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Is CIP2A a biomarker for poor prognosis in cancer? – A systematic review with meta-analysis

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Background: Cancerous inhibitor of PP2A (CIP2A) is a trimeric protein phosphatase inhibitor. CIP2A acts on the tumor suppressor PP2A, controlling cell survival and proliferation. Several studies have demonstrated that CIP2A is aberrantly overexpressed in both hematological cancers and solid tumors and may be a predictive biomarker for poor prognosis. On the other hand, there are several studies that show conflicting evidence. This comprehensive systematic review aims to evaluate the predictive significance of CIP2A in cancer.
Methods: 34 studies published from 2013 to 2026, were selected for the examination of the potential relationship between CIP2A and various clinical milestones in solid and hematological cancers. Searches of PubMed, EBSCO (Medline) and Web of Science (core collection) were conducted until 01/06/2026. The Newcastle-Ottawa scale was used to assess risk of bias. Meta-analysis was performed to evaluate the use of CIP2A as a predictive biomarker for clinical outcome.
Results: At 5 years, the random effects model revealed a significant difference between low and high CIP2A expression and overall survival (OS) ($p < 0.001$). At one and 5 years, there were significant differences in progression free survival (PFS) between low and high CIP2A expression ($P = 0.001$ and $P < 0.001$, respectively). Subgroup analysis revealed that, in the context of both the colorectal and breast cancer groups, there were significant differences between the low and high CIP2A groups at the five-year milestone and in CML and AML at 1 year.
Conclusion: Elevated CIP2A expression at diagnosis was associated with poor overall survival and progression-free survival, although this association should be interpreted cautiously due to heterogeneity between cancer types, limited subgroup data, and methodological limitations. When compared to several other cancers, it was discovered that this association was stronger in specific cancers, such as leukemia, colorectal and breast cancer.

KEYWORDS
biomarker, cancer, CIP2A, CML, prognosis

Introduction

Cancer continues to represent one of the greatest global health challenges, according to the WHO, cancer was one of the primary causes of death in 2020, accounting for approximately 10 million deaths worldwide [1]. In terms of prognosis, many cancers including prostate and thyroid cancer have an approximate 97.5% [2] and 98.4% [3] 5 year survival rate respectively. However, in contrast to these cancers, oesophageal [4], bladder [5] and pancreatic cancer [6] have some of the lowest overall prognosis, where the 5 year

survival rate is less than 15%. A means to improve patient outcomes is by screening for predictive biomarkers. A predictive prognostic biomarker forecasts a future patient outcome connected to the disease [5]. As a result, clinicians are better equipped to decide on treatment options that optimise the results for patients and increase survival rates. The quantity of biomarkers discovered has grown exponentially during the last 10 years, evidenced by the growth in publications linked to the 'biomarker' key word. As of 2016 there were 768,259 publications on PubMed connected to biomarkers [7], upon searching for this keyword in 2026 there is 1,378,460. Few of the molecular biomarkers reported in these publications are currently being used in clinical settings, even though many of them claim to be clinically beneficial.

One biomarker that is of interest is cancerous inhibitor of PP2A (CIP2A). Among the numerous molecular biomarkers investigated in cancer, CIP2A was selected as the focus of this review because of its broad involvement in oncogenic signaling and its reported association with clinical outcomes across multiple cancer types [8]. Across most cancers, nearly 70% of cancer patient samples demonstrate significant CIP2A expression [8]. Numerous studies have shown that CIP2A is aberrantly overexpressed in solid tumours as well as haematological cancers [9]. Importantly, unlike many candidate biomarkers, CIP2A has been investigated as a potential prognostic marker across both solid and haematological malignancies, with studies reporting associations with clinical outcomes including overall survival (OS) and progression-free survival (PFS) [10]. However, the reported prognostic significance of CIP2A has not been consistent across cancer types and study populations [11–13]. This combination of biological relevance, broad investigation across malignancies and conflicting clinical evidence provided the rationale for selecting CIP2A for the present systematic review.

CIP2A contributes to dysregulated cell growth through disruption of key tumour suppressor pathways involved in cellular growth [14]. Constitutively active protein kinases, which promote mutations, are discovered in most malignancies. As a result, these protein kinases are regarded as crucial targets for cancer therapy. An example of this is a common serine/threonine phosphatase known as protein phosphatase 2A (PP2A) which has been identified as a tumour suppressor protein and PP2A mutations have been found in a number of cancers [15]. Signalling pathways important in cell survival, proliferation, and growth are negatively regulated by PP2A [15]. The catalytic (C) subunit, scaffolding (A) subunit and regulatory (B) subunit make up the three subunits that form the phosphatase PP2A [16]. Among PP2A's inhibitors is the oncoprotein CIP2A. This oncoprotein was originally discovered as an autoantigen in gastric cancer. Since it was 90 kD in size, it was first given the name 'p90' [17]. Direct interaction between CIP2A and the oncogenic transcription factor MYC results in inhibition of PP2A activity towards phosphorylated MYC serine sixty-two, which in turn stops MYC from being proteolytically degraded [9]. As a transcription factor known for its carcinogenic potential MYC regulates cell division, metabolism, and apoptosis. By the stimulation of genes such as cyclin D and cyclin-dependant kinase 4 (CDK4), MYC is able to promote the advancement of the cell cycle [18]. This inhibition of PP2A activity towards MYC impacts several signalling pathways, including the PI3K-AKT-mTOR and RAS-MEK-ERK pathways as seen in Figure 1 [10]. Phosphatidylinositol 4,5-bisphosphate (PIP2) can be converted by activated phosphatidylinositol 3-kinase (PI3K) to PIP3, a second messenger that, via 3-phosphoinositide dependent kinase 1 (PDK1), indirectly activates AKT. Different substrates, including mTOR and glycogen synthase kinase-3β (GSK-3β), are acted upon by AKT, which controls many processes such as cell growth and proliferation [21]. By phosphorylating cAMP response element-binding protein (CREB) via the PI3K/AKT signalling pathway, IL-10 controls the expression of the CIP2A gene [22] (Figure 1). In most human malignancies, oncogenic signalling pathways including E2F1 overexpression, P53 inactivation, and MYC activation drive CIP2A expression, promoting uncontrolled cell cycle progression, cellular growth, and proliferation [23, 24] (Figure 1).

CIP2A has been discovered as a biomarker in cancer including nasopharyngeal [25], breast [26], ovarian [27] and both chronic [28] and acute myeloid leukemias (AML) [29, 30]. A number of papers have reported the overexpression of CIP2A to be closely linked to the stage of certain tumours and CIP2A has been reported as a prognostic indicator for various clinical milestones such as overall survival (OS) and progression free survival (PFS) in a number of cancers [27, 28, 31–33]. Conversely, a few papers and publicly available datasets have reported inconsistent or limited associations between CIP2A expression and patient prognosis [11–13, 34]. These discrepancies may reflect differences in tumour subtypes, analytical methodologies, cohort selection and transcriptomic versus protein-level analyses. Therefore, despite substantial evidence supporting CIP2A as a potential prognostic biomarker, its prognostic significance across cancer types remains unclear. To address this, we conducted a systematic review to assess the association between CIP2A expression and clinical outcomes across multiple malignancies and to determine the consistency of reported survival associations.

