Original Article

Association of a genetic variant in the adenosine triphosphate transmembrane glycoprotein and risk of pancreatic cancer

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Background: Pancreatic cancer (PC) is one of the most aggressive neoplasms with a poor prognosis. The association of multidrug resistance genes, *MDR1/ABCB1*, with the poor outcomes of several malignancies has been reported, which can be explained at least in part by a reduction in the transportation of drugs and their metabolites. Here, we explore the association of a genetic variant, rs2032582, in the *ABCB1* gene with the risk of developing PC.

Methods: Seventy-five patients and 188 controls were recruited. DNA was extracted followed by genotyping using Taqman® real-time polymerase chain reaction-based method. Kaplan-Meier and Cox models analysis showed that there is no significant association between genetic models and overall survival (OS) (P=0.32).

Results: The frequencies of AA, AC, and CC genotypes of the variant were 29.7%, 42.2%, and 28.1%, respectively in the PC group, while the frequencies of the genotypes were 32.4%, 54.8%, and 12.8%, respectively, in the control group. Individuals with the AA genotype had an increased risk of developing PC {e.g., dominant genetic model [CC versus AA + AC: OS ± standard deviation (SD): 28±5.8 versus 50.8±6.7 months] with odds ratio (OR) of 2.67 (CI =1.33–5.34, P=0.005)}.

Conclusions: Our findings demonstrated the association of the *ABCB1* variant with an increased risk of PC. Further studies in a larger sample size and multi-center setting are suggested to explore the prognostic value of emerging marker PC.

Keywords: Pancreatic cancer (PC); *ABCB1*; *MDR1*; polymorphism; rs2032582

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Introduction

As one of the most aggressive neoplasms with a poor prognosis, pancreatic cancer (PC) is the seventh leading cause of cancer-related deaths worldwide. The incidence rate is slightly higher in men than women, as it is the twelfth most common cancer in men and eleventh in women. Moreover, age plays a role in this disease (1,2). As this disease is asymptomatic or non-specific symptoms are seen, most PC patients are diagnosed at an advanced stage (3,4). Although many efforts have been made to improve its 5-year survival rate, this remains at lower than 9% (2). The only current treatment is surgical resection followed by adjuvant chemotherapy with gemcitabine or S-1, an oral fluoropyrimidine derivative (5). *KRAS*, *CDKN2A*, *TP53*, and *SMAD4* are the four primary driver genes for PC: one oncogene and three tumor suppressor genes. The most commonly mutated oncogene is *KRAS*; it encodes a small GTPase facilitating downstream signaling from growth factor receptors. The *CDKN2A* gene encodes the most frequently altered tumor suppressor gene which is an essential cell-cycle regulator; as in ductal adenocarcinomas, it loses function in more than 90% of cases (6). There are often somatic mutations in the *TP53* tumor suppressor gene; it encodes a protein with a critical role in the cellular stress response and is mutated in a wide range of tumor types. The tumor suppressor gene *SMAD4* moderates signaling downstream responsible for changing the growth factor β (*TGFβ*) receptor and is inactivated in about 50% of tumors (3,6).

The *ABCB1* gene encodes an adenosine triphosphate (ATP) transmembrane glycoprotein, called p-glycoprotein (P-gp) or multidrug resistance 1 (*MDR1*), which is an efflux pump and removes toxic endogenous materials, drugs, and xenobiotics from cells (7,8). The location of the *ABCB1* gene is in the 7q21.12 region, comprising a total of 209 Kb, and has 29 exons and more than 40 identified single nucleotide polymorphisms (9,10). One variant of the *ABCB1* gene is the rs2032582 polymorphism (2677G>T/A) in exon 21. This variant can change protein function by amino acid exchange from alanine to serine or threonine (11,12), which facilitates P-gp expression (8,13). *ABCB1* polymorphism is highly associated with different cancers, including PC, in women (14). Moreover, G2677T variant is notably linked to a high risk of lung cancer (10,15). Due to the involvement of the *ABCB1* in the metabolism of exogenous and endogenous compounds, related polymorphism may potentially cause carcinogenesis; accordingly, we aimed to investigate the association between rs2032582 in this gene with clinical features and risk of PC.

Highlight box

Key findings

- The *ABCB1* polymorphism (rs2032582) with increased risk of PC is associated. But this variant does not significantly associate with OS.

