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ORIGINAL ARTICLE

Retrospective Cohort Study

Influence of proton pump inhibitors in the development of spontaneous bacterial peritonitis

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Author contributions: Mattos AA conceptualized and designed this study; Miozzo SAS, John JA, Appel-da-Silva MC and Dossin IA collected the data; Miozzo SAS reviewed the literature and wrote the manuscript with substantial contribution of Mattos AA; Mattos AA and Tovo CV reviewed the manuscript critically for important intellectual content; all authors approved the final version of the manuscript.

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Abstract

AIM

To investigate whether the use of proton pump inhibitors (PPIs) increases the incidence of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis and ascites.

METHODS

An historical cohort study was carried out in cirrhotic outpatients with ascites followed in a specialized clinic at a tertiary hospital in Southern Brazil. Patient charts were reviewed to collect information on the variables of interest as the use of PPIs. Primary outcome was defined as development of SBP during the study period. SBP was diagnosed based on ascitic fluid polymorphonuclear cell count $\geqslant$ 250 cells/mm^3 without evidence of an intra-abdominal, surgically treatable source of infection.

RESULTS

Of 738 cirrhotic patients, 582 (58.2% male) were enrolled, with mean age of 53.6 ± 12 years. Hepatitis C virus infection (36.2%) and alcohol abuse (25.6%) were the main etiologies of cirrhosis. The presence of ascites was detected in 299 (51.4%) patients during the development of the study. Nineteen patients with previous diagnosis of SBP undergoing secondary prophylaxis and 22 patients with insufficient PPI data were further excluded. Of 258

patients with ascites, 151 used PPIs, and 34 developed SBP (22.5%). Among 107 non-users of PPIs, 23 developed SBP (21.5%) (HR = 1.44, 95%CI: 0.85-2.47, *P* = 0.176). The median follow-up time of patients using PPI was 27 mo *vs* 32 mo for non-users. Univariate analysis of the risk factors associated with the development of SBP revealed a significant association of SPB with the severity of liver disease according to the Child-Turcotte-Pugh (CTP) score. Multivariate analysis confirmed that CTP score was the only independent variable influencing the occurrence of SBP. Survival at 60 mo (Kaplan-Meier analysis) was similar in users and non-users of PPI, independently of the presence of SBP (58.4% *vs* 62.7% respectively, *P* = 0.66). For patients with SBP, survival at 60 mo was 55.1%, *vs* 61.7% in patients without SBP (*P* = 0.34).

CONCLUSION

In conclusion, the rate of SBP was not significantly different in users or non-users of PPIs in this cohort of cirrhotic with ascites.

Key words: Cirrhosis; Bacterial infection; Spontaneous bacterial peritonitis; Proton pump inhibitors; Ascites

Core tip: The aim of the present study was to investigate whether the use of proton pump inhibitors (PPIs) increases the incidence of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis and ascites. An historical cohort study was carried out with cirrhotic patients. The primary outcome was development of SBP. Of 258 patients with ascites, 151 used PPIs, and 34 developed SBP (22.5%). Among 107 non-users of PPIs, 23 developed SBP (21.5%) (HR = 1.44, 95%CI: 0.85-2.47, *P* = 0.176). In conclusion, the use of PPIs does not increase the incidence of SBP in patients with cirrhosis and ascites.

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INTRODUCTION

The incidence and severity of bacterial infections have been reported to be greater in cirrhotic patients as compared to the general population[1]. In fact, there is evidence that bacterial infections are the cause of death in up to 25% of patients with cirrhosis[2], leading to a four-fold increase in mortality in this population[3]. Supporting this information, a study conducted in our center analyzed 541 consecutively hospitalized cirrhotic patients, revealing the presence of infection in 25% of the cases. In that study, the mortality of infected patients was also four-fold higher as compared to non-infected patients[4]. In addition, infection may trigger other typical complications associated with increased morbidity and mortality in cirrhosis[5,6].

Spontaneous bacterial peritonitis (SBP) is the most characteristic infection in cirrhosis, and prompt recognition and treatment are required to reduce the associated morbidity and mortality.

Bacterial translocation has been described as a key mechanism in SBP development. Small intestinal bacterial overgrowth potentially promotes bacterial translocation[7,8]. Thus, it has been speculated that chronic acid suppression by proton pump inhibitors (PPIs) - which favors gastric and duodenal bacterial colonization - may contribute to small intestinal bacterial overgrowth and consequently increase the incidence of SBP[9].

Nevertheless, there is some controversy regarding the role of PPIs in SBP. The findings of observational studies suggesting PPIs as a risk factor for SBP[10-12] have been supported by retrospective studies[13-19] and meta-analyses[20,21] providing evidence of increased SBP incidence associated with PPI use; however, recent studies by Mandorfer *et al*[22] and Terg *et al*[23] have not observed this relationship. The present study aimed to investigate the association of PPI treatment with the incidence of SBP in a cohort of outpatients with cirrhosis and ascites.

MATERIALS AND METHODS

This historical cohort study included outpatients with a diagnosis of cirrhosis treated in the Portal Hypertension Clinic at Hospital Santa Casa de Misericórdia de Porto Alegre, a tertiary hospital in the Southern Brazil, between March 2005 and March 2014.

The diagnosis of cirrhosis was confirmed by clinical, laboratory, and imaging data, endoscopy or histologic examination. Outpatient follow-up of at least 1 year was required for inclusion in the study. Primary outcome was defined as development of SBP during the study period.

Patient charts were reviewed to collect information on the variables of interest: Age, sex, etiology of liver disease, Child-Turcotte-Pugh (CTP) score[24] and Model for End-Stage Liver Disease (MELD) score[25], comorbidities, continuous medications (including but not restrict to PPIs), lifetime, hospital admissions, and complications including ascites, SBP, upper gastrointestinal bleeding. At each outpatient visit, serum levels of albumin, creatinine, bilirubin, platelets, and prothrombin time were recorded.