Methods

Publication search

This systematic review was conducted according to the PRISMA guidelines [35]. PubMed, EBSCO (Medline), and Web of science (core collection) were all searched by two reviewers (up to 1st June 2026). The PubMed search strategy was ("CIP2A"[All Fields] OR "Cancerous inhibitor of PP2A"[All Fields]) AND ("Neoplasms"[MeSH Terms] OR cancer[All Fields] OR tumour [All Fields] OR malignancy[All Fields] OR neoplasm[All Fields]) AND ("Survival"[MeSH Terms] OR prognosis[All Fields] OR outcome[All Fields]). Equivalent search strategies were used for the remaining databases. The filters applied were: Free full-text and publication date ≥2013. The literature search was restricted to studies published ≥2013 to provide an updated assessment of prognostic significance of CIP2A following the previous review by Khanna and Pimanda [8], which evaluated the earlier clinical literature on CIP2A in human cancers. The present review was therefore designed to extend, rather than duplicate, the existing evidence synthesis by quantitatively analysing the subsequent literature and incorporating studies published over approximately the following 13 years. Figure 2 shows the PRISMA flow diagram for systematic reviews which includes searches of databases only [37]. A

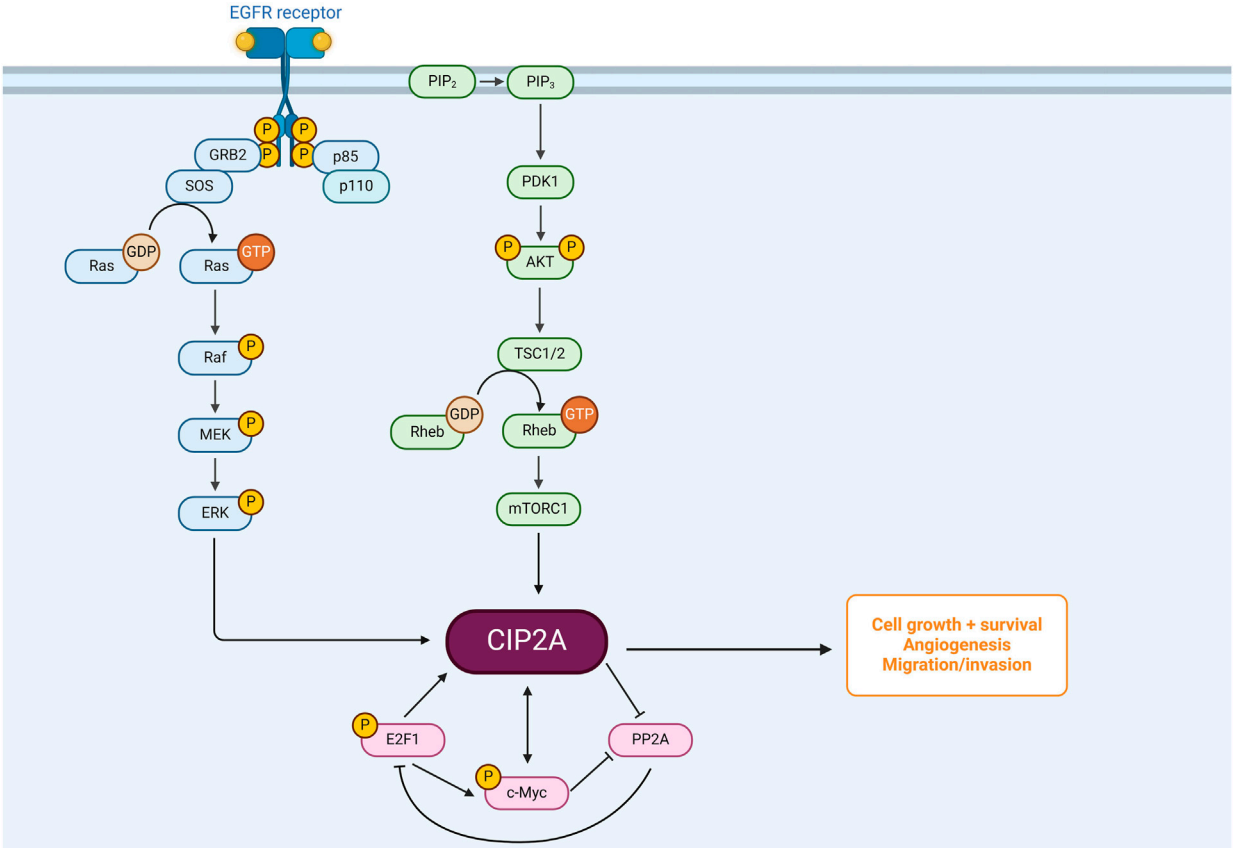


FIGURE 1
A diagram to show the signalling pathways of CIP2A. Including the Ras/Raf/MEK/ERK pathway, the PI3K/AKT/mTOR pathway and the E2F1 feedback loop. All pathways of which cause increased CIP2A activity and consequently increased cell growth, survival, angiogenesis, and migration. Adapted from Beibei et al and Lucas et al. [19, 20].

total of 560 papers were identified from the aforementioned databases. Database filters were applied prior to screening, and duplicate records were identified and removed using EndNote 2025 3.1 reference management software. A total of 228 papers were screened for eligibility using their title and abstracts and eventually full texts. Papers were excluded if they did not fit the inclusion criteria. Papers were excluded if they reviewed drug resistance, provided no clinical data or were not in the English language. 4401 patients/samples were made available by the thirty-four studies that were chosen for analysis of the connection, if any, between CIP2A and clinical outcome in cancer (Figure 2).

Study selection and eligibility

The inclusion criteria included papers published from 2013, with full text accessible to the reviewers. The papers must include clinical data regarding the following clinical milestones: OS and PFS regarding CIP2A protein or mRNA expression. Studies reporting either a hazard ratio (HR) with a 95% confidence interval (CI), or survival data from which an effect estimate could be obtained, were considered eligible. Papers studying both solid tumours and haematological cancers were included. This systematic review excluded: case studies, review articles and letters. Papers reviewing CIP2A regarding drug resistance were also excluded as well as papers not in the English language (Figure 2). This selection process was conducted by both reviewers in two stages: firstly, titles and abstracts were screened to remove irrelevant studies. In the second stage, the full texts of the remaining articles were assessed against the eligibility criteria to determine inclusion in the final meta-analysis. To minimize bias, these inclusion and exclusion criteria were predefined prior to the screening process. Both reviewers independently assessed studies against the inclusion and exclusion criteria.

Data extraction, quality assessment and statistical analysis

Author, year of publication, cancer type, number of patients, the detection method, percentage of CIP2A positive patients/samples and the studies' clinical outcomes were extracted from the papers selected and recorded in Table 1. Different methods of CIP2A measurement were not used as separate effect estimates where studies reported the same clinical outcome; studies using protein- and mRNA-based measures were included in the overall analysis, with the detection method recorded to assess potential methodological heterogeneity. The research quality of all studies was assessed by a standardised tool, the Newcastle-Ottawa Scale (NOS), studies with a score of six or higher were considered a high-

