Site-specific PKM2 phosphorylation in cancer: a systematic review of its role in metabolic plasticity and precision therapy

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Abstract

Pyruvate kinase M2 (PKM2), a central enzyme in glycolysis, plays a key role in tumor metabolism and growth. Its activity is tightly regulated through site-specific phosphorylation at residues such as Tyr105, Ser37, and Thr454. These modifications influence metabolic plasticity, tumor progression, and therapy resistance. This systematic review consolidates current evidence on PKM2 phosphorylation in cancer, its metabolic and signaling implications, and potential as a biomarker and therapeutic target in precision oncology. A systematic search of PubMed, Scopus, and Embase was conducted in accordance with the PRISMA 2020 guidelines. Studies investigating site-specific PKM2 phosphorylation and its functional or clinical relevance in cancer were included. Data extraction focused on phosphorylation sites, signaling pathways, metabolic and tumor-related effects, and therapeutic applications. Study quality and bias risk were assessed using standardized tools. Fifty-eight studies met the inclusion criteria. Tyr105, Ser37, and Thr454 were the most frequently reported phosphorylation sites, each significantly influencing PKM2 activity, localization, and oncogenic interactions. Their modification consistently enhanced glycolysis, plasticity, tumor growth, and resistance to therapy across cancers. Site-specific PKM2 phosphorylation regulates metabolism and tumor behavior, underscoring its value as a biomarker and therapeutic target for precision-based cancer management.

Key words: pyruvate kinase M2 (PKM2), site-specific phosphorylation, cancer metabolism, tumor growth and therapy resistance, metabolic plasticity, precision oncology.

Introduction

Cancer cells undergo radical metabolic reprogramming to fuel fast growth, withstand hypoxia, respond to shifts in nutrients, and evade therapeutic pressure. Typical of the reprogramming is upregulated aerobic glycolysis, or the Warburg effect, so that cancer cells may meet their biosynthetic as well as energy needs [1, 2]. Pyruvate kinase M2 (PKM2), the glycolysis rate-controlling enzyme, is the linchpin. Characteristic of PKM2, compared to its isoform PKM1, is the ability to exist in multiple conformations, so that it must switch between energy output as well as anabolic metabolism [3]. Furthermore, PKM2 is localized to the nucleus, where regulation of gene expression as well as oncogenic signal sup-

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port takes place [4]. Recent findings postulate that post-translational modifications (PTMs), most notably site-specific phosphorylation, substantially influence PKM2's enzymatic activity, cellular localization, and non-metabolic activities [4, 5]. Phosphorylation on specific sites including Tyr105, Ser37, and Thr454 has been postulated to foster metabolic plasticity, tumor growth, chemotherapy resistance, and immune evasion [6]. Because of these pleiotropic activities, phosphorylated PKM2 has emerged as both a biomarker and a therapeutic target in precision oncology.

Despite a growing body of literature, there is currently no comprehensive synthesis of evidence focusing specifically on site-specific PKM2 phosphorylation and its implications in cancer metabolism and targeted therapy. To address this gap, the present systematic review aims to summarize current evidence on site-specific phosphorylation of PKM2 across different cancer types; evaluate the functional impact of specific phosphorylation events on PKM2-mediated metabolic reprogramming and oncogenic signaling; assess the clinical relevance of phosphorylated PKM2 as a diagnostic, prognostic, or predictive biomarker; and explore its potential as a therapeutic target within the framework of precision medicine. By consolidating these findings, this review seeks to support translational efforts toward the development of targeted metabolic interventions and personalized therapeutic strategies in oncology.

Methods

Protocol and registration

This systematic review was conducted in accordance with PRISMA 2020 guidelines. A comprehensive literature search was conducted using major electronic databases: PubMed, Scopus, Embase, and Web of Science. The search encompassed all relevant studies published up to August 31, 2025. The protocol was developed prior to data extraction. PROSPERO registration, although attempted, was not accepted as the data extraction had already commenced at the time of submission. No changes were made to the predefined methodology after data extraction began (Figure 1).

