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Prognostic significance of cyclin-dependent kinase subunit 2 (CKS2) in malignant tumours: a meta-analysis and bioinformatic analysis

Yi Zhang ,[1] Zheng Li,[1] Ying Huang,[2] Bingwen Zou,[1] Yong Xu[1]

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[1]Department of Radiation Oncology, Division of Thoracic Oncology, Sichuan University West China Hospital, Chengdu, Sichuan, China
[2]College of Management, Sichuan Agricultural University, Yaan, Sichuan, China

Correspondence to
Professor Bingwen Zou; zoubingwen81@163.com and Dr Yong Xu; xy868996@163.com

ABSTRACT

Objectives This study aimed to systematically elucidate the prognostic significance of cyclin-dependent kinase subunit 2 (CKS2) expression in various cancers and its correlation with their clinicopathological characteristics.

Design In this meta-analysis and bioinformatic analysis, articles were identified through searches of multiple databases and meta-analysed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols. Data from The Cancer Genome Atlas were examined using UCSC Xena tools to further confirm the prognostic effect of CKS2.

Data sources The PubMed, Embase, Web of Science and Cochrane Library databases were searched for articles published from their inception to 1 January 2023, using a combination of subject terms and free words, including 'CKS2', 'cancer', 'tumor', 'neoplasm', 'carcinoma', 'malignancy' and 'prognosis'.

Eligibility criteria The analysis included cohort or case–control studies, reported in English, with malignancy diagnoses confirmed by pathological methods, available HRs and 95% CIs for overall survival (OS) or extractable Kaplan-Meier curves, and a sample size of ≥20 patients. Reviews, commentaries, letters, conference reports, case reports, in vitro and animal studies, studies of *CKS2* gene variants, studies with sample cases from public databases and studies with unavailable survival or duplicated data were excluded.

Data extraction and synthesis Two researchers independently screened the articles, extracted the data and evaluated the quality of included studies using the Newcastle-Ottawa Scale. Meta-analysis and bioinformatic analyses were performed using the STATA and R software, respectively.

Results The analysis included 13 retrospective studies encompassing 1348 cases across 10 cancer types. Nine studies involving 1124 patients examined the correlation between CKS2 expression levels and OS. A fixed-effects model analysis revealed a significant association between high CKS2 expression and reduced OS (HR=2.27, 95% CI=1.87 to 2.77, p<0.001). Furthermore, high CKS2 expression was significantly associated with advanced tumour stage (relative risk (RR) = 1.82, 95% CI=1.57 to 2.11, p<0.001), lymph node metastasis (RR=1.68, 95% CI=1.38 to 2.04, p<0.001), larger tumour size (RR=1.60, 95% CI=1.27 to 2.03, p<0.001) and lower differentiation grade (RR=1.57, 95% CI=1.29 to 1.90, p<0.001). CKS2 expression levels were not significantly correlated with patients' age (RR=1.11, 95% CI=0.99 to 1.26, p=0.071) or sex (RR=0.98, 95% CI=0.90 to 1.07, p=0.653). An assessment of the articles showed no significant publication bias, confirming the robustness of these findings. The bioinformatic analysis further confirmed CKS2 upregulation in the examined cancer types and its association with poor OS in glioma (HR=1.97, 95% CI=1.78 to 2.18, $p=3.70\times10^{-42}$), liver hepatocellular carcinoma (HR=1.56, 95% CI=1.31 to 1.86, $p=3.50\times10^{-7}$) and lung adenocarcinoma (HR=1.27, 95% CI=1.10 to 1.48, $p=1.70\times10^{-3}$).

Conclusions Elevated CKS2 expression is associated with poor prognosis in a subset of malignant tumours, highlighting its potential as a prognostic marker.

PROSPERO registration number CRD42023394038.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Including a bioinformatic analysis alongside a traditional meta-analysis enabled a robust evaluation of CKS2's prognostic value in various cancers.
⇒ This study was limited by the retrospective nature of the included studies, which might introduce biases and limited the strength of the evidence.
⇒ This study includes limited cancer types and relies heavily on studies from specific geographical regions, potentially affecting the generalisability of its findings to other cancer types and to broader populations.

INTRODUCTION

Cancer, a leading cause of mortality worldwide, is fundamentally driven by aberrant cell proliferation—a process governed by the meticulous regulation of the cell division cycle.[1 2] The fidelity of this cycle is vital for cell survival and proliferation, ensuring orderly growth, DNA replication and cell division.[3] A complex regulatory network of cell cycle proteins ensures the seamless sequential repetition of phases in the cell division cycle.[3] However, disruptions within this network can lead to the uncontrolled cell proliferation characteristic of cancerous growths.

Understanding the molecular intricacies of this regulation is crucial since it holds the key to unlocking novel therapeutic targets and prognostic markers in oncology.

