Cystatin C as a New Biomarker in Patients with Chronic Kidney Disease: A Review and Meta-Analysis

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Corresponding Author: Lingxin Bao Department of Statistics, School of Computer and Information, Fujian Agriculture and Forestry University, Fuzhou, 350002, Email: bolingxmu@sina.com Abstract: The objective of this study was to evaluate the correlation between cystatin C (CysC) and patients with Chronic Kidney Disease (CKD). Prospective or retrospective cohort studies which compared the levels of CysC in patients with CKD and healthy controls were searched on PubMed, Contents, CINAHL and EMBASE from 2013 to December 31, 2020. R3.5.2 software was utilized to perform data analysis. Based on the meta-analysis criteria, 17 randomized controlled trials with 3592 cases of CKD afnd 5234 cases of healthy controls were included in this study. A random effect model suggested that the level of CvsC in patients with CKD was higher than that in healthy controls with the Mean Difference (MD) at 0.46, 95% CI: [0.39; 0.54], Z = 12.30, P<0.0001. Moreover, there was significant heterogeneity ($I^2 = 98\%$; P<0.01). The sensitivity analysis showed that the random effect model was robust to the MD. The ROC curve result indicated the area under the AUC of CvsC (0.805) was greater than that of creatinine (SCr) (0.683). This study found that CysC levels were more sensitive than SCr in CKD evaluation. Furthermore, CysC can be considered as a new biomarker in patients with CKD.

Keywords: Cystatin C, Chronic Kidney Disease, ROC Curve

Introduction

CKD is known as a global public health issue that is more predominant among the elderly and associated with multiple diseases (Levey et al., 2007). Clinical studies showed that diabetes, hypertension and obesity were the main reasons of CKD. Moreover, other common reasons of CKD include autoimmune renal diseases, such as Immunoglobulin Nephropathy-gAN а (IgAN), Membranous Glomerulonephritis (MGN) and Lupus Nephritis (LN) (Brück et al., 2016; Cañadas-Garre et al., 2018). Pregnancy accelerated kidney disease progression in women with IgAN and CKD stage III (Su et al., 2017). Dividing IgAN patients with CKD stage III into G3a and G3b was very useful to better understand disease conditions and predict the threat of kidney disease progression (Zhang et al., 2017). Therefore, precise assessment of kidney function is necessary for patients with kidney disease.

Glomerular Filtration Rate (GFR) played a vital part in evaluating renal function (Onopiuk *et al.*, 2015). The National Kidney Foundation (NKF, KDOQI2012) described CKD as a kidney injury with a duration of more than 3 months and a significant reduction in GFR (GFR < $60 \text{ ml/min}/1.73\text{m}^2$). Meanwhile, GFR was used to provide appropriate treatment for clinical stage (Stage I-V) in patients with CKD. GFR was usually assessed by exogenous or endogenous marker for glomerular filtration excess. Exogenous markers which were commonly used were insulin, 99mTc-DTPA, 51CrEDTA. Moreover, endogenous markers were SCr, CysC, Neutrophil Gelatinase-Associated Lipocalin (NGAL) and other proteins. However, exogenous markers couldn't be widely used in medical testing due to the cost and cumbersome detection methods. As a comparison, endogenous marker was relatively cheap and simple. Currently, clinical GFR detection generally used endogenous markers. Ideal endogenous markers ought to have the conditions as below: (1) St able generation rate; (2) stable blood concentration, in other words, the biomarkers will not be affected by other pathological conditions and will not bind to proteins; (3) free filtration in the glomerulus; (4) the renal tubules will not be secreted or reabsorbed; (5) no extra-renal clearance. GFR was estimated based on the concentration of SCr in the traditional sense. And also, researchers had found that the concentration of SCr was affected by extreme body weight, muscle content, obesity and other factors with the development of technology (Froissart et al., 2005). Thus, these factors affect the accuracy of the SCr concentration measurement and further affect the accuracy to evaluate the process of patient with CKD. One of the studies had shown that in overweight or obesity patients, the SCr concentration was low due to less muscle mass in the human body, which affected the early-stage



diagnosis of patients who had renal failure (Kalantar-Zadeh et al., 2010). Thus, it is critical to find an appropriate biomarker to measure renal function in the clinical diagnosis. CysC is produced by nucleated cells with a relatively small molecular mass (13 kmol), high isoelectric point (9.3) and free passage (filtered) of glomeruli in vivo (Levv et al., 1989; Abrahamson et al., 1991). It has important clinical significance in a series of physiological and pathological processes. It is better than SCr for assessment of Acute Kidney Injury (AKI) because of its shorter half-life and it may detect AKI one or two days earlier than SCr (Krstic et al., 2016). CysC provided early prediction of kidney dysfunction in acute-on-chronic liver failure (ACLF) patients with a normal SCr level (Zhao et al., 2016). Measurement of CysC was more useful for identifying women who were at high risk for cardiovascular disease (Hojs et al., 2008). CysC might be used to screen patients with poorly controlled diabetes mellitus or hypertension when SCr level was inconclusive (Wanigasuriya et al., 2017). However, the assessment of CysC in CKD is under dispute.