Selection criteria

Studies were considered eligible for inclusion if they met the following criteria: original research articles, including *in vitro*, *in vivo*, and clinical studies, that specifically investigated site-specific phosphorylation of PKM2 in the context of cancer. Eligible studies were required to report on the functional, mechanistic, metabolic, or therapeutic relevance of phosphorylated PKM2. Only peer-reviewed, full-text articles published in English were included.

Studies were excluded if they focused solely on other post-translational modifications of PKM2 without providing relevant phosphorylation data. Additionally, reviews, meta-analyses, editorials, commentaries, conference abstracts, and case reports were excluded. Studies that did not involve cancer or did not establish a clear link between PKM2 phosphorylation and cancer-related outcomes were also excluded. Articles not available in full text or published in languages other than English were not considered for review.

Search strategy

The search strategy combined Medical Subject Headings (MeSH) with free-text terms that related to PKM2, phosphorylation, cancer, and metabolism. Keywords and Boolean operators used were: ("PKM2" OR "pyruvate kinase M2") AND ("phosphorylation" OR "site-specific phosphorylation") AND ("cancer" OR "tumor" OR "neoplasm" OR "malignancy") AND ("metabolism" OR "glycolysis" OR "Warburg effect" OR "metabolic plasticity"). To ensure the relevance of the results, search filters were applied to include only full-text freely accessible, peer-reviewed original research articles published in English. The search strategy was then narrowed as necessary, on a specific database basis. In addition, reference listings of all the retrieved studies were scrutinized exhaustively by hand to identify any other shortlisted articles that may have been missed during the database search. All the results were subsequently imported into reference management programs, awaiting the exclusion of the duplicates before screening. In PubMed, the following combination of MeSH (Medical Subject Headings) and free-text terms was used to conduct, on a comprehensive basis, a survey of the pertinent literature: ("Pyruvate Kinase" [MeSH] or "PKM2" or "pyruvate kinase M2") and ("Phosphorylation" [MeSH] or "site-specific phosphorylation" or "post-translational phosphorylation") and ("Neoplasms" [MeSH] or "cancer" or "tumor" or "malignancy" or "carcinoma") and ("Neoplastic Cell Metabolism" [MeSH] or "metabolism" or "glycolysis" or "Warburg effect" or "metabolic reprogramming" or "metabolic plasticity").

Selection process

All retrieved articles were imported into reference management software to remove duplicates automatically. The selection process was carried out in two stages. In the first stage, the author screened the titles and abstracts of all retrieved records to identify potentially eligible studies. In the second stage, full-text articles of shortlisted studies

were assessed for inclusion based on predefined eligibility criteria. The screening decisions were independently reviewed by two researchers after completion of the primary screening phase to ensure accuracy and consistency with the predefined eligibility criteria. The reviewers verified inclusion and exclusion decisions. Any discrepancies were resolved through discussion and consensus. The selection process was documented in accordance with the PRISMA 2020 guidelines, and a flow diagram was generated to illustrate study identification, screening, eligibility, and inclusion [7].

Data collection process

Data extraction was performed independently by MMA using a standardized data extraction form developed and explicitly piloted for this review, and following completion of the initial data extraction, independently reviewed by two researchers to verify accuracy, completeness, and consistency with the original studies. The form was designed to capture relevant information on study characteristics, methodological details, and key findings. Specifically, the following data were extracted: study details, cancer type, phosphorylation site, experimental model, functional outcomes, mechanistic insights, and clinical relevance.

Risk of bias analysis

For preclinical studies, the SYRCLE Risk of Bias tool was used, which evaluates bias across domains such as random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases specific to animal research [8] (Figure 2) [9–38]. For clinical studies, the Cochrane Risk of Bias 2 (RoB 2) tool was used. Each study was graded as having low, moderate, or high risk of bias. Any uncertainties in the assessments were resolved through discussion with the methodological reviewers [39]. The results of the risk of bias assessments were presented in tabular form and considered in the interpretation of the findings (Figure 3) [6, 40–46].

