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ORIGINAL ARTICLE

The value of serum cystatin C in early evaluation of renal insufficiency in patients undergoing chemotherapy: a systematic review and meta-analysis

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Abstract

Purpose Several studies have shown that cystatin C levels can be used to detect decline in renal function in cancer patients receiving chemotherapy, and can serve as a supplement to creatinine level measurement for early detection of renal insufficiency. Nevertheless, use of the parameter remains controversial. This study aimed to assess the value of serum cystatin C levels in evaluation of early renal insufficiency due to chemotherapy.

Methods Studies were retrieved from PubMed, Ovid Embase, the Web of Science, the Cochrane Library, Ovid, and the CNKI databases up to May 15, 2018. Serum levels of cystatin C before and after chemotherapy were evaluated for its ability to assess renal function.

Results A total of 12 studies, including 1775 participants, met our inclusion and exclusion criteria. Pooled analysis revealed that the levels of serum cystatin C in cancer patients after chemotherapy were significantly higher than those of patients prior to treatment [standard mean difference (SMD) = 0.54, 95% CI 0.34–0.74, $P = 0.0000$]. Compared to creatinine, serum cystatin C increased significantly in the early phases of glomerular filtration rate (GFR) change before and after chemotherapy (GFR ≥ 90 ml/min/1.73 m^2, $P < 0.05$ vs. $P > 0.05$, 5.83%; 60 < GFR < 90 ml/min/1.73 m^2, $P < 0.01$ vs. $P > 0.01$, 38.83%) and increased more substantially in the later phases (GFR < 60 ml/min/1.73 m^2, $P < 0.01$ vs. $P < 0.01$, 70.87% vs. 23.09%). However, creatinine decreased even in the early phases and did not increase in an obvious manner until the later phases (GFR < 60 ml/min/1.73 m^2, $P < 0.01$, 23.09%). The GFR values were derived from measured methods.

Conclusions Cystatin C may be superior to creatinine for the detection of minor changes in GFR in early stages of renal insufficiency secondary to chemotherapy. More studies are needed to further verify this result.

Keywords Cystatin C · Renal insufficiency · Chemotherapy · Meta-analysis

Introduction

Cancer patients receiving chemotherapy are at significant risk for renal insufficiency because of the nephrotoxicity of chemotherapy drugs (such as carboplatin and cisplatin) [1–3]. Close monitoring of renal function is required to detect early renal damage in a timely fashion [4, 5], because optimization of drug dosing is based on the assessment of renal function [6]. However, glomerular filtration rate (GFR), the most important parameter of renal function, is rarely measured directly in practice owing to methodological complexity [7]. The gold standard method for measuring GFR is to assess GFR through the clearance of an exogenously administered infused substance such as inulin. Confined with its insusceptibility to

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physiological variability in kidney function [8], the gold standard method is also inappropriate for general use [9].

Given the recent growth of the spectrum of drug therapies in oncology, there is a growing demand for efficient and robust diagnostics. Therefore, a simple, accurate means of estimating GFR is critically important [10].

Creatinine is an imperfect biomarker, since it does not predict the early stages of chemotherapy-induced renal damage. Nevertheless, creatinine is used most commonly in clinical practice. Its serum levels are often influenced by many non-renal factors including sex, age, diet, muscle mass, and metabolism [11]. Moreover, after serial analysis, creatinine was shown to be an inadequately sensitive marker for detection of mild-to-moderate changes in GFR, since serum levels do not significantly increase until GFR decreases substantially (< 60 ml/min/1.73 m^2) [12]. Nevertheless, it is critically important to predict early renal damage during drug treatment.

Cystatin C, a cysteine proteinase inhibitor with low relative molecular mass (12.8 kDa), is produced at a invariant rate in all karyocytes in humans [13]. Cystatin C passes freely through the glomerular filter and is almost entirely resorbed in the proximal tubule, because of its relatively low molecular mass, its positive charge, and its lack of contact with other proteins [14]. In addition, cystatin C is only reabsorbed but not secreted by tubule epithelial cells, and is subsequently metabolized [15]. As a result, cystatin C is cleared by kidney and its serum levels are only determined by GFR. The relationship between cystatin C and renal function has gained considerable attention in the literature [7, 16]. Because of these many advantages over creatinine, including fewer non-renal determinants, cystatin C is considered an alternative for estimation of GFR [17].