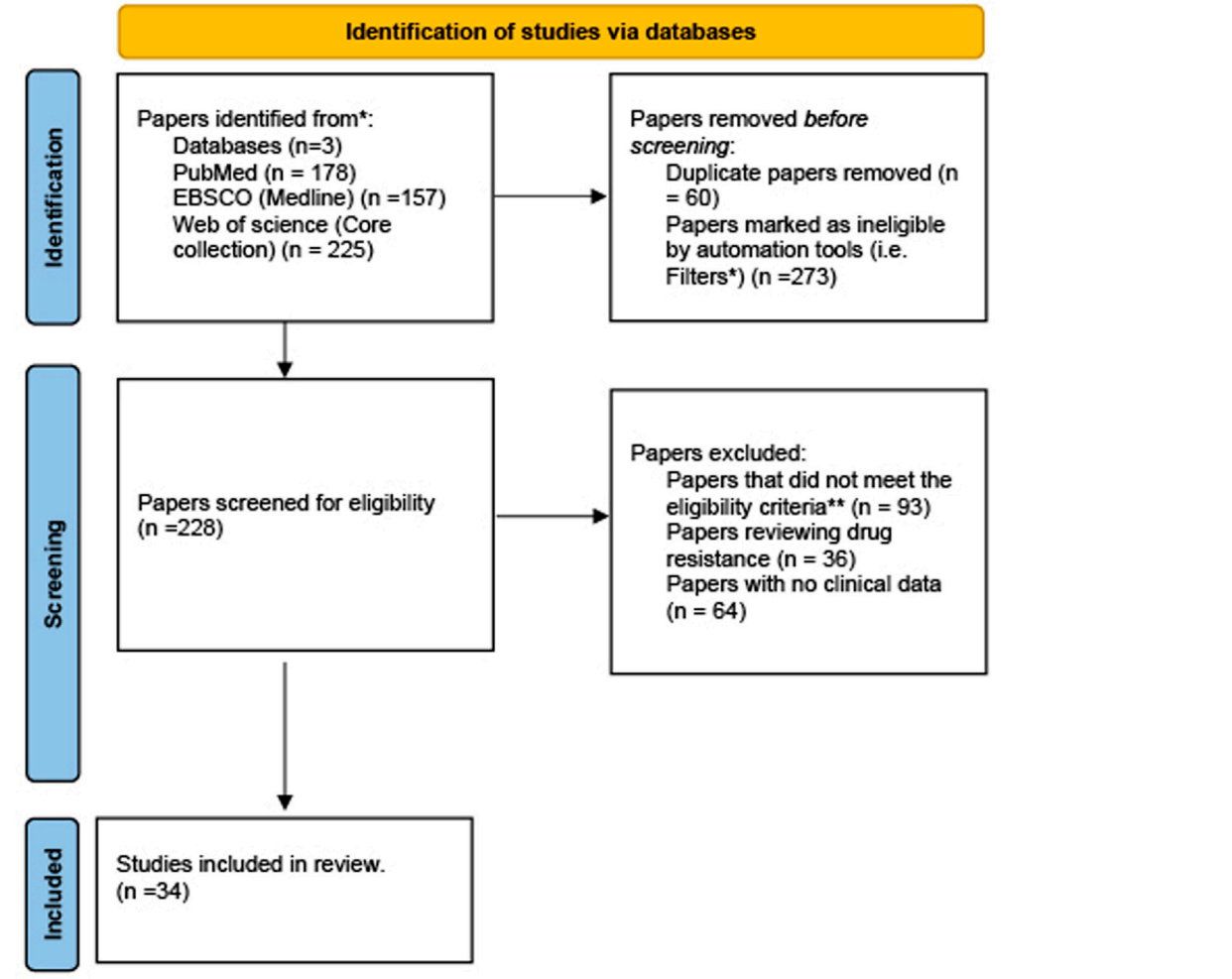


FIGURE 2
PRISMA 2020 flow diagram for new systematic reviews which includes the searches of databases only, created using the PRISMA Flow Diagram tool [36]. Database filters included the following–Full text available, published within 13 years (2013 >) Eligibility criteria–Papers reporting clinical milestones (OS, EFS, DFS, PFS) regarding CIP2A expression in cancer.

quality research paper (Table 1) [68]. The analysis in this review was based on OS and PFS data (where applicable), as these were the most common clinical outcomes among the included papers. Where reported, HRs and corresponding 95% CIs were extracted directly from the published studies. Where HRs were not reported, available numerical survival data were extracted. Where numerical survival data were unavailable, one-year and five-year survival estimates were obtained by manually reading survival probabilities from published Kaplan–Meier curves at the corresponding time points. These time points were selected because they were commonly reported across studies and allowed comparison between studies. Statistical analysis was performed using Jamovi version 2.5 [69]. A p-value <0.05 was considered statistically significant. Each eligible study's OS and/or PFS endpoints (where available) were used to assess the association between CIP2A expression and prognosis at one and/or 5 years. For analysis, risk ratios (RRs) with corresponding 95% CIs were calculated. To account for potential heterogeneity given the anticipated clinical and methodological variability between cancer types and study populations, all pooled analyses were performed using a random-effects model. For each meta-analysis, the effect measure was the RR, with analyses performed and displayed on the logarithmic scale as log risk ratios (log RR) with corresponding 95% confidence intervals. A log RR of 0 represents the null effect, equivalent to an RR of 1. Negative log RR values indicate an RR below 1, whereas positive values indicate an RR above 1. Pooled estimates were calculated using a random-effects model to account for anticipated clinical and methodological differences between studies. Individual studies were weighted according to the precision of their effect estimates, such that studies with more precise estimates contributed more strongly to the pooled estimate.

We computed the I^2 statistic using the Q-test for heterogeneity, an I^2 value between 30% and 60% may represent moderate heterogeneity, I^2 between 50% and 90% may represent substantial

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TABLE 1 Characteristics of papers included in systematic review.

Author (s)	Year	Cancer type	Patients/ Samples	CIP2A positive (%)	Study endpoint	Quality of paper (NOS score)
Alzahrani et al.	2020 [38]	Oral squamous cell carcinoma	35	68.57	OS	6
Baldacchino et al.	2015 [39]	Breast	48	20.83	OS, DFS	5
Barragán et al.	2015 [40]	AML	203	25.12	OS, DFS, RFS	6
Cha et al.	2017 [41]	Non-small cell lung cancer	209	38.76	OS	6
Chao et al	2016 [42]	Papillary thyroid carcinoma	178	51.12	PFS	6
Chen et al.	2020 [43]	Colorectal	390	40.26	OS, DFS	7
Chen et al.	2021 [44]	Colorectal	61	45.90	OS	6
Chen et al.	2015 [45]	Colorectal	220	41.36	OS	7
Chen et al.	2015 [46]	Gastric	37	67.57	OS	7
Chen et al.	2023 [47]	Non-small cell lung cancer	151	60.93	OS	6
Chuang et al.	2022 [48]	Prostate	62	66.13	PFS	7
Clark et al.	2021 [49]	CML	172	49.42	PFS, FFP	7
Cristobal et al.	2017 [33]	TNBC	61	27.87	OS, EFS	6
Gao et al.	2020 [50]	Renal clear cell carcinoma	80	50.00	OS	6
Li et al.	2019 [51]	Esophagogastric junction adenocarcinoma	65	64.62	OS, DFS, TTP	5
Liu et al.	2018 [52]	Colon	165	37.58	OS	7
Liu et al.	2017 [53]	Multiple myeloma	41	46.34	OS	7
Liu et al.	2014 [25]	Nasopharyngeal carcinoma	280	65.71	OS, DFS	7
Lucas et al.	2015 [20]	CML	74	29.72	OS, PFS, MR, CR	7
Luque et al.	2022 [54]	Breast	220	18.18	OS, EFS	5
Nishio et al.	2020 [55]	Breast	424	49.50	OS	7
Seppälä et al.	2015 [56]	Tongue squamous cell carcinoma	92	46.74	OS	7
Shafik et al.	2020 [11]	AML	60	35.00	OS, PFS	5
Tang et al.	2015 [57]	Renal clear cell carcinoma	148	65.54	OS, DFS	7
Velmurugan et al.	2019 [58]	Oral squamous cell carcinoma	133	56.39	OS	7
Ventelä et al.	2015 [59]	Head and neck	20	95.00	OS	6
Wang et al.	2017 [60]	Cervical	184	20.65	OS, DFS	5
Wang et al.	2019 [61]	Renal clear cell carcinoma	110	50.00	OS	6
Wiegering et al.	2013 [62]	Colon	73	56.16	OS	6
Xu et al.	2017 [63]	Gallbladder carcinoma	65	64.62	OS	6
Xu et al.	2016 [64]	Pancreatic	72	70.83	OS	7
Xue et al.	2013 [65]	Bladder urothelial cell carcinoma	117	72.65	OS	6
Xue et al.	2018 [66]	Hepatocellular carcinoma	31	67.74	OS, RFS	6
Zhang & Wang	2020 [67]	Glioma	120	64.17	OS	7