The cyclin-dependent kinase (CDK) subunits are central to cell cycle regulation, playing an integral role in modulating various phases in the cell division process.[4] Among them, CDK subunit 2 (CKS2) has emerged as a protein of significant interest due to its critical involvement in the G2/M transition of the cell cycle.[5] Beyond its role in cell cycle regulation, CKS2 is implicated in various physiological processes, including mitosis, cellular differentiation and cell proliferation.[6] This multifaceted involvement underscores the potential of CKS2 as a key player in cancer pathophysiology.

Recent scientific studies have revealed that CKS2 is differentially overexpressed in multiple malignancies, including non-small-cell lung cancer, gastric cancer and glioma.[7–9] This differential expression is not merely a consequence of but is closely associated with tumour progression and aggressiveness.[10] Despite these revelations, the specific physiological roles and detailed molecular mechanisms by which CKS2 influences tumour cell proliferation remain largely unknown. Filling this knowledge gap is essential since it could facilitate the development of targeted therapies and enable CKS2's use as a prognostic marker. Consequently, there is an urgent need for a comprehensive synthesis of the available data to elucidate the clinical relevance of CKS2 in oncology.

Given the critical role of CKS2 in cancer biology, this study pioneers a dual approach, combining a meta-analysis with bioinformatic analysis, to determine the prognostic significance of CKS2 in malignant tumours. This study is not merely academic; it is a clarion call to validate the prognostic potential of CKS2, understand its clinical implications and pave the way for its integration into personalised cancer care. By unravelling the correlation between CKS2 expression levels and various cancer prognostic factors, such as tumour stage, differentiation, lymph node metastasis and distant metastasis, this study seeks to establish CKS2 as a prognostic marker, setting the stage for its potential clinical use in personalised cancer care.

METHODS

Meta-analysis

Study design and registration

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11] and was preregistered with PROSPERO (ID: CRD42023394038). The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) table is provided as online supplemental table S1.

Literature search strategy

Two researchers independently searched the PubMed, Embase, Web of Science and Cochrane Library databases for articles published from their inception to 1 January 2023. All searches combined subject terms and free words. The search term was as follows: ('CKS2' OR 'cyclin-dependent kinase subunit 2') AND ('cancer' OR 'tumor' OR 'neoplasm' OR 'carcinoma' OR 'malignancy') AND 'prognosis'. Details of the search strategy are provided in the supplementary material (online supplemental tables S2–S5). The reference lists in the retrieved articles were also manually searched to identify any missing articles.

Inclusion and exclusion criteria

Inclusion criteria

This study's inclusion criteria were as follows: (1) cohort or case–control studies; (2) malignancy diagnoses confirmed by pathological methods; (3) available HRs and 95% CIs for overall survival (OS) or extractable Kaplan-Meier curves; (4) sample size of ≥20 patients and (5) publication in the English language.

Exclusion criteria

This study's exclusion criteria were as follows: (1) reviews, commentaries, letters, conference reports and case reports; (2) in vitro or animal studies; (3) studies with studies of haematological tumours; (4) studies of genetic *CKS2* gene variants (eg, polymorphisms or methylation patterns); (5) studies with sample cases from public databases; and (6) unavailable survival data or duplicated data.

Data extraction

Two researchers independently screened the articles according to the inclusion and exclusion criteria and extracted the desired information. The information extracted from the articles included the first author, publication year, country, tumour type, sample size, follow-up duration, outcome indicators and clinically relevant pathological features. Specifically, clinically relevant pathological features were extracted: tumour differentiation, tumour size, lymph node involvement and distant metastasis. These features are paramount since they provide insights into tumour aggressiveness and stage, which can significantly impact prognosis and therapeutic decisions. Result indicators included OS. HRs and their 95% CIs for OS already provided in the articles were directly extracted. If the outcomes were only represented by Kaplan-Meier curves and no specific values were reported, the data from the Kaplan-Meier curves were extracted using the Engauge Digitizer software (V.4.1; http://markummitchell.github.io/engauge-digitizer) according to the method reported by Tierney *et al*.[12] In case of disagreement during the extraction process, a joint decision was made after a discussion between the two investigators, and a third investigator ruled if the decision was not unanimous. The article screening process is illustrated in figure 1.

Evaluation of the quality of the literature

Two investigators independently evaluated the quality of the included articles using the Newcastle-Ottawa Scale (NOS).[13] Each item was scored, and the