These advantages notwithstanding, the use of cystatin C for assessment of renal function in post-chemotherapy cancer patients has not been precisely studied and thus remains controversial. Some studies showed no significant increase of cystatin C after chemotherapy and concluded that cystatin C may not be useful for estimation of GFR in oncology patients [18]. In this study, we conducted a systematic review and meta-analysis to further explore the value of cystatin C in assessing renal function in cancer patients receiving chemotherapy.

Materials and methods

The present meta-analysis and systematic review was based on the preferred reporting items for systematic review and meta-analysis (PRISMA) [19] (Table S1).

Search strategies

Two investigators (He L. and Li J.) performed independent systematic literature retrievals from PubMed, Ovid MEDLINE, Ovid Embase, Web of Science, Science Direct, The Cochrane Library, and CNKI up to May 15, 2018. Search terms were as follows: “cystatin C”, “cisplatin, carboplatin, drug therapy, chemotherapy, pharmacotherapy” and “tumor, cancer, neoplasm”. The complete search terms for PubMed included: (cystatin C OR cys C) AND [drug therapy (MeSH Terms) OR pharmacotherapy OR chemotherapy OR chemotherapies] OR (carboplatin OR cisplatin) AND [tumor OR cancer OR neoplasms (MeSH Terms)]. The search was confined to only human subjects and studies published in the last 10 years. Additionally, the references of the acquired studies were reviewed to determine if any other qualified studies had been missed. The search strategy flowchart is shown in Fig. 1.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) publication in the last 10 years without limits to published language; (2) case–control, cohort, or randomized clinical trials with sample size not less than 20; (3) measurement of serum cystatin C; (4) subjects were cancer patients receiving chemotherapy, without other serious systemic or severe organ disease; and (5) complete data for pooling, reported as mean and standard deviation, or providing the ability for means to be calculated using formulas (obeying normal distribution). Exclusion criteria were as follows: (1) conference abstracts, letters, meta-analyses, and reviews; (2) animal studies; (3) studies with incomplete data or partially unusable data; and (4) without available statistics or with insufficient data.

The abstracts and titles of every screened study were reviewed to identify potentially qualified studies. Discrepancies were resolved by consensus.

Quality assessment

The methodological quality of the eligible studies was judged using the Newcastle–Ottawa scale (NOS), which applied a score ranking system with three aspects: selection, comparability, and exposure. The three aspects are accorded maximum scores of 4, 2, and 3, respectively. The quality of each study was judged as low, moderate, or high, by scores of 0–3, 4–6, and 7–9, respectively. There were additional discussions to settle discrepant opinions regarding methodological quality.