OS, EFS (Event free survival), DFS (disease free survival), PFS, FFP (freedom from progression), TTP (time to progression), RFS (relapse free survival), MR (Molecular response), CR (cytogenic response), AML (acute myeloid leukemia), CML (Chronic myeloid leukemia).

heterogeneity and $I^2 > 75\%$ shows considerable heterogeneity [70]. These ranges intentionally overlap because I^2 thresholds are not absolute or mutually exclusive cut-offs; rather, they provide general guidance for interpreting the magnitude of heterogeneity. As outlined in the Cochrane Handbook for Systematic Reviews of Interventions, I^2 values should therefore be interpreted cautiously and considered alongside the magnitude and direction of the effect estimates, the precision of the estimates, and the statistical evidence for heterogeneity [71]. Funnel plots and Egger's regression test for publication bias were performed to determine the potential for publication bias amongst papers [72]. Subgroup analysis was performed on groups of the same cancer type where there were three or more papers with the same data sets, using the same statistical methods as previously mentioned. No formal sensitivity analysis was performed because of the limited number of studies available for individual outcomes and cancer types.

Results

Study characteristics

A total of 4401 patients were included in the sample from the thirty-four trials, published between 2013–2026. The median number of patients within each study was 101 with an average of 129 and a range of 11–390 patient samples per paper. There are twenty-four different cancer types represented in the thirty-four papers included in this review, this comprises both solid tumours studies (n = 29) and haematological cancer studies (n = 5). The most common cancer types across the papers were breast cancer (n = 4) and myeloid leukemia's (n = 4), followed by colorectal (n = 3), Oral cancer (n = 3) and renal clear cell carcinoma (n = 3). A total of thirty-four papers included OS data, of these papers however, only twenty-nine included data 5 years and above. Five papers included PFS data, three of these included data 5 years and above. The study characteristics are summarised in Table 1. OS is defined as the amount of time that passed between the commencement of the study and the patient's death (of any cause) [73]. PFS is defined as the interval between the commencement of the study and the date of an incidence of disease advancement/progression, such as the progression into an advanced disease phase or death [74]. NOS score ranged from 5–7, with limited variability, indicating all studies were of a moderate to high quality. Therefore, a formal sensitivity analysis was not undertaken. Instead, study quality was assessed descriptively, with no clear relationship observed between NOS score and effect estimates, suggesting that study quality did not notably influence findings.

Overall analysis

At five years, OS and PFS was reduced in patients with elevated CIP2A expression. There was minimal heterogeneity between OS and CIP2A expression at 1 year ($I^2 = 0.02\%$, $P = 0.001$) and the random effects model showed no statistical difference (pooled log RR = −0.004, 95% CI = −0.014 to 0.003, P = 0.310) as seen in the forest plot (Figure 3). Nevertheless, at 5 years there was minimal heterogeneity between OS and CIP2A expression ($I^2 = 16.54\%$, P = 0.010) and the random effects model showed a significant difference between low and high CIP2A expression and OS (pooled log RR = −1.27, 95%CI = −1.440 to −1 .081, $P < 0.001$) (Figure 4). Regarding PFS there were significant differences between low and high CIP2A expression at both one (pooled log RR = −1.24, 95% CI = −1.973 to −0.499, p = 0.001) and 5 years (pooled log RR = −1.13, 95% CI = −1.702 to −0.551, $P < 0.001$). There was no heterogeneity at 1 ($I^2 = 0.00\%$, P = 0.602) and 5 years ($I^2 = 0.00$, P = 0.164) (Figures 5, 6). Publication bias was assessed using funnel plots and Egger regression tests for asymmetry. Most analyses demonstrated no significant evidence of asymmetry; however, significant asymmetry was observed in the one- and five-year OS analyses as well as the oral cancer subgroup analyses ($p < 0.05$). Funnel plots are provided in the Supplementary Material.

Subgroup analysis

Subgroup analysis was performed on groups of cancers where there were three or more papers in that group (Table 2). For the breast cancer group there was no heterogeneity ($I^2 = 0\%$, P = 0.680)) and no statistical differences (pooled log RR = −0.385, 95% CI: −1.471 to 0.702; P = 0.488) between low and high CIP2A expression and OS at 1 year (Figure 7A). At 5 years, there was no heterogeneity ($I^2 = 0\%$, P = 0.895) and the random effects model showed a statistically significant difference between groups of low and high CIP2A expression (pooled log RR = −1.151, 95% CI: −1.560 to −0.743; $P < 0.001$) (Figure 7B). There was moderate heterogeneity ($I^2 = 29.86\%$, P = 0.299) and no significant differences (pooled log RR = 0.32, 95% CI = −0.316 to 0.949, P = 0.327) between CIP2A expression and OS at 1 year in patients/samples with colorectal cancer (Figure 8A). However, there was no heterogeneity ($I^2 = 0\%$, P = 0.828) but a significant difference (pooled log RR = −0.90, 95% CI = −1.235 to −0.565, $P < 0.001$) between CIP2A expression and OS in the colorectal cancer group at 5 years (Figure 8B). In the renal clear cell carcinoma group at 1 year there was no heterogeneity ($I^2 = 0\%$, P = 0.956) when comparing CIP2A expression with OS and no significant differences between CIP2A expression groups (pooled log RR = 0.07, 95%CI = −1.225 to 1.362, P = 0.917) (Figure 9A). Likewise, at 5 years in the renal clear cell carcinoma group there were no significant differences (pooled log RR = −2.09, 95%CI = −4.350 to 0.176, P = 0.071) but there was considerable heterogeneity between elevated CIP2A expression and OS ($I^2 = 90.15\%$, P = 0.008) (Figure 9B). Oral squamous cell carcinomas and tongue squamous cell carcinomas were grouped into an oral cancer group, with only 1 year follow up data. There was considerable heterogeneity between increased CIP2A expression and OS at 1 year (Figure 10) ($I^2 = 95.77\%$, $P < 0.001$) and no significant differences between groups of CIP2A expression (pooled log RR = −2.59, 95%CI = −7.435 to 2.252, P = 0.294) (Figure 10). Finally, CIP2A expression and OS at 1 year in patients/samples with myeloid leukemias showed moderate heterogeneity ($I^2 = 66.12\%$, P = 0.031) but a statistically significant difference between low and high CIP2A expression (pooled log RR = −1.17, 95%CI = −2.257 to −0.077, P = 0.024) (Figure 11).

Discussion

This systematic review suggests that elevated CIP2A expression may be associated with poor OS and PFS, particularly at 5 years.

