Prognostic significance of anti-diabetic medications in pancreatic cancer: A meta-analysis

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ABSTRACT

The role of anti-diabetic medications in pancreatic cancer remains conflicting. We carried out a systematic search of Pubmed and Embase databases for studies published before August 2016, which assessed the associations between anti-diabetic medications (metformin, sulfonylureas, thiazolidinediones and insulin) intake and pancreatic cancer prognosis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using the random-effects model. The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS). Fourteen studies enrolling 94778 participants were eligible for inclusion, with 12 cohort studies and 2 randomized controlled trials (RCTs). Significant association between metformin (adjusted HR=0.77, 95% CI=0.68-0.87) use and OS was found in cohort studies, whereas no significant association between metformin use and PFS (HR=1.22; 95% CI=0.76-1.95) or OS (HR=1.20, 95% CI=0.84-1.72) in RCTs. No significant survival benefits were identified for insulin (HR=1.18, 95% CI=0.83-1.69), sulfonylureas (HR=1.03, 95% CI=0.81-1.30), or thiazolidinediones (HR=0.84, 95% CI=0.58-1.22). The trim-and-fill method and subgroup analyses stratified by the study characteristics confirmed the robustness of the results. Our findings provide strong evidence that metformin is associated with improved OS in pancreatic cancer patients in cohort studies. However, the effect of other anti-diabetic medications should be interpreted with caution owing to the limited number of studies.

INTRODUCTION

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in the United States [1]. Owing to late stage at the time of diagnosis, there are just 10%-20% of patients eligible for surgical treatment [2]. Although the surgical procedure of pancreatic cancer over the last decades has improved strongly, it needs some more effective treatments and adjuvant therapies against PC.

The relationship between PC and diabetes mellitus (DM) has been increasingly recognized over the past decades. Studies suggest that DM plays a pivotal role in cancer risk and progression [3–5]. Although we have not fully understood the mechanisms of increased risk of cancer incidence with DM, hyperinsulinemia may influence the neoplastic process through its effects on enhancing cancer cell proliferation, survival, and invasion and inhibiting apoptosis in the insulin-like growth factor-I (IGF-I) signaling pathway [6, 7]. There are an increasing number of experimental evidence and epidemiologic studies to show that ADMs may modify the prognosis of PC. Some studies suggest that metformin may improve outcome of patients with diabetes and pancreatic cancer [8–13], whereas others have not revealed beneficial effect [14–18]. Besides, some studies suggest that insulin may highlight risk of PC mortality [19, 20], whereas others have not affected the survival [8, 11]. Due to controversial results among studies, we thus carry out this meta-analysis to investigate the prognostic value of ADMs use (as compared with non-user) among PC patients.
RESULTS

Description of the included studies

The initial database search yielded a total of 3326 references for eligibility. After excluding the duplicates and screening the remaining title and abstract, 42 potentially relevant studies were identified for further review. After selection, a total of 14 publications met our inclusion criteria (Figure 1). The clinical features of included studies were summarized in Table 1. In summary, 13 studies investigated the survival outcomes for patients of metformin use, 5 for insulin use, 2 for SUs use and 2 for TZDs use. The median follow-up time ranged from 0.77 to 12 years. 5 studies were carried out in USA, 3 in Europe and 2 in Asia. Several cohorts were adjusted for some conventional influential factors, including age, sex, disease stage. Six studies involved PC patients with I-IV disease stages, and two with stage IV. Assessment of methodological quality for cohort studies yielded a score range of 7 to 9, and 7 of 12 studies had a score of 8 or above (Supplementary Table 1).

Metformin use and PC survival

The combined HR for the OS comparing metformin use versus non-use was 0.77 (95% CI=0.68-0.87) with moderate inter-study heterogeneity ($I^2=52.9\%$, $p=0.02$) (Figure 2A) for cohort studies. Figure 2B presents the HR (HR=1.22; 95% CI=0.76-1.95) for PFS. No significant

