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Anticancer Benefit of Metformin in Patients With Early-Stage Pancreatic Cancer: A Retrospective Cohort Study

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Abstract

Background: Epidemiologic studies have produced conflicting results on the effects of metformin on pancreatic cancer. This study aimed to observe and analyze whether metformin use is associated with better prognosis in pancreatic cancer. **Materials and Methods:** In this retrospective cohort study, all baseline data were retrieved from The Chinese Medicine Information Retrieval System (https://dc.wzhospital.cn/vpn/index.html) of The First Affiliated Hospital of Wenzhou Medical University. Survival data were collected by follow-up visits and medical records. Overall survival was the primary endpoint, while progression-free survival and disease-free survival were secondary endpoints. Progression or recurrence was assessed with radiologic images. **Results:** Seventy-six metformin users and 92 metformin nonusers diagnosed with pancreatic cancer from 2012 to 2020 in this hospital were enrolled. The adjusted hazard ratio for overall survival for metformin users was 0.50 (95% confidence interval = 0.33-0.76), where median overall survival was 16.0 months for metformin users versus 11.5 months for metformin nonusers. The protective effect was also found by analyzing progression-free survival (adjusted hazard ratio = 0.39, 95% confidence interval = 0.18-0.86) and disease-free survival (adjusted hazard ratio = 0.30, 95% confidence interval = 0.14-0.68). In the subgroup analysis, metformin use had a statistically significant association with prolongation of survival in stage I to II pancreatic cancer patients (hazard ratio = 0.47, 95% confidence interval = 0.25-0.91), but not for advanced tumor stage (hazard ratio for IV stage = 0.62, 95% confidence interval = 0.33-1.19), after adjustment for other risk factors. **Conclusion:** Metformin use is related to favorable survival outcomes of pancreatic cancer, especially in early tumor stage.

Keywords

pancreatic cancer, metformin use, cancer survival, cancer treatment, retrospective cohort study

Abbreviations

AMPK, AMP-activated protein kinase; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IGF-1, insulin-like growth factor; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; T2DM, type 2 diabetes mellitus.

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Introduction

Pancreatic cancer is one of the most lethal solid malignancies, with an overall 5-year survival rate of less than 10%.[1] It is considered as the second leading cause of cancer-related death in developed countries.[2] The incidence and mortality rates of pancreatic cancer nearly mirror each other. The global age-standardized incidence of pancreatic cancer is 4.8 per 100,000 persons, and the mortality rate is 4.4.[3] Alarmingly, the median time from diagnosis to death from untreated advanced pancreatic cancer is about 3.5 months.[4] More effective prevention and treatment strategies are urgently needed.

As known, diabetes is a risk factor for pancreatic cancer. The incidence of pancreatic cancer is higher in patients with type 2 diabetes mellitus (T2DM),[5] as a result of high level of insulin and insulin-like growth factor (IGF-1), which activates PI3K/Akt/mTOR and AMP-activated protein kinase (AMPK) signaling pathways, enhances growth and metabolism of cancer cells.[6] In addition, pancreatic cancer–related death in T2DM patients goes up steeply to 30% to 40% compared with those without diabetes.[7]

Interestingly, several studies reported that metformin exerted antitumorigenic effects via inhibiting the LKB1-AMPK-mTOR signaling pathway, suppressing the JNK pathway, and lowering insulin and IGF-1 levels.[8–10] Metformin, a relatively cheap, safe, and well-tolerated medication in the biguanide class, is used as an oral antidiabetic drug for the treatment of T2DM. In the past decade, many epidemiologic studies reported that metformin rendered anticancer effects in several types of cancers, such as breast cancer and colorectal cancer.[11–13]

Nonetheless, its benefit on pancreatic cancer was controversial.[14–17] Two prospective cohort studies supported that metformin users had a relatively lower risk for pancreatic cancer compared to metformin nonusers.[15,16] Conversely, a large cohort study from the Netherlands did not detect a reduced risk of gastrointestinal cancers in current metformin users compared with those users of other nonsteroidal anti-inflammatory drugs, including pancreatic cancer.[14] Toriola *et al* also reported that there were no associations between metformin use and survival in patients with pancreatic ductal adenocarcinoma (PDAC) among African American patients.[17]

Herein, we retrospectively comprised a cohort of pancreatic cancer patients who were exposed to metformin before cancer diagnosis to evaluate the effect of metformin use on the prognosis of pancreatic cancer. In this study, we investigated the overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS) outcomes in diabetic patients with and without metformin treatment.