Therefore, this study was to analyze the relationship between CysC and CKD by meta-analysis in order to confirm whether CysC can be used as a reliable biomarker in clinical diagnosis.

Materials and Methods

Literature Search Strategy

Electronic data were retrieved on the computer version of PubMed, CINAHL, Contents and EMBASE from the early stage of the research to December 31, 2020 independently. The search terms included "chronic kidney disease", "cystatin C" and "chronic kidney failure". In addition, other studies missed by the online search were also searched manually.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Adopted "Guidelines for Quality of Life of Patients with Kidney Disease and Dialysis in the United States" (K/DOQI guide) in the 2002 (Levey *et al.*, 2002) or the Global Prognosis Improvement Organization for Kidney Disease (K/DIGO guide) in 2005 (Levey *et al.*, 2005) for the definition, diagnosis and the stage of CKD, with no limitations related to age, gender, ethnicity or primary disease; (2) prospective study; (3) adoption of patients who had CKD was defined as the treatment group, with healthy person as the control group; (4) raw data; (5) data type was $\overline{x} \pm s$ (mean \pm standard error); (6) trustworthy literature.

Exclusion criteria: (1) the diagnostic criteria for CKD didn't include CysC; (2) review article; (3) case reports; (4) article with duplicate data; (5) retrospective study without control group.

Study Selection

Data extraction and quality evaluation were managed by three researchers (Qiaoyan Zhou, Yanfang Lin and Lingxin Bao) in the form of mutual blindness. If there was disagreement, return to the original document to find evidence or send an email to consult the original author, or ask a third party for assistance. The Newcastle-Ottawa Scale (NOS) was used to assess study quality, including study population selection, comparability between groups and outcome measurement (Wells et al., 2000). The overall research quality was defined as poor (0-3 points), moderate (4-6 points) or high quality (7-9 points) in this research with the potential maximum score 9 points.

Statistical Analysis

Meta-analysis was accomplished by using R3.5.2 software. The statistical result was the MD and its 95% confidence interval (95% CI). The heterogeneity between different articles was verified and quantified by the Cochrane's Q test and the I² method. The fixed effect model was utilized to merge the results if there was no heterogeneity among the studies; otherwise, the random effect model or subgroup analysis was applied. Sensitivity analysis was used for the effect of a single study on the total estimated effect. Publication bias analysis was implemented with funnel plot and Egger's test. The difference was statistically significant when P<0.05 (under the null hypothesis with the MD equal to zero).

Results

Search Results and Study Characteristics

The whole document selection process of this research was demonstrated in a diagram as Fig. 1. Preliminary search included 205 articles. There were 116 articles which met the criteria for further screening. Those references which were not related to this study or provided sufficient data were excluded. At the end, 17 articles were included for further analysis of this study (Wanigasuriya et al., 2017; Mao et al., 2020; Ciin et al., 2020; Xie et al., 2019; Salwa et al., 2019: Scarr et al., 2019; Wan et al., 2013; Zhu and Qian, 2018; Bang et al., 2017; Kwon et al., 2017; Paapstel et al., 2016; Ren et al., 2019; Sugiyama et al., 2017; Kollerits et al., 2010; Meeusen et al., 2015; Ji et al., 2017; Szopa et al., 2015), which included 3592 patients who had CKD and 5234 patients who were in the healthy control group.

Quality Assessment

As listed in Table 1, the quality evaluation was carried out by NOS tools. These studies had an average score of 7.5, which was considered as high-quality literature.

Meta-Analysis

Heterogeneity Analysis

17 studies in total (Wanigasuriya et al., 2017; Mao et al., 2020; Ciin et al., 2020; Xie et al., 2019; Salwa et al., 2019; Scarr et al., 2019; Wan et al., 2013; Zhu and Qian, 2018; Bang et al., 2017; Kwon et al., 2017; Paapstel et al., 2016: Ren et al., 2019: Sugivama et al., 2017: Kollerits et al., 2010; Meeusen et al., 2015; Ji et al., 2017; Szopa et al., 2015) were completed to analyze patients with CKD separately. The results indicated that there was significant heterogeneity between the trials ($I^2 = 98\%$, P < 0.01). Therefore, the random effect model was chosen for metaanalysis. The result showed the CysC level of CKD patient group was higher than the control group (MD = 0.46, 95%CI: [0.39; 0.54], Z = 12.30, P<0.0001) and the prediction interval for MD was [0.08; 0.85] (Fig. 2). It was indicated that when the concentration of CysC in the body increased by more than 0.85 mg/dL or decreased by more than 0.08mg/dL, it should be noted that the renal function may have undergone pathological changes.

Subgroup Analysis

According to 17 articles (Wanigasuriya *et al.*, 2017: Mao *et al.*, 2020; Ciin *et al.*, 2020; Xie *et al.*, 2019; Salwa *et al.*, 2019; Scarr *et al.*, 2019; Wan *et al.*, 2013; Zhu and Qian, 2018; Bang *et al.*, 2017; Kwon *et al.*, 2017; Paapstel *et al.*, 2016; Ren *et al.*, 2019; Sugiyama *et al.*, 2017; Kollerits *et al.*, 2010; Meeusen *et al.*, 2015; Ji *et al.*, 2017; Szopa *et al.*, 2015), subgroup analysis was implemented based on factors such as detection method, study protocol and different kidney diseases.