Figure 1: Flow diagram of the selection process of studies investigating effect of anti-diabetic medications use on pancreatic cancer survival.
Table 1: Baseline characteristics of the included studies on survival outcomes of anti-diabetic medications use for pancreatic cancer patients

| Authors       | Study design | Country/ Setting                          | No. of hospitals involved | Study period | Exposure ascertainment              | Median follow-up (months) | ADMs user/non-user | Sample size | Types of ADMs | Disease stage | Survival end points | Adjusted variables                                                                 |
|---------------|--------------|------------------------------------------|---------------------------|--------------|--------------------------------------|---------------------------|---------------------|-------------|----------------|----------------|-------------------|-----------------------------------------------------------------------------------|
| Reni et al.   | RCT          | Italy; hospital based                     | Single                    | 2010-2014    | RCT                                  | NR                        | 31/29               | 60          | Metformin     | IV             | OS, PFS            | CA199 levels, tumor size and stage, performance status, DDP4 inhibitors           |
| Lee et al.    | Retrospective cohort | Korea; hospital based                  | Single                    | 2005-2013    | Medical records, self-reported        | 10.3                      | 117/120             | 237         | Metformin, TZDs, SU, insulin | I-IV             | OS                | Age, sex, smoking status, surgery, tumor stage, treatment regimen               |
| Kozak et al.  | Retrospective cohort | USA; hospital based                    | Single                    | 1998-2013    | Electronic medical records           | 11.23                     | 18/153              | 171         | Metformin     | I-IV             | OS, DFS            | Performance status, diabetes, cancer extent, weight loss during therapy          |
| Choi et al.   | Retrospective cohort | Korea; hospital based                  | Single                    | 2003-2010    | Electronic medical records           | 10.2                      | 56/127              | 183         | Metformin     | I-IV             | OS                | Age, sex, BMI, stage                                                   |
| Chaiterakij et al. | Retrospective cohort | USA; hospital based                     | Single                    | 2000-2011    | Electronic medical records           | 9.26                      | 366/614             | 980         | Metformin     | I-IV             | OS                | Age, sex, region, Charlson index, treatment regimen                              |
| Cerullo et al. | Retrospective cohort | USA; population based                 | Multiple                  | 2010-2012    | Electronic medical records           | 16.5                      | 456/2937            | 3393        | Metformin     | I-IV             | OS                | Age, BMI, surgery, diabetes, CA199 levels, stage, regional nodes                 |
| Ambe et al.   | Prospective cohort | USA; hospital based                    | Single                    | 1986-2013    | Electronic medical records           | 19                        | 19/25               | 44          | Metformin     | I-II             | OS                |                                                                                   |
| Kordes et al. | RCT          | Netherlands; hospital based             | Multiple                  | 2010-2014    | RCT                                  | 28.1                      | 61/60               | 121         | Metformin     | IV             | OS, PFS            | Age, sex, performance status, stage, tumor location, surgery, diabetes          |
| Tseng et al.  | Retrospective cohort | China; population based                | Multiple                  | 1995-2006    | Structured questionnaire interview   | 12 years                  | 5927/80970         | 86897       | Insulin       | I-IV             | OS                | Age, sex, diabetes, BMI, smoking, region                                           |
| Hwang et al.  | Retrospective cohort | United Kingdom; population based        | Multiple                  | 2003-2010    | Electronic medical records           | NR                        | 247/269             | 516         | Metformin     | I-IV             | OS                | Age, sex, diabetes duration and complications, Charlson index, BMI, GFR, smoking, other ADMs and HbA1c. |
| Sadeghi et al. | Retrospective cohort | USA; hospital based                    | Single                    | 2000-2009    | Interviews, medical records.         | 11.4                      | 117/185             | 302         | Metformin     | I-IV             | OS                | Disease stage, CA199 level, tumor size and site, performance status, Demographic factors, stage, income, diabetic complications, Charlson index, other ADMs |
| Amin et al.   | Retrospective cohort | USA; population based                  | Multiple                  | 2007-2011    | NR                                   | NR                        | 589/258             | 847         | Metformin     | I-IV             | OS                |                                                                                   |
| Jang et al.   | Prospective cohort | Korea; population based                | Multiple                  | 2005-2011    | Prescription information             | NR                        | 530/234             | 764         | Metformin     | I-IV             | OS                | NR                                                                |
| Jeon et al.   | Retrospective cohort | USA; population based                  | Multiple                  | 2008-2009    | NR                                   | NR                        | 132/131             | 263         | Insulin/ SU; metformin/ TZDs | I-IV             | OS                | Age, sex, race, stage and chemotherapy                                          |

ADMs, anti-diabetic medications; BMI, body mass index; DFS, disease-free survival; NR, not reported; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SUs, sulfonylureas; TZDs, thiazolidinediones.
Figure 2: Meta-analysis of the associations between metformin use and pancreatic cancer overall survival (A), and progression-free survival (B). CI, confidence interval; HR, hazard ratio; W (random): Weights (random effects model).
analyses limited to studies with some of the main variable adjusted (age, sex and tumor stage) are also presented in Table 2. For studies with these three variables adjusted, a null prognostic association of metformin use was noted. Nevertheless, further studies should be conducted to examine the true survival benefit of metformin in PC patients due to the small number of studies involved in these subgroups.