Materials and Methods

Participants

A retrospective cohort study was conducted using The Chinese Medicine Information Retrieval System (https://dc.wzhospital.cn/vpn/index.html) of The First Affiliated Hospital of Wenzhou Medical University. The analysis included patients diagnosed with pancreatic cancer from January 1, 2012, to December 31, 2020. All pancreatic cancer patients were diagnosed by pathological biopsy. The vital status of the participants was determined directly by their own medical records.

From the electronic medical record management system, we could get relevant information such as gender, age at diagnosis, date of diagnosis, tumor TNM classification, the primary tumor site (head, body, or tail of pancreas), the treatment modality (surgery, chemotherapy, targeted therapy, immunotherapy, or radiotherapy), and the history of drinking and smoking.

Metformin users were defined as participants who had been prescribed continuous oral metformin before pancreatic cancer diagnosis. Participants who were never prescribed metformin were defined as nonusers. The date of prescription was compared with the date of diagnosis to assess whether metformin was administered before or after diagnosis.

Patients excluded were as follows:

1. Follow-up less than 1 month after diagnosis.
2. Incomplete medical records.
3. Diagnosis as metastatic lesion from another primary cancer.
4. Suffered from multiple primary cancers.
5. Post-diagnostic metformin use.
6. Died from other specific causes (not from pancreatic cancer).

The participants were selected randomly according to the following procedure (Figure 1). A total of 892 patients with pancreatic cancer were identified from The Chinese Medicine Information Retrieval System of The First Affiliated Hospital of Wenzhou Medical University. After application of the inclusion and exclusion criteria, the participants, in the final analysis, included 76 metformin users and 92 metformin nonusers.

Exposure

To further analyze the relationship between metformin use and pancreatic cancer survival, and to reduce or avoid the confounding effects of other anti-hyperglycemic drugs, in this retrospective cohort study, patients who had been prescribed at least one dispensing record of oral metformin before pancreatic cancer diagnosis were defined as metformin users, while concurrent or previous use of other anti-hyperglycemic agents, including sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, D-phenylalanine derivatives, dipeptidyl peptidase 4 inhibitors, incretin mimetic agents and insulins were excluded. According to the dispensing record, the metformin dosage form was extended-release tablets, with the dose ranging from 250 to 1000 mg orally once a day. Patients who never prescribed metformin before pancreatic cancer diagnosis were defined as nonusers.