What is known and what is new?

- *ABCB1* polymorphism is highly associated with different cancers, including PC, in women.
- This manuscript adds there is a relationship between the *ABCB1* polymorphism (rs2032582) and nodal status with an increased risk of PC.

What is the implication, and what should change now?

- Further studies in larger populations and at different geographical locations are required to confirm our findings and evaluate the prognostic potentials of rs2032582 in determining the risk of PC.

Methods

Patient samples

In this case-control study, we have 75 PC patients and 188 age-matched healthy from Emamreza Hospital of Mashhad, Iran. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Mashhad University of Medical Sciences Ethics Committee (ID: IR.MUMS.MEDICAL.REC.1400.709). The Mashhad University of Medical Sciences Ethics Committee guidelines were used to obtain informed consent from all the participants. All the samples were obtained from the patients with PC from May 2006 to August 2020 and confirmed with histological diagnosis. All the patients undergo surgical resection and survival time was calculated from the date of surgery to the date of death. Formalin-fixed, paraffin-embedded (FFPE) samples of PC tissues were obtained and used in this study. The control group was collected from the Mashhad cohort study, individuals had no diseases.

DNA extraction and genotyping

First, paraffin-embedded tissue samples were de-paraffinized by xylene and absolute ethanol solution. Genomic DNA was then extracted from FFPE tissue samples by the PZP kit, according to the provided protocol for the kit. The sample concentration and purity of DNA were assessed,

Table 1 Demographic and clinicopathological characteristics

Characteristic	Mean ± SD or n (%)	
	Patient	Control
Age (years)	61.04±11.99	57.00±9.71
Sex		
Female	31 (48.0)	90 (47.9)
Male	33 (52.0)	98 (52.1)
TMN classification		
Stage I–II	33 (52.0)	
Stage III–IV	31 (48.0)	
Tumor size		
T1	0 (0.0)	
T2	32 (50.0)	
T3	23 (36.0)	
T4	9 (14.0)	
Nodal status		
Yes	41 (64.0)	
No	23 (36.0)	
Distant metastasis		
Yes	9 (14.0)	
No	55 (86.0)	
Grade		
Poor-differentiated	0 (0.0)	
Moderated-differentiated	3 (4.7)	
Well-differentiated	7 (11.0)	
Undifferentiated	54 (84.3)	

Cases with unclear properties were excluded from the study. SD, standard deviation.

then genotype analysis of rs2032582 polymorphism was carried out using Taqman®-based assay; PCR reactions were carried out in 12.5 µL total volume, using ~10 ng/µL DNA in TaqMan® Universal Master Mix with specific primer and probe (C-11711720c-30; Applied Biosystems Foster City, CA). The evaluation of the allelic content for each sample was done using the ABIPRISM-7500 tool equipped with SDS software version-2.0.

Statistical analysis

The data distribution within the subgroups was analyzed using the Kolmogorov-Smirnov tests. Normally distributed continuous data were assessed using Student's *t*-tests. The comparison between the frequencies of *ABCB1* gene rs2032582 polymorphisms was assessed using χ^2 tests. We used independent *t*-test and Pearson chi-squared tests to evaluate the demographic and clinicopathological data of 252 individuals in various genotypes. The Hardy-Weinberg test was used to evaluate the genotype and allele frequency using the Pearson χ^2 test. Odds ratio (OR), 95% confidence intervals (CIs), and P value were calculated to estimate the correlation of genotypes on different genetic models, using logistic regression. The data analysis was performed by SPSS-22 software with a P values less than 0.05, and all tests were two-sided.

Results

Clinicopathological characteristics of patients

The demographic, clinical, and genetic characteristics of the population are shown in *Table 1*. Forty-six percent of the patient samples were female, and 54% were male, with an overall mean age of 61.49±11.38 years. Moreover, 50%, 36%, and 14% of PC patients were T2, T3, and T4, respectively. Fifty-two percent of patients were in stage I–II, and 48% of patients were in stage III–IV (*Table 1*).

Association of the rs2032582 genetic variant with PC

We performed genotyping on genomic DNAs extracted from cancer patients' tissues; hence the association between *ABCB1* polymorphism (rs2032582) and susceptibility to PC was explored. As sown in the *Table 2*, the frequencies of AA, AC, and CC genotypes in the total population were calculated as 31.7%, 51.6%, and 16.7%, respectively which was in Hardy-Weinberg equilibrium (HWE). The frequencies of A and C alleles were 0.42 for rs2032582. The frequencies of AA, AC, and CC genotypes for rs2032582 were 29.7%, 42.2%, and 28.1%, respectively in the PC group while these frequencies in control group were 32.4%, 54.8%, and 12.8%, respectively (*Table 2*).

