RESEARCH ARTICLE

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Prognostic and Clinical Significance of Circulating Cystatin C Levels in Cancer Patients: A Meta-Analysis

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Abstract

Background: Cystatin C (CysC) exhibits both tumor-promoting and tumor-suppressing effects. Although elevated circulating CysC levels have been reported in multiple cancer types, studies assessing its prognostic value have produced conflicting results. This study aims to resolve these discrepancies and clarify the role of CysC as a prognostic marker. **Methods:** A literature search was conducted in multiple databases. The pooled Hazard Ratio (HR) with a 95% confidence interval (CI) was calculated to assess the prognostic significance of CysC, while the Odds Ratio (OR) with a 95% CI was used to evaluate its clinicopathological associations in various cancers. Sources of heterogeneity were identified by performing subgroup and meta-regression analyses. The study was registered in PROSPERO. **Results:** Twelve studies comprising 7678 patients were included in the analysis. The study found that elevated CysC levels were associated with worse overall survival (OS); pooled HR = 1.60, 95% CI = 1.22–2.10; p = 0.0006, I^2 = 84%. Subgroup analyses indicated that renal cancer, follow-up time >2.5 years, and study location (China) were linked to worse survival, and all subgroups contributed to significant heterogeneity. Sensitivity analysis confirmed the robustness of the pooled results. Additionally, CysC levels correlated with T stage, N stage, TNM stage, and sex, but not with smoking. **Conclusion:** Elevated CysC is associated with worse overall survival, but significant heterogeneity warrants cautious interpretation.

Keywords: Cystatin C- CysC- prognostic role- cancer- meta-analysis

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Introduction

Cancer continues to be a critical global health problem, affecting people of any age, sex, race, and ethnicity, and manifests in numerous forms. Asia experienced the highest rate of cancer-related fatalities in 2022, accounting for 56.1%, while Europe and the Americas had 20.4% and 14.9%, respectively. For men, the cancers causing the most deaths were the lungs (22.7%), liver (9.6%), and colorectal (9.2%). In women, the leading fatal cancers were breast (15.4%), lungs (13.6%), and colorectal (9.4%) [1]. Although therapies such as immunotherapy and targeted treatments have progressed, they have not significantly reduced overall cancer mortality [2]. This has prompted researchers to focus on identifying new cancer biomarkers to predict prognosis as well as for targeted therapies [3]. However, nearly all cancer biomarkers reported to date fall short of accurately assessing prognosis [4]. Therefore, the search for novel cancer biomarkers is critically needed.

CysC is a 13-kDa nonglycosylated protein consisting of 120 amino acids and belonging to the cysteine protease inhibitor family. It is encoded by the *CST3* gene on chromosome 20. CysC is secreted by all nucleated cells and is detectable in all body fluids [5-8]. Circulating CysC is not influenced by factors such as age, race, or muscle mass, and its level remains stable up to the age of 50 [8-10]. This characteristic makes serum CysC a reliable diagnostic and predictive marker for various conditions, including cirrhosis, inflammation, Parkinson's disease, kidney disease, and cardiovascular disease [11-15]. Researchers have also been investigating the role of CysC in cancer. B. Zhang reported that CysC is involved in cancer-related pathways [16]. CysC exhibits dual roles in cancer: it can act as both a tumor suppressor and a promoter. As a tumor promoter, it facilitates tumor progression by triggering p38 mitogen-activated protein kinase (MAPK) signaling, blocking lysosomal cathepsin-driven apoptosis, altering 14-3-3 (ζ.B) adaptor protein levels, disrupting

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the endothelial glycocalyx, weakening T cell–mediated antitumor responses, and increasing the expression of tumor-promoting proteases including cathepsins B, K, L, S, and legumain [17]. A study reported that the loss of CysC in breast cancer leads to suppression of tumor growth [18]. CysC accelerates myeloma bone disease by inhibiting legumain and decreasing homocysteine [19]. It also inhibits apoptosis in cancer cells (5). Consistently, an animal study demonstrated that tumor proliferation, size, and volume were significantly reduced in CysC-deficient ($CstC^{-/-}$) mice [18].

