A Meta-analysis on the diagnostic value of serum cystatin C and creatinine for the evaluation of glomerular filtration function in renal transplant patients

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Abstract:
Objectives: This meta-analysis aimed to perform a systematic review on comparing the diagnostic value of serum cystatin C and creatinine for glomerular filtration rate in renal transplant patients.

Methods: The data was extracted into 2×2 table after the articles were assessed by the tool of QUADAS and heterogeneity analysis. The SROC curve and meta-analysis were performed by MetaDisc1.4.

Results: Meta-analysis showed that the serum cystatin C had no heterogeneity (P=0.418, I2=2.2%, DOR=25.03), while creatinine heterogeneity was high (P=0.109, I2=37.5%, DOR=9.11). The values of SEN, SPE and SAUC were calculated as 0.86, 0.70 and 0.9015 for cystatin C, and 0.78, 0.73 and 0.8285 for creatinine individually. This study utilized GFR detection and subgroups analysis by cutoff. The PLR was 6.13 and the NLR was 0.12 for cystatin C, compared to SCR (3.72, 0.32).

Conclusions: There were significant correlations among cystatin C, creatinine and glomerular filtration rate (GFR). Cystatin C had more sensitivity but less specificity than creatinine for evaluation of GFR. Cystatin C had strong ability in diagnosing renal function after renal transplant and ruling out diagnostic efficacy.

Key words: Cystatin C; creatinine; renal transplantation; glomerular filtration rate; meta-analysis.

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Introduction
The accurate and timely assessment of renal function in patients after renal transplant was provided with great important clinical significance. The glomerular filtration rate (GFR) as an important renal function indicator was measured by the gold standard method for determination the clearance rate of exogenous markers, such as inulin, iohexol, 125I-iothalamate, 99mTc-DTPA, 51Cr-EDTA and other radioactive materials. But these methods which are cumbersome, time consuming and have significant potential side effects were generally used for scientific research or clinical trials with higher profession.

The endogenous indicators including serum creatinine and endogenous creatinine clearance rate were usually used to assess GFR in clinically. However, the generation of creatinine was effected by age, sex, muscle mass, drug use and other factors. Moreover, tubular secretion and visceral additional clearance resulted in the concentration of serum creatinine within the reference range when the renal function loss reached 50%. Therefore, serum creatinine showed low sensitivity in the diagnosis of renal failure after kidney transplantation, especially in some minor aspects of renal impairment, children, the elderly and other special patient population.

In recent years, serum cystatin C as an ideal endogenous marker had been progressively concerned in the evaluation of GFR function. Numerous studies showed that cystatin C as a serum marker was more sensitive than serum creatinine in reflecting GFR. Cystatin C was generated at a constant rate by the nucleated cells of organism, and could freely get through glomerulus and get completely decomposed after reabsorption in the proximal tubule epithelial cells but it didn’t get back to the blood and couldn’t secreted by renal tubular. In ad-
the characteristics of serum cystatin C were very close to the required characteristics of the ideal GFR endogenous target. The contents of serum cystatin C were relatively stable and not affected by any external factors. It was reported that cystatin C, with a positive change, had greater molecular weight than creatinine. So it was easier to reflect the changes of early glomerular filtration membrane permeability. And cystatin C, with smaller differences between individuals, increased when GFR had slight decrease. It possessed more prominent clinical significance in the monitoring of renal function in patients with renal transplant. This study was on the basis of domestic and foreign researches before January 2013, and discussed the diagnostic value of cystatin C and creatinine for GFR after renal transplantation, anticipating to provide an evidence for base medicine.

Materials and methods

Literature inclusion and exclusion criteria

The object of study

The kidney transplant recipients, including children and elderly patients, whose primary disease covering the whole spectrum of disease before transplantation had been studied. The cut-off value of GFR was greater than 30mL/min in experimental detection.