Effect measures

Given the heterogeneous nature of the included studies, spanning *in vitro* experiments, *in vivo* models, and clinical data, effect measures were extracted and reported in accordance with the type of outcome presented. For *in vitro* and *in vivo* studies, effect measures included relative changes in metabolic activity (e.g., glycolysis rate, lactate production), gene/protein expression levels (e.g., fold change in PKM2 or downstream targets), and cellular outcomes such as proliferation, apoptosis, migration, and invasion. These were typically reported as mean ± standard deviation (SD) or standard error (SE), with corresponding *p*-values or confidence intervals (CIs) where available. For clinical studies, quantitative outcomes such as hazard ratios (HRs), odds ratios (ORs), relative risks (RRs), and their corresponding 95% confidence intervals were extracted to assess associations between site-specific PKM2 phosphorylation and clinical endpoints (e.g., overall survival, disease-free sur-

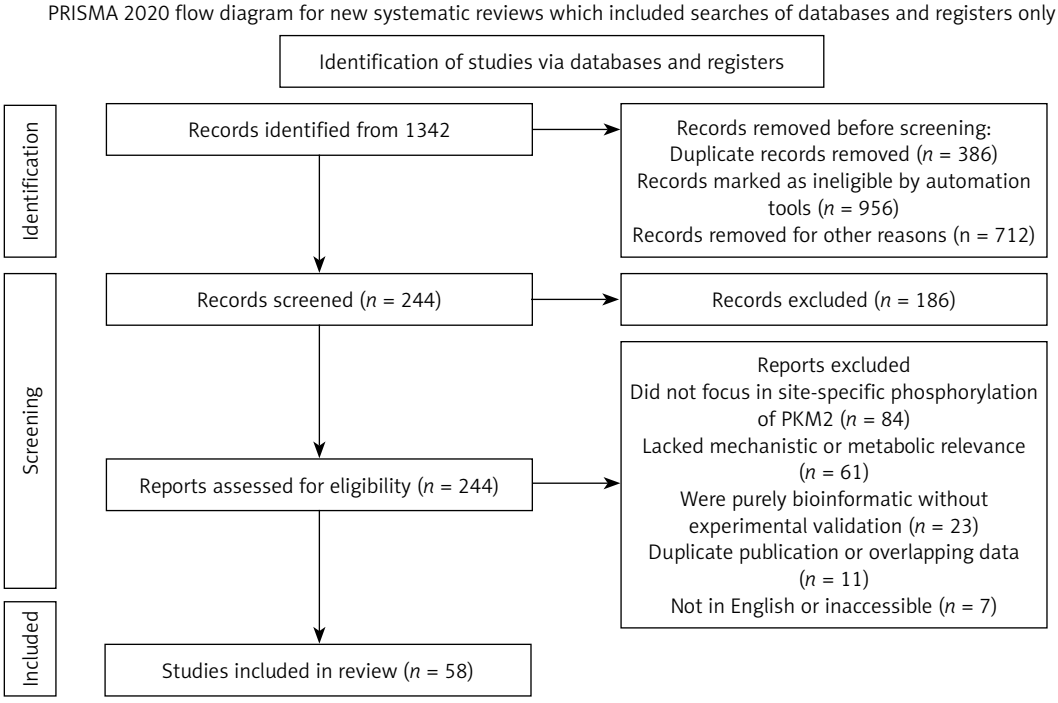