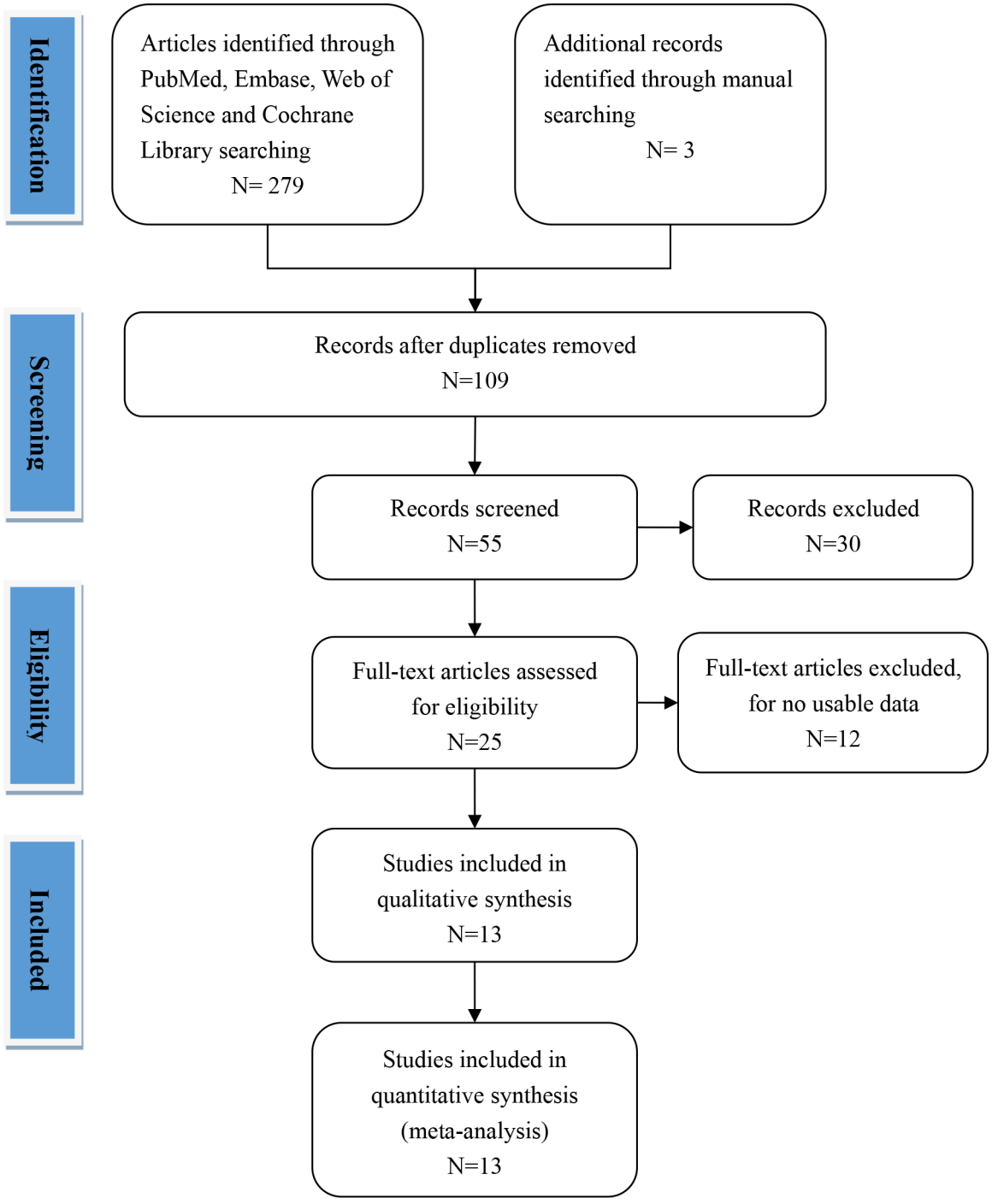


Figure 1 Flowchart of article identification and selection.

maximum NOS score is 9. The two investigators jointly decided each article's final NOS quality score, and disagreements were resolved through mutual discussion or by a third researcher. Articles with a NOS score of ≥6 were considered high quality and selected for this study.

Statistical analyses

Data analyses were conducted using the STATA software (V.12.0). HRs and their 95% CIs were used to assess the relationship between CKS2 expression levels and the survival of patients with cancer. Relative risk (RRs) and their 95% CIs were used to assess the correlation between CKS2 expression levels and clinicopathological features. The heterogeneity in the studies was assessed using the χ^2 test and the inconsistency index (I^2).[14] Heterogeneity was considered high when the χ^2 test p value was <0.05 and the I^2 value was ≥50%. HR and RR were combined using a random-effects model when I^2 was ≥50% and a fixed-effects model when I^2 was <50%.[15] Begg's and Egger's tests were used to detect significant publication bias.[16 17] A p<0.05 was considered statistically significant, except for the heterogeneity test.

Bioinformatic analysis

Data extraction and preprocessing

To further examine the prognostic effect of CKS2, we downloaded the unified and standardised pan-cancer dataset from the UCSC database. Then, we extracted and $\log_2(x+0.001)$ transformed the gene expression data for ENSG00000123975 (CKS2) for each sample. Finally, we obtained the expression data of cancer types included in this study and the OS data of the corresponding samples: invasive breast carcinoma (BRCA), cholangiocarcinoma (CHOL), colon/rectum adenocarcinoma (COADREAD), oesophageal carcinoma (ESCA), glioma (GBMLGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), ovarian serous cystadenocarcinoma (OV), stomach adenocarcinoma (STAD) and uterine corpus endometrial carcinoma (UCEC).

Differential CKS2 expression analysis

In order to further explore CKS2 expression levels in different tumour and cancer tissues, we calculated the difference in expression between normal and tumour samples for each tumour using the R statistical software (V.3.6.4), conducted difference significance analyses using unpaired Wilcoxon rank-sum and signed-rank tests and created violin plots to visualise the results.

