

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer, and its incidence and mortality have been steadily increasing in recent decades. This type of cancer typically develops in individuals with chronic liver diseases, which account for 70-90% of HCC cases. The primary causes of these liver conditions are persistent infections from hepatitis B virus (HBV) or hepatitis C virus (HCV), and alcohol abuse.¹⁻³

However, in recent years, non-alcoholic fatty liver disease (NAFLD) and its more severe form, non-alcoholic steatohepatitis (NASH), have emerged as significant risk factors for HCC, surpassing viral and alcohol-related liver diseases, particularly in developed countries where these are less common. NAFLD, a key feature of metabolic syndrome, is closely associated with obesity, hypertension, dyslipidemia, and diabetes.⁴⁻⁶

Type 2 diabetes mellitus (T2DM) is a condition characterized by high blood sugar, insulin resistance, and hyperinsulinemia, and it represents a major health challenge

worldwide. There is compelling evidence linking diabetes to an increased risk of various cancers, including those of the breast, pancreas, lung, colorectal, and kidneys.⁷ Of particular concern is the strong association between T2DM and HCC, as research has shown that people with diabetes have a 2- to 3-fold greater risk of developing HCC compared to non-diabetic individuals, regardless of the presence of cirrhosis or the underlying cause of liver disease. Additionally, longer duration of diabetes is associated with an increased risk of HCC, and diabetes also negatively impacts survival rates in individuals with HCC.⁸⁻¹⁰

The connection between diabetes and the risk of HCC is largely attributed to conditions commonly associated with diabetes, such as insulin resistance and NAFLD. Insulin resistance, a defining feature of T2DM, promotes the development of NAFLD, which in turn is a well-established risk factor for liver fibrosis and cirrhosis, both of which can progress to HCC.^{11,12}

Numerous studies have shown that individuals with diabetes are more likely to develop NAFLD, and

that diabetes accelerates the progression of liver fibrosis, further heightening the risk of cirrhosis and HCC. This connection is particularly evident in the liver's role in glucose metabolism, where insulin resistance leads to fat buildup, inflammation, and liver damage, all of which contribute to HCC development.¹³ Additionally, over the past two decades, the proportion of HCC cases among diabetic individuals, particularly those without viral hepatitis, has notably risen, further emphasizing the importance of diabetes as a risk factor for non-viral liver cancer.¹⁴ This systematic review aims to evaluate the association regarding the role of diabetes in the development and progression of HCC based on literatures of the last decade.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the association regarding the role of diabetes in the development and progression of HCC based on literatures of the last decade. The review aimed to provide insights to improve patient treatment strategies, with an emphasis on the significance of key findings in the reviewed studies. Inclusion criteria for the study included: 1) Papers published in English, and 2) Papers published between 2014 and 2024. Exclusion criteria were: 1) Editorials, 2) Papers without a DOI, 3) Previously published review articles, and 4) Duplicate entries in journals.

Search Strategy

The keywords used for this research are hepatocellular carcinoma, diabetes mellitus, insulin resistance, hyperinsulinemia. The Boolean MeSH keywords inputted on databases for this research are: *("carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All*

Fields] AND *"carcinoma"[All Fields])* AND *("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) OR ("insulin resistance"[MeSH Terms] OR ("insulin"[All Fields] AND "resistance"[All Fields]) OR "insulin resistance"[All Fields]) OR ("hyperinsulinaemia"[All Fields] OR "hyperinsulinism"[MeSH Terms] OR "hyperinsulinism"[All Fields] OR "hyperinsulinemia"[All Fields]).*

