Impact of Hepatitis B Virus on Clinicopathological Features and Outcomes After Resection for Pancreatic Adenocarcinoma

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Abstract. *Background/ Aim: Chronic hepatitis B virus (HBV) infection is sometimes considered a risk factor for pancreatic cancer (PDAC), but the prognostic value of its presence has only rarely been investigated. The present study aimed to explore the impact of HBV after resection for PDAC. Materials and Methods: According to HBV surface antigen seroreactivity, 343 patients were classified as having non-viral or HBV-related cases of PDAC. Clinicopathological data and outcomes were comparatively assessed between the groups. Results: Chronic HBV infection was observed in 16 patients (4.5%). No significant differences between the HBV and non-viral cases of PDAC were observed. Tumor diameters (3.4 vs. 3.0, p=0.092) and stages at diagnosis (31 vs. 14% T1-T2, p=0.082) tended to differ between the groups, albeit without reaching significance. Completion of adjuvant therapy (63 vs. 54%, p=0.612), as well as median overall survival (15 vs. 17 months, p=0.346) was similar in the HBV and non-viral PDAC groups. Conclusion: HBV-positive and virus-free patients with PDAC generally shared the same demographic, clinical and pathological profiles. HBV did not appear to have a detrimental effect on either early or long-term outcomes after resection for PDAC. Future studies searching for occult infection might, however, shed a different light on the role of HBV in PDAC.*

Pancreatic adenocarcinoma (PDAC) is a disease with dismal prognosis, and most patients will die within one year after diagnosis (1). PDAC represents an important healthcare problem with a predicted mortality rate in Europe of approximately 8 per 100,000 in men and approaching 6 per 100,000 in women for 2014 (2). Resection with adjuvant chemotherapy represents the single hope for a better prognosis (3-5), but long-term survival has been observed in only a minority of patients (6).

Hepatitis B virus (HBV) infection is also an important healthcare problem worldwide, although geographical disparities have been observed (7). HBV and hepatitis C virus (HCV) are widely considered to be the most prevalent risk factors for hepatocellular carcinoma worldwide, including Romanian patients (8, 9). The effects of viral hepatitis status on clinical, pathological and outcomes after curative-intent approaches for hepatocellular carcinoma have been previously explored to a great extent (9, 10).

Regarding PDAC, although several studies, mostly from East Asia, have identified HBV as a risk factor (11-16), only a few works published thus far have explored the effects of HBV infection on clinical, pathological and outcomes after therapy (17-19), and none has included patients in whom disease was only resected. Remarkably, no specific surveys have been conducted in a European context. Furthermore, patients with PDAC and HBV are considered to constitute a particular subset of patients with early onset (17, 18) and male predominance (18).

The aim of the present study was to assess the effects of HBV infection on demographics, clinical, and pathological data, and on early and long-term outcomes in a single surgical Center including a relatively large number of patients resected for PDAC.

Patients and Methods

Patients. Between 2002 and 2013, 348 patients underwent different types of pancreatectomy due to a final pathological diagnosis of PDAC at our Department of Surgery. HBV infection was tested using a serum enzyme immunoassay test for hepatitis B surface antigen (HBsAg). Hepatitis C virus infection was tested using a serum enzyme immunoassay test for hepatitis C virus antibody (anti-HCV).

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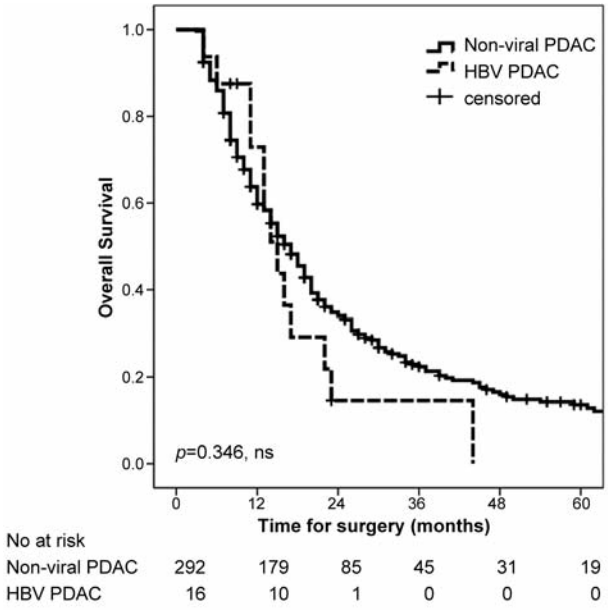