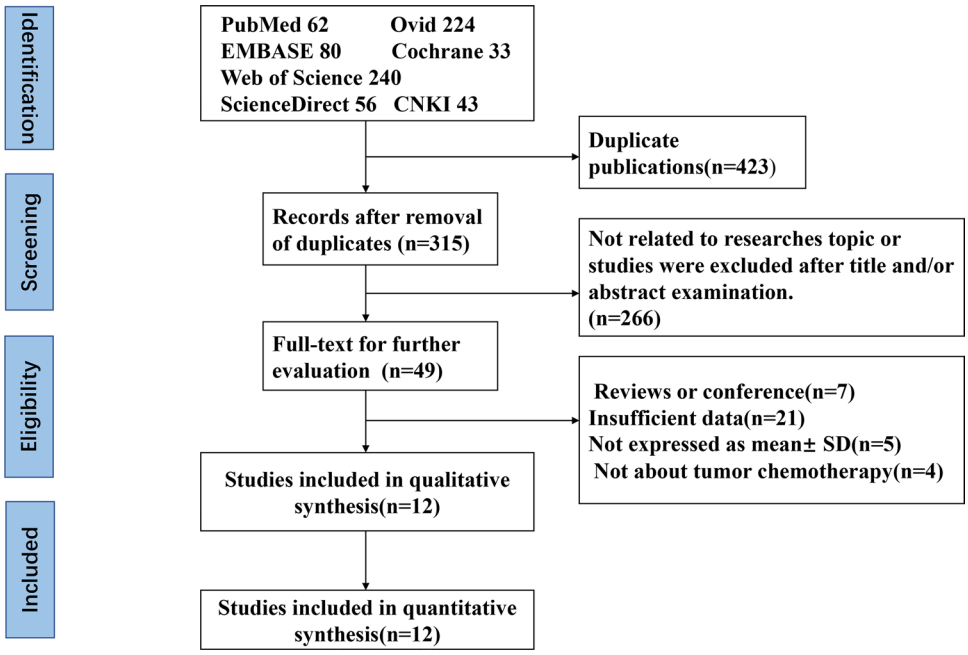

Fig. 1 Search strategy flowchart

Data extraction

The relevant data extracted by the two investigators (He L. and Li J.) from eligible studies were checked by a third investigator (Zhang W.). A collection form was constructed on the basis of extracted data. Disagreements were again settled by consensus after discussion. The following variables were collected: (1) name of the first author, publication year, country, age of patients; (2) number of the study objectives, cancer types, and detection methods; (3) serum levels of cystatin C before and after chemotherapy; (4) equations for estimating GFR; and (5) time of blood sample examination after chemotherapy.

Statistical analysis

All statistical analyses were conducted by STATA 12.0 statistical software, with $P < 0.05$ indicating statistical significance. Between-study heterogeneity was evaluated on the basis of the Chi square-based Q test, with $P < 0.10$ indicating apparent heterogeneity. If there was large heterogeneity ($P < 0.10$), the random-effects model was applied, otherwise, the fixed-effects model was used. The value of serum cystatin C in diagnosis of early renal insufficiency in patients receiving chemotherapy was assessed using standard mean differences (SMDs) and their 95% confidence interval (CI). All quantitative variables were shown as mean ± SD. The significance of the overall results was judged by the Z test with $P < 0.05$ indicating statistical significance. The stability of the results was evaluated by sensitivity analysis. Egger's test and Begg's test was used to estimate latent publication bias.

Results

Study characteristics

As is shown in the flowchart outlining the literature search, a total of 738 studies were acquired. Of these, 726 studies were ruled out by inclusion and exclusion criteria. The remaining 12 studies [15, 20–30] with a total of 1775 cancer patients, were brought into the meta-analysis. These studies were conducted in China, Poland, Italy, France, Turkey, and Iran. They involved various type of cancers, including lung and ovarian cancer. The major characteristics of eligible studies are displayed in Table 1. The quality assessment is displayed in Table 2.

Outcomes for meta-analysis

We first examined heterogeneity among the eligible studies. The I^2 value of 81.1% ($P < 0.001$) suggested the existence of considerable heterogeneity among eligible studies. Therefore, we performed a meta-analysis using a random-effects model. The studies showed that serum cystatin levels in cancer patients after chemotherapy were significantly higher than were levels prior to chemotherapy, while the loss of renal function remained small [standard mean difference (SMD) = 0.54, 95% CI 0.34–0.74, $P < 0.001$, Fig. 2].

Comparison between cystatin C and creatinine levels

There was one study that elaborated the comparison between serum cystatin C and creatinine levels in detail

Table 1 Characteristics of the studies included in the meta-analysis

First author	Years	Country	Chemotherapy	Cancer type	Time (after chemotherapy)	Equation	Sample size	Age (years)	Detection assay	Cystatin C (mg/L)	
										Before	After
Tong [20]	2017	China	Diverse chemotherapy	Various cancers	Sixth cycle	Various	771	60.2 ± 10.4	ITA	1.01 ± 0.37	1.19 ± 0.49
Bretagne [21]	2017	France	Diverse chemotherapy	Various cancers	First cycle	CG CKD-EPI	131	61.5 ± 13	LEITA	1.12 ± 0.42	1.44 ± 0.72
Houshang [22]	2015	Iran	Cisplatin	Various cancers	Third cycle	CG	70	51 ± 11	ITA	1.15 ± 0.33	1.21 ± 0.28
Murat [23]	2014	Turkey	Cisplatin	Lung cancer	Third cycle	Various	20	55.6 ± 7.49	ITA	0.96 ± 0.27	1.01 ± 0.35
F.T. Kos [24]	2013	Turkey	Cisplatin	Various cancers	Third cycle	CG MDRD	34	54 (14–70)	ITA	1.10 ± 0.3	1.22 ± 0.31
Qin [25]	2013	China	Diverse chemotherapy	Lung cancer	First cycle	CG	96	56 (42–79)	LEITA	1.20 ± 0.37	1.78 ± 0.56
Wang [26]	2013	China	Diverse chemotherapy	Various cancers	First cycle	CG	88	42–74	LEITA	1.36 ± 0.22	1.70 ± 0.52
Zhao [27]	2012	China	Diverse chemotherapy	Various cancers	Sixth cycle	CG	82	54 ± 5	LEITA	1.03 ± 0.21	1.10 ± 0.30
Cai [28]	2011	China	Diverse chemotherapy	Various cancers	Second cycle	CG	110	59 ± 10	LEITA	1.49 ± 0.50	1.80 ± 0.84
Jin [29]	2010	China	Diverse chemotherapy	Various cancers	First cycle	CG	54	59 (41–83)	LEITA	1.23 ± 0.45	1.68 ± 0.62
Lubomir [15]	2010	Poland	Diverse chemotherapy	Ovarian cancer	Sixth cycle	CG MDRD	34	54 (28–68)	ITA	0.70 ± 0.20	0.80 ± 0.30
Wojciech [30]	2009	Poland	Cisplatin	NSCLC	Second cycle	NR	40	62.1 ± 4	ELISA	1.64 ± 0.51	1.71 ± 0.4

