Research Article

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Efficacy and safety of PD-1/PD-L1 inhibitors in pancreatic ductal adenocarcinoma: a systematic review and Meta-analysis of randomized controlled trials

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Abstract

Objectives: The clinical benefit of PD-1/PD-L1 inhibitors in unselected PDAC remains uncertain. To quantify the efficacy and safety of PD-1/PD-L1 inhibitors in PDAC compared with non-immunotherapy regimens and to explore sources of heterogeneity.

Methods: We conducted an electronic database search and a systematic review and meta-analysis. Our primary outcome was overall survival, along with secondary outcomes including progression-free survival, objective response rate, and adverse events.

Results: Seven RCTs (n=754) met inclusion criteria. PD-1/PD-L1 therapy was associated with a modest improvement in OS vs. active comparators (mean difference [MD] =0.92 months, 95 % CI 0.04–1.81; p=0.041; I^2=97.0 %). No significant benefit was observed for PFS (MD=−0.19 months, 95 % CI=−1.32 to 0.94; p=0.740; I^2=99.6 %) or ORR (OR=1.32, 95 % CI=0.69–2.53; p=0.402; I^2=39.2 %). Rates of grade ≥3 AEs were similar between groups (OR=1.36, 95 % CI=0.95–1.95; p=0.098; I^2=0 %).

Conclusions: PD-1/PD-L1 inhibitors confer a small OS benefit in PDAC, but conclusions are constrained by small phase II studies, study-level data, high heterogeneity, non-standardized survival/AEs, and exploratory subgroup signals that need validation in phase III trials.

Keywords: pancreatic ductal carcinoma; oncology; cancer; immune checkpoint inhibitor; prognosis

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Introduction

By 2030, pancreatic cancer is projected to rank among the leading causes of cancer-related mortality, reflecting its aggressive biology and late presentation [1]. Characterized by high malignant potential and often asymptomatic progression, pancreatic cancer is notably aggressive and has the lowest 5-year survival rate among all cancers. As the most prevalent pathological subtype of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC) responds poorly to treatment [1]. In addition to a paucity of broadly targetable oncogenic alterations, PDAC is characterized by an immunologically tumor immune microenvironment with dense desmoplastic stroma, limited effector T-cell infiltration, dominant immunosuppressive myeloid populations, and stromal–immune cross-talk that excludes or disables T cells

[2]. Cancer-associated fibroblasts remodel extracellular matrix and secrete chemokines (e.g., CXCL12) that physically and functionally bar cytotoxic lymphocytes; concurrently, myeloid-derived suppressor cells and M2-like macrophages enforce local tolerance [2, 3], while low tumor mutational burden limits neoantigenicity [4]. Collectively these features blunt checkpoint blockade in unselected PDAC. Currently, the first-line treatments for PDAC include chemotherapy and radiotherapy. The standard chemotherapy options include folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX), and gemcitabine with nab-paclitaxel [5]. Additional ongoing approaches include concurrent targeted therapy [6]. Despite these efforts, clinical outcomes have not improved significantly, and PDAC remains one of the cancers with the least favorable prognosis.

Programmed cell death-1 (PD-1) and its ligand PD-L1 constitute a key inhibitory axis restraining antitumor T-cell function. Consequently, PD-1/PD-L1 inhibitors have become the first line of treatment for various cancers [7]. Additionally, PD-1 is a negative regulator expressed on reactive anti-tumor T cells, and its ligand, meanwhile, PD-L1, which is prevalent in tumor cells, suppresses cytotoxic T cell activity [8]. Furthermore, PD-1/PD-L1 inhibitors alleviate immune suppression of anti-tumor T cells, resulting in their proliferation and infiltration into the tumor microenvironment, thereby initiating an anti-tumor response [9]. Hence, these inhibitors function by "awakening" dormant immune responses and facilitating the immune-mediated destruction of tumor cells by obstructing checkpoint receptors or ligands and disrupting co-inhibitory signaling within the tumor cells. This proves particularly effective in cancers characterized by a highly immunosuppressive tumor microenvironment [10].