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further

analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) OR ("insulin resistance"[MeSH Terms] OR ("insulin"[All Fields] AND "resistance"[All Fields]) OR "insulin resistance"[All Fields]) OR ("hyperinsulinaemia"[All Fields] OR "hyperinsulinism"[MeSH Terms] OR "hyperinsulinism"[All Fields] OR "hyperinsulinemia"[All Fields])</i>	466
Springer Link	<i>((((hepatocellular carcinoma) AND (diabetes mellitus)) OR (insulin resistance)) OR (hyperinsulinemia))</i>	402
Sagepub	<i>((((hepatocellular carcinoma) AND (diabetes mellitus)) OR (insulin resistance)) OR (hyperinsulinemia))</i>	500
Google Scholar	<i>((((hepatocellular carcinoma) AND (diabetes mellitus)) OR (insulin resistance)) OR (hyperinsulinemia))</i>	804

Table 2. JBI *Critical appraisal of Study*

Parameters	Simon (2018)	Yang (2020)	Dyson (2014)	Chen (2017)	Younossi (2015)	Ajmera (2023)	Wang (2024)	Hu (2023)
1. Bias related to temporal precedence								
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation								
Was there a control group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No.	No.	No.	No.	No.	No.	No.	No.
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes of participants included in any comparisons measured in the same way?	No.	No.	No.	No.	No.	No.	No.	No.
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

