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Long-term aspirin use influences the probability of distant metastases and operability in patients with pancreatic ductal adenocarcinoma: a single-center retrospective study

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ABSTRACT

Background: Aspirin, a non-steroidal anti-inflammatory drug and platelet inhibitor, has been shown to reduce cancer incidence, lower metastatic rates and improve survival in certain cancer types. However, data on the effect of aspirin on prognosis in pancreatic ductal adenocarcinoma (PDAC) are limited. Therefore, we conducted a retrospective, single-center study to evaluate the impact of aspirin use on disease characteristics and survival in PDAC patients.

Materials and methods: The study analyzed data from all consecutively treated PDAC patients over a 6-year period. Operability, Tumor–Node–Metastasis (TNM) stage, and survival endpoints were compared between patients who had used aspirin for 2 or more years prior to their diagnosis (ASA ≥ 2) and those who did not (ASA 0).

Results: A total of 182 patients were included. In the ASA ≥ 2 group, significantly fewer patients had metastatic disease at diagnosis, and a significantly larger proportion presented in the operable stages, compared to the ASA 0 group. No significant differences were observed between the two groups in the T or N stages, overall survival, disease-free survival, or time to progression-free survival.

Conclusions: Although long-term aspirin use did not influence survival endpoints, it was associated with a significantly lower probability of demonstrable distant metastases at diagnosis and a higher rate of resectable disease. This finding warrants further research to explore new therapeutic approaches for the treatment of PDAC.

Keywords: pancreatic adenocarcinoma; aspirin; metastasis; operability

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Introduction

Pancreatic cancer, with pancreatic ductal adenocarcinoma (PDAC) being the most common form, is the fifth leading cause of cancer-related deaths in Europe and the United States [1, 2]. Its incidence has risen in recent decades, and with advances in oncology extending survival for other cancers, PDAC is projected to become the second leading cause of cancer deaths by 2030 [3]. The Czech Republic is

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one of the most affected countries globally, with an age-standardized incidence of 9.3/100,000 and a mortality rate of 8.9/100,000 [4, 5].

The prognosis of patients with PDAC remains poor, with a 5-year survival between 5–10%, despite improvements in surgical techniques and modern chemotherapy regimens [1, 6]. Contributing factors to this low survival rate include late diagnosis due to the absence of effective screening programs to aid early detection, early disease recurrence after curative surgical resection, resistance to standard chemotherapy and radiotherapy, and limited success with modern targeted therapies and immunotherapy.

Aspirin, a non-steroidal anti-inflammatory drug and platelet inhibitor, is recommended for the prevention of cardiovascular events in patients with atherosclerotic vascular disease [7]. However, current guidelines emphasize individualized use due to potential complications, especially gastrointestinal bleeding [8].

Several studies have demonstrated aspirin's effects on cancer development and progression. It has been associated with a reduced risk of developing various malignancies, especially tumors of the gastrointestinal tract [9, 10]. Aspirin has also been linked to reduced mortality rates in cancer patients, with most clinical data derived from colorectal and breast cancers [11]. A reduction in the risk of distant metastasis has been observed in some cancers, notably colorectal cancer, but also in other malignancies, such as breast or esophageal cancer [12–14].

The potential of aspirin to reduce the risk of PDAC has been discussed in the literature for many years, with some studies confirming this effect [15–17], while others not [18–20]. However, considerably less data exists on the effect of aspirin use on prognosis in PDAC patients. To date, only three published studies have evaluated the effect of aspirin use in PDAC patients, but these studies included only those who had undergone primary surgery [21–23]. Additionally, one large retrospective analysis from a cancer registry studied the effects of aspirin use in PDAC but also included patients with other gastrointestinal malignancies [24].

Therefore, this single-institution retrospective study was conducted to evaluate the effect of aspirin use on tumor characteristics at the time of diagnosis and disease prognosis in all patients treated for PDAC.