An increased risk of PC (dominant model: OR =2.67, CI =1.33–5.34, P=0.005, and recessive model: OR =1.13, CI =0.61–2.10, P=0.68) (*Table 3*) was observed in the individuals with an AA genotype of the *ABCB1* rs2032582. We also evaluated the genotype distribution of the *ABCB1* polymorphism in relation to the clinicopathological features of patients with PC using a recessive genetic model, which showed that rs2032582 has a significant correlation with

Table 2 Allele and genotype frequencies of rs2032582 polymorphisms

Gene	SNP	Control (N=188)	Case (N=64)	Total (N=252)	MAF	HWE (P value)
ABCB1	rs2032582				0.42	0.37
	AA	61 (32.4)	19 (29.7)	80 (31.7)		
	AC	103 (54.8)	27 (42.2)	130 (51.6)		
	CC	24 (12.8)	18 (28.1)	42 (16.7)		

SNP, single-nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 3 The analysis of rs2032582 polymorphism under various genetic models

Models	Genotype	Case, n (%)	Control, n (%)	OR (95% CI)	P value
Allele	A	65 (50.8)	225 (59.8)	–	–
	C	63 (49.2)	151 (40.2)	–	
Dominant	AA + AC	46 (72.0)	164 (87.0)	2.67 (1.33–5.34)	0.005
	CC	18 (28.0)	24 (13.0)	1.00 (reference)	
Recessive	AC + CC	45 (70.0)	127 (68.0)	1.13 (0.61–2.10)	0.68
	AA	19 (30.0)	156 (32.0)	1.00 (reference)	
Co-dominant	AA + CC	37 (58.0)	85 (45.0)	1.66 (0.93–2.94)	0.08
	AC	27 (42.0)	103 (55.0)	1.00 (reference)	

OR, odds ratio; CI, confidence interval.

nodal status (P=0.04) (*Table 4*). The mean range of CC genotype (28±5.8 months) was compared to AA + AC genotypes (50.8±6.7 months) and showed no significant association between the dominant genetic model and their OS (P=0.42) (*Figure 1*). Cox plot analysis was also performed, but like OS, this genetic model did not show a significant association with Cox regression (P=0.32).

Discussion

The *ABCB1* polymorphism is associated with a reduction in drug and metabolites transportation, so they accumulate in the extracellular environment leading to cancerous conditions. However, this polymorphism does not alter any of its encoded amino acids; it dramatically decreases mRNA expression and the stability of the protein and may be associated with tumorigenesis (16). Our results showed that PC is more common in male than in female. Our data are in line with a previous study in Tehran population. Sheikh *et al.* revealed that most patients were male (61.1%) with lower overall survival (OS) (17).

An important recent finding has shown the significant association between a genetic variant (rs2032582) and the risk of PC. Individuals with an AA genotype are more susceptible to PC. There is a piece of emerging evidence supporting the notion that the rs2032582 genetic variant plays a role in the development of several malignancies (18), such as lung cancer (15) and colorectal cancer (10,14). Consistent with our results, a recent study by ShahidSales *et al.* in 2020 on 88 breast cancer and 200 healthy individuals reported no statistically significant association between *CYP1B1*/rs1056836 and the type and the risk of breast cancer. At the same time, *ABCB1*/rs2032582 was potentially associated with breast cancer tumor size (P<0.05) (10). Regarding the association between the *ABCB1* gene rs1045642 polymorphism, a meta-analysis consisting of 3,175 colorectal cancer patients and healthy controls in 2012 was undertaken. The result showed that neither *ABCB1* rs2032582 nor *ABCB1* rs3789243 were associated with colorectal cancer risk (P=0.03). Neither *ABCB1* rs2032582 nor *ABCB1* rs3789243 were associated with colorectal cancer risk. He *et al.* found an increased frequency of alleles (rs2032582G/rs1045642C) in Caucasian CRC patients (P=0.02) (8). In a study done by Panczyk

Table 4 Frequency of the demographic and pathological information in dominant genetic model

