REVIEW

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Effect of *HER3* Overexpression on Survival Outcomes in Pancreatic Cancer Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Pancreatic cancer (PC) is a highly aggressive malignancy known for its late diagnosis and poor prognosis, making it one of the leading causes of cancer-related mortality worldwide. Identifying the molecular alterations involved in the prognosis of PC is essential. One such factor is *HER3* overexpression, which can contribute to cancer cell survival, metastasis, and reduced overall survival (OS) in patients by activating cellular signaling pathways. This meta-analysis investigates the rate of *HER3* overexpression in pancreatic cancer patients and examines how this overexpression affects their survival rates. **Materials and Methods:** A comprehensive search was conducted across PubMed, Embase, Web of Science, and Scopus databases up to August 2024. Studies evaluating the association between *HER3* overexpression and PC were collected following specific inclusion and exclusion criteria. The rate ratio (RR) with 95% confidence intervals (CI) was calculated. Heterogeneity and publication bias were evaluated, and the extent of *HER3* overexpression in patients with PC was analyzed. Also, the studies' quality was evaluated using the Newcastle-Ottawa Quality Assessment Scale. The research protocol has been registered on PROSPERO under the registration number CRD42024584939. **Results:** Four studies involving 345 patients with PC were selected for analysis to assess the role of *HER3* overexpression on OS. Seven studies involving 536 patients were also included to evaluate the rate of *HER3* overexpression in PC patients. Findings indicate that 47.8% of PC patients showed overexpression of *HER3* (CI 95%: 34.1-61.9). Additionally, *HER3* overexpression was significantly linked to a poorer overall survival rate of patients with PC (OR: 0.605, 95% CI: 0.401-0.913, P= 0.017). **Conclusion:** In summary, our results reveal that a significant proportion of PC patients show overexpression of *HER3*, suggesting its potential role as a target for immunotherapy. The findings also highlight the promise of *HER3* as a prognostic biomarker in PC.

Keywords: *HER3*- meta-analysis- overexpression- pancreatic cancer- survival rate

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Introduction

Pancreatic cancer (PC) is one of the most aggressive and deadly types of cancer worldwide due to its poor prognosis and late-stage and metastatic diagnosis [1-3]. There are several types of PC. The most common type is pancreatic ductal adenocarcinoma, which originates from epithelial cells and is associated with a poor prognosis [4]. Another type, Pancreatic Neuroendocrine Tumors, is less common but tends to have a better prognosis and originates from hormone-producing cells [5]. Acinar Cell Carcinoma is a rare form of PC that develops in the cells that produce digestive enzymes [6].

In the tumor microenvironment, interactions between cancerous and non-cancerous cells play a pivotal role in tumorgenicity [7]. These interactions are often mediated by the overexpression of molecules like *HER2*, *HER3*, and MUC4, which activate specific signaling pathways involved in cancer cell survival and proliferation [8]. One key group of molecules involved is the HER family (human epidermal growth factor receptor or ErbB) of cell surface receptors, which includes four members: EGFR (ErbB1or *HER1*), *HER2* (ErbB2), *HER3* (ErbB3), and *HER4* (ErbB4) [9]. Unlike other members of the HER family, *HER3* lacks intrinsic kinase activity. As a result, it needs to form heterodimers with other HER family

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proteins for effective functioning. Notably, no ligand has yet been identified for *HER2*. Among the most active complexes is the *HER2-HER3* heterodimer, where the binding of the ligand heregulin to *HER3* triggers the PI3K/AKT/mTOR signaling pathway via *HER2* [8, 10]. Under normal conditions, binding these receptors to their ligands activates signaling pathways responsible for physiological functions such as cell survival, migration, proliferation, and differentiation. However, overexpression of *HER2* is linked to tumorigenesis, while overexpression of *HER3* promotes tumor cell proliferation and treatment resistance, contributing to the development of cancers. These disruptions can hinder apoptosis, increasing cancer cell survival and poorer patient outcomes [11]. Consequently, targeted therapies that inhibit these receptors have emerged as promising treatment candidates for patients with overexpression of these receptors [12].

Although several studies have examined the effect of *HER3* overexpression on overall survival in PC patients, a comprehensive analysis of the available data has not been conducted. In this study, we performed a meta-analysis with two main objectives: first, to determine the prevalence of *HER3* overexpression in patients with PC, and second, to evaluate how *HER3* overexpression impacts the survival rates of these patients.