Materials and methods

The analyzed cohort included all consecutive patients regardless of age or sex, with histologically or cytologically confirmed pancreatic adenocarcinoma treated in the University Hospital Hradec Králové (UHHK) and diagnosed within a 6-year period between January 2011 and December 2016. The diagnosis of PDAC was either made at UHHK or patients were referred for treatment from other centers. Standard diagnostic procedures were performed in accordance with internationally and nationally accepted guidelines and included ultrasound and iodine contrast-enhanced computed tomography (CT) of the pelvis, abdomen, and chest. Tumor tissue for histological evaluation was obtained by surgical resection, endoscopic ultrasound (EUS) with biopsy, or biopsy of liver metastases under CT guidance. If material for histological verification could not be obtained, cytological verification was accepted (using either EUS or paracentesis/thoracocentesis). The diagnosis was established after histopathological or cytopathological confirmation. Hematological and biochemical laboratory blood tests, including liver function tests and baseline CA 19-9 tumor marker levels, were performed on all patients. In cases of biliary obstruction, endoscopic retrograde cholangiopancreatography with stent placement was performed. Based on the standard diagnostic procedures mentioned above, the Tumor Node Metastasis (TNM) staging was determined according to the American Joint Committee on Cancer/ International Union Against Cancer staging system, 7th edition. Treatment and post-treatment follow-up of all patients adhered to contemporary national and international guidelines, considering the extent of the disease, the patient's biological status, any secondary diseases, and their individual preferences.

The inclusion criteria required clear documentation of aspirin use (or lack thereof) including details on dosage and duration of therapy. Patients who had used aspirin for ≥ 2 years prior to their PDAC diagnosis were assigned to the "ASA ≥ 2" group, while those who had not used aspirin or any other antiplatelet therapy, or had used aspirin

for < 2 years were assigned to the "ASA 0" group. The aspirin dosage used by all patients was 100 mg once daily, with indications for aspirin use varying between patients, including primary cardiovascular prevention and secondary prevention for cardiac or cerebrovascular comorbidities. Additionally, patients' medical records needed to include comprehensive details of their past medical and pharmacological history as well as previous therapeutic and surgical interventions. The exclusion criteria included multiple malignancies, a history of other malignancies with or without medical and/or surgical interventions, neuroendocrine tumors (NET) of the pancreas, tumors of uncertain histology possibly originating from other tissues, and histologically unverified tumors. Additionally, patients with poorly documented medical histories or insufficient data regarding aspirin use, its dosage or duration were also excluded. Patients were not excluded based on any treatment modality for their current PDAC, nor for any other non-malignant co-morbidities. All patients underwent standard PDAC treatment according to national and international guidelines, irrespective of whether they had received aspirin therapy.

The study compared the following characteristics and survival endpoints between the ASA ≥ 2 and ASA 0 groups: operability, TNM stages, overall survival (OS) [time from diagnosis to death], progression-free survival (PFS) [time from diagnosis to progression or death], and disease-free survival DFS [time from curative resection to recurrence or death]

The impact of aspirin therapy on metastatic risk was further assessed separately in subgroups of patients stratified according to primary tumor location (head *vs*. body and tail of the pancreas).

Data were systematically collected by reviewing the patient registry from the Department of Clinical Oncology and Radiotherapy, selecting the diagnosis timeframe (2011–2016), and evaluating revised medical records available through the computerized hospital information system (NIS).

Statistical analysis

Statistical analysis for this study was performed using NCSS Statistical Software 2022. Prior to conducting the main analyses, the normality of continuous variables was assessed using the Shapiro–Wilk test. For normally distributed data, parametric tests were applied, while non-normally distributed data were analyzed using non-parametric tests.

Logistic regression analysis was employed to compare operability and N and M stages between the ASA ≥ 2 and ASA 0 groups. This analysis was conducted using binary data.

The results were reported as odds ratios (OR) with 95% confidence intervals (CI). A p-value of < 0.05 was considered statistically significant.

Linear regression analysis was used to compare the T stage between the two groups. The results were reported as regression coefficients with 95% CI, and a p-value of < 0.05 was considered statistically significant.

