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Correlation between Angiotensin Inhibitor Administration and Longer Survival in Patients Who Underwent Curative Resection for Pancreatic Cancer

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Purpose: The microenvironment of pancreatic ductal adenocarcinoma (PDAC) with extensive desmoplastic stroma contributes to aggressive cancer behavior. Angiotensin system inhibitors (ASIs) reduce stromal fibrosis and are a promising therapeutic strategy. The purpose of this study was to examine how ASIs affected the oncological results of patients who had their PDAC removed.
Materials and Methods: A retrospective assessment was conducted on the clinicopathological and survival data of patients who received curative resection for PDAC at Severance Hospital between January 2012 and December 2019.
Results: A total of 410 participants (228 male and 182 female), with a median follow-up period of 12.8 months, were included in this study. Patients were divided into three groups, based on ASI use and history of hypertension: group 1, normotensive and never used ASI (n=210, 51.2%); group 2, ASI non-users with hypertension (n=50, 12.2%); and group 3, ASI users with hypertension (n=150, 36.6%). The three groups did not differ significantly in terms of age, sex, kind of operation, T and N stages, or adjuvant and neoadjuvant therapy. Moreover, there was no discernible difference in disease-free survival between those who used ASI and those who did not (p=0.636). The 5-year overall survival (OS) rates in groups 1, 2, and 3 were 52.6%, 32.3%, and 38.0%, respectively. However, the OS rate of ASI users was remarkably higher than that of non-users (p=0.016).
Conclusion: In patients with resected PDAC, ASI is linked to longer survival rates. Furthermore, for individuals with hypertension, ASI in conjunction with conventional chemotherapy may be an easy and successful treatment option.

Key Words: Angiotensin system inhibitor, survival, pancreatic cancer, ductal adenocarcinoma

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a malignant tumor that is extremely fatal, with a 5-year survival rate of <10% without surgery and <20%–30% after surgery.[1,2] More than half of patients with pancreatic cancer experience recurrence within 1–2 years following surgical resection, despite the availability of multiple treatment alternatives, such as new chemotherapy regimens and surgical procedures.[3,4] The current standard of care for curative treatment is neoadjuvant chemotherapy followed by surgical resection. However, only about 20% of patients are thought to be viable candidates for complete tumor resection.[5-7]

Dense fibroinflammatory stroma and desmoplastic reactions associated with pancreatic cancer cause hypovascularity and a hypoxic microenvironment that evoke acquired chemoresistance by blocking drug delivery, and play a significant role in the progression of cancer, leading to poor prognosis. Pancreatic cancer is a unique type of solid tumor that adapts to hypoxic physiological responses by creating a favorable hypovascular tumor microenvironment for its growth.[8,9] Hence, for decades, several oncological studies have focused on understanding the

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tumor microenvironment for pancreatic cancer tumorigenesis. However, unlike the overwhelming success of immunotherapeutic approaches for other cancers, including melanoma and lung cancer, PDAC patients have demonstrated modest responses.[10]

The renin-angiotensin system (RAS) is the primary regulator of cell proliferation, metabolism, and growth. The RAS is associated with tumor progression in various malignancies, particularly in tumor cell expression.[11-13] Some cancer cells utilize angiotensin II signaling pathways, which are the primary effectors of the RAS, for survival. Fibrotic changes in tumors and desmoplasia proliferate due to the activation of RAS system via the transforming growth factor (TGF)-β. As a result of the inhibition of the angiotensin-II-receptor-1, angiotensin system inhibitors (ASIs) lower stromal fibrosis signaling, which is correlated with decreased profibrotic signal production, including TGF-1, connective tissue growth factor (CCN2), and endothelin-1 (ET-1).[14]

In pancreatic cancer models, ASIs enhance oxygen and medication transport to tumors, thereby increasing the effectiveness of treatment.[14-16] According to Liu, et al.,[17] chronic ASI are associated with longer survival. The malignant potential of cancer cells from patients with pre-existing cardiovascular disease who were already taking ASI was reduced in these cohorts. In a phase II clinical trial, Murphy, et al.[18] suggested that ASIs in combination with neoadjuvant chemotherapy might help downstage locally advanced pancreatic cancer. Using a single-center database, we aimed to determine the oncological effects and significance of ASIs in Korean patients undergoing radical surgery for pancreatic cancer.

