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【 ORIGINAL ARTICLE 】

# ABO Blood Type and the Long-term Outcomes of Pancreatic Cancer

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on behalf of the Ehime Pancreato-Cholangiology (EPOCH) Study Group

**Abstract:**

**Objective** The long-term effect of the ABO blood type on the clinical course of patients with pancreatic cancer (PC) is inconclusive. This study aimed to determine whether or not the ABO blood type influences the long-term outcomes of PC in Japanese patients.

**Methods** The medical records of Japanese patients with PC were reviewed. Data, including the age, sex, and outcomes, from the Ehime Pancreato-Cholangiology Study Group were analyzed.

**Results** The mean age of the 406 patients was 71.0±10.5 years, and 220 (54.2%) were men. A total of 44.6%, 20.7%, 22.4%, and 12.3% had blood type A, B, O, and AB, respectively. The median survival time (MST) of patients with A alleles was shorter than that of patients with non-A alleles (p=0.048), especially among those who underwent resection (p=0.031). In contrast, no marked difference in the MST was noted among those who underwent chemotherapy and palliative care. Finally, a multivariate analysis confirmed A alleles as an independent factor associated with the long-term outcome of PC (p<0.05 in 2 different models).

**Conclusion** The ABO blood type influenced the long-term outcomes of Japanese patients with PC, presumably due to its impact on disease onset and tumor behavior.

**Key words:** pancreatic cancer, ABO blood type, long-term outcomes, tumor behavior

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## Introduction

Pancreatic cancer (PC) has the worst prognosis of all cancers (1). PC is the seventh-most common cancer and the fourth leading cause of cancer death in Japan (1). Although various risk factors for developing PC have been determined, such as familial PC (2), there are no simple surrogate markers for efficiently diagnosing PC at an early stage (3). Furthermore, the predisposing environmental and genetic factors for most patients are not well understood.

The ABO blood type has been associated with the risk of developing cancers, including PC and gastric cancer (4-6). In addition, the long-term effects of the ABO blood type on the clinical course of various cancers, such as esophageal squamous cell carcinoma (7), colon cancer (8), renal cell carcinoma (9), and bladder cancer, have been reported (10). ABO gene variants have recently been identified as susceptibility factors for PC (4). Serological evidence of non-type O having an increased risk of PC supports this finding (11).

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However, the majority of western studies on the effect of the ABO blood type on the PC survival enrolled resected patients (12, 13). In Asia, only three studies have been conducted: two from China and one from Turkey (14-16). The results of these studies are inconclusive, and the impact of the ABO blood type on the prognosis of Japanese patients with PC remains unknown. Furthermore, the role of the ABO blood type in the pathogenesis of PC and its effect on the long-term outcomes of different PC treatments are not fully understood.

The present study explored whether or not the ABO blood type influences the long-term outcomes of PC in Japanese patients.

## Materials and Methods

### Patients and study design

The Ehime Pancreato-Cholangiology (EPOCH) Study Group studied the impact of the ABO blood type on the long-term outcomes of Japanese patients with PC and in the pathogenesis of PC. The current retrospective study examined data from consecutive patients diagnosed with PC between January 1, 2011, and December 31, 2013, at Ehime University Hospital and its affiliated centers (EPOCH Study Group). Data, including the age, sex, body mass index (BMI), serological ABO blood type, serum carcinoembryonic antigen (CEA) level, serum carbohydrate antigen 19-9 (CA19-9) level, tumor size, lymph node metastasis, distant metastasis, Union for International Cancer Control (UICC) stage (7th edition) (17) at the PC diagnosis, treatments (resection, chemotherapy, radiation, and palliative care), and the outcome, were analyzed. The diagnosis of PC was based on tumor markers (CEA, CA19-9), abdominal imaging, and/or histological findings as previously described (18). Lymph node metastasis was considered positive when the size was greater than 1 cm in diameter on abdominal imaging for patients without resection. The classification of stage 0 was determined pathologically. Patients without data on their ABO blood type were excluded.