Prognostic analysis of CKS2 expression

To acquire a more comprehensive understanding of CKS2's prognostic value, we used the coxph function of the R survival package (V.3.2.7) to establish a Cox proportional hazards regression model to analyse the relationship between *CKS2* gene expression and prognosis in each tumour.[18] We assessed prognostic significance using the log-rank test.

Patient and public involvement

None.

RESULTS

Meta-analysis results

Literature screening results and the included articles' basic characteristics

Our search strategy identified 124, 61, 94 and 0 articles from the PubMed, Embase, Web of Science and the Cochrane Library databases, respectively, of which 13 were selected for inclusion in this study based on its inclusion and exclusion criteria. The article screening process is shown in figure 1. Of the 13 included articles,[8 9 19–29] 10 were from China, 2 were from Japan and 1 was from South Korea. Their sample size ranged from 38 to 345, with a mean of 103.7. The included articles covered 11 types of cancer, comprising 1348 cases. The features of all eligible articles are shown in table 1.

Relationship between CKS2 expression levels and OS

Nine articles reported a correlation between CKS2 expression levels and OS among 1124 patients with cancer, with minor heterogeneity between studies (I^2=0.0%, p=0.940). Therefore, an analysis was performed with a fixed-effects model, revealing that high CKS2 expression was significantly correlated with OS (HR=2.27, 95% CI=1.87 to 2.77, p<0.001; figure 2), with patients with low CKS2 expression having better OS. A subgroup meta-analysis was performed by cancer type. The classification of all cancer types into two categories (digestive tract and non-digestive tract) showed a positive association in patients with non-digestive tract tumours (HR=2.47, 95% CI=1.71 to 3.58, p<0.001; online supplemental table S6). Subgroup meta-analyses stratified by country, sample size and follow-up times were also performed. Similar results were found regarding the effects of increased CKS2 expression on OS (online supplemental table S6).

Relationship between CKS2 expression levels and clinicopathological characteristics

Some of the included studies had examined the relationship between CKS2 expression levels and the clinicopathological traits of patients with tumours. Our results showed that high CKS2 expression was significantly associated with tumour stage (RR=1.82, 95% CI=1.57 to 2.11, p<0.001; online supplemental figure S1), lymph node metastasis (RR=1.68, 95% CI=1.38 to 2.04, p<0.001; online supplemental figure S2), tumour size (RR=1.60, 95% CI=1.27 to 2.03, p<0.001; online supplemental figure S3) and differentiation grade (RR=1.57, 95% CI=1.29 to 1.90, p<0.001; online supplemental figure S4). However, high CKS2 expression was not significantly associated with patients' age (RR=1.11, 95% CI=0.99 to 1.26, p=0.071; online supplemental figure S5) or sex (RR=0.98, 95% CI=0.90 to 1.07, p=0.653; online supplemental figure S6 and table S7).

Publication bias and sensitivity analysis

We assessed publication bias in the included studies using Begg's test (Z=1.36, Pr>Z = 0.175; figure 3A) and Egger's test (p=0.160; figure 3B). Both tests indicated no significant publication bias in the included studies. The sensitivity analysis (figure 3C) also showed no significant effect on the combined HR after eliminating each study, indicating the relative robustness of our results.

Bioinformatic analysis results

Differential CKS2 expression analysis

Data from the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression Project (GTEx) were used to quantitatively confirm CKS2 expression in the cancer types included in this study. Figure 4A shows a significant difference in CKS2 expression between normal and tumour samples. In addition, CKS2 expression was significantly upregulated in all 11 cancers included in this study: BRCA, CHOL, COADREAD, ESCA, GBMLGG, LIHC, LUAD, LUSC, OV, STAD and UCEC. CKS2 expression levels in different cancers are shown in online supplemental table S8.

Table 1 Key information on the articles included in the meta-analysis

Study	Country	Cancer type	Sample size	Follow-up (months)	Tumour stage (I/II/III/IV)	Outcome measures	Gender (female/male)	NOS
Kang *et al* 2009[19]	South Korea	Gastric cancer	60	–	24/12/12/12	–	48/12	7
Shen *et al* 2010[20]	China	Hepatocellular carcinoma	48	–	–	–	10/38	7
Tanaka *et al* 2011[21]	Japan	Gastric cancer	109	134	57/51(I–II/III–IV)	OS	35/74	8
Shen *et al* 2013[22]	China	Cholangiocarcinoma	62	19 (12–36)	–	OS	14/48	7
Wang *et al* 2013[23]	China	Oesophageal carcinoma	56	–	5/10/35/6	–	8/48	7
Wang *et al* 2014[25]	China	Breast cancer	126	111 (2–131)	10/76/40(I/II/III)	OS	126/0	8
Kita *et al* 2014[24]	Japan	Oesophageal carcinoma	121	24 (1–181)	58/63(I–II/III–IV)	OS	12/109	8
Yu *et al* 2015[26]	China	Colorectal cancer	345	120	85/119/117/24	OS	146/199	8
Xu *et al* 2019[29]	China	Epithelial ovarian cancer	127	60	89/38(I–II/III–IV)	OS	127/0	8
Deng *et al* 2019[27]	China	Uterine leiomyosarcoma	38	5	26/3/5/4	OS	38/0	8
Wan *et al* 2022[8]	China	NSCLC	60	–	12/35/13(I/II/III)	–	26/34	7
Feng *et al* 2022[28]	China	Glioma	70	80	28/42(I–II/III–IV)	OS	38/32	7
Zhou *et al* 2022[9]	China	Gastric cancer	126	46.5	37/48/41(I/II/III)	OS	48/78	8

