DOI: https://doi.org/10.53350/pjmhs2023171339

**ORIGINAL ARTICLE**

# A Cross-Sectional Study on Association between Metabolic Syndrome and Hepatobiliary Cancers

MUHAMMAD IRFAN SHEHZAD[1], ANWAR UL HAQ[2], IKRAM ZADA[3], MUHAMMAD ADNAN SHAHID[4], NOMAN KAREEM QURESHI[5], SHAH BAKHT AZEEM[6]

[1]*Consultant Gastroenterologist, Central Hospital, Stadium Road, Sargodha*
[2]*Associate Professor Medicine, Khyber Girls Medical College, Peshawar/ Medical-A Unit, Hayatabad Medical Complex, Peshawar*
[3]*Associate Physician Gastroenterology, Federal Government Polyclinic, Islamabad*
[4]*Registrar Internal Medicine, PIMS, Islamabad*
[5]*Assistant Professor Gastroenterology, AJK Medical College/ CMH / Shaikh Khalifa bin Zayed Hospital, Muzaffarabad AJK*
[6]*Medical Officer, MBBS, MCPS, (Family Medicine), Master in Community Health Education (USA), CMH Okara*
*Corresponding author: Anwar ul Haq, Email: doctoranwar@live.com*

## ABSTRACT

**Background and Aim:** Several studies have supported the idea that a metabolic abnormality contributes to expansion of hepatocellular carcinoma (HCC). To date, metabolic factors have not been shown to be associated with hepatocellular carcinoma (HCC). Therefore, the present study aimed to assess the metabolic syndrome association with hepatocellular carcinoma.

**Patients and Methods:** This cross-sectional study was carried out on surgically treated and radiologically confirmed 360 HCC cases in Gastroenterology Department of Central Hospital, Sargodha and Hayatabad Medical Complex Peshawar, during the period from January 2022 June 2022. Study protocol was approved by the research and ethical committee. Informed written consents were taken from each individual. Body mass index, blood pressure, medical history, and other related information were gathered from medical records. Patients were categorized into different groups based on their BMI: i) <18.5 kg/m2, ii) 18.5-23.9 kg/m2, iii) 24-29.9 kg/m2, Fiv) 30-34.9 kg/m2 and ≥ 35 kg/m2. A routine biochemical or immunological analytic method was used to determine all metabolic parameters and liver function tests. The metabolic-associated factors were associated with HCC-related different liver function's test and stratified for BMI, free fatty acids, and Glycated Albumin (GA). Chemical analysis was used to detect antioxidant capacity (TAOC) and malondialdehyde (MDA). Data analysis was done in SPSS version 27.

**Results:** Of the total 360 HCC patients, there were 234 (65%) male and 126 (35%) females. The overall mean age was 68.62±6.4 years. The association between hepatobiliary cancer and body mass index (BMI), smoking, ischemic heart disease, hypertension, and diabetes was found in a univariate analysis of the data. Based on BMI, patients were categorized as follows: 35 (9.7%) in (<18.5 kg/m2), 70 (19.4%) in (18.5-23.5 kg/m2), 118 (32.8%) in (24-29.9 kg/m2), 88 (24.4%) in (30-34.9 kg/m2), and 49 (13.7%) in (≥ 35 kg/m2). The incidence of smokers, non-smokers, and ex-smokers were 146 (40.6%), 60 (16.7%), and 154 (42.8%) respectively. The prevalence of different risk factors such as hypertension, diabetes, ischemic heart disease, Aspirin use, and statin use was 188 (52.2%), 124 (34.4%), 66 (18.3%), 148 (41.1%), and 142 (39.4%) respectively. The HCC group had significantly higher mean body mass index, glucose level, and lipid level than controls (P <0.05). HCC patients showed a significant association between liver function and metabolic factors. A significant association between high level of GA and increased cancer risk were found between cases and control.

**Conclusion:** The present study concluded that hepatobiliary carcinoma may be caused by metabolic syndrome, which includes dyslipidemia, a high body mass index, and high serum glucose levels as independent risk factors. This finding supports previous research and emphasizes that the connection between hapotabiliatry cancer and increased BMI remains for liver tumors, bile duct cancer, and gallbladder cancers.

