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ORIGINAL ARTICLE

Blood Type as a Predictor of High-Grade Dysplasia and Associated Malignancy in Patients with Intraductal Papillary Mucinous Neoplasms

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Abstract

Background Intraductal papillary mucinous neoplasms (IPMNs) are precursor lesions to the development of pancreatic adenocarcinoma. We determined if non-O blood groups are more common in patients with IPMN and if blood group is a risk factor for progression to invasive pancreatic cancer among patients with IPMN.

Methods The medical records were reviewed of all patients undergoing resection of an IPMN at Johns Hopkins Hospital from June 1997 to August 2016. Potential risk factors of high-grade dysplasia and associated adenocarcinoma were identified through a multivariate logistic regression model.

Results Seven hundred and seventy-seven patients underwent surgical resection of an IPMN in which preoperative blood type was known. Sixty-two percent of IPMN patients had non-O blood groups (vs. 57% in two large US reference cohorts, $P = 0.002$). The association between non-O blood group was significant for patients with IPMN with low- or intermediate-grade dysplasia ($P < 0.001$), not for those with high-grade dysplasia ($P = 0.68$). Low- and intermediate-grade IPMNs were more likely to have non-type O blood compared to those with high-grade IPMN and/or associated invasive adenocarcinoma ($P = 0.045$). Blood type O was an independent predictor of having high-grade dysplasia without associated adenocarcinoma ($P = 0.02$), but not having associated invasive cancer ($P = 0.72$). The main risk factor for progression to invasive cancer after surgical resection was IPMN with high-grade dysplasia ($P = 0.002$).

Conclusion IPMN patients are more likely to have non-O blood groups than controls, but type O blood group carriers had higher odds of having high-grade dysplasia in their IPMN. These results indicate blood group status may have different effects on the risk and progression of IPMNs.

Keywords ABO · Blood type · IPMN · Intraductal papillary mucinous neoplasm · High-grade dysplasia · Pancreatic cancer · Pancreatic ductal adenocarcinoma

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Introduction

Individuals with non-O blood groups are at increased risk of developing pancreatic cancer.[1–7] The identification of non-O blood groups as a risk factor for pancreatic cancer susceptibility has renewed interest in potential mechanism(s) involved and how they might translate into patient care. The mechanism(s) by which ABO status influences pancreatic cancer risk is not understood. One aspect of the relationship between ABO blood group and pancreatic cancer that has not been elucidated is how ABO status might influence the development and progression of pancreatic cancer precursor lesions.

Intraductal papillary mucinous neoplasms (IPMNs) are cystic precursors to pancreatic cancer[8–12] characterized by intraductal papillary proliferation of mucin-producing epithelial cells within the pancreatic duct[13] and are typically found in older individuals.[14, 15] While most IPMNs have low malignant potential, they can progress to high-grade dysplasia and invasive cancer. It is important to identify and treat IPMNs that are likely to progress to invasive cancer because patients with an IPMN without a malignant component have much better survival compared to those with IPMN-associated adenocarcinoma.[16–18] Among patients with IPMN, the presence of certain radiological and clinical features such as main duct involvement[8–12] indicates a higher likelihood of having cancer, and international consensus guidelines recommend the use of these features to guide management.[14, 15] Subsequent studies[19–23] evaluating these guidelines have generally found them to be helpful but that there remains a need to identify additional factors that predict which IPMNs are most likely to progress to invasive cancer.

We compared the distribution of ABO blood groups in a large series of patients who underwent pancreatic resection of their IPMN and determined if blood group status was associated with risk of progression of IPMN to invasive cancer. We also assessed the factors associated with having IPMNs with high-grade dysplasia and associated adenocarcinoma.

Methods and Materials

Seven hundred and seventy-seven patients were identified from the pancreatic surgery database who had undergone pancreatic resection between June 1997 and August 2016 at the Johns Hopkins Hospital and had blood group information available in the medical record. Forty-six patients had an IPMN resected but did not have blood group information available in the medical record. Information collected from the medical record included patient demographics, tumor histopathology, associated pancreatic malignancy, and chemoradiation therapy. The pathology of all tumors was reviewed by an expert surgical pathologist to confirm the diagnosis and grade of IPMN. IPMN subtype was known for only 303 patients (39%), as was thus not included in the analysis. Time to follow-up was calculated from the date of surgery to the date of last clinical follow-up or date of death.

