ORIGINAL ARTICLE

Does blood group affect survival following pancreatoduodenectomy for periampullary malignancy?

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Abstract

Background: Blood group is reported to have an effect upon survival following pancreatoduodenectomy for pancreatic ductal adenocarcinoma. The effect of blood group is not known, however, among patients with other periampullary cancers. This study sought to review this.

Methods: Data were collected for a range of factors and survival outcomes from patients treated at two centres. Those with blood groups B and AB were excluded, due to small numbers. Patient survival was compared between patients with blood groups O and A using multivariable analysis which accounted for confounding factors.

Results: Among 431 patients, 235 (54.5%) and 196 (45.5%) were of blood groups A and O respectively. Baseline comparisons found a significant difference in the distribution of tumour types (p = 0.011), with blood group O patients having more ampullary carcinomas (33.2% vs 23.4%) and less pancreatic ductal adenocarcinomas (45.4 vs 61.3%) than group A. On multivariable analysis, after accounting for confounding factors including pathologic variables, survival was found to be significantly shorter in those with blood group A than group O (p = 0.047, HR 1.30 [95%CI: 1.00–1.69]).

Conclusions: There is a difference in the distribution of blood groups across the different types of periampullary cancers. Survival is shorter among blood group A patients.

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Introduction

Survival among patients with resectable periampullary tumours remains poor, particularly among those with pancreatic adenocarcinoma.[1] Risk factors for periampullary malignancy are multifactorial. These include some modifiable risk factors, such as cigarette smoking and obesity,[2] and non-modifiable risk factors including race and genetic predisposition.[3] However, causal factors remain largely unknown and, given the lack of improvement of outcomes, there is a need to understand underlying mechanisms more clearly. There is tangible evidence to suggest a relationship between blood group and the incidence of pancreatic adenocarcinoma.[4–7] A smaller number of studies have also shown a relationship between prognosis of pancreatic adenocarcinoma and blood group, suggesting that blood group O has a favourable impact on outcome.[8,9] However, to date, there have been no studies correlating incidence or survival of patients with other periampullary adenocarcinomas such as ampullary carcinoma, duodenal carcinoma and cholangiocarcinoma with blood group.

ABO blood group antigens are surface markers encoded by alleles located on chromosome nine.[10] These are expressed on red blood cells, as well as on a number of endodermal epithelial cells, including those in the gastrointestinal, bronchopulmonary and urogenital tracts.[10] The blood group antigens are classed as glycoconjugates – molecules which play an important role in the pathogenesis of malignancy, including the pivotal stages of intercellular adhesion and membrane signalling.[10] There have been numerous studies linking ABO to other carcinomas such as those of the stomach,[11] breast[12] and ovary.[13]

The aim of this study was to assess the prognostic significance of blood group among patients undergoing pancreatoduodenectomy for periampullary malignancy.

Methods

Data were collected from two pancreatic surgery departments between February 2007 and February 2017. Both sites gathered data prospectively to institutional databases. Institutional approval was obtained for this study. Adult patients undergoing pancreatoduodenectomy for pancreatic adenocarcinoma, cholangiocarcinoma, ampullary carcinoma or duodenal carcinoma were included, with all other patients, including those undergoing surgery for cystic lesions, excluded. A total of 570 patients were identified. Of these, patients who either died within 90 days of surgery (N = 38, 6.7%), or had less than 90 days of post-surgical follow-up (N = 15, 2.6%) were excluded. Of the remainder, those of blood group B (N = 66, 12.8%) or group AB (N = 20, 3.9%) were also excluded, due to the small sizes in these groups. A similar method has been employed by other research groups in order to minimise the number of patient cohorts for comparison.[6,9,14]

Pancreatoduodenectomy was performed by consultant (attending) surgeons. Pylorus preserving resections were the standard approach at both sites and the majority of surgeons preferred pancreatojejunostomy over pancreatogastrostomy. Enhanced recovery programmes were introduced during the study period, and neoadjuvant FOLFIRINOX therapy was used towards the end of the period for patients with borderline resectable arterial involvement of disease. It was departmental practice to perform upfront venous resection for those patients with reconstructable venous involvement on preoperative CT scan. Post-operative pancreatic fistula was defined in line with the relevant definitions from the International Study Group for Pancreatic Surgery.[15]

Statistical analysis

Patient demographics, disease and treatment factors were compared between patients in blood groups O and A. Continuous variables were reported as medians and interquartile ranges (IQRs), with comparisons between groups made using Mann–Whitney tests. Categorical variables were compared using Fisher's exact test, with Kendall's tau used for ordinal variables. Univariable analysis of patient survival was performed using Kaplan–Meier curves, with Cox regression models used to calculate hazard ratios (HR) and p-values. In addition, a Cox regression model was produced with the blood group, tumour type and an interaction term as factors, to test whether the effect of blood group differed by the type of tumour.