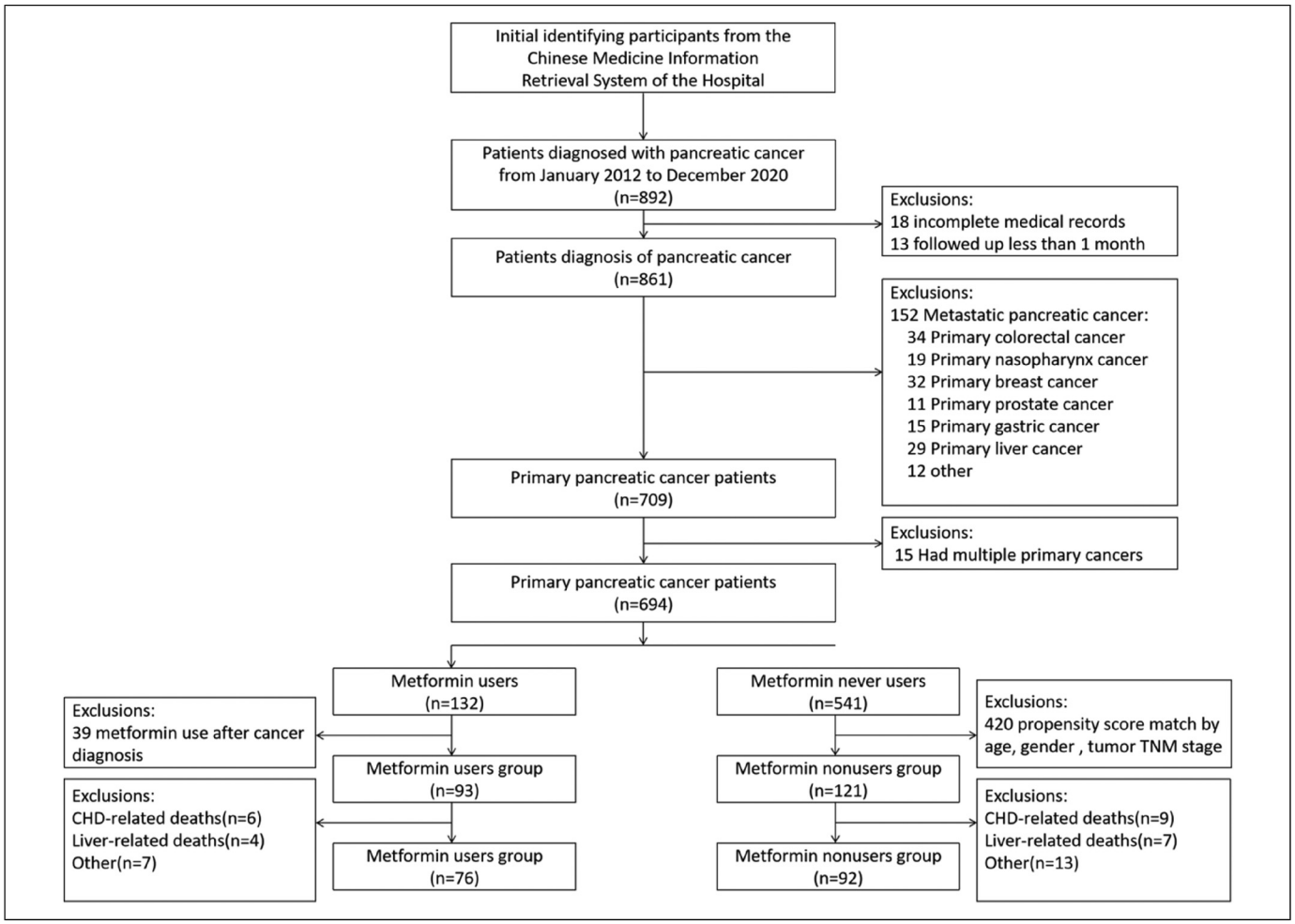

Figure 1. The selection process of the study population.

Outcome Measures

Follow-up of the cohort started on the date of diagnosis of pancreatic cancer, and ended at the time of death, or the deadline of follow-up (October 22, 2021). The survival outcomes in pancreatic cancer patients were analyzed based on OS as the primary outcome, which measured from the date of diagnosis of pancreatic cancer to the date of death, or the last contact date (for the 18 patients who were lost to follow-up). Patients who did not die were censored at the close date of follow-up (October 22, 2021). Progression-free survival was analyzed as a secondary outcome and defined as the time from the first chemotherapy to disease progression or death from any cause. The last outcome was DFS, which was defined as the interval between the date of surgery and the date of the last follow-up or recurrence/progression. Progression or recurrence was assessed with radiologic images.

Statistical Analysis

PASS software (PASS 15. NCSS, LLC.) was used to calculate the minimum required sample size. Categorical variables, chiefly baseline characteristics, were analyzed and compared by Chi-square test, including Pearson Chi-square test, continuity correction Chi-square test, and Fisher exact test. Rank-sum test was applied to examine the differences in grade variables. Continuous variables were analyzed and compared by independent sample *t* test. We used Kaplan-Meier plot to do univariate survival analyses, with comparison by log-rank test. Median OS, DFS, and PFS were estimated at the same time. Cox proportional hazards regression model for univariate and multivariate analyses was used to measure the association between metformin use and tumor survival after adjustment, and the effect of metformin on tumor survival was valued by hazard ratio (HR) and 95% confidence interval (CI). Subgroup analyses were also carried out with this model. A 2-sided *P* value <.05 was defined as statistically significant. Statistical analyses were done by SPSS® version 25 (IBM) and R version 4.1.0 (R Foundation for Statistical Computing).

Ethical Statement

The reporting of this study conformed to the STROBE (Strengthening the Reporting of Observational Studies in

Epidemiology) guidelines.[18] We obtained the patients' verbal consent to use their data for this cohort study, and all patients were anonymous and arranged with ID for the purpose of protecting their privacy.

Results

Baseline Characteristics of the Cohort Study

One hundred sixty-eight patients with pancreatic cancer (median age = 63.3 ± 10.7) were recruited in total, consisting of 76 cases in the group of metformin use (45.2%) and 92 cases of metformin nonuse (54.8%). They were 57 female patients (33.9%) and 111 male ones (66.1%). The baseline characteristics of participants with pancreatic cancer who used or did not use metformin are presented in Table 1. Between the two groups, there were no significant differences in baseline age, gender, tumor stage, primary tumor site, treatment modality, comorbid disease, smoking, and drinking status. Seventy-five cases (44.7%) were diagnosed as stage I-II pancreatic cancer, 31 cases (18.5%) as stage III pancreatic cancer, and 56 cases (33.3%) as stage IV pancreatic cancer. In this cohort, metformin users were significantly more likely to be diagnosed with advanced pancreatic cancer than nonmetformin users. In addition, in both groups, only a few participants received radiotherapy (6.0%), immunotherapy (1.8%), and/or targeted therapy (3.0%).