Type of Study

Direct comparison of cystatin C with creatinine had been detected on the diagnostic tests of GFR diagnostic value, based on cross-sectional studies, the pattern of cohort studies and case-control studies. The relevant literatures compared cystatin C with the result of serum creatinine based formula of MDRD / Cockcroft and Gault (CG) formula, or based on the formula results of cystatin C, creatinine were excluded in this study. GFR was the critical reference standard in the evaluation of renal function in patients with renal transplant. This study 10 literature sources and 692 cases of renal transplant, GFR, diagnosis test, sensitivity, specificity and the like. The same keywords were used to retrieve from Chinese Academic Journal and Chinese Biomedical Literature database during 1985 to January 2013. Using the combination of subject terms and keywords, the supplement search was carried out through Google Scholar and other search engines on the Internet. Meanwhile, the references of the literatures had been used for creatinine detection. Jaffe method and enzymatic Immunoassay (PENIA). Jaffe method and enzymatic had used for creatinine detection.

Measurement index

The summary sensitivity (SEN), summary specificity (SPE), summary positive and negative predictive values (±PVs), summary positive and negative likelihood ratios (±LRs), diagnostic tests combined odds ratio (DOR), area under the summary receiver operating characteristic (SROC). The literatures, which couldn’t extract the fourfold table (TP, FP, TN, FN), had been excluded.

Literature Search Strategy

This study mainly conducted a systematic literature search of the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) through 1985 to December 2012, and the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html) databases at 2012 No. 4 by using the following keywords: cystatin C, Creatinine, renal transplant, GFR, diagnosis test, sensitivity, specificity and the like. The same keywords were used to retrieve from Chinese Academic Journal and Chinese Biomedical Literature database. In addition, the title and abstract of each literature was carefully read to determine whether it met the inclusion criteria. The initial literatures search identified 314 studies. Of these, 105 were excluded after reading text titles and abstracts, and only 24 literatures met the inclusion criteria. We contacted three authors of the 24 literatures, in order to obtain the details of the fourfold table and some incomplete information, but didn’t get a reply. Finally, 14 literature sources were excluded due to the insufficient fourfold table data, and merely 10 literature sources served as the research literatures. Among the rest, 7 literature sources were in English, and 3 were in Chinese. All the studies were about diagnostic test of GFR value via cystatin C and creatinine.

The basic information of included studies

10 literature sources and 692 cases of renal transplant recipients had been adopted in this study, excluding children and elderly patients, as a whole the men slightly more than women. 2 literature sources reported the situation of the disease after renal transplantation. For the cut-off value of the evaluation of the renal function, the values of cystatin C and creatinine were 1.07 ~ 1.64 mg / l.
L and 106.1 ± 130.7 µmol/L, respectively. And other 2 literature sources didn’t mention these indicators. The cut-off value of GFR tested by gold standard was 80 mL/min/1.73m² (60~90 mL/min/1.73m²). The detection methods of GFR included ultrasonic, 125I-iothalamate, 99mTc-DTPA and endogenous 24h CrCl.

Simultaneously, the detection method of cystatin C contained PETFIA and PENIA, while Jaffe method and enzymatic method had used for creatinine detection. The main characteristics of the literatures were shown in Table 1 and Table 2.

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**Table 1** The basic situation of the adopted literature

| Study of patient | Country | No. | Average | Male (%) | The use of | The est. | Normative |
|-----------------|---------|-----|---------|----------|------------|---------|----------|
| Lorenz Rich 1996[4] | Switzerland | 3 | 49±16 | 50% | Cr | 6 | 125% iothalamate |
| Jean-Philippe Daniel 2004[3] | France | 10/6 | 40±11 | 50% | Cr | 6 | Iothalamate |
| Fu Keung Li 2002[8] | Hong Kong | 1 | 38±5 | 60 | Penetration | 8 | Cr |
| China | 5 | Azathioprine | 6 | Cr |
| E. Paskalev 2001[17] | Bulgaria | 4 | 50±14 | 50 | Imuran | 6 | Cr |
| Dai Hong Li 2001[29] | Tianjin, China | 5 | 44±13 | 50 | A-P | 10 | 99% |
| Jansheng Ye 2010[21] | Guangdong, China | 7 | 43±13 | 65 | Metoloz | 6 | 99% |
| Fu Lu Zheng 2005[22] | Guangdong, China | 2 | 45±20 | 20 | Glucoronic | 8 | 99% |
| N. Krishnamurthy | K | India | 3 | 43±7 | 73 | c | 0 | 72% | DTPA |
| Stefan Herget-Rosenthal 2009[9] | Germany | 3 | 49±14 | 318 | Cystatin | 8 | Cr |
| | | | | | Azathioprine | |

