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

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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 CysC 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 CysC (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 a Nephropathy-gAN (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 ml/min/1.73m^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, ^{99m}Tc-DTPA, ^{51}CrEDTA. 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

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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 (Levy *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 ± 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 I^2 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; Sugiyama *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 meta-analysis. 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 0.08 mg/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 I^2 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.

Table 1: Quality valuation of included studies

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 *et al*.	2020	3	1	1	5	Medium quality
Xie *et al*.	2019	4	2	2	8	High quality
Salwa *et al*.	2019	3	1	1	5	Medium quality
Scarr *et al*.	2019	4	2	2	8	High quality
Wan *et al*.	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 *et al*.	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 *et al*.	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

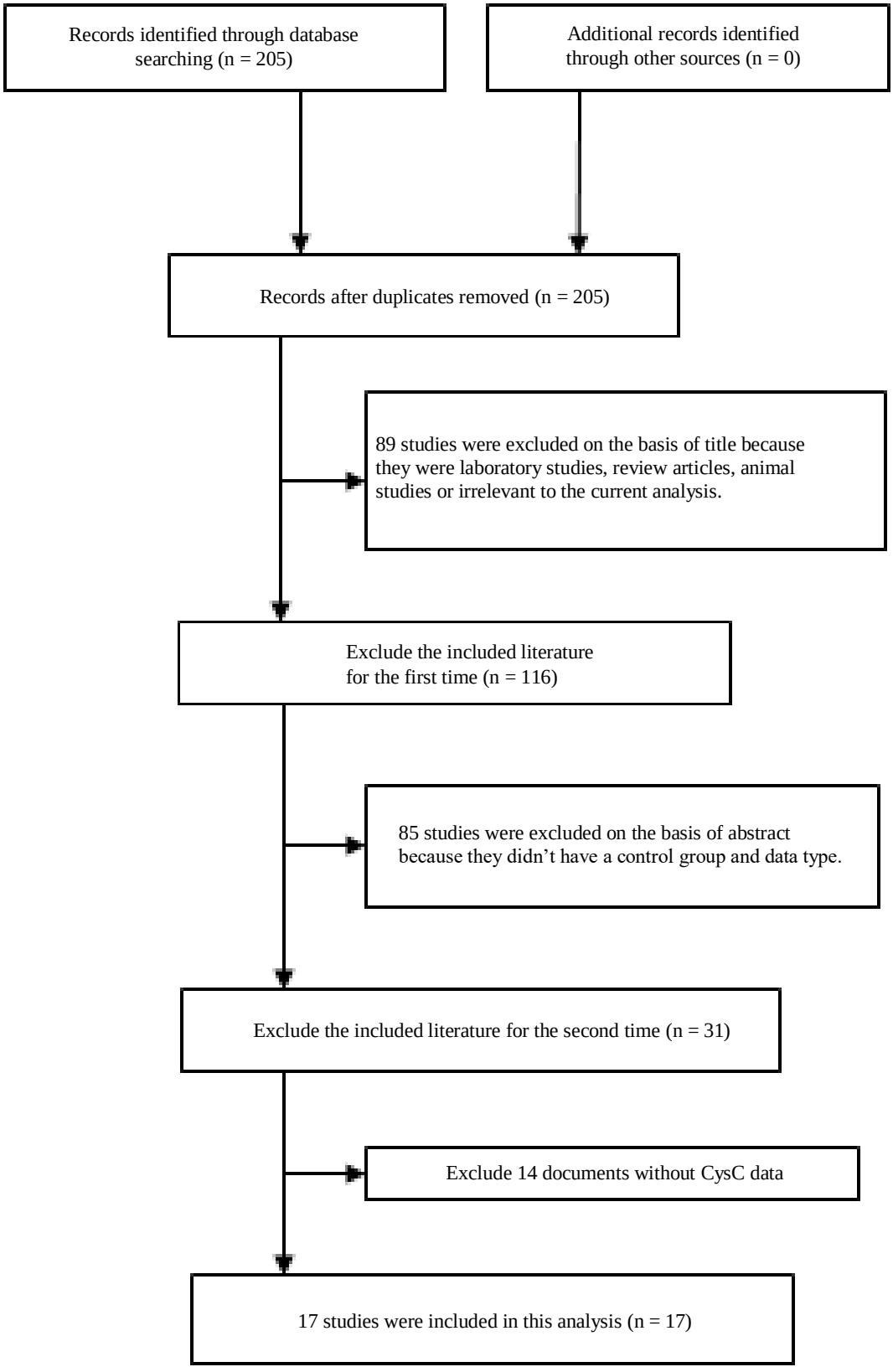

Fig. 1: Flow chart details the study selection process

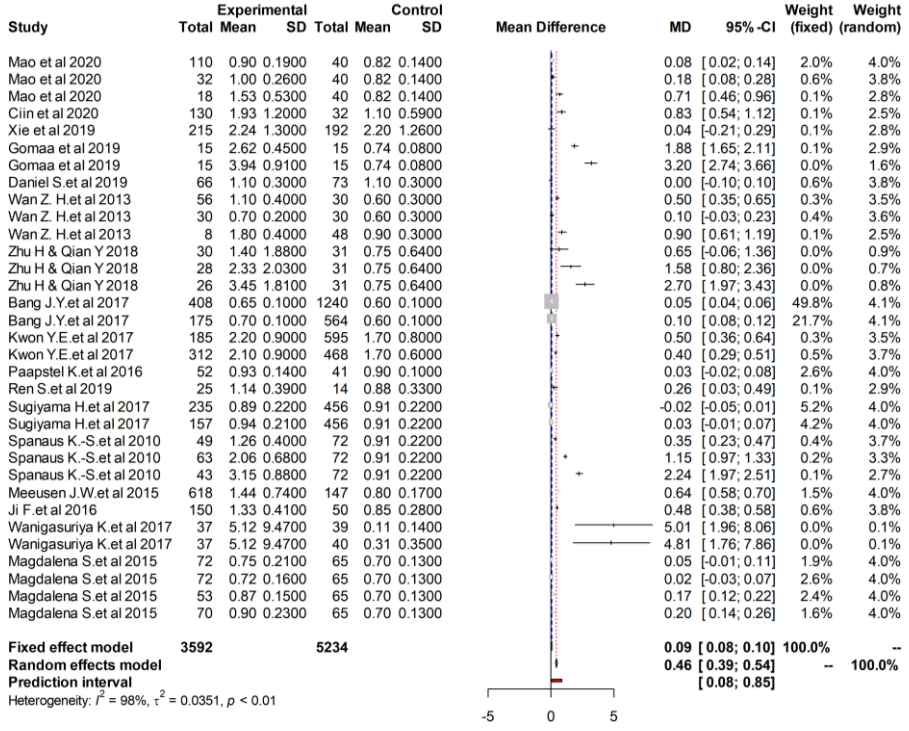

Fig. 2: The meta-analysis with Forest plot of CysC concentration

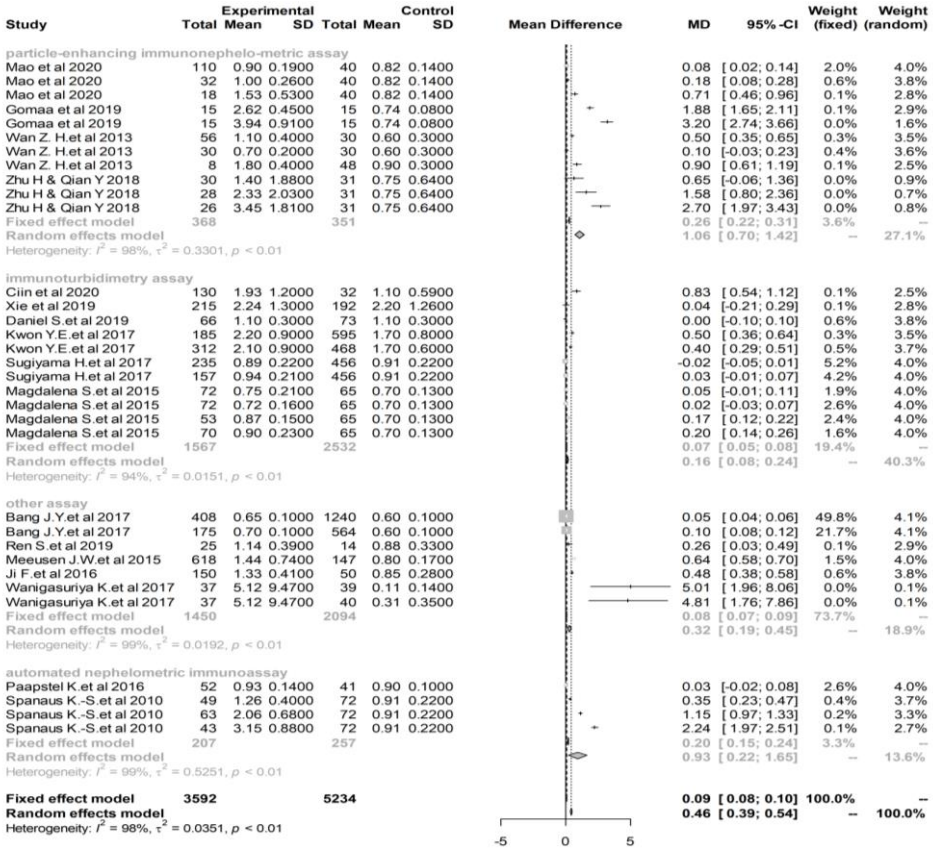

Fig. 3: Subgroup analysis of detection method data

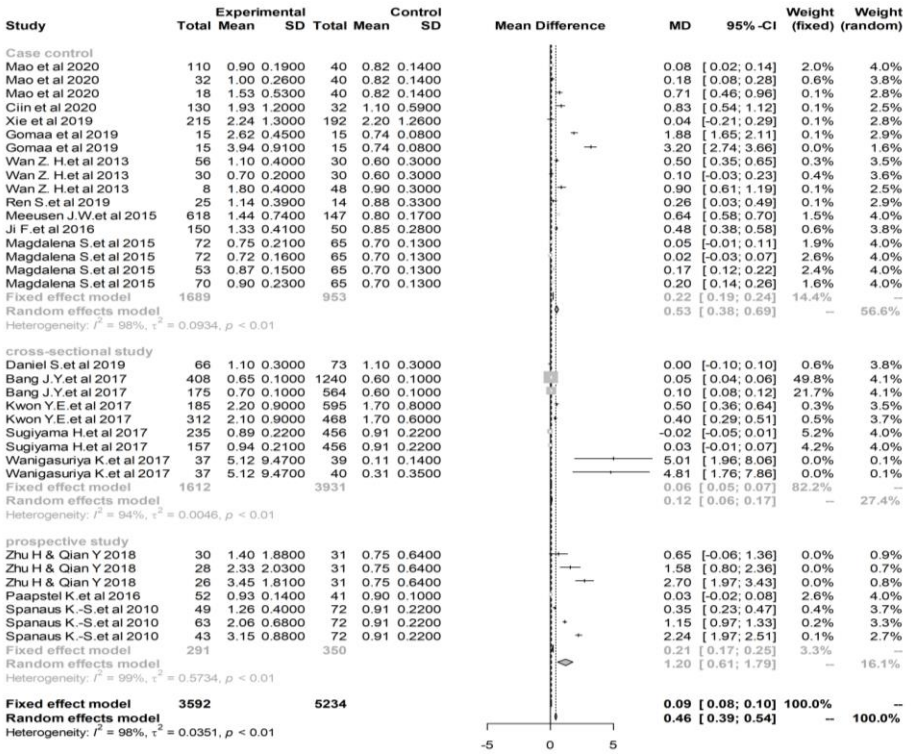