Survival endpoints OS, PFS, and DFS were analyzed using the log-rank test. Kaplan–Meier survival curves were generated for visualization, and hazard ratios (HR) with 95% CI were reported. A p-value of < 0.05 was considered statistically significant.

Results

During the defined period, 333 patients were treated or consulted for PDAC at UHHK. Of these, 151 patients were excluded from the analysis for the following reasons: history of NET (34 patients), multiple malignancies (58 patients), tumors of uncertain histology (12 patients), histologically unverified tumors (41 patients; typically for poor performance status), and poorly documented or insufficient data regarding aspirin use (6 patients). A total of 182 patients (55% of the initial cohort) met the inclusion criteria and were included in this study. A flowchart outlining the selection process is presented in Figure 1. The patient and treatment characteristics are shown in Tables 1 and 2; 154 patients were assigned to the ASA 0 group and 28 were assigned to the ASA ≥ 2 group.

Aspirin and tumor operability

Aspirin use was associated with a higher likelihood of tumor operability. In the ASA 0 group, only 25% of the 154 patients presented with operable tumors at diagnosis, while 75% presented with inoperable tumors. In contrast, in the ASA ≥ 2 group, 46% of patients presented with operable tumors and 54% were inoperable (Fig. 2A). Logistic regression analysis revealed a statistically significant association, with p-value 0.026 [haz-

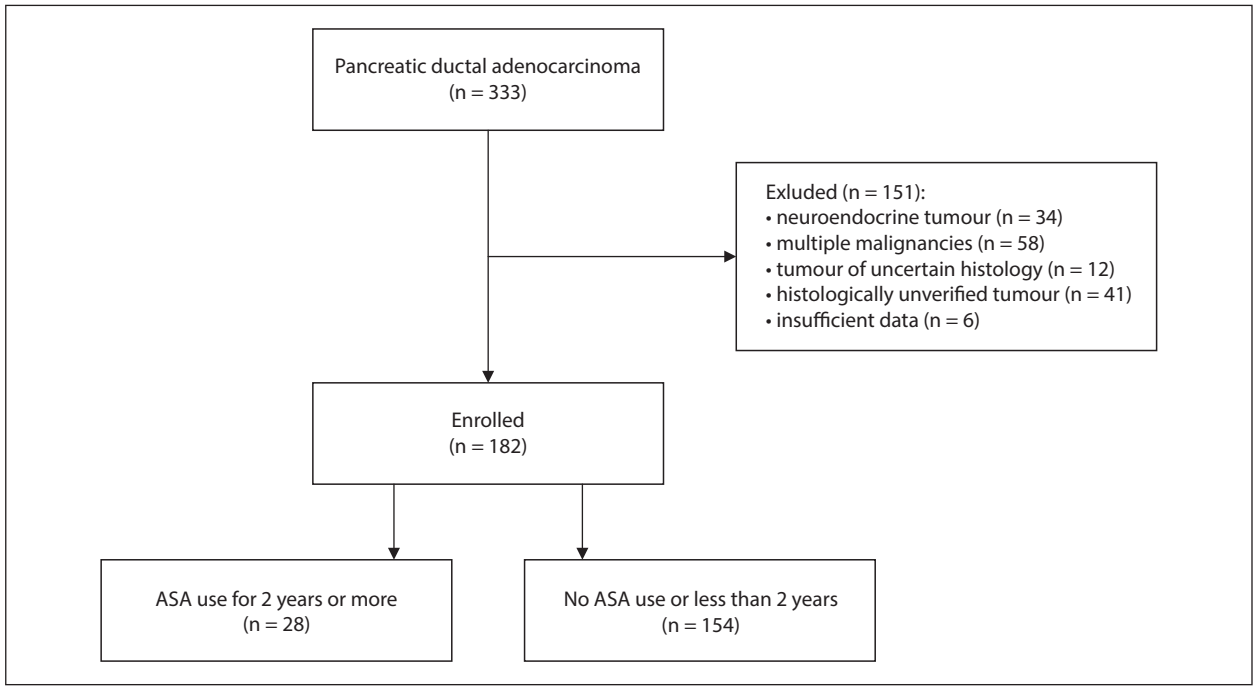

Figure 1. Flowchart of patients selected for analysis. ASA — aspirin

Table 1. Patient characteristics — Tumor–Node–Metastasis (TNM) classification 7th edition