Further Egger’s test ($P=0.135$) or Begg’s test ($P=0.436$) also did not found a certain degree publication bias.

### Other ADMs use and PC survival

Five studies investigated the impact of insulin use and PC survival and there was no significant association between insulin use and PC survival (HR=1.18, 95% CI=0.83-1.69; Figure 4A). We also did not find significant association between SUs (HR=1.09, 95% CI=0.80-1.48; Figure 4B) or TZDs (HR=0.84, 95% CI=0.58-1.22; Figure 4C) use and PC survival.

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### Table 2: Subgroup analyses of the associations between metformin use and overall survival for cohort studies

| Comparison variables | No. of studies | $I^2$ statistics; % | HR (95% CI) | $P_{\text{interaction}}$ |
|----------------------|----------------|---------------------|-------------|--------------------------|
| Total                | 11             | 52.9                | 0.77(0.68 - 0.87) | NA                       |
| Study design         |                |                     |             | 0.534                    |
| Prospective cohort   | 2              | 0                   | 0.72(0.61 - 0.86) |             |
| Retrospective cohort | 9              | 58.9                | 0.78(0.67 - 0.90) |             |
| Study setting        |                |                     |             | 0.111                    |
| Hospital based       | 6              | 64.5                | 0.67(0.53 - 0.85) |             |
| Population based     | 5              | 33.6                | 0.84(0.73 - 0.96) |             |
| Study region         |                |                     |             | 0.214                    |
| USA                  | 7              | 47.2                | 0.78(0.67 - 0.92) |             |
| Europe               | 1              |                     | 1.09(0.80 - 1.48) |             |
| Asia                 | 3              | 0                   | 0.69(0.60 - 0.79) |             |
| Hospital number      |                |                     |             | 0.111                    |
| Single               | 6              | 64.5                | 0.67(0.53 - 0.85) |             |
| Multiple             | 5              | 33.6                | 0.84(0.73 - 0.96) |             |
| Sample size          |                |                     |             | 0.0024                   |
| ≥500                 | 5              | 44.1                | 0.86(0.76 - 0.97) |             |
| <500                 | 6              | 0                   | 0.63(0.54 - 0.74) |             |
| Main variable adjusted* |            |                     |             | 0.276                    |
| Yes                  | 5              | 57.8                | 0.83(0.68 - 1.03) |             |
| No                   | 6              | 30.8                | 0.73(0.64 - 0.83) |             |
| NOS scale            |                |                     |             | 0.359                    |
| ≥8                   | 6              | 59.4                | 0.73(0.59 - 0.90) |             |
| <8                   | 5              | 36.2                | 0.82(0.71 - 0.94) |             |

CI, confidence interval; HR, hazard ratio; Main variable adjusted*, Age, sex, stage; NA; not available.
DISCUSSION

This meta-analysis investigated the association between ADMs (metformin, insulin, SUs and TZDs) treatment and survival of PC. We found metformin treatment was significantly associated with favorable OS of PC patients (HR=0.77, 95% CI=0.68-0.87) in cohort studies, but was not significantly associated with PFS (HR=1.22; 95% CI=0.76-1.95) for RCTs. We also found no survival benefits of other ADMs, such as insulin, SUs or TZDs, for PC patients.

Several potential mechanisms may explain the associations for the fact that conventional ADMs may alter the risk of multiple malignancies. It was reported that metformin has been shown to play an important anticancer role in multiple ways including insulin-dependent or independent manners [21]. A recent study found that SUs can induce cell proliferation and had an effect of carcinogenesis by promoting insulin secretion [22]. Moreover, previous in vitro studies showed that TZDs had an impact on cell growth arrest and apoptosis and the inhibition of cancer cell invasion [23].

Several important strengths of this meta-analysis should be addressed. Firstly, to the best of our knowledge, this is the first systematic review regarding the associations between the use of ADMs and prognosis of PC. Secondly, comprehensive and reproducible search strategies were developed to identify all relevant studies or trials in the major databases without language limitations. Thirdly, we investigated the most commonly used ADMs including metformin, SUs, TZDs and insulin and conducted a meta-analysis for both RCTs and cohort studies. Fourthly, more than 90000 participants were included to quantitatively assess the association between ADMs use and PC prognosis, which was the most comprehensive synthesis of the evidence on this topic ever today. Finally, several subgroup analyses were carried out for some of the important variables, such as study design and setting, research region, number of research hospital, main variable adjusted and quality score. The results showed consistency across subgroups.