ELISA enzyme-linked immunosorbent assay, *ITA* immunologic turbidimetric assay, *LEITA* latex-enhanced immunologic turbidimetric assay, *NSCLC* non-small cell lung cancer, *NR* not reported, various cancers: including lung cancer; *CG* Cockcroft–Gault, *MDRD* modification of diet in renal disease, *CKD-EPI* chronic kidney disease epidemiology collaboration

Table 2 Quality assessment of all included studies

First author	Published year	Selection	Comparability	Exposure	Total
Tong [20]	2017	★★★★	★★	★★★	9
Bretagne [21]	2017	★★	★★	★★★	7
Houshang [22]	2015	★★★	★★	★★★	8
Murat [23]	2014	★★	★★	★★	6
Kos [24]	2013	★★★	★★	★★	7
Qin [25]	2013	★★	★	★★	5
Wang [26]	2013	★★	★★	★★	6
Zhao [27]	2012	★★★	★	★★	6
Cai [28]	2011	★★	★★	★★	6
Jin [29]	2010	★★	★	★★	5
Lubomir [15]	2010	★★	★★	★★	6
Wojciech [30]	2009	★★	★★	★★	6

Each star represents one point. Selection: it has four questions and the maximum score was 4. Comparability: it has one question and the maximum score was 2. Exposure: it has three questions and the maximum score was 3