Exclusion criteria were lack of diagnostic confirmation of cirrhosis, co-infection with human immunodeficiency virus (HIV), diagnosis of advanced hepatocellular carcinoma (beyond the Milan criteria)[26] at the first outpatient consultation, and missing clinical data. In addition, in patients with ascites at the moment of enrolment and those undergoing secondary prophylaxis

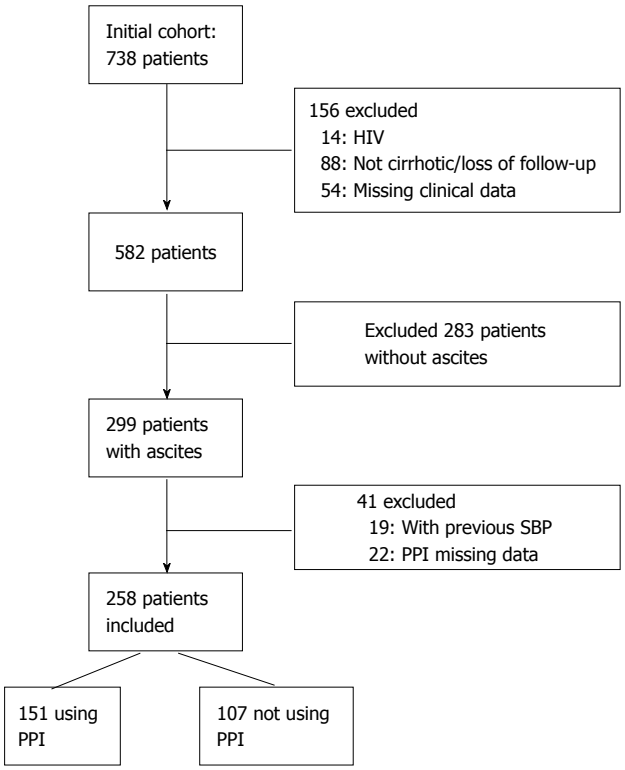

Figure 1 Flow diagram of inclusion. PPI: Proton pump inhibitor; HIV: Human immunodeficiency virus.

due to prior diagnosis of SBP were excluded. PPI treatment was defined as continuous when in use for at least 3 mo. Indications for PPI treatment were determined based on chart review.

The primary outcome, SBP, was diagnosed based on ascitic fluid polymorphonuclear cell count $\geqslant$ 250 cells/mm^3 without evidence of an intra-abdominal, surgically treatable source of infection[7,27,28]. The study was approved by the Research Ethics Committee at Hospital ISCMPA (protocol 3675/11).

Statistical analysis

Continuous data were expressed as means and SD or medians and interquartile range in case of non-Gaussian distribution. Categorical variables were expressed as numbers and percentage. Student's *t* test was used for comparison of means, and Mann-Whitney's *U* test for comparison of medians. Categorical data were compared using the χ^2 test or Fisher's exact test. The incidence of SBP during the follow-up period was estimated using the Kaplan-Meier (KM) method. The comparison of KM curves of users *vs* non-users of PPI was performed using the log-rank test. The magnitude of the association between PPI use and presence of SBP was expressed as hazard ratio (HR) with 95%CI, and calculated using a Cox proportional hazards model adjusted for CTP and MELD scores and the presence of upper gastrointestinal bleeding. Data were processed and analyzed using SPSS v. 22.0 at a significance level of $P = 0.05$.

RESULTS

Of 738 eligible patients, 156 were excluded: 14 patients with HIV, 88 without diagnostic confirmation of cirrhosis or loss of follow-up, and 54 with missing clinical data. The mean age of the 582 patients included in the initial sample was 53.6 ± 12 years, and 58.2% were male. Hepatitis C infection (36.2%) and alcohol abuse (25.6%) were the main etiologies of cirrhosis. Median outpatient follow-up was 5 years.

The presence of ascites was detected in 299 (51.4%) patients during the development of the study. A further 19 patients with a previous diagnosis of SBP undergoing secondary prophylaxis and 22 patients with insufficient PPI data were excluded. Thus, 258 patients with ascites were selected for follow-up (Figure 1). The median follow-up time of patients using PPI was 27.1 (3-60) mo *vs* 32.2 (7-60) mo for non-users of PPI. The patients were using a standard dose of 20 mg qd of omeprazole, the medication available free of charge in the public health system.

Demographic, clinical, and laboratory data of users and non-users of PPI are shown in Table 1. No significant differences were detected between the groups. Of 151 users of PPI, 34 (22.5%) developed SBP *vs* 23 (21.5%) of 107 non-users of PPI. This comparison was not statistically significant (HR = 1.44, 95%CI: 0.85-2.47, $P = 0.176$) (Figure 2).

Univariate analysis of the risk factors associated with the development of SBP revealed a significant association with the severity of liver disease according to the CTP score. Multivariate analysis confirmed that CTP score was the only independent variable influencing the occurrence of SBP. Patients with CTP-B and C had a two-fold and three-fold increase, respectively, in the risk of SBP as compared to patients with CTP-A (HR = 2.16, 95%CI: 1.14-4.09, $P = 0.018$ in CTB B patients and HR 3.77, 95%CI: 1.66-8.59, $P = 0.002$ in CTP C patients) (Table 2). Using the COX model, the events occurred in Child A 18.2%; Child B 35.6%; and Child C 52.7%; $P < 0.001$. Throughout the follow-up period, the Child C patients presented a higher mortality.

Survival at 60 mo (Kaplan-Meier analysis) was similar in users and non-users of PPI, independently of the presence of SPB (58.4% *vs* 62.7% respectively, $P = 0.66$). For patients with SBP, survival at 60 mo was 55.1%, *vs* 61.7% in patients without SBP ($P = 0.34$).

In the group of 151 patients using PPI, 19 patients had a diagnosis of peptic ulcer (12.6%), 20 presented gastric esophageal reflux (13.1%) and 17 used PPI to treat dyspepsia (11.3%). Evidence of formal indication for PPI treatment was not found in the chart of 95 patients (63%).

DISCUSSION

Given the importance of SBP in the context of liver disease, the identification of possible risk factors is crucial to prevent this infection. Among possible risk

Table 1 Sociodemographic and clinical characteristics of patients classified according to the use or not of proton pump inhibitors

Characteristic	Use of PPI		*P*
	Yes (*n* = 151)	No (*n* = 107)	
Age (yr)	54.7 ± 11.2	53.1 ± 11.3	0.26[1]
Male sex (%)	63.30%	62.60%	> 0.99[2]
Etiology of liver disease (%)			0.53[2]
Hepatitis C virus	34.50%	34.00%	
Alcohol	27.00%	34.90%	
Alcohol + hepatitis C virus	24.30%	19.80%	
Other	14.20%	11.30%	
Platelet count, × 10^3/mm^3	126 ± 81	112 ± 56	0.13[1]
Creatinine, mg/dL	1.07 ± 0.69	0.97 ± 0.27	0.15[1]
Albumin, g/dL	3.4 ± 0.6	3.3 ± 0.6	0.70[1]
Total bilirubin, mg/dL	1.30 (0.80-2.60)	1.40 (0.90-2.60)	0.59[3]
Prothrombin time, INR	1.34 ± 0.29	1.41 ± 0.26	0.24[1]
Child-Turcotte-Pugh score (%)			0.37[2]
A	42.40%	36.40%	
B	42.40%	51.40%	
C	15.20%	12.10%	
MELD score	12.5 ± 3.9	12.7 ± 3.8	0.71[1]
Upper gastrointestinal bleeding (%)	21.90%	18.70%	0.64[2]

Data expressed as mean ± SD, median (25-75 interquartile range) or *n* (%). [1]Student's *t* test; [2]Fisher's exact test; [3]Mann-Whitney's *U* test. MELD: Model for end-stage liver disease.

