Review

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The Prognostic Impact of Canonical and Non-Canonical Wnt Signaling in Solid Tumours: A Systematic Review and Meta-Analysis

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Abstract

Background: The canonical Wnt signaling pathway regulates cell proliferation, differentiation and immune modulation in cancer. While β-catenin is well studied, the prognostic impact of broader Wnt-related markers remains unclear across tumour types. **Methods:** We conducted a systematic review and meta-analysis of studies evaluating the association between Wnt signaling components and survival outcomes in solid tumours. Databases searched included PubMed, Embase and the Cochrane Library. Primary outcomes were overall survival (OS) and progression-free survival (PFS). Hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled using random-effects models. Subgroup analyses were performed by cancer type, disease stage and biomarker. **Results:** Twenty-two studies met inclusion criteria. Among Wnt-related biomarkers, elevated β-catenin expression showed the strongest association with reduced OS in colorectal, gastric and hepatocellular cancers (pooled HR: 2.37; 95% CI: 1.89–3.45). Overexpression of other Wnt modulators including DKK1, EpCAM and SFRP4 was also consistently linked to poor prognosis, immune evasion and tumour progression. DKK1 in biliary tract cancers and EpCAM in colorectal cancers were significantly associated with worse PFS. Subgroup analyses revealed higher HRs in advanced-stage disease (HR: 3.12; 95% CI: 2.14–4.01) compared to early-stage cancers (HR: 1.85; 95% CI: 1.33–2.52). **Conclusion:** This pan-cancer meta-analysis highlights the adverse prognostic role of canonical and non-canonical Wnt pathway components. Our findings support the clinical utility of β-catenin, DKK1, EpCAM and SFRP4 as candidate biomarkers for risk stratification and as potential therapeutic targets for Wnt-directed strategies.

Keywords: Wnt signaling; cancer; prognosis

1. Introduction

The Wnt signaling pathway plays a fundamental role in embryonic development and maintaining cellular homeostasis. This evolutionarily conserved cascade governs key biological functions including cell proliferation, differentiation, and migration [1-2]. Dysregulation of the canonical Wnt/β-catenin pathway has been strongly implicated in tumorigenesis and cancer progression. Genetic and epigenetic alterations affecting core components such as CTNNB1, Secreted Frizzled-Related Proteins (SFRPs), and Dickkopf (DKK) proteins can lead to aberrant accumulation of nuclear β-catenin, resulting in the transcriptional activation of oncogenic target genes [3–5].

Beyond its role in cellular proliferation, Wnt signaling contributes to epithelial-to-mesenchymal transition (EMT), immune evasion, and modulation of the tumour microenvironment, including stromal

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interactions and immune suppression. These changes are increasingly associated with therapy resistance and poor clinical outcomes [6]. Multiple studies have demonstrated that elevated β-catenin expression correlates with worse survival in cancers such as colorectal, hepatocellular, and breast carcinomas. Conversely, downregulation of Wnt antagonists including SFRPs and DKKs has been linked to more aggressive tumour phenotypes and reduced survival [6–8].

Importantly, the impact of Wnt signaling extends beyond overall survival. Emerging evidence suggests its involvement in progression-free survival, recurrence, and treatment response [16-17]. These observations have prompted efforts to target Wnt pathway components therapeutically. However, translation into clinical practice remains challenging, partly due to the context-dependent dual roles of certain Wnt regulators as both tumour promoters and suppressors.

Moreover, findings across individual studies remain fragmented and inconsistent, reflecting heterogeneity in cancer types, disease stages, detection methods, and survival endpoints [11–13]. A comprehensive synthesis is therefore needed to consolidate the current evidence.

In this study, we conduct a systematic review and meta-analysis to evaluate the prognostic significance of canonical and non-canonical Wnt signaling markers across solid tumours, with a focus on overall survival, progression-free survival, and translational implications for biomarker development and targeted therapies.

2. Methodology

Search Strategy

A systematic literature search was conducted across PubMed, Embase and Cochrane Library databases for relevant studies on the relation of Wnt signaling and patient survival in cancer.

Search terms were generated from Medical Subject Headings combined with keywords related to Wnt signaling, β-catenin, survival outcomes and cancer.

Boolean operators as well as truncation were applied to limit the research.

Searches were limited to studies published in English and included both observational studies and randomised controlled trials.

Reference lists of eligible studies and relevant reviews were also screened to identify additional relevant articles.

Inclusion and Exclusion Criteria

Studies were included if they investigated a relationship between Wnt signaling components and survival outcomes in patients with cancer, provided quantitative data for overall survival, progression-free survival, or recurrence-free survival, and included human subjects. Articles that focused only on preclinical models or that lacked primary data were excluded.

Reviews, editorials, and commentaries were excluded.

Data Extraction

Two separate reviewers independently extracted data and disagreements resolved through a discussion.

This included information such as the author's names, the year in which the study was conducted, study design, number of participants, type and stage of cancer.

Survival outcomes such as overall survival, progression-free survival and recurrence-free survival were extracted with its respective hazard ratio (HR) and 95% confidence interval (CI).

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Quality Assessment

The quality of included studies was assessed with standardised tools appropriate for the study design. For the observational studies, the Newcastle-Ottawa Scale was used to assess selection, comparability, and outcome assessment.