**Keywords:** Hepatobiliary carcinoma, metabolic syndrome, Obesity, Diabetes

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most prevalent malignancy and the third leading cause of cancer mortality globally [1]. The higher occurrence of HCC is caused by HBV and HCV. Other numerous factors contribute to higher incidence and progression of chronic liver disorders [2]. Hepatocellular carcinoma (HCC) and liver cirrhosis (LC) of chronic types has been significantly correlated with metabolic disorders [3]. Hepatobiliary and gallbladder malignancies have been steadily growing over the last two decades. Since the last few decades, the liver cirrhosis cases increased by 200% with age-standardization [4, 5]. The prevalence of gallbladder and bile duct malignancies are also increasing [6]. There is uncertainty regarding the HCC increased cases caused by metabolic syndrome and obesity [8]. HCC pathogenesis and risk factors are well understood. HCV, hereditary factors, HBV, lifestyle variables (smoking and nutritional determinants), NAFLD, and other less prevalent causes are among them.

Metabolic syndrome is a group of clinical disorders defined by insulin resistance, including obesity, hypertension, dyslipidemia, and type II diabetes mellitus [9]. Numerous malignancies could be caused by metabolic syndrome. Type II diabetes is related with an increased risk of hepatocellular carcinoma [10]. Another study found a relation between metabolic syndrome and biliary tract malignancies [11]. Laboratory testing might reveal metabolic disorders or impairments in liver function. Liver function impairment could be caused by bilirubin and abnormal levels of aminotransferase (ALT). Several studies have recently indicated that g-glutamyltransferase (GGT) and ALT can predict the development of MS [12, 13]. Although the associations between metabolic variables and hepatocellular carcinoma (HCC) have steadily become apparent, very few studies has been carried out on HCC and metabolic indicators [14]. Therefore, we aimed to investigate the relationship between HCC development and metabolic syndrome.

## METHODOLOGY

This cross-sectional study was carried out on surgically treated and radiologically confirmed 360 HCC cases in Gastroenterology Department of Central Hospital, Sargodha and Hayatabad Medical Complex Peshawar, during the period from January 2022 June 2022. Study protocol was approved by the research and ethical committee. Informed written consents were taken from each individual. Body mass index, blood pressure, medical history, and other related information were gathered from medical records. Patients were categorized into different groups based on their BMI: i) <18.5 kg/m2, ii) 18.5-23.9 kg/m2, iii) 24-29.9 kg/m2, iv) 30-34.9 kg/m2 and ≥ 35 kg/m2. A routine biochemical or immunological analytic method was used to determine all metabolic parameters and liver function tests. The metabolic-associated factors were associated with HCC-related different liver function's test and stratified for BMI, free fatty acids, and Glycated Albumin (GA).

Chemical analysis was used to detect antioxidant capacity (TAOC) and malondialdehyde (MDA).

After 12 hours of fasting, blood samples were collected and examined. Prior to surgery, all blood samples were collected. Total bilirubin (TBIL), total protein (TP), direct bilirubin (DBIL), albumin (ALB), aspartate aminotransferase (AST), and GGT were the liver function markers examined. Data analysis was done in SPSS version 27. Non - parametric data were reported as median and range, and parametric data as mean SD. A Mann-Whitney U test was used to compare categorical variables. The relative risk of HCC was estimated using the OR. All p-values were calculated with two tails, and p-values less than 0.05 were considered significant.

## RESULTS

Of the total 360 HCC patients, there were 234 (65%) male and 126 (35%) females. The overall mean age was 68.62±6.4 years. The association between hepatobiliary cancer and body mass index (BMI), smoking, ischemic heart disease, hypertension, and diabetes was found in a univariate analysis of the data. Based on BMI, patients were categorized as follows: 35 (9.7%) in (<18.5 kg/m2), 70 (19.4%) in (18.5-23.5 kg/m2), 118 (32.8%) in (24-29.9 kg/m2), 88 (24.4%) in (30-34.9 kg/m2), and 49 (13.7%) in (≥ 35 kg/m2). The incidence of smokers, non-smokers, and ex-smokers were 146 (40.6%), 60 (16.7%), and 154 (42.8%) respectively. The prevalence of different risk factors such as hypertension, diabetes, ischemic heart disease, Aspirin use, and statin use was 188 (52.2%), 124 (34.4%), 66 (18.3%), 148 (41.1%), and 142 (39.4%) respectively.