Table 2 Relationship between selected variables and presence of spontaneous bacterial peritonitis

Variable	*n*	Events *n* (%)	Bivariate analysis		Multivariate analysis	
			HR (95%CI)	*P*	HR (95%CI)	*P*
PPI use						
Yes	151	34 (22.5)	1.44 (0.85-2.47)	0.176	1.50 (0.87-2.58)	0.142
No	107	23 (21.5)	1		1	
CTP						
A	103	15 (26.3)	1		1	
B	119	30 (52.6)	2.10 (1.12-3.92)	0.020	2.16 (1.14-4.09)	0.018
C	36	12 (21.1)	3.62 (1.69-7.78)	0.001	3.77 (1.66-8.59)	0.002
MELD						
⩾ 15	78	19 (33.3)	1.41 (0.81-2.45)	0.226	0.95 (0.52-1.72)	0.854
< 15	180	38 (66.7)	1		1	
UGB						
Yes	53	11 (19.3)	0.92 (0.48-1.79)	0.808	0.99 (0.51-1.92)	0.967
No	205	46 (83.7)	1			

PPI: Proton pump inhibitor; CTP: Child-Turcotte-Pugh; MELD: Model for end-stage liver disease; UGB: Upper gastrointestinal bleeding.

factors, the role of PPIs has been recently discussed. To our knowledge, this is the first study conducted in Brazil in a cohort representing a population with typical environment and demographic characteristics as racial heterogeneity, probably traducing a differentiation in the gut microbiota.

The gastric acidity exerts a defense of the host against enteric pathogens, supporting the hypothesis of an influence of acid suppression on the development of secondary infections resulting from increased bacterial populations in the gastrointestinal tract. As in the pathogenesis of other bacterial infections in patients with cirrhosis, bacterial translocation plays a key role in the genesis of SBP, and has been described as the main trigger of SBP development[29-31]. The increased prevalence of bacterial overgrowth and intestinal dysmotility in cirrhotic patients with SBP when compared to cirrhotic patients without SBP underscores the role of intestinal microbiota in the pathogenesis of this infection[32]. A prospective study with 70 patients with cirrhosis analyzed jejunal secretion cultures and observed an association of bacterial overgrowth with acid-suppressive therapy ($P = 0.01$) and hypochlorhydria ($P < 0.001$); nevertheless, no statistical association was detected between the presence of SBP and bacterial overgrowth or acid-suppressive therapy[8]. With regard to the microbiota, few studies[33-35] were carried out in Brazil, making interesting the pioneer knowledge of the impact of the PPIs in cirrhosis.

In the present study, a cohort of patients with cirrhosis was followed-up, allowing the estimation of

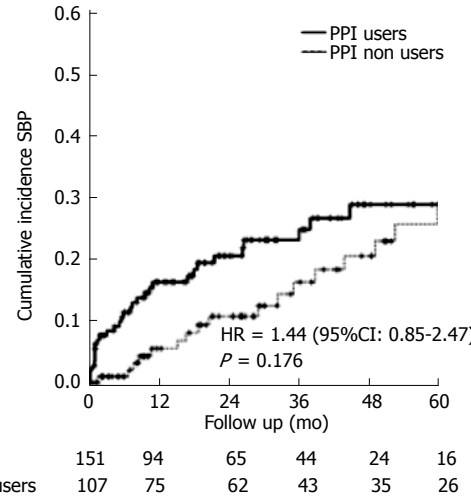

Figure 2 Kaplan-Meier curves of the cumulative incidence of spontaneous bacterial peritonitis events in patients with ascites using or not proton pump inhibitors. PPI: Proton pump inhibitor; SBP: Spontaneous bacterial peritonitis.

the incidence of SBP in users or non-users of PPI. We did not observe an association between the use of PPI and the incidence of SBP. However, the degree of liver dysfunction expressed as CTP score was strongly related to incidence of SBP, with a three-fold increase in risk of SBP in patients with more severe disease (CTP C), as reported in other studies[22,36]. This association is also emphasized by previous observations showing that liver dysfunction is related to increased bacterial translocation[7,37].

It should be noted that some studies suggesting an association between PPIs and SBP did not achieve statistically significant results[8,13], or were unable to confirm this association in multivariate analyses[17]. It is important to emphasize that the studies linking the use of anti-secretory therapy to increased frequency of SBP are mostly retrospective or case-control in design[13-19,38].

Bajaj *et al*[38] have not observed significant associations between the use of PPI and the rate of severe infections (HR = 1.08, 95%CI: 0.90-1.30) or infections related to acid-suppressive therapies (HR = 1.22, 95%CI: 0.97-1.52), except when the duration of PPI treatment was taken into account. In this study the authors do not describe the severity of liver disease of patients.

Min *et al*[39] reported an association between PPIs and SBP based on results from 1554 patients with cirrhosis and ascites. There were 90 cases of SBP among 512 users of PPI (10.6%) and 146 cases of SBP among 1042 non-users (5.8%). The annual incidence rate of SBP was higher in those using PPIs (HR 1.396, 95%CI: 1.057-1.843, $P = 0.019$).

Regarding the influence of acid-suppressive therapies on the development of SBP, some works have described different results for PPI and histamine-2 receptor antagonists (H2RA)[15,21,38], with no reported influence of H2RA. This has prompted a discussion regarding whether the difference between these acid-suppressive therapies results from a stronger acid-suppressive effect and greater delay in gastric emptying with PPIs[40,41] or from weaknesses in the hypothesis of acid-suppressive therapy as an independent risk factor for SBP. In the present study, all patients received omeprazole 20 mg qd, since this is the medication available free of charge in the Public Health System.

Meta-analyses[20,21,42] carried out to evaluate the association between acid-suppressive therapies and SBP have confirmed a relationship. The first of these[20] meta-analyzed case-control and retrospective studies with hospitalized patients. The meta-analyzed studies involved 772 individuals with cirrhosis using PPIs, for and odds ratio (OR) of 2.77 (95%CI: 1.82-4.23). A second meta-analysis[21] involved 3815 patients with cirrhosis, and showed significantly higher risk of SBP in users of PPIs *vs* non-users (OR = 3.15, 95%CI: 2.09-4.74, $P < 0.00001$); however, once again that study included mostly retrospective, case-control studies of hospitalized patients. Other limitations included the lack of information regarding dose and duration of PPI and H2RA treatment. The more recent meta-analysis[42] evaluated 7822 patients from 14 studies (6 case-control studies with 817 patients and 8 cohort studies with 7005 patients). The authors found statistically significant but quantitatively small associations between SBP and the use of PPIs. After adjustment for publication bias, there was very low-quality evidence per the GRADE approach in favor of this association. Therefore, they suggest that patients with cirrhosis who have indications for the use of PPI should not be denied because of concern for precipitating SBP.