Characteristics	AA + AC (N=46)	CC (N=18)	P value
Age (years)	47.5±11.7	51.0±14.4	–
Sex			0.13
Female	25 (54.0)	6 (33.0)	
Male	21 (46.0)	12 (67.0)	
Tumor size			0.81
T1–T2	24 (52.0)	9 (50.0)	
T3–T4	22 (48.0)	9 (50.0)	
Distant metastasis			0.6
Yes	6 (13.0)	3 (17.0)	
No	40 (87.0)	15 (83.0)	
Nodal status			0.04
Yes	26 (56.0)	15 (83.0)	
No	20 (44.0)	3 (17.0)	
TMN classification			0.81
Stage I–II	24 (52.0)	9 (50.0)	
Stage III–IV	22 (48.0)	9 (50.0)	
Grade			0.53
WD, MD	8 (17.0)	2 (11.0)	
UD	38 (83.0)	16 (89.0)	

Data are presented as mean ± standard deviation or n (%). WD, well-differentiated; MD, moderately differentiated; UD, undifferentiated.

et al. in the Netherlands, 95 patients with colorectal cancer and 95 healthy blood samples, every 3 SNP were tested (*ABCB11236*C>T, *ABCB12677*G>T/A, and *ABCB13435*C>T). Haplotypes were significantly distributed among colorectal patients and the healthy population (P=0.03). Differences in haplotype distributions between colorectal cancer patients and healthy populations suggested that other potential SNPs, especially in the regulatory region of the *ABCB1* gene, may influence P-glycoprotein expression and function (19). The association of *ABCB1* 3435>T polymorphism and treatment outcomes in advanced gastric cancer patients was observed in a study by Chang *et al.* In this study, 43 gastric cancer patients were treated with paclitaxel-based chemotherapy and a control group of 11 healthy volunteers (20). In 2019, Zhao showed the effects of *OPRM1* and *ABCB1* gene polymorphisms

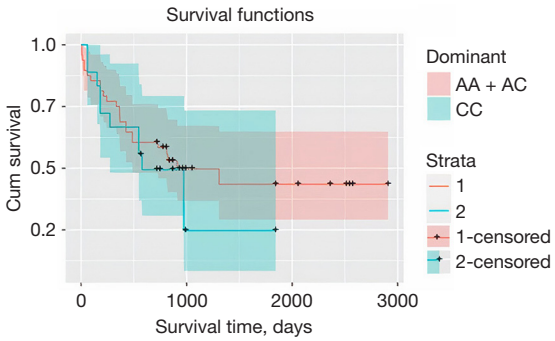

Figure 1 Association between *ABCB1* rs2032582 polymorphism and Kaplan-Meier plot of overall survival in patients with pancreatic cancer.

(rs2032582 and rs1128503) on the analgesic effect and dose of sufentanil after thoracoscopic-assisted radical resection of lung cancer. In this study, 225 patients were included (132 men and 93 women). The results showed that the sufentanil doses at T1 (doses and side effects of sufentanil consumed 6 h), T2 (24 h), and T3 (48 h) were significantly higher in radical-operation lung cancer patients with mutant homozygous rs2032582 and rs1128503 loci in the *ABCB1* gene. Patients at T1, T2, and T3 took higher doses of sufentanil in comparison to patients without mutations, with a statistically significant difference (P<0.05). In the current study, there was no significant difference between rs1045642 and sufentanil consumption (P>0.05), while previous investigation showed a positive association between the variation and PC (21). Pang *et al.*, in 2014, investigated the potential relationship between the progression of PC and chemical resistance. In this study, 4 SNPs in different genes, including *ABCB1*, and the expression of 3 transporters were investigated in healthy and cancerous samples (22).

Conclusions

Our outcomes show a relationship between the *ABCB1* polymorphism (rs2032582) and nodal status and an increased risk of PC. Further studies in larger populations and at different geographical locations are required to confirm our findings and evaluate the prognostic potentials of rs2032582 in determining the risk of PC.

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Footnote

Data Sharing Statement: Available at https://apc.amegroups.org/article/view/10.21037/apc-22-7/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Mashhad University of Medical Sciences Ethics Committee (ID: IR.MUMS.MEDICAL.REC.1400.709). The Mashhad University of Medical Sciences Ethics Committee guidelines were used to obtain informed consent from all the participants.

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