Multivariable Cox regression analyses were then used to consider the association between blood group and mortality, whilst accounting for a range of potentially confounding factors. Continuous factors were categorised into three groups prior to analysis, and categorical variables had groups combined where the within-group sample sizes were small. All factors where data were available in at least 90% of cases were considered for inclusion in this analysis. A backwards stepwise approach was used to select independent predictors of patient survival. The factors present in the final model of the stepwise procedure were then entered into a new model, in order to prevent list-wise exclusion of cases with missing data on other variables.

Sensitivity analyses were then performed, to consider the potential impact of those factors that were not included in the main analysis due to large quantities of missing data. Separate models were produced where these factors were individually included alongside the factors in the final model, to ensure that they were not significant independent predictors of survival.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY). Patients with missing data were excluded on a per-analysis basis, and $p < 0.05$ was deemed to be indicative of statistical significance throughout. All analyses were performed by a medical statistician (JH).

Results

After exclusions, data for 431 patients were available for analysis, of whom 196 (45.5%) were blood group O and 235 (54.5%) group A (Table 1a,b). Patient demographics and comorbidity were similar in the two groups. A significant difference in the distribution of tumour types was detected, with blood group O patients having higher rates of ampullary tumours and lower rates of pancreatic ductal adenocarcinomas (PDAC) (45.4% vs 61.3%) than those with blood group A. Patients with blood group O were significantly more likely to have a soft gland on intra-operative assessment, and less likely to require associated venous reconstruction, than those from blood group A. The differences observed for these two variables related to the underlying difference in tumour type, with venous reconstruction being significantly more common in PDAC (22.8% vs. 3.3%–9.6% in other types, $p < 0.001$) and soft glands significantly less common in PDAC (19.8% vs. 47.4%–66.7% in other types, $p < 0.001$).

Survival by blood group

Univariable analysis found patient survival to be significantly shorter for patients in blood group A than for group O (median 23.7 vs 37.7 months, $p = 0.004$, Fig. 1), with a hazard ratio (HR) of 1.43 (95% CI: 1.12–1.84). Subgroup analysis found this to be similar for the two hospital sites, with hazard ratios of 1.44 (95% CI: 1.11–1.86) for the N = 391 patients from University Hospitals Birmingham, and 1.47 (95% CI: 0.52–4.21) for the N = 40 patients from University Hospitals Coventry and Warwickshire. No significant interaction was detected between the blood group and tumour type ($p = 0.326$), with a subgroup analysis (Table 2) showing that the effect of blood group was in the same direction for all four tumour types, with hazard ratios ranging from 1.06 in the PDAC group to 2.44 in duodenal tumours.

A multivariable analysis was then performed, which considered all of the variables in Table 1a,b for inclusion in the model as potentially confounding factors, alongside the blood group