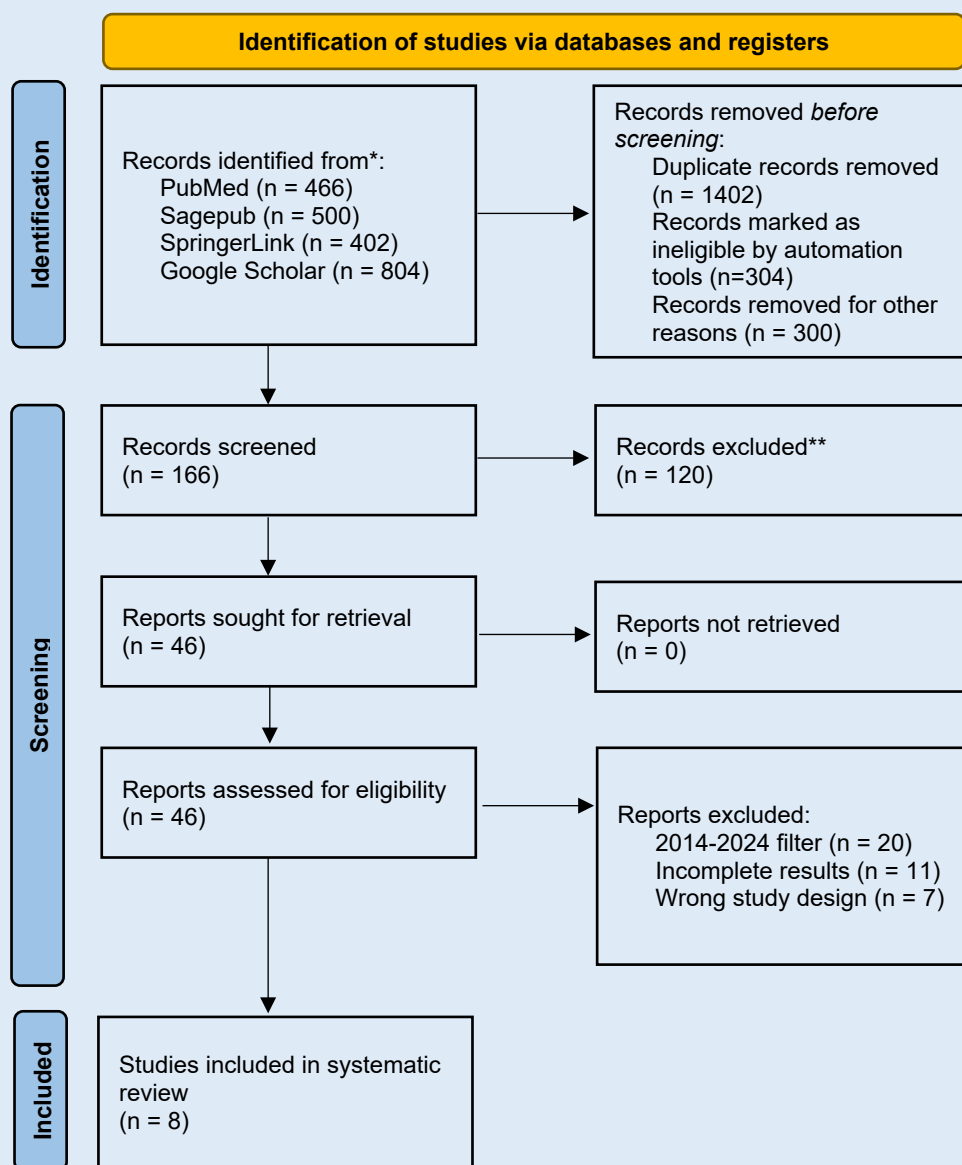


Figure 1. Article search flowchart

RESULT

The initial number of articles retrieved from online databases (PubMed, SagePub, SpringerLink, and Google Scholar) is 2,172 articles. After conducting three levels of screening, eight articles that directly relate to the current systematic review have been chosen for further assessment through full-text reading and analysis. Table 3 presents the selected literature included in this analysis.

Table 3. The literature included in this study

No.	Author	Origin	Method	Sample	Result
1.	Simon, et al. ¹⁵ (2018)	Multicenter	Retrospective cohort	112	Over 32 years of follow-up (4,488,410 person-years), 112 cases of hepatocellular carcinoma (HCC) were documented. Type 2 diabetes (T2D) was found to significantly increase the risk of HCC, with a multivariable hazard ratio (HR) of 4.59. The risk was higher with longer T2D duration: 2.96 for 0-<2 years, 6.08 for 2-<10 years, and 7.52 for ≥10 years. Additionally, the presence of multiple metabolic comorbidities (T2D, obesity, hypertension, dyslipidemia) further elevated HCC risk, with an 8.1-fold increased risk for those with all four comorbidities. Neither insulin nor oral hypoglycemic use was significantly linked to HCC risk.
2.	Yang, et al. ¹⁶ (2020)	USA	Retrospective cohort	354	In a study of 354 Mayo Clinic patients with NASH cirrhosis, 71% had diabetes, with a mean age of 62 at cirrhosis evaluation. During a median follow-up of 47 months, 30 patients developed hepatocellular carcinoma (HCC). Diabetes was linked to a significantly higher risk of HCC, with hazard ratios (HR) of 3.6 in univariate and 4.2 in multivariable

					analysis. Additionally, age and low serum albumin levels were associated with increased HCC risk. Other metabolic risk factors like BMI, hyperlipidemia, and hypertension were not linked to HCC. In a larger cohort of 6,630 UNOS NASH registrants, 58% had diabetes, and the risk of HCC was similarly increased with HRs of 1.4 and 1.3 in univariate and multivariable analysis, respectively.
3.	Dyson, et al. ¹⁷ (2014)	UK	Retrospective cohort	632	Hepatocellular carcinoma (HCC) mortality in the region increased 1.8-fold over 10 years, rising from 2.0 to 3.7 per 100,000. A review of 632 cases revealed significant increases in HCC linked to hepatitis C, alcoholic liver disease, and, notably, non-alcoholic fatty liver disease (NAFLD), which accounted for 34.8% of cases by 2010. Metabolic risk factors, including obesity and diabetes, were present in 66.1% of cases in 2010. The median overall survival was just 10.7 months. While patients with NAFLD-associated HCC were older and had less frequent surveillance detection, their survival was similar to other etiologies, likely due to higher incidental presentation and a lower prevalence of cirrhosis.