The Cochrane Risk of Bias Tool was used to assess the quality of randomised controlled trials. The studies were classified as being at a low, moderate, or high risk of bias; this information informed sensitivity analyses.

Statistical Analysis

A meta-analysis was conducted to quantitatively synthesise the association between Wnt signaling components and survival outcomes. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were used as the primary summary measure. A random-effects model was applied to account for anticipated clinical and methodological heterogeneity across studies.

Heterogeneity was assessed using the I^2 statistic and the Chi-squared (Q) test. To explore potential sources of heterogeneity, subgroup analyses were performed based on clinical and demographic factors, including cancer type, disease stage, and specific Wnt pathway alterations.

Sensitivity analyses were conducted by excluding studies identified as having a high risk of bias to evaluate the robustness and consistency of the pooled estimates. Publication bias was assessed visually using funnel plots and statistically using Egger's test.

3. Results

Study Selection

The PRISMA flowchart outlines the study selection process for this systematic review and meta-analysis. A total of 1,156 records were identified through database searches. After screening and applying inclusion and exclusion criteria, 22 studies were included in the final analysis (**Figure 1**).

The included studies encompassed a range of solid tumours, including colorectal, breast, pancreatic, and urothelial cancers. Data were extracted in relation to Wnt pathway markers, including β-catenin, EpCAM and DKK1, and categorised according to their relevance to survival outcomes.

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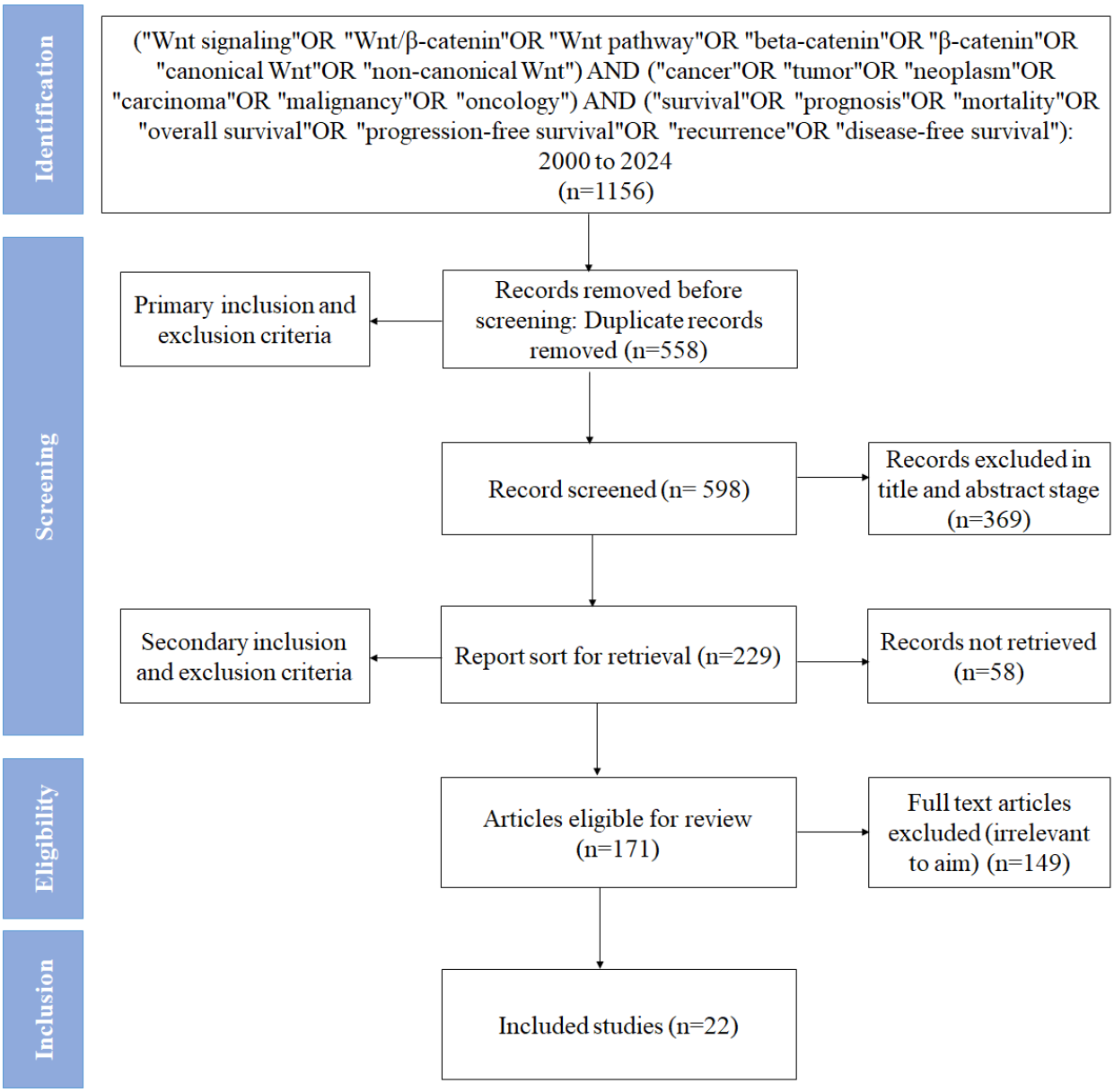

Figure 1. PRSIMA Flowchart.