In the same way, van Vlerken *et al*[36] did not observe an influence of PPIs on bacterial infection in a prospective analysis of cirrhotic patients receiving outpatient follow-up (HR = 1.2, 95%CI: 0.5-3.0, $P = 0.72$). It should be noted, however, that those authors had only a small number of cases of SBP. More recently, Mandorfer *et al*[22] carried out a retrospective cohort analysis of 607 patients submitted to paracentesis and did not identify PPIs as a risk factor for SBP. Similarly, in a multicenter study with 521 cirrhotic patients, Terg *et al*[23] reported similar SBP rates in patients at increased risk of SBP infection - 79.5% in users and 78.7% in non-users of PPIs.

The low mortality observed in patients with SBP in relation to the group without this infection is probably related to the fact that these infections are community-acquired, which results in a lower severity. We recently published a study showing the relevance of multiresistant bacteria in patients with nosocomial SBP, which certainly worsens the prognosis of these patients[43]. However, when patients with a greater impairment of hepatocellular function were evaluated (Child C), mortality was higher.

One aspect that deserves attention is the high prevalence of PPI use (58%) in our patients, and the fact that 63% of those using PPI did not have evidence of formal indication for PPI therapy. Similar data have been previously described, with PPI used by as many as 86% of patients[23] and used by as many as 63% patients without documented indications[16,19,23,36,44-46]. PPIs have been used to prevent gastroesophageal reflux and worsening of inflammation and esophageal ulceration following band ligation and sclerotherapy in cirrhotic patients; however, this practice is questionable[45-47]. As possible limitations of the present study we should note that most of the data were obtained from reviewing the charts, which is important to remark thus we are aware of the potential biases.

In conclusion, considering the current uncertainty regarding PPIs as a risk factor for SBP in patients with cirrhosis, the present study evaluated an historical cohort of cirrhotic outpatients with ascites and did not find evidence of increased incidence of SBP with the use of PPIs. In addition, the CTP score was strongly related to incidence of SBP.

COMMENTS

Background

Spontaneous bacterial peritonitis (SBP) is the most characteristic infection in cirrhosis, and has been associated to morbidity and mortality. Small intestinal bacterial overgrowth potentially promotes bacterial translocation. Thus, it has been speculated that chronic acid suppression by proton pump inhibitors (PPIs) - which favors gastric and duodenal bacterial colonization - may contribute to small intestinal bacterial overgrowth and consequently increase the incidence of SBP. Nevertheless, there is some controversy regarding the role of PPIs in SBP.

Research frontiers

The increased prevalence of bacterial overgrowth and intestinal dysmotility in cirrhotic patients with SBP when compared to cirrhotic patients without SBP underscores the role of intestinal microbiota in the pathogenesis of this infection. However, few studies evaluating the gut microbiota were carried out in cirrhotic patients, mainly in Brazil, making interesting the pioneer knowledge of the impact of the PPIs in cirrhosis.

Innovations and breakthroughs

To the knowledge, this is the first study conducted in Brazil in a cohort representing a population with typical environment and demographic characteristics as racial heterogeneity, probably traducing a differentiation in the gut microbiota. Considering the current uncertainty regarding PPIs as a risk factor for SBP in patients with cirrhosis, the present study evaluated an historical cohort of cirrhotic outpatients with ascites and did not find evidence of increased incidence of SBP with the use of PPIs.

Applications

One aspect that deserves attention is the high prevalence of PPI use (58%) in the patients, and the fact that 63% of those using PPI did not have evidence of formal indication for PPI therapy. Similar data have been previously described in the literature, with PPI used by as many as 86% of patients and used by as many as 63% patients without documented indications. So, it is possible that these results may alert and promote the correct use of PPI in cirrhotics.

Peer-review

The study is well conducted and statistical methods are sound.

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ORIGINAL ARTICLE

Retrospective Study

Occult hepatitis B virus infection and surgical outcomes in non-B, non-C patients with curative resection for hepatocellular carcinoma

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Abstract

AIM

To investigate the prevalence, clinicopathological characteristics and surgical outcomes of occult hepatitis B virus (HBV) infection (OBI) in patients with non-B, non-C (NBNC) hepatocellular carcinoma (HCC).

METHODS

This study retrospectively examined the cases of 78 NBNC

patients with curative resection for HCC for whom DNA could be extracted from formalin-fixed paraffin-embedded tissue. OBI was determined by the HBV-DNA amplification of at least two different sets of primers by TaqMan real-time polymerase chain reaction. Possibly carcinogenetic factors such as alcohol abuse, diabetes mellitus, obesity and non-alcoholic steatohepatitis (NASH) were examined. Surgical outcomes were evaluated according to disease-free survival (DFS), overall survival (OS) and disease-specific survival (DSS).

RESULTS

OBI was found in 27/78 patients (34.6%) with NBNC HCC. The OBI patients were significantly younger than the non-OBI cases at the time of surgery (average age 63.0 *vs* 68.1, P = 0.0334) and the OBI cases overlapped with other etiologies significantly more frequently compared to the non-OBI cases (P = 0.0057). OBI had no impact on the DFS, OS or DSS. Only tumor-related factors affected these surgical outcomes.

CONCLUSION

Our findings indicate that OBI had no impact on surgical outcomes. The surgical outcomes of NBNC HCC depend on early tumor detection; this reconfirms the importance of a periodic medical examination for individuals who have NBNC HCC risk factors.

Key words: Hepatocellular carcinoma; Non-B non-C; Occult hepatitis B virus infection; Surgery; Surgical outcome

Core tip: We analyzed the occult hepatitis B virus infection (OBI) status of 78 cases of non-B, non-C hepatocellular carcinoma (NBNC HCC). OBI was found in 27/78 patients (34.6%). The OBI patients were significantly younger than the non-OBI patients at the time of surgery, and the OBI cases were frequently overlapped with other etiologies. OBI had no impact on surgical outcomes. Only tumor-related factors affected the surgical outcomes. The surgical outcomes of NBNC HCC thus depend in part on the early detection of the tumor.

Koga H, Kai K, Aishima S, Kawaguchi A, Yamaji K, Ide T, Ueda J, Noshiro H. Occult hepatitis B virus infection and surgical outcomes in non-B, non-C patients with curative resection for hepatocellular carcinoma. *World J Hepatol* 2017; 9(35): 1286-1295 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i35/1286.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i35.1286

INTRODUCTION

Although the most major risk factors for hepatocellular carcinoma (HCC) are hepatitis C virus (HCV) infection and hepatitis B virus (HBV) infection, the prevalence of non-B, non-C (NBNC) HCC patients who are negative for both hepatitis C antibody (HCVAb) and hepatitis B surface antigen (HBsAg) has gradually increasing. In a 2010 Japanese survey, the prevalence of NBNC HCC were 24.1% of all HCC patients[1].