Figure 1. *Kaplan–Meier survival curves: hepatitis B virus group (16 patients) vs. non-viral (292 patients) group, resected for pancreatic adenocarcinoma. n.s.: Not significant.*

HBV infection was defined as the presence of HBsAg, while HCV infection was defined as the presence of anti-HCV antibody.

Patients with HBV infection with or without HCV co-infection were considered the HBV group (16 patients) while patients without HBV or HCV infection were considered the non-viral group (327 patients). The demographics, clinical, pathological and outcome data were comparatively assessed between the two groups. Notably, five patients with HCV infection only were excluded from the comparative analysis. The data were retrospectively assessed from a prospectively gathered electronic database established at our Department of Surgery. The study was approved by the Ethics Committee at our institution (No 1015-13).

Statistical analysis. Statistical analyses were performed with Statistical Packages for Social Sciences version 17.0 software (SPSS Inc., Chicago, IL, USA). The data are expressed as the numbers (percentages) for categorical variables and medians (ranges) for continuous variables. Fisher's exact test (two-tailed) was used to compare the categorical variables, while the Mann–Whitney test (two-tailed) was used for continuous variables. Median follow-up time was estimated using reversed Kaplan–Meier curves and median overall survival time was estimated using Kaplan–Meier curves; comparisons were performed using the log-rank test. Overall survival time was considered as the time from resection to death or last follow-up (July 1, 2014). *p*-Values less than 0.05 were considered statistically significant.

Results

Demographics. The non-viral group represented the majority of patients who underwent resection for PDAC (327 patients, 94.1%). HBV was present alone in 13 patients (3.7%), while HCV was present alone in five patients (1.4%). HBV and HCV co-infection was present in three patients (0.8%). Thus, overall HBV was present in 16 patients (4.5%) and HCV in 8 (2.2%). There were no significant differences between the HBV and non-viral PDAC groups regarding their age or gender, as shown in Table I. No differences between groups were observed for body-mass index, smoking and alcohol abuse (data not shown).

Table I. *Demographic data. Comparative analysis between the hepatitis B virus (HBV) pancreatic ductal adenocarcinoma (PDAC) and non-viral PDAC groups.*

Parameter	HBV PDAC group (16 patients)	Non-viral PDAC group (327 patients)	*p*-Value
Median (range) age, years	56 (47-75)	60 (34-85)	0.604[a]
Male sex, n (%)	8 (50%)	193 (59%)	0.604[b]

[a]Mann-Whitney test (two-tailed); [b]Fisher's exact test (two-tailed).

Clinical and pathological results. No differences were observed between the HBV and non-viral PDAC groups regarding associated diabetes mellitus, chronic pancreatitis or cardiovascular co-morbidities (Table II). Furthermore, no differences were observed regarding clinical signs and symptoms, serum carbohydrate antigen 19-9 (CA 19-9) level, operative procedures, associated vascular resection, operative time, blood loss, histological type and grade of differentiation, as shown in Table II. None of the patients in the HBV PDAC group presented clinical or laboratory signs of liver cirrhosis, while six patients (1.8%) in the non-viral group presented Child A toxic-nutritional cirrhosis ($p=1$). In addition, no differences were observed regarding the presence of lymph node or distant metastases, American Joint Commission on Cancer stages, or negative resection margin rates (Table II). Finally, two features, tumor diameter (3.4 *vs*. 3.0 cm, $p=0.092$) and T-stage (31 *vs*. 14.4% T1-T2, $p=0.082$), displayed trends toward differences, but without reaching the accepted level of statistical significance.