### Statistical analyses

All statistical analyses were performed using the JMP software program (version 13; SAS, Cary, USA). The data were reported as the mean±standard deviation or the number and percentage, as appropriate. Variables were compared using Student's *t*-test. Intergroup comparisons were performed using the chi-square test. Outcomes were analyzed using the Kaplan-Meier method. To determine whether or not different ABO blood types were independently associated with the long-term outcomes of PC, a multivariate analysis was performed using a logistic regression model adjusted for the following variables: age, sex, and BMI (model 1); and age, sex, BMI, tumor size, lymph node metastasis, and distant metastasis (model 2). Differences were considered statistically significant at a two-tailed p value of $<0.05$.

### Ethics

The study's protocol complied with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of the Ehime University Graduate School of Medicine. Written informed consent was waived owing to the retrospective nature of the study.

## Results

### Patient characteristics

Of the 517 consecutive patients, 111 were excluded due to missing data on ABO blood type. Thus, 406 patients (220 men and 186 women) with PC were included in the analysis. The mean patient age was 71.0±10.5 years (range: 33-89 years). Of the enrolled patients, 181 (44.6%), 84 (20.7%), 91 (22.4%), and 50 (12.3%) had blood type A, B, O, and AB, respectively. The mean age (71.1±10.6, 73.2±9.5, 72.9±9.2, and 70.5±10.1), percentage of men (53.0%, 52.4%, 60.4%, and 50.0%), and BMI (21.0, 20.6, 21.8, and 20.7) did not differ markedly between the patients according to the blood type distribution (Table 1).

### Tumor characteristics at the PC diagnosis among the different ABO blood types

Tumor markers did not differ among the blood types. The median tumor size was 3.0 cm (range, 0.6-10.0 cm), and the size of each blood type was as follows: type A, 3.0 cm (range, 0.6-10.0 cm); type B, 3.0 cm (range, 1.0-7.0 cm); type O, 3.0 cm (range, 1.0-10.0 cm); and type AB, 3.4 cm (range, 0.7-7.0 cm). Lymph node metastasis and distant metastasis were compared, but there was no marked difference among the different ABO blood types: lymph node metastasis (p=0.353) and distant metastasis (p=0.325).

Although data on lymph node metastasis were missing in seven patients, they all had distant metastasis, which did not influence their UICC staging. The distribution of the UICC stage at the PC diagnosis of the entire cohort was as follows: stage 0, 7 patients (1.7%); stage IA, 20 (4.9%), stage IB, 22 (5.4%); stage IIA, 103 (25.4%); stage IIB, 50 (12.3%); stage III, 63 (15.5%); and stage IV, 141 (34.7%) (Table 1).

Similarly, when the ABO blood types were combined, there were no marked differences in characteristics between A alleles and non-A alleles and between B alleles and non-B alleles (Table 2a, b). However, there was a significant difference in the BMI only between type O and non-type O (p =0.016, Table 2c).

### Long-term outcomes of PC among the different ABO blood types

When the ABO blood types were combined and the median survival time (MST) of the entire treatment was compared, the results were as follows: A alleles vs. non-A alleles (361 days vs. 494 days, p=0.048 ; Fig. 1); B alleles vs.