Materials and Methods

Design and search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, and the study protocol was registered in the PROSPERO database under the registration number CRD42024584939. To access relevant studies, we performed a systematic search across four scientific databases: PubMed, Embase, Web of Science, and Scopus, covering up to August 2024. The search was conducted using the keywords "pancreatic cancer," "*HER3*," and "overexpression" along with their synonyms. The search was not restricted to studies published in English but was limited to research involving human subjects. We also conducted a manual search in Google Scholar and the references of the relevant studies to increase search sensitivity. One of the researchers conducted the search (MHM), and the search results were efficiently managed using EndNote software (Clarivate Analytics, Philadelphia, PA, USA).

Study Selection Criteria

The primary aim of this study was to identify and evaluate studies examining *HER3* expression level in PC patients. The secondary aim was to identify studies that assessed the association between *HER3* overexpression and the survival rates of PC patients. Accordingly, this meta-analysis included all qualified, relevant research evaluating the rate of *HER3* overexpression in PC patients and examined the association between *HER3* overexpression and survival in these individuals. Exclusion Criteria for this study include (1) Abstracts, case reports, conference proceedings, editorials, letters to the editor, review articles, systematic reviews, and comments; (2) Duplicate studies or studies that report on overlapping populations; (3) Studies conducted on pediatric patients or conducted in vitro; (4) Studies that employ irrelevant methods or report outcomes that are not applicable; (5) Studies with incomplete data.

Data extraction process

Two reviewers, RHM and NA, independently selected eligible studies and ZJ and SS extracted the necessary data for analysis using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Any disagreements were resolved through consensus and discussion with a third reviewer, MHM. The collected data was entered into an Excel spreadsheet containing the following information: the last name of the primary author, the location and date of the study, the total number of cancer patients, the number of patients with *HER3* overexpression, the ages of the patients, their ethnicities, the methods used to evaluate *HER3* expression and data related to the overall survival of patients categorized into *HER3* positive and *HER3* negative groups. The main features of the selected studies have been summarized in Table 1.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) for non-randomized studies was utilized to evaluate the methodological quality of the studies reviewed [13]. This tool assesses three primary domains: "Selection of Studies," "Comparability of Groups," and "Outcome Ascertainment." Each domain is assigned a score, with a maximum of four stars for selection, two stars for comparability, and three stars for outcome, resulting in a total score for each study that ranges from 0 to 9. Studies are classified as "High Quality" if they receive a score of 7–9, "Moderate Quality" if they score between 4–6, and "Low Quality" if they score between 0–3. In this research, two authors (RHM and NA) independently assessed the quality of each article. In cases of disagreement, a third reviewer (MHM) was consulted.

Statistical analysis

The data for this meta-analysis were analyzed using the Comprehensive Meta-Analysis software, version 3 (Biostat, USA). In order to calculate the odds ratios and their associated 95% confidence intervals, the statistical analysis incorporated the sample sizes, the count of *HER3*-positive patients, and the overall survival data of the patients. P-values less than 0.05 are considered statistically significant. The studies' heterogeneity was evaluated using Cochrane Q and I^2 statistics. A random-effects model was applied to estimate the outcome data when the Cochrane Q P-value was less than 0.1, and the I^2 value was greater than 50%, indicating statistical heterogeneity. In other cases, a fixed-effects model was used. Subgroup analysis was conducted to assess the influence of confounding variables on the meta-analysis results. Additionally, we performed a random-effects meta-regression using the Knapp-Hartung adjustment to evaluate whether the year of publication influenced the *HER3* overexpression in pancreatic cancer. Also, Egger's regression asymmetry test was conducted, and a funnel plot was created to evaluate

publication bias. Additionally, a sensitivity analysis was performed by systematically excluding each study to evaluate the results' consistency.