Early and late postoperative outcomes. No differences were observed between the HBV and non-viral PDAC patients regarding overall and severe postoperative complications, 90-day mortality, postoperative clinically relevant pancreatic fistulae, delayed gastric emptying, post-pancreatectomy hemorrhage or re-laparotomy rates, as shown in Table III. Nor were there any differences between the groups regarding the completion of adjuvant therapy rates (Table III).

Table II. *Clinical and pathological data. Comparative analysis between the hepatitis B virus (HBV) pancreatic ductal adenocarcinoma (PDAC) and non-viral PDAC groups.*

Parameter	HBV PDAC group (16 patients) (327 patients)	Non-viral PDAC group	*p*-Value
Diabetes mellitus, n (%)	4 (25%)	87 (27%)	1[b]
Chronic pancreatitis, n (%)	4 (25%)	67 (20%)	0.751[b]
Cardiovascular co-morbidities, n (%)	3 (19%)	95 (29%)	0.571[b]
Jaundice, n (%)	7 (44%)	161 (49%)	0.799[b]
Weight loss, n (%)	4 (25%)	138 (42%)	0.202[b]
Abdominal pain, n (%)	10 (63%)	174 (53%)	0.609[b]
Median (range) serum CA 19-9 level, ng/ml	182 (4-3794)	192 (1-5772)	1[a]
Type of surgical procedure, n (%)			0.343[b]
Pancreatico-duodenectomy	11 (69%)	244 (75%)	
Distal pancreatectomy	5 (31%)	67 (20%)	
Total pancreatectomy	0 (0%)	16 (5%)	
Vascular resection, n (%)	2 (13%)	71 (22%)	0.538[b]
Median (range) operative time, min	240 (120-360)	250 (110-600)	0.190[a]
Median (range) estimated blood loss, ml	375 (200-1400)	400 (100-4000)	0.935[a]
Median (range) tumor diameter, cm	3.4 (1-7)	3 (0.3-14)	0.092[a]
Histology, n (%)			0.346[b]
Ductal adenocarcinoma	14 (88%)	303 (93%)	
Cystadenocarcinoma	2 (12%)	24 (7%)	
Grade of differentiation, n (%)			1[b]
G1	10 (63%)	201 (61%)	
G2	5 (31%)	92 (28%)	
G3	1 (6%)	34 (11%)	
T-Stage, n (%)			0.082[b]
Cis	0 (0%)	1 (0.3%)	
T1	2 (12%)	9 (2.4%)	
T2	3 (19%)	38 (12%)	
T3	11 (69%)	271 (83%)	
T4	0 (0%)	8 (2.3%)	
Lymph node metastases (N1), n (%)	5 (31%)	163 (50%)	0.200[b]
Distant metastases (M1), n (%)	2 (12%)	28 (9%)	0.640[b]
AJCC stage, n (%)			0.305[b]
0	0 (0%)	1 (0.3%)	
1a	2 (12.5%)	6 (1.8%)	
1b	2 (12.5%)	18 (5.5%)	
2a	6 (37.5%)	127 (39%)	
2b	4 (25%)	140 (42.8%)	
3	0 (0%)	5 (1.5%)	
4	2 (12.5%)	29 (8.8%)	
NA		1 (0.3%)	
Resection margins, n (%)			1[b]
R0	10 (63%)	207 (63%)	
R1	4 (25%)	100 (31%)	
R2	2 (12%)	20 (6%)	

AJCC: American Joint Commission on Cancer; [a]Mann–Whitney test (two-tailed); [b]Fisher's exact test (two-tailed).