Sensitivity Analysis

In univariate analysis, age, tumor stage, and radical surgery were more likely to be associated with survival outcomes in patients with pancreatic cancer (Table 2). Of note, metformin exposure was associated with a trend toward a lower risk of death (HR = 0.71, 95% CI = 0.48-1.04, $P = .081$). In the Cox proportional hazards model, 113 deaths (67.3%) were observed at the end of follow-up, while 37 cases (22.0%) were still alive. Metformin use was significantly associated with lower overall mortality when adjusted for tumor stage, age, and radical surgery (adjusted HR = 0.50, 95% CI = 0.33-0.76, $P = .001$).

Survival Outcomes of the Cohort Study

A Kaplan-Meier curve can be seen in Figure 2. The earliest time of death was day 64, and the last observed time of failure was day 1941. The median OS in the group of metformin use and metformin nonuse was 481 days (95% CI = 295-667) and 345 days (95% CI = 279-410), respectively. As to the median DFS, it was prolonged by 167 days in the group of metformin use, compared with that of metformin nonuse (Figure 3). Moreover, the median PFS was significantly longer in patients who received metformin than those did not, that was 219 days and 136 days, respectively (Figure 4). In conclusion, our findings suggested that metformin use was associated with improved survival outcomes in patients with pancreatic cancer.

Subgroup Analysis

Furthermore, after stratification for various factors, it was found that metformin users still held a better OS (Table 3). There was a strong association between metformin exposure and survival among participants with lower disease stage, male and the elders. In subgroup analyses according to the clinical cancer stage, metformin exposure in stage I-II pancreatic cancer resulted in favorable survival outcomes (adjusted HR 0.47, 95% CI = 0.25-0.91) compared with those with advanced stage (adjusted HR for Stage IV = 0.62, 95% CI = 0.33-1.19). The efficacy of metformin was found to be more pronounced in patients over 60 years of age (HR = 0.37, 95% CI = 0.22-0.60). The association between metformin use and tumor survival persisted in individuals undergoing radical surgery (adjusted HR = 0.40, 95% CI = 0.20-0.79).

Discussion

Metformin, a recognized prescription drug for the prevention and treatment of T2DM, has attracted worldwide attention for its anticancer activity. Although some epidemiologic researches have reported a protective effect of metformin on pancreatic cancer risk,[19,20] the relationship between metformin use and the survival of pancreatic cancer is still controversial. Some studies revealed positive effects,[15,16,21] whereas others demonstrated different outcomes.[17,22,23] Of note, a nationwide cohort study from New Zealand showed insulin use was associated with lower mortality risk in individuals with pancreatic cancer–related diabetes.[24] Lee *et al* also found that metformin, thiazolidinedione, and dipeptidyl peptidase-4 inhibitor exposure were associated with decreased risk for future pancreatic cancer.[25] So, in order to eliminate the confounding factors of other anti-diabetic drugs, we used data on dispensed drugs to determine concomitant use. In our study, metformin users were defined as participants who had been prescribed continuous oral metformin before pancreatic cancer diagnosis (those who concurrently or previously used other antihyperglycemic drugs were excluded), which would guarantee the exclusive use of metformin during the entire course of cancer treatment. Notably, we found that pancreatic cancer patients who received metformin had improved survival outcomes compared with patients who did not.

In subgroup analysis based on the clinical stage of pancreatic cancer, the survival benefits of metformin use were statistically significant in the I-II Stage subgroup (adjusted HR for I-II stage = 0.47, 95% CI = 0.25-0.91). These findings were in concordance with the study conducted by Shi *et al*[26] and Sadeghi *et al*.[16] In contrast to our study, a retrospective cohort study in South Korea suggested that metformin exposure was associated with survival benefits in patients with pancreatic cancer and preexisting T2DM, especially among those with an advanced cancer stage.[27] In the subgroup analysis of age, we found that the relative benefit of metformin may be higher in patients older than 60 years of age (adjusted HR 0.37, 95% CI = = 0.22-0.60). We hypothesized that the treatment modality and age could affect the antitumor effect of metformin. Patients

Table 1. Baseline Characteristics of the Study Population.[a]