Results

Study selection

For this meta-analysis, we thoroughly reviewed the results from our search using specified keywords, which initially yielded a total of 387 studies. After removing 142 duplicate articles, 245 articles remained. We then screened the titles and abstracts of these articles, excluding 228 that were deemed irrelevant. In the second phase, we performed an in-depth review of the full texts of the remaining 17 articles to identify relevant ones. The reasons for exclusion at each stage included overlapping patient data, insufficient sample sizes, and other factors. In the final phase, we selected all relevant and eligible studies, resulting in the following findings: - Seven case-control studies aligned with the paper's first objective, which examined patients with PC and *HER3* overexpression, with a total sample size of 536. - Four case-control studies related to the second objective, focusing on the association between *HER3* overexpression and patient survival in PC, with a sample size of 345. The search strategy and study selection process are illustrated in Figure 1.

Study selection and characteristics

The selected studies were published between 1995 and 2016. Among these, three studies were conducted in Asia [14-16], three in Europe [17, 12, 11], and one in North America [18]. The basic characteristics of these studies are summarized in Table 1. All studies included in this analysis confirmed PC diagnoses through histopathological evaluations and assessed *HER3* overexpression using the immunohistochemistry (IHC) technique. Each study was assigned a quality rating ranging from zero to nine based on the Ottawa-Newcastle Scale for case-control studies. As shown in Table 1, six studies were rated as high quality, while one study was assessed as moderate quality.

Quantitative synthesis

The analysis of the seven studies included in this review found that *HER3* overexpression was present in 47.8% of patients with prostate cancer (PC) [95% Confidence Interval: 34.1% - 61.8%]. Furthermore, the examination of four studies investigating the relationship between *HER3* overexpression and overall survival rates indicated a significant association (Odds Ratio: 0.605, 95% CI: 0.401 - 0.913, P = 0.017). This suggests that *HER3* overexpression is linked to reduced patient survival and overall lifespan. Figure 2 presents two forest plots that illustrate these findings.

Heterogeneity test

The heterogeneity of the studies included in this meta-analysis was evaluated using the I^2 statistic and the Q test. In the analysis of *HER3* overexpression in PC, the I^2 value was found to be 86.85%, indicating a high level of heterogeneity among the studies. This suggests that a significant portion of the variability in effect estimates is due to differences between the studies rather than chance. In the analysis of the effect of *HER3* overexpression on PC patients, the I^2 statistic reached an even higher value of 98.60%, reflecting substantial heterogeneity. This indicates that the studies in this analysis showed considerable variation in their findings regarding the impact of *HER3* overexpression on patient outcomes. Furthermore, the Q test results produced p-values of $P < 0.001$ for both analyses, reinforcing the presence of significant heterogeneity. These findings underscore the need for caution when interpreting the overall effect estimates, as the variability among studies may affect the conclusions drawn from this meta-analysis. Future research should investigate the sources of this heterogeneity to better understand the role of *HER3* in PC.

A subgroup analysis was conducted according to region to investigate the cause of heterogeneity based on the availability of data. The findings indicated that the mean effect size of *HER3* overexpression rates did not differ significantly among the various regions of the studies, suggesting that the region is not a source of heterogeneity for the first analysis (P=0.485). However, the results of the subgroup analysis for the second investigation, which examined the association between *HER3* overexpression and survival in PC patients, showed that the region was a source of heterogeneity (P<0.001).

Table 1. Basic Information of the Studies Included in the Meta-Analysis

First author	Year	Country	Region	Age Range (mean or median)	Used for evaluation of Overexpression or Survival	Number of HER3 positive cases	Number of HER3 negative cases	Method of HER3 evalustion	NOS Score**
Friess (18)	1995	USA	North American	31-77(63)	Overexpression and Survival	27	31	IHC*	7
Vaidya (14)	1996	Japan	Asian	-	Overexpression	27	30	IHC	7
Velde (17)	2009	Netherlands	European	33-76(62)	Overexpression	33	45	IHC	8
Hirakawa (15)	2011	Japan	Asian	33-84(67)	Overexpression and Survival	52	74	IHC	7
Thomas (12)	2014	France	European	-	Overexpression	12	44	IHC	5
Bittoni (11)	2015	Italy	European	48-87(69)	Overexpression and Survival	37	54	IHC	7
Li (16)	2016	China	Asian	18-80(62)	Overexpression and Survival	17	53	IHC	8

* IHC, Immunohistochemistry; **NOS, The Newcastle-Ottawa Quality Assessment Scale