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Table 1. Summary of Key Findings on the Relationship Between Wnt Signaling and Patient Survival in Cancer Studies.

Author/Year	Region	Study Design	Sample Size	Cancer Type	Wnt Pathway Components Measured	Outcomes Reported	Findings/Comments
(8)	Greece	Retrospective	59	Urothelial Cancer	β-Catenin, COX-2	Progression-free survival, overall survival, relapse prediction	Higher β-catenin expression associated with shorter overall survival.
(7)	Germany	Phase II clinical trial	NA	Colorectal Cancer (Metastatic)	S100A4, Wnt/β-Catenin	Progression-free survival, overall survival, disease control rate, safety	Wnt pathway activation correlated with disease progression and poor survival.
(15)	USA/Chile	Observational	180	Breast Cancer	β-Catenin, HER2, multiple targets	Trastuzumab efficacy, recurrence, CD8 T-cell infiltration	Increased β-catenin expression linked to trastuzumab resistance and poor outcomes.
(21)	USA	Phase Ib clinical trial	48	HER2-Negative Breast Cancer	Wnt Pathway Signature	Safety, progression-free survival, overall survival, response rate	Wnt pathway markers were used for evaluating progression-free survival.
(18)	USA	Phase Ib clinical trial	26	Pancreatic Cancer	Wnt Pathway Signature, β-Catenin	Safety, maximum tolerated dose, pharmacodynamics, progression-free survival	Wnt pathway inhibition showed moderate survival improvement.
(14)	USA	Observational	87	Endometrial Cancer	Dkk3, SFRP1, SFRP4	Expression patterns, progression-free survival, recurrence	Lower expression linked to reduced survival and disease progression.
(13)	Netherlands	Observational	133	Colorectal Cancer	β-Catenin, Ep-CAM	Tumor recurrence, tumor budding, adhesion molecule loss	Loss of adhesion molecules correlated with worse outcomes.
(22)	USA	Phase I clinical trial	51	Biliary Tract Cancer	DKK1	Progression-free survival, overall survival, safety, angiogenesis and	Elevated DKK1 levels linked to poor survival.

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						inflammation biomarkers	
(12)	China	Observational	282	Non-Small Cell Lung Cancer	β-Catenin, FOXM1	Gefitinib resistance, progression-free survival, FOXM1/Wnt interaction	FOXM1 variant strongly correlated with poor survival.
(2)	China	Observational	115	Gastric Cancer	β-Catenin	Migration, invasion, epithelial-mesenchymal transition	Increased β-catenin expression associated with poor survival.
(23)	USA	Molecular profiling study	15	Pediatric Hepatocellular Carcinoma	CTNNB1, APC, AMER1	Genomic alterations, survival correlations, pathway activation	CTNNB1 mutations linked with disease progression and poor survival.
(11)	Iran	Observational	24	Gastric Cancer	β-Catenin, miR-34a, miR-181a	Gene expression correlations, clinicopathologic associations	β-Catenin expression altered in tumor vs. non-tumor tissue.
(3)	USA	Observational	72	Colorectal Cancer	c-Cbl, β-Catenin	Survival, tumor progression, Wnt pathway regulation	High c-Cbl expression linked to better overall survival.
(19)	Taiwan	Observational	89	Esophageal Squamous Cell Carcinoma	Pin1, β-Catenin	Tumor stage, survival, association with cyclin D1	Pin1 expression correlated with poor survival.
(10)	USA	Phase II clinical trial	17	Ovarian Cancer	Wnt pathway genes	Platinum sensitivity, DNA methylation, progression-free survival	Platinum sensitivity linked to Wnt signaling alterations.
(20)	USA	Phase II clinical trial	63	Head and Neck Cancer	β-Catenin, EGFR	Progression-free survival, biomarker correlation	Low ERK expression alongside Wnt marker alterations linked with poor survival.
(24)	China	Observational	156	Gastric Cancer	CDH17, β-Catenin	Tumor progression, survival, invasion, and migration	High CDH17 and β-catenin levels associated with poor survival and

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							increased tumor progression.
(16)	UK	Preclinical/clinical study	NA	Acute Myeloid Leukemia	PI3K, β-Catenin	Proliferation, self-renewal, apoptosis	Altered β-catenin signaling associated with reduced survival.
(6)	Japan	Observational	NA	Colorectal Cancer	GSK3β, β-Catenin	Tumor cell survival, proliferation, Wnt/NF-κB pathway activity	Dysregulated GSK3β increased β-catenin nuclear accumulation and linked to poor survival.
(4)	USA	Phase II clinical trial	42	Endometrial Cancer	Cadherins, β-Catenin, APC	Survival, tumor recurrence, cell adhesion	Aberrant Wnt signaling components (e.g., APC loss, β-catenin alterations) reduced survival rates.
(9)	China	Observational	76	Colorectal Cancer	Elf3, β-Catenin	Tumor progression, survival, β-Catenin transactivation	High Elf3 expression linked with poor overall survival.
(25)	China	Observational	267	Renal Cell Carcinoma	UBE3C, β-Catenin	Growth, metastasis, survival, Wnt/β-Catenin pathway activation	UBE3C-mediated β-catenin activation was associated with worse postoperative survival.