Characteristic	N	%
Patients	182	
Median age, years (range)	66 (37–86)	
Sex		
Male	100	55
Female	82	45
Primary tumor location		
Head	120	66
Body and tail	62	34
T stage		
T1	2	1
T2	27	15
T3	74	41
T4	79	43
N stage		
N0	41	23
N1	141	77
M stage		
M0	87	48
M1	95	52

Characteristic	N	%
Stage		
IA	1	1
IB	7	4
IIA	11	6
IIB	25	14
III	44	24
IV	94	52
Grade		
1	8	4
2	47	26
3	89	49
4	2	1
X	35	19
Operability		
Yes	52	29
No	130	71
Aspirin use		
≥ 2 years	28	15
< 2 years	154	85

ard ratio (HR): 2.55, 95% confidence interval (CI): 1.12–5.84; power of the test = 0.36). Using Pearson's Chi-squared test (power of the test 0.61), the p-value was 0.023 indicating a 28% relative risk reduction in aspirin users. A correlation test was performed to rule out potential bias, demonstrating no significant correlation between age and tumor operability.

Table 2. Treatment characteristics

Treatment	N	%
Surgical resection	49	
Adjuvant chemotherapy	23	47
Adjuvant chemoradiotherapy	7	14
No adjuvant treatment	19	39
Palliative chemotherapy		
Yes	115	63
No	67	37

Aspirin and TNM stage

Aspirin use was associated with a decreased risk of metastatic disease. In the ASA 0 group, 88 patients (57%) presented with metastasis (M1 stage) at diagnosis, while 66 patients (43%) presented with no metastasis at diagnosis (M0 stage). In the ASA ≥ 2 group, however, 7 patients (25%) presented with M1 stage, while 21 (75%) presented with M0 stage (Fig. 2B). This difference was statistically significant (logistic regression: HR: 0.25 95% CI: 0.10–0.62, p = 0.002; power of the test > 0.80; relative risk reduction = 56%). The reduction of metastatic risk with aspirin use was observed across primary tumor locations: head of the pancreas (HR: 0.28, 95% CI: 0.08–0.91; p = 0.03; power of the test = 0.7) and body/tail of the pancreas (HR: 0.18, 95% CI: 0.03–0.82; p = 0.03; power of the test = 0.7).

Aspirin use was not significantly associated with a difference in T (p = 0.2) or N stages (p = 0.94).

Survival analysis

The log-rank test did not show significant OS benefit in the ASA ≥ 2 group compared with the ASA 0 group (HR: 1.10; 95% CI: 0.72–1.68; p = 0.66) (Fig. 3A). OS was also compared separately for operable and inoperable PDAC patients in the two groups (ASA ≥ 2 and ASA 0), but no significant difference was observed.