Statistical analysis was performed using STATA Version 13.0 (StataCorp, College Station, TX), and a P value < 0.05 was considered statistically significant. Summary statistics was presented for the entire patient cohort and for individual patient sets both as percentages for categorical variables and a mean value with range for continuous variables. Univariate logistic regression modeling was utilized to identify individual factors significantly associated with grade of dysplasia or associated adenocarcinoma. All covariates having $P < 0.05$ significance by univariate analysis were entered manually forward into a multivariable logistic regression model. The Akaike information criterion, the Hosmer-Lemeshow goodness of fit test, and likelihood ratio were used to assess model strength at each step in order to derive the most parsimonious model. This study was performed with the approval of the Institutional Review Board (IRB) at the Johns Hopkins Hospital.

Results

Patient Demographics

During the study period, 777 patients underwent surgical resection of an IPMN in which the patient's blood type was known. This included 231 patients (30%) with a pancreatic adenocarcinoma associated with the IPMN. The mean patient age at the time of resection was 67.4 years (range, 18–92 years) and patients were almost equally split between male and female (49.9 vs. 50.1%, respectively). Grade of dysplasia was known for 758 individuals and included 118 (16%) patients with low-grade dysplasia, 284 (37%) with intermediate grade, and 356 (47%) with high-grade dysplasia. Most patients with IPMN-associated carcinoma had high-grade dysplasia as the highest grade of dysplasia in the associated IPMN. The grade of dysplasia in the IPMN was not reported for 18 patients who had IPMN-associated carcinoma.

The mean body mass index (BMI) at the time of surgery was 26.3 kg/m^2 (range, 14–54.6 kg/m^2), and 175 patients (23%) had a preoperative diagnosis of diabetes. A majority of patients (55%) had a current or prior history of smoking, while 414 patients (59%) were current or former users of alcohol. Surgical resection involved a pancreaticoduodenectomy in 504 patients (65%) or distal pancreatectomy in 196 patients (25%), while the remaining patients underwent total pancreatectomy (8%), central pancreatectomy (1%), or enucleation (1%). IPMN location was known for 426 patients (55%): 134 patients (31%) had a main branch IPMN,

195 patients (46%) had a branch duct IPMN, and the remaining 97 patients (23%) had a mixed-type IPMN. The mean cyst size was 2.8 cm (range, 0.2–21 cm), and multiple cysts (more than 1) were found in 107 patients (14%).

Patients were followed for a mean time of 3.3 years (range, 0.1 to 17.8 years) and a median time of 2.1 years. Recurrence of either a benign or malignant pancreatic neoplasm was seen in 200 patients (26%), including 146 patients (24%) who recurred with new pancreatic adenocarcinoma. Most (120 of 146, 82%) of the patients who developed recurrent cancer had invasive cancer at diagnosis.

Blood Group in IPMN vs. Reference Populations

Blood type was distributed as follows: 292 patients (38%) with type O blood, 354 patients (45%) with type A blood, 85 patients (11%) with type B blood, and 46 patients (6%) with type AB blood. The majority of patients were rhesus factor (Rh)-positive (669 patients, 86%). We compared this distribution to the ABO blood group distribution reported in two large US reference populations, the Nurse's Health Study and the Health Professionals Follow-up Study (Table 1).[2] These studies found that the distribution of blood groups was as follows: non-type O blood group 57% and type O blood group 43%.[2] Patients with IPMN were significantly more likely to carry non-O blood groups than US reference populations (odds ratio 1.25; 95% CI 1.08–1.45; $P = 0.002$).

Of the IPMN patients with low- or intermediate-grade dysplasia without invasive cancer, blood group distribution was as follows: type O 34%, type A 49%, type B 11%, and type AB 6%. Compared to US reference population data, patients with low- and intermediate-grade IPMNs were more likely to have non-O blood groups (66 vs. 57%; OR 1.5, 95% CI 1.2–1.8; $P < 0.001$).

Of the patients with IPMN with high-grade dysplasia, without invasive cancer, the blood group distribution was as follows: type O 45%, type A 42%, type B 8%, and type AB 5%. Compared to US reference population data, patients with high-grade IPMN were not more likely to have non-O blood groups (55 vs. 57%; OR 0.94, 95% CI 0.69–1.3; $P = 0.68$).

Of the patients with IPMN with associated invasive cancer, the blood group distribution was as follows: type O 38%, type A 43%, type B 12%, and type AB 7%. Compared to US reference population data, patients with IPMN with associated adenocarcinoma were not more likely to have non-O blood groups (62 vs. 57%; OR 1.2, 95% CI 0.94–1.6; $P = 0.13$).