Figure 1. PRISMA flow diagram

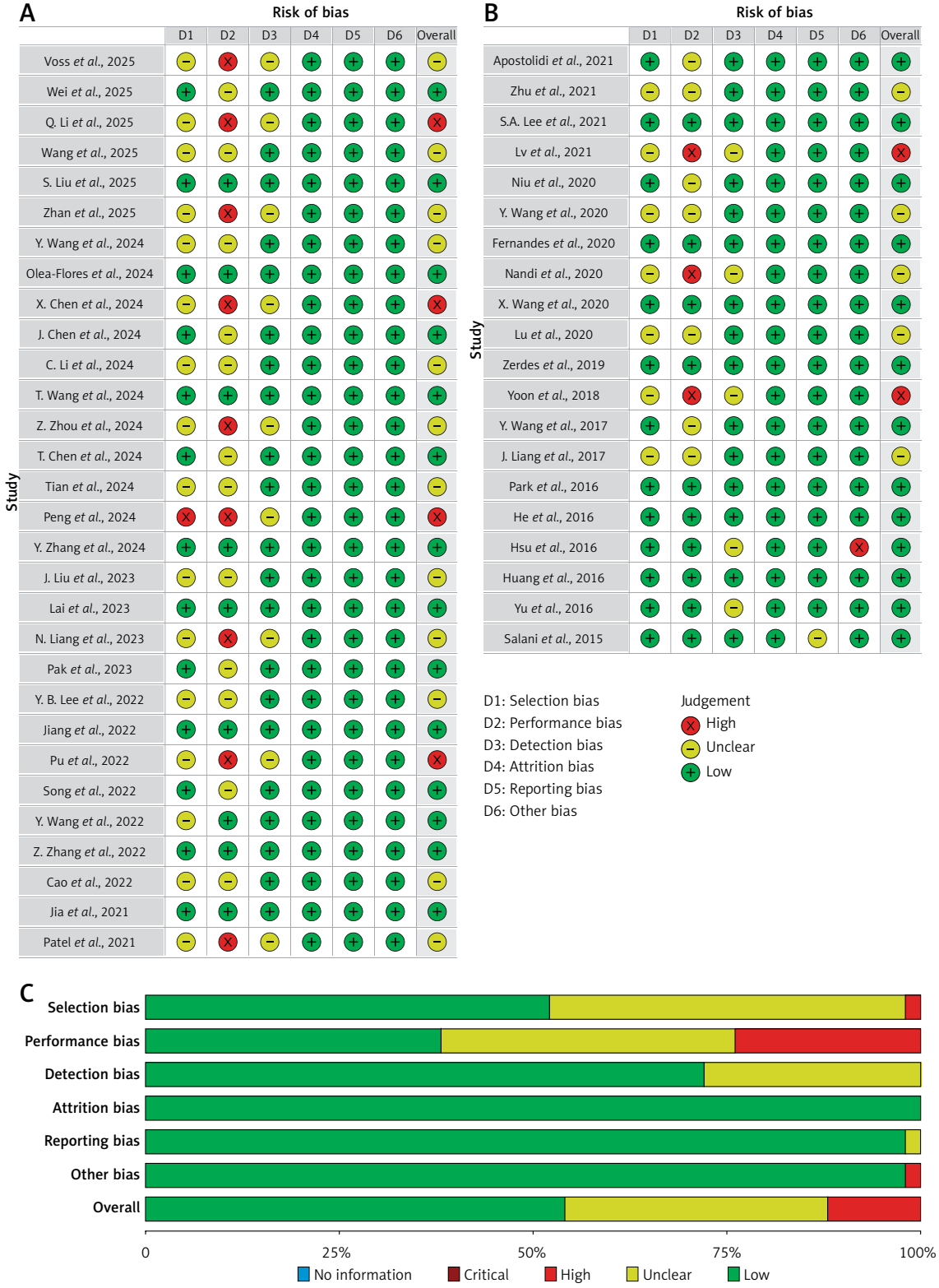

Figure 2. SYRCLE Risk of Bias for preclinical studies. **A** – Studies 1-30. **B** – Studies 31-50. **C** – Summary plot

vival, therapeutic response). When multiple studies reported similar quantitative data for a particular phosphorylation site and outcome, the data were qualitatively synthesized and, where appropriate, the direction and magnitude of effect were summarized narratively.

Results

Study selection and characteristics

The literature search identified 1,342 records, of which 58 studies fulfilled the inclusion criteria after screening and eligibility assessment. The

majority were preclinical (44 studies), complemented by 8 clinical/translational investigations and 6 multi-omics/in silico analyses. Most studies focused on lung, colorectal, breast, glioblastoma, and hepatocellular carcinoma. The included works were published between 2005 and 2025. Key study features are summarized in Supplementary Table SI [6, 11, 40, 45–53], and the PRISMA flow chart is shown in Figure 1.