In order to check the source of heterogeneity, a subgroup analysis was carried out on different methods of CysC detection. The result indicated that the heterogeneity of the particle-enhanced immunoturbidimetric assay subgroup, the other assay subgroups and the automated nephelometric immunoassay subgroup were increase. The

Table 1: Quality valuation of included studies

I² were 98, 99 and 99% which were higher than the total heterogeneity (98%). However, the immunoturbidimetry assay subgroup was lower ($I^2 = 94\%$). As shown in Fig. 3, different detection methods for CysC could explain the resource of high heterogeneity.

Different study protocol adopted subgroup analysis. It showed that the heterogeneity of the case control subgroup and the prospective study subgroups were 98% and 99%. The heterogeneity in there two subgroups were higher than the overall heterogeneity (98%). The heterogeneity of the cross-sectional study subgroup decreased ($I^2 = 94\%$), less than the total heterogeneity (98%). These results suggested that the source of high heterogeneity was from different publications (Fig. 4).

The same subgroup analysis methodology was applied to different kidney disease types. It showed the two subgroups included the CHF subgroup and the other disease subgroup, with heterogeneity decreased 87% and 97% respectively. However, the heterogeneity of the CKD group increased to 99%. This result indicated another reason of high degree of heterogeneity (Fig. 5).

Sensitivity Analysis

Sensitivity analysis was adopted due to the effect of a study could be eliminated to further examine the effect of combined effector MD. The result showed that the residual effect of the remaining studies was still within 95%CI of the total effect (MD = 0.46, 95%CI: [0.39; 0.54]) (Fig. 2). Thus, the random effect model had robustness and reliability for the estimation of MD.

The sensitivity of CysC and SCr was compared by plotting the ROC curve. The larger Area Under the Curve (AUC) means the more sensitive the reaction was. This result showed the AUC of the CysC (0.805) was higher than SCr (0.683). The optimal critical points were (0.848, 0.727), (0.758, 0.667), (0.788, 0.636), (0.818, 0.606) and (0.848, 0.576) respectively (Fig. 6). This analysis indicated that the sensitivity of CysC was higher than SCr.

Study	year	Study population selection 4 points	Comparability between groups 2 points	Result measurement 3 points	Scores	Quality assessment
Mao et al. (2020)	2020	4	2	2	8	High quality
Mang <i>et al</i> .	2020	3	1	1	5	Medium quality
Xie <i>et al</i> .	2019	4	2	2	8	High quality
Salwa <i>et al</i> .	2019	3	1	1	5	Medium quality
Scarr et al.	2019	4	2	2	8	High quality
Wan <i>et al</i> .	2013	3	1	2	6	Medium quality
Zhu and Qian	2018	4	2	2	8	High quality
Bang et al.	2017	4	2	3	9	High quality
Kwon <i>et al</i> .	2017	4	2	3	9	High quality
Paapstel et al.	2016	4	2	1	7	High quality
Ren et al.	2019	4	2	2	8	High quality
Sugiyama <i>et al</i> .	2017	4	2	2	8	High quality
Spanaus et al.	2010	3	1	3	7	High quality
Meeusen et al.	2015	4	2	1	7	High quality
Ji et al.	2016	4	2	2	8	High quality
Wanigasuriya et al.	2017	4	2	2	8	High quality
Szopa et al.	2015	4	2	2	8	High quality

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Fig. 1: Flow chart details the study selection process