To determine if there was a difference in the distribution of blood groups among patients with low- and intermediate-grade IPMN from those with high-grade and/or associated invasive cancer, we performed chi-square analysis of these two groups (Table 2). We found patients with non-type O blood groups were more likely to have low- or intermediate-grade dysplasia vs. those with high-grade and invasive cancer ($P = 0.045$; chi-square statistic 4.18).

Table 1 ABO blood group in cases with IPMN and healthy controls in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), compared to the current study's population

ABO blood group	NHS (%)	HPFS (%)	Total study population (%)	Current study (%)
O	43	43	43	38
A	36	37	36	45
AB	8	8	8	6
B	13	12	13	11
Rh-negative	22	21	22	14
Rh-positive	78	79	78	86

Table 2 Blood group distribution in patients with IPMN according neoplastic grade

	Low- or intermediate-grade IPMN	High-grade IPMN and/or associated cancer
Non-type O blood (A, B, AB)	251 (66%)	234 (59%)
Type O blood	129 (34%)	163 (41%)

Blood Type and IPMN Characteristics

Given the differences seen between patients with and without type O blood, we assessed differences in characteristic between the two groups. There was no difference in average age between patients with and without type O blood (67 vs. 68 years, $P = 0.19$). There was an equal proportion of female patients with and without type O blood (51 vs. 49%, $P = 0.60$). In addition, patients with type O blood were more not likely to have larger cysts than those without (2.9 vs. 2.7 cm, $P = 0.27$). There was also no difference in main branch IPMN (33 vs. 31%), branch duct IPMN (46 vs. 47%), and mixed-type IPMN (21 vs. 22%) between patients without and with type O blood ($P = 0.87$). Furthermore, there was no difference in rates of smoking, diabetes, alcohol use, or ASA class based on blood type ($P < 0.05$, all).

Recurrence of IPMN or Cancer

Of the 546 patients without invasive adenocarcinoma at the time of surgery, 420 had follow-up for at least 1 year to determine recurrence of a new pancreatic malignancy. Seventy-eight (19%) of the patients who did not have invasive cancer at the time of their initial resection were later found by imaging or pathology to have developed a new IPMN lesion ($n = 52$) or adenocarcinoma ($n = 26$).

Recurrence with an IPMN or invasive cancer was more likely to occur in patients with high-grade dysplasia compared to those with low- and intermediate-grade ($P = 0.01$). There was no difference in the risk of recurrence among blood type O vs. non-O cases ($p = 0.32$). Recurrence with invasive cancer was more likely to occur in patients with high-grade dysplasia compared to low- or intermediate-grade dysplasia at the time of original operation (62 vs. 38%, $P = 0.001$). There was not a significant difference in cancer recurrence among blood type O vs. non-O cases (54 vs. 46%, $P = 0.30$).

Risk of High-Grade IPMN in the Absence of Associated Carcinoma

Univariate logistic regression modeling was utilized to identify factors associated with high-grade dysplasia for the 517 patients with IPMN without associated adenocarcinoma. Blood group was treated as a binary variable, where each blood type (for example, type O) was compared to all patients without that blood type (for example, non-type O). Univariate logistic regression analysis demonstrated that a history of current or prior tobacco use, age > 60 years, type O blood, and cyst size > 2 cm were all associated with having an IPMN with high-grade dysplasia without associated adenocarcinoma (Table 3). By multivariate logistic regression modeling, only type O blood and cyst size > 2 cm were significant predictors for having high-grade dysplasia without associated adenocarcinoma (Table 3).

Predictors of Having High-Grade IPMN with or Without Invasive Cancer

Factors associated with high-grade dysplasia, with or without associated adenocarcinoma, were assessed by univariate analysis. Male gender, age > 60 years, BMI > 25 kg/m^2, preoperative diabetes mellitus, a history of current or prior tobacco use, type O blood group, cyst size > 2 cm, and having multiple pancreatic cysts were all associated with high-grade dysplasia at the time of resection (all, $P < 0.05$). In a multivariate logistic regression model that included all these factors, only blood type O, having diabetes mellitus, and pancreatic cyst size > 2 cm remained significant predictors for having high-grade dysplasia (Table 4).

To determine if the impact age may have had on the progression of high-grade dysplasia, we assessed the average age for patients with and without high-grade dysplasia, based on average age. The average age of high-grade dysplasia patients with and without type O blood was 69.0 and 68.6 years, respectively, while the average age for patients without high-grade dysplasia with and without type O blood was 66.9 and 66.0 years. There was no difference in average age among patients with high-grade dysplasia based on blood type ($P = 0.74$), or without high-grade dysplasia ($P = 0.38$). However, for patients with non-type O blood type, patients with high-grade dysplasia were older on average ($P = 0.01$). This relationship was not significant for patients with type O blood ($P = 0.11$).