Phosphorylation sites and functional roles

The most frequently studied residue was Tyr105 (in 31 studies), where phosphorylation disrupted PKM2 tetramerization, favoring glycolytic reprogramming and biomass accumulation. Elevated Tyr105-PKM2 was consistently associated with aggressive tumor behavior and poor survival in NSCLC, glioblastoma, and colorectal cancer. Ser37 phosphorylation (14 studies), mainly mediated by ERK, facilitated nuclear translocation of PKM2 and activation of oncogenic transcriptional programs such as c-Myc and cyclin D1, contributing to proliferation, epithelial–mesenchymal transition, and chemoresistance.

Thr454 (6 studies) was linked to CDK1-driven cell cycle regulation and stem-like properties in pancreatic and prostate cancer models. Emerging residues such as Ser202/204 were implicated in mitochondrial localization, DNA repair, and redox balance, though the findings remain preliminary. A few studies also demonstrated multisite phosphorylation patterns (e.g., Tyr105 + Ser37) that synergistically promoted metabolic plasticity, immune evasion, and resistance to EGFR inhibitors.

Experimental and clinical evidence

Preclinical data consistently showed that phosphorylated PKM2 enhanced aerobic glycolysis, lactate output, anabolic biosynthesis, and redox regulation. In its nuclear form, phospho-PKM2 interacted with β-catenin, HIF-1α, and STAT3, amplifying transcriptional programs supporting tumor growth and immune escape.

In clinical settings, high expression of Tyr105- and Ser37-phosphorylated PKM2 was associated with unfavorable prognosis, higher tumor grade, and resistance to chemotherapy (oxaliplatin, anthracyclines). However, all clinical studies were retrospective, with small sample sizes, and no randomized controlled trials were identified.

Risk of bias and quality of evidence

Most preclinical studies lacked randomization, blinding, and adequate sample size justification, while clinical studies showed variability in antibody validation, endpoint reporting, and handling of confounders. Overall, both preclinical and clinical evidence were graded as moderate-to-high risk of bias. Using the GRADE framework, the certainty of evidence was rated moderate for metabolic effects, low for prognostic associations, and very low for predictive or clinical utility in therapy selection. The RoB 2 assessment revealed a moderate risk of bias across most retrospective clinical studies. The primary concerns were confounding factors, incomplete adjustment for clinicopathological variables, and variability in antibody validation for phosphorylated PKM2 detection. No randomized interventional studies were identified, limiting causal inference.

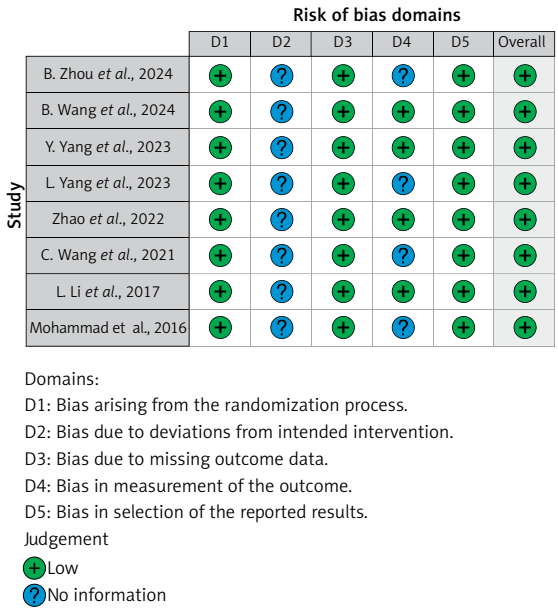

Figure 3. ROB analysis of clinical articles

Results of individual studies

A total of 58 individual studies were included in the final synthesis. The findings reflect a consistent focus on the functional impact of site-specific phosphorylation of PKM2 on tumor metabolism, growth, and therapeutic response. The key individual studies are organized below by phosphorylation site and cancer context (Supplementary Table SII).