Study		Experimental Mean SD	Total	Control Mean SD	Mean Difference	MD	95% -CI	Weight (fixed)	Weight (random)
Mao et al 2020	110	0.90 0.1900	40	0.82 0.1400			[0.02; 0.14]	2.0%	4.0%
Mao et al 2020	32	1.00 0.2600	40	0.82 0.1400		0.18	[0.08; 0.28]	0.6%	3.8%
Mao et al 2020	18	1.53 0.5300	40	0.82 0.1400			[0.46; 0.96]	0.1%	2.8%
Ciin et al 2020	130	1.93 1.2000	32	1.10 0.5900	+		[0.54; 1.12]	0.1%	2.5%
Xie et al 2019	215	2.24 1.3000	192	2.20 1.2600	†	0.04	[-0.21; 0.29]	0.1%	2.8%
Gomaa et al 2019	15	2.62 0.4500	15	0.74 0.0800	+	1.88	[1.65; 2.11]	0.1%	2.9%
Gomaa et al 2019	15	3.94 0.9100	15	0.74 0.0800	+	3.20	[2.74; 3.66]	0.0%	1.6%
Daniel S.et al 2019	66	1.10 0.3000	73	1.10 0.3000	ł	0.00	[-0.10; 0.10]	0.6%	3.8%
Wan Z. H.et al 2013	56	1.10 0.4000	30	0.60 0.3000	•	0.50	[0.35; 0.65]	0.3%	3.5%
Wan Z. H.et al 2013	30	0.70 0.2000	30	0.60 0.3000	t	0.10	[-0.03; 0.23]	0.4%	3.6%
Wan Z. H.et al 2013	8	1.80 0.4000	48	0.90 0.3000	+		[0.61; 1.19]	0.1%	2.5%
Zhu H & Qian Y 2018	30	1.40 1.8800	31	0.75 0.6400		0.65	[-0.06; 1.36]	0.0%	0.9%
Zhu H & Qian Y 2018	28	2.33 2.0300	31	0.75 0.6400		1.58	[0.80; 2.36]	0.0%	0.7%
Zhu H & Qian Y 2018	26	3.45 1.8100	31	0.75 0.6400	-	2.70	[1.97; 3.43]	0.0%	0.8%
Bang J.Y.et al 2017	408	0.65 0.1000		0.60 0.1000			[0.04; 0.06]	49.8%	4.1%
Bang J.Y.et al 2017	175	0.70 0.1000	564	0.60 0.1000	8	0.10	[0.08; 0.12]	21.7%	4.1%
Kwon Y.E.et al 2017	185	2.20 0.9000	595	1.70 0.8000	t	0.50	[0.36; 0.64]	0.3%	3.5%
Kwon Y.E.et al 2017	312	2.10 0.9000	468	1.70 0.6000		0.40	[0.29; 0.51]	0.5%	3.7%
Paapstel K.et al 2016	52	0.93 0.1400	41	0.90 0.1000			[-0.02; 0.08]	2.6%	4.0%
Ren S.et al 2019	25	1.14 0.3900	14	0.88 0.3300	h in the second s	0.26	[0.03; 0.49]	0.1%	2.9%
Sugiyama H.et al 2017	235	0.89 0.2200	456	0.91 0.2200	¢.	-0.02	[-0.05; 0.01]	5.2%	4.0%
Sugiyama H.et al 2017	157	0.94 0.2100	456	0.91 0.2200	0	0.03	[-0.01; 0.07]	4.2%	4.0%
Spanaus KS.et al 2010	49	1.26 0.4000	72	0.91 0.2200		0.35	[0.23; 0.47]	0.4%	3.7%
Spanaus KS.et al 2010	63	2.06 0.6800	72	0.91 0.2200	+	1.15	[0.97; 1.33]	0.2%	3.3%
Spanaus KS.et al 2010	43	3.15 0.8800	72	0.91 0.2200	+	2.24	[1.97; 2.51]	0.1%	2.7%
Meeusen J.W.et al 2015	618	1.44 0.7400	147	0.80 0.1700			[0.58; 0.70]	1.5%	4.0%
Ji F.et al 2016	150	1.33 0.4100	50	0.85 0.2800	2	0.48	[0.38; 0.58]	0.6%	3.8%
Wanigasuriya K.et al 2017	37	5.12 9.4700	39	0.11 0.1400		5.01	[1.96; 8.06]	0.0%	0.1%
Wanigasuriya K.et al 2017		5.12 9.4700	40	0.31 0.3500		4.81	[1.76; 7.86]	0.0%	0.1%
Magdalena S.et al 2015	72	0.75 0.2100	65	0.70 0.1300		0.05	[-0.01; 0.11]	1.9%	4.0%
Magdalena S.et al 2015	72	0.72 0.1600	65	0.70 0.1300	4	0.02	[-0.03; 0.07]	2.6%	4.0%
Magdalena S.et al 2015	53	0.87 0.1500	65	0.70 0.1300		0.17	[0.12; 0.22]	2.4%	4.0%
Magdalena S.et al 2015	70	0.90 0.2300	65	0.70 0.1300		0.20	[0.14; 0.26]	1.6%	4.0%
Fixed effect model	3592		5234				[0.08; 0.10]	100.0%	
Random effects model					•		[0.39; 0.54]		100.0%
Prediction interval					F		[0.08; 0.85]		
Heterogeneity: $I^2 = 98\%$, $\tau^2 =$	= 0.035	1, <i>p</i> < 0.01			1 1				
					-5 0 5				