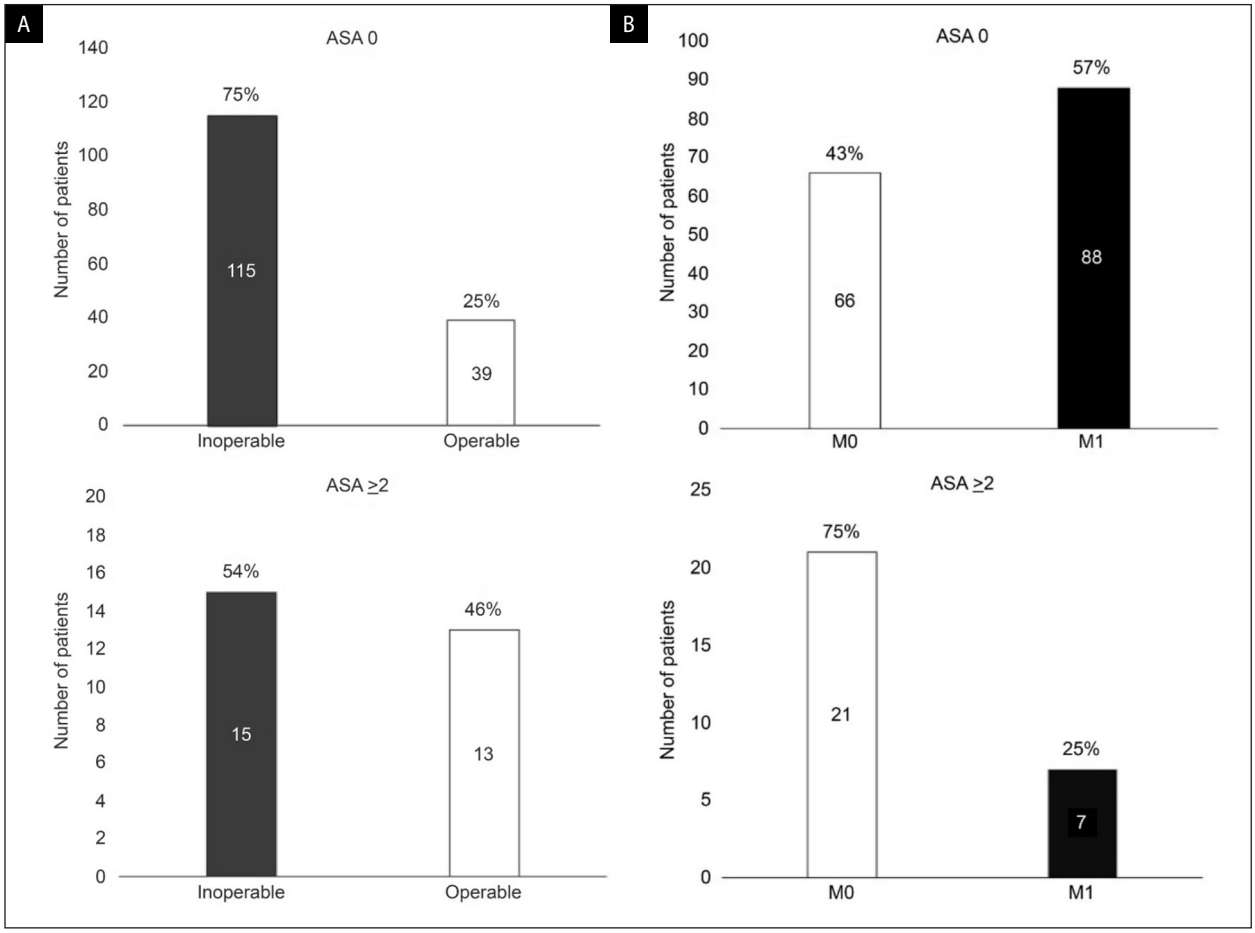

Figure 2. Proportion of patients with inoperable disease (**A**) and distant metastases (**B**). Patients in the ASA ≥ 2 group were more likely to have inoperable disease (p = 0.026) and evidence of distant metastases (p = 0.002). ASA — aspirin

