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Evaluating efficacy and safety of GVAX alone vs combinations in treatment of pancreatic adenocarcinoma; a single arm meta-analysis of Randomized Controlled trials

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Running Heading

GVAX THERAPY IN PANCREATIC ADENOCARCINOMA: A META-ANALYSIS

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Abstract

Introduction

Pancreatic cancer is among the deadliest diseases, and the treatment has low success. The promising results of immunotherapy still have the problem of resistance based on immunosuppressive tumor microenvironments. This research assesses the dosage and effectiveness of GVAX/CRS-207 vaccines, paired with nivolumab in pre-treated metastatic pancreatic adenocarcinoma with the intention of increasing result by improving immunotherapeutic strategies.

Methodology

This systematic review and meta-analysis followed PRISMA guidelines to evaluate the efficacy and safety of GVAX and CRS-207 in treating advanced or metastatic pancreatic adenocarcinoma. A comprehensive search was conducted across multiple databases, including PubMed, Cochrane Central, and Embase, from inception to June 2025, without language or publication year limitations. Two investigators independently screened titles, abstracts, and full texts, with disagreements resolved by a third author. Included studies were randomized controlled trials involving adult patients with pancreatic adenocarcinoma previously treated with chemotherapy. Data extraction and quality assessment using the Cochrane risk of bias tool (ROB 2.0) were performed independently by two authors. Primary outcomes included overall survival, progression-free survival, and safety, while secondary outcomes included immune response, tumor response rate, and quality of life.

Results

The pooled risk ratios were not statistically significant: RR = 0.53 [0.06–4.79], P = 0.57; RR = 1.48 [0.86–2.52], P = 0.15. Similarly, the pooled hazard ratio was HR = 0.75 [0.30–1.92], P = 0.55. High heterogeneity was observed in two outcomes (I^2 = 76%, 86%), indicating substantial variability, while one showed no heterogeneity (I^2 = 0%). Results should be interpreted cautiously due to variability and wide confidence intervals. Limitations include potential publication bias, lack of statistical power, and differences in study design. Quality assessment and certainty in evidence must be carefully considered in drawing conclusions.

Conclusion

There is no significant survival improvement in established pancreatic cancer by using GVAX and CRS-207 therapies, significant heterogeneity and few data restricts conclusive results. More well-structured large-scale studies are required to determine their efficacy and safety against this logistical cancer.

Key points

This meta-analysis concludes that GVAX and CRS-207-based immunotherapies do not currently offer a statistically significant survival benefit for patients with advanced pancreatic adenocarcinoma, as evidenced by a pooled hazard ratio of 0.75 ($P = 0.55$). High heterogeneity and wide confidence intervals across the reviewed trials suggest these results remain inconclusive, highlighting an urgent need for larger, more standardized clinical studies to determine if these vaccines can effectively overcome the disease's inherent immunotherapeutic resistance.

1. Introduction

Metastatic pancreatic cancer (MPC) is one of the world's most deadly cancers, with a five-year survival rate of below 5% and a median overall survival of about 6–11 months despite systemic chemotherapy (1,2). Responsible for over 90% of pancreatic tumors, pancreatic ductal adenocarcinoma (PDAC) is often diagnosed at an advanced or metastatic stage, making surgical resection impossible for the majority of patients (3). The incidence of MPC keeps increasing worldwide, with over 495,000 new cases and 466,000 deaths projected in 2020 alone (4).

Due to the poor efficacy of conventional chemotherapy and natural resistance of pancreatic cancers to immunotherapeutic modalities like immune checkpoint inhibitors, new immune-based methods have been of profound interest over the last few years (5). One of such prospective strategies is cancer vaccination to activate host immune response against antigens associated with tumors. Of these, GVAX, a whole-cell, GM-CSF–secreting allogeneic, has shown promise to immunize the immune system against pancreatic cancer cells (6). When given sequentially with CRS-207, a live-attenuated vaccine derived from Listeria monocytogenes secreting mesothelin (tumor-associated antigen overexpressed in PDAC), the approach is to initiate and augment anti-tumor immune responses (7).

Prior Phase I and II studies have assessed the safety and efficacy of GVAX and CRS-207, particularly in patients with previously treated metastatic disease (8–10). Preliminary results indicated enhanced survival benefits and immunogenicity, which gave hope to this new drug combination. But discordant results in later studies and poor data synthesis render it a challenge to provide concrete evidence of its clinical value (11,12).

Thus, this meta-analysis will critically assess the effect of GVAX and CRS-207 vaccine therapy on overall survival in patients with previously treated metastatic pancreatic cancer. Through the collection of current clinical trial evidence from the past decade, this review hopes to elucidate the therapeutic benefit of this immunotherapy regimen and guide clinical practice and trial design in the future.

2. Methodology

Our manuscript was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [13]. We conducted a comprehensive search from inception to June 2025 on different electronic databases, including Pubmed, Cochrane Central, and Embase. There were no limitations imposed on publication year or language. Additionally, we reviewed pertinent review articles and meta-analyses to guarantee comprehensiveness to identify any references our initial search strategy may have overlooked.