**Table 1. Tumor Characteristics of the Patient with Pancreatic Cancer according to the ABO Blood Type.**

| | | Total (n=406) | Type A (n=181, 44.6%) | Type B (n=84, 20.7%) | Type O (n=91, 22.4%) | Type AB (n=50, 12.3%) | p value |
|---|---|---|---|---|---|---|---|
| M/F | | 220/186 (54.2%) | 96/85 (53.0%) | 44/40 (52.4%) | 55/36 (60.4%) | 25/25 (50%) | 0.571 |
| Age | | 71.0±10.5 | 71.1±10.6 | 73.2±9.5 | 72.9±9.2 | 70.5±10.1 | 0.266 |
| BMI (95%CI) | | 21.1 (20.7-21.4) | 21.0 (20.4-21.6) | 20.6 (19.9-21.4) | 21.8 (21.1-22.6) | 20.7 (19.7-21.9) | 0.085 |
| CEA level (ng/mL) Median (range) | | 4.4 (0.1-1,452) | 4.0 (0.6-1,452) | 4.7 (1.1-327.6) | 4.8 (0.1-140) | 3.5 (0.9-65) | 0.275 |
| CA19-9 level (U/mL) Median (range) | | 217.5 (-390,822) | 155 (-144,370) | 324 (-390,822) | 239 (-313,740) | 238.6 (-98,586) | 0.465 |
| Tumor size (cm) Median (range) | | 3.0 (0.6-10.0) | 3.0 (0.6-10.0) | 3.0 (1.0-7.0) | 3.0 (1.0-10.0) | 3.4 (0.7-7.0) | 0.174 |
| LN Metastasis No/Yes | | 246/153 | 102/75 | 53/30 | 61/28 | 30/20 | 0.353 |
| Distant Metastasis No/Yes | | 264/142 | 119/62 | 51/33 | 65/6 | 29/21 | 0.325 |
| Resection+chemotherapy/ Chemotherapy/ Palliative care | | 172/161/73 | 76/71/34 | 38/28/18 | 41/37/13 | 17/25/8 | 0.567 |
| Stage, n (%) | 0 | 7 (1.7%) | 4 (2.2%) | 1 (1.2%) | 1 (1.1%) | 1 (2%) | 0.503 |
| | IA | 20 (4.9%) | 6 (3.3%) | 3 (3.6%) | 8 (8.8%) | 3 (6%) | |
| | IB | 22 (5.4%) | 12 (6.6%) | 3 (3.6%) | 6 (6.6%) | 1 (2%) | |
| | IIA | 103(25.4%) | 45 (24.9%) | 22 (26.2%) | 28 (30.8%) | 8 (16%) | |
| | IIB | 50 (12.3%) | 28 (15.5%) | 9 (10.7%) | 7 (7.7%) | 6 (12%) | |
| | III | 63 (15.5%) | 24 (13.3%) | 13 (15.5%) | 15 (16.5%) | 11 (22%) | |
| | IV | 141(34.7%) | 62 (34.3%) | 33 (39.3%) | 26 (28.6%) | 20 (40%) | |

M/F: male/female, BMI: body mass index, CI: confidential interval, LN: lymph node, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

**Table 2a. Clinical Characteristics of the PC Patient between a Alleles and Non-A Alleles.**

| Characteristic | Total (n=406) | A alleles (n=231, 56.9%) | Non-A alleles (n=175, 43.1%) | p value |
|---|---|---|---|---|
| M/F | 220/186 (54.2%) | 121/110 (52.4%) | 99/76 (56.6%) | 0.401 |
| Age | 71.0±10.5 | 71.0±10.5 | 73.0±9.3 | 0.058 |
| BMI (95%CI) | 21.1 (20.7-21.4) | 20.9 (20.4-21.5) | 20.6 (20.7-21.8) | 0.312 |
| CEA level (ng/mL) Median (range) | 4.4 (0.1-1,452) | 3.8 (0.6-1,452) | 4.7 (0.1-327.6) | 0.06 |
| CA19-9 level (U/mL) Median (range) | 217.5 (-390,822) | 162.9 (-144,370) | 263 (-390,822) | 0.149 |
| Tumor size (cm) Median (range) | 3.0 (0-10.0) | 3.0 (0-10.0) | 3.0 (0-10.0) | 0.065 |
| LN Metastasis No/Yes | 246/153 | 132/95 | 114/58 | 0.097 |
| Distant Metastasis No/Yes | 264/142 | 148/83 | 116/59 | 0.643 |
| Resection+chemotherapy/ Chemotherapy/ Palliative care | 172/161/73 | 93/96/42 | 79/65/31 | 0.588 |

PC: pancreatic cancer, M/F: male/female, BMI: body mass index, CI: confidential interval, LN: lymph node, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

non-B alleles (394 days vs. 429 days, p=0.625; Fig. 2); and type O vs. non-type O (521 days vs. 383 days, p=0.063; Fig. 3).