Table 1a Patient and disease-related factors

	N	Blood Group		p-Value
		Group O	Group A	
Patient Demographics				
Age (Years)	431	67.6 (61.2–74.8)	67.0 (61.0–72.6)	0.325
Gender (% Male)	431	100 (51.0%)	134 (57.0%)	0.244
Body Mass Index	425	25.5 (22.5–28.3)	24.5 (22.0–27.8)	0.169
Ethnicity (% White)	431	186 (94.9%)	226 (96.2%)	0.639
Smoking Status	402			0.618
No		106 (58.6%)	126 (57.0%)	
Ex		47 (26.0%)	66 (29.9%)	
Yes		28 (15.5%)	29 (13.1%)	
Past Medical History				
Cerebrovascular Accident	422	4 (2.1%)	11 (4.7%)	0.190
Asthma	422	14 (7.4%)	9 (3.9%)	0.133
Atrial fibrillation/angina	422	10 (5.3%)	9 (3.9%)	0.490
Chronic Obstructive Pulmonary Disease	422	7 (3.7%)	10 (4.3%)	0.809
Hypertension	422	75 (39.7%)	72 (30.9%)	0.065
Diabetes	422	34 (18.0%)	43 (18.5%)	1.000
Renal Failure	421	3 (1.6%)	3 (1.3%)	1.000
Previous Myocardial Infarction	421	5 (2.7%)	5 (2.1%)	0.757
Disease-Related Factors				
Tumour Type	431			**0.011**
PDAC		89 (45.4%)	144 (61.3%)	
Duodenal Carcinoma		15 (7.7%)	11 (4.7%)	
Cholangiocarcinoma		27 (13.8%)	25 (10.6%)	
Ampullary Carcinoma		65 (33.2%)	55 (23.4%)	
T-stage	420			0.648*
T1		12 (6.4%)	12 (5.2%)	
T2		24 (12.8%)	22 (9.5%)	
T3		135 (71.8%)	183 (78.9%)	
T4		17 (9.0%)	15 (6.5%)	
N-stage	423			0.088*
N0		55 (28.9%)	53 (22.7%)	
N1		129 (67.9%)	167 (71.7%)	
N2		6 (3.2%)	13 (5.6%)	
R-status	414			0.323
R0		155 (82.4%)	177 (78.3%)	
R1		33 (17.6%)	49 (21.7%)	

PDAC – pancreatic ductal adenocarcinoma.
Data reported as N (%), with p-values from Fisher's exact test, or median (IQR), with p-values from Mann–Whitney tests, as applicable, unless stated otherwise.
*p-Value from Kendall's tau, to account for the ordinal nature of the factor.
Bold p-Values are significant at $p < 0.05$.

(Table 3). This found increasing T-stage ($p = 0.001$) and N-stage ($p < 0.001$) to be associated with significantly shorter survival, whilst patients with a past history of myocardial infarction ($p = 0.020$) and those of non-white ethnicity ($p = 0.039$) had significantly improved survival. In addition, patient age ($p = 0.052$) and the tumour type ($p = 0.089$) were selected for inclusion, but did not reach statistical significance in the final model. After accounting for these factors, the association

Table 1b Treatment and operative factors

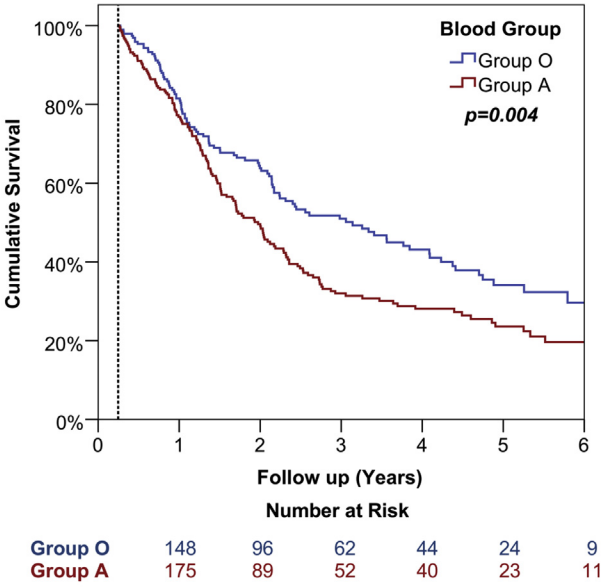
	N	Blood Group		p-Value
		Group O	Group A	
Pre-operative biliary stent	430	131 (67.2%)	168 (71.5%)	0.345
Neoadjuvant Chemotherapy	391	4 (2.2%)	3 (1.4%)	0.707
Venous Reconstruction	430	21 (10.8%)	42 (17.9%)	**0.041**
Pancreatoduodenctomy Type	431			0.691
PPPD		164 (83.7%)	200 (85.1%)	
Whipple		32 (16.3%)	35 (14.9%)	
Pancreatic Reconstruction	431			0.281
Pancreatojejunostomy		147 (75.0%)	165 (70.2%)	
Pancreatogastrostomy		49 (25.0%)	70 (29.8%)	
Anastomosis Style	233			0.790
Duct to Mucosa		71 (62.3%)	72 (60.5%)	
Dunking		43 (37.7%)	47 (39.5%)	
Intra-operative Gland Consistency	184			**0.006**
Soft		44 (46.8%)	24 (26.7%)	
Hard/Firm		50 (53.2%)	66 (73.3%)	
Intra-operative PD Width (mm)	164	4^{3-5}	4^{3-6}	0.058
Postoperative Pancreatic Fistula	386			0.244*
No		140 (81.9%)	185 (86.0%)	
A		13 (7.6%)	15 (7.0%)	
B		12 (7.0%)	10 (4.7%)	
C		6 (3.5%)	5 (2.3%)	
Adjuvant Chemotherapy	403	114 (61.6%)	149 (68.3%)	0.173
PERT After Discharge	269	91 (74.0%)	113 (77.4%)	0.568