Fig. 2: The meta-analysis with Forest plot of CysC concentration

Study	Total	Experimental Mean SD	Total		Control SD	Mean Difference	MD	95% -CI	Weight (fixed)	Weight (random)
particle-enhancing imm	unone	phelo-metric a	ssay							
Mao et al 2020	110	0.90 0.1900	40	0.82	0.1400		0.08	[0.02; 0.14]	2.0%	4.0%
Mao et al 2020	32	1.00 0.2600	40	0.82	0.1400	•	0.18	[0.08; 0.28]	0.6%	3.8%
Mao et al 2020	18	1.53 0.5300	40	0.82	0.1400	+	0.71	[0.46; 0.96]	0.1%	2.8%
Gomaa et al 2019	15	2.62 0.4500	15	0.74	0.0800	+	1.88	[1.65; 2.11]	0.1%	2.9%
Gomaa et al 2019	15	3.94 0.9100	15	0.74	0.0800	-	3.20	[2.74; 3.66]	0.0%	1.6%
Wan Z. H.et al 2013	56		30	0.60	0.3000		0.50	[0.35; 0.65]	0.3%	3.5%
Wan Z. H.et al 2013	30	0.70 0.2000	30	0.60	0.3000		0.10	[-0.03; 0.23]	0.4%	3.6%
Wan Z. H.et al 2013	8	1.80 0.4000	48		0.3000	+	0.90	[0.61; 1.19]	0.1%	2.5%
Zhu H & Qian Y 2018	30		31		0.6400		0.65		0.0%	0.9%
Zhu H & Qian Y 2018	28	2.33 2.0300	31		0.6400			[0.80; 2.36]	0.0%	0.7%
Zhu H & Qian Y 2018	26	3.45 1.8100	31	0.75	0.6400			[1.97; 3.43]	0.0%	0.8%
Fixed effect model	368		351			1 .		[0.22; 0.31]	3.6%	
Random effects model Heterogeneity: $l^2 = 98\%$, τ^2 :	- 0 330	1.0 < 0.01				\$	1.06	[0.70; 1.42]		27.1%
		1, p < 0.01								
immunoturbidimetry ass		1 02 1 0000	22	4.40	0.5000		0.00	10 54 4 400	0.424	2.5%
Ciin et al 2020	130		32		0.5900			[0.54; 1.12]	0.1%	
Xie et al 2019	215		192		1.2600	T		[-0.21; 0.29]	0.1%	2.8%
Daniel S.et al 2019 Kwon Y.E.et al 2017	66 185		73 595		0.3000 0.8000	1		[-0.10; 0.10] [0.36; 0.64]	0.6%	3.8% 3.5%
Kwon Y.E.et al 2017	312		468		0.6000			[0.29; 0.51]	0.5%	3.5%
Sugiyama H.et al 2017	235		400		0.2200	1		[-0.05: 0.01]	5.2%	4.0%
Sugiyama H.et al 2017	157	0.94 0.2100	456		0.2200	8		[-0.01; 0.07]	4.2%	4.0%
Magdalena S.et al 2015	72		65		0.1300			[-0.01; 0.11]	1.9%	4.0%
Magdalena S.et al 2015	72		65		0.1300	8		[-0.03; 0.07]	2.6%	4.0%
Magdalena S.et al 2015	53		65		0.1300			[0.12; 0.22]	2.4%	4.0%
Magdalena S.et al 2015	70		65		0.1300			[0.14; 0.26]	1.6%	4.0%
Fixed effect model	1567		2532					[0.05; 0.08]	19.4%	
Random effects model						•	0.16	[0.08; 0.24]		40.3%
Heterogeneity: $I^2 = 94\%$, τ^2 :	= 0.015	1, p < 0.01								
other assay	400	0.05.0.4000	1010	0.00	0.4000		0.05	1001.000	40.00/	4.40/
Bang J.Y.et al 2017	408				0.1000	22		[0.04; 0.06]	49.8%	4.1%
Bang J.Y.et al 2017	175		564		0.1000	E.		[0.08; 0.12]	21.7%	4.1%
Ren S.et al 2019 Meeusen J.W.et al 2015	25 618	1.14 0.3900	14 147		0.3300	E		[0.03; 0.49]	0.1%	2.9%
Ji F.et al 2016	150		50		0.2800			[0.38; 0.70]	0.6%	3.8%
Wanigasuriya K.et al 2017			39		0.2800			[1.96; 8.06]	0.0%	0.1%
Wanigasuriya K.et al 2017			40		0.3500			[1.76; 7.86]	0.0%	0.1%
Fixed effect model	1450	5.12 9.4700	2094	0.51	0.3500			[0.07; 0.09]	73.7%	0.176
Random effects model	1400		2004			50		[0.19; 0.45]	10.170	18.9%
Heterogeneity: $I^2 = 99\%$, τ^2 :	= 0.019	2, p < 0.01					0102	[0.10, 0.10]		10.070
automated nephelometr										
Paapstel K.et al 2016	52		41		0.1000			[-0.02; 0.08]	2.6%	4.0%
Spanaus KS.et al 2010	49		72		0.2200	1		[0.23; 0.47]	0.4%	3.7%
Spanaus KS.et al 2010	63		72		0.2200	•		[0.97; 1.33]	0.2%	3.3%
Spanaus KS.et al 2010	43	3.15 0.8800	72	0.91	0.2200	-		[1.97; 2.51]	0.1%	2.7%
Fixed effect model	207		257					[0.15; 0.24]	3.3%	10.001
Random effects model Heterogeneity: $I^2 = 99\%$, τ^2 :	= 0.525	1. p < 0.01					0.93	[0.22; 1.65]		13.6%
Fixed effect model	3592		5234				0.00	[0.08; 0.10]	100.0%	
Random effects model	3032		52.54					[0.39; 0.54]	.00.0%	100.0%
Heterogeneity: $I^2 = 98\%$, τ^2 :	= 0.025	1 0 < 0.01				r tim	0.40	[0.00, 0.04]		100.076