### *Long-term outcome of PC among the different ABO blood types and different treatments*

Of the 406 patients, 172 (42.4%), 161 (38.8%), and 73 (18.0%) underwent surgical resection, chemotherapy, and

**Table 2b. Clinical Characteristics of the PC Patient between B Alleles and Non-B Alleles.**

| Characteristic | Total (n=406) | B alleles (n=134, 33.0%) | Non-B alleles (n=272, 67.0%) | p value |
|---|---|---|---|---|
| M/F | 220/186 (54.2%) | 69/65 (51.5%) | 151/121 (55.5%) | 0.445 |
| Age | 71.0±10.5 | 72.1±9.7 | 71.7±10.2 | 0.902 |
| BMI (95%CI) | 21.1 (20.7-21.4) | 20.6 (20.0-21.3) | 21.3 (20.9-21.8) | 0.075 |
| CEA level (ng/mL) Median (range) | 4.4 (0.1-1452) | 4.5 (0.9-327.6) | 4.4 (0.1-1,452) | 0.335 |
| CA19-9 level (U/mL) Median (range) | 217.5 (-390,822) | 280.9 (-390,822) | 182.8 (-313,740) | 0.629 |
| Tumor size (cm) Median (range) | 3.0 (0-10.0) | 3.0 (0-7.0) | 3.0 (0-10.0) | 0.471 |
| LN Metastasis No/Yes | 246/153 | 83/50 | 163/103 | 0.827 |
| Distant Metastasis No/Yes | 264/142 | 80/54 | 184/88 | 0.116 |
| Resection+chemotherapy/ Chemotherapy/ Palliative care | 172/161/73 | 55/53/26 | 117/108/47 | 0.858 |

PC: pancreatic cancer, M/F: male/female, BMI: body mass index, CI: confidential interval, LN: lymph node, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

**Table 2c. Clinical Characteristics of the PC Patient between Type O and Non-type O.**

| Characteristic | Total (n=406) | Type O (n=91, 22.4%) | Non-type O (n=315, 77.6%) | p value |
|---|---|---|---|---|
| M/F | 220/186 (54.2%) | 55/36 (60.4%) | 165/150 (52.4%) | 0.172 |
| Age | 71.0±10.5 | 72.9±9.2 | 71.5±10.2 | 0.244 |
| BMI (95%CI) | 21.1 (20.7-21.4) | 21.8 (21.1-22.5) | 20.9 (20.4-21.3) | 0.016 |
| CEA level (ng/mL) Median (range) | 4.4 (0.1-1452) | 4.8 (0.1-140) | 4.1 (0.6-1,452) | 0.46 |
| CA19-9 level (U/mL) Median (range) | 217.5 (-390,822) | 239 (-313,740) | 217 (-390,821) | 0.222 |
| Tumor size (cm) Median (range) | 3.0 (0-10.0) | 3.0 (0-10.0) | 3.0 (0-10.0) | 0.091 |
| LN Metastasis No/Yes | 246/153 | 61/28 | 185/125 | 0.126 |
| Distant Metastasis No/Yes | 264/142 | 65/26 | 199/116 | 0.141 |
| Resection+chemotherapy/ Chemotherapy/ Palliative care | 172/161/73 | 41/37/13 | 131/124/60 | 0.558 |

PC: pancreatic cancer, M/F: male/female, BMI: body mass index, CI: confidential interval, LN: lymph node, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

palliative care, respectively (Table 1). The pathological diagnosis was made for 279 patients with PC (68.7%): 172 patients (100%) for surgical resection, 86 patients (53.4%) for chemotherapy, and 21 patients (28.8%) for palliative care. The surgical resection group included 115 patients (66.9%) who received adjuvant chemotherapy (including 8 who received radiation). Of the 115 patients, gemcitabine-based chemotherapy, S-1-based chemotherapy, and gemcitabine plus S-1 were administered to 64 (55.7%), 40 (34.8%), and 6 (5.2%) patients, respectively.

The regimen for the chemotherapy group was gemcitabine-based in 123 patients (77.8%), including 23 who had combined radiation treatment; S-1 based in 27 patients (17.1%); and gemcitabine plus S-1 in 7 patients (4.4%).