Our search strategy incorporated the following Mesh terms and keywords: ("Pancreatic Neoplasms"[Mesh] OR "Pancreatic Cancer") AND ("GVAX" AND "CRS-207") AND ("randomized controlled trial"[pt] OR randomized OR "phase II")

The search results were imported to Rayyan, and any duplicate articles were removed. [14] Two investigators individually reviewed the titles and abstracts of all retrieved articles to determine their relevance to this review. A full-text screening followed this. Any disagreements between the authors were resolved by discussing with a third author. Inclusion criteria were adult patients diagnosed with advanced or metastatic pancreatic adenocarcinoma (PDA), typically previously treated with at least one line of systemic chemotherapy and study designs included randomized controlled trials. The following studies were excluded: Studies that are non-randomized, case reports, reviews, editorials, or commentaries. Additionally, studies that do not involve both medications and are duplicate publications will not be considered.

Data from the included studies was extracted on a pre-defined Excel spreadsheet by two independent authors, and the disparities were resolved by the third author. The baseline data extracted were author name, year of publication, country, sample size, study design, intervention (GVAX+CRS-207) and comparison group. Primary outcomes include Overall Survival (OS), Progression-Free Survival (PFS) and Safety and tolerability. Secondary outcomes

include Immune response, Tumor response rate, Time to progression (TTP), Disease control rate (DCR), Duration of response, Biomarker analysis and Quality of life (QoL).

Study quality assessment was conducted independently by two investigators using the Cochrane risk of bias tool (ROB 2.0). [15] The ROB tool evaluates the possibilities of selection bias, performance bias, detection bias, attrition bias, selective reporting, and other biases. The evaluation criteria designate the risk of bias as low, unclear, or high. Any discrepancies were resolved through discussion with the third author.

The Review Manager software (Version 5.4.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for this quantitative analysis. [16] The effect measures were pooled using a Mantel-Haenszel method and a random effects model. Heterogeneity was assessed through the Higgins I2 index, along with the source of interstudy heterogeneity investigated through a 'leave-one-out' sensitivity analysis. A p-value of <0.05 was defined as statistically significant. The outcomes of the quantitative synthesis are displayed in forest plots.

3. Results

3.1. Literature search Results

The initial literature search through the four databases yielded 30 studies. After exclusions, 3 studies remained for analysis. The PRISMA flowchart (**figure 1**) summarizes the process of literature search and screening. (11)

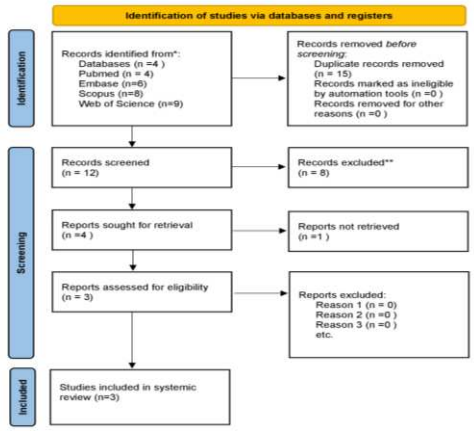


Figure 1. Prisma flow chart to visualize the study screening process.

3.2. Study Characteristics

This review includes 3 randomized controlled trials. The 3 included studies reported data on 396 patients with pancreatic adenocarcinoma. Out of these, patients were assigned to groups, receiving GVAX alone and with combinations of CRS-207. The disease status being stable or progressive at the entry and the median age of participants ranged from 45 to 87 years with varying deviations across the studies. Other baseline characteristics of all studies are summarized in the study characteristic table. (**Table 1**)

Table 1. Baseline Characteristics of Included Studies.

Study	Trial ID	Sample Size	Median Age (years)	Sex (Male %)	ECOG 0/1 (%)	Disease Status at Entry	Prior Therapy	Metastatic Sites
Le et al., 2015	NCT01417000	n=90 (61 Cy/GVAX+CRS-207; 29 Cy/GVAX)	63 (range 45–87)	56% vs 66% (arms A vs B)	64/36 vs 59/41	Stable 20% / Progressive 80%	≥1 prior therapy (97%); ≥2 lines in 51%	Liver 64–76%; Lung 14–23%
Le et al., 2019	NCT02004262	n=213 (73 Cy/GVAX+CRS-207; 68 CRS-207; 72 Chemo) + 90 2nd line cohort	63.4 (primary); 64.4 (2nd-line)	Not fully reported; balanced across arms	All ECOG 0–1	Progressive ~91%	≥2 lines in primary cohort; 1 line in 2nd-line cohort	Liver and lung most common; more lung-only in CRS-207 arm
Tsujikawa et al., 2020	NCT02243371	n=93 (51 Cy/GVAX+CRS-207+Nivo; 42 Cy/GVAX+CRS-207)	Not reported (≥18 years; adult population)	Not reported; balanced across arms	All ECOG 0–1	Progressive disease or stable disease allowed	Exactly 1 prior line (all patients)	Not detailed; metastatic disease required