Several randomized controlled trials (RCTs) have been conducted to evaluate the efficacy of combining chemotherapy, radiotherapy, and PD-1/PD-L1 inhibitors for treating patients with cancer. We performed a meta-analysis to thoroughly investigate the efficacy of PD-1/PD-L1 inhibitors compared to that of conventional chemotherapy in patients with PDAC. By incorporating the most recent trials and organizing analyses around mechanisms relevant to PDAC's immune-resistant microenvironment, this review extends prior syntheses and clarifies where PD-1/PD-L1 blockade may yield clinical benefit and where evidence remains limited.

Materials and methods

General guidelines

This meta-analysis adhered to the most recent 2020 revision of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [11], as delineated in Table S1. The review protocol was prospectively registered on Inplasy.com under registration number (INPLASY202450109). Two independent researchers (T.-C.C. and W.-H.W.) conducted comprehensive electronic searches across Embase, PubMed, Web of Science, Cochrane CENTRAL, and ClinicalTrials.gov databases. They utilized a robust and exhaustive search strategy employing the following keywords: "pancreatic cancer," "PD-1," "PD-L1," "checkpoint inhibitor," and related terms. The search covered the period from the inception of each database until April 20, 2024. The detailed search methodology, including specific search strings, is provided in Table S2. The two researchers independently screened the retrieved citations at the title and abstract levels for eligibility. This was followed by full-text reviews of potentially relevant studies. No language restrictions were applied. Non-English articles were translated and screened at the title/abstract level or in full text, and eligible studies were subsequently included. To further enhance the search, they manually examined additional databases and reference lists of relevant meta-analyses. Our study included publications from all languages. The entire process of data extraction, conversion to a standardized metric when necessary, and synthesis of results across studies was conducted in strict adherence to the rigorous guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and relevant best practices within the medical literature [12–14].

Inclusion and exclusion criteria

The PICOS framework included the following [1]: population, human participants with PDAC [2]; intervention, PD-1 or PD-L1 inhibitor alone or in combination with chemotherapy or radiation therapy [3]; comparison, active comparator without any use of PD-1 or PD-L1 inhibitor [4]; outcome, overall survival, progression-free survival, objective response rate, or adverse events; and [5] studies, published and unpublished RCTs. We also included conference abstract data and data available from clinicaltrials. gov for eligible RCTs.

The articles adhered to the following criteria: (I) being an RCT, including both double-blind and open-label designs; (II) involving patients with PDAC; and (III) including a treatment group that used at least one PD-1 or PD-L1 inhibitor, along with a comparator group that did not use any PD-1 or PD-L1 inhibitor. Unpublished data were included when sufficient methodological details and outcome data were available from trial registries or conference proceedings. The exclusion criteria were as follows: (I) lack of a fully documented cohort comprising solely patients with

PDAC and (II) not including any of the following efficacy outcomes: overall survival, progression-free survival, and objective response rate.

Methodological quality appraisal

We employed the Cochrane risk-of-bias tool for randomized trials (RoB 2, London, UK) [15] to critically evaluate the methodological quality of the included studies. This tool assesses six critical components that define the quality of a study: randomization methods, intervention compliance, measurement of outcomes, completeness of outcome data, selective outcome reporting, and overall risk of bias.

Primary and secondary outcomes

The primary outcome was overall survival, defined as the duration (in months) from a patient's initial PDAC diagnosis to their current state of health. Secondary outcomes included [1]: progression-free survival, which refers to the duration (measured in months) a patient remains free from symptoms of disease progression during a medical therapy or clinical trial [2]; objective response rate, the percentage of people in a study or a treatment group who either experience a partial or complete response to the treatment within a certain period; and [3] adverse events. We recorded treatment-related grade 3/4 adverse events according to the Food and Drug Authority definitions (grade 3: prevents everyday activity and necessitates medical intervention; grade 4: emergency room visit or hospitalization) [16]. For cells with zero events, zero was replaced by 0.5 to incorporate the study into the analysis [17].