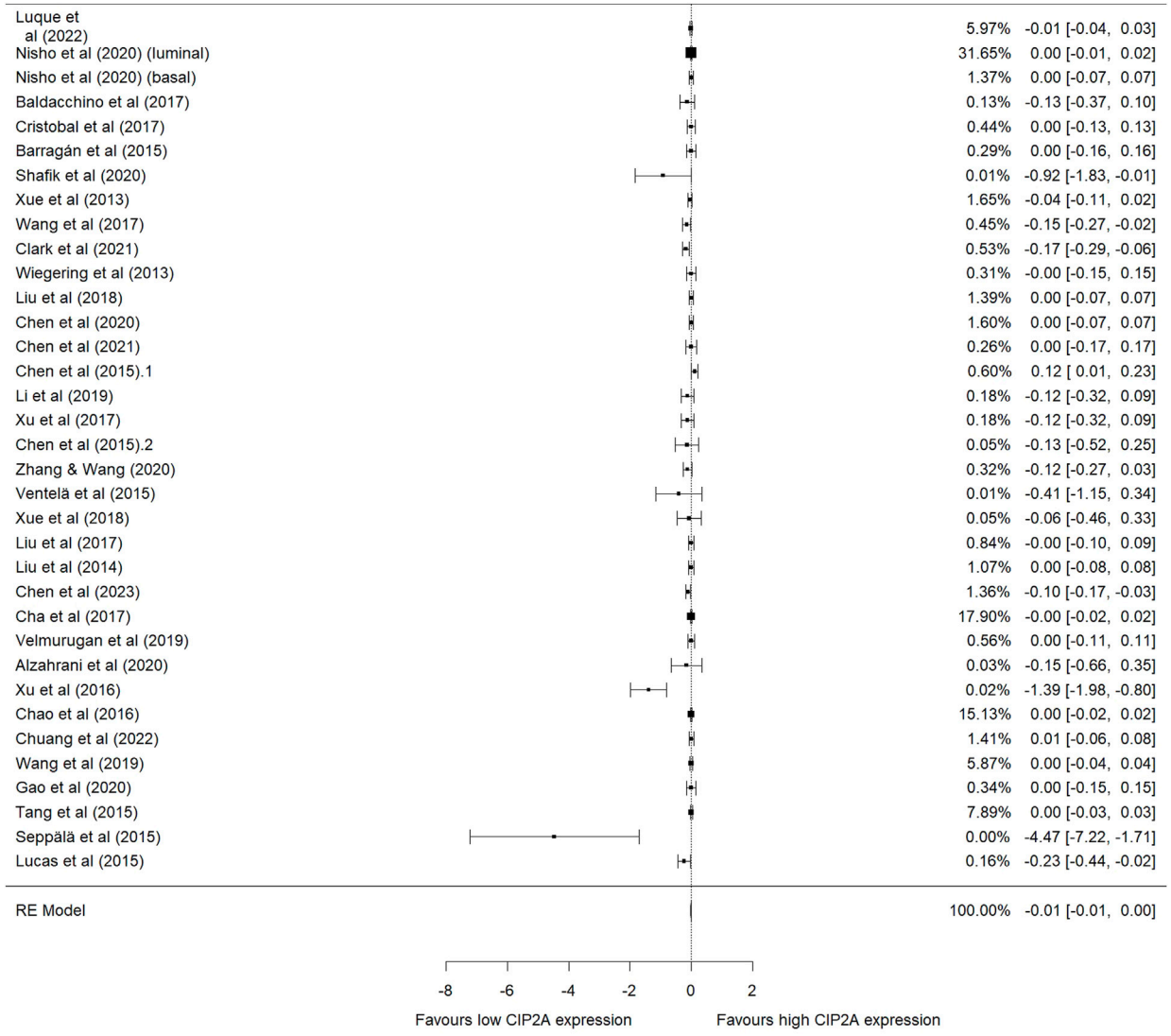


FIGURE 3
A forest plot to show the pooled effect between CIP2A expression and OS at 1 year using a random effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

These findings suggest that CIP2A may be a good biomarker to predict cancer patient prognosis. There were significant differences between low and high CIP2A expression and OS and PFS at 5 years. There were also significant differences between low and high CIP2A expression and PFS at 1 year. Specifically, in the sub -group analysis, at 5 years there were significant differences between low and high CIP2A groups in both the breast cancer group and the colorectal cancer group. This is consistent with the only other review on CIP2A in cancer, where they explored CIP2A's prognostic significance in solely solid tumours. Similarly, this review reported that high CIP2A expression in solid tumours was associated with poorer prognosis, indicating it potential utility as a prognostic biomarker [75].

The findings of this review are broadly consistent with prior literature describing CIP2A as a poor prognostic biomarker in several different cancers. However, they contrast with survival analyses in the Human Protein Atlas, which in certain datasets (including colorectal and breast cancer) suggest improved survival outcomes in patients with high CIP2A expression [34]. This discrepancy likely reflects differences in cohort composition, expression thresholds, and the use of data types (e.g., RNA-seq versus immunohistochemistry), highlighting the context-dependant nature of CIP2A-associated prognostic effects.

One cancer where CIP2A has been validated as a biomarker for cancer progression is chronic myeloid leukaemia (CML). It was suggested that diagnostic levels of CIP2A protein expression may be used as a possible biomarker to forecast treatment failure and disease progression [49]. This is consistent with the results of this review (Figure 11). Included in this review were various papers investigating CIP2A and survival in many different cancers (including CML). This review is consistent with previous studies investigating the prognostic value of CIP2A in cancer. An example of this is the paper by Liu et al (2017) where they concluded that in