4.	Chen, et al. ¹⁸ (2017)	Asia	Retrospective cohort	112,686	During a mean follow-up of 12.7 years, 37,343 cancer deaths were identified, with 36,667 in East Asians and 676 in South Asians. Diabetes was significantly associated with an increased risk of death from any cancer (HR 1.26). Strong associations were found between diabetes and higher cancer mortality from cancers of the colorectum, liver, bile duct, gallbladder, pancreas, breast, endometrium, ovary, prostate, kidney, thyroid, and lymphoma. However, diabetes was not significantly linked to death from leukemia, bladder, cervix, esophagus, stomach, or lung cancers
5.	Younossi, et al. ¹⁹ (2015)	USA	Retrospective cohort	4929	A study of 4,929 HCC cases and 14,937 controls revealed that 54.9% of HCC cases were linked to HCV, 16.4% to alcohol-related liver disease (ALD), 14.1% to NAFLD, and 9.5% to HBV. Over six years (2004–2009), NAFLD-related HCC cases increased by 9% annually. NAFLD-HCC patients were older, had shorter survival times, more heart disease, and were more likely to die from liver cancer. Only 5% of those who received liver transplants for HCC had NAFLD-related HCC. Multivariate analysis showed that NAFLD

					increased the risk of 1-year mortality (OR 1.21), with older age, lower income, and unstaged HCC also increasing mortality risk. Receiving a liver transplant or having localized tumors was protective
6.	Ajmera, et al. ²⁰ (2023)	USA	Retrospective cohort	524	In a study of 501 adults (63% female) with type 2 diabetes mellitus (T2DM), the mean age was 64.6 years and the average BMI was 31.4 kg/m ² . The prevalence of non-alcoholic fatty liver disease (NAFLD) was 65%, with 14% having advanced fibrosis and 6% having cirrhosis. Obesity and insulin use were both significantly associated with an increased risk of advanced fibrosis, with odds ratios of 2.50 and 2.71, respectively. Among 29 patients with cirrhosis, two had hepatocellular carcinoma, and one had gallbladder adenocarcinoma.
7.	Wang, et al. ²¹ (2024)	USA	Retrospective cohort	1890020	The study found that GLP-1 receptor agonists (GLP-1RAs) were associated with a significantly lower risk of incident hepatocellular carcinoma (HCC) compared to insulin, sulfonylureas, and metformin, with hazard ratios of 0.20, 0.39, and 0.63, respectively. GLP-1RAs also showed a reduced risk of hepatic decompensation compared

					to six other anti-diabetes medications. The reduced risks were observed across various stages of fatty liver disease, with the most pronounced effects in patients without liver disease. Combination therapies involving GLP-1RAs further decreased the risks of HCC and hepatic decompensation.
8.	Huo, et al. ²² (2023)	China	Retrospective cohort	1866	The study used Mendelian randomization (MR) analysis to investigate the association between type 2 diabetes (T2D) and hepatocellular carcinoma (HCC) in East Asian populations. The results from the inverse variance weighting (IVW) method indicated an inverse association between T2D and HCC, with a risk odds ratio of 0.86, even after adjusting for factors like BMI, chronic hepatitis B, and alcohol intake. Additional MR methods and sensitivity analyses confirmed the robustness of these findings. However, reverse MR analysis did not show a significant impact of genetic risk for HCC on T2D.

Simon, et al.¹⁵ (2018) concluded that T2D independently increases the risk of HCC, with longer duration and multiple metabolic conditions enhancing this risk,

highlighting the role of insulin resistance in HCC development.

Yang, et al.¹⁶ (2020) concludes that diabetes is a significant

risk factor for HCC in patients with NASH cirrhosis.

Dyson, et al.¹⁷ (2014) concludes that while HCC-related mortality is rising, elderly patients with metabolic comorbidities can have a better prognosis if their cancer is detected early and managed by a specialist team.

Chen, et al.¹⁸ (2017) concludes that diabetes increases the risk of cancer-related mortality by 26%, emphasizing the need for improved diabetes and obesity management to reduce cancer deaths in Asia.

Younossi, et al.¹⁹ (2015) concludes that NAFLD associated with T2DM is becomes a major cause of HCC in the U.S. and is associated with poorer survival outcomes and lower transplant rates.

Ajmera, et al.²⁰ (2023) highlights the high prevalence of advanced liver disease in adults aged 50 and older with T2DM.