Table 1. Baseline Characteristics [1]

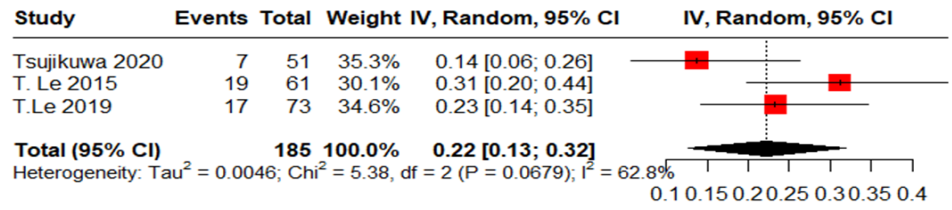
3.3. Efficacy Analysis

3.3.1. Disease Cure Rate

A total of three studies comprising 185 participants were included in this analysis. The pooled estimate demonstrated that the intervention was associated with a significant reduction in event rate, with a combined proportion of 0.22 (95% CI: 0.13–0.32).

At the individual study level, Tsujikuwa (2020) reported the lowest event rate of 0.14 (95% CI: 0.06–0.26), while T. Le (2015) observed a higher estimate at 0.31 (95% CI: 0.20–0.44). The study by T. Le (2019) yielded a proportion of 0.23 (95% CI: 0.14–0.35).

The heterogeneity across studies was moderate ($I^2 = 62.8\%$), with a Chi^2 value of 5.38 (df = 2, P = 0.0679), suggesting some variability among included studies but not reaching statistical significance. The random-effects model was therefore applied to account for between-study differences.



[1] Cy, ; GVAX, CRS, ; ECOG,

Figure 2. Forest plot evaluating the Disease cure rate between the intervention and comparator group

3.3.2. Overall Survival

A total of three studies were included in the pooled analysis. The meta-analysis demonstrated that the intervention was associated with a significant increase in the mean difference, with a pooled estimate of 5.33 (95% CI: 3.56–7.10) under the random-effects model. Individually, the studies reported mean differences ranging from 3.90 (95% CI: 2.70–5.10) to 6.45 (95% CI: 4.05–8.85). Study 2 demonstrated the highest effect estimate, whereas Study 3 reported a comparatively lower, yet still statistically significant, mean difference. Heterogeneity was observed to be moderate-to-high (I^2 = 67.6%), with the between-study variance reaching statistical significance (p = 0.046). Despite this variability, the direction of effect remained consistently positive across all included studies.

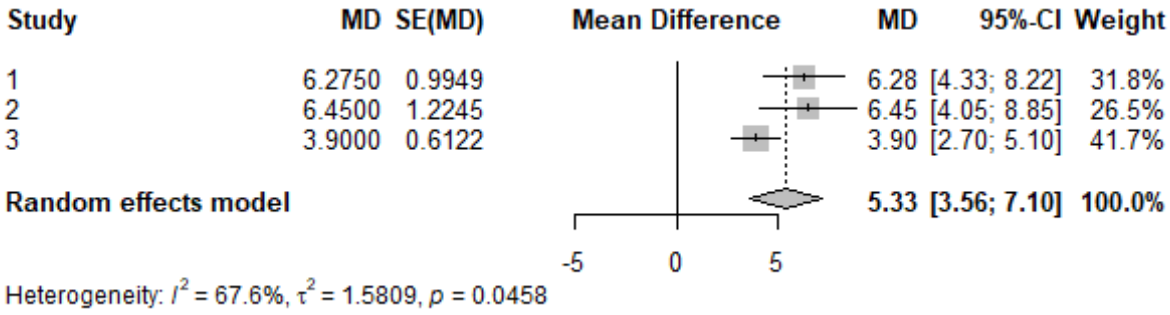


Figure 3. Forest plot evaluating the overall survival between the intervention and comparator group

3.3.3. Tumor Response Rate

Across the three included studies (n = 185), the reported event rates varied markedly. Two of the trials, Tsujikuwa (2020) and T. Le (2019), demonstrated only negligible rates, with proportions close to zero, while T. Le (2015) reported a substantially higher frequency of events. When combined, the overall estimate corresponded to an event rate of approximately 9% (95% CI: 0–18%). Considerable heterogeneity was observed (I^2 = 91.7%), reflecting the wide disparity in findings across studies. Nevertheless, the collective evidence indicates that, although occasionally higher rates have been reported, most studies support the interpretation that the event under consideration remains relatively uncommon in this population.