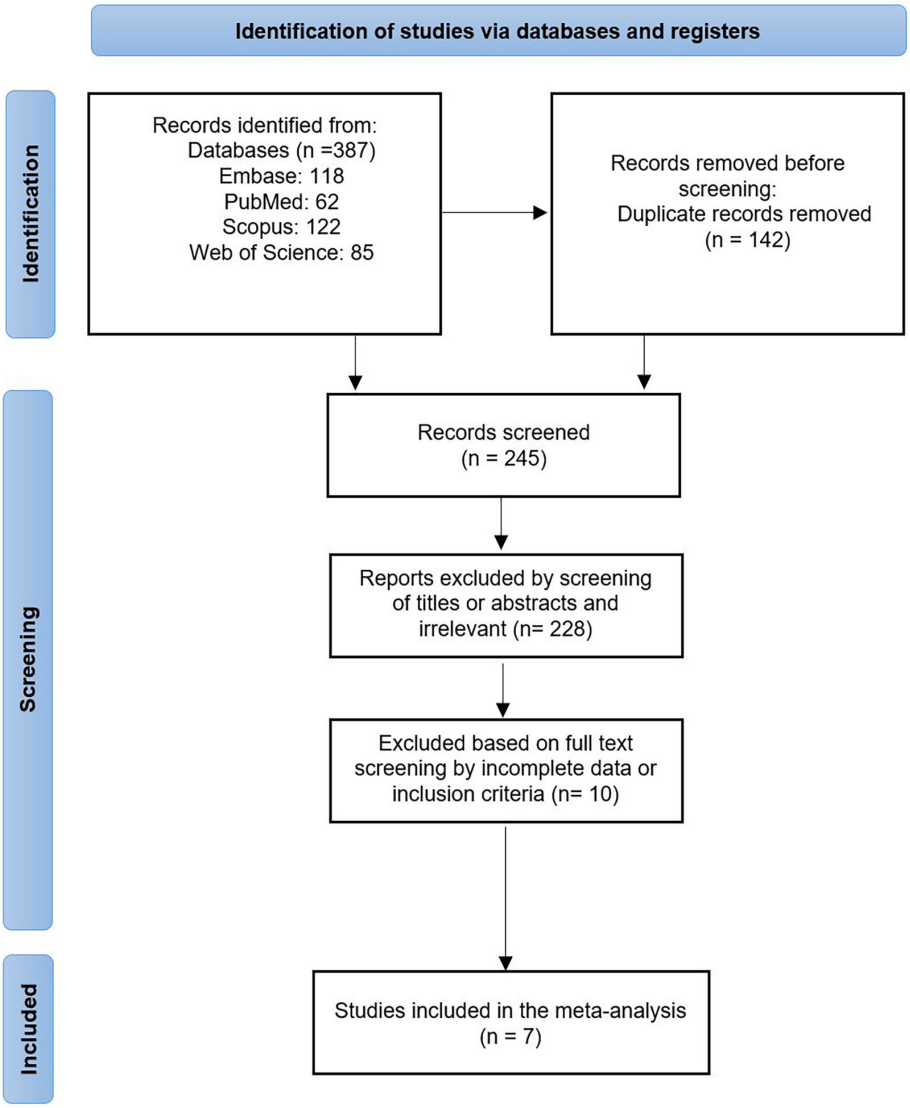

Figure 1. The Flowchart Illustrates the Search Strategy Methodology and Study Selection Process

Nevertheless, the number of studies included in this subgroup analysis needed to be higher.

The meta-regression analysis aimed to determine if the year of publication affected the overexpression of *HER3* in pancreatic cancer. The results indicated a coefficient of -0.0764 (SE = 0.0436) for the variable "Year," suggesting a slight decline in *HER3* overexpression rates over time. However, this finding was not statistically significant, with a p-value of 0.0703. Between-study heterogeneity remained high (I^2=85.3%, Tau^2=0.436), with 'Year' explaining only 11% of variance (Figure 3).

Sensitivity analysis

To ensure the reliability of the study findings and to assess the impact of each study on the overall results of the meta-analysis, a sensitivity analysis was conducted. In this process, each study was removed one at a time, and the changes in the meta-analysis results were evaluated. The results indicated that there were no significant changes after the removal of any single study, demonstrating the stability and robustness of the findings from this analysis.