Wang, et al.²¹ (2024) suggest that GLP-1RAs may offer protective benefits for liver health in patients with type 2 diabetes, warranting further research into their mechanisms and clinical application.

Huo, et al.²² (2023) suggests that T2D may be inversely associated with HCC, but further research is needed to confirm these results.

DISCUSSION

The association between Type 2 Diabetes Mellitus (T2DM) and hepatocellular carcinoma (HCC) has been a subject of growing concern and research in recent years. Studies consistently suggest that T2DM increases the risk of developing HCC, with several studies focusing on metabolic factors and long-term complications of the disease. This systematic review aims to explore the intricate relationship between T2DM and HCC by synthesizing findings from multiple retrospective cohort studies that evaluate the impact of diabetes on the risk of HCC development and mortality.

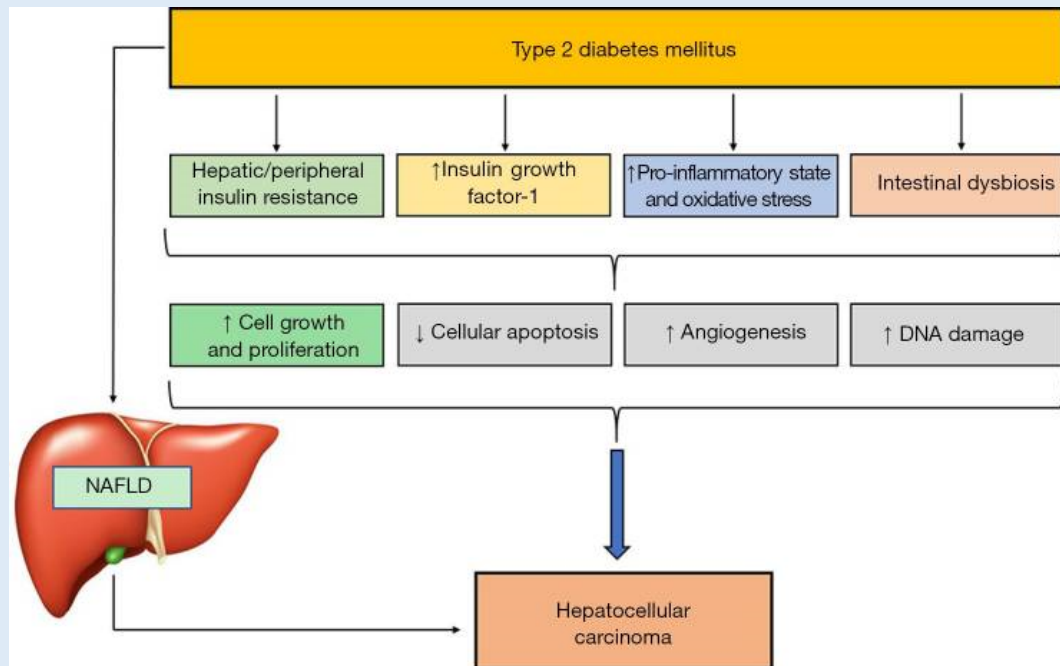


Figure 2. The schematic association between T2DM and hepatocellular carcinoma.³

Simon et al. (2018) identified a strong association between T2DM and HCC, with a multivariable hazard ratio of 4.59 over a 32-year follow-up period. The study highlighted that the risk of HCC increases significantly with the duration of diabetes, suggesting that longer duration T2DM contributes to the higher incidence of liver cancer. Additionally, the presence of multiple metabolic comorbidities such as obesity, hypertension, and dyslipidemia further exacerbated this risk. These findings underscore the role of insulin resistance in the

pathogenesis of liver cancer, a crucial factor in the diabetic population.¹⁵

Further evidence from Yang et al. (2020) reinforces this association in a cohort of patients with non-alcoholic steatohepatitis (NASH) cirrhosis. The study reported a hazard ratio of 4.2 for HCC in diabetic patients, with diabetes remaining a significant risk factor even after controlling for other factors like BMI and hyperlipidemia. This study also highlighted that the presence of diabetes in patients with NASH cirrhosis is a particularly strong predictor of HCC

development, further emphasizing the need for closer monitoring of these high-risk individuals.¹⁶