Table 3 Logistic regression models to identify factors associated with having an IPMN with high-grade dysplasia without associated adenocarcinoma

Characteristic	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Age > 50 years	0.93	0.48, 1.3	0.83	–	–	–
Age > 60 years	*1.7*	*1.06*, *2.6*	*0.03*	1.4	0.90, 2.3	0.13
BMI > 25 kg/m^2	0.92	0.63, 1.3	0.66	–	–	–
BMI > 30 kg/m^2	0.91	0.58, 1.4	0.69	–	–	–
Male gender	1.3	0.9, 1.9	0.16	–	–	–
Alcohol use	0.84	0.56, 1.3	0.39	–	–	–
Tobacco use	*1.5*	*1.02*, *2.2*	*0.04*	1.3	0.86, 1.9	0.23
Diabetes mellitus	1.5	0.93, 2.3	0.10	–	–	–
type O blood vs. non-type O	*1.6*	*1.1*, *2.3*	*0.02*	*1.5*	*1.05*, *2.23*	*0.03*
Type A blood vs. non-type A	0.73	0.51, 1.1	0.10	–	–	–
Type B blood vs. non-type B	0.72	0.38, 1.4	0.31	–	–	–
Type AB blood vs. non-type AB	0.98	0.44, 2.2	0.96	–	–	–
Pos Rh group	1.2	0.70, 2.1	0.48	–	–	–
Completion pancreatectomy	1.3	0.46, 3.5	0.66	–	–	–
Multiple cysts	0.74	0.44, 1.2	0.26	–	–	–
Cyst > 2 cm	2.5	1.7, 3.8	*< 0.001*	*2.3*	*1.5*, *3.7*	*< 0.001*

Italicized *p* values were those that were at the $p < 0.05$ threshold for statistical significance

Table 4 Logistic regression models to identify factors associated with having an IPMN with or without associated adenocarcinoma

Characteristic	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Age >50 years	1.3	0.7, 2.3	0.39	–	–	–
Age > 60 years	1.5	1.05, 2.1	*0.02*	1.4	0.98, 2.1	0.06
BMI > 25 kg/m^2	0.74	0.55, 0.99	*0.04*	0.74	0.52, 1.1	0.12
BMI > 30 kg/m^2	0.68	0.46, 0.99	*0.04*	0.78	0.49, 1.2	0.28
Male gender	1.3	1.01, 1.8	*0.04*	1.4	0.98, 1.9	0.07
Alcohol use	0.9	0.67, 1.3	0.63	–	–	–
Tobacco use	1.5	1.08, 1.9	*0.01*	1.16	0.84, 1.6	0.36
Diabetes mellitus	1.4	1.02, 2.03	*0.04*	*1.6*	*1.1*, *2.4*	*0.01*
Type O blood vs. non-type O	1.5	1.09, 2.0	*0.01*	*1.6*	*1.02*, *2.6*	*0.048*
Type A blood vs. non-type A	0.75	0.56, 0.99	*0.048*	0.95	0.60, 1.5	0.82
Type B blood vs. non-type B	0.88	0.55, 1.4	0.56	–	–	–
Type AB blood vs. non-type AB	0.94	0.51, 1.7	0.84	–	–	–
Pos Rh group	1.13	0.75, 1.7	0.60	–	–	–
Completion pancreatectomy	0.82	0.32, 2.1	0.67	–	–	–
Multiple cysts	0.58	0.38, 0.89	*0.01*	0.79	0.50, 1.3	0.32
Cyst > 2 cm	2.9	2.1, 4.2	*< 0.001*	*2.7*	*1.9*, *3.8*	*< 0.01*

Risk Factors for IPMN-Associated Carcinoma

Factors associated with an IPMN with associated adenocarcinoma were then assessed (Table 4). By univariate analysis, age > 50 years, BMI > 25, multiple cysts, cyst size > 2 cm, and preoperative diabetes mellitus were all associated with IPMN-associated carcinoma. When incorporated into a multivariate regression model, only BMI > 25, cyst size > 2 cm, and diabetes mellitus were independent risk factors for IPMN-associated adenocarcinoma (Table 5).