'–' indicates not available/not reported.
NOS, Newcastle-Ottawa Scale; NSCLC, Non-small cell lung cancer; OS, overall survival.

Prognostic analysis of CKS2 expression

To acquire a more comprehensive understanding of the prognostic value of CKS2, we performed separate Cox analyses of OS for each cancer type. CKS2 expression levels were significantly associated with OS in patients with GBMLGG (HR=1.97, 95% CI=1.78 to 2.18, $p=3.70\times10^{-42}$), LIHC (HR=1.56, 95% CI=1.31 to 1.86, $p=3.50\times10^{-7}$) and LUAD (HR=1.27, 95% CI=1.10 to 1.48, $p=1.70\times10^{-3}$; figure 4B).

DISCUSSION

The regulation of the cell division cycle is essential for cell survival and proliferation, and the sequential repetition of the phases in the cell division cycle is achieved through a complex regulatory network of cell cycle proteins.[4] Therefore, tumours are caused by aberrant cell proliferation due to disruptions in cell cycle regulation.[3] The CKS family comprises a group of small proteins that play important roles in regulating the cell division cycle.[6] Both CKS1 and CKS2 are reportedly involved in regulating cell proliferation, playing distinct roles in different cell cycle phases.[30] A component essential for the Skp, Cullin, F-box containing complex including S-phase kinase-associated protein 2 (SCF^{Skp2})-mediated degradation of p27 ubiquitination, CKS1 is mainly involved in regulating the G1/S transition of the cell cycle, whereas CKS2 is essential for the G2/M transition.[31 32] CKS2 is also involved in regulating several physiological processes, including mitosis, cellular differentiation and cell proliferation. Recent studies have shown that CKS2 is differentially overexpressed in several cancer types, and this differential expression is closely associated with the progression of various cancers, including prostate cancer, nasopharyngeal carcinoma and glioma.[33–36] CKS2 promotes cancer cell proliferation by regulating cell cycle proteins, including cyclin A, cyclin B1 (CCNB1) and CDK1.[9] Nonetheless, the specific physiological roles of CKS2 and the detailed molecular mechanisms underlying its involvement in tumour cell proliferation remain largely unknown.

This is the first meta-analysis to integrate the outcomes of existing studies on CKS2 to further validate its potential