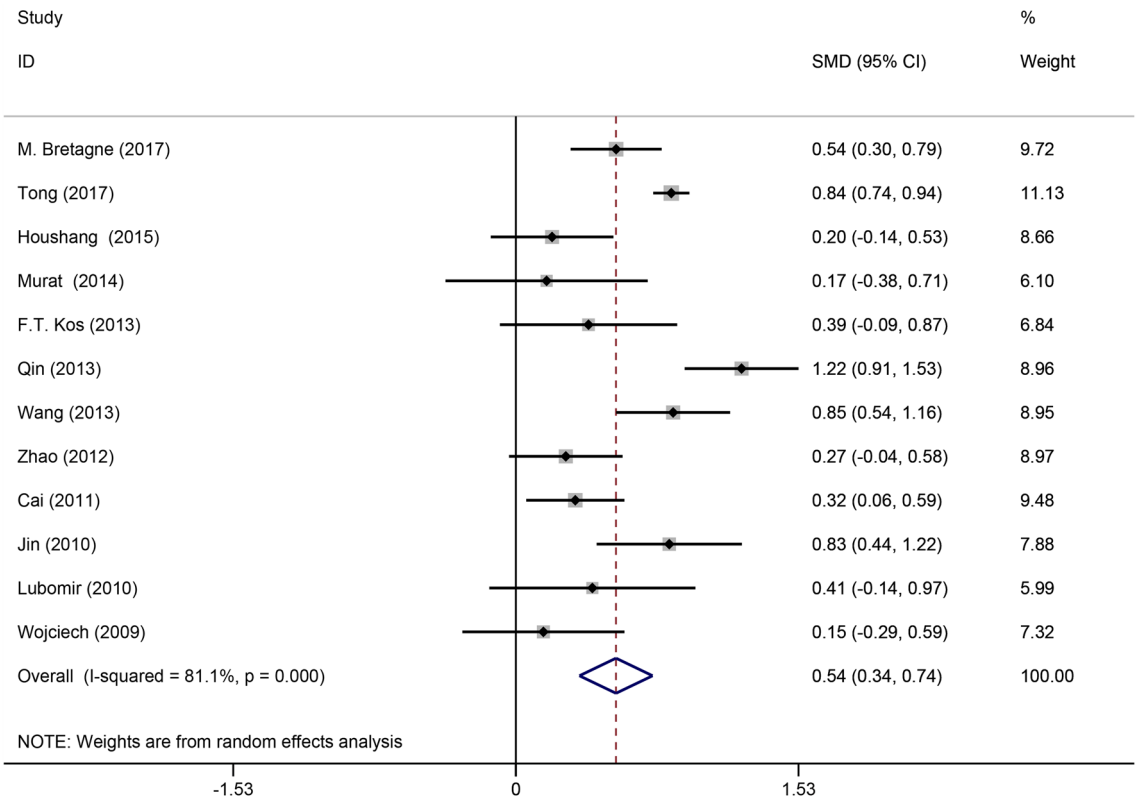

Fig. 2 Forest plot of the serum cystatin C for early predicting renal insufficiency

[20]. Three phases of GFR values were classified according to the GFR measurement reference (clearance of radionuclide), GFR ≥ 90 ml/min/1.73 m^2, 60 < GFR < 90 ml/min/1.73 m^2 and GFR ≤ 60 ml/min/1.73 m^2. The former two phases (GFR ≥ 90 ml/min/1.73 m^2 and 60 < GFR < 90 ml/min/1.73 m^2) were considered the early phases. Table 3 shows that serum cystatin C levels indicated minor changes in GFR in the early phases (GFR ≥ 90 ml/min/1.73 m^2, $P < 0.05$) with a minor increase of 5.83% before and after chemotherapy. Serum cystatin C was elevated substantially ($P < 0.05$) in the later phase (60 < GFR < 90 ml/min/1.73 m^2, $P < 0.01$) with an increase of 38.83%, and more significantly

Table 3 Comparison of cystatin C and creatinine with various GFR values

GFR (ml/min/1.73 m^2)	Before chemotherapy	After chemotherapy		
	91.48 ± 24.26	GFR ≥ 90	60 < GFR < 90	GFR ≤ 60
Cystatin C (mg/L)	1.03 ± 0.34	1.09 ± 0.20	1.43 ± 0.27	1.76 ± 0.42
Creatinine (μmol/L)	72.38 ± 21.12	52.07 ± 9.96	66.10 ± 10.88	89.09 ± 16.19
P (cystatin C)	–	< 0.05	< 0.01	< 0.01
P (creatinine)	–	> 0.05	> 0.01	< 0.01
N	545	57	184	304
Percent (cystatin C)	–	5.83%	38.83%	70.87%
Percent (CREATINE)	–	–	–	23.09%

As creatinine even decreased in early phases while GFR > 60 ml/min/1.73 m^2, the increase in percent which was minus, was abandoned. The GFR was measured by the clearance of radionuclide (99mTc-DTPA)

in the third phase (GFR < 60 ml/min/1.73 m^2, $P < 0.01$) with an increase of 70.87%. However, creatinine decreased even in the early phases and only increased with an apparently minor increase of 23.09%, when GFR values decreased to 60 ml/min/1.73 m^2.

Subgroup analysis

To identify possible factors contributing to heterogeneity, we performed subgroup analysis among the eligible studies. Subgroup analysis was stratified by chemotherapy types, tumor types, and sample size (Table 4). We found that tumor and therapy types showed relatively substantial influence on overall SMD.

The pooled levels of cystatin C were roughly parallel in large ($N > 100$) and small ($N < 100$) sample size groups, whereas the pooled levels of cystatin C of the cisplatin group were significantly lower than that of various chemotherapy groups. There were also no obvious discrepancies between the pooled cystatin C levels in the groups according to cancer type.

Meta-regression analysis

To explore the sources of high heterogeneity in the present study, a meta-regression analysis with single factors and multiple factors was conducted (Table 5). From a single covariate regression model, we found that research region, language and research type were probably related to the heterogeneity, whereas publication year, cystatin C detection assay, mGFR (corrected vs. uncorrected), research quality and initial renal function (corrected vs. uncorrected) were less relevant. With respect to multiple covariates, publication year and research type might be sources of substantial heterogeneity.

Sensitivity analysis

The influence of each study on the pooled results was evaluated to evaluate stability and sensitivity (Fig. 3). The figure suggests that deleting any individual study did not affect the overall results significantly, and the outcomes of this meta-analysis were stable as a whole.