Alcoholic liver disease (ALD)[2] and non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)[3,4] are well-known etiologies of NBNC HCC. Other known etiologies of NBNC HCC include hemochromatosis[5], Budd-Chiari syndrome[6], metabolic disease, autoimmune hepatitis, primary biliary cirrhosis, parasitic disease, congestive disease and unknown etiology[7]. Occult HBV infection (OBI) was also recognized as one of the risk factors for the development of HCC[8,9]. OBI is considered one of the possible phases in the natural history of chronic HBV infection[10], and it reflects the persistence of HBV genomes in the hepatocytes of individuals who test negative for HBsAg[11]. The gold standard to diagnose OBI is the detection of HBV DNA in the hepatocytes by highly sensitive and specific techniques such as real-time polymerase chain reaction (PCR) using the sets of specific primers for different HBV genomic regions[11-14].

The virology and pathogenesis of OBI have been well investigated[15,16], and many epidemiological and molecular biological studies have addressed that OBI is an important risk factor for developing HCC[9]. However, the clinical characteristics and surgical outcomes of OBI-associated HCC have not been well-investigated. We could not find any study that investigated in detail a surgical series of OBI-associated HCC. It is quite important to determine the clinical characteristics and surgical outcomes of OBI-associated HCC among cases of NBNC HCC or HCV-associated HCC because different etiologies of HCC may modulate the clinical characteristics and outcomes, thereby requiring different preventive and therapeutic strategies.

Our aim in the present study was to clarify the prevalence, clinicopathological characteristics and surgical outcomes in patients with OBI-associated HCC in our surgical series of NBNC HCC patients. To the best of our knowledge, this is the first study investigating the surgical outcomes in OBI-associated NBNC HCC.

MATERIALS AND METHODS

Patients

Initially, 477 patients with HCC who underwent curative surgical resection for the primary lesion at Saga University Hospital between 1984 and 2012 were enrolled the study. All patients enrolled in this study had no lymph node metastasis or distant metastasis at the time of surgery. Of these, 83 cases of NBNC HCC were identified and subjected to DNA extraction from formalin-fixed paraffin-embedded (FFPE) tissue blocks. These 83 NBNC HCC cases were same population of previous our study[17]. We retrospectively examined a

final total of 78 cases of NBNC HCC (in the other five cases, DNA was unavailable). Written informed consent for the use of their liver tissues and clinical information was obtained from all patients. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine at Saga University (Approval No. 27-18).

Nucleic acid extraction from liver tissues

Sections cut from FFPE tissue blocks of noncancerous liver tissue were used. The NucleoSpin® DNA FFPE system (Takara Bio, Shiga, Japan) was used to extract the nucleic acid from liver tissues (< 10 mg) per the manufacturer's instructions. The DNA was eluted in 20 μL of Tris Borate EDTA (TBE) buffer. The amount and quality of extracted DNA was confirmed by NanoDrop® (Thermo Fisher Scientific, Yokohama, Japan).

Detection of HBV DNA and definition of occult HBV infection

The regions of HBs, hepatitis B core (HBc), and hepatitis B x (HBx) in the HBV DNA were analyzed by TaqMan real-time PCR per the manufacturer's guidelines (TaqMan Fast Universal PCR Master Mix; Applied Biosystems, Foster City, CA). The oligonucleotide primers and probes which were specific for the S, X and C regions of HBV were as described by Kondo *et al*[18]. Plasmid pBRHBadr72 (full-length HBV DNA) was used as an internal standard. The detection limit of our TaqMan real-time PCR was 100 copies/mL. Only the cases in which HBV DNA was detected by the TaqMan real-time PCR using at least two different sets of primers were considered to exhibit OBI[11].

Analyses of alcohol abuse, obesity, diabetes mellitus

To analyze the relationships between OBI and other etiologies of NBNC HCC, we also investigated the patients' alcohol consumption status and metabolic factors such as diabetes mellitus, obesity and NASH. The patients who were clinically diagnosed as having diabetes mellitus were categorized as diabetes mellitus group. A body mass index (BMI) > 25 kg/m^2 in both genders was defined as obesity. We defined an alcohol abuse as a daily ethanol consumption of > 40 g for men and > 20 g for women.

Histopathological analysis

To pathologically assess the degree of fibrosis in noncancerous liver tissues, we used the new Inuyama classification system which is widely used in Japan: F0, no fibrosis; F1, portal fibrosis widening; F2, portal fibrosis widening with bridging fibrosis; F3, bridging fibrosis plus lobular distortion; and F4, cirrhosis[19]. The diagnoses of NASH were pathologically confirmed. These histopathological analysis and classification were performed by two pathologists (Keita Kai and Shinichi Aishima).

Table 1 Status of occult hepatitis B virus infection (n = 78)

Occult HBV infection (%)	
(+)	27 (34.6)
(−)	51 (65.4)
Details of HBV amplification	
HBc lesion (%)	23 (29.4)
HBs lesion (%)	50 (64.1)
HBx lesion (%)	32 (41.0)
Amplification of at least one lesion (%)	64 (82.1)

HBV: Hepatitis B virus.

Statistical analysis

All statistical analyses were supervised by a statistician (Atsushi Kawaguchi). The statistical analysis was performed using JMP ver. 12 software (SAS Institute, Cary, NC) and SAS software ver. 9.4 (SAS Institute, Cary, NC). Continuous variables are expressed as the mean ± SD and were compared using the Student's t test. Categorical variables were compared using the χ^2 test and Fisher's exact test, as appropriate. Disease-free survival (DFS), overall survival (OS) and disease-specific survival (DSS) was determined according to our previous report[17]. The uni- and multi-variate analyses were performed using a Cox proportional hazards model. To adjust the potential covariates for the comparison of OBI status in the multivariate analysis, age, gender and OBI status were always kept in the model and other parameters were selected by the stepwise procedure with the P-value threshold of 0.2. P-values < 0.05 were considered as statistically significant.

RESULTS

Status of OBI

The OBI status of the patients is summarized in Table 1. Twenty-seven patients (34.6%) were categorized as having an OBI in this study. The details of HBV-DNA amplification were HBc lesion, 23 cases (29.4%); HBs lesion, 50 cases (64.1%); and HBx lesion, 32 cases (41.0%). The number of cases with amplification of at least one lesion was 64 cases (82.1%).

Clinicopathological features of NBNC HCC according to OBI status

Table 2 demonstrates the summary of the clinico-pathological features. The 78 patients with NBNC HCC were consisted of 61 men (78.2%) and 17 women (21.8%). The mean age at the time of surgery was 66.3 years. Alcohol abuse was identified in 19 patients (24.4%). Twenty-seven patients (34.6%) had diabetes mellitus and obese was found in 24 patients (30.8%). NASH was pathologically confirmed in eight patients (10.3%).