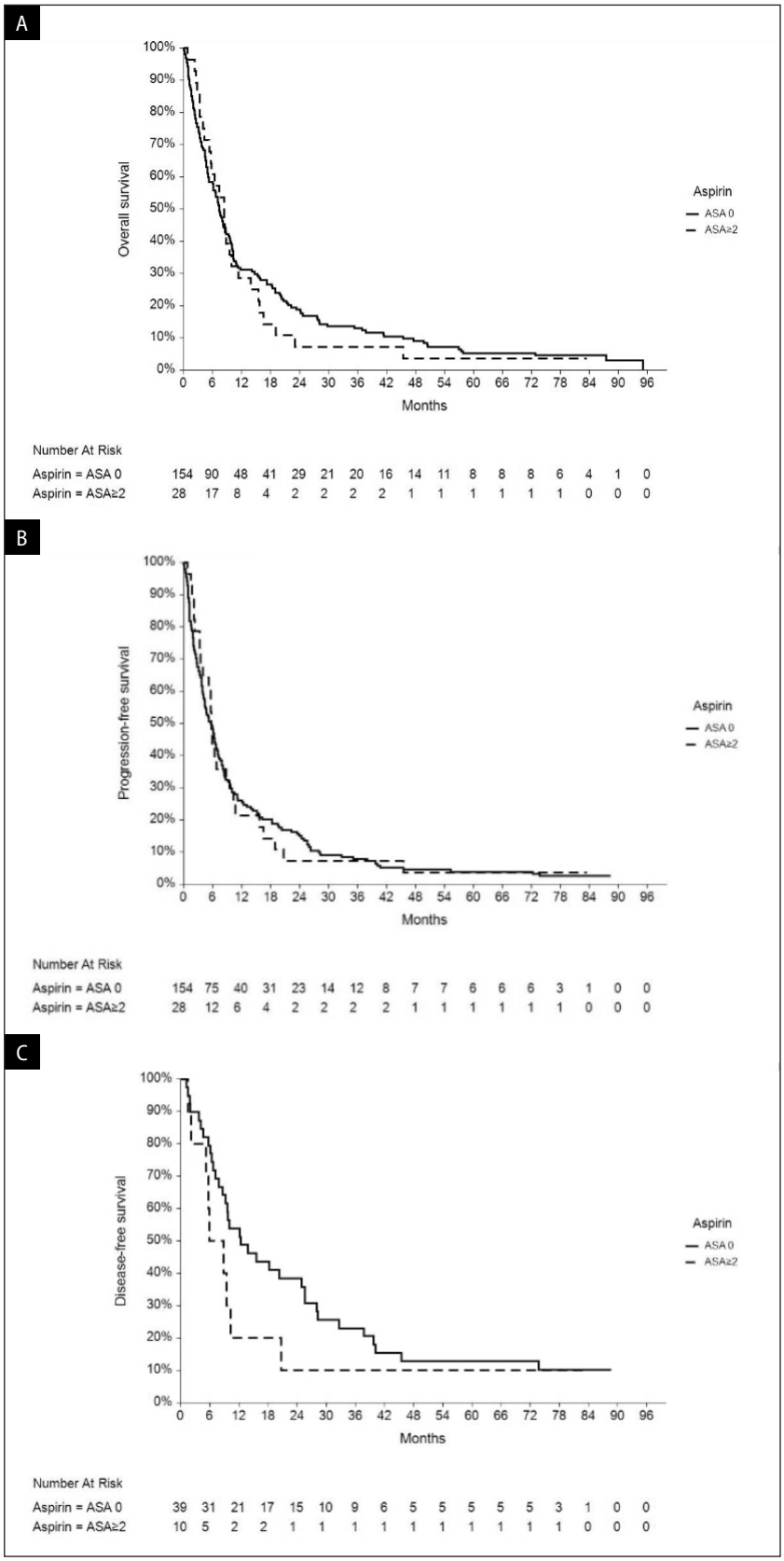

Figure 3. Overall survival (OS) and progression-free survival (PFS) in all patients (**A**) and (**B**), and disease-free survival (DFS) in operated patients (**C**). Kaplan–Meier survival curve shows no significant difference in OS (p = 0.66), PFS (p = 0.99) or DFS (p = 0.2) between patients in the ASA ≥ 2 group (dashes) and the ASA 0 group (full line). ASA — aspirin

DFS was analyzed in patients with resected PDAC using the log-rank test. No significant difference in DFS was found between the ASA ≥ 2 group and the ASA 0 group (HR: 1.59 95% CI: 0.68–3.74; p = 0.2) (Fig. 3B). Progression-free survival (PFS) was similarly analyzed using the log-rank test, and no significant difference was observed between the ASA ≥ 2 group and the ASA 0 group (HR: 1.0; 95% CI: 0.66–1.50); p = 0.99) (Fig. 3C).