Table 4 Subgroup analysis

Subgroup	Number of studies	Cystatin C (95% CI)	*P*	Model	Heterogeneity	
					I^2	*P*
Cancer types						
Lung cancer	4	0.53 (−0.25–1.32)	0.184	Random	90%	< 0.001
Ovarian cancer	1	0.41 (−0.14–0.97)	0.146	–	–	–
Various cancers	7	0.54 (0.33–0.76)	< 0.001	Random	80.90%	< 0.001
Therapy types						
Cisplatin	4	0.22 (0.01–0.43)	0.044	Fixed	0.00%	0.883
Combination therapies	8	0.67 (0.46–0.89)	< 0.001	Random	80.70%	< 0.001
Sample size						
$N >= 100$	3	0.59 (0.26–0.91)	< 0.001	Random	87.50%	< 0.001
$N < 100$	9	0.52 (0.24–0.80)	< 0.001	Random	78.40%	< 0.001

Table 5 Meta-regression analysis

Covariate	Coef.	*Z* value	*P* value	95% CI
Single covariate regression model				
Research regions	−0.1389549	−1.77	0.076	(−0.2924486, 0.0145388)
Published year	0.0280295	0.69	0.487	(−0.0510374, 0.1070964)
Cystatin C detection assays	−0.2391608	−1.51	0.131	(−0.549194, 0.0708723)
mGFR(corrected vs. uncorrected)	−0.0655458	−0.23	0.816	(−0.6164994, 0.4854078)
Languages (English vs. Chinese)	−0.3781916	−1.91	0.056	(−0.7657941, 0.0094109)
Research quality (high vs. moderate)	0.2722819	1.35	0.178	(−0.1238884, 0.6684523)
Research types (cohort vs. case–control)	0.4895866	6.24	0	(0.3357334, 0.6434398)
Initial renal function (corrected vs. uncorrected)	0.2956872	1.55	0.122	(−0.0788725, 0.6702468)
Multiple covariates regression model				
Research regions	0.2544114	1.71	0.87	(−0.0369936, 0.5458163)
Published year	0.0906751	2.4	0.017	(0.0165193, 0.1648309)
Cystatin C detection assays	−0.5209606	−1.58	0.115	(−1.168366, 0.1264443)
mGFR (corrected vs. uncorrected)	0.106865	0.34	0.732	(−0.5037636, 0.7174937)
Languages (English vs. Chinese)	−0.0471286	−0.13	0.9	(−0.7834359, 0.6891788)
Research quality (high vs. moderate)	−0.0055951	−0.02	0.986	(−0.632226, 0.6210358)
Research types (cohort vs. case–control)	0.6191762	3.12	0.002	(0.2302442, 1.008108)
Initial renal function (corrected vs. uncorrected)	0.2029318	1.08	0.282	(−0.1668112, 0.5726748)

While $P < 0.10$, it is shown that the covariate is related to the heterogeneity of the study; initial renal function refers to how the renal function of patients was before chemotherapy; if initial renal function was administrated in good state, it was corrected, conversely uncorrected. ****If there was mGFR values by gloden methods to abtain precise GFR values, it was corrected, conversely uncorrected