Still there are limitations in our systematic review. Firstly, the number of studies for each medication involved in this meta-analysis was relatively small except for metformin, and thus it is difficult to draw definite conclusions for the limited statistical power in SUs, TZDs or insulin subset. Secondly, almost none of the included studies had dose or duration-response analysis for certain ADMs, so it is impossible for us to perform this kind of analysis. Therefore, further study should be focused on this aspect. Thirdly, although some major confounders including age, sex and disease stage were identified and adjusted for some of the included studies, some other variables (such as tumor size, body mass index or chemotherapy) could influence our exploration of associations between ADMs and PC survival. Last but not

Figure 3: Funnel plot of studies investigating association between metformin use and pancreatic cancer survival for cohort studies.
Figure 4: Meta-analysis of the associations between insulin (A), sulfonylureas (B), and thiazolidinediones (C) use and pancreatic cancer overall survival. CI, confidence interval; HR, hazard ratio; W (random): Weights (random effects model).

In summary, the results from this meta-analysis revealed that in cohort studies, metformin, not other ADMs was associated with improved OS in PC patients. However, due to limited number of studies investigating other ADMs, further large-scale studies are warranted to determine these associations.
MATERIALS AND METHODS

Literature search and study selection

Based on the PRISMA statement [24], we performed a comprehensive literature search in Pubmed and Embase databases up to August 2016 for relevant citations without language restrictions. We used the search strategies (Supplementary Table 2 and Table 3) that included Medical Subject Headings and Emtree headings combined key words relating to the prognostic effect of ADMs among PC patients. We also manually scanned the reference lists from the extracted relevant research papers, previous reviews and meta-analysis for additional possible publications.

We included published studies providing aggregate data if they met the following criteria: (1) evaluated any prognostic information in PC patients comparing ADMs users with non-users, (2) reported a summary statistic of hazard ratios (HRs) with 95% confidence intervals (CIs) or provided data for calculation as described by Parmar et al [25]. RCTs or observational studies were eligible for this meta-analysis. If there were more than one studies from the same cohort, we selected the most detailed or recent one for analysis. All the studies reporting prognostic information, including overall survival (OS), and progression-free survival (PFS), were selected in the main analyses (Supplementary Table 4). Two independent investigators (Zhou and Gong) conducted the study selection from eligible studies.

Data extraction

Two independent investigators (Zhou and Gong) selected articles and extracted data from eligible studies, evaluated the quality of each study and any discrepancies were resolved by a consensus discussion with a third investigator (Tan). The characteristics recorded were the first author’s last name, publication year, country of the population studied, study design, study setting, number of hospitals involved, time period of study, information source for exposure ascertainment and outcome assessment, total number of persons in each group (exposed vs. not exposed), sample size, types of ADMs, stage, mean F/U (months), survival endpoints and adjustment variables HR, and 95% confidence intervals (CIs) with adjustment for confounding factors. The methodological quality of each study was evaluated using the Newcastle-Ottawa quality assessment scale [26], in which three domains including cohort selection, comparability, and outcome were evaluated with a score range of 0 to 9 with nine representing the highest quality.

Statistical analysis

We used STATA statistical software (version 12.0, StataCorp LP, College Station, TX) and R statistical software (version 3.3.1) to perform the meta-analysis. Survival estimates with full adjustments for known confounders of included studies were abstracted. Summary data reporting HRs with corresponding 95% CIs estimated from Cox proportional hazards models were pooled with random-effects model [27]. The data regarding the association of ADMs (use vs. no use) with survival outcomes were pooled separately. We used the Cochrane Q statistic (with a P value less than 0.10 considering statistically significant) and the F statistic (with an F exceeding 50% indicating significant heterogeneity) to test for between-study heterogeneity [28]. Metformin usage and OS for PC patients were explored for primary meta-analysis. Other outcome measures such as PFS and Disease-free survival (DFS) were also evaluated. Owing to the limited studies for PFS and DFS, we combined the data of PFS and DFS as one outcome for the meta-analysis. We performed sensitivity analyses to explore the reasons for statistical heterogeneity. The risk of publication bias was assessed visually by inspecting of a funnel plot and statistically by using Egger’s or Begg’s regression model [29]. We further ascertained the number of missing studies using Duval and Tweedie’s trim and fill method to adjust the summary hazard ratio based on all the studies including the hypothesized missing ones [30]. All statistical analyses were two-sided and a P-value less than 0.05 was considered significant.

Abbreviations

ADMs: anti-diabetic medications; SUs: sulfonylureas; TZDs: thiazolidinediones; DM: diabetes mellitus; PC: Pancreatic cancer; HRs: hazard ratios; CIs: confidence intervals; OS: overall survival; PFS: progression-free survival. RCTs: randomized controlled trials.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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