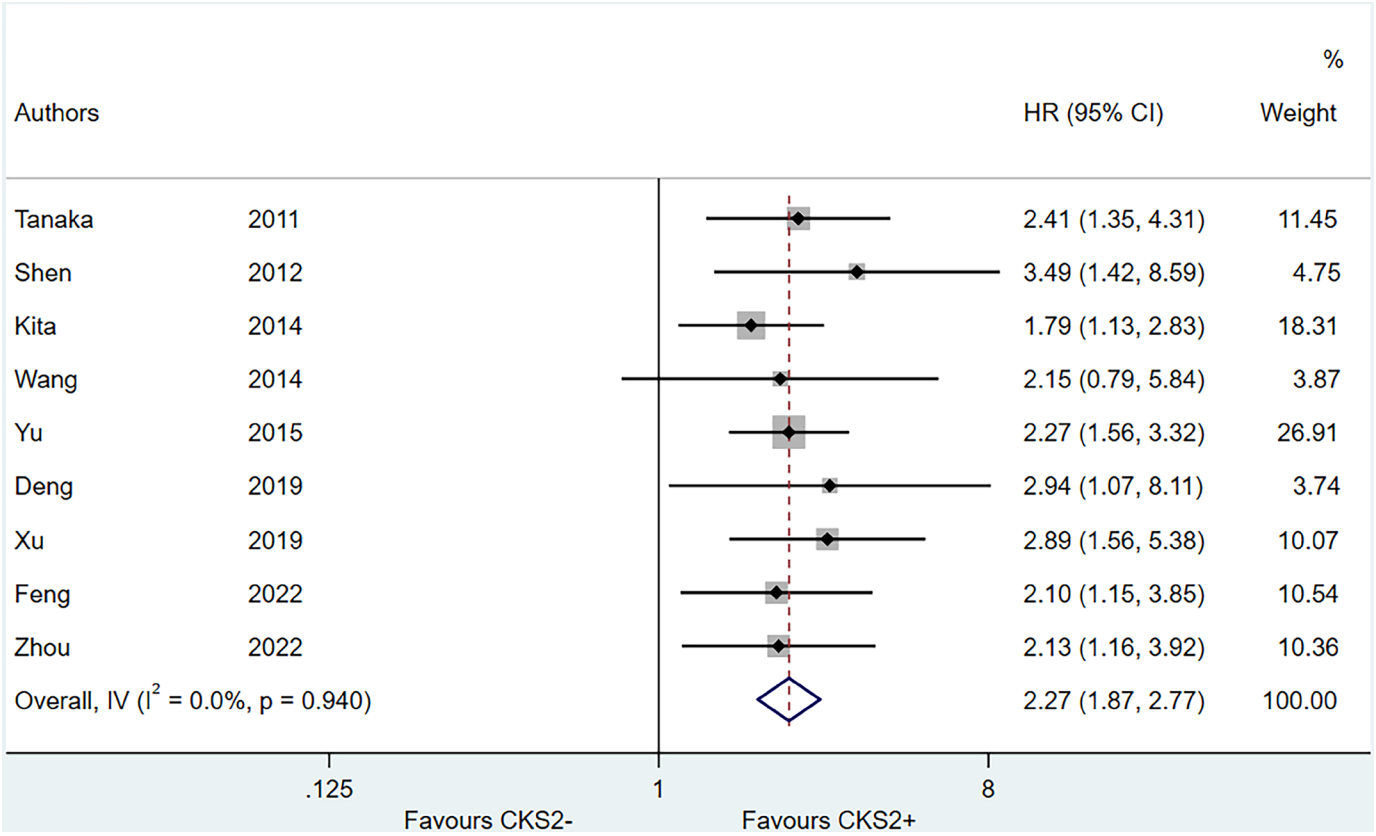


Figure 2 Meta-analysis of the pooled HRs for OS in patients with cancer. CKS2, cyclin-dependent kinase subunit 2; OS, overall survival.

prognostic value in tumours. It showed that a high CKS2 expression is unfavourable for survival in various cancers. High CKS2 expression correlated with patients' tumour stage, the degree of tumour differentiation, lymph node metastasis and distant metastasis, further underscoring the critical correlation between high CKS2 expression and poor prognosis in patients with cancer. Bioinformatic analysis revealed significant overexpression of CKS2 in various cancers, consistent with the findings of several other studies, further solidifying the idea that CKS2 plays a critical role in different cancer types. In addition, it indicated that elevated CKS2 expression was significantly associated with worse OS in patients with glioma, liver hepatocellular carcinoma and lung adenocarcinoma. This finding is consistent with Yu *et al*,[7] who also reported that high CKS2 expression was associated with reduced survival in patients with glioma. Similarly, Zhi *et al*[37] found that increased CKS2 expression was a marker of poor prognosis in patients with hepatocellular carcinoma. These corroborative findings from diverse cancer types suggest that CKS2 might have a universal role in cancer biology, making it a promising candidate for further research and clinical application.

The clinical implications of our findings extend beyond mere prognostication. The clinical utility of this study lies in its potential to transform current oncological practices. By establishing CKS2 as a prognostic marker, this research provides a foundation for personalised medicine approaches in cancer care. Clinicians could use CKS2 expression levels as a biomarker to stratify patients based on their prognostic risk, enabling more tailored and potentially effective treatment strategies. For example, patients with high CKS2 expression might benefit from more aggressive treatment regimens or closer monitoring, while those with lower CKS2 expression could avoid excessive treatment. Furthermore, CKS2's role in cell cycle regulation presents an opportunity for targeted therapies. CKS2 inhibitors could be developed as novel anticancer agents, potentially offering new treatment avenues for patients currently with limited options. Additionally, the early detection of CKS2 overexpression could facilitate the diagnosis of aggressive cancer subtypes, leading to earlier intervention and improved patient outcomes. Overall, our study underscores the importance of biomarker research in advancing precision oncology and improving cancer prognosis. Despite these promising prospects, there remains a long way to go. Further research, clinical trials and the development of targeted therapies are essential to fully realise the potential of CKS2 as a cornerstone in cancer diagnosis, treatment and management.

Our study observed a significant correlation between CKS2 expression levels and the prognosis of patients with malignant tumours, consistent with recent research. However, it had the following limitations. First, the included studies only represented 11 cancer types,