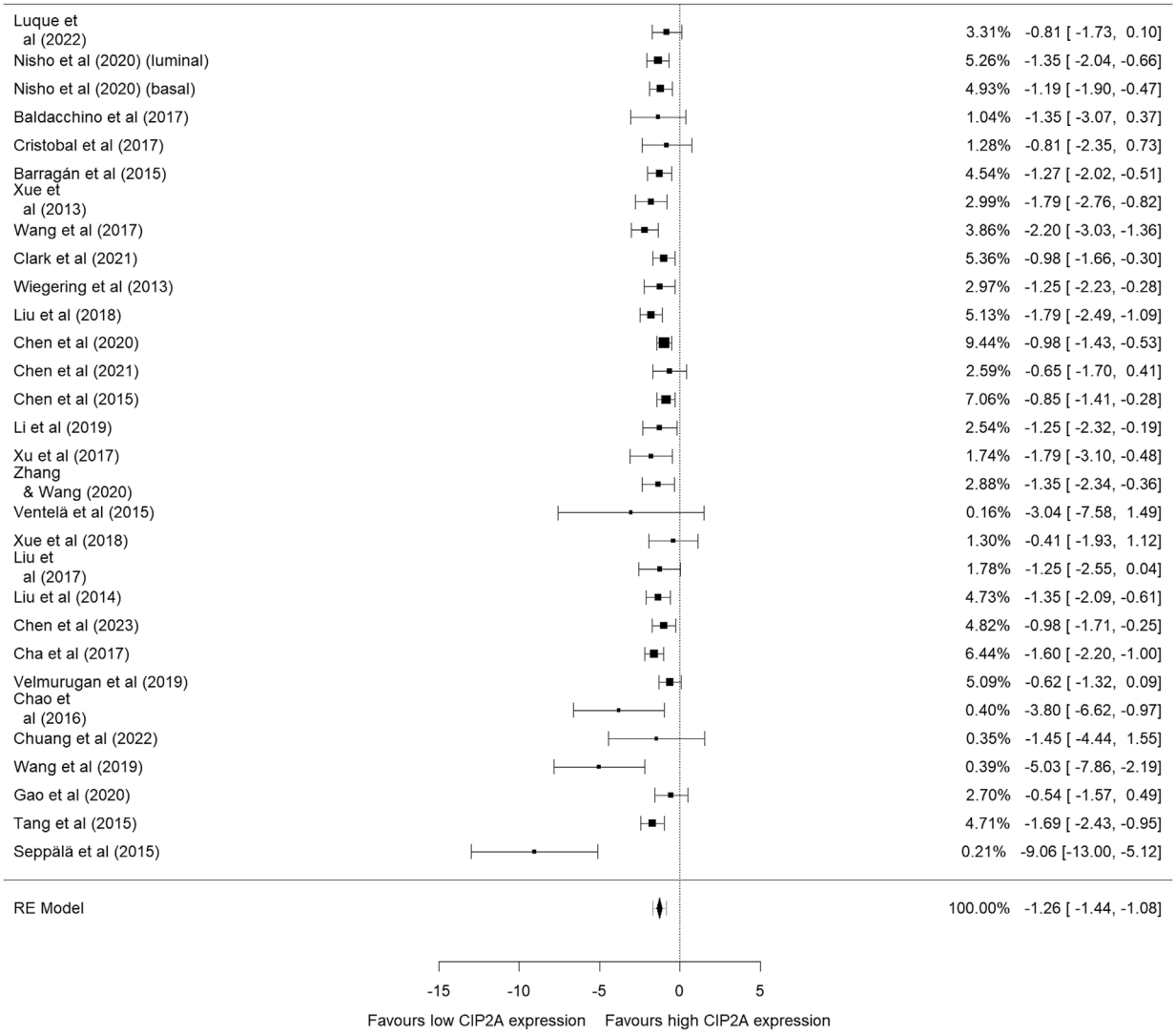


FIGURE 4
A forest plot to show the pooled effect between CIP2A expression and OS at 5 years using a random effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

multiple myeloma patients CIP2A functions as an oncogene and inhibiting CIP2A could be a crucial therapeutic approach for treating multiple myeloma [53]. On the contrary, it was found that in the paper by Bockelman et al. in colorectal cancer there was no correlation between CIP2A and the prognosis of the patient [12]. This opposes the findings of this review where subgroup analysis of different cancer types revealed that at 5 years there was a significant difference between high and low CIP2A expression and OS in colorectal cancer patients among the papers included in this review ($P < 0.001$) (Figure 8). This variation in results could stem from the large variation in patient/sample size. Bockelman et al had a sample size of 752 [12] compared with a range of 61–390 samples in the papers reporting on colorectal cancer in this review [43–45]. In addition to differences in sample sizes contributing to heterogeneity between studies, variation in the methods used to assess CIP2A expression may have also influenced the conclusions. Specifically, while many studies measured CIP2A expression at the protein level, others assessed expression at the mRNA level or incorporated both approaches. This distinction is important because mRNA and protein expression may not always correlate, due to post-transcriptional regulation, differences in protein stability and degradation, and other biological mechanisms. Côme et al [26] demonstrates this difference in their study on CIP2A expression in breast cancer. They found that CIP2A mRNA was overexpressed in 159 breast cancer samples and that this correlated with a more aggressive tumour. However, overexpressed CIP2A at a protein level was only found in 39% of a smaller subgroup of breast cancer patients. This highlights the need to incorporate both molecular approaches, as mRNA and protein levels may not always correlate with one another. These findings highlight that mRNA and protein measurements may capture different aspects of CIP2A biology and may therefore have different prognostic implications. Although protein expression may provide a more direct

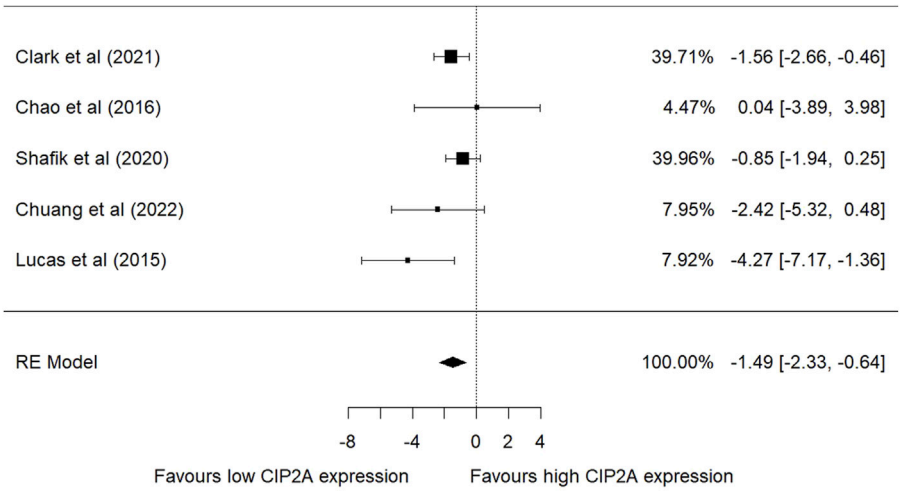


FIGURE 5
A forest plot to show the pooled effect between CIP2A expression and PFS at 1 year using a random effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

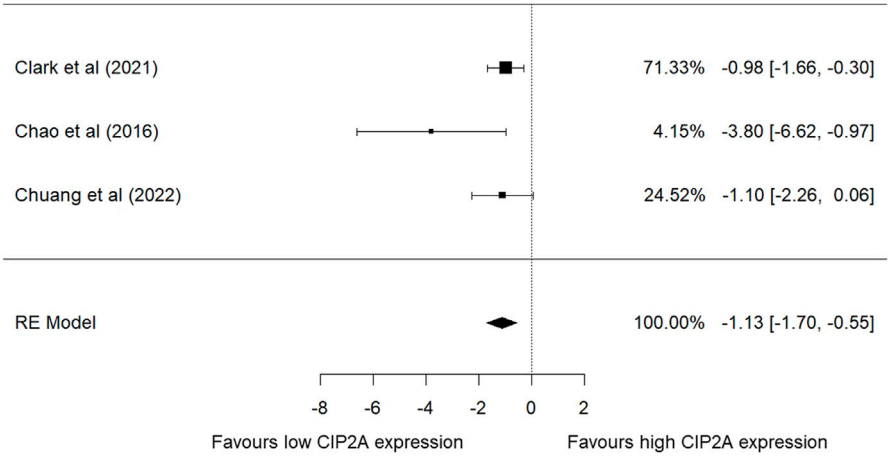


FIGURE 6
A forest plot to show the pooled effect between CIP2A expression and PFS at 5 years using a random effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

representation of CIP2A's functional activity, the current evidence is insufficient to conclude that protein expression is consistently superior to mRNA expression for predicting survival or disease progression across cancer types. Where both measurements are available, the prognostic value of each should be assessed independently, with preference given to the measure that has demonstrated the strongest and most reproducible association with clinical outcome within the relevant cancer type. Further studies directly comparing CIP2A mRNA and protein expression within the same patient cohorts are required to determine which provides the most robust prognostic information.

In addition to supporting CIP2A as a potential prognostic biomarker, this review suggests that CIP2A may represent a candidate therapeutic target. This is supported by its overexpression in normally transformed/cancerous cells but is minimally detected in non-cancerous or non-transformed cells [17], highlighting its potential use as a therapeutic target. Further studies are required to confirm this.