MATERIALS AND METHODS

Patients selection and evaluation

A total of 423 patients with histologically proven PDAC, who had pancreatic resection at Yonsei University Severance Hospital between January 2012 and December 2019, were initially included in this retrospective single-center cohort analysis. The exclusion criteria included histology other than adenocarcinoma, palliative surgery, multiple primary malignancies, and mortality within three months of surgery. Finally, this study included 410 patients (Fig. 1). Information on each patient was retrieved from the electronic medical records system and retrospectively reviewed. The Institutional Review Board of Yonsei University College of Medicine approved this study (IRB number 4-2023-0898 in 2023).

Statistical analysis

IBM SPSS Statistics for Windows, version 26 (IBM Corporation, Armonk, New York, USA) was used for all statistical analyses. Values are presented as means, standard deviations, or, when appropriate, medians and ranges. The chi-square test was used to compare categorical variables, and presented as numbers (n) and percentages (%). As appropriate, the independent t-test or Mann-Whitney U test was used to compare continuous variables. The t-test or chi-square test was used for statistical analysis, as appropriate. Kaplan–Meier analysis was used to evaluate survival. Log-rank tests were used to compare the survival outcomes. The period from study enrollment to recurrence of near or distant disease was defined as disease-free survival (DFS). The period from study enrollment to death from any cause was referred to as overall survival (OS). The cutoff for statistical significance was set at $p<0.05$. The risk factors affecting DFS and OS were assessed using the Cox proportional hazard model, and variables that had a p-value of 0.05 or below in the univariate analysis were included in the multivariate analysis.

RESULTS

Clinicopathologic characteristics of patients with PDAC

Three groups of PDAC patients were created based on the types of medication and antihypertensive medication use. The clinicopathological features and results of these patients are shown in Table 1. Of 410 patients included in this study,

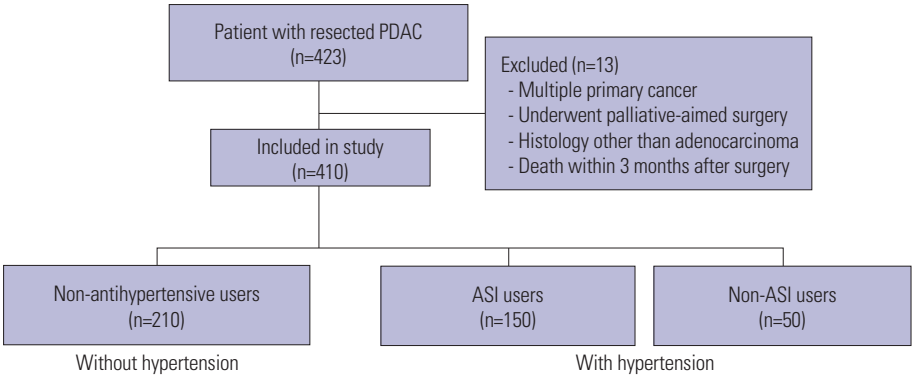

Fig. 1. Study flowchart. PDAC, pancreatic ductal adenocarcinoma.

Table 1. Clinicopathologic Characteristics of the Patients (n=410)