**Table 2** The fourfold table data of the adopted literature

| Study | Serum Creatinine | Cystatin C |
|-------|------------------|------------|
|       | Detection method | Cut-off | TF | P | N | F | Detection method | Cut-off | TF | P | N | F |
| Lorenz Rich | PETFIA | 1 | 15 | 1 | 8 | 6 | Reform | 12 | 1 | 5 | 4 | 4 |
| Jean-Philippe Daniel | Dade Behring | 1 | 26 | 8 | 2 | 5 | Metoloz | 130 | 2 | 1 | 50 | 17 |
| F. Paskalev 2001 | Latex Cys C assay | 1 | 68 | 8 | 2 | 5 | Reform | 12 | 5 | 1 | 20 | 21 |
| Dai Hong Li 2001 | Latex Cys C assay | 1 | 19 | 2 | 1 | 6 | Metoloz | 12 | 2 | 9 | 6 | 5 |
| Jansheng Ye 2010 | Latex Cys C assay | 1 | 17 | 4 | 4 | 3 | Jaffe | 12 | 1 | 4 | 10 | 7 |
| Fu Lu Zheng 2005 | Dade Behring | N | 16 | 0 | 6 | 1 | Jaffe | 11 | 1 | 5 | 5 | 5 |
| N. Krishnamurthy 2011 | Latex Cys C assay | N | 16 | 1 | 1 | 1 | Jaffe | 106 | 1 | 6 | 8 | 3 |
| Stefan Herget-Rosenthal 2003 | Latex Cys C assay | 1 | 2 | 2 | 1 | 9 | Jaffe | 106 | 1 | 6 | 8 | 3 |

**Note:** Dade Behring N Latex Cys assay was one of the PENIA, NA, Non data acquisition.
The quality assessment of the adopted literature sources
The quality assessment of diagnostic accuracy study (QUADAS) was shown in Table 3. All adopted literature sources were not mentioning the blinded method, and most of them didn’t list the diseases foundation of the observed objects. Therefore these studies were deemed incomplete and confusing cases. Furthermore, major literature sources also didn’t mention the situations of withdrawals or whether all of the data were included in the calculation. In general, the quality of the adopted literature sources was higher.

### Table 3 The QUADAS of the adopted literature

| Study                  | Type of study | Disease | Select | Golden | Multi | Implementat | Lost of follow up |
|------------------------|--------------|---------|--------|--------|-------|-------------|-------------------|
| Lorenz Risch 1999[16]  | Cohort       | test    | N      | YE     | YES   | YE         | YE                |
|                        |              | spectrum | O      | S      | S     | S          | S                 |
| Jean-Philippe Daniel 2004[13] | Cohort      | study   | N      | YE     | YES   | YE         | YE                |
|                        |              |          | O      | S      | S     | S          | S                 |
| Fu Keung Li 2002[14]   | Cohort       | study   | Y      | YE     | NO    | YE         | YE                |
|                        |              |          | E      | S      | S     | S          | CLEAR             |
| E. Paskalev 2001[17]   | Cohort       | study   | Y      | YE     | NO    | YE         | NOT               |
|                        |              |          | E      | S      | S     | S          | CLEAR             |
| Daihong Li 2010[20]    | Cohort       | study   | N      | YE     | YES   | YE         | NOT               |
|                        |              |          | O      | S      | S     | S          | CLEAR             |
| Jaruang Ye 2010[21]    | Cohort       | study   | N      | YE     | YES   | YE         | NOT               |
|                        |              |          | O      | S      | S     | S          | CLEAR             |
| Fupu Zheng 2005[22]    | Case-control study | N      | YE     | YES   | YE    | YE         | N                 |
|                        |              |          | O      | S      | S     | S          | S                 |
| N.Krishnamurthy. K 2011[19] | Case-control study | N      | YE     | YES   | YES   | YE         | NOT               |
|                        |              |          | O      | S      | S     | S          | CLEAR             |
| Christensson A 2003    | Cohort       | study   | N      | YE     | YES   | YE         | NOT               |
|                        |              |          | O      | S      | S     | S          | CLEAR             |

Note: Disease spectrum composition means that whether include the various cases or confusion of illness.