Interestingly, one of the papers included in this review, investigated the prognostic significance of CIP2A and neutrophil lymphocyte ratio (NLR) as prognostic biomarkers alone and in combination with one another in colorectal cancer patients' serum [44]. Inflammation plays a significant role in the development and progression of colorectal cancer and has been shown as a marker for poor prognosis in 20%–40% of colorectal cancer patients [76]. NLR is an accurate indicator of inflammation, and it is used in many other

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TABLE 2 **Subgroup meta-analysis summary table.**

Cancer type	Outcome	Time point	Studies (n)	Pooled log RR	95% CI	P-value	I^2 (%)	Heterogeneity P-value
Breast	OS	1 Year	4	−0.38	−1.47 to 0.70	0.488	0	0.680
Breast	OS	5 Years	4	−1.15	−1.56 to −0.74	<0.001	0	0.895
Colorectal	OS	1 Year	3	0.32	−0.32 to 0.95	0.327	29.86	0.299
Colorectal	OS	5 Years	3	−0.90	−1.24 to −0.57	<0.001	0	0.828
RCCC	OS	1 Year	3	0.07	−1.22 to 1.36	0.917	0	0.956
RCCC	OS	5 Years	3	−2.09	−4.35 to 0.18	0.071	90.15	0.008
Oral	OS	1 Year	3	−2.59	−7.44 to 2.25	0.294	95.77	<0.001
Myeloid leukemias	OS	1 Year	4	−1.17	−2.26 to −0.08	0.024	66.12	0.031

Pooled log RRs with corresponding 95% Cis, P-values, and measures of between study heterogeneity are summarized for cancer subgroups containing three or more studies. I^2 represents the percentage of total variation across studies attributable to heterogeneity, while the heterogeneity P-value represents the statistical significance of between-study heterogeneity. OS, overall survival; RCCC, renal clear cell carcinoma.

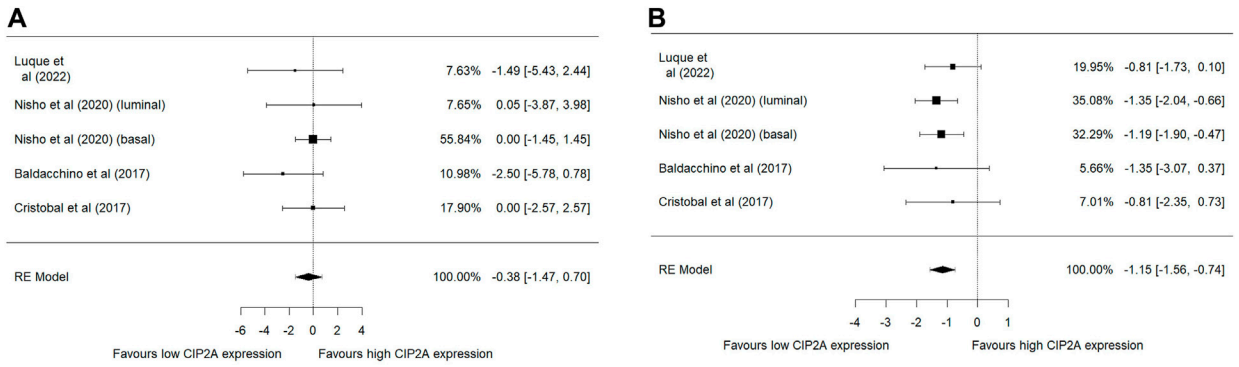


FIGURE 7
Forest plot showing the pooled effect of high versus low CIP2A expression on 1 year **(A)** and 5 year **(B)** overall survival in breast cancer patients, including luminal, basal, and triple-negative subtypes, using a random-effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

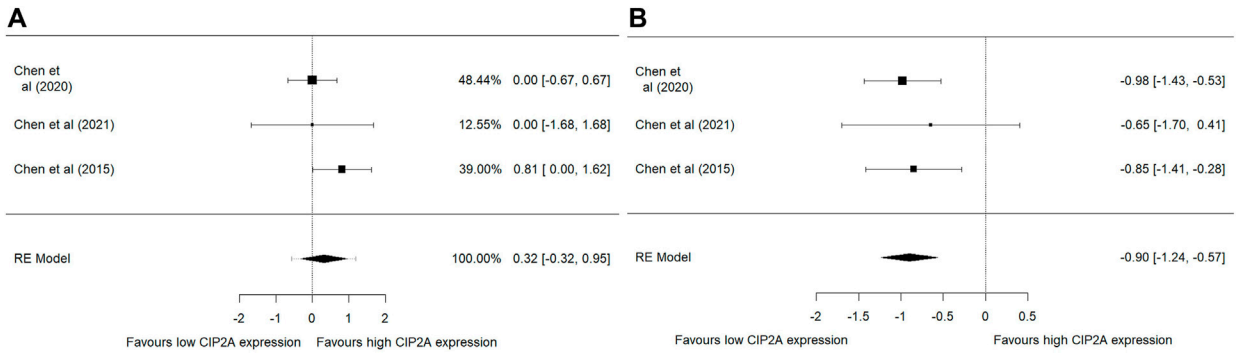


FIGURE 8
Forest plot showing the pooled effect of high versus low CIP2A expression on 1 year **(A)** and 5 year **(B)** overall survival in colorectal cancer patients using a random-effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

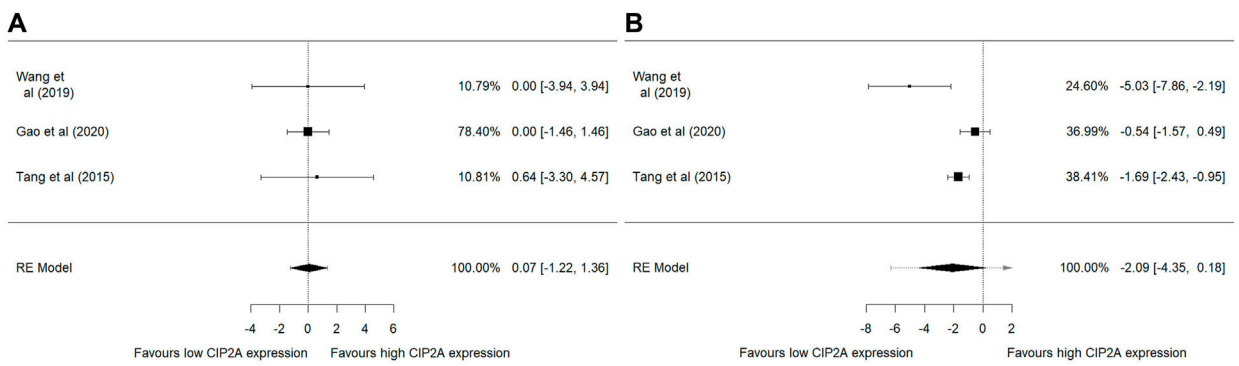


FIGURE 9
Forest plot showing the pooled effect of high versus low CIP2A expression on 1 year **(A)** and 5 year **(B)** overall survival in renal clear cell carcinoma using a random-effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

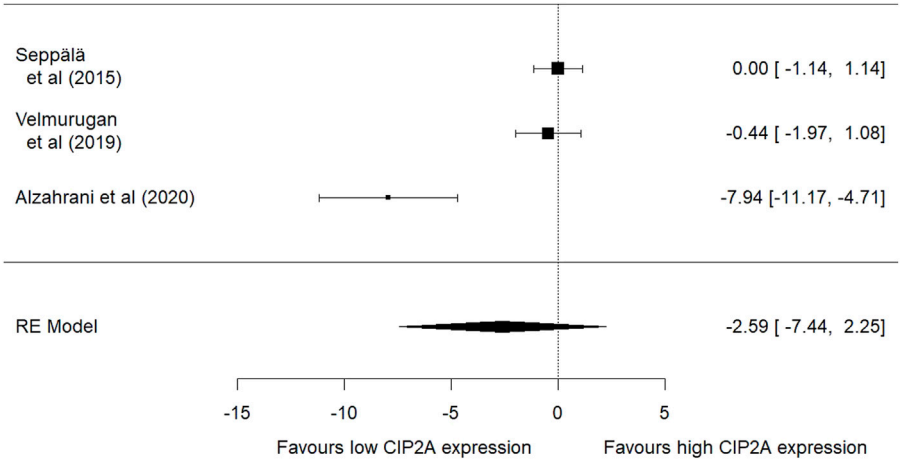


FIGURE 10
Forest plot showing the pooled effect of high versus low CIP2A expression on one-year overall survival in oral cancer patients, including oral squamous cell carcinoma and tongue squamous cell carcinoma, using a random-effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

cancers as a prognostic biomarker [77, 78]. It was found that combining various variables for prognostic evaluation of patients with colorectal cancer is beneficial, as evidenced by the fact that CIP2A and NLR together disclose the long-term prognosis of patients with colorectal cancer more accurately than using each one alone [44]. Future research should aim to explore other combinations of biomarkers to further improve their use to predict clinical outcome, allowing clinicians to make informed decisions on treatment options and thus improving patient outcomes and quality of life.