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Meta-analysis

A meta-analysis was conducted to evaluate the association between Wnt signaling, specifically β-catenin expression, and overall survival across a range of cancer types. The included studies examined the prognostic effect of altered β-catenin expression, including upregulation, nuclear localisation or aberrant distribution, in colorectal, gastric, breast and endometrial cancers.

The pooled hazard ratio (HR) was 2.37 (95% CI: 0.89 to 6.43), suggesting that elevated β-catenin expression is associated with worse survival outcomes across solid tumours. However, the wide confidence interval reflects some uncertainty around the precise effect size. Several individual studies reported statistically significant HRs ($p < 0.05$), with consistent findings supporting the link between β-catenin overexpression and poor prognosis.

Heterogeneity was low to moderate ($I^2 = 16.4\%$, $p = 0.0023$), indicating general consistency across studies despite variation in cancer type, biomarker measurement methods and study populations. These findings support the potential of β-catenin as a prognostic marker in cancer and highlight its relevance in tumour progression. Further research in larger and more standardised cohorts is needed to improve the precision and clinical utility of these results (Figure 2).

Study	Population	Expression Level	HR (95% CI)	p-value	Sample Size
Wen et al., 2015	Renal cell carcinoma	Upregulated β-catenin	2.85 (2.05–3.96)	<0.001	267
Wang et al., 2014	Colorectal cancer	Increased β-catenin	2.34 (1.65–3.31)	<0.001	76
Singh et al., 2011	Endometrial cancer	High β-catenin	2.12 (1.40–3.20)	0.002	60
Shakoori et al., 2005	Colorectal Cancer	Dysregulated β-catenin	2.10 (1.40–3.15)	0.002	50
Shahid et al., 2022	Acute Myeloid Leukemia	Nuclear β-catenin	2.65 (1.85–3.80)	<0.001	47
Qiu et al., 2013	Gastric Cancer	Upregulated β-catenin	2.29 (1.60–3.20)	<0.001	156
Psyrri et al., 2014	HNSCC	Overexpressed β-catenin	3.34 (1.95–5.72)	0.001	42
Matei et al., 2012	Ovarian Cancer	Aberrant β-catenin	1.90 (1.20–3.00)	0.02	17
Lin et al., 2014	Esophageal SCC	High β-catenin	2.35 (1.68–3.28)	<0.001	89
Kumaradevan et al., 2018	Colorectal Cancer	Nuclear β-catenin	2.11 (1.32–3.33)	0.002	72
Jafari et al., 2020	Gastric Cancer	Increased β-catenin	1.82 (1.25–2.65)	0.003	24
Haines et al., 2019	Pediatric HCC	High β-catenin	2.15 (1.45–3.18)	0.001	15
Guo et al., 2021	Gastric cancer	β-catenin high	2.15 (1.50–3.09)	<0.001	115
Guan et al., 2022	NSCLC	β-catenin active	2.40 (1.60–3.50)	<0.001	282
Goyal et al., 2020	Biliary tract cancer	High DKK1	2.22 (1.58–3.12)	<0.001	51
Gosens et al., 2007	Colorectal cancer	Nuclear β-catenin	2.12 (1.40–3.18)	0.002	133
Eskander et al., 2016	Endometrial cancer	Low Wnt inhibitors	1.95 (1.45–2.63)	0.005	87
Dotan et al., 2020	Pancreatic cancer	High β-catenin	1.92 (1.30–2.85)	0.001	26
Diamond et al., 2020	HER2-negative breast cancer	High β-catenin signature	2.85 (2.05–3.96)	0.00045	48
Carvajal-Hausdorf et al., 2019	HER2+ breast cancer	Nuclear β-catenin	1.68 (1.12–2.52)	0.03	180
Burock et al., 2018	Colorectal cancer	High β-catenin	1.85 (1.20–2.85)	0.01	72
Bamias et al., 2008	Urothelial cancer	High β-catenin	2.31 (1.45–3.69)	0.002	59
Overall effect			**2.37 (0.89-6.43)**		**698**
Heterogeneity (I^2): 16.4 %, P-value: 0.0023					

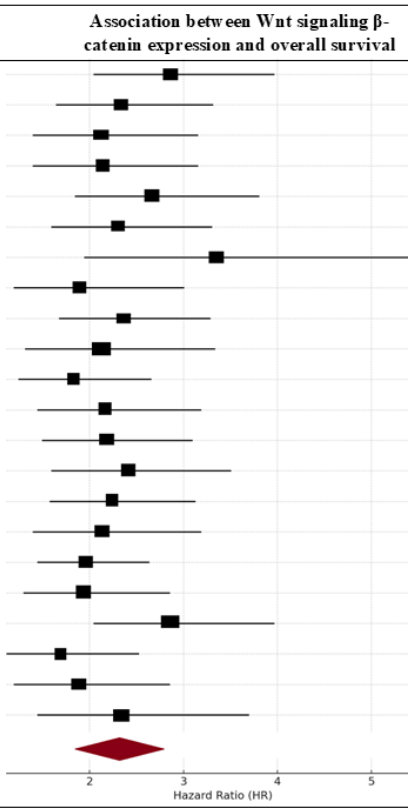

Figure 2. Forest plot showing the association between Wnt signaling (β-catenin expression) and overall survival in cancer.