PERT – pancreatic enzyme replacement therapy; PPPD – pylorus preserving pancreatoduodenectomy. Data reported as N (%), with p-values from Fisher's exact test, unless stated otherwise.
*p-Value from Kendall's tau, to account for the ordinal nature of the factor.
Bold p-Values are significant at $p < 0.05$.

between blood type and patient survival remained significant ($p = 0.047$), with a hazard ratio of 1.30 (95% CI: 1.00–1.69) for blood group A, relative to the group O. Therefore there appears to be a modest effect of blood group upon survival, an effect which is less powerful than that of T or N stage.

Discussion

This was a retrospective analysis of risk factors for survival following pancreatoduodenectomy for periampullary malignancy, with a particular focus upon the effect of blood group. Established patient and pathological variables were considered in the analyses. One of the main findings was that distribution of tumour types varied significantly by blood group. Patients with



Excludes 90-day mortality, and patients with less than 90 days of follow up.

Figure 1 Kaplan Meier curve of survival by blood group

blood group A were found to be more likely to undergo surgery for pancreatic ductal adenocarcinoma, and this is in line with findings of previous studies which have demonstrated that the risk of pancreatic cancer is lower among patients with blood group O.[4–7] Since this study is not a population based analysis, we cannot relate the occurrence of the various tumour types to blood group, but it is clear that the distribution of tumour type varies by blood group.

Survival following surgery was found to differ significantly by blood group on both univariable and multivariable analyses. These observations are in line with other published data, suggesting that blood type has a significant effect upon survival following resection of pancreatic ductal adenocarcinoma.[8,9] No significant interaction between blood group and tumour type was detected, implying that the difference in survival by blood group was similar, regardless of tumour type. On subgroup analysis, whilst no significant differences in survival by blood group were detected for any of the individual tumour types, on account of insufficient statistical power due to small sample sizes, the tendency was for shorter survival in group A patients in all cases. To our knowledge, there have been no studies that have reported the effect of blood type upon survival following resection of distal cholangiocarcinoma, ampullary carcinoma or duodenal carcinoma. Among these subgroups, patient survival was in favour of those with blood group O and with hazard ratios of 1.33, 1.72 and 2.44 respectively.

The exact mechanism by which blood group antigens influence survival remains incompletely understood. Pre-clinical studies have shown a relationship between the levels of molecules such as soluble Intercellular Adhesion Molecule-1 (sICAM-1),[16] TNF-α,[17] E-selectin,[18] P-selectin[19] and variations in the ABO gene. sICAM-1 inhibits the adhesion of lymphocytes to

Table 2 Subgroup survival analysis by tumour type

	Number of Cases		Median Survival (Months)		HR (95% CI)	p-Value
	Group O	Group A	Group O	Group A		
Overall	196	235	37.7	23.7	1.43 (1.12–1.84)	**0.004**
Pancreatic Ductal Adenocarcinoma	89	144	20.1	20.3	1.06 (0.77–1.46)	0.724
Duodenal Carcinoma	15	11	>85.6[a]	23.1	2.44 (0.77–7.73)	0.130
Cholangiocarcinoma	27	25	25.7	16.2	1.33 (0.70–2.52)	0.382
Ampullary Carcinoma	65	55	74.0	52.7	1.72 (0.96–3.07)	0.067

Median survival times are Kaplan Meier estimates. Hazard ratios are for blood group A, relative to group O, and are based on univariable Cox regression models.
In a Cox regression model containing the blood group, tumour type and an interaction term, no significant interaction was detected (p = 0.326).
Bold p-values are significant at p < 0.05.
[a] Cumulative survival rate was >50% at the end of follow up. Quoted value is the point that the last patient was lost to follow up.