Publication bias assessment

Funnel plots, Begg's rank correlation, and Egger's regression tests were employed to evaluate the potential for publication bias. The findings related to publication bias are illustrated in Figure 4. Begg's and Egger's tests indicated no publication bias when analyzing *HER3* overexpression in PC, with P-values of 0.452 and 0.247, respectively. Similarly, there was no evidence of publication bias in the analysis of the correlation between *HER3* overexpression and the survival of PC patients, as indicated by P-values of 0.734 for Begg's test and 0.838 for Egger's test. The funnel plots indicated no evidence of publication bias. While some asymmetry was observed in the graphs, it was not significant and likely resulted from the limited number of studies included in the analysis. The funnel plot diagrams were modified using Duval and Tweedie's trim and fill test. These modifications did not lead to any significant changes in the studies that examined *HER3* overexpression and its effects on the survival of PC patients (Data not shown).

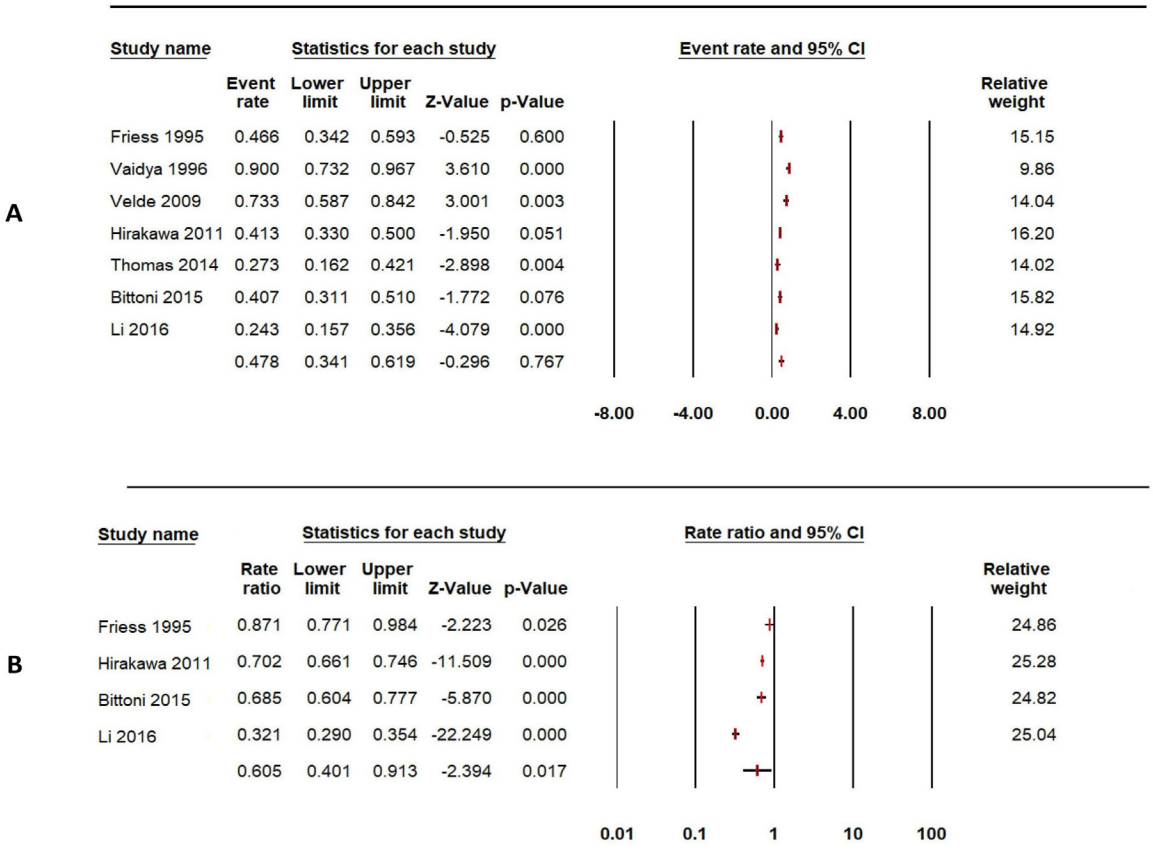

Figure 2. Forest plots: (A) examining the prevalence of *HER3* overexpression in pancreatic cancer patients; (B) evaluating the relationship between *HER3* overexpression and overall survival in prostate cancer.