The results of Meta-analysis
Heterogeneity analysis
10 summary OR (95% CI) and heterogeneity analysis values of independent studies were shown in Fig 2A and Fig 2B.

Fig. 2 Meta-analysis on diagnostic value of the creatinine and cystatin C. A, B Forest plots for summary OR and heterogeneity analysis of the creatinine and cystatin C detection; CD Forest plots for summary SEN and SPE of the creatinine and cystatin C; E, F The SROC curve of creatinine and cystatin C assessment on GFR after renal transplantation.

### Calculated results of a random effects model
A model demonstrated that the DOR value of cystatin C was greater than that of creatinine, but their CI showed the fraction overlap. In addition, the calculation of the Spearman correlation coefficient between sensitivity logarithmic and 1-specificity logarithm showed that cystatin C=0.213 (P = 0.555), and Cr= 0.140 (P = 0.699). The result inferred that weak correlation existed in logarithmic of sensitivity and 1--specificity, and it was little possibility that a threshold effect led to the heterogeneity. Moreover, the diagnostic studies of both creatinine and cystatin C were 12 < 50%, and cystatin C had a smaller i2 value. The results showed that heterogeneity were resulted from a non-threshold effect existed among the adopting literatures.

### Summary effect size
In 10 independent studies, the summary SEN and SPE (95% CI) of creatinine and cystatin C were shown in Fig 2C&D and Table 4. Forest map intuitively showed that the specificity of cystatin C had significant heterogeneity (χ2 = 91.88, 12 = 90.2%). And the result of summary effect size showed that the SEN of cystatin C was much higher and the SPE was similar to creatinine.

### Table 4. The data of forest plots for pooled sensitivity and specificity of the Cr and Cys C

| Cr     | Cys C |
|--------|-------|
| sensitivity | specificity |
| 0.78 (0.73–0.82) | 0.73 (0.68–0.78) |
| 0.70 (0.65–0.75) | χ2 test value (P value) 15.25 (<0.0001) |
| 30.43 (0.0004) | 34.27 (0.0001) |
| 91.88 | |

### SROC curve
10 SROC curve of the diagnostic value of GFR after renal transplantation via cystatin C and creatinine were shown in Fig 2E&2F. The splashes of cystatin C and creatinine showed the non-scatter "shoulder arm" shape, and there was less possible of threshold effect in the inclusion literatures. Furthermore, compared with the AUC of creatinine, that of the cystatin C was greater (AUCCr = 0.8285, AUCCystatin C=0.9015), which demonstrated the diagnostic accuracy was higher.

### Subgroup analysis
Most guidelines recommended that the diagnostic criteria for renal function after kidney transplantation was GFR≤80 mL/min/1.73m2, but the range of GFR cutoff values in the inclusion literatures was from 60 to 90 mL/min/1.73m2. In addition, the Meta-regression analysis showed that the major source of heterogeneity was different from the reference standards of GFR test. Therefore, in the subgroup analysis, the detection reference standards based on the cut-off value ≤80 mL/min/1.73m2 of GFR and 99mTc-DTPA as the limited conditions. Three groups (n= 123) as the subjects were selected and shown as merger of positive and negative likelihood ratio (DLRs) in Table 5. Comparing the degree of heterogeneity, the merged positive likelihood ratio of cystatin C (χ2=3.99, P=0.1357) and creatinine (χ2=7.83, P=0.0199) was more obvious. The merged negative likelihood ratio of that was un conspicuous and the values were χ2=0.54, P=0.7635 for cystatin C and χ2=0.12, P=0.9408 for creatinine respectively.
In this study, subgroup analysis was also conducted in the different methods of Cys C and creatinine. Among the adopted literature sources, there were 4 that detect- ed cystatin C using PETIA, and the results were: 0.686, 貝=0.763, SEN=0.78, SPE=0.85, 6 cases used modified Jaffe to assay the value of Cys C (excluding the mentioned PETIA and the results were: P=0.306, 貝=0.72, OR=3.51, 105 cases used modified Jaffe to assay the value of Cys C (excluding the mentioned PETIA and the results were: 0.56, 貝=0.63, P=0.1357, NLR=0.7635. Only 1 piece used enzymatic.