Statistical analyses

This meta-analysis was conducted using Comprehensive Meta-Analysis software (version 3; Biostat, Englewood, NJ, United States) due to the heterogeneous nature of the study populations [18]. The mean difference (MD) and 95 % confidence interval (CI) were calculated for all continuous outcomes (overall survival and progression-free survival). Odds ratios (OR) and their corresponding 95 % CIs were used to analyze categorical outcomes (i.e., objective response rate and rates of adverse events), such as the rates of treatment-related adverse events. We performed a sensitivity analysis using the "one-study removal" method to assess the robustness of the overall effect size. This involved excluding each study individually to determine whether the omission of any single study significantly impacted the results [17]. In addition, heterogeneity was quantified using the I^2 statistic.

To detect potential publication bias, we visually inspected the funnel plot for asymmetries and applied Egger's regression test to statistically determine any systematic deviations in effect sizes [11].

Ethics statement

Ethical review and approval were not required for this meta-analysis because it synthesized data from previously published studies and contained no individual patient identifiers. The protocol was registered with INPLASY (INPLASY202450109) and the review followed PRISMA 2020 guidelines.

Results

Study selection

The initial search yielded 2,259 articles. After removing duplicates and screening titles and abstracts, 2,227 articles were identified to be irrelevant and excluded. Full texts of the remaining 32 studies were reviewed. Of these, 25 articles were excluded for various reasons: 13 did not provide data exclusively for patients with PDAC, and insufficient outcome data were available for 12 studies (Table S3). This resulted in seven RCTs for the final quantitative analysis [19–25] (Figure 1). Study characteristics are presented in Table 1.

Study characteristic

The seven RCTs included a total of 754 participants, published between 2020 and 2023, all of which were phase II trials enrolling patients with metastatic or advanced PDAC. Detailed study features are summarized in Table 1.

Quality assessment

Five studies [19–22, 24] were classified as having some bias risk as they did not provide information on allocation concealment. The remaining two studies [23, 25] were rated as having a low risk of bias, and none of the studies exhibited a high risk of bias (Figure S1, Table 2).

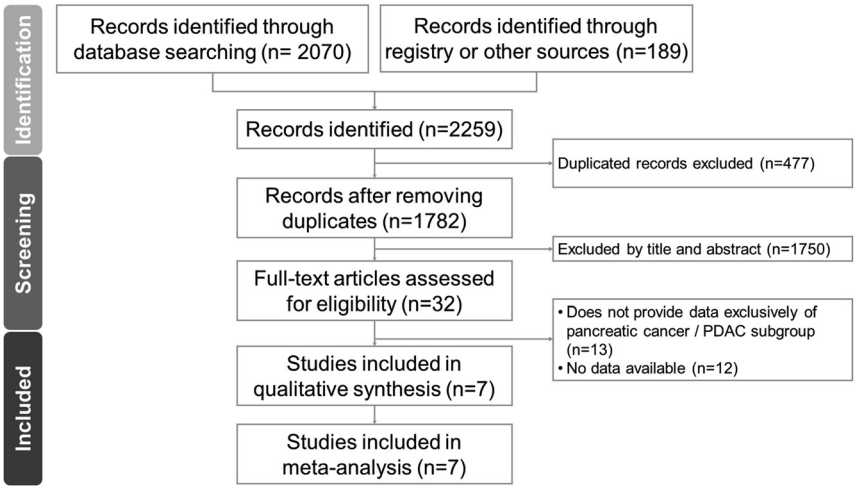

Figure 1: PRISMA flow diagram of the current network meta-analysis.

Table 1: Summary of the retrieved trials investigating the effect of ICI on PDAC in the enrolled participants.