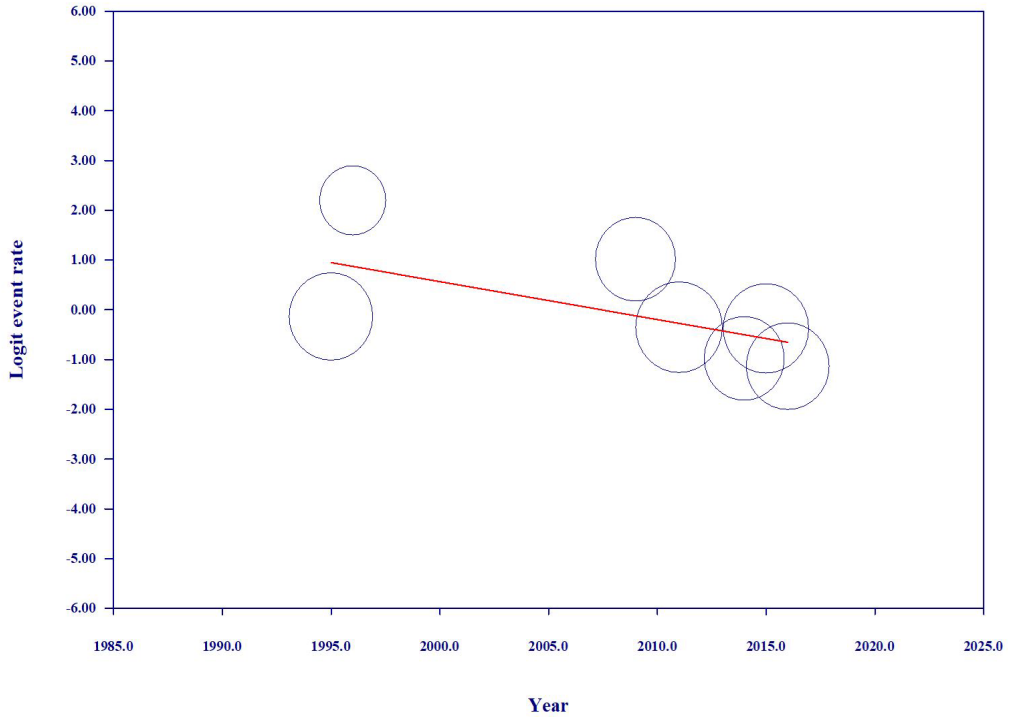

Figure 3. Bubble Plot of the Meta-Regression Analyzing the Association between Publication Year (1995–2016) and Logit-Transformed *HER3* Overexpression Rates in Pancreatic Cancer Patients. Each circle represents a study, with size proportional to its weight in the analysis. The solid line indicates the estimated trend ($\beta = -0.076$, $p = 0.070$), and the shaded area represents the 95% confidence interval. No significant temporal trend was observed, though high heterogeneity persisted ($I^2 = 85.3\%$).