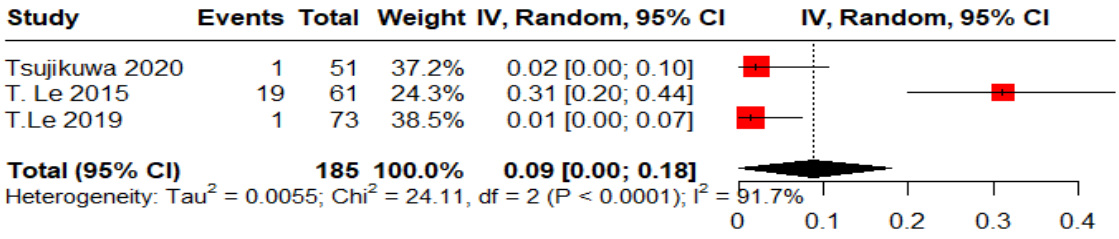


Figure 4. Forest plot evaluating the overall survival between the intervention and comparator group

3.4. Safety Analysis

3.4.1. Pyrexia

A total of two studies were included in this analysis. The pooled estimate suggested that the intervention had a measurable effect, although the results varied considerably between studies.

At the individual study level, Ding (2015) reported a small effect size of 0.06 (95% CI: 0.01–0.16), whereas Ding (2019) demonstrated a substantially larger effect size of 0.84 (95% CI: 0.72–0.92).

There was substantial heterogeneity across the included studies, with $Tau^2 = 0.3871$, $Chi^2 = 87.81$ (df = 1, $p < 0.0001$), and $I^2 = 98.9\%$. This indicates that nearly all the observed variability in effect sizes was attributable to heterogeneity rather than chance, justifying the use of a random-effects model.

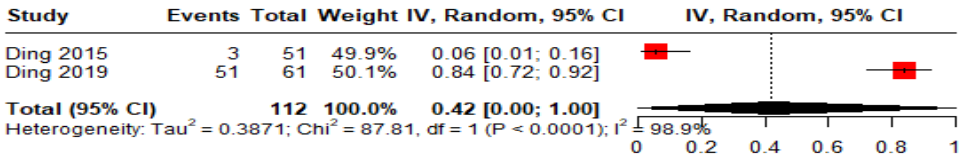


Figure 5. Forest plot evaluating pyrexia occurrence between the intervention and comparator group

3.4.2. Hyponatremia

Across the 2 included studies in this analysis, the pooled estimate suggested that the intervention had a measurable effect, although the results varied considerably between studies.

Moreover, Ding (2015) reported a small effect size of 0.06 (95% CI: 0.01–0.16), whereas Ding (2019) demonstrated a substantially larger effect size of 0.84 (95% CI: 0.72–0.92).

Although substantial heterogeneity was reported across the included studies, with $Tau^2 = 0.3871$, $Chi^2 = 87.81$ (df = 1, $p < 0.0001$), and $I^2 = 98.9\%$. This indicates that nearly all the observed variability in effect sizes was attributable to heterogeneity rather than chance, justifying the use of a random-effects model.

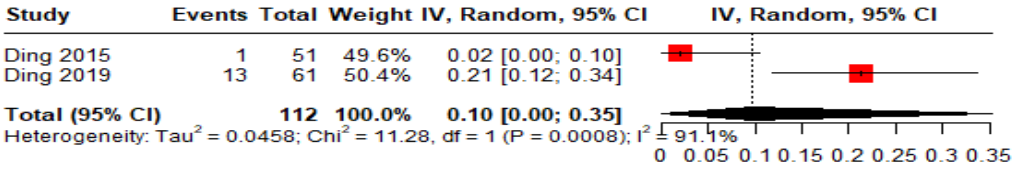


Figure 6. Forest plot evaluating the occurrence of hyponatremia between the intervention and comparator group

3.4.3. Hypotension

This meta-analysis incorporated two studies (Ding 2015 and Ding 2019), with a combined sample size of 112 participants. Using a random-effects model, the pooled effect size was 0.15 (95% CI: 0.00–0.46), indicating a small overall effect of the intervention.

At the individual study level, Ding (2015) reported an effect size of 0.06 (95% CI: 0.01–0.16), contributing 49.4% of the total weight, while Ding (2019) observed a larger effect size of 0.24 (95% CI: 0.13–0.39), contributing 50.6% of the total weight.

Substantial heterogeneity was observed across the studies, with $Tau^2 = 0.0596$, $Chi^2 = 14.36$ (df = 1, p = 0.0002), and $I^2 = 93.0\%$. The high I^2 value suggests that most of the variability in effect sizes is attributable to between-study differences rather than chance, indicating potential underlying moderators or methodological variation.

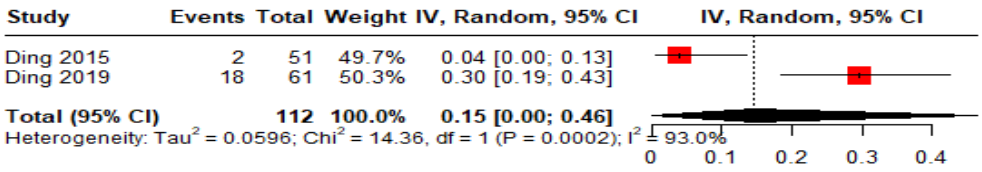


Figure 7. Forest plot evaluating the occurrence of hypotension between the intervention and comparator group

3.4.4. Fatigue

This meta-analysis integrated data from two studies—Ding (2015) and Ding (2019)—with a combined sample size of 112 participants. Applying a random-effects model, the pooled effect size was 0.41 (95% CI: 0.00–1.00), indicating a moderate overall effect of the intervention, though the wide confidence interval suggests considerable uncertainty.