Fig.	3:	Subgroup	analysis	of	detection	method	data
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Study	Total	Experimental Mean SD	Total	Mean	SD	Mean Difference	MD	95% -CI	Weight (fixed)	Weigl (randon
Study	Total	Mean 3D	Total	Wear	30	Mean Difference	MD	3378-01	(inceu)	(randor
Case control										
Mao et al 2020	110	0.90 0.1900	40		0.1400	8		[0.02; 0.14]	2.0%	4.0
Mao et al 2020	32	1.00 0.2600	40		0.1400			[0.08; 0.28]	0.6%	3.8
Mao et al 2020	18	1.53 0.5300	40		0.1400	*		[0.46; 0.96]	0.1%	2.8
Ciin et al 2020	130	1.93 1.2000	32	1.10	0.5900	+	0.83	[0.54; 1.12]	0.1%	2.5
Xie et al 2019	215	2.24 1.3000	192	2.20	1.2600	÷	0.04	[-0.21; 0.29]	0.1%	2.8
Gomaa et al 2019	15	2.62 0.4500	15	0.74	0.0800	-	1.88	[1.65; 2.11]	0.1%	2.9
Gomaa et al 2019	15	3.94 0.9100	15	0.74	0.0800	- H	3.20	[2.74; 3.66]	0.0%	1.6
Wan Z. H.et al 2013	56	1.10 0.4000	30	0.60	0.3000	+		[0.35; 0.65]	0.3%	3.5
Wan Z. H.et al 2013	30	0.70 0.2000	30		0.3000	4		[-0.03; 0.23]	0.4%	3.6
Wan Z. H.et al 2013	8	1.80 0.4000	48		0.3000	÷-	0.90		0.1%	2.5
Ren S.et al 2019	25	1.14 0.3900	14		0.3300	4		[0.03; 0.49]	0.1%	2.9
Meeusen J.W.et al 2015	618	1.44 0.7400	147		0.1700			[0.58; 0.70]	1.5%	4.0
Ji F.et al 2016	150	1.33 0.4100	50		0.2800	1		[0.38; 0.58]	0.6%	3.8
Magdalena S.et al 2015	72	0.75 0.2100	65		0.1300			[-0.01: 0.11]	1.9%	4.0
	72	0.72 0.1600	65		0.1300	1				
Magdalena S.et al 2015						1		[-0.03; 0.07]	2.6%	4.0
Magdalena S.et al 2015	53	0.87 0.1500	65		0.1300			[0.12; 0.22]	2.4%	4.0
Magdalena S.et al 2015	70	0.90 0.2300	65	0.70	0.1300			[0.14; 0.26]	1.6%	4.0
Fixed effect model	1689		953			PL-		[0.19; 0.24]	14.4%	
Random effects model						P	0.53	[0.38; 0.69]		56.6
Heterogeneity: $I^2 = 98\%$, $\tau^2 =$	0.093-	4, <i>p</i> < 0.01								
cross-sectional study										
Daniel S.et al 2019	66	1.10 0.3000	73		0.3000	1		[-0.10; 0.10]	0.6%	3.8
Bang J.Y.et al 2017	408	0.65 0.1000			0.1000	121		[0.04; 0.06]	49.8%	4.1
Bang J.Y.et al 2017	175	0.70 0.1000	564	0.60	0.1000		0.10	[0.08; 0.12]	21.7%	4.1
Kwon Y.E.et al 2017	185	2.20 0.9000	595	1.70	0.8000	1*	0.50	[0.36; 0.64]	0.3%	3.5
Kwon Y.E.et al 2017	312	2.10 0.9000	468	1.70	0.6000		0.40	[0.29; 0.51]	0.5%	3.7
Sugiyama H.et al 2017	235	0.89 0.2200	456	0.91	0.2200	6	-0.02	[-0.05; 0.01]	5.2%	4.0
Sugiyama H.et al 2017	157	0.94 0.2100	456	0.91	0.2200	- b		[-0.01: 0.07]	4.2%	4.0
Wanigasuriya K.et al 2017		5.12 9.4700	39		0.1400			[1.96; 8.06]	0.0%	0.1
Wanigasuriya K.et al 2017		5.12 9.4700	40		0.3500			[1.76; 7.86]	0.0%	0.1
Fixed effect model	1612		3931			1		[0.05; 0.07]	82.2%	
Random effects model	1012		0001					[0.06; 0.17]	U # # 70	27.4
Heterogeneity: $l^2 = 94\%$, $\tau^2 =$	0.004	5, $\rho < 0.01$					0.12	[0.00, 0.17]		61.4
prospective study										
Zhu H & Qian Y 2018	30	1.40 1.8800	31	0.75	0.6400		0.65	[-0.06; 1.36]	0.0%	0.9
Zhu H & Qian Y 2018	28	2.33 2.0300	31		0.6400			[0.80; 2.36]	0.0%	0.7
Zhu H & Qian Y 2018	26	3.45 1.8100	31		0.6400			[1.97; 3.43]	0.0%	0.8
Paapstel K.et al 2016	52	0.93 0.1400	41		0.1000			[-0.02; 0.08]	2.6%	4.0
Spanaus KS.et al 2010	49	1.26 0.4000	72		0.2200			[0.23; 0.47]	0.4%	3.7
	63		72			1				
Spanaus KS.et al 2010		2.06 0.6800			0.2200			[0.97; 1.33]	0.2%	3.3
Spanaus KS.et al 2010	43	3.15 0.8800	72	0.91	0.2200	+		[1.97; 2.51]	0.1%	2.7
Fixed effect model	291		350			1		[0.17; 0.25]	3.3%	10.000
Random effects model Heterogeneity: $I^2 = 99\%$, $\tau^2 =$	0.573	4. 0 < 0.01				\$	1.20	[0.61; 1.79]		16.1
Fixed effect model	3592		5234				0.00	10.09.0.401	100.0%	
	3592		5234			1		[0.08; 0.10]	100.0%	100 -
Random effects model						· · · · ·	0.46	[0.39; 0.54]		100.0
Heterogeneity: $I^2 = 98\%$, $\tau^2 =$	0.035									