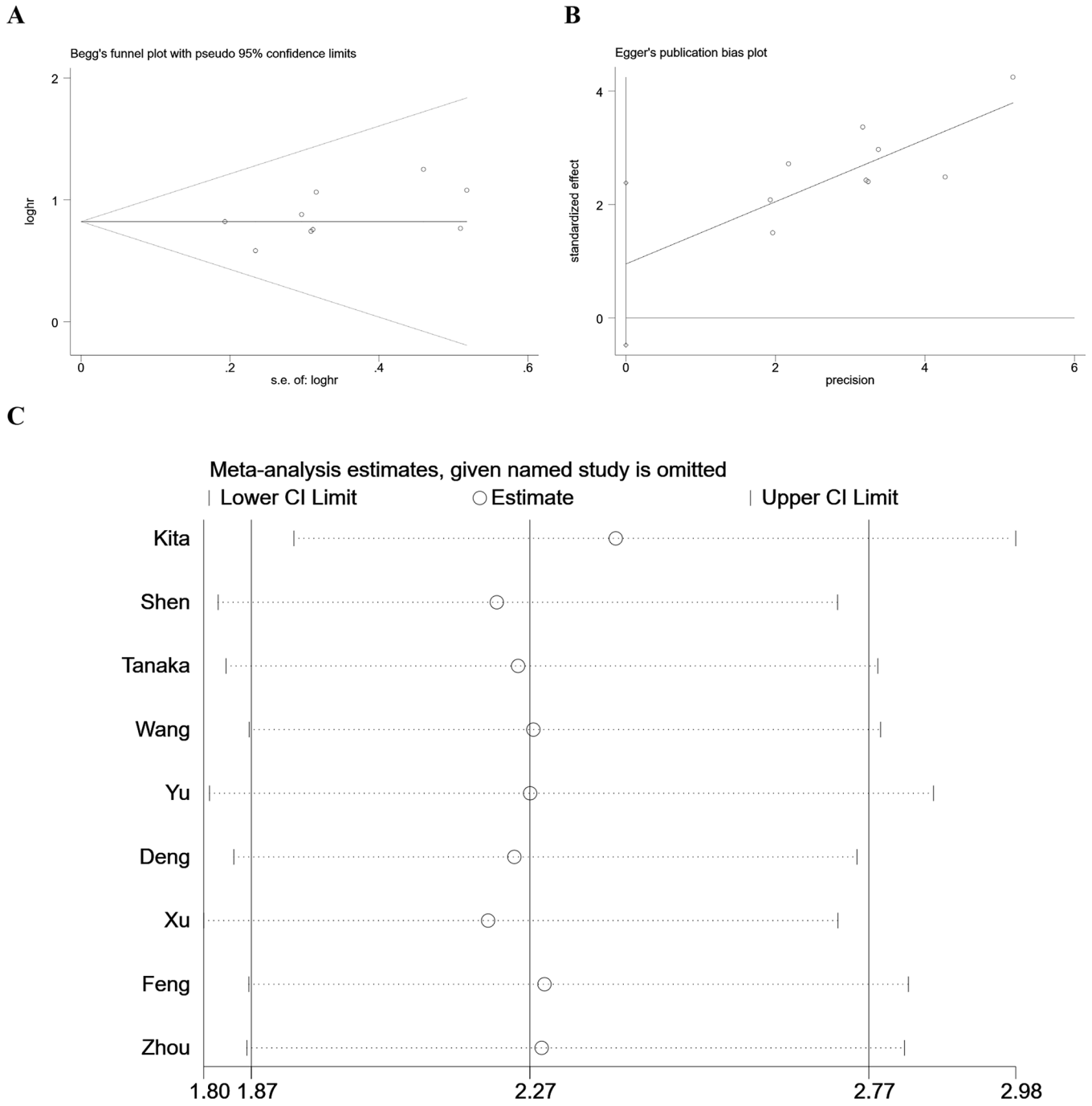
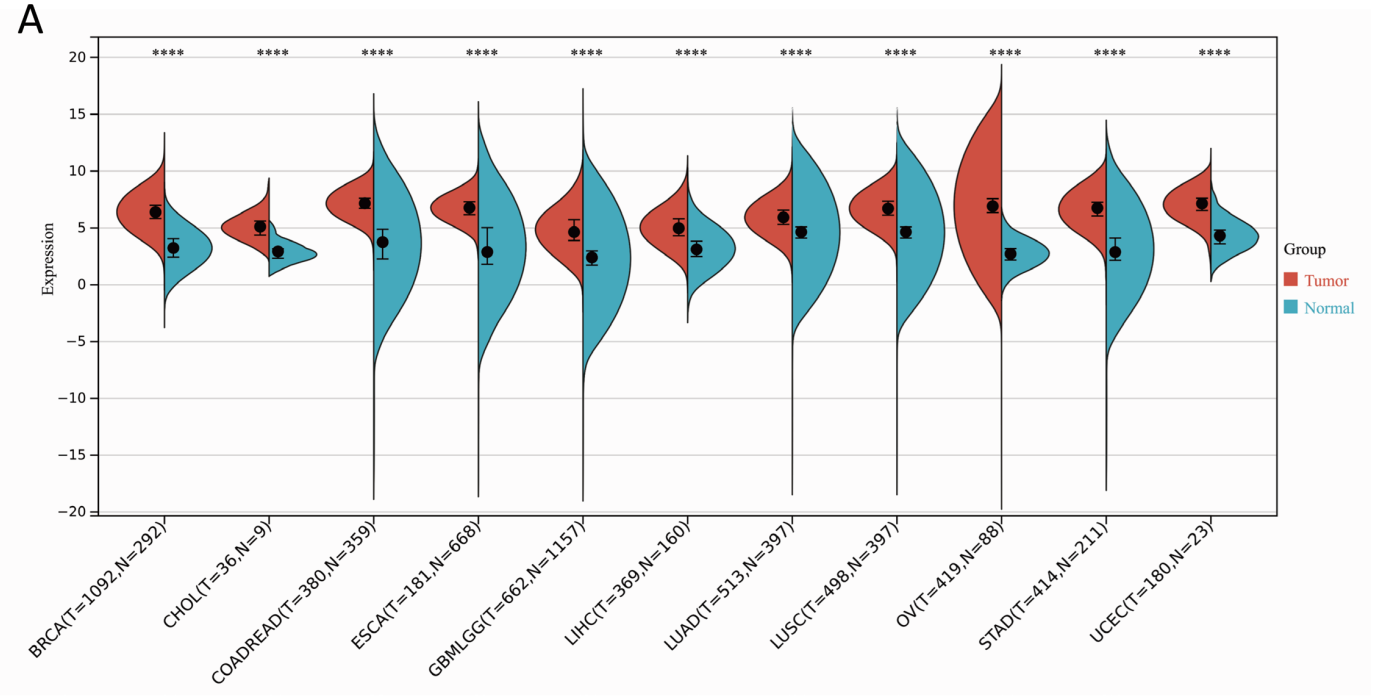