According to treatments, those with A alleles who under-

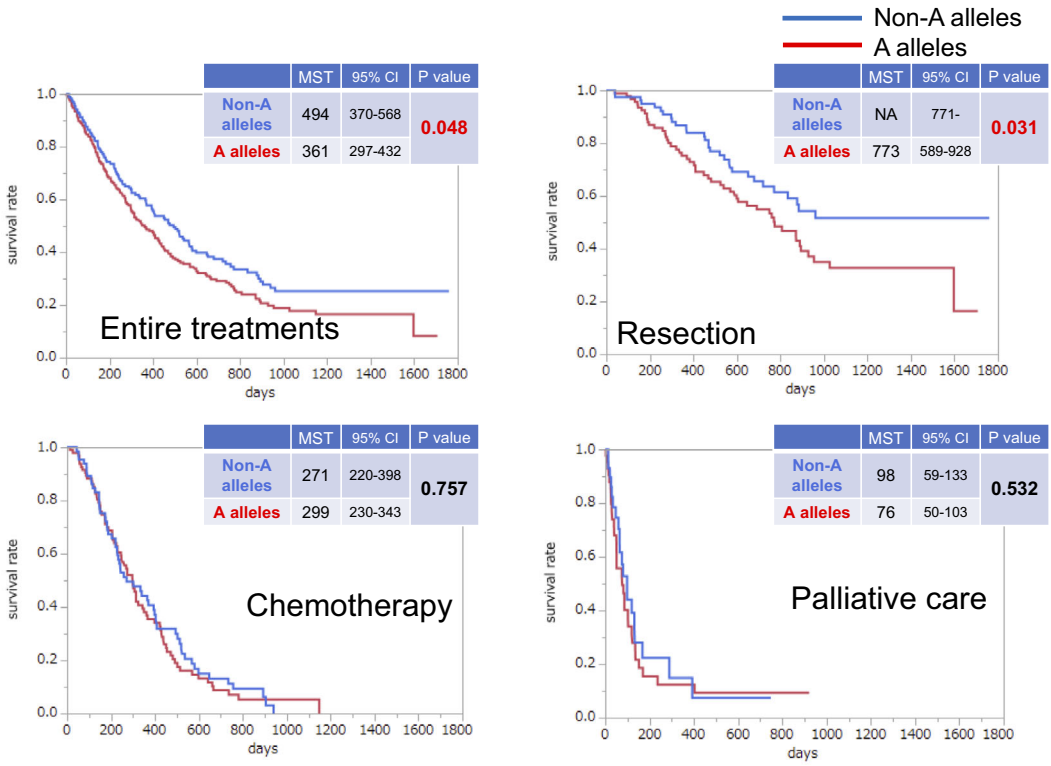


**Figure 1. Comparison of long-term outcome of patients with pancreatic cancer between A alleles and non-A alleles according to treatments [entire treatments (p=0.048), resection (p=0.031), chemotherapy (p=0.757), and palliative care (p=0.532)].**

went resection had worse long-term outcomes than those with non-A alleles (A alleles, 773 days; non-A alleles, days not available, p=0.031). However, the MST of those who underwent chemotherapy (A alleles, 299 days; non-A alleles, 271 days, p=0.757) and palliative care (A alleles, 76 days; non-A alleles, 98 days, p=0.532) did not differ markedly between those with A alleles and non-A alleles (Fig. 1). There was no significant difference in the MST between those with B alleles and non-B alleles among those who underwent resection (B alleles, 834 days; non-B alleles, 877 days, p=0.839), chemotherapy (B alleles, 299 days; non-B alleles, 299 days, p=0.784), and palliative care (B alleles, 98 days; non-B alleles, 80 days, p=0.683) (Fig. 2). When type O and non-type O were compared, no marked difference was seen in those who underwent resection (type O, days not available; non-type O, 807 days, p=0.063), chemotherapy (type O, 271 days; non-type O, 299 days, p=0.719), or palliative care (type O, 80 days; non-type O, 86 days, p=0.905) (Fig. 3).

### *The association between different ABO blood types and the long-term outcomes of PC*

A alleles were significantly associated with the long-term outcome of PC in 2 different models [model 1, hazard ratio (HR) 1.317, 95% confidence interval (CI) 1.018-1.710, p=0.036; model 2, HR 1.454, 95% CI 1.101-1.928, p=0.008]. However, B alleles were not associated with the long-term outcome of PC. Model 1 showed that type O was significantly associated with the long-term outcome of PC compared to type non-O (HR 0.719, 95% CI 0.521-0.974, p=0.033), while the association disappeared when model 2 was applied (Table 3).