Table III. *Postoperative outcomes data. Comparative analysis between the hepatitis B virus (HBV) pancreatic ductal adenocarcinoma (PDAC) and non-viral PDAC groups.*

Parameter	HBV PDAC group (16 patients)	Non-viral PDAC group (327 patients)	*p*-Value
Postoperative complications, n (%)	8 (50%)	153 (47%)	0.804[b]
Severe complications, n (%)[‡]	3 (19%)	49 (15%)	0.718[b]
90-Day mortality, n (%)	0 (0%)	26 (7.9%)	0.621[b]
Clinically relevant POPF, n (%)[§]	4 (25%)	56 (17%)	0.496[b]
Clinically relevant DGE, n (%)[§]	4 (25%)	65 (20%)	0.538[b]
Clinically relevant hemorrhage, n (%)[§]	1 (6%)	34 (10%)	1[b]
Re-laparotomy for complications, n (%)	3 (19%)	33 (10%)	0.229[b]
Median (range) hospital stay, days	14 (10-58)	13 (1-80)	0.169[a]
Adjuvant therapy, n (%)	10 (63%)	178 (54%)	0.612[b]
Median (range) follow-up time, months	NR (4-44)	59 (3-146)	0.308[c]
Median (range) overall survival, months	15 (4-44)	17 (3-146)	0.346[d]

POPF: Postoperative pancreatic fistula; DGE: delayed gastric emptying; NA: not available; NR: not reached. [‡]Grade III-V Dindo-Clavien (6); [§]grade B-C by the International Study Group for Pancreatic Surgery (9). [a]Mann–Whitney test (two-tailed); [b]Fisher's exact test (two-tailed); [c]reversed Kaplan–Meier with log rank test; [d]Kaplan–Meier with log-rank test.

A total of 37 patients (11%) from the non-viral PDAC group (26 postoperative deaths and 11 patients lost from the follow-up) were excluded from the survival analysis. No differences between the HBV and non-viral PDAC groups were observed regarding the median follow-up time (Table I) or median overall survival time (Figure 1).

Discussion

The prevalence of viral hepatitis infection in the adult general population in Romania has been reported to be between 4.4% and 5.6% for HBV (7, 20, 21) and from 3.2% to 4.5% for HCV (21, 22). Immunization has been associated with a significant decrease in HBV infection in the Romanian population over the past two decades (20, 23). In the present series, the incidences of HBV and HCV infection (4.5% and 2.2%, respectively) shared the same trends as those in the adult general population in Romania, even when adjusted for age in the cohort of patients who underwent resection for PDAC (7, 20).

HBV represents an important cause of liver cirrhosis worldwide (24). The presence of liver cirrhosis has been associated with increased morbidity and mortality rates after pancreatectomy (25, 26). Interestingly, in the present series, none of the HBV group presented with liver cirrhosis, while 1.8% of the patients in the non-viral PDAC group presented with toxic-nutritional liver cirrhosis.

HBV is no longer considered strictly hepatotropic (27), and it has been also detected in pancreatic juice (28) and tissue (17, 27, 29-33), suggesting possible implications in the pathogenesis of pancreatic diseases such as acute pancreatitis (29) and PDAC (17, 30, 31). It appears, in fact, that pancreatic disorders are frequently encountered in patients with chronic HBV infection (34).

Previous studies have identified chronic/active HBV infection, past exposure to HBV, the presence of HBsAg (11-16) and chronic infection and past exposure to HCV infection (15, 16, 35, 36) as risk factors for PDAC development. The association of HCV with PDAC appeared to be influenced significantly by other factors, such as alcohol abuse and HBV co-infection (35). Furthermore, occult HBV infection was found to be highly prevalent in patients diagnosed with PDAC (11, 37). However, there are also studies that did not find a significant correlation between HBV and PDAC occurrence (36, 38-40), while others identified chronic HBV infection as a risk factor for PDAC, particularly in a population under the age of 50 years (41). Nevertheless, the presence of anti-HBV antibody was associated with a decreased risk of PDAC in a meta-analysis (15). Recent studies have shown that patients with HBV and PDAC are significantly younger than non-viral patients, suggesting an earlier onset of the disease in the former sub-group (17-19). In the present series, no significant differences were observed regarding age between the HBV and non-viral groups of patients (Table I). Interestingly, previous studies have shown that patients with HBV infection who underwent curative-intent therapy for hepatocellular carcinoma were significantly younger and with a predominance of male sex compared to non-viral patients (9).

Regarding the patients' sex, data from the literature have shown conflicting results. Some studies have indeed shown a significant male predominance in patients with PDAC and HBV (18, 19), although others have not (17), as was the case in the present cohort of patients.