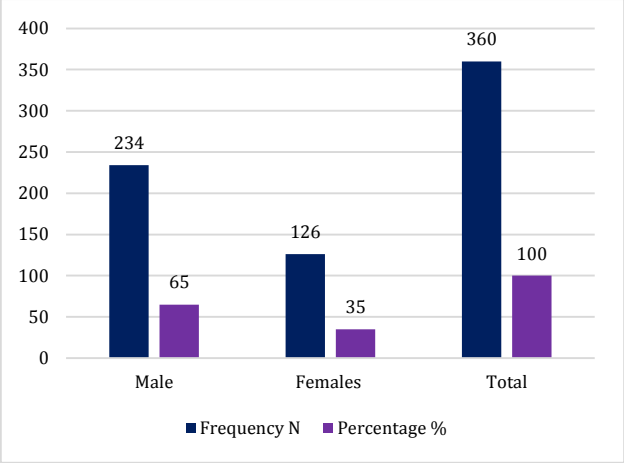


Figure-1: Gender's distribution (n=360)

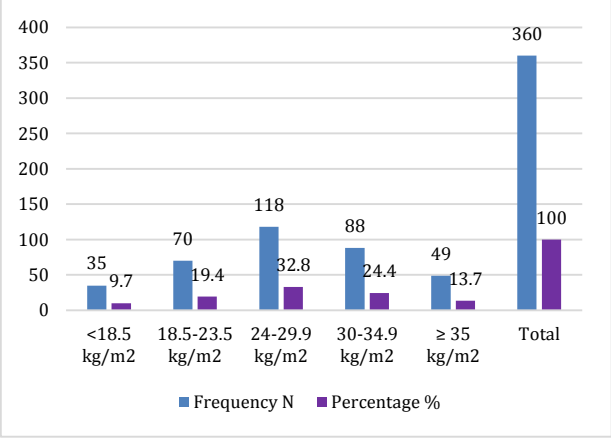


Figure-2: Patient's distribution based on BMI (kg/m2) (n=360)

The HCC group had significantly higher mean body mass index, glucose level, and lipid level than controls (P <0.05). HCC patients showed a significant association between liver function and metabolic factors. A significant association between high level of GA and increased cancer risk were found between cases and control. Gender's distribution is shown in Figure-1. Distribution of patients based on BMI is shown in Figure-2. Figure-3 illustrate the incidence of smokers, non-smokers, and ex-smokers. Prevalence of various risk factors are depicted in Figure-4. Table-I represents the demographic details and laboratory characteristics of cases. Univariate study of risk variables for hepatobiliary cancer is shown in Table-II.

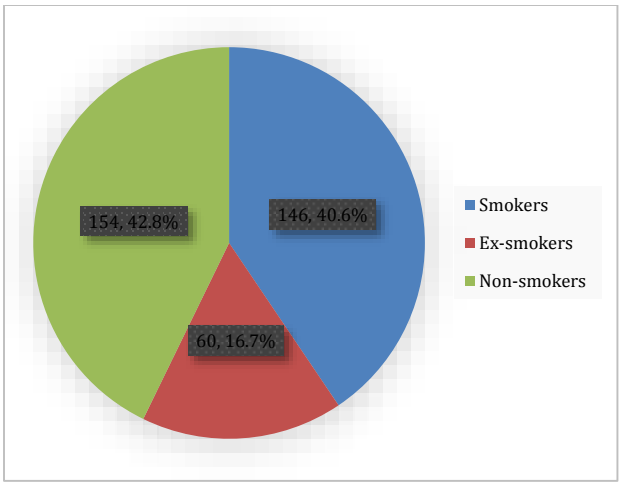


Figure-3: Prevalence of smokers, non-smokers, and ex-smokers (n=360)