## Discussion

The present study is the first study to show the influence of the ABO blood type in the clinical course of PC in Japanese patients. There were two main findings in our study: the long-term outcome of the entire cohort as well as the long-term outcomes among the patients who underwent resection differed according to the ABO blood type.

Some previous studies have investigated the association of the ABO blood type with PC stage or treatment choice at the diagnosis (resection vs. no resection). Although the results were inconclusive, they mainly showed no association (12, 14-16). A population study conducted in Norway showed a higher prevalence of type A among those with unresected PC than in the general population. However, when the prevalence of resection and no resection was compared between those with type A and non-type A, no marked difference was noted (data not shown in the manuscript, but a chi-square analysis comparing type A and non-type A among unresected PC patients showed p=0.223) (13).

Previous studies comparing the overall survival among patients with different ABO blood types have reported conflicting findings (12-16). A German group that investigated

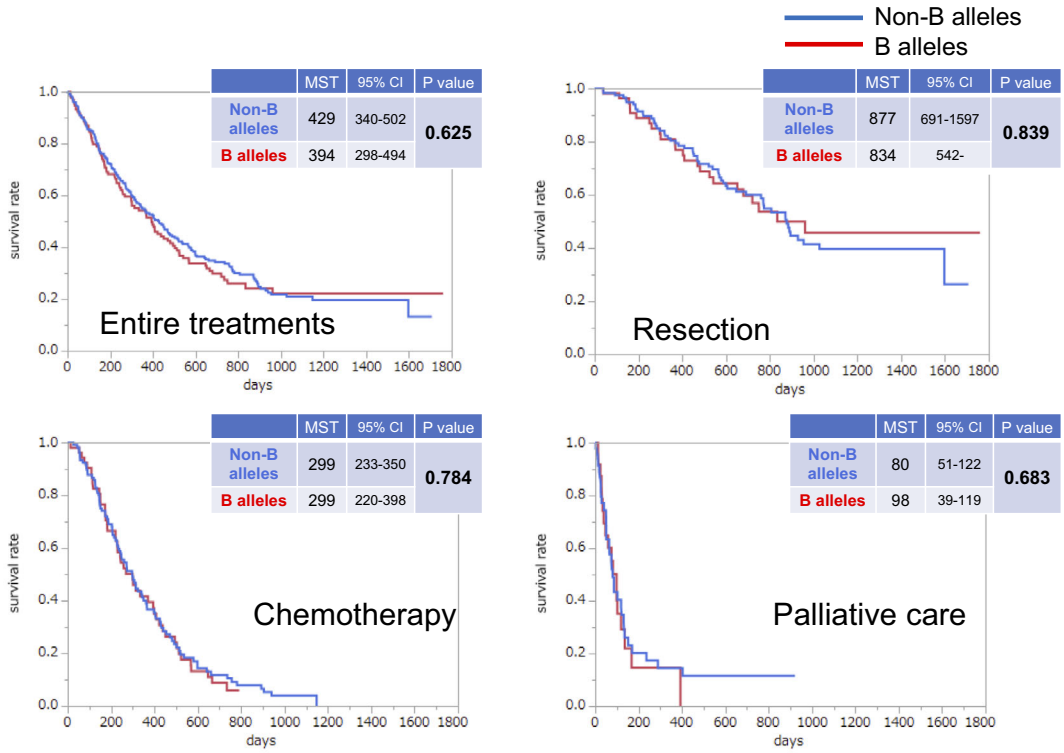


**Figure 2.** **Comparison of long-term outcome of patients with pancreatic cancer between B alleles and non-B alleles according to treatments [entire treatments (p=0.625), resection (p=0.839), chemotherapy (p=0.784), and palliative care (p=0.683)].**