The funnel plot in Figure 4 displays the distribution of effect sizes from 58 individual studies included in the systematic review. The *x*-axis represents the estimated effect sizes (e.g., log hazard ratios or standardized mean differences) associated with site-specific PKM2 phosphorylation, while the *y*-axis indicates the corresponding standard errors. The red dashed vertical line denotes the pooled effect size. The dotted lines represent the pseudo 95% confidence intervals around the pooled estimate, forming the expected funnel shape in the absence of publication bias. Visual asymmetry in the scatter distribution may

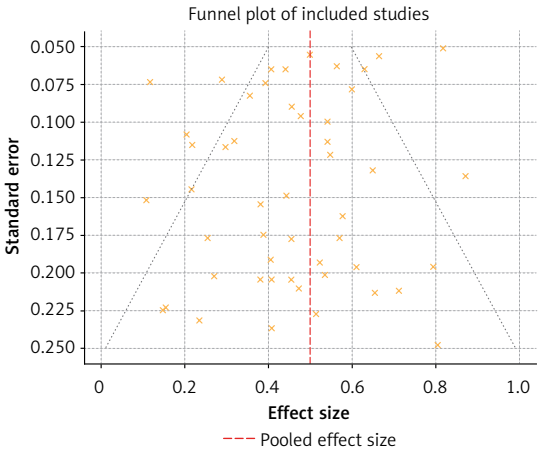

Figure 4. Funnel plot of included studies evaluating site-specific PKM2 phosphorylation in cancer

suggest potential small-study effects or reporting bias. The heterogeneity observed in the funnel plot may partly reflect the inclusion of both preclinical and clinical studies with differing outcome measures, experimental designs, and sample sizes. As these studies do not share a uniform effect metric, the funnel plot should be interpreted as an exploratory visualization rather than a formal assessment of publication bias.

Discussion

This systematic review synthesizes the current evidence on the role of site-specific phosphorylation of pyruvate kinase M2 (PKM2) in cancer metabolism, tumor progression, and therapeutic responsiveness. Across 58 studies, our analysis highlights the central role of PKM2 as a dynamic metabolic regulator whose activity and localization are modulated by phosphorylation at key residues, most notably tyrosine 105 (Y105), serine 37 (S37), threonine 45 (Thr45), and tyrosine 148 (Y148) [6, 31, 50]. Phosphorylation at specific PKM2 residues alters its oligomeric state and subcellular localization, thereby influencing cancer cell metabolism [1]. For instance, Y105 phosphorylation disrupts tetramer formation, shifting PKM2 to a dimeric state with lower catalytic activity. This facilitates the accumulation of glycolytic intermediates that fuel anabolic biosynthesis, a hallmark of the Warburg effect [21]. Similarly, S37 phosphorylation promotes PKM2 nuclear translocation, where it functions as a coactivator of oncogenic transcription factors such as β-catenin and HIF-1α [4]. These mechanisms collectively enhance tumor cell adaptability under hypoxic and nutrient-deprived conditions, underscoring phosphorylation-dependent metabolic plasticity as a survival advantage in diverse malignancies.

Several studies link high levels of phosphorylated PKM2 to aggressive tumor phenotypes and poor clinical outcomes. Y105 phosphorylation was associated with increased invasion, epithelial–mesenchymal transition (EMT), and metastasis in hepatocellular, breast, and colorectal cancers [54].

Table I. Roles of PKM2 phosphorylation in cancer and non-oncological diseases

Disease category	Condition	Phosphorylation mechanism	Functional consequence	Clinical/ pathological relevance	Reference
Cancer	NSCLC/ breast cancer/ glioblastoma	Tyr105/Ser37 phosphorylation	Enhanced aerobic glycolysis, nuclear translocation	Associated with tumor growth, proliferation, and poor prognosis	Hitosugi *et al.* (2009). Yang *et al.* (2012) [47, 48]
Inflammatory disease	Sepsis	Nuclear PKM2–STAT3 pathway	Induces pro-inflammatory cytokine production	Drives systemic inflammation	Yu *et al.* (2014). [55]
Autoimmune disease	Rheumatoid arthritis	PKM2-mediated metabolic reprogramming	Enhances glycolysis in activated immune cells	Sustains synovial inflammation	Liao *et al.* (2025). [56]
Dermatological disease	Psoriasis	Nuclear PKM2 activation	Keratinocyte metabolic shift and proliferation	Contributes to hyperproliferative lesions	Yang *et al.* (2023). [43]
Infectious disease	Viral infection/ macrophage activation	PKM2 nuclear signaling	Regulates inflammatory gene transcription	Supports immune activation response	Toller-Kawahisa *et al.* (2025) [57]
Metabolic disease context	Chronic inflammatory metabolic states	PKM2-dependent glycolytic reprogramming	Alters glucose metabolism in immune cells	Associated with sustained inflammation	Xie *et al.* (2016) [58]