	No HTN[1] (n=210)	HTN without ASI[2] (n=50)	HTN with ASI[3] (n=150)	*p* value	*p* [1) vs. 2)]	*p* [2) vs. 3)]	*p* [1) vs. 3)]
Age (yr)	61.6±9.38	65.9±8.1	66.6±8.5	<0.001	0.008	0.904	<0.001
Sex				0.501	0.526	0.325	0.521
Male	118 (56.1)	31 (62.0)	79 (52.7)				
Female	92 (43.9)	19 (38.0)	71 (47.3)				
Neoadjuvant chemotherapy				0.566	0.373	0.356	>0.999
Yes	53 (25.2)	16 (32.0)	37 (24.7)				
No	157 (74.8)	34 (68.0)	113 (75.3)				
Operation method				0.788	0.845	0.859	0.478
Open	155 (73.8)	36 (72.0)	105 (70.0)				
Minimally invasive	55 (26.2)	14 (28.0)	45 (30.0)				
Operation type				0.136	0.029	0.197	0.589
PD/PPPD	125 (59.5)	24 (48.0)	83 (55.4)				
Distal pancreatectomy	74 (35.2)	26 (52.0)	62 (41.3)				
Total pancreatectomy	11 (5.4)	0	5 (3.3)				
Tumor size (cm)	2.7±1.3	2.9±1.2	2.7±1.6	0.617	0.616	0.633	>0.999
T stage				0.384	0.218	0.318	0.656
T0	5 (2.4)	0	2 (1.3)				
T1	55 (26.2)	11 (22.0)	33 (22.0)				
T2	121 (57.6)	28 (56.0)	95 (63.3)				
T3	29 (13.8)	11 (22.0)	20 (13.3)				
N stage				0.486	0.671	0.293	0.338
N0	107 (50.9)	22 (44.0)	82 (54.7)				
N1	76 (36.2)	21 (42.0)	56 (37.3)				
N2	27 (12.9)	7 (14.0)	12 (8.0)				
LVI				0.092	0.249	0.053	0.170
Yes	74 (35.2)	22 (44.0)	42 (28.0)				
No	136 (64.8)	28 (56.0)	108 (72.0)				
PNI				0.995	0.948	>0.999	>0.999
Yes	146 (69.5)	35 (70.0)	105 (70.0)				
No	64 (30.5)	15 (30.0)	45 (30.0)				
R status				0.753	0.496	0.406	0.887
R0	176 (83.8)	45 (90.0)	125 (83.3)				
R1	30 (14.3)	4 (8.0)	23 (15.3)				
R2	4 (1.9)	1 (2.0)	2 (1.4)				
Adjuvant therapy				0.756	0.831	>0.999	0.556
Yes	175 (83.3)	43 (86.0)	129 (86.0)				
No	35 (16.7)	7 (14.0)	21 (14.0)				

HTN, hypertension; ASI, angiotensin system inhibitor; PD, pancreaticoduodenectomy; PPPD, pylorus preserving pancreaticoduodenectomy; LVI, lympho-vascular invasion; PNI, perineural invasion.
Data are presented as mean±standard deviation or n (%). Bonferroni correction was used to obtain pairwise *p*-values. Tumor stage was assessed according to the tumor-node-metastasis classification, the American Joint Committee on Cancer 8th edition.

210 (51.2%) patients were normotensive and never used ASI [group 1, no angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEi)]; 50 (12.2%) had pre-existing hypertension but were treated using alternative medications (group 2, ASI non-users with hypertension); and 150 (36.6%) were ASI users with hypertension (group 3) (Fig. 1). There were no appreciable gender disparities found in any of the three groups. The group of non-users was significantly younger than the ASI group (61.6±9.38 year vs. 66.6±8.5 year; $p<0.001$). The rates of use of neoadjuvant chemotherapy before surgical resection were similar in all three groups, including 53 (25.2%) in group 1, 16 (32.0%) in group 2, and 37 (24.7%) in group 3 ($p=0.566$). No discernible variations were observed in the operation methods or pathological severities among the three groups, except that no patient in group 2 underwent total pancreatectomy. The rates of use of gemcitabine-based adjuvant chemotherapy

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after resection, which occurred every 4 weeks for up to six cycles, were similar among the groups (p=0.756) (Table 1).[19,20]

Comparison of survival outcomes

This study analyzed the 5-year DFS and OS according to the three groups. In the entire study population, neither the DFS among all three groups [28.5% (group 3) vs. 29.7% (group 2) vs. 32.8% (group 1); p=0.462] nor among the two hypertensive groups (group 3 vs. group 2, p=0.636) showed significant differences (Fig. 2A).