As a tumor suppressor, CysC limits tumor growth by inhibiting cathepsin activity, blocking transforming growth factor beta (TGF-β) interaction with its type II receptor, and modulating the MAPK/ERK signaling pathway [17]. CysC deficiency promotes the activity of MAPK/Erk signaling cascades, resulting in enhanced prostate cancer invasion [20]. CysC prevents angiogenesis in breast cancer by inhibiting TGF-β signaling, which results in the suppression of tumor progression [21]. CysC inhibits the progression of cancer's invasion and metastasis in ovarian cancer [22]. In melanoma cells, CysC inhibits proliferation by prolonging cell division [23].

Researchers have observed elevated CysC levels in various cancers, including head and neck, lung, gastrointestinal, ovarian, prostate, kidney, and breast cancers [24-30]. Additionally, CysC has been identified as a valuable prognostic predictor in several cancers, including myeloma, esophageal, renal, upper tract urothelial, and colorectal carcinomas, as well as non-Hodgkin's B-cell lymphoma [31-38]. Nevertheless, evidence also indicates that lower CysC expression correlates with poor breast cancer prognosis and increased risk in prostate cancer and glioma [20, 39].

This study aims to evaluate the prognostic and clinicopathological significance of elevated circulating CysC levels in cancer patients. The prognostic value of CysC was assessed by examining the association between elevated CysC levels and OS in cancer patients. OS is regarded as the most reliable and accessible measure of patient outcomes [40]. It denotes the duration between the diagnosis of cancer and death [41].

Materials and Methods

The study was registered with PROSPERO (CRD42023470689) and followed PRISMA guidelines [42].

Literature search

Web of Science, PubMed, Scopus, and Medline databases were searched for articles published up to January 5, 2024. The search strategy used the following keywords: (((Cystatin C) OR (Cys-C) OR (CST3)) AND ((Cancer) OR (Carcinoma) OR (Malignancy)) AND ((Prognosis) OR (Survival))). The search was updated on September 1, 2025.

Criteria for inclusion and exclusion

The inclusion criteria for eligible studies were as follows: (I) Original research involving cancer patients (II) Measurement of CysC in the blood (III) Use of a defined cutoff value to determine elevated CysC levels (IV) Investigation of the association between elevated CysC levels and OS (V) HRs with corresponding 95% CIs were calculated using the multivariate Cox proportional hazards model.

The exclusion criteria were as follows: animal studies; non-English publications; theses or dissertations; reviews, conference papers, letters, editorials, abstracts, books, documents, case reports, comments, or duplicate articles; and studies that used patient data from the Cancer Genome Database.

Data Extraction & Quality assessment

The titles, abstracts, and full texts of potentially relevant articles were independently screened by two authors & any conflicts were resolved by a third author. After the initial screening, irrelevant articles were excluded, and the full texts of the remaining studies were assessed. Data extracted from the included studies comprised the first author, publication year, study location, patient inclusion period, sample size, cancer type, CysC high and low patient groups, and HRs with 95% CIs. The calculation of the HR and its 95% CI from the data extracted from the Kaplan-Meier curve was not conducted in this meta-analysis due to lower reliability [43]. Two authors independently evaluated the methodological quality of the included studies using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Based on their scores, studies were categorized as low quality, poor (0–4), moderate quality, fair (5–8), or high quality, good [9–14].

Statistical Analysis

All statistical analyses were conducted using Review Manager version 5.4 and Comprehensive Meta-Analysis. Prognostic value was evaluated using pooled HRs with 95% CIs, while the clinicopathological significance of CysC in cancer was assessed using ORs with 95% CIs. Heterogeneity was assessed using I^2 and Cochran's Q statistics; I^2 >50% or $p < 0.05$ indicating high heterogeneity. A random-effects method was used in the statistical analysis. Meta-regression and subgroup analyses were utilized to identify potential contributors to heterogeneity. Publication bias was evaluated using funnel plots, Egger's regression test. Publication bias was addressed using the Duval and Tweedie trim-and-fill technique. To test the stability of the findings, sensitivity analyses were carried out. A p-value below 0.05 was regarded as statistically significant.