Discussion

Data on the effect of aspirin use on the prognosis of PDAC are still insufficient. Three retrospective studies investigated the impact of aspirin on survival following pancreatic surgery for PDAC. One study reported an association between aspirin use and improved disease free-survival (DFS) [21], while another noted better DFS, hematogeneous metastasis-free survival, and overall survival (OS) in patients taking aspirin [22]. However, a third study did not find any association between aspirin use and OS or DFS [23]. A retrospective analysis of data from the Eindhoven Cancer Registry found no significant difference in OS among 25 of 692 PDAC patients treated with aspirin before and after their cancer diagnosis. This outcome was most likely due to the small sample size. However, when the analysis was limited to the 195 patients who used aspirin prior to their PDAC diagnosis, the effect on OS was statistically significant compared to those not taking aspirin [24].

This single-center retrospective study demonstrates that patients with PDAC who had used aspirin for ≥2 years before diagnosis were almost twice as likely to present with operable tumors. To our knowledge, this is the first study to specifically demonstrate the effect of aspirin use on metastasis and operability in pancreatic adenocarcinoma.

Numerous studies, particularly on gastrointestinal adenocarcinomas, have shown that aspirin, a unique irreversible cyclooxygenase-1 inhibitor, may play a role in reducing tumor incidence and progression through its inhibition of platelet function [25]. The reciprocal relationship between cancer and platelets has been well-documented in preclinical research for several decades [26]. Tumor cells have the ability to activate platelets through a process known as tumor cell-induced platelet aggregation [27]. In the tumor microenvironment, platelets promote tumor growth by paracrine production of several growth factors, including platelet-derived growth factors A and B, insulin-like growth factor I, platelet factor 4, vascular endothelial growth factor, and transforming growth factor-β [28]. Platelets can also regulate tumor proliferation by direct interaction with tumor cells [26]. Additionally, activated platelets facilitate tumor cell invasion and dissemination by promoting epithelial-mesenchymal transition [29], a process by which tumor cells acquire a mesenchymal phenotype enabling them to enter the circulation [30].

Preclinical data suggest that platelets play a pivotal role in aiding metastasis at distant sites by promoting the formation of the early metastatic niche [31]. This is achieved by secreting chemokines, which recruit host cells (including granulocytes) that are necessary for creating the extracellular matrix [32], and by releasing several pro-angiogenic factors essential for tumor neovascularization [33]. Some of these pro-angiogenic factors have clinical relevance as predictors of cancer progression [34].

Although preclinical studies have long suggested that aspirin may influence cancer metastasis [35, 36], clinical evidence supporting this effect remains limited. A reduced risk of initial distant metastases has been reported in breast cancer and prostate cancer patients taking aspirin [37, 38]. Patients with stage II and III triple-negative breast cancer using aspirin had shown improved DFS and a lower risk of metachronous distant metastases [13]. Additionally, aspirin use following the diagnosis of stage I, II, or III colorectal cancer was associated with a lower risk of cancer-specific and overall mortality [39]. A meta-analysis of five randomized trials comparing aspirin use versus non-use for preventing vascular events also addressed the impact of aspirin on distant metastasis. The analysis found that aspirin use reduced the risk of cancer with distant metastasis in all solid tumors (HR: 0.64, 95% CI: 0.48–0.84, p = 0.001), particularly in adenocarcinomas (HR: 0.54, 95% CI: 0.38–0.77, p = 0.0007). However, this reduction was not statistically significant in non-adenocarcinomas (HR: 0.82, 95% CI: 0.53–1.28, p = 0.39). And while this effect was statistically significant for colorectal cancer (HR: 0.36, 95% CI: 0.18–0.74, p = 0.005), non-significant trends were observed for other gas-

trointestinal cancers (HR: 0.39, 95% CI: 0.12–1.23, p = 0.07) [14].

In this study, aspirin use was associated with a significant reduction in metastatic disease at diagnosis (56% relative risk reduction) but did not influence either T-stage or N-stage. These findings suggest that the increased likelihood of operability with aspirin use may be attributed to a reduction in metastatic spread via the hematogenous route rather than through lymph node invasion.