Although certain studies have observed increased rates of synchronous liver metastases in patients with HBV and PDAC (19), other studies have not identified significant differences in tumor stages in patients resected for PDAC with or without HBV infection (17, 18).

In the present series, patients with HBV infection displayed trends toward increased rates of early T-stage tumors, albeit without reaching the accepted level of statistical significance. A simple explanation for this finding could be the fact that patients with a HBV infection or chronic liver disease are more often investigated in a hospital and therefore any pathology has the potential to be detected in an early stage. A more biological explanation could also be speculated: viral hepatitis produces an immunological and tissular storm that might have a toxic effect for the tumoral process ongoing in the pancreas. This pathogenesis was found to be responsible for the lower incidence of colorectal liver metastases in patients with chronic liver disease shown in a recent meta-analysis (42).

Up to now, no comparative data have been reported in the literature regarding potential differences of chronic/active, past exposure or occult HBV infection rates in patients with PDAC, with and without resection. Further studies are needed to assess if HBV infection could play a role in patients with unresectable PDAC.

Studies from the literature have shown no correlations with serum CA 19-9 level, tumor location, size or grading in patients with HBV and PDAC (17-19), as in the present study. Interestingly, the patients of the HBV group more frequently had chronic pancreatitis and diabetes compared with the non-viral patients in a recent study (17). Thus, the chronic inflammation induced by HBV was proposed as a potential pathogenic mechanism for the development of PDAC (17). In the present cohort, no significant differences between the non-viral and HBV groups were observed for associated chronic pancreatitis or diabetes mellitus rates.

Present or past exposure to HBV might potentially influence the therapeutic approach for a patient diagnosed with cancer. Thus, increased HBV reactivation rates have been reported during chemotherapy for solid cancer, including PDAC (43-47). HBV reactivation was associated with delays in or disruption of chemotherapy protocols (46); thus, the prognosis of these patients might potentially be jeopardized (44). Screening for HBV before chemotherapy is recommended (46), particularly in areas in which it is endemic.

For patients who underwent resection for PDAC, adjuvant treatment, mainly based on a gemcitabine protocol, has been associated with prolonged survival (4, 5). Some studies have suggested prevention of viral reactivation before chemotherapy in patients with PDAC and past exposure to HBV (11). A meta-analysis suggested not only the benefits of lamivudine as a preventive therapy for HBV re-activation but also a decrease in HBV-related liver insufficiency and lower death rates in HBsAg-positive patients who underwent chemotherapy (48). However, some studies have shown that a gemcitabine-based chemotherapy protocol was not associated with an increased risk of HBV re-activation; thus, screening does not appear to be cost-effective (45). In the present series, the presence of HBV had no detrimental impact on the rate of completion of adjuvant therapy after resection for PDAC (Table III), as previous studies have already shown (17-19). Unlike previously published studies (17-19), the present series included patients who underwent resection only.

A trend toward a worse prognosis in HBsAg-positive patients with PDAC has been reported, but statistical significance was not reached (18, 19), as was the case for the present cohort.

The present study was limited by its retrospective design and by the relatively small number of patients with a viral infection. Furthermore, the study did not address the issue of past HBV infection, which is reported in 27% of the adult general population in Romania (20). Occult HBV infection and HBV–Hepatitis D virus co-infection were also overlooked. Considering these limitations, the results of the present study should be interpreted with caution.

Conclusion

HBV-positive and virus-free patients with PDAC shared the same demographic, clinical and pathological profile. HBV did not appear to have a detrimental effect on either early or long-term outcomes after resection for PDAC, in this single-Center series of patients. The usefulness of screening and prevention of HBV re-activation in patients with PDAC submitted to adjuvant chemotherapy remain matters of debate. The assessment of pancreatectomy specimens for HBV infection is a promising field for research and might potentially clarify the relationship between the HBV and PDAC, with valuable information for clinical decision-making. Future studies searching for occult infection might also shed some light on the role of HBV in PDAC.

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Conflicts of Interest

The Authors declare no conflicts of interest with regard to this study.

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