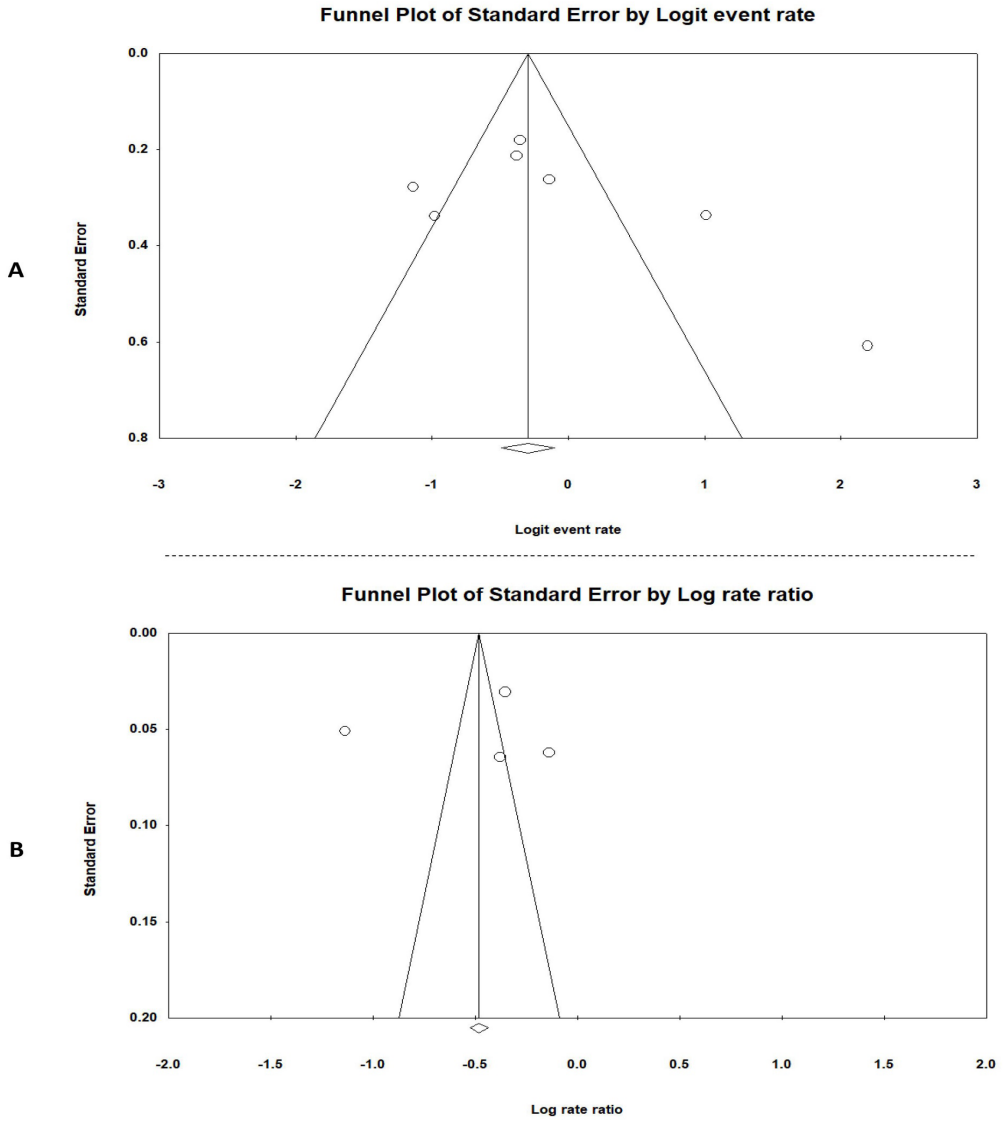

Figure 4. Funnel Plots for Publication Bias Assessment: (A) studies examining the prevalence of *HER3* overexpression in pancreatic cancer patients; (B) studies evaluating the relationship between *HER3* overexpression and overall survival in prostate cancer.

Discussion

In this meta-analysis, we examined the prevalence of *HER3* overexpression in PC and discovered that it occurs in 47.8% of patients with the disease. Our findings also indicate that *HER3* overexpression is consistently linked to poorer overall survival among PC patients. This supports the receptor's role in cancer cell proliferation, survival, and invasion, as it is involved in activating various cellular signaling pathways.

In accordance with the findings from our study on the overexpression of *HER3* in PC, previous research has also shown that *HER3* is overexpressed in various other cancer types, including breast [19], cervical [20], gastric [21], head and neck [22], lung [23], melanoma [24], ovarian [25], and prostate [26] cancers. Although the HER receptor family naturally plays a critical role in cellular signaling, growth, and proliferation, studies have shown that abnormal expression of HER family members can contribute to the pathogenesis of various cancers [27]. *HER3*, a member of the HER family, lacks intrinsic phosphorylation activity. Therefore, it requires heterodimerization with other HER family members, such as *HER2* or *HER1*, to achieve activation and perform its functions [28]. Previous research has shown the co-expression of *HER2* and *HER3* in several cancers, including PC [29]. *HER3* forms heterodimers with *HER2*, leading to enhanced signaling through pathways like the PI3K/AKT and MAPK pathways and promoting cell proliferation and survival [30].