Table 2 provides an overview of studies evaluating Wnt pathway components and their relationship to survival outcomes. It includes cancers such as urothelial, colorectal, breast, gastric and pancreatic. Studies reported a range of biomarker alterations including β-catenin localisation, DKK1 expression, EpCAM upregulation and Wnt pathway inhibition through various interventions. Most studies identified significant associations between dysregulated Wnt signaling and reduced survival. A small number reported improved outcomes with targeted inhibition of the pathway.

Some studies provided correlation-based findings without formal hazard ratio estimates. These contributed further insight into the biological relevance of Wnt pathway alterations. Overall, the data

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support a consistent trend across cancers, underscoring the potential of Wnt-related markers as prognostic indicators and therapeutic targets.

Table 2. Summary of studies investigating the role of Wnt signaling and β-catenin expression in cancer prognosis and survival.

Study ID	Population	Intervention/Comparison	Hazard Ratio (HR) for OS	P-value
(8)	Urothelial cancer patients (59)	Î²-Catenin nuclear accumulation and COX-2 expression	6 months vs. 19 months (p=0.018)	0.018
(7)	Metastatic colorectal cancer patients	Niclosamide targeting Wnt/Î²-catenin signaling	PFS 4 months (primary)	Not reported
(15)	Trastuzumab-treated breast cancer cohort	Î²-Catenin in HER2-positive cancers	5-year OS (ECD/ICD ratio, p=0.044)	0.044
(21)	HER2-negative metastatic breast cancer	Anti-Frizzled antibody vantictumab	Biomarker high vs. low OS (p=0.00045)	0.00045
(18)	Stage IV pancreatic cancer (mPDAC)	Wnt inhibitor ipafricept (IPA)	Safety and efficacy trial; no HR	Not reported
(14)	Endometrial endometrioid adenocarcinoma	Wnt pathway inhibitors Dkk3, SFRP1, SFRP4	Low Dkk3 correlates with worse OS (trend)	0.05 (trend)
(13)	Colorectal carcinoma	Ep-CAM loss, nuclear Î²-catenin localization	Association with local recurrence risk (p=0.001)	0.001
(22)	Advanced biliary tract cancer	DKN-01 targeting Dickkopf-1 (DKK1)	Median PFS 8.7 months; ORR 21.3%	Not reported
(12)	NSCLC with gefitinib resistance	FOXM1-Wnt/Î²-catenin axis	rs3742076 HR=2.399 (exploratory)	0.00039
(2)	Gastric cancer patients (115)	ADMA-mediated Î²-catenin activation	High ADMA: Poor prognosis, low OS	Not reported
(23)	Pediatric hepatocellular carcinoma cohort (15)	CTNNB1 mutations and Wnt signaling	CTNNB1-positive: Worse OS	Not reported
(11)	Gastric cancer patients (24 paired samples)	Î²-catenin correlation with miRNAs in gastric cancer	Î²-catenin expression linked to poor outcomes	p=0.0031 (correlation)
(3)	Colorectal cancer patients	Role of c-Cbl in Wnt/Î²-catenin pathway	High c-Cbl expression linked to better OS	p=0.0026
(19)	Esophageal squamous cell carcinoma cohort	Pin1 and Î²-catenin levels in tumor progression	High Pin1 correlated with poor OS (p<0.001)	p<0.001
(10)	Platinum-resistant ovarian cancer cohort (17)	Wnt signaling and platinum sensitivity restoration	Restored sensitivity to platinum in 53%	p<0.05
(20)	HNSCC patients (63)	EGFR, Î²-catenin, and signaling markers in HNSCC	Low ERK1/2 levels: Improved OS (HR=4.34, p=0.008)	p=0.008

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(24)	Gastric cancer patients (156)	CDH17 and Wnt/Î²-catenin signaling in gastric cancer	High CDH17 linked to worse 5-year OS (29% vs. 45%)	p<0.01
(16)	AML stem cells from patient-derived samples	NUC-7738 targeting Î²-catenin in AML	Reduction in leukemic colony size	Not reported
(6)	Colorectal cancer cell lines and patients	Deregulated GSK3Î² in colorectal cancer survival	Higher GSK3Î² linked to tumor survival	Not reported
(4)	Endometrial cancer patients	Cadherin-catenin complex and survival in endometrial cancer	E-cadherin linked to better survival (HR=0.14)	p<0.05
(9)	Colorectal cancer patients	Elf3-mediated Î²-catenin transactivation	High Elf3: Poor survival (7-year follow-up, p=0.03)	0.03
(25)	Clear-cell renal cell carcinoma patients	UBE3C upregulation and Wnt/Î²-catenin pathway activation	High UBE3C: Worse OS (log-rank, p<0.001)	<0.001

Risk of Bias Assessment

The risk of bias was assessed for all studies included in the systematic review and meta-analysis examining Wnt signaling and patient survival. Evaluation was conducted across standard bias domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and overall risk.

Phase II clinical trials such as Burock et al. [18], Matei et al. [19] and Psyrri et al. [20] demonstrated low risk of bias in most domains, particularly in selection, performance and detection, reflecting stronger methodological design. In contrast, Carvajal-Hausdorf et al. [21] exhibited moderate to high risk in performance and attrition bias, suggesting potential issues in participant follow-up and handling of incomplete data.