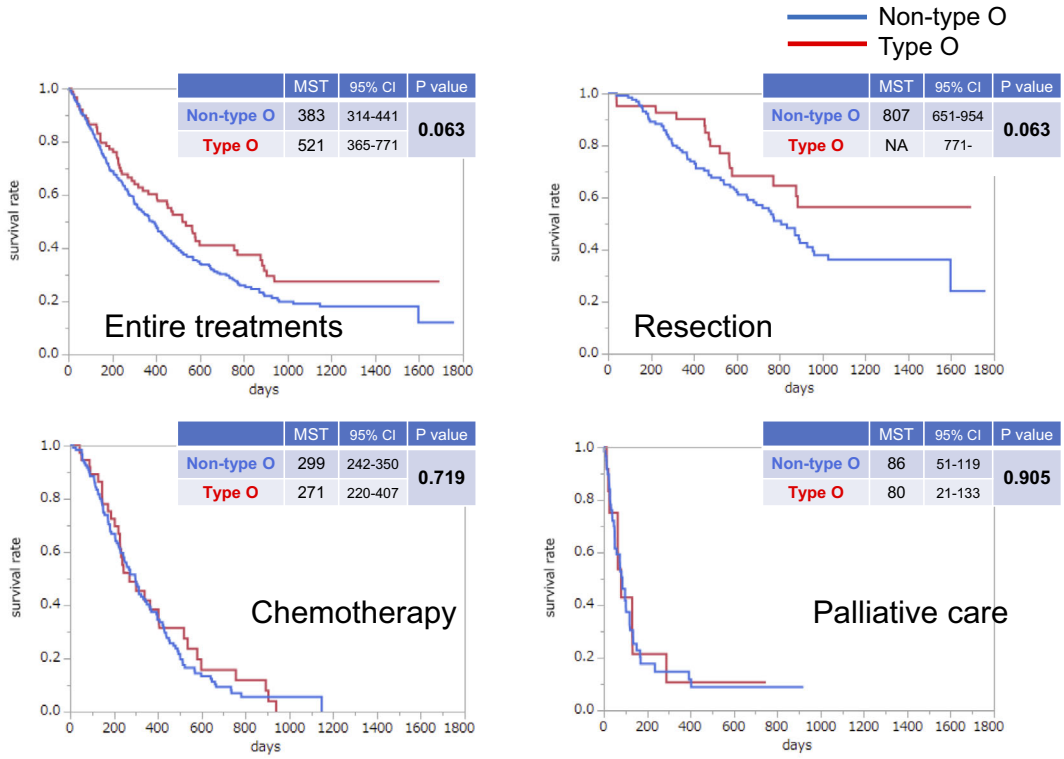


**Figure 3.** **Comparison of long-term outcome of patients with pancreatic cancer between type O and non-type O according to treatments [entire treatments (p=0.063), resection (p=0.063), chemotherapy (p=0.719), and palliative care (p=0.905)].**

resected PC patients reported a favorable and independent impact of type O on the survival (12). However, two Chinese studies reported no association between type O and PC (14, 15). These differing findings are not surprising,

**Table 3. Association between Different ABO Blood Types and Long-term Outcome of Pancreatic Cancer.**

| a. A alleles (n=231) vs. non-A alleles (n=175) | | |
|---|---|---|
| | HR (95% CI) | p value |
| Model 1 | 1.317 (1.018-1.710) | 0.036 |
| Model 2 | 1.454 (1.101-1.928) | 0.008 |

| b. B alleles (n=134) vs. non-B alleles (n=272) | | |
|---|---|---|
| | HR (95% CI) | p value |
| Model 1 | 1.114 (0.848-1.451) | 0.434 |
| Model 2 | 0.956 (0.716-1.264) | 0.754 |

| c. Type O (n=91) vs. non-type O (n=315) | | |
|---|---|---|
| | HR (95% CI) | p value |
| Model 1 | 0.719 (0.521-0.974) | 0.033 |
| Model 2 | 0.746 (0.527-1.035) | 0.081 |

Model 1: adjusted for age, sex and BMI

Model 2: adjusted for age, sex, BMI, tumor size, LN metastasis and distant metastasis

HR: hazard ratio, CI: confidential interval, BMI: body mass index, LN: lymph node

since the stage at the diagnosis is generally associated with the prognosis in any disease. Regarding the influence of different treatment modalities on the long-term outcome, one study showed a difference in the MST between unresected PC patients with type O and non-type O (6.7 months vs. 5.5 months, p=0.040), while no marked difference was observed in resected PC patients (13). These results suggest a difference in the affinity to chemotherapy between those with type O and non-type O.