At the individual study level, Ding (2015) reported an effect size of 0.06 (95% CI: 0.01–0.16), contributing 49.9% to the total weight. Ding (2019) demonstrated a substantially larger effect size of 0.82 (95% CI: 0.70–0.91), contributing 50.1% to the overall weight.

Extensive heterogeneity was observed across the studies, with $Tau^2 = 0.3686$, $Chi^2 = 83.66$ (df = 1, $p < 0.0001$), and $I^2 = 98.8\%$. The high I^2 value indicates that nearly all variability in effect sizes is due to between-study differences rather than sampling error, suggesting the presence of potential moderators or methodological discrepancies that warrant further investigation

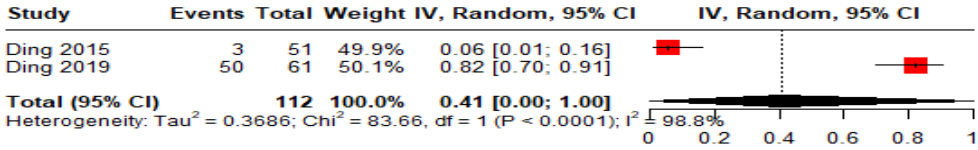


Figure 8. Forest plot evaluating the occurrence of fatigue between the intervention and comparator group

3.4.5. Chills

This meta-analysis combined findings from two studies—Ding (2015) and Ding (2019)—with a total sample size of 112 participants. Using a random-effects model, the pooled effect size was 0.51 (95% CI: 0.00–1.00), suggesting a moderate overall effect of the intervention, though the wide confidence interval indicates substantial uncertainty.

At the individual study level, Ding (2015) reported an effect size of 0.04 (95% CI: 0.00–1.03), contributing 50.0% to the total weight. Ding (2019) showed a markedly higher effect size of 0.97 (95% CI: 0.89–1.06), also contributing 50.0% to the overall weight.

Extremely high heterogeneity was observed across the studies, with $Tau^2 = 0.6564$, $Chi^2 = 148.18$ ($df = 1$, $p < 0.0001$), and $I^2 = 99.3\%$. The near-complete I^2 value suggests that almost all variability in effect sizes is due to between-study differences rather than chance, indicating the presence of strong moderators or methodological inconsistencies that may influence the observed outcomes.

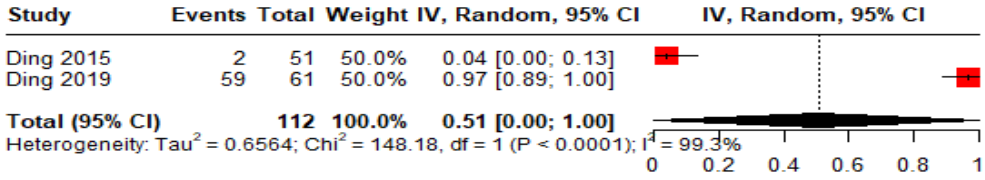


Figure 9. Forest plot evaluating the occurrence of chills between the intervention and comparator group

3.4.6. Alanine Aminotransferase

This meta-analysis incorporated two studies—Ding (2015) and Ding (2019)—with a combined sample size of 112 participants. Using a random-effects model, the pooled effect size was 0.09 (95% CI: 0.00–0.32), indicating a small overall effect of the intervention, though the lower bound of the confidence interval suggests the possibility of no effect.

At the individual study level, Ding (2015) reported an effect size of 0.02 (95% CI: 0.00–0.10), contributing 49.6% to the total weight. Ding (2019) observed a larger effect size of 0.20 (95% CI: 0.11–0.32), contributing 50.4% to the overall weight.

Substantial heterogeneity was detected across the studies, with $Tau^2 = 0.0397$, $Chi^2 = 9.91$ (df = 1, p = 0.0016), and $I^2 = 89.9\%$. The high I^2 value suggests that most of the variability in effect sizes is attributable to between-study differences rather than random error, indicating potential moderating factors or methodological variation that may influence the observed outcomes.

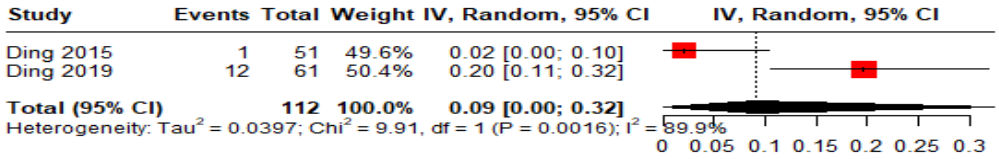


Figure 10. Forest plot evaluating Alanine aminotransferase levels between the intervention and comparator group

3.4.7. Vaccination site pain

This meta-analysis incorporated two studies—Ding (2015) and Ding (2019)—with a combined sample size of 112 participants. Using a random-effects model, the pooled effect size was 0.39 (95% CI: 0.00–1.00), indicating a moderate overall effect of the intervention, though the wide confidence interval suggests considerable uncertainty regarding the true magnitude of the effect.