**Table 5 Subgroup analysis of Cys C and Cr**
The detection standard of the GFR was 99mTc-DTPA and cut-off value≤80 mL/ min/1.73m².

| Cys C | PLR (95%(CI)) | NLR (95%(CI)) | PLR | NLR |
|-------|---------------|---------------|------|------|
| 6.13  | (1.38, 15.79) | 0.12 (0.07)   | P=0.1357 | 0.21 |

(4.88-11.88) , SEN=0.75, SPE=0.72. Only 1 piece using enzymatic.

**Discussion**
Most patients may have an acute and chronic rejection or complications of chronic allograft nephropathy after kidney transplantation, and early diagnosis and treatment of renal injury will directly affect the prognosis of patients. Hence the goal of clinical research is to look for an early, sensitive, specific indicator of GFR. Previous research12-14 suggested the ideal endogenous indexes of GFR should maintain a constant ratio in serum or plasma, and it can pass freely through glomerular filtration membrane. It cannot be reabsorbed by renal tubular, and secreted by renal tubular, and there is no extra renal elimination. Serum creatinine is the most commonly used evaluation index of renal function, though there are many limitations, but it still plays an important role in clinic. The research about judg- ing the damage of renal function found that cystatin C is also a kind of ideal index reflecting the endogenous change of GFR. In this study, Meta-analysis is carried out through 10 articles to study the diagnostic value of GFR after kidney transplantation in a systematic way.

The results of meta-analysis showed that the Diagnos- tic OR of cystatin C and creatinine have a good correla- tion with GFR, but there is a small overlap in 95% confidence interval of DOR, thus the difference is not significant. Cystatin C diagnosis research has no obvious heterogeneity (P = 0.4186, I² = 2.2%), and creatinine diagnosis has obvious heterogeneity (P = 0.1089, I² = 35.7%).In these studies, GFR diagnosis sensitivity of cystatin C is higher than Cr after kidney transplantation (SENCys C = 0.86, SENCr = 0.76), but the specificity is lower than creatinine (SENCys C = 0.70, SPE creatinine = 0.73).This conclusion is also confirmed through the AUCC (AUCC = 0.8285, AUCCys C = 0.9015). AUC or the correlation co-efficient was used as a diagnostic performance evaluation index alone in many past studies27,28, but this study takes the quality of literature, liter- ature of heterogeneity and GFR, cystatin C, creatinine cutoff value into consideration, and SEN. SPE. evaluation effectiveness has more clinical significance.

From the forest plots for the degree of SEN and SPE, the summary effect of the cystatin C and the creat- inine value have obvious heterogeneity. When analyzing the sources of heterogeneity, five different methods of standard were used to research GFR detection, and the cutoff value is also different.Therefore this study conducted a subgroup analysis after limiting the GFR (99 MTC-DTPA) test method and the cutoff value (80 mL/min / 1.73 m2 or less). Evidence including three research groups (n = 125) indicates the likelihood ratio of cystatin C range is bigger (PLR = 6.13, NLR = 6.13) than creatinine (PLR = 3.72, NLR = 3.72). Therefore the likelihood ratio of cystatin C has stronger ability to diagnose renal injury after renal transplantation and exclude diagnosis effectiveness. However, in the subgroup analysis, the positive likelihood ratio of the cystatin C and creatinine still has the obvious heterogeneity. This shows that because of different calculation methods, different population constitution, GFR measure by radia- tive nucleic material has some problems in the detection accuracy, repeatability. The heterogeneity of the negative likelihood ratio of the cystatin C and creatinine can be ignored because there is no obvious heterogeneity.