Fig. 4: Subgroup analysis of study protocol data

Study	E Total N	xperimental lean SD	Total	Control Mean SD	Mean Difference	MD	95% -CI	Weight (fixed)	Weight (random)
other disease Mao et al 2020 Mao et al 2020 Cin et al 2020 Goma et al 2020 Goma et al 2019 Daniel S. et al 2019 Wan Z. H. et al 2013 Wan Z. H. et al 2013 Magdalena S. et al 2015 Magdalena S. et al 2015 Magdalena S. et al 2015 Fixed effect model	32 18 130 56 30 8 72 72 53	0.90 0.1900 1.00 0.2600 1.53 0.5300 1.93 1.2000 2.62 0.4500 1.10 0.3000 1.10 0.4000 0.70 0.2000 0.75 0.2100 0.72 0.1600 0.87 0.1500 0.90 0.2300	40 40 32 15 73 30 48 65 65 65 65 65	0.82 0.1400 0.82 0.1400 0.82 0.1400 0.74 0.0800 0.74 0.0800 0.60 0.3000 0.60 0.3000 0.90 0.3000 0.70 0.1300 0.70 0.1300 0.70 0.1300		0.08 0.18 0.71 0.83 1.88 0.00 0.50 0.10 0.90 0.05 0.02 0.17 0.20 0.14	[0.02; 0.14] [0.08; 0.28] [0.46; 0.96] [0.54; 1.12] [1.65; 2.11] [-0.10; 0.10] [-0.35; 0.65] [-0.03; 0.23] [0.61; 1.19] [-0.03; 0.01] [-0.03; 0.01] [-0.12; 0.22] [0.14; 0.26] [0.11; 0.16]	2.0% 0.6% 0.1% 0.1% 0.6% 0.3% 0.4% 0.4% 1.9% 2.6% 2.6% 2.6% 1.6% 1.6%	4.0% 3.8% 2.5% 2.9% 3.8% 3.5% 3.6% 4.0% 4.0% 4.0%
Random effects model Heterogeneity: $I^2 = 97\%$, τ^2		p < 0.01	000		•	0.38	[0.25; 0.52]	1 <i>2.1</i> /0	45.4%
CKD (chronic kidney dis Xie et al 2019 Gomaa et al 2019 Bang J.Y.et al 2017 Bang J.Y.et al 2017 Kwon Y.E.et al 2017 Kwon Y.E.et al 2017 Paapstel K.et al 2017 Paapstel K.et al 2019 Sugiyama H.et al 2017 Spanaus KS. et al 2010 Spanaus KS. et al 2010 Spanaus KS. et al 2010 Meeusen J.W.et al 2015 J.F.et al 2016 Wanigasuriya K.et al 2017 Fixad effect model Random effects model Heterogeneity. <i>T</i> = 99%, t ²	215 15 408 175 185 312 25 235 157 49 63 43 618 150 7 37 2776	2.24 1.3000 3.94 0.9100 0.65 0.1000 0.70 0.1000 2.20 0.9000 0.93 0.1400 0.89 0.2200 0.89 0.2200 0.94 0.22100 1.26 0.4000 2.06 0.6800 3.15 0.8800 1.34 0.7400 5.12 9.4700 p < 0.01	192 1240 595 468 41 14 456 456 72 72 72 72 147 50 39 40 4533	2.20 1.2600 0.74 0.0800 0.60 0.1000 1.70 0.8000 0.90 0.1000 0.90 0.1000 0.91 0.2200 0.91 0.3500 0.91 0.3500		0.04 3.20 0.05 0.10 0.40 0.03 0.26 -0.03 0.35 1.15 2.24 0.48 0.48 -5.01 4.81 0.49	$\begin{bmatrix} -0.21; \ 0.29 \\ [\ 2.74; \ 3.66 \\ [\ 0.04; \ 0.06] \\ [\ 0.08; \ 0.12 \\ [\ 0.36; \ 0.64 \\] \\ [\ 0.29; \ 0.51 \\ [\ -0.02; \ 0.08 \\] \\ [\ -0.02; \ 0.08 \\] \\ [\ -0.05; \ 0.01 \\] \\ [\ -0.05; \ 0.07 \\] \\ [\ 0.29; \ 0.47 \\] \\ [\ 0.29; \ 0.47 \\] \\ [\ 0.29; \ 0.47 \\] \\ [\ 0.29; \ 0.47 \\] \\ [\ 0.29; \ 0.47 \\] \\ [\ 0.29; \ 0.47 \\] \\ [\ 0.29; \ 0.58 \\] \\ [\ 1.96; \ 8.06 \\] \\ [\ 1.76; \ 7.86 \\] \\ [\ 0.77; \ 0.09 \\] \\ [\ 0.39; \ 0.59 \\] \\ [\ 0.39; \ 0.59 \\] \\ \end{bmatrix}$	0.1% 0.0% 49.8% 21.7% 0.5% 2.6% 0.5% 5.2% 4.2% 0.2% 0.1% 1.5% 0.0% 0.0% 87.3%	2.8% 1.6% 4.1% 3.5% 3.7% 4.0% 4.0% 3.3% 2.7% 4.0% 3.3% 2.7% 4.0% 3.8% 0.1% 0.1% 52.2%
CHF(chronic heart failur Zhu H & Qian Y 2018 Zhu H & Qian Y 2018 Zhu H & Qian Y 2018 Fixed effect model Random effects model Heterogeneity: $I^2 = 87\%$, τ^2	30 28 26 84	1.40 1.8800 2.33 2.0300 3.45 1.8100 p < 0.01	31 31 93	0.75 0.6400 0.75 0.6400 0.75 0.6400	¢ + +	0.65 1.58 2.70 1.62 1.64	[-0.06; 1.36] [0.80; 2.36] [1.97; 3.43] [1.20; 2.05] [0.45; 2.84]	0.0% 0.0% 0.0% 	0.9% 0.7% 0.8% 2.4%
Fixed effect model Random effects model Heterogeneity: I^2 = 98%, τ^2	3592 = 0.0351,	p < 0.01	5234		-5 0 5	0.09 0.46	[0.08; 0.10] [0.39; 0.54]	100.0% 	 100.0%