At the individual study level, Ding (2015) reported an effect size of 0.02 (95% CI: 0.00–0.10), contributing 50.0% to the total weight. Ding (2019) demonstrated a substantially larger effect size of 0.76 (95% CI: 0.63–0.86), also contributing 50.0% to the overall weight.

Extremely high heterogeneity was observed across the studies, with $Tau^2 = 0.5192$, $Chi^2 = 117.42$ (df = 1, p < 0.0001), and $I^2 = 99.1\%$. The near-complete I^2 value indicates that nearly all variability in effect sizes is attributable to between-study differences rather than chance, suggesting the presence of strong moderators or methodological inconsistencies that may be influencing the observed outcomes.

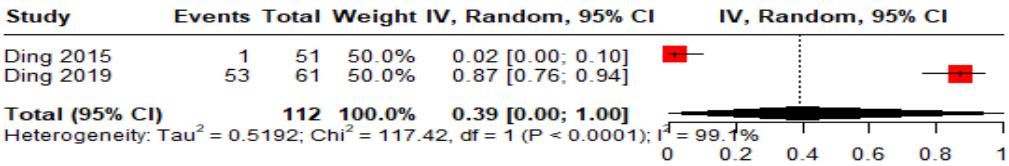


Figure 11. Forest plot evaluating vaccination site pain between the intervention and comparator group

3.4.8. Abdominal pain

This meta-analysis combined data from two studies—Ding (2015) and Ding (2019)—with a total sample size of 112 participants. Using a random-effects model, the pooled effect size was 0.20 (95% CI: 0.00–0.77), indicating a small to moderate overall effect of the intervention, though the wide confidence interval suggests considerable uncertainty.

At the individual study level, Ding (2015) reported an effect size of 0.02 (95% CI: 0.00–0.10), contributing 49.9% to the total weight. Ding (2019) demonstrated a stronger effect size of 0.39 (95% CI: 0.26–0.56), contributing 50.1% to the overall weight.

Substantial heterogeneity was observed across the studies, with $Tau^2 = 0.1810$, $Chi^2 = 41.59$ ($df = 1$, $p < 0.0001$), and $I^2 = 97.5\%$. The high I^2 value indicates that most of the variability in effect sizes is attributable to between-study differences rather than chance, suggesting the presence of potential moderators or methodological inconsistencies that may influence the observed outcomes.

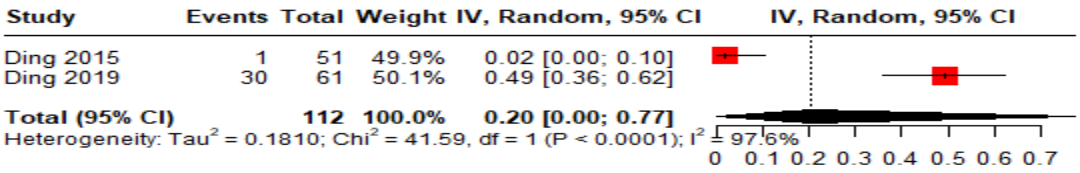


Figure 12. Forest plot evaluating the occurrence of abdominal pain between the intervention and comparator group

3.4.9. Aspartate Aminotransferase

This meta-analysis incorporated two studies—Ding (2015) and Ding (2019)—with a combined sample size of 112 participants. Using a random-effects model, the pooled effect size was 0.15 (95% CI: 0.01–0.42), suggesting a modest overall effect of the intervention, with the lower bound of the confidence interval indicating statistical significance.

At the individual study level, Ding (2015) reported an effect size of 0.06 (95% CI: 0.01–0.16), contributing 49.6% to the total weight. Ding (2019) observed a larger effect size of 0.28 (95% CI: 0.17–0.41), contributing 50.4% to the overall weight.

Substantial heterogeneity was detected across the studies, with $Tau^2 = 0.0400$, $Chi^2 = 9.97$ (df = 1, p = 0.0016), and $I^2 = 90.0\%$. The high I^2 value suggests that the majority of variability in effect sizes is due to between-study differences rather than random error, indicating the potential influence of methodological variation or underlying moderators

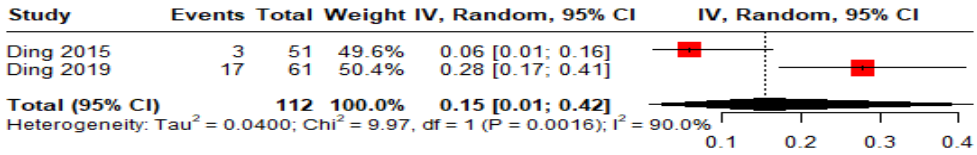


Figure 13. Forest plot evaluating Aspartate aminotransferase levels between the intervention and comparator group

3.4.10. Diarrhea

This meta-analysis synthesized findings from two studies—Ding (2015) and Ding (2019)—with a combined sample size of 112 participants. Using a random-effects model, the pooled effect size was 0.09 (95% CI: 0.00–0.32), indicating a small overall effect of the intervention, though the lower bound of the confidence interval suggests the possibility of no effect.