Table 3 Multivariable analysis

	HR (95% CI)	p-Value
Blood Group		**0.047**
Group O	–	–
Group A	1.30 (1.00–1.69)	**0.047**
Age (Years)		0.052
<65	–	–
65–74	1.34 (1.02–1.76)	0.038
75+	1.45 (1.01–2.08)	0.047
Previous Myocardial Infarction	0.25 (0.08–0.80)	**0.020**
Tumour Type		0.089
Pancreatic Ductal Adenocarcinoma	–	–
Duodenal Carcinoma	0.53 (0.29–0.96)	0.037
Cholangiocarcinoma	0.99 (0.69–1.42)	0.943
Ampullary Carcinoma	0.73 (0.50–1.06)	0.096
T-Stage (T3/T4)		**0.001**
T0-T2	–	–
T3-T4	2.47 (1.44–4.25)	**0.001**
N-Stage (N1/N2)		**<0.001**
N0	–	–
N1-N2	3.88 (2.64–5.70)	**<0.001**
Ethnicity (Non-White)	0.42 (0.19–0.96)	**0.039**

Results are from a multivariable Cox regression analysis. An initial model was created which considered the blood group, and all factors from Table 1a,b for inclusion, with the exception of PD width, gland consistency, anastomosis style and PERT usage, due to missing data. A backwards stepwise approach was used to identify significant independent predictors of patient survival. The factors in the final model were then entered into a new model to prevent list-wise exclusions of patients with missing data for variables not selected for the final model. This increased the included sample size from N = 269 to 418, and the latter model is reported above. Sensitivity analyses on the four excluded factors did not find any significant associations between these factors and patient survival, after accounting for the factors in the final model (p = 0.571, 0.609, 0.187 and 0.122 respectively).
Bold p-values are significant at p < 0.05.

endothelial cells and subsequent extravasation by binding to lymphocyte function-associated antigen (LFA-1).[20] The levels of sICAM-1 are reduced in non-O groups when compared to blood group O.[16] Cancer cells that have successfully invaded the basement membrane and intravasated to reach the blood stream must now extravasate into a favourable environment to fully metastasise. They do so in a fashion very similar to that of inflammatory cells[21] and thus, the hypothesis is that the lower levels of sICAM-1 in patients with blood group A may provide the right environment to promote metastasis of circulating cancer cells.

Single nucleotide polymorphisms also significantly influence the levels of serum TNF-α,[17] a molecule that is known to accelerate epithelial–mesenchymal transition,[22] a process which is essential to metastasis.[23] Understanding biochemical or genetic differences that relate to a survival advantage of one blood group over another may yield therapeutic options in the future.

There are clear limitations of this study. By excluding patients with blood groups B and AB, the study does not consider patients with all blood groups. The rationale for these exclusions was that the small sample sizes in these groups would result in low statistical power for comparisons, hence would add complexity to the analysis with little chance of yielding useful results.

It is unclear why a prior history of myocardial infarction was associated with improved survival within the multivariable analysis. It is worth noting that the number of patients with a history of myocardial infarction is low (n = 10, 2.3%). In addition, although it may seem unusual that chemotherapy was not identified as being independent predictor of patient survival on multivariable analysis, this is likely a result of selection bias. Whilst chemotherapy was used routinely among patients with pancreatic ductal adenocarcinoma, it was used selectively among those with ampullary carcinoma where patients with early stage disease did not receive chemotherapy. Thus, chemotherapy usage was associated with T- and N-staging, and so did not add significantly to these in the model.

Understanding the biological mechanisms that underpin the observed differences in survival between the blood groups could potentially provide options for therapeutic intervention in the future. In the short-term, ABO blood group information can be integrated along with other prognostic factors into a predictive tool that stratifies patients according to their risk of recurrence after resection. Such tools can prove to be more discriminative than TNM staging alone,[24] although it is accepted that this will have limited or no clinical impact for the majority of patients.

In summary, this study has demonstrated a significant survival advantage among patients with blood group O who have undergone pancreatoduodenectomy for periampullary malignancy, compared to those with blood group A. While this effect was observed in all tumour types, subgroup analysis suggests that the influence of blood group upon survival may be greater for tumours other than pancreatic ductal adenocarcinoma. However, the sample sizes on subgroup analyses gave insufficient statistical power to detect this difference, hence this would be an interesting target for a future study.

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Disclosure of interest

None.

Conflicts of interest

None declared.

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