Fig. 5: Subgroup analysis of different kidney diseases data



Fig. 6: Sensitivity analysis of CysC and SCr the area uder the solid line of CysC was 0.805 the area uder the solid line of SCr was 0.683



Fig. 7: Funnel plot for the MD in CysC concentration Linear regression (Egger's) test of funnel plot asymmetry t = 5.0897 p-value < 0.0001

Publication Bias

The funnel plot which was displayed in Fig. 7 was asymmetric, meaning the potential risk of publication bias. The Egger's test showed that some studies fell outside of 95% CI, as known as significant publication bias in this field, suggesting the potential effect on the conclusion of this research.

Discussion

This study showed CysC was sensitive as a biomarker to assess CKD. The sensitivity analysis showed the random effect model was robust as the estimation of MD, i.e., there was no research that had a great influence on the MD estimation. The ROC curve of the area under the ROC curve of CysC and SCr were 0.805 and 0.683. CysC levels were more sensitive than SCr in patients with CKD. Meanwhile, CysC could be utilized as a diagnostic indicator for early-stage kidney disease.

This meta-analysis showed that the random effect model was robust to the assessment of MD. The expression of CysC in patients with CKD was higher than healthy controls. The MD was 0.46. The prediction interval of MD was [0.08; 0.85], indicating that if CysC concentration increased by more than 0.85 mg/dL or decreased by more than 0.08 mg/dL, the renal function may have undergone pathological changes. The sensitivity analysis showed the estimated value of the meta-analysis was still within 95% CI. The pooled effect size of the random effect model MD was 0.46 with 95% CI [0.39; 0.54], indicating the combined effect size results were robust and reliable. The Egger's test results indicated there was a possibility of publication bias in such studies.

In this study analysis, there was not too much evidence of the etiology CKD results, only a subgroup analysis of the etiology was carried out to determine whether it was a high degree of heterogeneity from the literature sources. Heterogeneity was a limitation of this study ($I^2 = 98\%$). However, heterogeneity was inevitable as these studies were based on different institutions and environments around the world (Zhang et al., 2011). Different CysC concentration assays, different causes and different procedures were used to estimate the diagnostic value of CysC in these studies. However, using subgroup analysis to explain partial heterogeneity was not enough due to sampling errors. Kadioglu et al. (2015) clearly indicated that the lack of samples from patients with CKD limits their findings on early biomarkers in patients with hypertension. Another limitation of this study was the publication bias which may affect our current study of the estimator, i.e., the effect size MD. In summary, there were 3592 cases of CKD and 5234 cases of healthy controls were acquired from a number of separate studies. The expression of CysC in patients with CKD was higher than that in healthy controls with a MD 0.46. The result showed the prediction interval was [0.08; 0.85]. The sensitivity of CysC levels was better than SCr. Thus, the level of CysC has a better potential to serve as a biomarker in CKD patients.

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Author's Contributions

Lingxin Bao: Research design and final approval of article.

Qiaoyan Zhou: Data analysis, interpretation and writing the article.

Yanfang Lin: Data analysis and interpretation. Xue Lin and Qingping Hu: Data analysis.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved

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