Figure 3 Begg's funnel plot (A), Egger's test (B) and sensitivity analysis (C) for publication bias of the correlation between *cyclin-dependent kinase subunit 2* expression and overall survival.

primarily digestive malignancies. Consequently, it may not comprehensively represent the full spectrum of malignancies, and the observed associations should be interpreted cautiously and may not be universally prognostic. Second, no clinical trials were identified in our search, which is a significant limitation. The studies included in our analysis were retrospective, so their evidence was weak due to the lack of randomised controlled trials. Consequently, the findings of our meta-analysis are based on associations and correlations observed in cohort studies rather than definitive causation. Third, the included patients with cancer were clinically heterogeneous, with different tumour stages, surgical approaches and adjuvant treatments. Fourth, inconsistent measurement procedures and criteria for quantifying CKS2 expression levels may have increased heterogeneity in our study, leading to measurement bias. Fifth, the corresponding data obtained from Kaplan-Meier curves may have contained errors, possibly impacting our final results. Sixth, our study had some heterogeneity and bias that could not be avoided altogether. Therefore, while our study provides valuable insights into CKS2's role in cancer prognosis, prospective studies with standardised assessment methods are imperative to validate our findings and explore the therapeutic



B

CancerCode	pvalue	Hazard Ratio(95%CI)
TCGA-BRCA(N=1044)	0.27	1.10(0.93,1.30)
TCGA-CHOL(N=33)	0.11	1.85(0.86,3.95)
TCGA-COADREAD(N=368)	0.88	0.98(0.73,1.30)
TCGA-ESCA(N=175)	0.3	1.16(0.88,1.52)
TCGA-GBMLGG(N=619)	3.70E-42	1.97(1.78,2.18)
TCGA-LIHC(N=341)	3.50E-07	1.56(1.31,1.86)
TCGA-LUAD(N=490)	1.70E-03	1.27(1.10,1.48)
TCGA-LUSC(N=468)	0.84	1.02(0.87,1.19)
TCGA-OV(N=407)	0.13	0.92(0.83,1.02)
TCGA-STAD(N=372)	0.09	0.88(0.75,1.02)
TCGA-UCEC(N=166)	0.39	0.87(0.63,1.20)

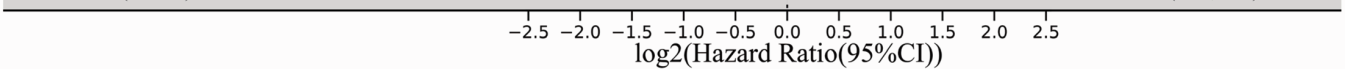


Figure 4 Bioinformatic analysis of CKS2: (A) differential expression and (B) prognostic analysis.

potential of CKS2 in cancer management. Furthermore, in this study, we focused primarily on the expression levels and prognostic significance of CKS2 in various malignancies. A strategic decision was made to concentrate on gene expression rather than epigenetic modifications, such as gene methylation. This choice was driven by our objective to provide a streamlined examination of CKS2's role within a specific scope, aiming for clear insights into its expression patterns and implications in cancer. Future studies may involve a comparative analysis of gene expression and methylation patterns, potentially offering novel insights into cancer biology and aiding in the development of targeted therapeutic strategies.

In conclusion, high CKS2 expression may result in a reduced OS in patients with cancer and correlate with their tumour stage, degree of tumour differentiation, lymph node metastasis and distant metastasis. Therefore, CKS2 could be a potential prognostic marker for various cancers. Regarding future perspectives, the prognostic value of CKS2 should be further validated in multiple cancers using larger sample sizes, broader population sources and standardised clinical trials.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study did not require ethical approval since it was based on published data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

ORCID iD

Yi Zhang http://orcid.org/0009-0000-5564-1209

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