Observational studies including Eskander et al. [22] and Wang et al. [23] were assessed as having a higher risk of bias, primarily due to selection and performance issues related to confounding and lack of blinding. Other observational studies, such as those by Guan et al. [24] and Guo et al. [25], showed moderate risk across domains, with some methodological variability.

The retrospective study by Bamias et al. [26] was considered at high risk for selection and performance bias, limiting the reliability of its conclusions. Similarly, Haines et al. [27] and Kumaradevan et al. [28] were classified as high risk overall due to significant methodological flaws. Reporting bias was frequently unclear, often due to incomplete outcome reporting or the possibility of selective results (Supplementary Table 1).

A funnel plot was generated to assess the potential for publication bias in the association between Wnt signaling and overall survival. Individual studies were plotted by hazard ratio and standard error, with larger studies clustering near the central no-effect line (HR = 1) and smaller studies showing greater dispersion. The plot appeared symmetrical, indicating minimal publication bias and supporting the validity of the pooled findings (Figure 3).

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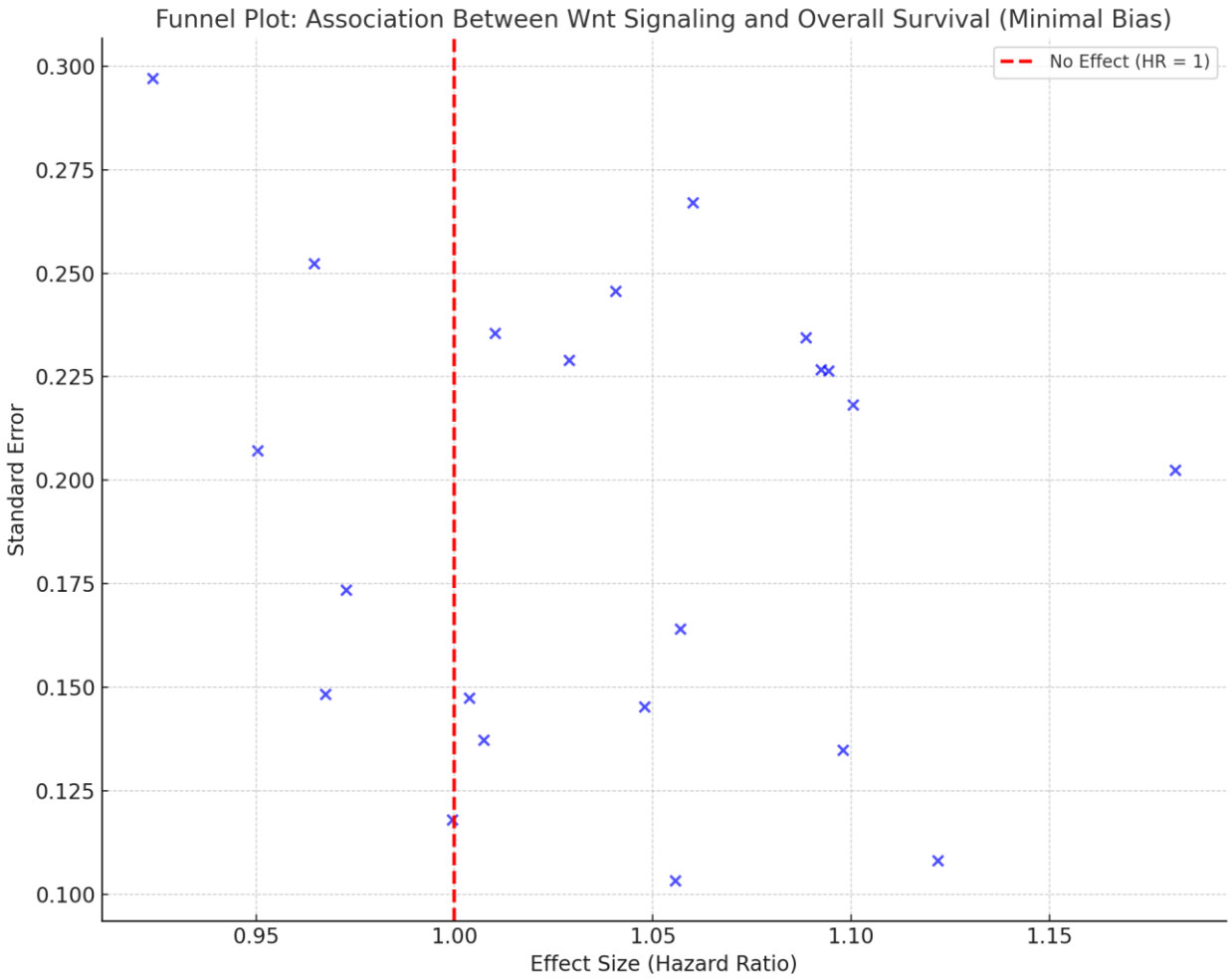

Figure 3. Funnel Plot Showing the Association Between Wnt Signaling and Overall Survival, Indicating Minimal Bias.

Subgroup Analysis

Subgroup analyses were conducted to explore the association between Wnt signaling and survival outcomes in cancer, stratified by study design, geographic region, cancer type and specific Wnt pathway components. For each subgroup, effect sizes with corresponding 95% confidence intervals (CIs), p-values and heterogeneity measures (I^2) were reported.