We compared the OBI cases (n = 27) with the non-OBI cases (n = 51) regarding clinicopathologic

Table 2 Clinicopathologic features of the patients with non-B, non-C hepatocellular carcinoma (*n* = 78) according to occult hepatitis B virus infection status

	Total cases (*n* = 78)	OBI (*n* = 27)	Non-OBI (*n* = 51)	*P*[1]
Age (mean ± SD)	66.3 ± 11.9	63.0 ± 17.0	68.1 ± 7.6	0.0334
Gender (%)				0.6066
Male	61 (78.2)	22 (81.5)	39 (79.5)	
Female	17 (21.8)	5 (18.5)	12 (20.5)	
Alcohol abuse (%)				0.8151
(+)	19 (24.4)	7 (25.9)	12 (23.5)	
(-)	59 (75.6)	20 (74.1)	39 (77.1)	
Diabetes mellitus (%)				0.106
(+)	27 (34.6)	10 (37.0)	17 (33.3)	
(-)	51 (65.4)	17 (63.0)	34 (66.7)	
Obesity (%)				0.4966
(+)	24 (30.8)	7 (25.9)	17 (33.3)	
(-)	54 (69.2)	20 (74.1)	34 (66.7)	
BMI (mean ± SD)	22.7 ± 4.56	22.1 ± 3.67	23.1 ± 4.97	0.3537
Size (mean ± SD), mm	64.2 ± 41.8	72.7 ± 45.6	59.8 ± 39.4	0.1955
Solitary/multiple (%)				0.8959
Solitary	47 (60.3)	16 (59.3)	31 (60.8)	
Multiple	31 (39.7)	11 (40.7)	20 (39.2)	
Vp (%)				0.7217
(+)	31 (39.7)	10 (37.0)	21 (41.2)	
(-)	47 (60.2)	17 (60.3)	30 (58.8)	
Liver fibrosis (%)				0.2851
F0-2	44 (56.4)	13 (48.2)	31 (60.8)	
F3-4	34 (43.6)	14 (51.8)	20 (39.2)	
NASH (%)				0.007
(+)	8 (10.3)	0	8 (15.7)	
(−)	70 (89.7)	27	43 (84.3)	
No. of etiologies				0.0057[2]
Single	38 (48.7)	11 (40.7)	27 (52.9)	
Multiple	25 (32.1)	16 (59.3)	9 (17.7)	
Unknown	15 (19.2)	0	15 (29.4)	

[1]Comparison between OBI and non-OBI cases; [2]Analysis excluding unknown cases. OBI: Occult HBV infection; Vp: Portal vein invasion; NASH: Non-alcoholic steatohepatitis; BMI: Body mass index.

factors (age, gender, alcohol abuse, diabetes mellitus, obesity, BMI, tumor size, solitary/multiple, portal vein invasion, degree of background liver fibrosis, NASH and number of etiologies). Significant differences were observed in age, NASH and the number of etiologies. The OBI patients were significantly younger than the non-OBI patients at the time of surgery (P = 0.0334): 63.0 ± 17.0 and 68.1 ± 7.6 years (mean age ± SD), respectively. All eight NASH cases were non-OBI cases (P = 0.007). The OBI patients had multiple etiologies for HCC significantly more frequently compared to the non-OBI patients, and high significance was observed even in the analysis excluding etiology-unknown cases (P = 0.0057).

Etiologies for NBNC HCC

As shown in Table 2, the etiologies of our NBNC HCC cases consisted of 38 (48.7%) single-etiology cases, 25 (32.1%) multiple-etiology cases, and 15 (19.2%) unknown-etiology cases. The Venn diagram for the etiologies of NBNC HCC is given as Figure 1. OBI and alcohol abuse were frequently associated with other etiologies. The Venn diagram for the metabolic factors (obesity, diabetes mellitus and NASH) is given as Figure 2. NASH was frequently associated with other metabolic factors.

Univariate and multivariate analyses for DFS, OS and DSS

Table 3 demonstrates the results of the uni- and multivariate analyses for DFS by Cox's proportional hazards model. The significant factors which correlated with DFS by the univariate analyses were portal vein invasion, T factor of TMN classification, and multiple tumors at the time of surgery (P = 0.0013, P = 0.0006 and P = 0.0002, respectively). The factors significantly correlated with DFS by the multivariate analysis were portal vein invasion (P = 0.0217) and multiple tumor (P = 0.0499). No patient had undergone adjuvant therapy after curative surgery until recurrence.

The results of the univariate and multivariate analyses for OS are summarized in Table 4. Only the factors of portal vein invasion (P = 0.022) and multiple tumors (P = 0.0334) correlated with OS by the univariate analyses. The multivariate analysis for OS indicated only one significant correlation of portal vein invasion (P = 0.0378). Table 5 demonstrates the results of the uni- and multi-variate analyses for DSS. In the univariate analysis, only the factor "multiple

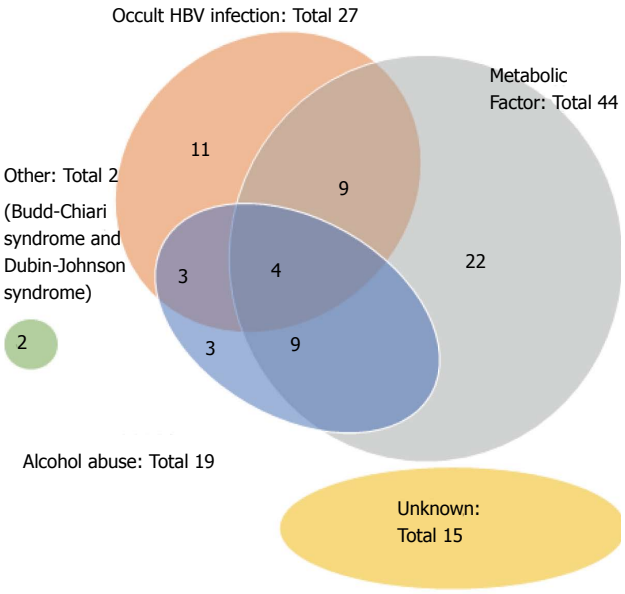

Figure 1 Venn diagram of the etiologies of non-B, non-C hepatocellular carcinoma. Occult hepatitis B virus infection and alcohol abuse were frequently associated with other etiologies.