Our analysis results are consistent with previous studies that emphasize the role of *HER3* in the progression of certain cancers. For instance, Li et al. [31] discovered that *HER3* overexpression significantly affects the survival rates of gastric cancer patients. Furthermore, a meta-analysis conducted by Ocana et al. [32] showed that the median percentage of solid tumors exhibiting *HER3* overexpression was 42.2%, which is similar to our finding of 47.8% in PC. This meta-analysis also explored the correlation between *HER3* overexpression and patient

survival, concluding that *HER3* overexpression is linked to poorer overall survival in patients with breast, gastric, and ovarian cancers. *HER3* is involved in the epithelial-to-mesenchymal transition, a process that enables cancer cells to gain migratory and invasive characteristics [10]. In addition, many targeted therapies, particularly those directed at *HER2*, can lead to the upregulation of *HER3* as a compensatory response. This upregulation can result in resistance to treatments such as trastuzumab (Herceptin) in *HER2*-positive cancers. *HER3* has the ability to activate alternative signaling pathways that bypass the inhibited *HER2* receptor, allowing cancer cells to survive and proliferate even in the presence of therapy [33].

We attempted to reduce potential heterogeneity by including only studies that employed the same methodology for *HER3* assessment (IHC method) and that used nearly identical standard cut-off values for identifying *HER3*-positive cases. However, we still observed significant heterogeneity among the included studies. This variation highlights the complexity of *HER3*'s role in PC. Differences in patient demographics (such as age, sex, and ethnicity), the grade and stage of cancer, treatment protocols, and sample sizes across studies can all impact the statistical power and reliability of the findings. Smaller studies may produce results that differ from those of more extensive studies. To further investigate this, we performed a subgroup analysis based on the regions of the studies. This aimed to identify the potential influence of variations in healthcare systems, access to treatment, and institutional protocols on patient outcomes. However, the results of the regional subgroup analysis indicated that the region is not a significant source of heterogeneity in this study. Our meta-regression analysis indicated that the overexpression of *HER3* does not show significant changes over time, though there is a slight decline in its expression. The lack of a clear temporal trend suggests that the prevalence of this biomarker in pancreatic cancer may remain stable over decades. However, the observed high heterogeneity highlights the need to explore additional moderators, such as differences in methodology or population characteristics. Future research should focus on elucidating the mechanisms behind these discrepancies, particularly regarding the abovementioned factors.

This meta-analysis includes data from more than 20 years of research. The selection of studies and data analysis guarantees that the findings are based on high-quality evidence, which minimizes bias and strengthens the validity of the results. By including studies from various geographical locations and diverse demographics in our meta-analysis, we enhance the generalizability of the findings, making them relevant to a broader patient population. Our study has some limitations that need to be addressed. In this meta-analysis, a significant level of heterogeneity was identified, complicating the interpretation of the results. The reliance on a limited amount of published data restricts the ability to conduct more detailed analyses, such as subgroup analyses and meta-regression, which could help identify possible sources of heterogeneity in this study. Addressing these sources of heterogeneity could provide deeper insights into the associations examined. Future studies should focus on exploring these aspects further. The number of studies included in this analysis was limited due to the lack of research in this area. This limitation may reduce the statistical power to identify significant associations and increase the risk of publication bias. Additionally, the small sample size could enhance the influence of individual studies on the overall estimates, potentially affecting the reliability of our conclusions. Therefore, it is crucial to conduct future meta-analyses with larger sample sizes.

In conclusion, the analyses revealed that *HER3* overexpression was observed in nearly half of PC patients and was associated with poor overall survival. These findings suggest that the development of new targeted therapies and the expansion of current treatments aimed at inhibiting *HER3* could potentially improve the survival of PC patients. Due to their lack of systemic side effects commonly associated with traditional cancer treatments and their higher safety profile, such targeted therapies could serve as an alternative to conventional PC therapies. However, further studies and clinical trials are necessary to confirm their efficacy in this context.

Author Contribution Statement

MHM and SF developed the study design. MHM conducted the literature search, while RHM and NA were responsible for study selection and quality control. ZJ and SS were responsible for data extraction. Additionally, MHM and SF performed the statistical analysis. All authors contributed to data interpretation and manuscript preparation and approved the final version of the manuscript.

Acknowledgements

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Ethical Considerations

Ethical approval was not needed for this meta-analysis, which did not directly involve human or animal subjects.

Study Registration Status

This systematic review and meta-analysis was registered in the PROSPERO international prospective register of systematic reviews (registration number: CRD42024584939).

Conflict of interest

The study authors declare no conflicts of interest related to this research.

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