Patients with PDAC that affects the head of the pancreas typically present in earlier, more treatable, or curable stages, largely due to the symptoms caused by biliary obstruction. In contrast, those with tumors located in the body or tail of the pancreas tend to present at more advanced stages due to a lack of specific early symptoms [40]. We, therefore, analyzed whether the reduction of metastatic disease associated with aspirin use was consistent across different tumor localizations. We hypothesized that if aspirin reduced metastatic risk even in tumors located farther from the head of the pancreas, it may indeed play a role in slowing tumor dissemination independent of tumor location and time of presentation. We observed that aspirin use was associated with a significant reduction in metastatic risk regardless of the primary tumor's location. This finding supports the hypothesis that aspirin may delay or inhibit metastasis, as evidenced by its effect on tumors that are usually discovered at more advanced stages.

In this study, use of aspirin for ≥ 2 years was not associated with significant changes in OS, PFS, or DFS. However, one important limitation was the relatively small sample size, which may limit the ability to accurately draw conclusions regarding survival endpoints. As such, whether the use of aspirin had a role in preventing or delaying recurrence in operable patients remains inconclusive.

Additionally, survival analyses, when considering aspirin use, may be heavily influenced by the fact that a large proportion of the patients using aspirin have cardiac or cerebrovascular comorbidities naturally creating a bias towards worsened survival. To tackle this bias, future studies should stratify patients based on the indication for aspirin use, differentiating between primary or secondary prophylaxis, as well as distinguish cancer-related mortality from deaths due to other causes. Moreover, it would be beneficial to evaluate patients' performance statuses and determine whether their cardiovascular comorbidities interfered with their qualification and adherence to standard adjuvant and palliative systemic therapies compared to those without these morbidities.

Although our study did not show a significant survival benefit of aspirin use in PDAC patients, likely due to the above-mentioned limitations, our data indicates that aspirin or related agents may indeed offer a clinical and therapeutic advantage by increasing the likelihood of presenting at curable or treatable stages possibly through delaying the metastatic process. Therefore, larger, prospective studies to evaluate aspirin's impact on survival endpoints as well as recurrence prevention or delay are justified. Furthermore, our data may shed light on the crucial relationship between platelets and metastasis in PDAC by supporting the hypothesis that aspirin may reduce metastatic spread likely through platelet inhibition. Given the established preclinical and clinical evidence, this platelet-cancer relationship is an area currently under growing scrutiny in oncologic research, with novel implications emerging regarding its potential role in aiding cancer diagnostics, prognostication, and identifying therapeutic targets. Taken together, these findings highlight the need for further studies investigating platelet interactions in cancer and metastasis to improve the current understanding of the mechanisms involved in the metastatic process and identify strategies to influence them.

Conclusions

This retrospective study demonstrated that patients with PDAC who have used aspirin for ≥ 2 years prior to diagnosis had a significantly higher likelihood of presenting at operable stages. Aspirin use was associated with a lower risk of presenting with metastasis at diagnosis, regardless of tumor location with respect to the head of the pancreas. However, aspirin use did not significantly impact T or N stages, suggesting that it influences hematogenous spread rather than lymphatic. This aligns with existing data on the mechanism of aspirin's anti-metastatic effect, which involves interfering with platelets' central role in supporting hematogenous metastasis. Given the very poor prognosis of PDAC, our findings emphasize the importance of further preclinical and clinical research aimed at

influencing the formation of metastases in pancreatic cancer.

Ethical statement

The authors are accountable for all aspects of the work and have ensured that questions related to the accuracy or integrity of any part of the work were 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 institutional/regional/national ethics/committee/ethics board of University Hospital Hradec Králové (Organization Office for Human Research Protections accreditation number IORG0008813), and the need for individual consent for this retrospective analysis was waived.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

Conception and design: A.M.B., S.J., I.S., and M.V. Administrative support: M.V. Provision of study materials and patients: S.J., I.S., F.Č., M.H., and M.V. Collection and assembly of data: A.M.B., S.J., L.H., and M.H. Data analysis and interpretation: A.M.B., S.J., I.S., O.S., and M.V. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Data availability statement

Datasets used and analyzed for this study could be provided upon reasonable request from the corresponding author.

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