Results

Literature search and selection

In total, 915 articles were identified from the four databases, of which 372 duplicates were removed. Titles and abstracts of the remaining 543 articles were screened, resulting in the exclusion of 509 articles: 371 were irrelevant, 101 were reviews, 22 were other types of publications (including three book chapters, five letters, five case reports, two editorials, and seven conference

papers), 12 were non-English, and three lacked full text. Full texts of the remaining 34 articles were assessed, and 22 were excluded for the following reasons: two lacked HRs with 95% CIs, two used univariates rather than multivariate Cox models, three did not report survival outcomes, one did not provide a confidence interval, seven used genome database data, six were animal studies, and two used tissues instead of blood samples. Ultimately, 11 articles were included in the analysis, with an additional one article identified from the updated search on September 1, 2025. One study [44] was not included in this study for measuring the low CysC value to see the prognosis [44]. The 12 studies included in the meta-analysis were: [16, 24, 29, 31, 35, 37, 45-50]. Figure 1 displays the articles search approach.

Characteristics of included studies

Data from twelve studies, encompassing a total of 7,678 patients, were included in this meta-analysis. Among them, nine studies were conducted in China, and one study each was from Greece, Poland, and the USA. The studies investigated various types of cancer: five focused on renal cell carcinoma, two on nasopharyngeal carcinoma, and one each on colorectal cancer, small cell lung cancer, multiple myeloma, and upper tract urothelial cancer. One study examined multiple cancer types, including gastrointestinal tumors, thoracic cancers, urogenital neoplasms, and head and neck neoplasms. Extracted data from the included studies were presented in Table 1.

Assessment of the quality of the included studies

Assessment with the NIH Quality Assessment Tool indicated that all included studies were of adequate methodological quality (Supplementary File 1).

Association between elevated Cystatin C level and OS

The results indicated that elevated CysC was associated with shorter OS in cancer patients (pooled HR = 1.60, 95% CI: 1.22–2.10; p = 0.0006), as shown in Figure 2. Significant heterogeneity was observed ($p < 0.00001$, $I^2 = 84\%$). Sensitivity analysis was conducted by systematically excluding each study to assess its individual impact on the overall results. The findings indicated that no single study had a significant influence on the pooled effect size. The lowest pooled HR was 1.46 [1.14, 1.86] when [49] was excluded, and the highest was 1.73 [1.30, 2.32] when [16] was excluded. Publication bias was detected,