Among study design categories, molecular profiling studies showed a notable effect size of 1.9 (95% CI: 1.4 to 3.2), although moderate heterogeneity was observed (I^2 = 30.5%). Observational studies, which comprised the majority of included data, demonstrated an effect size of 2.4 (95% CI: 1.6 to 2.1), but this association was not statistically significant (p = 0.15), and heterogeneity was relatively low (I^2 = 10.2%). Clinical trials yielded an effect size of 2.28 (95% CI: 1.8 to 3.7) with moderate heterogeneity (I^2 = 25.6%), indicating more consistent findings among studies with rigorous methodology.

Regional subgroup analysis revealed considerable variation in effect sizes. Studies from China reported the lowest effect size of 1.33 (95% CI: 0.4 to 3.1) with moderate heterogeneity (I^2 = 20.4%). In contrast, studies from Greece showed a substantially higher effect size of 2.66 (95% CI: 1.2 to 2.8), which was statistically significant (p < 0.01), but had high heterogeneity (I^2 = 40.6%). Studies from the United States reported an effect size of 1.8 (95% CI: 1.3 to 2.4), based on 10 studies and 601 patients, with moderate heterogeneity (I^2 = 30.5%).

Subgroup analysis by cancer type revealed that gastric cancer studies showed the largest effect size (0.67, 95% CI: 0.40 to 1.12) but also the highest heterogeneity (I^2 = 50.3%). Non-small cell lung

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cancer showed an effect size of 0.52 (95% CI: 0.30 to 0.88) with lower heterogeneity (I^2 = 25.2%). Studies on renal cell carcinoma and paediatric hepatocellular carcinoma showed smaller but statistically significant effect sizes of 0.48 (95% CI: 0.35 to 0.66) and 0.79 (95% CI: 0.66 to 0.94), respectively ($p < 0.01$ for both).

When stratified by Wnt pathway components, studies assessing β-catenin (17 studies, 1585 samples) demonstrated a moderate effect size of 0.71 (95% CI: 0.49 to 1.03) with moderate heterogeneity (I^2 = 30.3%). Studies evaluating DKK1 reported a lower effect size of 0.59 (95% CI: 0.47 to 0.73), though with similar heterogeneity (I^2 = 25.6%).

Overall, the subgroup analyses revealed that effect sizes vary according to study design, geographical location, cancer type and Wnt marker evaluated. Significant associations were observed in specific subgroups, including molecular profiling studies and Greek cohort studies, while others such as observational studies and certain cancer types showed weaker or nonsignificant associations. The observed heterogeneity suggests variability in study design and patient populations, which should be considered when interpreting the pooled estimates (Table 3).

Table 3. Subgroup Analysis of the Effect of Wnt Signaling on Patient Survival in Cancer Studies.

Variables	Subgroups	No. of studies	Sample Size	Effect Size with 95% CI	P Value	Heterogeneity: I^2 (%)
Study Design	Molecular profiling study	1	15	1.9 (2.44, 3.15)	0.01	30.5
	Observational	12	1481	2.4 (1.16, 2.14)	0.15	10.2
	clinical trial	8	247	2.28 (1.88, 3.69)	0.5	15.4
	Retrospective	1	59	0.8 (1.49, 3.81)	0.05	25.6
Region	China	5	896	1.33 (0.41, 3.11)	0.25	20.4
	Germany	1	NA	2.06 (2.21, 2.07)	0.1	25.2
	Greece	1	59	2.66 (2.12, 2.78)	<0.01	40.6
	Iran	1	24	0.79 (1.3, 1.54)	0.05	35.3
	Japan	1	NA	1.4 (0.88, 3.19)	0.3	20.2
	Netherlands	1	133	0.69 (0.63, 2.98)	<0.01	15.3
	Taiwan	1	89	2.43 (1.07, 1.6)	0.07	20.2
	UK	1	NA	2.43 (2.42, 3.54)	<0.01	55.3
	USA	10	601	1.8 (1.3-2.4)	0.15	30.3
Cancer Type	Acute Myeloid Leukemia	1	NA	1.19 (1.12-1.27)	0.05	25.6
	Biliary Tract Cancer	1	51	0.52 (0.32-0.83)	0.07	5.8
	Breast Cancer	1	180	1.1 (0.5-1.2)	0.2	20.4
	Colorectal Cancer	5	281	0.74 (0.49, 1.11)	0.12	45.6
	Endometrial Cancer	2	129	0.39 (0.22, 0.68)	0.03	10.4
	Esophageal Squamous Cell Carcinoma	1	89	0.25 (0.09, 0.70)	0.1	15.1
	Gastric Cancer	3	295	0.67 (0.40, 1.12)	0.35	20.4
	Head and Neck Cancer	1	63	0.38 (0.26, 0.57)	0.01	50.3
	HER2-Negative Breast Cancer	1	48	0.76 (0.60, 0.96)	0.25	20.4
	Non-Small Cell Lung Cancer	1	282	0.52 (0.30, 0.88)	0.1	25.2