The 5-year OS outcomes did not differ between the three groups [52.6% (group 3) vs. 32.3% (group 2) vs. 38.0% (group 1), respectively; p=0.053]. However, between group 3 (52.6%) and group 2 (32.3%), the survival rates differed significantly (p=0.016) (Fig. 2B).

Comparison of survival outcomes in patients receiving neoadjuvant chemotherapy

To report the effectiveness of ASI and neoadjuvant chemotherapy efficacy, 106 patients who underwent neoadjuvant chemotherapy were grouped into three subgroups according to the use of antihypertensive medication and types of medication [group 1 (normotensive and never used ASI), group 2 (ASI non-users with hypertension), and group 3 (ASI users with hypertension)]. Subsequently, we compared the 5-year DFS and OS among the three subgroups. In the neoadjuvant chemotherapy groups, neither DFS [30.9% (group 3) vs. 60.2% (group 2) vs. 37.8% (group 1); p=0.518] nor OS [47.7% (group 3) vs. 56.4% (group 2) vs. 33.7% (group 1); p=0.694] showed any significant differences (Fig. 3).

When comparing the two subsets of hypertension patients treated with neoadjuvant chemotherapy by antihypertensive medication usage, no discernable variations were observed in the 5-year DFS (p=0.523) and 5-year OS (p=0.599) between groups 2 and 3 (Fig. 3).

Risk factors impacting survival outcomes

Risk factors affecting OS were evaluated in the entire study population (Table 2). In univariate analysis, pN1 [odds ratio (OR): 1.717, p=0.001], pN2 (OR: 2.614, p<0.001), and lymphovascular invasion (LVI) (OR: 1.773; p<0.001) were significant risk factors for OS. Conversely, adjuvant chemotherapy (OR, 0.678; p=0.042) reduced the effect of the risk factors on survival outcomes. In the multivariate analysis, pN1 (OR: 1.704; p=0.003), pN2 (OR: 2.456, p<0.001), and LVI (OR: 1.441, p=0.026) remained significant risk factors for poor OS. Adjuvant chemotherapy (OR: 0.544; p=0.002) reduced the risk of poor OS.

We repeatedly evaluated the risk factors in patients with prediagnosed hypertension (Table 3). Univariate analysis identified pN1 (OR: 2.182; p=0.001), pN2 (OR: 2.499; p=0.009), and LVI (OR: 1.978, p=0.003) as significant risk factors for OS in the hypertensive groups. Adjuvant chemotherapy (OR: 0.564; p=0.046) and ASI (OR: 0.571; p=0.018) both reduced the risk of OS in univariate analysis. In the multivariate analysis, pN1 (OR: 2.301; p=0.001) and pN2 (OR: 2.959; p=0.003) remained important risk variables. In multivariate analysis, reduced risk rates for adjuvant chemotherapy (OR: 0.484, p=0.019) and ASI (OR: 0.582, p=0.023) were observed.

DISCUSSION

Poor overall prognosis and a low incidence of resection are main characteristics of pancreatic cancer. Long-term survival is expected only in patients who undergo surgical resection.[5,21,22] According to the findings of this single-center investigation, for individuals whose pancreatic cancer has been removed, ASIs increase the likelihood of survival.