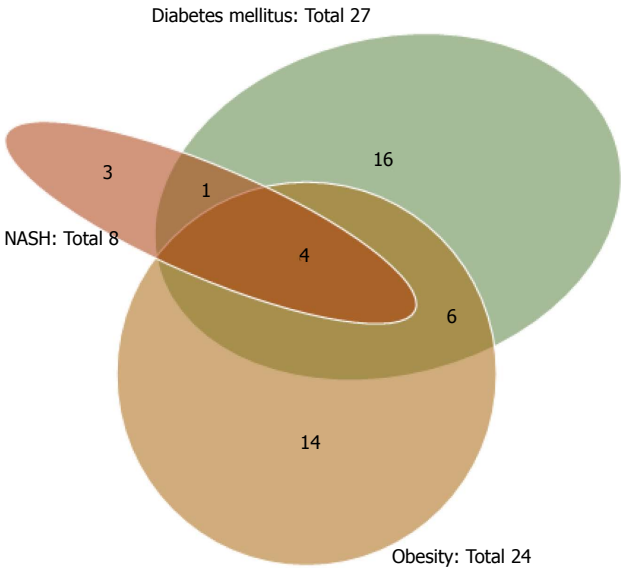

Figure 2 Venn diagram of metabolic factors (obesity, diabetes mellitus and non-alcoholic steatohepatitis). Non-alcoholic steatohepatitis (NASH) was frequently associated with other metabolic factors.

Table 3 Uni- and multi-variate analyses for disease-free survival after hepatic resection

Characteristic	*n*	Univariate analysis		Multivariate analysis	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age			0.316		0.1007
≤ 69	39	1		1	
> 69	39	0.74 (0.40-1.33)		0.58 (0.30-1.11)	
Gender			0.4847		0.298
Female	17	1		1	
Male	61	0.78 (0.41-1.60)		0.66 (0.31-1.41)	
Occult HBV infection			0.8739		0.7096
Absent	51	1		1	
Present	27	1.05 (0.55-1.93)		1.13 (0.59-2.17)	
Alcohol abuse			0.2752		
Absent	59	1			
Present	19	0.66 (0.28-1.35)			
Diabetes mellitus			0.8853		
Absent	51	1			
Present	27	0.95 (0.49-1.78)			
NASH			0.6226		
Absent	70	1			
Present	8	1.25 (0.47-2.75)			
Obesity			0.7641		
Absent	54	1			
Present	24	1.10 (0.57-2.02)			
Fibrosis			0.1477		0.2273
F0-2	44	1		1	
F3, 4	34	1.54 (0.86-2.80)		1.54 (0.78-2.81)	
Vp			0.0013		0.0217
Absent	47	1		1	
Present	31	2.90 (1.53-5.50)		2.52 (1.15-5.50)	
T12/T34			0.0006		0.4074
T12	38	1		1	
T34	40	3.14 (1.62-6.43)		1.57 (0.53-4.67)	
Solitary/multiple			0.0002		0.0499
Solitary	47	1		1	
Multiple	31	3.23 (1.73-6.14)		2.32 (0.99-5.42)	

HR: Hazard ratio; CI: Confidence interval; Vp: Portal vein invasion; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus.

Table 4 Uni- and multi-variate analyses for overall survival after hepatic resection

Characteristic	*n*	Univariate analysis		Multivariate analysis	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age			0.8321		0.6843
⩽ 69	39	1		1	
> 69	39	0.94 (0.50-1.73)		0.87 (0.45-1.67)	
Gender			0.2713		0.342
Female	17	1		1	
Male	61	1.54 (0.73-3.80)		1.51 (0.68-3.85)	
Occult HBV infection			0.6039		0.5263
Absent	51	1		1	
Present	27	1.18 (0.61-2.20)		1.23 (0.63-2.31)	
Alcohol abuse			0.3061		
Absent	59	1			
Present	19	1.45 (0.69-2.82)			
Diabetes mellitus			0.2441		
Absent	51	1			
Present	27	1.45 (0.76-2.67)			
NASH			0.7366		
Absent	70	1			
Present	8	0.84 (0.25-2.10)			
Obesity			0.9432		
Absent	54	1			
Present	24	1.02 (0.51-1.93)			
Fibrosis			0.7084		
F0-2	44	1			
F3,4	34	1.12 (0.60-2.06)			
Vp			0.022		0.0378
Absent	47	1		1	
Present	31	2.06 (1.11-3.81)		2.34 (1.05-5.24)	
T12/T34			0.0767		0.3344
T12	38	1		1	
T34	40	1.73 (0.94-3.27)		0.58 (0.20-1.73)	
Solitary/multiple			0.0334		0.0809
Solitary	47	1		1	
Multiple	31	1.94 (1.05-3.58)		2.17 (0.92-5.25)	

HR: Hazard ratio; CI: Confidence interval; Vp: Portal vein invasion; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus.

tumors" was significantly correlated with DSS (P = 0.0173). No significant factor was determined by the multivariate analysis.

DISCUSSION

Many studies have reported an association between OBI and HCC[9]. A meta-analysis in 2012 demonstrated that OBI increases the risk of developing HCC in both HCV- and non-HCV-infected patients[20]. However, other studies did not find such an association[21,22]. Although the debate remains, OBI has been recognized as a possible etiology in the development of HCC. Pathogenetic mechanisms of HCC development *via* OBI would be implicated in HBV-induced hepatocarcinogenesis, namely chronically sustained inflammation and direct oncogenic effect through integration into the host genome[9,23].

If OBI is an important etiology of HCC, it is quite important to clarify the clinical characteristics and outcomes of OBI-related HCC because different etiologies of HCC may modulate the clinical characteristics and outcomes, thereby requiring different preventive and therapeutic strategies. We therefore focused on NBNC HCC cases which were not influenced by HCV or overt HBV infection.

The prevalence of OBI in this study was 27/78 patients (34.6%). The prevalence of OBI has varied widely among the reported case series[8,24]. The difference in the prevalence of OBI may be due to the lack of methodological uniformity among the different studies[11]. Although the gold standard to diagnose OBI is the detection of HBV DNA in hepatocytes, studies testing OBI by using serum samples have been reported, and the methods of DNA detection varied widely. In addition, the detection of HBc antibody in the serum of HBsAg-negative patients has been used as a surrogate serum marker of OBI[12]. The previous reported prevalence of OBI varied from 12.1% to 78.0% in an anti-HBc positive patient series and from 5.7% to 50.0% in a series in which HBV-DNA was detected in hepatocytes or serum samples[12].