Table-1: Demographic details and laboratory characteristics of cases

| Laboratory parameters | Value (Mean ± SD) | P-value |
|---|---|---|
| Age (years) | 48.76 ± 10.92 | 0.01 |
| Gender N (%)<br>Male<br>Females | <br>234 (65)<br>126 (35) | 0.01 |
| ALT (U/L) | 53.21 ± 66.21 | 0.00 |
| AFP (µg/L) | 33.8 (4-1209) | 0.00 |
| ALB(g/L) | 41.46 ± 4.21 | 0.00 |
| TBIL(µmol/L) | 15.42 ± 13.26 | 0.007 |
| TP(g/L) | 70.42 ± 5.16 | 0.00 |

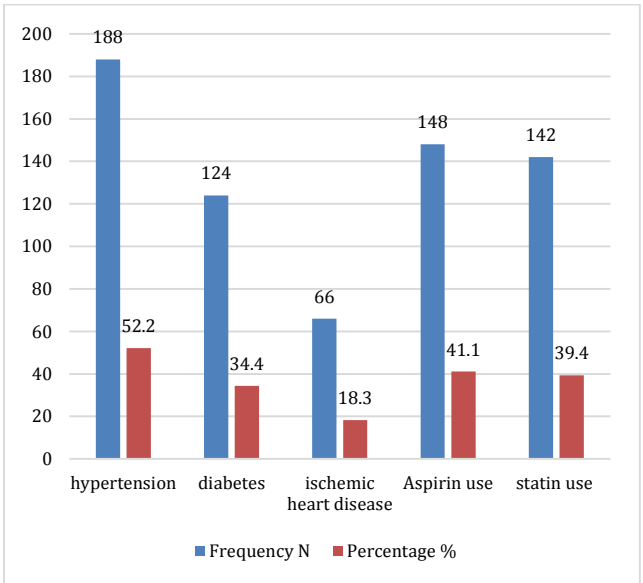


Figure-2: Prevalence of various risk factors

Table-2: Univariate study of risk variables for hepatobiliary cancer

| Parameters | OR (95% CI) | P-value |
|---|---|---|
| Age (years) | 0.99 (0.972–0.995) | <0.001 |
| BMI (kg/m2) | 3.19 (2.61–4.28) | <0.001 |
| Smoking | 1.91 (1.68–2.03) | <0.001 |
| Diabetes | 2.18 (1.87–2.29) | <0.001 |
| Hypertension | 1.19 (1.12–1.35) | <0.001 |
| Ischemic heart disease | 2.15 (1.9–2.31) | <0.001 |
| Aspirin | 0.98 (0.97–1.00) | 0.05 |
| Statin | 0.99 (0.992–0.997) | <0.001 |

## DISCUSSION

The present study mainly focused on association of hepatobiliary cancer with metabolic syndromes and found that Gallbladder cancer has been caused by hypertension, obesity, diabetes, and ischemic heart disease. Hepatocellular carcinoma and gallbladder cancer were shown to be inversely related to age and statin usage. Extrahepatic cholangiocarcinoma was linked to an increase in BMI, diabetes, ischemic heart disease, and insulin usage, but not smoking was protective. Increased BMI and insulin usage were also related to hepatic cholangiocarcinoma. Hepatobiliary carcinoma may be caused by metabolic syndrome, which includes dyslipidemia, a high body mass index, and high serum glucose levels as independent risk factors. Obesity and metabolic syndrome are linked to an increased hepatobiliary cancer risk. The present study found a substantial relation between hepatobiliary carcinoma and metabolic syndrome. This finding supports previous research and emphasizes that the connection between hepatobiliary cancer and increased BMI remains for liver tumors, bile duct cancers, and gallbladder cancers.

Numerous studies investigated the liver-related malignancies association with metabolic syndrome and the relationship intensity appears to be caused by type 2 diabetes and insulin resistance [15, 16]. Type 2 diabetes patients with insulin resistance promote the increasing cellular proliferation and cancer by blocking apoptosis via the formation of reactive oxygen species, which can promote cellular lipid peroxidation and damage [17].

The present study observed that the hepatobiliary cancer risk had inverse association with age. Age is recognized to be hepatobiliary cancer development risk factor [18]. This impact might be explained by a hepatobiliary malignancies higher incidence in 60 to 80-year age range and a decline with age advancement. The persistence odd ratio approximately 1 and age had inverse association with hepatobiliary carcinoma increasing risk [19].