Characteristics	Overall n = 168	Metformin User, n = 76	Metformin Nonuser, N = 92	*P* Value[b]
Age, mean ± SD	63.3 ± 10.7	64.3 ± 10.3	62.5 ± 11.0	.276
Gender, n (%)				
Female	57 (33.9)	27 (35.5)	30 (32.6)	.691
Male	111 (66.1)	49 (64.5)	62 (67.4)	
Stage, n (%)				.114
I	48 (28.6)	16 (21.1)	32 (34.8)	
II	27 (16.1)	17 (22.4)	10 (10.9)	
III	31 (18.5)	11 (14.5)	20 (21.7)	
IV	56 (33.3)	30 (39.5)	26 (28.3)	
Unknown[c]	6 (3.5)	2 (2.5)	4 (4.3)	
Tumor location, n (%)				.520
Head and neck	94 (56.0)	42 (55.3)	52 (56.5)	
Body	52 (31.0)	21 (27.6)	31 (33.7)	
Tail	19 (11.3)	11 (14.5)	8 (8.7)	
Unknown	3 (1.7)	2 (2.6)	1 (1.1)	
Chemotherapy, n (%)				.518
Yes	93 (55.4)	40 (52.6)	53 (57.6)	
No	75 (44.6)	36 (47.4)	39 (42.4)	
Radiotherapy, n (%)				.195
Yes	10 (6.0)	7 (9.2)	3 (3.3)	
No	158 (94.0)	69 (90.8)	89 (96.7)	
Targeted therapy and/or immunotherapy, n (%)				.730
Yes	8 (4.8)	3 (3.9)	5 (5.4)	.
No	160 (95.2)	73 (96.1)	87 (94.6)	
Radical surgery, n (%)				.107
Yes	80 (47.6)	31 (40.8)	49 (53.3)	
No	88 (52.4)	45 (59.2)	43 (46.7)	
Palliative surgery, n (%)				.525
Yes	30 (17.9)	12 (15.8)	18 (19.6)	
No	138 (82.1)	64 (84.2)	74 (80.4)	
Cardiovascular disease, n (%)				.132
Yes	69 (41.1)	36 (47.4)	33 (35.9)	
No	99 (58.9)	40 (52.6)	59 (64.1)	
Cerebral infarction, n (%)				.329
Yes	4 (2.4)	3 (3.9)	1 (1.1)	
No	164 (97.6)	73 (96.1)	91 (98.9)	
Kidney disease, n (%)				.943
Yes	18 (10.7)	8 (10.5)	10 (10.9)	
No	150 (89.3)	68 (89.5)	82 (89.1)	
Hepatobiliary disease, n (%)				.420
Yes	54 (32.1)	22 (28.9)	32 (34.8)	
No	114 (67.9)	54 (71.1)	60 (65.2)	
Digestive system disease				.061
Yes	25 (14.9)	7 (9.2)	18 (19.6)	
No	143 (85.1)	69 (90.8)	74 (80.4)	
Smoking status, n (%)				.973
Current & former	44 (26.2)	20 (26.3)	24 (26.1)	
Never	124 (73.8)	56 (73.7)	68 (73.9)	
Drinking history, n (%)				.101
Current & former	41 (24.4)	14 (18.4)	27 (29.3)	
Never	127 (75.6)	62 (81.6)	65 (70.7)	

Abbreviation: SD, standard deviation.
[a]Data are number of participants enrolled/number eligible (%).
[b]*P* value indicated the difference between baseline data of the two groups.
[c]Number of "Unknown": the number of cases whose stage or tumor location could not be determined.

Table 2. The Factors Associated With OS.[a]

	Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Metformin	0.71 (0.48-1.04)	.081	0.50 (0.33-0.76)	.001
Age	1.05 (1.02-1.07)	.000	1.05 (1.03-1.07)	.000
Gender				
Female	1			
Male	1.58 (1.05-2.40)	.028		
Tumor stage		.000		.002
I	1		1	
II	0.80 (0.42-1.50)	.480	1.08 (0.57-2.05)	.818
III	2.04 (1.16-3.57)	.013	2.38 (1.34-4.22)	.003
IV	2.72 (1.68-4.42)	.000	2.39 (1.43-4.02)	.001
Tumor location		.572		
Head and neck	1			
Body	1.07 (0.71-1.63)	.741		
Tail	1.03 (0.56-1.92)	.921		
Treatment modality				
Chemotherapy	1.05 (0.72-1.53)	.810		
Targeted therapy & Immunotherapy	0.69 (0.25-1.87)	.466		
Radical surgery	0.34 (0.23-0.51)	.000	0.51 (0.33-0.79)	.002
Palliative surgery	1.77 (1.11-2.83)	.016		
Comorbid disease				
Cardiovascular disease	1.53 (1.04-2.25)	.030		
Kidney disease	1.20 (0.68-2.12)	.528		
Hepatobiliary disease	1.00 (0.67-1.49)	.996		
Digestive system disease	0.75 (0.43-1.29)	.292		
Lifestyle				
Smoking	1.25 (0.82-1.91)	.301		
Drinking	0.90 (0.57-1.40)	.635		

Abbreviations: CI, confidence interval; HRs, hazard ratios.