Coef coefficient, *mGFR* measured glomerular filtration rate

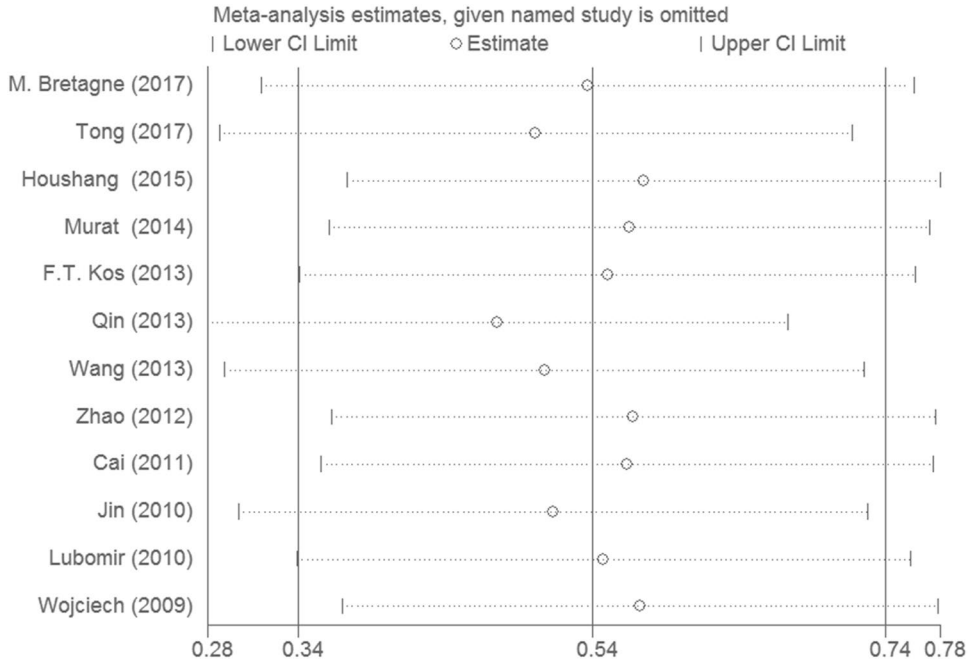

Fig. 3 Sensitivity analysis

Publication bias

We used Begg's test and Egger's test for estimation of latent publication bias. We found there might be latent publication bias among the eligible studies (Egger's test, $P = 0.05$; Begg's test, $P = 0.681$). Nevertheless, this bias would not have great influence on this study. Subsequently, the trim and fill method yielded no trimming and no

change in data, which denoted that publication bias was not influential.

Discussion

The particular characteristics of cystatin C are such that serum levels change with small changes in GFR [31]. Several studies observed that cystatin C levels were more sensitive and reliable than creatinine clearance measurements for adjusting doses of renally excreted drugs and for early detection of renal insufficiency in cancer patients receiving chemotherapy [12, 32, 33]. To our knowledge, this is the first meta-analysis to evaluate relevant studies of the value of serum cystatin C levels in early prediction of renal insufficiency in patients receiving chemotherapy. The overall results suggested that cystatin C levels were superior to creatinine levels for prediction of mild-to-moderate impairment in GFR. The authors believe, therefore, that cystatin C might be a promising marker for monitoring renal function during chemotherapy.

As renal injury is a potential complication in chemotherapy, cancer patients require close monitoring of renal function. Optimal dose carboplatin and cisplatin are critically dependent on accurate measurements of GFR. Although inulin clearance remains the standard GFR tracer, it is inconvenient and time-consuming. Clearance of radionuclide (^{51}Cr-EDTA or 99mTc-DTPA) is considered to be closest to that of inulin and is widely accepted as a reference technique [6]. Radionuclide is considered more reliable than cystatin C in lung cancer patients [23]. However, this method is not suitable for monitoring timely changes to guide chemotherapy, because of radioactivity time-consuming nature [6].

Compared with creatinine, cystatin C levels are a better choice for several reasons. First, cystatin C is more stable than creatinine with respect to non-renal factors, as it is not involved in the inflammatory processes. Many studies have shown that creatinine is easily influenced by muscle mass, sex, protein intake, and metabolism [11]. Cystatin C-based estimation might also produce bias during chemotherapy based on non-GFR determinants in some cases, for example, where there is enhanced cell turnover and inflammation, it has less influence than creatinine. Therefore, GFR estimation based on cystatin C is superior and has been advocated in recent years; new chronic kidney disease epidemiology equations may further improve the prediction of kidney function for guiding chemotherapy [34]. In non-chemotherapy patients such as those with acute pyelonephritis, GFR estimations based on cystatin C yield higher performance than that based on creatinine [35]. However, the variability of mathematical estimations of GFR should be considered in clinical practice, whether creatinine or cystatin C or a combination of both. Using various equations might have a significant effect on the final GFR estimations, and even clinical decisions about the utility of GFR. Among the various equations, the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation presents higher efficacy than the MDRD (Modification of Diet in Renal Disease) and CG (Cockcroft–Gault) equations for estimating the GFR, especially at high levels of GFR values [36], and had the least bias when based on cystatin C. Although many studies applied the MDRD equation (Table 1), the CKD-EPI equation is the current recommended application for estimating the GFR [35]. A recent study developed new, simple cystatin C-based equations for GFR, involving just two variables—cystatin C concentration and age—which avoids bias from race and sex [37]. In addition, creatinine values do not change until GFR declines to 1/3 or more of baseline [12], potentially overestimating GFR and obviating the possibility of early diagnosis. Nevertheless, it is crucially important to predict early renal damage during drug treatment in cancer patients. In our meta-analysis, serum cystatin C levels were able to detect mild changes in GFR (GFR > 60 ml/min/1.73 m^2), and even milder changes in GFR (GFR ≥ 90 ml/min/1.73 m^2), whereas serum creatinine levels showed poor performance in the early phases. As shown in the Table 3, cystatin C levels increased mildly (5.83%) when GFR > = 90 ml/min/1.73 m^2, and increased substantially (38.83%) when GFR > 60 ml/min/1.73 m^2. By contrast, serum creatinine levels did not increase until GFR had already declined to 60 mL/min/1.73 m^2 [20], which is the threshold for adjusting some chemotherapy agent dosages. It is important to note that this is the threshold for cisplatin dose reduction, according to several studies [10, 38]. Cystatin C levels have considerable potential to detect GFR changes in the range of 45–59 mL/min/1.73 m^2 [10]. In addition, cystatin C has a shorter plasma half-life than does creatinine [14]. Finally, there are many simple, convenient but sensitive methods for measurement of cystatin C levels.