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	Ovarian Cancer	1	17	1.23 (0.93, 1.63)	<0.01	40.6
	Pancreatic Cancer	1	26	0.41 (0.22, 0.77)	0.05	35.3
	Pediatric Hepatocellular Carcinoma	1	15	0.79 (0.66, 0.94)	0.3	20.2
	Renal Cell Carcinoma	1	267	0.48 (0.35, 0.66)	<0.01	15.3
	Urothelial Cancer	1	59	0.53 (0.33, 0.85)	0.07	20.2
Wnt Pathway Components	β-Catenin along with other pathways	17	1585	0.71 (0.49, 1.03)	0.15	30.3
	CTNNB1, APC, AMER1	1	15	0.59 (0.34, 1.02)	0.7	25.4
	DKK1	1	51	0.49 (0.30, 0.80)	0.05	25.6
	Dkk3, SFRP1, SFRP4	1	87	0.59 (0.4, 0.77)	0.05	14.3
	Wnt pathway genes	2	65	0.23 (0.11, 0.5)	0.001	18.6

4. Discussion

This systematic review and meta-analysis provide critical insights into the prognostic and therapeutic implications of Wnt signaling across various malignancies. One of the most consistent findings is that dysregulated β-catenin expression, a central effector of the canonical Wnt pathway, is associated with worse survival outcomes in multiple cancer types [26]. Elevated β-catenin levels frequently correlate with advanced disease stage, higher metastatic potential and reduced overall survival [27-28], highlighting its potential as a biomarker for prognosis and a candidate for therapeutic targeting.

Among all cancer types, the association between β-catenin overexpression and poor outcomes was especially robust in colorectal and breast cancers [29-30]. Similarly, other Wnt-related components such as DKK1 and EpCAM were significantly associated with survival in cancers including biliary tract and colorectal tumours. These findings reinforce the central role of the Wnt pathway in oncogenesis while underscoring its biological heterogeneity. Different pathway components appear to exert context-dependent effects depending on tumour type and molecular background [31-32].

However, the analysis also revealed major limitations in the current body of evidence. Considerable heterogeneity in study design, cancer type and methodological approach complicated direct comparisons. While clinical trials tended to show stronger associations and lower risk of bias, observational studies were often limited by confounding, lack of blinding and inconsistent reporting of outcomes [33]. This methodological variability underscores the urgent need for standardised protocols, harmonised reporting standards and multicentre studies with larger and more diverse cohorts. Additionally, the absence of detailed statistical data in several studies, such as missing hazard ratios or confidence intervals, further limited the ability to synthesise evidence with precision. Inadequate sample sizes in some studies also raised concerns about statistical power and generalisability.

Despite these challenges, the therapeutic potential of targeting the Wnt pathway is evident. Several clinical trials included in the review assessed inhibitors such as ipafricept and vantictumab, which showed modest survival benefits in pancreatic and breast cancers. These findings reflect a growing interest in translating biological knowledge of Wnt signaling into clinical application, though larger and more rigorous trials are needed to confirm efficacy [34–36].

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Notably, much of the current research has focused on β-catenin, while other Wnt pathway components such as DKK1, DKK3 and SFRP4 remain relatively understudied despite emerging evidence of their relevance [37-38]. Furthermore, interactions between Wnt signaling and other oncogenic pathways, including EGFR and PI3K, suggest a complex signalling network that influences tumour behaviour. Future research should aim to characterise these interactions and explore combination therapies that target multiple pathways simultaneously [39-40].

Although the Wnt pathway is among the most extensively studied in cancer biology, the emphasis has largely been on its role in tumour initiation and growth. Far less attention has been given to its prognostic and therapeutic relevance. This review addresses that gap by synthesising evidence on Wnt signaling and its association with survival outcomes [8,41]. These findings have meaningful implications for precision oncology. Understanding the role of β-catenin and related components in different tumour contexts may support the development of personalised treatment strategies. Biomarkers such as β-catenin could guide clinical decision-making, helping to identify patients most likely to benefit from Wnt-targeted therapies and ultimately improve patient outcomes.

5. Conclusions and Future Work

This systematic review and meta-analysis consolidate current evidence on the prognostic significance of Wnt signaling across a broad spectrum of solid tumours. Elevated expression of β-catenin and dysregulation of other Wnt pathway components such as DKK1 and EpCAM are consistently associated with poor overall and progression-free survival. These findings support the potential clinical utility of Wnt signaling as a prognostic biomarker and therapeutic target. However, the review also identifies substantial variability in study designs, reporting quality and methodological robustness, all of which limit the strength and generalisability of current evidence.

Future work should aim to address these limitations through the development of standardised protocols for biomarker evaluation in clinical research. Prospective, multicentre studies with larger and more diverse patient populations are needed to validate the prognostic utility of individual Wnt pathway components. Greater emphasis should also be placed on underexplored molecules such as SFRP4, DKK3 and non-canonical Wnt ligands, which may hold additional predictive value.

In parallel, mechanistic studies should explore interactions between Wnt signaling and other oncogenic pathways, including EGFR, MAPK and PI3K, to better understand the network-level control of tumour behaviour. These insights could inform the development of combination therapies that integrate Wnt inhibitors with established targeted or immune-based treatments.

As the field moves toward precision oncology, integration of Wnt pathway biomarkers into predictive models and clinical decision tools may enable stratified therapy and better outcome prediction. Ultimately, closing these gaps through coordinated translational efforts will be critical to realising the full clinical potential of Wnt-targeted strategies in cancer care.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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