[a]Values of HR and *P* values were obtained by univariate or multivariate Cox proportional hazards regression. If a variable had a relatively great significance in univariate analysis, or might be related to prognosis medically, it would be included in multivariate analysis. HR equaled to 1 indicated that this group was set as the reference. More specifically, for reference groups of these variables in the table, no metformin use, female, stage I, head and neck, no corresponding treatments, no corresponding comorbid diseases, and no smoking or drinking were set as the reference groups.

at early tumor stage had more opportunity for radical surgery, so they usually survived and lived longer, and the cumulative effect of metformin was stronger than in patients with advanced-stage cancer. In principle, metformin may help to alter the tumor immune microenvironment and improve the efficiency of immunotherapy.[28] Of note, metformin may mitigate the effects of chemotherapy by decreasing reactive oxygen species,[29] which may relatively weaken its anti-cancer role in advanced cancer patients. Additionally, the cancer of advanced stage is relatively denser than that of the early stage in biology, which makes the entry or accumulation of metformin in cancer cells became more difficult, thereby affects its anticancer action.[29,30] Moreover, we found that metformin seemed to have a better antipancreatic cancer effect in the aging male. Due that our current study was only observational, it was difficult to make an expanded explanation of why there was an association, and more prospective clinical trials would be needed to definitively address this issue.

Needless to say, there are some limitations to this study. First, given the small sample size in the subgroup analysis, the results had to be interpreted with caution, especially for stage III pancreatic cancer. Second, although PDAC accounts for more than 90% of pancreatic cancer cases in this cohort, some other histological types were also included. At last, data were limited to prescribed drugs, it was not possible to obtain information regarding metformin use at home.

In conclusion, our retrospective study of patients with pancreatic cancer elucidated that there was a strong association between longer survival and metformin exposure, especially for patients with early tumor stage. These suggested metformin use could be an adjuvant for pancreatic cancer treatment. However, more high-quality randomized controlled trials and prospective cohort studies are needed to confirm the conclusion.

Authors' Note

Ethical approval for this study was granted by the Ethics Committee in Clinical Research (ECCR) of the First Affiliated Hospital of Wenzhou Medical University (No. KY2022-R131).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