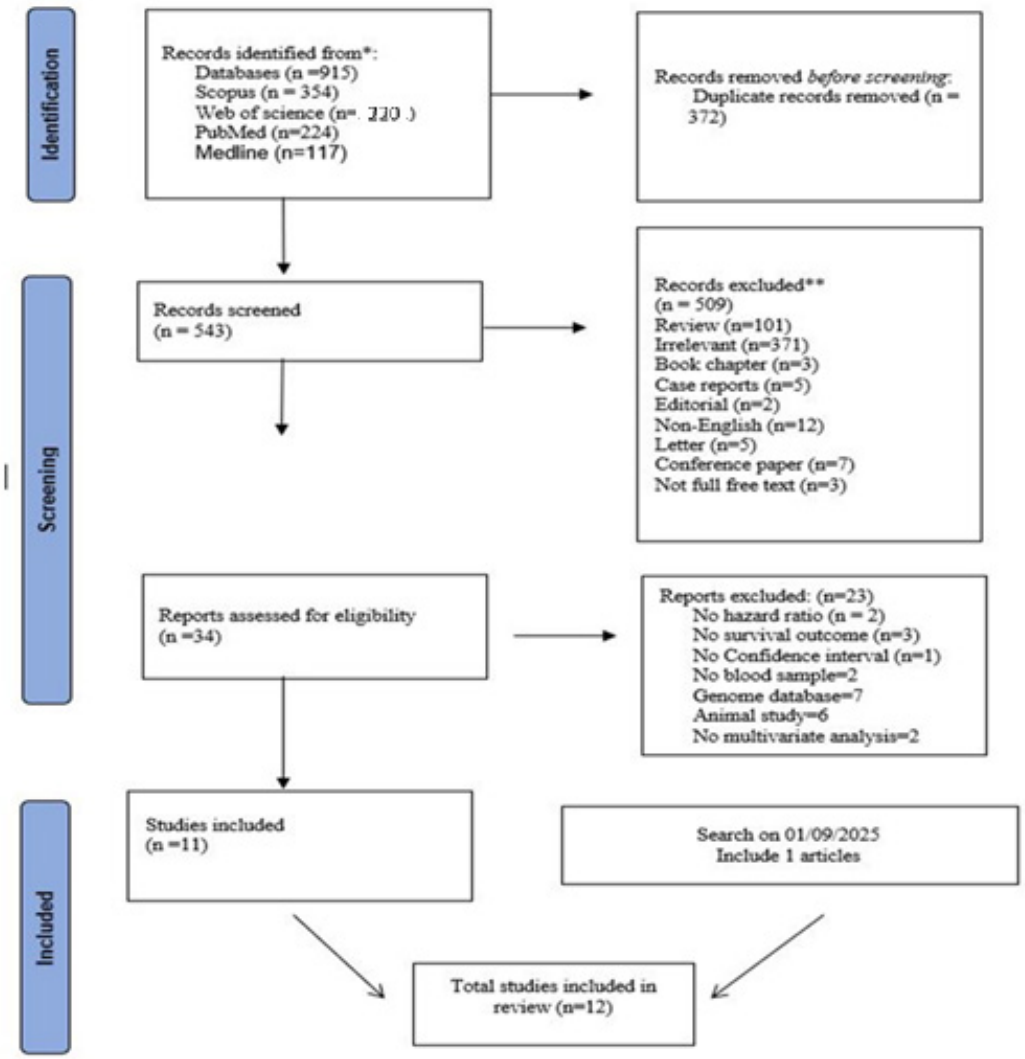

Figure 1. Visual Summary of Study Identification and Screening

Table 1. Characteristics of the Included Studies

Author	Study location	Publication year	Inclusion period	Sample size	Cancer type	Cut off value	Patients number		Mean/ median F/U time
							High CysC	Low CysC	
16	China	2023	2011-2020	2047	CRC	>1.09 mg/L	420	1627	35 months
24	China	2016	2006-2010	1063	NPC	≥0.945 mg/L	141	922	68.3 months
29	China	2017	2009-2013	325	RCC	>1.01 mg/L	109	216	48.74 months
31	Greece	2009	1995-2007	157	MM	>0.95 mg/L	NR	NR	20 months
35	China	2019	2005-2014	538	UTUC	≥1.4 mg/L	162	376	38 months
37	China	2021	2009-2012	2077	NPC	>1.03 mg/L	362	1715	96.3 months
45	China	2021	2008-2020	137	PRCC	≥1.25 mg/L	45	92	24 months
46	China	2020	2015-2018	152	SCLC	≥0.775 mg/L	83	69	NR
47	USA	2023	2018-2022	255	RCC	1.00 mg/L	NR	NR	16.6 months
48	Poland	2016	NR	56	mRCC	1.15 mg/L	44	12	NR
49	China	2019	2013-2014	247	multiple cancers	1.25 mg/L	NR	NR	598 days
50	China	2024	2013-2021	624	RCC	0.95 mg/L	164	460	40 months

Abbreviations: MM-multiple myeloma; RCC-Renal cell carcinoma; CRC-Colorectal carcinoma; PRCC-Papillary renal cell carcinoma; NPC-Nasopharyngeal carcinoma; SCLC-Small cell lung cancer; UTUC- Upper tract urinary carcinoma; mRCC-Metastatic kidney cancer; NR-Not reported, F/U: Follow up time.

as indicated by Egger's test (p = 0.047). Furthermore, the funnel plot was also asymmetrical (Supplementary File 2). Trim & fill method showed 3 studies were missing and the adjusted results indicated that the overall effect was not substantially altered (HR = 1.345; 95% CI = 1.025-1.765).

Subgroup analyses were performed based on cancer type (renal vs. other cancers), follow-up duration (>2.5 years vs. <2.5 years), and study location (China vs. other countries), and treatment status (no anti-cancer therapy & mixed or unclear treatment status). Significant heterogeneity was observed in all subgroups (Supplementary File 3, 4). Univariate meta-regression analysis was conducted using publication year, follow-up time, study location, treatment status, cut-off level, sample size and cancer type as covariates. The result showed that cancer type (p = 0.0465) as significant contributors to the observed high heterogeneity, whereas study location (p = 0.055), follow up time (p = 0.844), treatment status (p = 0.868), cut-off values (p=0.065), sample size (p=0.27), and publication year (p = 0.35) were not contributed to heterogeneity (supplementary File 5).