First author & year	NCT code	Trial name	Phase	Disease setting	Subjects recruited	Description of intervention
Chung et al. 2020	NCT03193190	N/A	II	Refractory metastatic PDAC	29	Group of PD-L1 inhibitor: Atezolizumab + RO6874281
					46	Group of active comparator: mFOLFOX6[d] or Gem[c]/Nab-Paclitazel
Tsujikawa et al. 2020	NCT02243371	N/A	II	Metastatic PDAC	51	Group of PD-1 inhibitor: Nivolumab + Cy-GVAX[e] + CRS-207
					42	Group of active comparator: Cy-GVAX[e] + CRS-207
Padrón et al. 2022	NCT03214250	PRINCE	II	Metastatic PDAC	69	Group of PD-1 inhibitor: Nivolumab + Gem[c]/Nab-Paclitazel + (sotigalimab)[f]
					36	Group of active comparator: Gem[c]/Nab-Paclitazel + sotigalimab
Renouf et al. 2022	NCT02879318	CCTG PA.7	II	Metastatic PDAC	119	Group of PD-L1 + CTLA-4 inhibitor: Durvalumab + tremelimumab + Gem[c]/Nab-Paclitazel
					61	Group of active comparator: Gem[c]/Nab-Paclitazel
Zhu et al. 2022	NCT02704156	RECIST	II	Metastatic PDAC	85	Group of PD-1 inhibitor: Pembrolizumab + SBRT[b] + trametinib
					85	Group of active comparator: SBRT + gemcitabine
Fu et al. 2023	NCT03977272	CISPD3	II	Metastatic PDAC	45	Group of PD-1 inhibitor: Sintilimab + mFFX[a]
					46	Group of active comparator: mFFX[a]
Heumann et al. 2023	NCT02451982	N/A	II	Resectable PDAC	24	Group of PD-1 inhibitor: Nivolumab + Cy-GVAX[e] + (Urelumab)[g]
					16	Group of active comparator: Cy-GVAX[g]

PDAC, pancreatic ductal adenocarcinoma; CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PDL-1, programmed cell death 1-ligand 1. [a]mFFX, modified FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin). [b]SBRT, stereotactic body radiation therapy. [c]Gem, gemcitabine. [d]mFOLFOX6, a combination of drugs, including: modified fluorouracil, leucovorin, and oxaliplatin. [e]Cy-GVAX, cyclophosphamide-GVAX. [f]Patients were randomly allocated into one of three treatment arms (nivolumab/chemo, sotigalimab/chemo and sotigalimab/nivolumab/chemo, respectively). [g]Patients were randomly allocated into one of three treatment arms (Cy-GVAX5, nivolumab/Cy-GVAX5, and nivolumab/Cy-GVAX5 + Urelumab, respectively).

Table 2: Detailed quality assessment of included studies using Cochrane risk of bias 2 tool.

First author	Year	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall RoB
Chung	2020	S[a]	L	L	L	L	S
Tsujikawa	2020	S[a]	L	L	L	L	S
Padrón	2022	S[a]	L	L	L	L	S
Renouf	2022	S[a]	L	L	L	L	S
Zhu	2022	L	L	L	L	L	L
Fu	2023	L	L	L	L	L	L
Heumann	2023	S[a]	L	L	L	L	S

H, high risk of bias; L, low risk of bias; RoB, risk of bias; S, some risk of bias. [a]The studies didn't provide allocation concealment details.