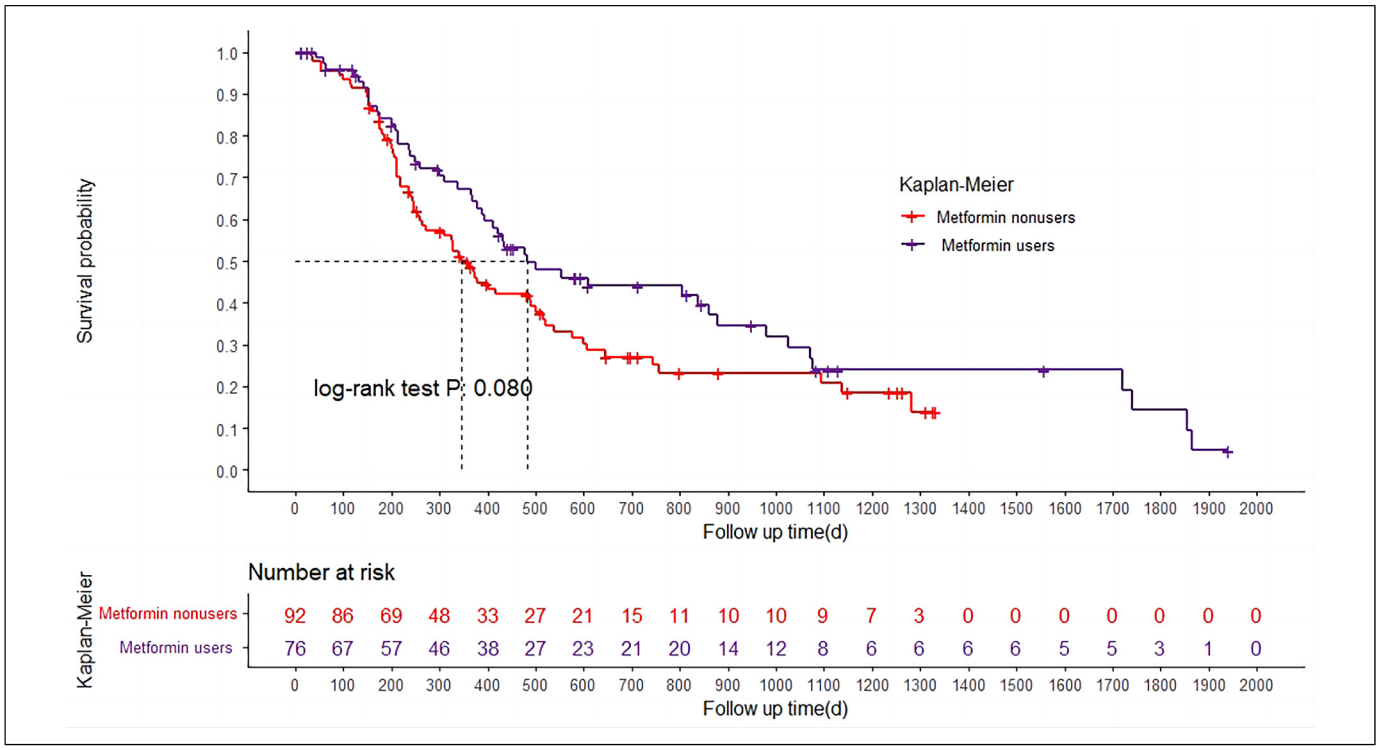

Figure 2. Kaplan-Meier curves for overall survival (OS) in the metformin-treated analysis. Log-rank test was carried out to estimate overall survival in Kaplan-Meier curves.

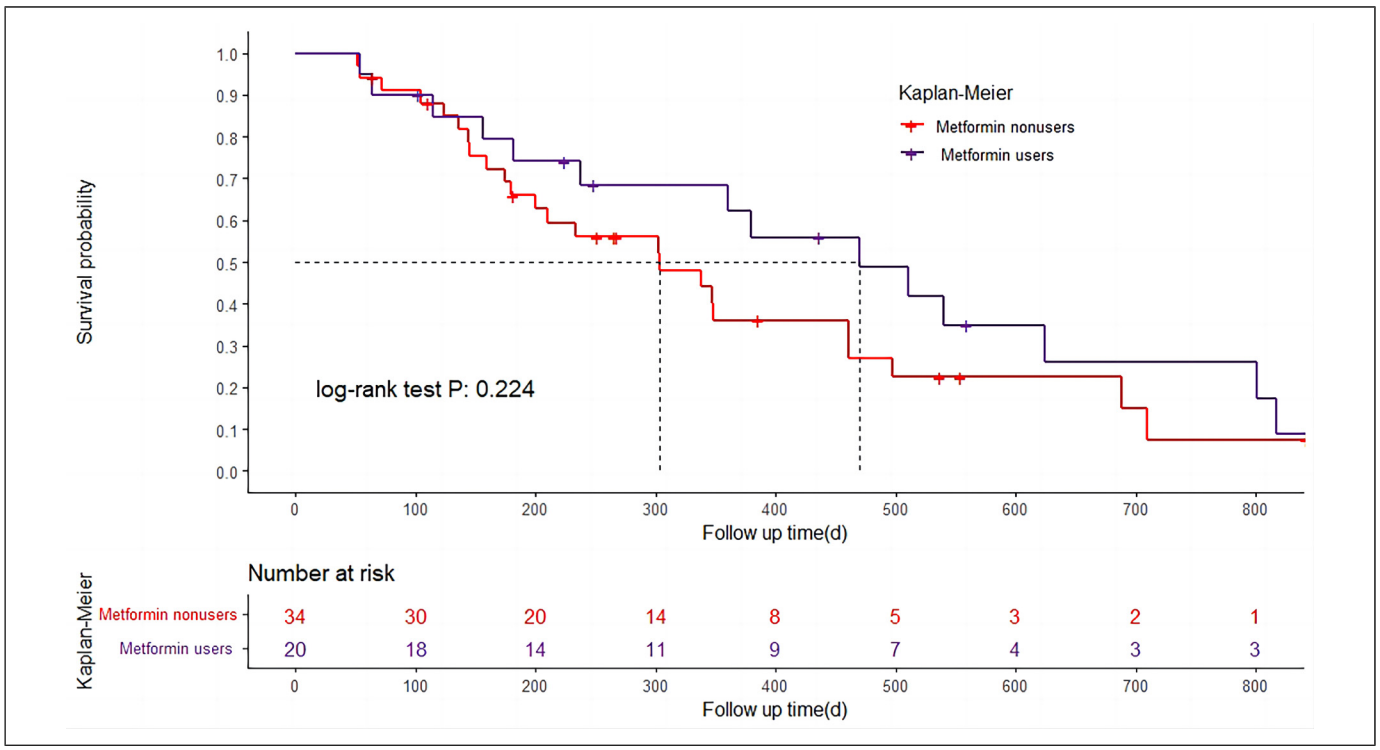

Figure 3. Kaplan-Meier curves for disease-free survival (DFS) in the metformin-treated analysis. Log-rank test was carried out to estimate disease-free survival in Kaplan-Meier curves.