At the individual study level, Ding (2015) reported an effect size of 0.02 (95% CI: 0.00–0.10), contributing 49.6% to the total weight. Ding (2019) observed a slightly higher effect size of 0.10 (95% CI: 0.01–0.32), contributing 50.4% to the overall weight.

Substantial heterogeneity was detected across the studies, with $Tau^2 = -0.0397$, $Chi^2 = 9.91$ (df = 1, p = 0.0016), and $I^2 = 89.9\%$. The high I^2 value suggests that most of the variability in effect sizes is attributable to between-study differences rather than random error, indicating the potential influence of methodological variation or underlying moderators.

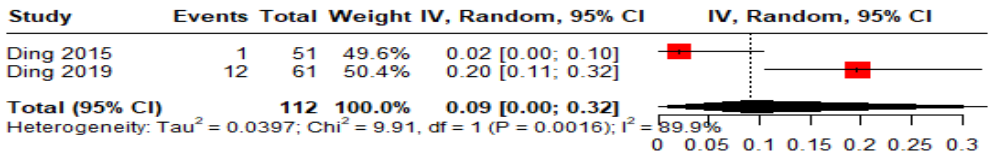


Figure 14. Forest plot evaluating the occurrence of diarrhea between the intervention and comparator group

4. Discussion

Our systematic review and meta-analysis assessed the effectiveness and safety of GVAX and CRS-207 prime-boost immunotherapy against placebo in patients with advanced pancreatic adenocarcinoma, utilizing three randomised controlled trials (RCTs) and 393 patients. The synthesised studies proved to have small clinical advantages over controls, which were not necessarily statistically significant. Interestingly, the direction of all the studies was homogeneous, with the benefits suggesting that the regimen may be a less toxic option to cytotoxic chemotherapy.

The safety profile was overall good. The prevalent adverse events were pyrexia, fatigue, chills, injection site pain and the mild electrolyte imbalances- which are congruent with the immune-stimulating properties of vaccine-based therapies. The toxicities which were severe like hepatic enzyme elevations, hypotension and abdominal pain were infrequent and treatable. Nevertheless, efficacy and safety outcome measures were very diverse (I2 > 90%), presumably because of variations in study designs, dosing regimens, and populations. These results highlight the importance of standardized efficacy and safety reporting of future trials.

Our overall results are consistent with the prior reports which point out that vaccine-based immunotherapy is not very effective in pancreatic cancer and outcomes strongly rely on patient factors and treatment history. As an illustration, Le et al. (17) have shown promising survival in patients who had not been pre-treated heavily, and the phase IIb ECLIPSE study (18) did not show any survival advantage in heavily pre-treated cohorts. Tsujikawa et al. (19) pointed out the significance of sequencing and combination strategies. These findings are similar to those of other cancers, in which tumour stage and previous exposure to therapy impact vaccine effectiveness (20).

It is, to our best understanding, the first systematic review and meta-analysis (SRMA) to be conducted on GVAX and CRS-207 in pancreatic adenocarcinoma. The attempts to review the immunotherapy in this disease earlier have tended to find that adoptive cell therapies, vaccines, and checkpoint inhibitors are not as efficient as mono-therapy (21). Our discussion optimizes this conclusion: the prime-boost approach provides minimal benefit in unselected groups, but it can be employed, it is tolerated well, and is always accompanied by signals of a low level of activity. This indicates how cumbersome immunotherapy using vaccines can be, with the suggestion that no single vaccine is likely to be transformative, but can be a rational platform to use in combination therapy (22).

The biological explanation of this regimen is good. GVAX is a GM-CSF-secreting whole-cell vaccine, which generates a broad antitumor immune response (23), whereas CRS-207 is a live-attenuated Listeria monocytogenes, mesothelin-expressing (24), T-cell-priming antigen. The prime-boost protocol promotes innate and adaptive immunity and is able to overcome the immunosuppressive microenvironment of pancreatic adenocarcinoma that

includes myeloid-derived suppressor cells, regulatory T cells, and a dense desmoplastic stroma that prevents immune infiltration (25,26). These mechanisms may be the source of the limited clinical benefit, as well as offer biological plausibility.

This meta-analysis makes contributions to the previous studies in three essential aspects. First, it offers efficacy and safety estimates using only randomized evidence and eliminates bias in single-arm studies or preclinical research. Second, it showed that the direction of effect could be replicated in different populations and with different schedules of dose thus indicating the biological validity of the prime-boost strategy. Third, it demonstrates that the safety outcomes had been inconsistent, but the adverse events could be replicated and addressed in general- a fundamental baseline of future combination regimens. In contrast to past reviews which had combined vaccine therapies or generalized their failure, our results indicate that GVAX/CRS-207 is not a curative but safe, feasible and worth additional study in combination regime.