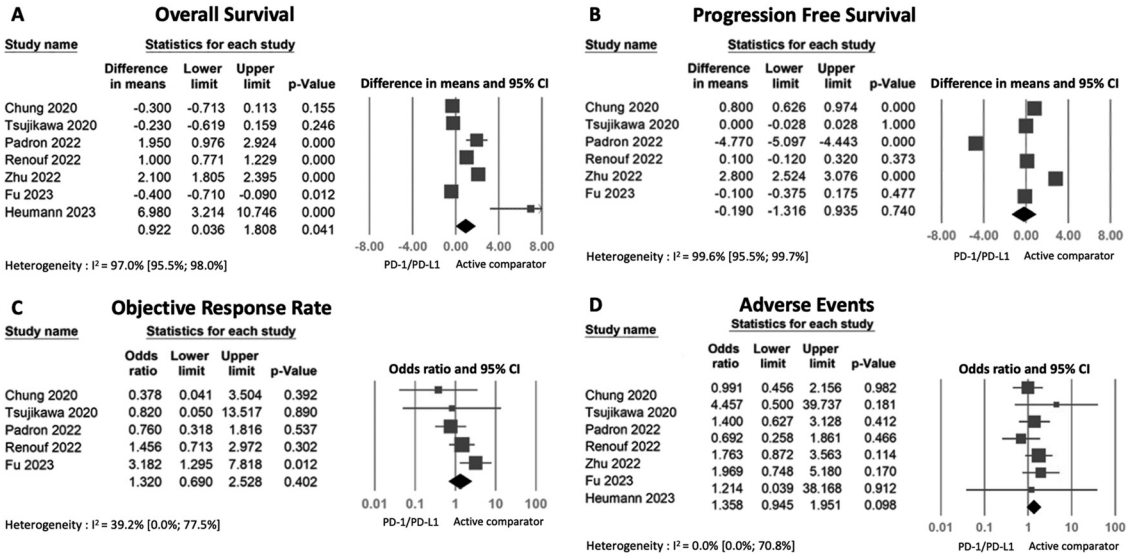

Figure 2: Forest plot of overall effects of PD – 1/PDL – 1 inhibitors compared with active comparator on (A) overall survival, (B) progression free survival, (C) objective response rate, and (D) adverse events in patients among PDAC patients.

Primary outcomes

Overall survival

PD-1/PD-L1 significantly increased overall survival compared with the survival observed with the active comparator (MD=0.922 months, 95 % CI=0.036–1.808, p=0.041, I^2=97.0 %) (Figure 2A). This finding remained robust in leave-one-out sensitivity analyses (Figure S2A).

Secondary outcomes

Progression-free survival

No statistically significant improvement in PFS was observed with PD-1/PD-L1 inhibitors compared with the active comparator (MD=−0.190 months, 95 % CI=−1.316 to 0.935, p=0.740, I^2=99.6 %) (Figure 2B). This result was consistent across sensitivity analyses (Figure S2B).

Objective response rate

Administration of PD-1/PD-L1 inhibitors did not significantly affect the objective response rate relative to the active comparator (OR=1.320, 95 % CI=0.690–2.528, p=0.402, I^2=39.2 %). Although the pooled effect size for the objective response rate alterations did not reach statistical significance, a trend toward an improved objective response rate was discernible among patients undergoing PD-1/PD-L1 treatment. (Figure 2C). Sensitivity analyses showed similar results (Figure S2C).

Adverse events

There was no significant difference in grade 3–4 treatment-related AEs (OR=1.358, 95 % CI=0.945–1.951, p=0.098, I^2=0.0 %) (Figure 2D). Sensitivity analyses showed similar findings (Figure S2D).

Publication bias

Funnel plots showed no substantial asymmetry, and Egger's regression tests indicated no significant publication bias for any endpoint (all p>0.5) (Figure S3).

Discussion

This review analyzed seven studies to evaluate the effects of PD-1/PD-L1 inhibitors in patients with PDAC. These findings indicate that PD-1/PD-L1 inhibitors resulted in an increase in overall survival compared to that observed with active comparators. However, these inhibitors did not significantly improve progression-free survival or objective response rate. PD-1/PD-L1 inhibitors did not exhibit an increase in adverse event occurrence compared to the active comparator.

Current standard first-line therapies for PDAC involve chemotherapeutic regimens such as gemcitabine, nab-paclitaxel,

and FOLFIRINOX. However, these approaches have limited efficacy, with a median overall survival of less than 1 year. Additionally, nearly all patients experience disease progression [26]. Although chemotherapy can cause tumor regression by driving the release of cancer cell antigens, its effects are often hindered by the immunosuppressive tumor microenvironment in PDAC, which impairs the anti-tumor immune response [27]. Given the inadequacy of current treatments to achieve a complete cure for pancreatic cancer, an urgent need exists for a more effective therapeutic approach.

Within our analysis, PD-1 and PD-L1 inhibitors demonstrated a marginally significant increase in overall survival, suggesting that reversing the suppressive tumor microenvironment to sensitize tumors to immune checkpoint inhibitor (ICI) therapy could be a promising treatment strategy for PDAC [28]. In the tumor microenvironment, the PD-1/PD-L1 signaling pathway crucially suppresses T cell-mediated immune responses. Disruption of these checkpoints and inhibitory signals may lead to the death of regulatory T cells and strengthen the activities of effector T cells that target tumor cells [29]. However, no universally accepted metric is available for assessing the effectiveness of ICI therapy. No improvement in progression-free survival was observed, suggesting that current combinations of ICIs extend survival without necessarily slowing disease progression. The objective response rate, which focuses solely on complete and partial tumor regression, may not fully reflect the potential benefits in terminal cancers, where maintaining a stable disease could be of relevant clinical value.