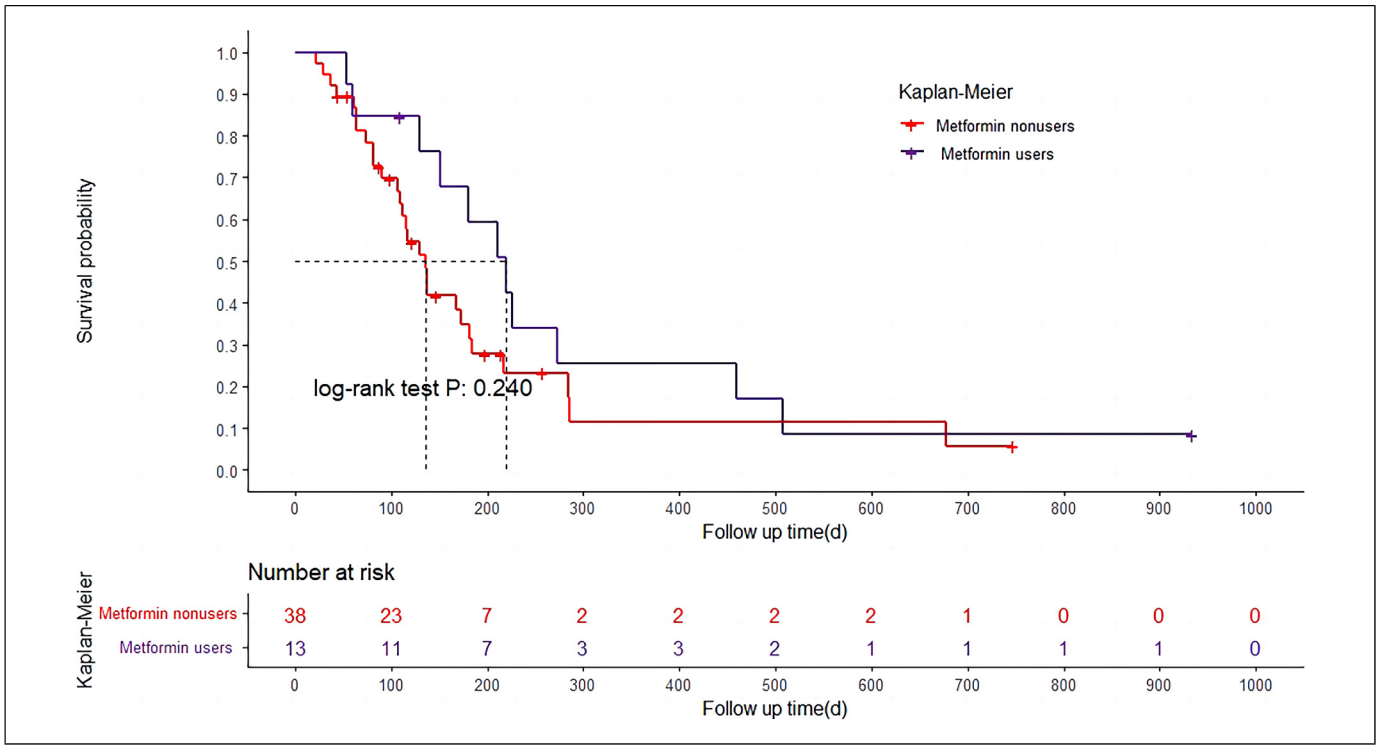

Figure 4. Kaplan-Meier curves for progression-free survival (PFS) in the metformin-treated analysis. Log-rank test was carried out to estimate progression-free survival in Kaplan-Meier curves.

Table 3. Subgroup Analysis of Overall Survival.[a]

	Metformin User	Metformin Nonuser		
Subgroup	No. of Patients		Hazard Ratio (95% CI)	*P* Value for Interaction
Overall information	76	92	0.50 (0.33-0.76)	
Gender				.183
Male	49	62	0.41 (0.24-0.69)	
Female	27	30	0.63 (0.27-1.46)	
Age				.127
<60 years	26	38	0.80 (0.40-1.61)	
≥60 years	50	54	0.37 (0.22-0.60)	
Stage[b]				.680
I-II	33	42	0.47 (0.25-0.91)	
III	11	20	0.57 (0.18-1.78)	
IV	30	26	0.62 (0.33-1.19)	
Smoking status				.604
Current & former	20	24	0.46 (0.21-1.03)	
Never	56	68	0.67 (0.42-1.08)	
Drinking status				.348
Current & former	14	27	0.26 (0.09-0.81)	
Never	62	65	0.61 (0.39-0.96)	
Chemotherapy				.096
Yes	40	53	0.41 (0.21-0.84)	
No	36	39	0.54 (0.28-1.05)	
Radical surgery				.751
Yes	31	49	0.40 (0.20-0.79)	
No	45	43	0.57 (0.34-0.98)	

[a]Effect of patient subgroup on OS. Adjusted for age, clinical stage, and radical surgery.
[b]Unknown cases of stage were excluded in the analysis of stage subgroup.

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