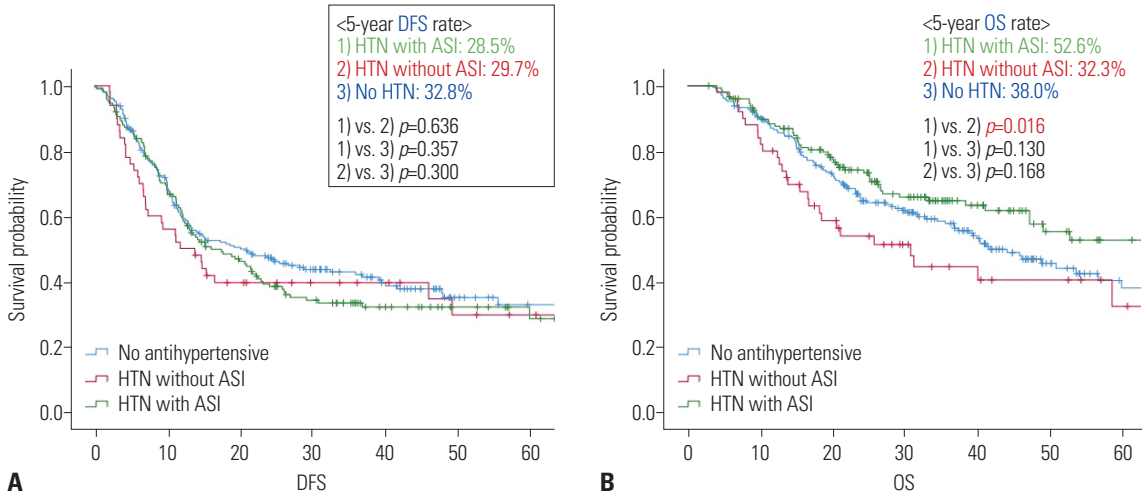

Fig. 2. Survival analysis according to hypertension (HTN) history and angiotensin system inhibitor (ASI) use of pancreatic cancer patients. A: Kaplan–Meier curves for disease-free survival (DFS) in pancreatic cancer patients with no HTN, ASI use, and without angiotensin inhibitor use with HTN. B: Kaplan–Meier curves for overall survival (OS) in pancreatic cancer patients with no HTN, ASI use with HTN, and without angiotensin inhibitor use with HTN.

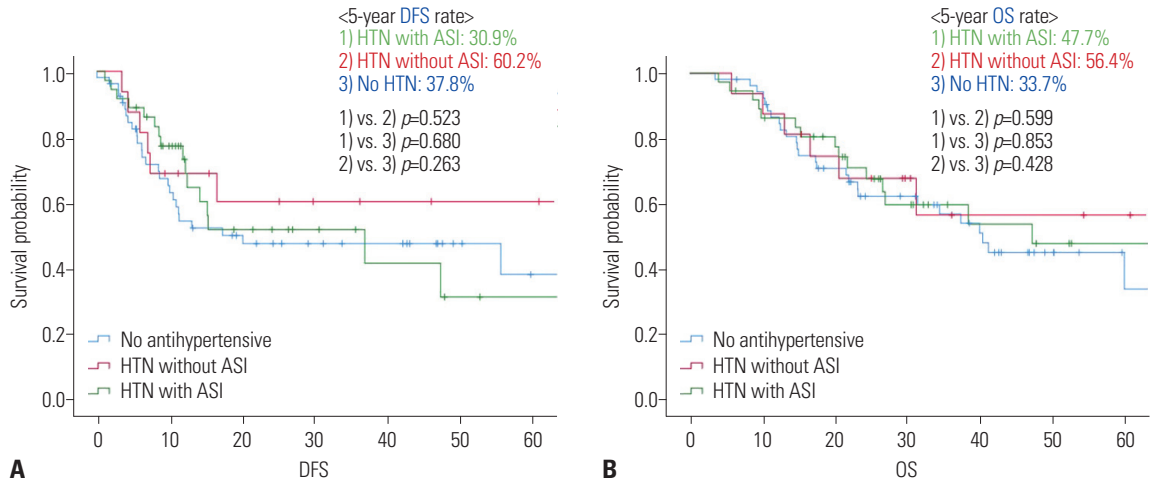

Fig. 3. Subgroup survival analysis according to hypertension (HTN) history and angiotensin system inhibitor (ASI) use of pancreatic cancer patients with neoadjuvant chemotherapy. A: Kaplan–Meier curves for disease-free survival (DFS) in pancreatic cancer patients receiving neoadjuvant chemotherapy with no HTN, ASI use, and without angiotensin inhibitor use with HTN. B: Kaplan–Meier curves for overall survival (OS) in pancreatic cancer patients receiving neoadjuvant chemotherapy with no HTN, ASI use with HTN, and without angiotensin inhibitor use with HTN.