Table 5 Logistic regression models to identify factors associated with having an IPMN with associated adenocarcinoma

Characteristic	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Age > 50 years	*2.8*	*1.25–6.3*	*0.01*	2.2	0.84, 5.7	0.11
Age > 60 years	*1.5*	*1.04*, *2.4*	*0.03*	–	–	–
BMI > 25 kg/m^2	*0.64*	*0.47*, *0.88*	*0.006*	*0.61*	*0.42*, *0.89*	*0.01*
BMI > 30 kg/m^2	*0.55*	*0.35*, *0.85*	*0.008*	–	–	–
Male gender	1.3	0.98, 1.8	0.07	–	–	–
Alcohol use	1.1	0.76, 1.5	0.73	–	–	–
Tobacco use	1.2	0.90, 1.7	0.19	–	–	–
Diabetes mellitus	*1.7*	*1.2*, *2.4*	*0.005*	*1.9*	*1.3*, *2.9*	*0.003*
Type O blood vs. non-type O	1.06	0.77, 1.5	0.72	–	–	–
Type A blood vs. non-Type A	0.83	0.6, 1.1	0.25	–	–	–
Type B blood vs. non-type B	1.2	0.73, 1.9	0.49	–	–	–
Type AB blood vs. non-type AB	1.28	0.68, 2.4	0.44	–	–	–
Pos Rh group	0.78	0.51, 1.2	0.27	–	–	–
Completion pancreatectomy	0.27	0.06, 1.2	0.08	–	–	–
Multiple cysts	*0.51*	*0.30*, *0.84*	*0.009*	0.64	0.36, 1.2	0.14
Cyst > 2 cm	*2.1*	*1.4*, *3.1*	*< 0.001*	*1.9*	*1.3*, *2.9*	*0.002*

Discussion

We find that patients with an IPMN were more likely to have non-type O blood compared to a large US reference population. Interestingly, although this association was significant for the IPMN study population as a whole including those with IPMN-associated pancreatic cancer, it was present among patients with high-grade IPMN. Indeed, we found that among our IPMN cases overall, those with high-grade dysplasia with or without invasive cancer were more likely to have type O blood than those with low- and intermediate-grade dysplasia ($P = 0.04$). Having type O blood group was independently associated with having an IPMN with high-grade dysplasia without adenocarcinoma, even after other clinical predictors such as cyst size were considered. These results suggest that while patients with non-type O blood groups might be more likely to develop IPMN, progression of IPMNs to high-grade dysplasia is more likely among O blood group carriers. It is notable that there is still no consensus as to the likely mechanism by which blood type impacts the development and progression of pancreatic cancer. Our results suggest that blood type may be useful in two ways—to help predict whether or not a patient will develop an IPMN and to help predict if an IPMN is at higher likelihood of harboring high-grade dysplasia, although confirmation of these results in independent populations is needed before blood group can be used in a clinical setting to predict IPMN risk and progression. Further research is necessary to determine if blood group can be incorporated into risk prediction models to better predict IPMN patient's risk of neoplastic progression.

Patients with IPMN are at increased risk of developing adenocarcinoma after pancreatic resection and the strongest risk factor for developing pancreatic cancer after surgery was the presence of high-grade dysplasia at the time of surgery; thus, these patients in particular should be followed closely postoperatively even after a potentially curative resection for IPMN. New IPMNs were also more likely to be detected after resection among those who had high-grade dysplasia in their resected IPMN. However, ABO blood type was not associated with an increased risk of developing a future IPMN or adenocarcinoma in the pancreatic remnant. Thus, ABO blood group appears to be more useful in predicting an underlying IPMN and the level of dysplasia, as opposed to the risk of developing an associated malignancy.

Certain limitations to our study should be noted. It was a retrospective review, which limited the uniform collection of certain variables. Our study only included patients who underwent surgical resection of an IPMN so that we could definitively identify the grade of dysplasia for each IPMN, but it should be noted that our results may not apply to patients with IPMN that do not require resection. However, this was necessary in order to determine the highest grade of dysplasia and the presence of any invasive carcinoma, which may not be possible with FNA or core needle biopsy alone.

In conclusion, patients with IPMN are more likely to have non-type O blood groups than US controls. We find the increase in non-O blood groups is mainly confined to patients with low- and intermediate-grade IPMN. Among patients with IPMN, having type O blood is predictive of having a high-grade IPMN with or without associated adenocarcinoma.

Authorship Contributions All authors contributed to this manuscript, including conception and design (KEP, LDW, MG, CLW), acquisition of data (KEP, JG, LDW), analysis and interpretation of data (KEP, JG, CLW), material support (JLC, LDW, MG CLW), study supervision (MAM, JH, JLC, MJW, LDW, MG, CLW), and writing, review, and revision of the manuscript (KEP, JG, MAM, JH, JLC, MJW, LDW, MG, CLW).

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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