Furthermore, subgroup analyses indicated that elevated CysC levels were associated with worse OS in studies conducted in China (HR=1.81, 95%CI=1.32-2.48, p = 0.0003), in studies with follow-up duration >2.5 years (HR=1.49, 95%CI=1.14-1.95, p = 0.003), renal cancer (HR=1.89, 95%CI=1.17-3.06, p = 0.010), no anti-cancer therapy (HR=1.56, 95%CI=1.07-2.28, p = 0.005), and mixed or unclear treatment status (HR=1.66, 95%CI=1.09-2.54, p <0.00001) and difference between the subgroup no anti-cancer therapy results and mixed or unclear treatment status was not also significant (p=0.83) (Supplementary File 3, 4).

The association between CysC level and clinicopathological features

Five clinicopathological parameters were analyzed for their association with CysC levels: T-stage (III–IV vs. I–II), N-stage (positive vs. negative), TNM stage (III–IV vs. I–II), smoking status (smoker vs. non-smoker), and sex (male vs. female). As shown in Figure 3 and Table 2, elevated CysC levels were significantly associated with advanced T-stage (p = 0.03), N-stage (p = 0.0007), TNM stage (p = 0.04), and sex (p < 0.00001). No significant

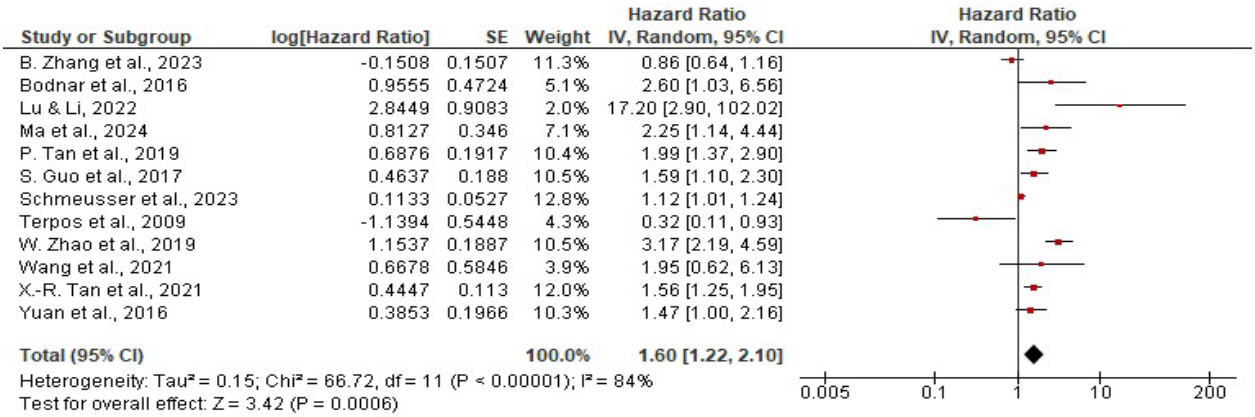

Figure 2. Forest Plot of Overall Survival in Relation to Elevated CysC Levels

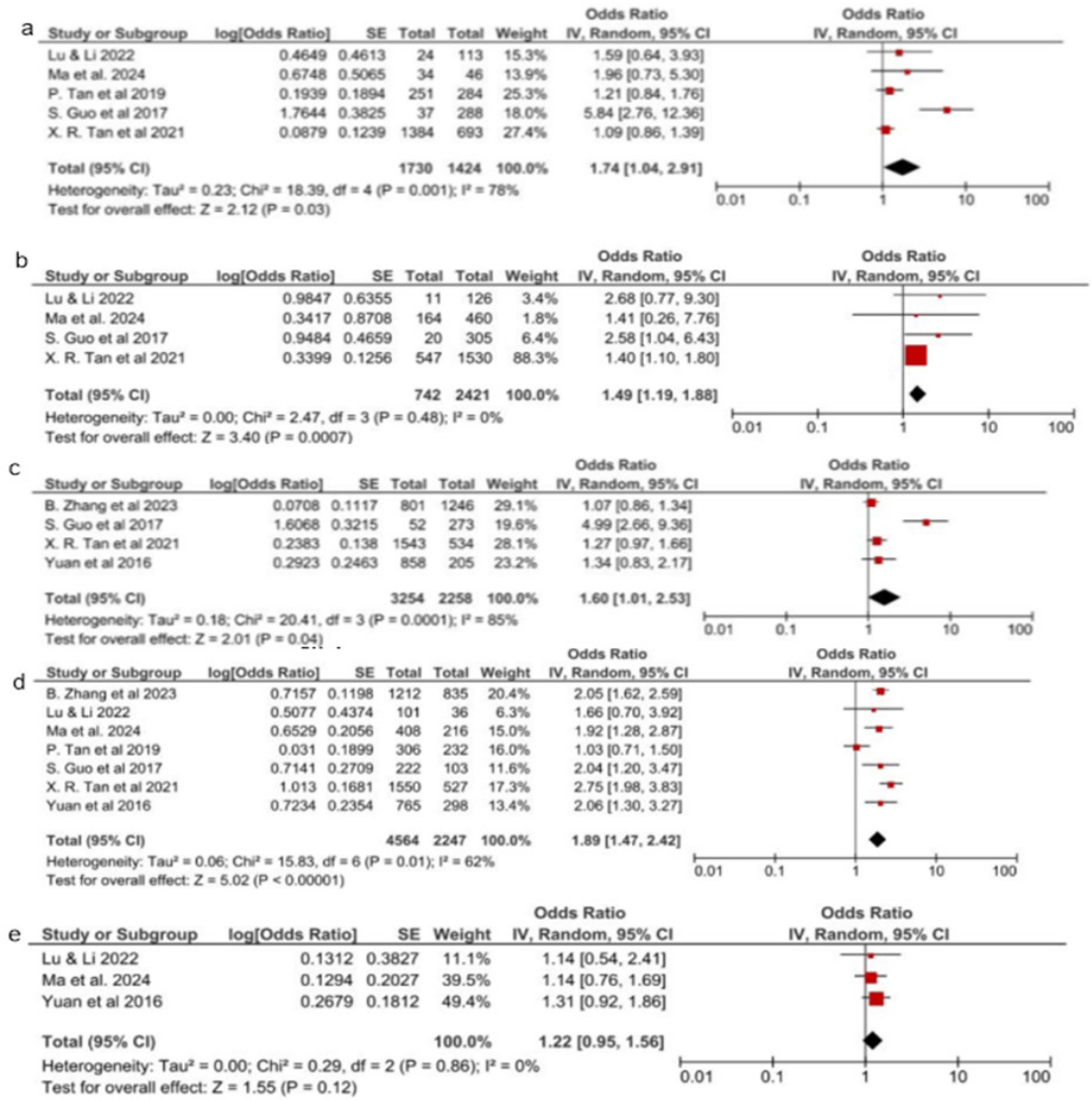

Figure 3. Forest Plots of the Association between CysC level & Clinicopathological Parameters: a. T-stage (grade III-IV vs. I-II), b. N stage (positive/negative), c. TNM staging (grade III-IV vs. I-II), d. sex (male vs. female), e. Smoking (yes/no).

Table 2. Clinicopathological Significance of Cystatin C

Clinicopathological features	No of studies	Sample size	p value	OR (95%CI)	Heterogeneity	
					I^2	p value
T-stage	5	3701	0.03	1.74 (1.04-2.91)	78%	0.001
N-stage	4	3163	0.0007	1.49 (1.19-1.88)	0%	0.480
TNM staging	4	5512	0.04	1.60 (1.01-2.52)	85%	0.0001
Sex (Male/Female)	6	6811	<0.00001	1.89 (1.47-2.42)	68%	0.007
Smoking (yes/no)	3	1824	0.12	1.22 (0.95-1.56)	0%	0.860

association was observed between CysC levels and smoking (p = 0.12).