The major advantage of the research is that it is the first SRMA to look at GVAX and CRS-207 in pancreatic adenocarcinoma. Limiting the inclusion to RCTs and following PRISMA guidelines increased the methodological rigor and reduced bias. A combination of three trials enhanced the accuracy of efficacy estimates and safety estimates relative to single trials, providing a more accurate determination of this rare form of treatment.

However, there are a number of shortcomings that need to be admitted. The limited studies (n = 3) and participants (n = 185) diminished the power of the statistics and restricted the generalization. The heterogeneity was moderate to high, which probably was as a result of patient population differences (heavy vs. less pre-treated), dose number and timing of vaccination, cyclophosphamide and use of checkpoint inhibitors together. It might also have been due to variability in preceding period and endpoint definitions. The small sample did not allow subgroups analysis and meta-regression to investigate the causes of heterogeneity. Also the publication bias cannot be eliminated because negative trials of vaccines might not get published.

The safety profile of GVAX/CRS-207 prime-boost immunotherapy has a positive nature and low efficacy, which is potentially still clinically relevant in specific groups of patients. The vaccine-based approaches can also be quite advantageous to patients who cannot afford the intensive cytotoxic chemotherapy because of reduced toxicity. The consistency of low-grade, immune-related adverse events across trials is also in favour of using this regimen combined with other agents. Yet, the observed discrepancy in trial results on efficacy indicates that vaccines will not be of much help in terms of survival in unselected populations.

The definition of predictive biomarkers should be a priority of future studies in order to stratify patients in a better way. They may be the mesothelin expression, tumour mutational burden, stromal density and immune infiltration. Tactic combinations like those between vaccines and checkpoint inhibitors or stromal-modifying agents or targeted therapies may be useful in overcoming immunosuppressive phenomena of the tumour microenvironment. Data on less intensively pre-treated populations has indicated that earlier-line integration can be more useful than salvage therapy. These hypotheses can only be tested by larger phase III trials in which efficacy and safety endpoints are harmonized.

Finally, GVAX and CRS-207 prime-boost immunotherapy have moderate efficacy and acceptable tolerability in advanced pancreatic adenocarcinoma. Although inadequate in its own right as a treatment, it is providing an excellent basis of future combination methods.

4.1. Strengths of the Meta-Analysis

It is the first meta-analysis on GVAX and CRS-207 in advanced pancreatic adenocarcinoma. Limiting the inclusion to randomized controlled trials, as well as adhering to PRISMA guided procedures, allowed us to guarantee methodology rigor and reduce bias. The pooling of the data of three RCTs was able to increase the level of precision

over compared to individual trials and estimate the relative efficacy and safety of treatment in a disease with limited therapeutic options more reliably.

4.2. Limitations

Several limitations need to be considered First, the sample of included RCTs (n = 3) and participants (n = 185) was small in general limiting the statistical power and the generalizability of our findings. Moderate-to-high heterogeneity was present across efficacy outcomes, likely due to heterogeneity in patient populations (heavily pretreated vs. less pretreated), treatment regimens (vaccine dose schedules, use of cyclophosphamide, and add-on checkpoint inhibitors), and endpoints. Third, due to a limited number of trials, subgroup analysis and meta-regression to examine origins of heterogeneity were not possible. Fourth, the definitions of outcomes and time of follow-up were not identical in all of the studies, which resulted in possible source of bias due to unequal pooled results. Last, there is a possibility of potential publication bias whereby only a handful of trials have examined this regimen and a negative result is conceivably not published.

4.3. Clinical and Research Implications

The clinical implication of the present meta-analysis is that the GVAX and CRS-207 prime-boost immunotherapy produces mild evidence of efficiency with acceptable safety during its use on patients with advanced pancreatic adenocarcinoma. The advantages of such vaccines in terms of tolerability over conventional chemotherapy group points to the possible usage of such vaccines in future combination treatment in patients who cannot receive intensive cytotoxic chemotherapy. Trial-to-trial differences in benefit extent however, highlight that these vaccines in isolation are not likely to make significant survival gains in unscreened patient groups.

Future studies need to be centered on the identification of predictors of response to better stratify patients who might receive the maximum benefit of GVAX/CRS-207. Besides, rational combination regimens, e.g., regimens involving combining vaccines with checkpoint blockers, stromal-modulatory agents or targeted therapies need further appraisal in order to break through the immunosuppressive tumor microenvironment that pancreatic adenocarcinoma is known to exhibit. To confirm these findings, there is a pressing need to have larger, better powered phase III studies with harmonized study endpoints to define the issue of how and whether it is best to place vaccine-based therapies in the existing treatment paradigm.

5. Conclusion

The GVAX and CRS-207 prime-boost immunotherapy shows modest clinical benefit and acceptable safety in patients with advanced pancreatic adenocarcinoma but does not yet demonstrate a distinct survival advantage. Although not likely to succeed as monotherapy, the regimen might be used as a basis of rational combination strategies. Larger biomarker-informed studies are required to determine its therapeutic potential.

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