There are other potential markers of renal insufficiency, including β2-MG and urinary neutrophil gelatinase-associated lipocalin (NGAL). β2-MG is considered a sensitive indicator of early renal damage in tumor chemotherapy [20], but its levels are easily altered by inflammation, hematopoietic cells, tumor changes, and immunosuppression, which indicates inadequate stability of the molecule. It has also been reported that β2-MG might be inferior to cystatin C for cancer patients who as a rule suffer from inflammation and various other metabolic changes [20, 26]. Besides, it has been suggested that urinary NGAL levels are more sensitive and specific than cystatin C [39]. However, the evidence is insufficient to merit widespread recognition and the relevant studies are insufficiently thorough to address the status of cystatin C. Although high-dose corticosteroids

might apparently influence the serum cystatin C levels in oncology, it remains very much a controversy among the authors [40, 41].

Assessments of cystatin C have already gained considerable recognition for the assessment of kidney function, following the suggestion of the KDIGO 2012 guidelines [42], and recent NICE guidelines [10]. Cystatin C measurements potentially overcome the limitations of creatinine measurements in potentially providing a more accurate evaluation of kidney function in cancer patients. A recent study found that cystatin C measurement in combination with creatinine measurement in prediction equations improved the prediction of GFR in the general population [43], but probably not sufficiently in patients receiving chemotherapy because of the great changes in patients' physical status caused by tumor, such as more oxidative stress, and more inflammation factor secretion. Another recent study showed that creatinine/cystatin C was useful in prediction chemotherapy-related renal insufficiency in patients with lung cancer [44]. Both require more evidence and research to further confirm these conclusions. Our results suggest the valuable efficacy of cystatin C levels in the early diagnosis of renal insufficiency in patients with cancer.

For reasons of scientific prudence and timeliness, we only extracted statistics from case–control studies or cohort studies or randomized clinical trials with sample size ≥ 20 from the last 10 years. The outcomes that were not denoted as mean $\pm$ SD (standard difference) were exclusive. The directly measured GFR values as a reference was obtained using "gold standard" methods, such as measuring radionuclide or inulin clearance, while the comparison of serum cystatin C and creatinine was performed to estimate GFR undertaken in the present study.

There are some limitations in this systematic review and meta-analysis. First, significant heterogeneity potentially affected the results to at least some extent. Difference in sample size, age, cultural background, cancer types, diversity of drugs, and duration of chemotherapy may contribute to heterogeneity. Subgroup analysis was conducted with regard to cancer type, therapy type, and sample size. We found that therapy types and cancer types might be the important sources of heterogeneity. Through meta-regression analysis, we found the research type had an obvious impact on heterogeneity. Language and region were also probable sources of heterogeneity. As our study only included full text articles published in English and Chinese, some inevitable publication bias might potentially cause heterogeneity, on account of missing some eligible studies. Furthermore, the inconsistency of the time of sample detection after the beginning of chemotherapy might contribute to high heterogeneity and introduce bias to some extent. Apart from that, the lack of calibration in assays of cystatin C might also be another important source of huge heterogeneity. Although the ITA (immunologic turbidimetric assay) and LEITA might not make a huge difference, LEITA could introduce some heterogeneity. The calibration of cystatin C could reduce bias and the detrimental effect on the compared results and the GFR estimations [45]. Even though the calibration of cystatin C has changed over time [46], the 2012 standardization has gained the most recommendations in recent years [47]. The cystatin C assays should be standardized by the internal reference material, i.e., ERM-DA471/IFCC, according to the 2012 standardization [48].

Conclusions

Cystatin C levels change substantially in early chemotherapy-induced renal impairment, while creatinine levels changed insignificantly. Serum cystatin C levels are therefore superior to creatinine levels for accurate and reliable detection of mild-to-moderate decrease in GFR. Nevertheless, further studies are needed to confirm these results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not required for this study.

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