Fig. 4: Subgroup analysis of study protocol data

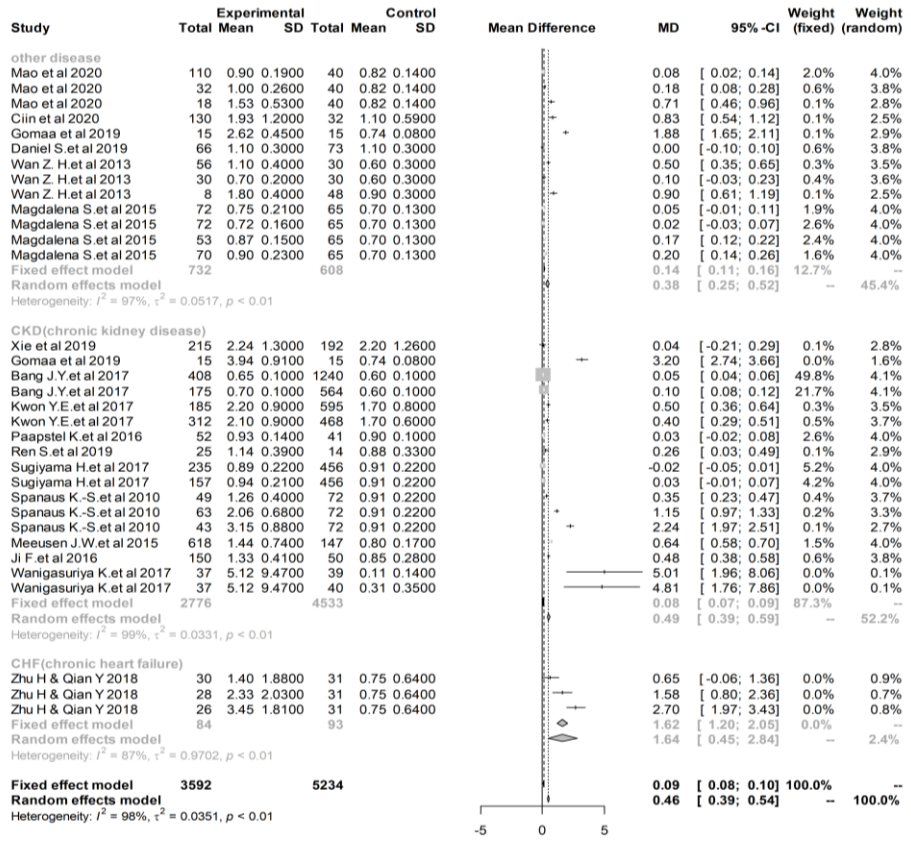

Fig. 5: Subgroup analysis of different kidney diseases data

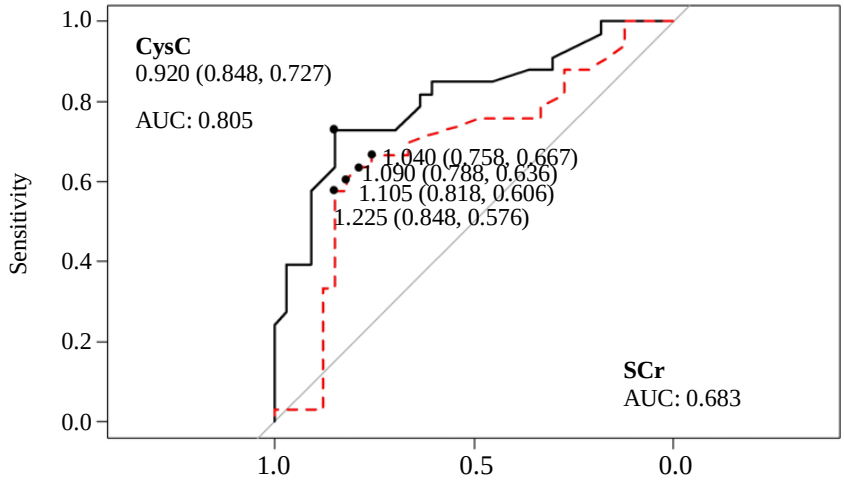

Fig. 6: Sensitivity analysis of CysC and SCr the area uder the solid line of CysC was 0.805 the area uder the solid line of SCr was 0.683

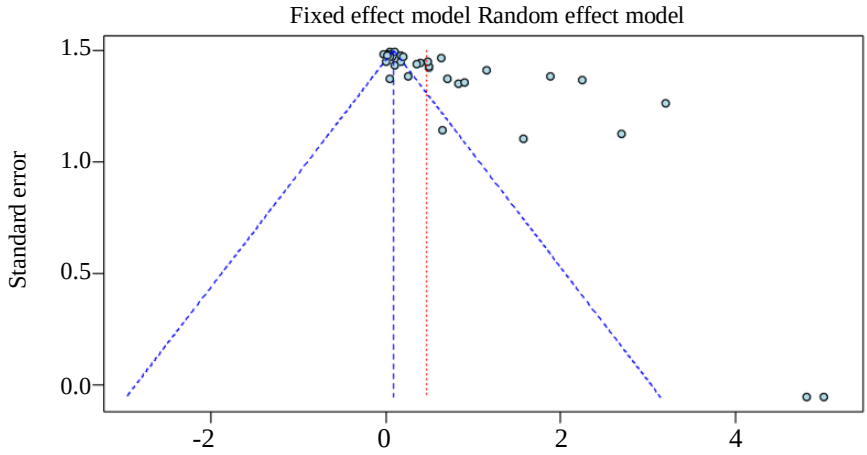

Fig. 7: Funnel plot for the MD in CysC concentration Linear regression (Egger's) test of funnel plot asymmetry t = 5.0897 p-value <0.0001

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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