Dyson et al. (2014) discussed the increasing incidence of HCC, particularly in patients with non-alcoholic fatty liver disease (NAFLD), which is strongly associated with T2DM. In their cohort, 66.1% of HCC cases had underlying metabolic risk factors, including diabetes. This study also suggested that the prognosis for HCC in patients with NAFLD might be somewhat more favorable compared to other etiologies, as early detection and appropriate management could improve survival rates. However, the study did not overlook the increased difficulty in detecting HCC early in these patients due to the often incidental nature of their presentation.¹⁷

The findings from Chen et al. (2017) contribute to the growing body of evidence that diabetes is not only linked to HCC but also increases the risk of death from various cancers, including liver cancer. The study showed that diabetes was associated with a 26% higher risk of cancer-related mortality in Asian

populations, with particularly strong associations with liver, colorectal, and pancreatic cancers. This highlights the broader public health implications of diabetes and the need for improved strategies for its prevention and management to reduce the risk of cancer deaths in diabetic populations.¹⁸

In the United States, the increasing prevalence of NAFLD as a cause of HCC, especially in patients with T2DM, was discussed by Younossi et al. (2015). NAFLD-HCC patients were found to have a significantly shorter survival time, poorer overall outcomes, and a lower likelihood of receiving liver transplants. The study highlighted the urgency of addressing NAFLD in the diabetic population to reduce the incidence of liver cancer. Interestingly, only 5% of NAFLD-related HCC patients received liver transplants, underscoring the challenges in managing advanced liver disease in diabetic individuals.¹⁹

Ajmera et al. (2023) explored the prevalence of advanced liver disease in adults aged 50 and older with T2DM. Their study found that 65% of diabetic patients had NAFLD,

with 14% showing advanced fibrosis and 6% presenting with cirrhosis. The authors concluded that the high prevalence of liver disease among older adults with T2DM puts them at considerable risk for HCC. Additionally, obesity and insulin use were identified as factors significantly associated with advanced fibrosis, which may eventually lead to liver cancer.²⁰

On a more promising note, Wang et al. (2024) reported that GLP-1 receptor agonists (GLP-1RAs) were associated with a significantly lower risk of incident HCC compared to other anti-diabetes medications. The study indicated that GLP-1RAs not only reduced the risk of HCC but also showed protective effects against hepatic decompensation in diabetic patients. These findings suggest that GLP-1RAs may offer a novel therapeutic avenue for reducing liver cancer risk in T2DM patient.²¹

In contrast, Huo et al. (2023) used Mendelian randomization (MR) analysis to explore the genetic basis of T2DM's relationship with HCC. Interestingly, their study found an inverse association between T2DM and HCC, which calls into question

the conventional understanding of the link between diabetes and liver cancer. The MR analysis did not show a significant effect of genetic risk for HCC on the development of T2DM, suggesting that the relationship may be more complex than previously thought.²²

Overall, the reviewed studies provide strong evidence supporting the association between T2DM and increased risk of HCC. The risk is particularly pronounced in patients with additional metabolic comorbidities such as obesity, hypertension, and NAFLD. However, studies also highlight the potential benefits of new therapeutic approaches, such as GLP-1RAs, in reducing the risk of HCC in diabetic patients. These findings emphasize the need for early detection, better management of metabolic conditions, and personalized treatment strategies to reduce the burden of HCC in diabetic populations. Furthermore, future studies should explore the mechanisms behind the potential inverse association between T2DM and HCC, as suggested by Mendelian randomization studies, to provide a

more comprehensive understanding of this complex relationship.²³

CONCLUSION

T2DM is a significant risk factor for HCC, especially with metabolic comorbidities. GLP-1RAs show promise in reducing this risk. Public health interventions are needed to improve diabetes management, and further research is essential to validate and explore these findings.

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