However, most of these findings are derived from preclinical models or small patient cohorts, and their clinical utility remains underexplored. The lack of standardized detection methods and heterogeneous scoring systems across studies also limits comparability and reproducibility.

Our review identifies a growing interest in targeting PKM2 phosphorylation as a therapeutic strategy. Preclinical studies suggest that inhibition of upstream kinases (e.g., FGFR1, ERK, c-Src) or stabilization of the PKM2 tetramer can reverse the pro-tumorigenic effects of phosphorylation [47, 48]. Moreover, phosphorylation status has emerged as a potential predictive biomarker for responsiveness to certain treatments, including tyrosine kinase inhibitors and metabolic modulators. However, few studies have validated these associations in clinical trials, and there is limited consensus on which phosphorylation sites offer the most predictive value [1, 45, 46]. PKM2 phosphorylation and nuclear signaling have also been implicated in several non-malignant diseases characterized by metabolic reprogramming and inflammatory activation (Table I). These findings indicate that PKM2 phosphorylation reflects a broader adaptive metabolic mechanism rather than a cancer-exclusive event.

Despite the promising findings, the overall certainty of the evidence remains low to very low, primarily due to the predominance of *in vitro* and animal studies, variability in study design, and potential publication bias. Many studies lacked adequate control groups, were not blinded, or did not assess long-term functional outcomes. Furthermore, the interactions between multiple post-translational modifications on PKM2 and their collective impact on tumor behavior remain poorly understood. Few studies addressed the effects of co-occurring genetic mutations, tumor heterogeneity, or tumor microenvironmental factors, all of which could modulate the functional impact of PKM2 phosphorylation. The funnel plot analysis further reflects this methodological heterogeneity. The visual dispersion and asymmetry likely arise from the combined inclusion of mechanistic *in vitro* studies, animal models, and retrospective clinical cohorts, each characterized by distinct outcome measures and sample size structures. As these study types do not share uniform effect metrics, the funnel plot should be interpreted cautiously as an exploratory visualization rather than definitive evidence of publication bias. Future analyses restricted to homogeneous clinical endpoints may provide more reliable bias assessment.

To advance this field, future research should focus on standardizing methodologies for detecting site-specific PKM2 phosphorylation in clinical samples. Studies should also elucidate mechanistic pathways downstream of each phosphorylation site using CRISPR-based gene editing and phosphomimetic models. Additionally, integrating PKM2 phosphorylation status into clinical trials, especially those targeting metabolic pathways or using biomarker-driven patient selection, will be valuable. Exploring combinatorial targeting strategies that inhibit PKM2 phosphorylation alongside immunotherapy or chemotherapy may enhance therapeutic efficacy.

In conclusion, site-specific phosphorylation of PKM2 plays a critical role in promoting metabolic reprogramming, tumor progression, and therapeutic resistance across multiple cancer types. While the existing preclinical data are compelling, the translation of these findings into clinical practice is still in its infancy. Rigorous validation and prospective studies are essential to determine whether PKM2 phosphorylation can serve as a reliable biomarker or therapeutic target in precision oncology. Given its involvement in inflammatory and autoimmune conditions, disease-specific validation is required before clinical implementation.

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Data availability statement

All data generated or analyzed during this study are included in this manuscript or supplementary information files.

Authors contribution

The author confirms sole responsibility for the conception, design, analysis, drafting, and finalization of the manuscript. All aspects of the work were performed independently by the author.

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Ethical approval

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Conflict of interest

The author declares no conflict of interest.

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