Discussion

This study represents the first meta-analysis to evaluate the prognostic and clinical significance of circulating CysC across various cancer types. Our findings indicate that elevated circulating CysC is associated with poor prognosis in cancer patients. However, significant heterogeneity (I^2=84%) was observed in the pooled results. Subgroup analysis revealed that cancer type (renal cancers vs. other cancers), follow-up duration (<2.5 vs. ≥2.5 years), study location (China vs. other countries), and treatment status (no anti-cancer therapy & mixed or unclear treatment status) contributed to the observed heterogeneity. Univariate meta-regression demonstrated that publication year, follow-up duration, treatment status,

cut-off values, sample size, and study location were not significant contributors, suggesting that other unmeasured covariates may account for the heterogeneity. Despite the heterogeneity, the pooled results remained robust, as confirmed by sensitivity analyses. Importantly, subgroup analyses indicated that elevated CysC was significantly associated with poor prognosis in studies conducted in China, in patients with follow-up durations longer than 2.5 years, in patients with renal cancer, no anti-cancer therapy and mixed or unclear treatment status. Our results are consistent with previous studies [29, 35, 37, 45, 47, 49], which reported a significant association between elevated circulating CysC and poor prognosis in cancer patients. However, several studies did not observe a prognostic significance of CysC [16, 31, 44 , 46]. These conflicting results may be attributed to shorter follow-up durations, smaller sample sizes, or differences in study populations. Additionally, cancer type appears to play a critical role; studies that did not find a significant association largely involved non-renal cancers, whereas prognostic significance was consistently observed in renal cancer patients. Furthermore, subgroup analysis demonstrated that follow-up duration>2.5 years, renal cancer, study location (China) and treatment status were significant moderators of the observed associations. CysC serves as a reliable biomarker of kidney function due to its low molecular weight and ease of measurement. It is freely filtered from the bloodstream by the kidneys, so impaired renal function leads to elevated serum CysC levels. Consequently, CysC is widely recognized as a sensitive indicator of glomerular filtration rate (GFR) and overall kidney health [51].

Several included studies stated renal function either by exclusion criteria or by direct measurement and statistical adjustment. Wang et al. [46] excluded patients with renal insufficiency; Schmeusser et al. [47] assessed eGFR using creatinine- and CysC-based CKD-EPI and excluded end-stage renal disease; Lu & Li [45], S. Guo et al. [29] and P. Tan et al. [35] measured serum creatinine and eGFR; Yuan et al. [24] excluded patients with eGFR ≤60 mL/min/1.73 m²; and Terpos et al. [31] measured creatinine and 24-h creatinine clearance. Bodner et al. [48] assessed renal function with multiple eGFR equations. Ma et al. [50] stated the renal function indirectly by measuring urea, creatinine, and uric acid levels and Zhao et al. [49] by measuring S. creatinine. In contrast, in XR Tan et al. [37] and Zhang et al. [16] renal function was not adjusted for in multivariable models.

The study also examined the clinicopathological associations of CysC across various cancers. The results indicated that advanced T-stage, N-stage, TNM stage, and sex were all significantly correlated with elevated CysC levels, suggesting a connection to tumor aggressiveness and progression; the absence of a correlation with smoking implies that CysC elevation is related to tumor biology rather than lifestyle factors. These findings indicate an association between CysC and both prognosis and tumor severity, but this should be interpreted cautiously given the high heterogeneity and renal confounding. This study has several limitations. Significant heterogeneity was observed, suggesting that other unmeasured factors may influence the prognostic association of CysC. Additionally, most of the included studies were conducted in China, and therefore associations with other ethnic groups could not be evaluated. Large-scale research including numerous ethnic groups are required to validate the prognostic importance of CysC in various malignancies. CysC is related to kidney function, we suggest that future studies should mention the renal function and adjust with eGFR and creatinine.

In conclusion, elevated circulating CysC levels are associated with poor overall survival in cancer patients, but significant heterogeneity warrants cautious interpretation. Moreover, high CysC levels are linked to advanced TNM stage, T stage, N stage, and patient sex.

Author Contribution Statement

S.T: Conceptualization, original draft, methodology, data curation, formal analysis, visualization and validation. M.M.H: Conceptualization, original draft, methodology, data curation, formal analysis, visualization and validation. Y.K.A, Y.S and Y.T: Supervision, writing-review and editing, and validation. All authors have read and agreed to the published version of the manuscript.

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Data availability statement

Data sharing is not relevant in this study because no datasets were created or analyzed.

Ethical statement

Since it is a meta-analysis that examined the previously published available data, it is not necessary.

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