Table 2. Univariate & Multivariate Analyses of Risk Factors Associated with Overall Survival for All Patients (n=410)

	Univariate			Multivariate		
	Exp (β)	95% CI	*p* value	Exp (β)	95% CI	*p* value
Age (yr)	1.001	0.985–1.018	0.875			
HTN						
No						
Yes	0.900	0.671–1.205	0.479			
ASI						
No						
Yes	0.730	0.531–1.004	0.053			
pN stage						
N0						
N1	1.717	1.246–2.367	0.001	1.704	1.202–2.416	0.003
N2	2.614	1.711–3.994	<0.001	2.456	1.565–3.852	<0.001
Adjuvant chemotherapy						
No						
Yes	0.678	0.466–0.986	0.042	0.544	0.368–0.802	0.002
LVI						
No						
Yes	1.773	1.316–2.389	<0.001	1.441	1.046–1.987	0.026

HTN, hypertension; ASI, angiotensin system inhibitor; LVI, lymphovascular invasion; CI, confidence interval.
Tumor stage was assessed according to the tumor-node-metastasis classification, the American Joint Committee on Cancer 8th edition.

The pancreatic cancer tumor matrix restricts treatment administration through vascular compression. This has the consequence of enlarging the tumor's local microenvironment and imposes significant desmoplastic stress, which represents 90% of the volume of the tumor. The vascular compression caused by ASIs improves vessel perfusion. Finally, ASIs restore stromal activity and matrix component production, resulting in stromal compression.[9,14]

As a downstream effect of angiotensin-II receptor-1 inhibition, ASIs diminish stromal fibrosis signaling, which is correlated with lower production of profibrotic signals TGF-1, CCN2, and ET-1. In pancreatic malignancies and other cancers, ASIs enhance medication, chemotherapy, and oxygen transport to tumors and lower hypoxia occurrences.[23-26]

Previous studies on pancreatic cancer with chronic ASI use range from preclinical to clinical studies.[24,27-31] The result of a meta-analysis conducted by Keith, et al.[30] indicated that while the survival outcomes of ASI intake in patients with PDAC are controversial, they are equivocal in that they do not lead to a negative prognosis for patients. Similarly, a single-center retrospective study targeting Americans revealed that ASI improves survival outcomes.[29] In a more sophisticated research

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Table 3. Univariate & Multivariate Analyses of Risk Factors Associated with Overall Survival for Patients with HTN (n=200)

	Univariate			Multivariate		
	Exp (β)	95% CI	*p* value	Exp (β)	95% CI	*p* value
Age (yr)	0.999	0.971–1.028	0.937			
HTN						
No						
Yes						
ASI						
No						
Yes	0.571	0.359–0.907	0.018	0.582	0.366–0.928	0.023
pN stage						
N0						
N1	2.182	1.361–3.498	0.001	2.301	1.427–3.709	0.001
N2	2.499	1.258–4.964	0.009	2.959	1.462–5.987	0.003
Adjuvant chemotherapy						
No						
Yes	0.564	0.321–0.990	0.046	0.484	0.271–0.864	0.019
LVI						
No						
Yes	1.978	1.267–3.088	0.003	1.451	0.900–2.340	0.126

HTN, hypertension; ASI, angiotensin system inhibitor; LVI, lymphovascular invasion; CI, confidence interval.
Tumor stage was assessed according to the tumor-node-metastasis classification, the American Joint Committee on Cancer 8th edition.

setting, a study targeting Europeans confirmed the postdiagnosis exposure period of ASI after PDAC diagnosis to be insignificant, suggesting that the use of ASI itself, rather than a specific post-exposure period, leads to better survival outcomes.[31]

In summary, the results varied, and no conclusions were drawn. Furthermore, to date, no research has shown a significant relationship between ASI and the mortality rate from pancreatic cancer in Asian populations following resection. This study was the first to examine the impact of ASIs in patients who had surgical resection. In the present study, ASI use following surgical resection in patients with pre-diagnosed hypertension was associated with a significant survival benefit, and the mortality reduction rate was equivalent to that reported in other hospitals.[31]

Tajaldini, et al.[32] presented a summary of the anticancer effects of repurposed drugs, demonstrating a decrease in drug resistance and an increase in efficacy. In their study, ASI also reduced tumor stromal fibrosis. Therefore, to ascertain the adjunct role of ASI in the efficacy of chemotherapy, we performed a survival analysis in the group that underwent neoadjuvant chemotherapy. However, there was no significant difference in survival between the three subgroups receiving neoadjuvant chemotherapy. Furthermore, patients with hypertension who did not receive ASI showed better 5-year DFS compared to those who did. It should be highlighted that the limited number of participants in this study, with only 106 people overall receiving neoadjuvant chemotherapy and only 16 in the group with hypertension but without ASI (group 2), raises concerns regarding the reliability of the findings. Consequently, it is necessary to accumulate a larger patient cohort for further analysis and refinement.