In the present study, OBI was determined by the HBV-DNA amplification of at least two different sets of primers by TaqMan real-time PCR using DNA extracted from FFPE tissues. It has been stated that the DNA extraction from frozen tissues was better than that

Table 5 Uni- and multi-variate analyses for disease-specific survival after hepatic resection

Characteristic	*n*	Univariate analysis		Multivariate analysis	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age			0.4181		0.2941
⩽ 69	39	1		1	
> 69	39	0.74 (0.34-1.54)		0.65 (0.27-1.44)	
Gender			0.3814		0.4598
Female	17	1		1	
Male	61	1.51 (0.62-4.48)		1.45 (0.56-4.56)	
Occult HBV infection			0.4661		0.4693
Absent	51	1		1	
Present	27	1.32 (0.60-2.78)		1.33 (0.60-2.88)	
Alcohol abuse			0.5064		
Absent	59	1			
Present	19	1.34 (0.52-3.02)			
Diabetes mellitus			0.4775		
Absent	51	1			
Present	27	1.31 (0.60-2.76)			
NASH			0.6755		
Absent	70	1			
Present	8	1.26 (0.37-3.27)			
Obesity			0.6466		
Absent	54	1			
Present	24	1.20 (0.53-2.53)			
Fibrosis			0.1392		0.2147
F0-2	44	1		1	
F3,4	34	1.74 (0.84-3.73)		1.62 (0.75-3.58)	
Vp			0.0806		0.1478
Absent	47	1		1	
Present	31	1.92 (0.91-4.03)		2.00 (0.78-5.08)	
T12/T34			0.0824		0.6238
T12	38	1		1	
T34	40	1.92 (0.92-4.15)		0.72 (0.19-2.75)	
Solitary/multiple			0.0173		0.0984
Solitary	47	1		1	
Multiple	31	2.44 (1.17-5.19)		2.55 (0.84-7.96)	

HR: Hazard ratio; CI: Confidence interval; Vp: Portal vein invasion; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus.

from FFPE[11]. In addition, all previous OBI studies using liver tissue were based on the frozen or raw liver tissue. Therefore, it was challenging to analyze the OBI status from FFPE samples. We have performed a pilot study using DNA extracted from FFPE tissues of overt HBV infection cases, and the results confirmed good HBV amplification in each primer set. Nevertheless, the possibility cannot be denied that the prevalence of OBI in this study would have been higher if frozen tissues were available. HBV covalently closed circular DNA (cccDNA) is harbored in the nucleus of HBV-infected hepatocytes, and therefore the results might have been affected if we had examined ccc DNA.

Our comparison of the OBI and non-OBI groups revealed that the patients with OBI were significantly younger than the patients without OBI at the time of surgery. This finding seems to support hepatocarcinogenesis of OBI. Recently, similar result has been reported. Coppola *et al*[25] analysed OBI in 68 consecutive HBsAg-negative patients with HCC by the presence of HBV DNA in at least two different PCRs and found that patients with OBI were significantly younger than the patients without OBI (mean age: 65.7 *vs* 71.2, $P = 0.03$). However, these results involving our series are not conclusive because the infection period of OBI was unknown. Additional studies are thus needed before a conclusion can be made regarding whether NBNC HCC develops more often in younger individuals with OBI compared to non-OBI patients.

The impact of OBI on liver fibrosis remains controversial. Several studies suggest an impact of OBI on the progression of liver fibrosis[25-29], whereas other studies found no association between OBI and liver fibrosis[29-32]. In the present study, we compared the degree of background liver fibrosis between the OBI and non-OBI cases, and we observed that the OBI group had a higher proportion (51.8%) of severe fibrosis cases (F3-4) compared to the non-OBI group (39.2%), although the difference was not significant.

Analyses of the surgical outcomes and clinicopathologic features according to OBI status were the main purpose of this study. Surgical outcomes according to known NBNC HCC etiologies such as alcohol, NAFLD/NASH, diabetes mellitus and obesity had been well investigated[1,33-36]. However, to the best of our knowledge, no previous study investigated the

association of OBI status and surgical outcomes in patients with NBNC HCC. Previous studies regarding OBI have been focused on the prevalence, the risk of developing HCC, and the prevalence of OBI in HCC cases[9,37,38].

Our present analyses of surgical outcome (DFS, OS and DSS) revealed that OBI status did not affect the surgical outcomes of NBNC HCC patients. The other analyzed etiologies also did not affect the surgical outcomes. Only tumor-related factors (*i.e.*, portal vein invasion, T-stage and multiple tumor) were associated with surgical outcomes of NBNC HCC. These findings indicate that the surgical outcome of NBNC HCC does not depend on the type of etiologies but that it does depend on the early detection of HCC. Therefore, a periodical screening of HCC using the abdominal echo and/or serum tumor markers is quite important for individuals who have one or more risk factors for NBNC HCC. For the early detection of NBNC HCC, the efficacy of the OBI screening using clinical samples (such as peripheral blood or liver biopsy specimen) should be discussed by accumulation of studies regarding OBI using clinical samples.

The limitations of our study were its retrospective nature, the long study period and the small number of patients. Information of actual number of tumors, viral serological markers except for HBsAg and HCVAb, and status of neoadjuvant treatments were not available. Diagnostic and therapeutic modalities also have changed in the recent decades. Our patients with NBNC HCC showed frequent overlapping in their etiology. Therefore, it is not an ideal method to compare OBI-associated patients to all the other NBNC patients. Association between metabolic factors (diabetes mellitus, NASH, and obesity) and HCC is considered much weaker than that of those of HBV and/or HCV. Therefore, it is doubtful these metabolic factors truly affected development of HCC.

In conclusion, the results of our study indicate that OBI was found in 34.6% of our series of patients with NBNC HCC. The patients with OBI were younger those without OBI at the time of surgery, and the OBI cases were frequently overlapped with other etiologies. The patients' surgical outcomes were not affected by the OBI status but were affected by only tumor-related factors, and thus the importance of the early detection of the tumors was reconfirmed. We hope to conduct larger retrospective or prospective studies to test our present findings.

COMMENTS

Research frontiers

Although many epidemiological and virological studies regarding occult HBV infection (OBI) have accumulated, the surgical outcomes of OBI-associated non-B, non-C (NBNC) hepatocellular carcinoma (HCC) have not been focused.

Innovations and breakthroughs

OBI was found in 27/78 (34.6%) patients with NBNC HCC. The OBI patients were significantly younger than the non-OBI patients at the time of surgery, and the OBI cases were frequently overlapped with other etiologies. OBI had no impact on surgical outcomes. Only tumor-related factors affected the surgical outcomes.

Applications

The results of present study indicated the possibility of OBI screening from formalin-fixed paraffin-embedded tissue. The importance of the early detection of HCC by a periodical checkup for individuals who have one or more risk factors for NBNC HCC was reconfirmed.

Terminology

In this study, OBI was determined by the HBV-DNA amplification of at least two different sets of primers by TaqMan real-time PCR using DNA extracted from FFPE tissues. NBNC-HCC is defined as hepatocellular carcinoma that has arisen in an individual who is negative for both hepatitis B surface antigen and hepatitis C antibody. Disease-free survival (DFS) was determined as the length of time after surgery that the patient survived without new lesions of HCC. Overall survival (OS) was determined from the time of surgery to the time of death or the most recent follow-up. Disease-specific survival (DSS) was determined from the time of surgery to the time of cancer-related death or the most recent follow-up.

Peer-review

It is a very interesting retrospective study in which they were able to show from the formalin-fixed paraffin-embedded tissue DNA of 78 patients that OBI had no impact on the surgical outcome and surgical outcomes of NBNC HCC depend on early tumor detection. This finding indicates that the importance of a periodic medical examination for individuals who have NBNC HCC risk factors. It is well-written, and presented.

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