Anti-hyperglycemic medications such as Insulin could be used to treat diabetes in turn associated to an increased risk of hepatocellular carcinoma [20]. Metformin, in particular, is considered to protect against the development of hepatocellular carcinoma [21]. Metabolic syndrome is characterized by a complicated set of variables, including glucose intolerance and insulin resistance, central obesity, dyslipidemia, and hypertension [22, 23]. Many studies have given preliminary evidence on the association between metabolic syndrome and hepatocellular cancer throughout the last decade [24, 25].

Statin usage was proven to be protective against hepatobiliary carcinoma. Statins have been studied for their chemo preventive effects in different cancers [26]. The inhibiting HMG-CoA acceleration, proapoptotic proteins, and proliferation in limited cell are pregulated by statins [27]. Statins have been shown in preclinical trials to promote apoptosis by decrease angiogenesis and suppress cancer [28, 29]. Statins have been shown to protect against colorectal and prostate cancer, but no association has been established with pancreatic cancer [29-31].

Subsequent studies, however, have found a statin is a considerable factor for reducing the risk for hepatocellular cancer [32], which is consistent with our findings. Obesity and insulin resistance the two most common components of MS, have been related to cancer and are now well recognized as substantial risk factors for HCC [32].

## CONCLUSION

The present study concluded that hepatobiliary carcinoma may be caused by metabolic syndrome, which includes dyslipidemia, a high body mass index, and high serum glucose levels as independent risk factors. This finding supports previous research and emphasizes that the connection between hapotabiliatry cancer and increased BMI remains for liver tumors, bile duct cancer, and gallbladder cancers.

## REFERENCES


1. Menon S, Mathew R. Association between metabolic syndrome and hepatobiliary cancers: A case-control study. Indian J Gastroenterol. 2019 Feb;38(1):61-68. doi: 10.1007/s12664-018-0925-y. Epub 2019 Jan 10. PMID: 30628006.
2. Menon S, Mathew R. Association between metabolic syndrome and hepatobiliary cancers: A case-control study. Indian Journal of Gastroenterology. 2019 Feb 14;38:61-8.
3. Yuan X, Wang X, Wu S, Chen S, Wang Y, Wang J, Lu Y, Sun Y, Fu Q, Wang L. Associations between metabolic dysfunction-associated fatty liver disease and extrahepatic cancers: a cohort in China. HEPATOBILIARY SURGERY AND NUTRITION. 2022 Apr 14.
4. Simon TG, King LY, Chong DQ, et al. Diabetes, metabolic comorbidities and risk of hepatocellular carcinoma: results from two prospective cohort studies. Hepatology. 2018;67:1797–806.
5. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. Hepatology. 2016;63:827–38.
6. Loomis AK, Kabadi S, Preiss D, et al. Body mass index and risk of nonalcoholic fatty liver disease: two electronic health record prospective studies. J Clin Endocrinol Metab. 2016;101:945–52.
7. Zhang W, Sun B. Impact of age on the survival of patients with liver cancer: an analysis of 27,255 patients in the SEER database. Oncotarget. 2015;6:633–41.
8. Peng YC, Lin CL, Hsu WY, et al. Statins are associated with a reduced risk of cholangiocarcinoma: a population-based case-control study. Br J Clin Pharmacol. 2015; 80:755–61.
9. Yokomichi H, Nagai A, Hirata M, et al. Statin use and all-cause and cancer mortality: BioBank Japan cohort. J Epidemiol. 2017;27:S84–91.
10. Shi M, Zheng H, Nie B, Gong W, Cui X. Statin use and risk of liver cancer: an update meta-analysis. BMJ Open. 2014;4:e005399.
11. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Metaanalytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
12. Li Z, Xue J, Chen P, et al. Prevalence of nonalcoholic fatty liver disease in mainland of China: a meta-analysis of published studies. J Gastroenterol Hepatol 2014;29:42-51.
13. Liu SS, Ma XF, Zhao J, et al. Association between nonalcoholic fatty liver disease and extrahepatic cancers: a systematic review and meta-analysis. Lipids Health Dis 2020;19:118.
14. Veracruz N, Hameed B, Saab S, et al. The Association Between Nonalcoholic Fatty Liver Disease and Risk of Cardiovascular Disease, Stroke, and Extrahepatic Cancers. J Clin Exp Hepatol 2021;11:45-81.
15. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-9.
16. Liu Z, Suo C, Shi O, et al. The Health Impact of MAFLD, a Novel Disease Cluster of NAFLD, Is Amplified by the Integrated Effect of Fatty Liver Disease-Related Genetic Variants. Clin Gastroenterol Hepatol 2022;20:e855-75.
17. Wang X, Wu S, Yuan X, et al. Metabolic Dysfunctionassociated Fatty Liver Disease and Mortality Among Chinese Adults: a Prospective Cohort Study. J Clin Endocrinol Metab 2022;107:e745-55.
18. Liu Z, Lin C, Suo C, et al. Metabolic dysfunctionassociated fatty liver disease and the risk of 24 specific cancers. Metabolism 2022;127:154955.
19. Lee H, Lee HW, Kim SU, et al. Metabolic DysfunctionAssociated Fatty Liver Disease Increases Colon Cancer Risk: A Nationwide Cohort Study. Clin Transl Gastroenterol 2022;13:e00435.
20. Yamamura S, Eslam M, Kawaguchi T, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int 2020;40:3018-30.
21. Tsutsumi T, Eslam M, Kawaguchi T, et al. MAFLD better predicts the progression of atherosclerotic cardiovascular risk than NAFLD: Generalized estimating equation approach. Hepatol Res 2021;51:1115-28.