According to our multivariate analysis, ASIs provided a significantly longer OS benefit after stratification of patients with hypertension according to medication usage. This result was confirmed in the multivariate risk factor analysis of patients with pre-diagnosed hypertension, as these patients were administered ASIs to control their high blood pressure prior to surgery. However, there was no significant effect on DFS. Further research, including a higher number of patients or by categorizing them into neoadjuvant and adjuvant chemotherapy groups, may show more meaningful results.

Patients with hypertension usually have more comorbidities than those without hypertension. Therefore, a poor survival prognosis is expected in patients with hypertension. Interestingly, our study showed the opposite results; the hypertension with ASI group (group 3) had a better 5-year survival rate compared to the non-hypertensive group (group 1). Furthermore, as angiotensin I and II act against tumor fibrosis in the RAS, their anti-desmoplastic effects may be stronger when angiotensin 1 is specifically inhibited. ACEi simultaneously inhibits angiotensin I and II, whereas ARBs specifically inhibit angiotensin I. Thus, their anti-desmoplastic effect is expected to be greater. As a result, a comparison of survival rates would be useful if patients are grouped into ACEi and ARB groups.

This study had some limitations. First, as this was a non-randomized, single-center retrospective research with a non-randomly selected population, selection bias may exist. Additionally, the current antihypertensive medication was assumed to be a long-term ASI, administered immediately before surgery; however, several patients switched to alternative medications

during the follow-up period. Moreover, due to the retrospective nature of this study, we were constrained to depend solely on existing records to confirm patients' medication histories. Thus, there was a limitation in determining the administration period.

However, this study was well-powered to examine the effects of ASI usage on survival during a cumulative study duration of approximately 10 years. Also, since we were able to confirm ASI use only in patients with hypertension, the survival benefit for patients without hypertension taking ASI should be considered. Furthermore, we plan to conduct a multilateral analysis using the national health insurance data. In addition, through a prospective study, we anticipate the ability to differentiate the timing of ASI exposure as either pre- or post-cancer, to discern the exposure period.

In conclusion, PDAC is an extremely dangerous malignancy with aggressive biology and dismal outlook. Our retrospective study revealed that ASIs were linked to significantly prolonged survival outcomes in individuals with resected PDAC. The use of ASIs may be a simple PDAC treatment strategy, especially in patients with hypertension. Hence, additional randomized prospective cohort studies are required to clarify the actual oncological impact of ASI on PDAC.

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AUTHOR CONTRIBUTIONS

Conceptualization: Ho Kyoung Hwang and Min Yu Kang. Data curation: Min Yu Kang and Ho Kyoung Hwang. Formal analysis: Hye Yeon Yang, Min Yu Kang, and Ho Kyoung Hwang. Funding acquisition: Hye Yeon Yang. Investigation: Hye Yeon Yang, Min Yu Kang, Chang Moo Kang, and Ho Kyoung Hwang. Methodology: all authors. Project administration: all authors. Resources: Hye Yeon Yang and Ho Kyoung Hwang. Software: all authors. Supervision: Hye Yeon Yang, Chang Moo Kang, Woo Jung Lee, and Ho Kyoung Hwang. Validation: Hye Yeon Yang, Min Yu Kang, and Ho Kyoung Hwang. Visualization: Hye Yeon Yang and Min Yu Kang. Writing—original draft: Hye Yeon Yang. Writing—review & editing: Hye Yeon Yang and Ho Kyoung Hwang. Approval of final manuscript: all authors.

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