In this regard, our first main finding is that A alleles had an association with the long-term outcomes (p=0.048). Our second main finding of a worse prognosis in those who underwent resection with A alleles than in those with non-A alleles (p=0.031) suggests that tumor invasive behavior may be more frequent in those with A alleles than in those with non-A alleles. Finally, our results derived from a multivariate analysis on different ABO blood types confirmed that A alleles had an association with the long-term outcomes ($P< 0.05$ in two different models).

Many studies have noted that changes in the expression of A, B, and H antigens on PC cell surfaces occur during pancreatic tumorigenesis, implying modifications in glycosyltransferase specificity (19-22). Beyond characterizing blood type, glycosyltransferase specificity influences a wide range of biological processes (23). For example, glycoconjugates play key roles in adhesion between cells and membrane signaling, which in turn influence progression to malignancy and metastasis (24). However, there are no data describing the role of A alleles in tumor behavior, such as their association with adhesion molecules.

ABO blood types may have an association with endothelial mesenchymal transition, which leads to spreading behavior in PC (25). A comparison of clinical data on the disease-free survival after resection among different ABO blood types might further help our understanding of tumor spread in PC, considering the relatively high rate of distant metastasis, especially to the liver, after resection. Marionneau et al. showed that the expression of A antigen increases resistance to apoptosis and facilitates escape from immune control among rat colon carcinoma cells (26). This may therefore be another mechanism explaining the association between the A allele and the long-term outcomes in PC.

The strength of our study is that we included a relatively large number of PC patients for our analysis compared to previous reports on the long-term outcomes, thereby allowing us to conduct a multivariate analysis to derive A alleles as an independent factor influencing the long-term outcomes in PC. However, the present study also has several limitations. First, unlike the study by Nakao et al. using single-nucleotide polymorphisms and genotypes (5), our data on the ABO blood type described the serological ABO blood type. Second, some data were missing due to the retrospective nature of the study. Third, a selection bias existed because we focused on the association between PC and ABO blood type; thus, we had more PC patients who underwent surgical resection (42.3%) than is seen in real-world clinical practice. Patients are tested for their ABO blood type prior to surgery, whereas such testing is not always performed in those who do not undergo resection. However, the distribution of the ABO blood type in our study was similar to that in the previous Japanese population study reported by Nakao et al. (46.0%, 21.6%, 20.5%, and 11.9% for type A, B, O, and AB, respectively), which slightly differed from the general distribution for the Japanese population (5). Finally, a pathological diagnosis was not made in all unresected PC patients; other rare pancreatic tumors may therefore have been included. However, the rate of 68.7% was comparable to that in the previous Japanese study (5), and the clinical diagnosis of PC is not difficult in the vast majority of PC patients. Furthermore, patients who are expected to have a poor prognosis and thus choose palliative care do not often undergo a pathological examination, as was noted in our cohort (28.8%). Limited access to endoscopic ultrasound-guided fine-needle aspiration during the study period might be another reason unable to make a pathological diagnosis of PC. Despite these limitations, this is the first study to show the long-term outcomes of Japanese patients with PC and to compare these outcomes according to the different treatment modalities and patients' ABO blood type.

In conclusion, the ABO blood type, particularly the A alleles, influences the long-term outcomes of Japanese patients with PC, presumably due to the impact of the blood type on the disease onset and tumor behavior. Understanding the mechanisms underlying differences in the clinical course of PC according to the ABO blood type may lead to the discovery of new drugs and improve the long-term outcomes.

Further studies are needed to address these issues.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethics committee at the Ehime University Graduate School of Medicine. All subjects were assigned a numerical code that was used throughout the study, and all data were stored in a secure database to maintain anonymity. Consent for publication was not necessary due to the retrospective approach of the research.

**The authors state that they have no Conflict of Interest (COI).**

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