As part of this review, it was also considered whether the role of CIP2A as a prognostic marker was independent or dependent on other clinical features such as age and tumour size. Most studies included in this review [25, 33, 38–41, 43–45, 47, 48, 51, 52, 54, 57, 58, 60–65, 67] suggest CIP2A to be an independent biomarker. For example, in the study by Xu et al [64] in pancreatic cancer, following multivariate analysis they concluded that CIP2A expression was an independent prognostic factor ($p = 0.008$). This is consistent with the findings of Zhang and Wang [67] who report that in glioma CIP2A is an independent prognostic marker for OS ($p = 0.003$). Nine of the studies included in this review did not report multivariate analyses. Therefore, it is concluded that CIP2A appears to be independent of other clinical features; confirmation of this could be obtained through a prospective study. Notably, none of the included studies assessed whether CIP2A improves prognostic performance beyond established clinical staging systems or existing prognostic tools. As a result, CIP2A's value for predicting prognosis remain uncertain, despite evidence suggesting it may function as an independent prognostic factor.

Not all cancer types demonstrated a significant association between CIP2A expression levels and survival outcomes. Subgroup analysis on renal clear cell carcinoma and oral cancer

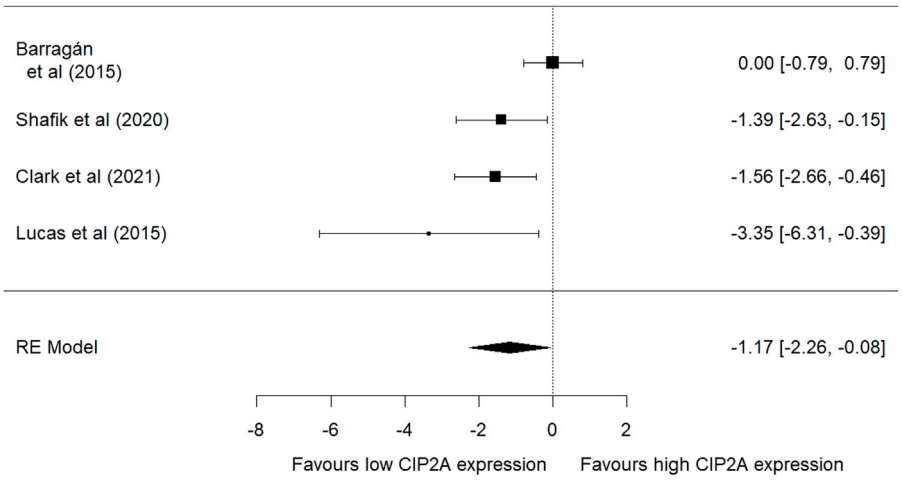


FIGURE 11
Forest plot showing the pooled effect of high versus low CIP2A expression on one-year overall survival in myeloid leukaemias, including acute and chronic myeloid leukaemia, using a random-effects model. Effect estimates are presented as log risk ratios (log RR) with 95% confidence intervals. A log RR of 0 represents no association between CIP2A expression and outcome; values below 0 indicate an association favouring low CIP2A expression, while values above 0 indicate an association favouring high CIP2A expression.

patients showed no significant prognostic effect. In renal clear cell carcinoma, the association between CIP2A expression and overall survival at 5 years did not reach statistical significance ($p = 0.071$), although a consistent trend towards poor survival with elevated CIP2A expression was observed. This is supported by the individual studies within this subgroup report associations between CIP2A expression and features including higher tumour grade, increased tumour size, lymph, and tumour node metastasis stage, as well as OS [50, 57, 61]. Similarly, in oral cancer, the pooled analysis from this review showed no statistically significant association between CIP2A expression and survival outcomes. However, individual studies reported that high CIP2A expression was associated with poor survival as well as increased tumour size, metastasis, and nodal involvement [38, 56, 58]. Additional findings also suggested that age (>60 years) and systemic inflammation were also associated with poor survival outcomes, with the study by Seppälä, Tervo [56] suggesting that there is a potential interaction between CIP2A expression and inflammation in tongue cancer progression.

Although several analyses demonstrated low statistical heterogeneity, this should be interpreted cautiously given the clinical and biological diversity of the included cancer types, which differ in overall biology and baseline prognosis. To partially address clinical heterogeneity, subgroup analyses by cancer type were performed however, I^2 estimates may be unreliable when based on small number of studies.

There are a few other limitations in this review to consider. Firstly, for this systematic review, only English-language research papers were selected, this excluded some papers that may have added more depth to the analysis. Secondly, due to the lack of reported descriptive statistics (e.g., mean and median survival data) in some of the selected studies, KM plots provided the data points for OS and PFS. In these cases, survival probabilities were read directly from published KM curves at predefined time points. This approach may introduce minor measurement error due to graphical resolution and scaling, increasing the potential for human error in extracted values. Future studies could use digital extraction tools for KM curves, alongside reporting numerical survival data to improve reproducibility and strengthen the reliability of future meta-analyses. The present analysis was also intentionally restricted to studies published from 2013 onwards to provide an updated quantitative synthesis following the earlier review by Khanna and Pimanda [8]. Earlier publications were therefore not included in the quantitative synthesis, although selected studies were discussed where necessary to provide historical context and to allow comparison with the earlier evidence base. Although this may limit the number of papers included, this approach enabled the present study to focus on the subsequent expansion of the clinical literature rather than duplicating the findings of the previous review. An additional limitation is the heterogeneity between publicly available databases such as the Human Protein Atlas, which report differing conclusions for CIP2A depending on cohort selection and expression quantification methods. Finally, papers lacking clinical data were excluded, clinical data is defined as data that was collected from patients and included data on survival milestones such as PFS, OS and EFS. This limited the scope of the study and may have impacted the results.

Conclusion

In conclusion, despite the methodological limitations of this systematic review, the findings suggest that CIP2A may have potential as a prognostic biomarker in cancer. Elevated CIP2A expression was associated with poor OS and PFS, with stronger association observed in breast cancer, colorectal cancer, and CML compared with other cancer types. Notably, the literature shows that CIP2A may provide an enhanced prognostic assessment when in combination with other markers such as NLR. Future research should focus on the validation of CIP2A as a prognostic biomarker in specific cancer types and explore its use in combination with other biomarkers to improve prognostic stratification.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization, AB and CML; methodology, AB; software, AB; validation, AB, CL; formal analysis, AB; investigation, AB, CL; resources, AB; data curation, AB, CL; writing – original draft preparation, AB; writing – review and editing, AB, CL, and CML.; supervision, CML; project administration, AB; funding acquisition, CML. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/bjbs.2026.17153/full#supplementary-material

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