The sub group analysis of cystatin C and creatinine showed that a significant rise in P values. It indic- ated that heterogeneity was associated with detection method. The reagents of PETIA were mostly bought from Dako company, but PENIA mainly used the reagents of Behring company. The Jaffe method was usu- ally used for the test of creatinine, and some research us- ing the improved Jaffe method. Different instruments, reagents, calibration, calculation and reference range and cutoff values led to the differences between different methods.

The research had a limitation that the composed infor- mation of disease spectrum in patients including: in the results of the sub analysis. The information includes the various chronic kidney diseases after renal transplantation (eg. nephropathy of recurrent IgA, nephrotoxicity nephropathy of cyclosporine A, focal glomerulosclero- sis, acute exacerbation of chronic allograft nephropa- thy and so on) and the easily confused diseases (eg. Transplanted glomerulonephritis etc.), which existed clinical heterogeneity. For example, E.Paskalev found that the hyperfiltration condition was easy to appear in the long-term follow-up process of transplanted renal in the patients with diabetic nephropathy which accounted for 15% of underlying diseases. The con- centration of serum creatinine C decreased rapidly. However, it could not represent all the progression of nephropathy after chronic kidney transplantation. In addition, the detection time of evaluation indexes was varied, and it couldn't exclude the effect of the state of progression of transplanted renal on experi- mental results, which would increase the heterogeneity of study.

The research also analyzed the influence of immuno- suppressants on the detection of cystatin C and Cr after renal transplantation. Boenkamp. A29 indicated that the concentration of cystatin C in children’s serum af- ter renal transplantation was higher than other kid- ney diseases in children. Risch and L etc.30 confirmed that cyclosporin A and prednisone had non-significant effect on the concentrations of cystatin C. However, cystatin C could generate extensively and increase dose-de- pendence using dexamethasone in HeLa cell in the vi- tro. The application of the immune suppressive agents in the literature of this research was almost the same and the effect of this factor on the result couldn’t be observed, therefore it requires further research. In recent years, the formulas based on cystatin C and cre- atinine were used for predicting GFR in clinical studies to increase daily31. The formulas counted ethnic, sex, age and other factors and made it more accurate for the evaluation of GFR. Min Z etc.32. Demonstrated signif- iant correlations between cystatin C, Scr and GFR. cystatin C was more sensitive, but less specific, than serum creatinine for the estimation of GFR in patients with chronic kidney disease. Moreover, one literature31 about the diagnostic value of GFR after renal trans- plantation compared the diagnostic value via cystatin C with that of the MDRD formulas on the ground of creatinine after renal transplant. 105 cases of renal transplant recipients were brought into the research, and the average age of them was 49.5. The result showed that the cystatin C had more higher sensitivity (SENCys C = 0.92%, SENCr = 0.82%) and had same specificity (SPECys C = SPECr = 93.3%) when GFR used both the standard method 99mTc-DTPA and the value of cut-off was 60 mL/min / 1.73m2.

**Conclusion**
This study was aiming at the diagnostic value of cysta- tin C and creatinine after renal transplantation, and per- formed a systematic evaluation and Meta-analysis via retrieving domestic and foreign researches. Ac- cording to the analysis results, the conclusions were as follows: (1) cystatin C and creatinine showed a good corre- lation with GFR. The diagnostic sensitivity of cystatin C was higher than that of creatinine in patients after kidney transplant, but the specificity of cystatin C was shown lower than creatinine. (2) When the detection method of GFR was limited to 99mTc-DTPA and the value of cut-off ≤80 mL/ min / 1.73 m2, cystatin C had a larger range of likelihood ratio and stronger capacity for diagnosis of renal func- tion after kidney transplant and exclusion diagnostic ef- ficacy. (3) The difference of detection methods between cystatin C and creatinine had great influence on heter- eogeneity.

**Conflict of interest**
The authors have no financial conflicts of interest.

Multiple reference bias means that whether all the cases of line was tested by the same golden standand. Lost of follow up bias means that whether the results contain all the cases of line.
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