22. Niriella MA, Ediriweera DS, Kasturiratne A, et al. Outcomes of NAFLD and MAFLD: Results from a community-based, prospective cohort study. PLoS One 2021;16:e0245762.
23. Wang, MD., Tang, SC., Li, C. et al. Association of Concurrent Metabolic Syndrome with Long-term Oncological Prognosis Following Liver Resection for Hepatocellular Carcinoma Among Patients with Chronic Hepatitis B Virus Infection: A Multicenter Study of 1753 Patients. Ann Surg Oncol 30, 346–358 (2023). https://doi.org/10.1245/s10434-022-12529-6.
24. Wu Y, Dong Y, Duan S, Zhu D, Deng L. Metabolic syndrome, inflammation, and cancer. Mediators Inflamm. 2017;2017:8259356.
25. Tian Y, Lyu H, He Y, Xia Y, Li J, Shen F. Comparison of hepatectomy for patients with metabolic syndrome-related HCC and HBV-related HCC. J Gastrointest Surg. 2018;22:615–23.
26. Jia HD, Liang L, Li C, Wu H, Wang H, Liang YJ, et al. Long-term surgical outcomes of liver resection for hepatocellular carcinoma in patients with HBV and HCV co-infection: a multicenter observational study. Front Oncol. 2021;11:700228.
27. Yoshida N, Takayama T, Midorikawa Y, Higaki T, Nakayama H, Moriguchi M, et al. Surgical outcomes in patients with hepatocellular carcinoma associated with metabolic syndrome. World J Surg. 2015;39:471–7.
28. Xing Y, Xu S, Jia A, Cai J, Zhao M, Guo J, et al. Recommendations for revision of Chinese diagnostic criteria for metabolic syndrome: a nationwide study. J Diabetes. 2018;10:232–9.
29. Yu JJ, Shen F, Chen TH, Liang L, Han J, Xing H, et al. Multicentre study of the prognostic impact of preoperative bodyweight on long-term prognosis of hepatocellular carcinoma. Br J Surg. 2019;106:276–85.
30. Du ZG, Wei YG, Chen KF, Li B. Risk factors associated with early and late recurrence after curative resection of hepatocellular carcinoma: a single institution's experience with 398 consecutive patients. Hepatobiliary Pancreat Dis Int. 2014;13:153–61.
31. Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol. 2019;16:411–28.
32. Wang MD, Li C, Liang L, Xing H, Sun LY, Quan B, et al. Early and Late Recurrence of Hepatitis B Virus-Associated Hepatocellular Carcinoma. Oncologist. 2020;25:e1541-1541e1551.