Compared with previous PDAC immunotherapy reviews [8], our findings are partly consistent. Both analyses concluded that unselected PDAC populations derive limited benefit from ICIs due to the “cold” tumor microenvironment. Our meta-analysis diverged from prior findings by demonstrating a modest but statistically significant OS benefit. Unlike the earlier study that reported no survival advantage, our analysis focused exclusively on RCTs, incorporated newer trials testing ICIs with chemotherapy or radiotherapy, and emphasized higher-quality trial designs, which likely accounts for the observed difference. The absence of significant improvement in PFS and ORR is consistent with prior reviews [6, 8]. From a methodological standpoint, the pooled sample sizes for these endpoints were modest, which may have limited statistical power. Biologically, PDAC’s dense desmoplastic stroma and low tumor-infiltrating lymphocyte content may delay radiographic tumor shrinkage, meaning OS benefits can occur without short-term PFS gains.

Regarding potential predictive biomarkers, KRAS wild-type status may be associated with better response to immune checkpoint blockade, as observed in the CCTG PA.7 trial [19]. However, this observation is currently supported by limited high-quality evidence. While other studies have hinted at enhanced immunotherapy responsiveness in KRAS wild-type PDAC [30–32], the available studies are small and heterogeneous. Thus, KRAS mutation status should be regarded as a hypothesis-generating biomarker, pending confirmation in prospective studies.

Tumor location may also influence ICI responsiveness. A pooled analysis found higher OS for pancreatic head cancers than for body/tail tumors (HR=0.95, 95 % CI=0.92–0.99, p=0.02), potentially due to differences in incidence, prognosis, and molecular features [33]. Overall survival is favorable with ICI treatment for primary tumors in the pancreatic head/uncinate region (HR=0.50, 95 % CI=0.23 to 1.23), while chemotherapy is advantageous for tumors in the body/tail (HR=1.53, 95 % CI=0.88 to 2.67) [25]. These results suggest that patients with pancreatic head tumors benefit particularly from ICI treatment and experience a significant extension of the survival period. Although these subgroup data are limited, they suggest that patients with both wild-type KRAS and pancreatic head tumors may have enhanced responsiveness to PD-1/PD-L1 inhibitors.

Additionally, PD-1/PD-L1 inhibitors do not cause more adverse events than those resulting from other active treatments. However, the types of adverse events associated with these ICIs are quite different from those typically observed with conventional chemotherapy. Moreover, ICIs can affect various organs, and their side effects can vary according to the severity and timing. Therefore, careful monitoring and timely intervention are essential to effectively manage these unique immune-related adverse events [34].

Although our meta-analysis provides valuable insights into the effectiveness of the interventions examined, several limitations should be acknowledged. First, our reliance on published findings rather than individual patient data may introduce biases in result interpretation owing to the limited sample size and number of trials. Furthermore, the trial Heumann et al. [24] had a wide OS confidence interval (3.214–10.746 months), likely due to its small sample size, early-phase design, and single-center recruitment, which may have increased statistical uncertainty and contributed to heterogeneity. Across studies, differences in patient demographics, disease stage, heterogeneity between studies presents a challenge, as differences in participant demographics, disease severity, treatment modalities, and other variables across studies can affect the consistency and reliability of the results.

Conclusions

This systematic review and meta-analysis of RCTs demonstrates that PD-1/PD-L1 inhibitors, compared with active

comparators, yield a modest but statistically significant improvement in overall survival in patients with PDAC, without significant gains in progression-free survival or objective response rate. The safety profile is comparable to standard chemotherapy, though the nature of adverse events differs. Emerging evidence suggests that patients with wild-type KRAS and tumors in the pancreatic head may derive greater benefit; however, these signals remain preliminary. Future large-scale, biomarker-stratified trials are essential to confirm these associations and refine the role of immune checkpoint inhibitors in PDAC treatment strategies.

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Data Availability Statement: The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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