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Serum Cystatin C Level as an Early Biomarker for Detecting Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis Study

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Abstract: ***There are many research addressed the importance of biomarkers for early prediction of diseases thus increasing the chance for treatment. This meta-analysis study aims to evaluate serum Cystatin C as early biomarker for predicting diabetic nephropathy in patients with type 2 diabetes. Methods: Searching on five database studies which carried out from 2019-2023. Ten studies included were analyzed using "meta", "metasens" and "diagmeta" packages. R version 4.2.2. We calculated values for serum cystatin C in DM and DM with nephropathy, cut-off value, specificity, sensitivity, the area under the curve (AUC) and Receiver operating characteristic curve (ROC). The Results showed level of cystatin C was significantly higher in DM with nephropathy group [MD = 1.22, 95% CI (-2.22,-0.23), p-value = 0.02]. The pooled data was heterogeneous (I^2 = 98%, p-value < 0.01and pooled sensitivity 0.73 and specificity 0.73. The pooled DOR of cystatin C was [69.9, 95% CI (4.68, 10.26). optimal cutoff point was [0.6932, 95% CI (0.2050; 0.9519). The pooled DOR of cystatin C was [69.9, 95% CI (4.68, 10.26). Conclusion: This study demonstrated that cystatin C is a potential early biomarker for predicting diabetic nephropathyin type 2 diabetic patients.***

Keywords: Cystatin C, Diabetic nephropathy, meta-analysis, biomarkers.

1. Introduction

Type 2 diabetes mellitus is characterized by hyperglycemia, which results from abnormal secretion, function, of insulin or both. (1). Long-term diabetes has been connected to microvascular issues such as retinopathy, neuropathy, and nephropathy. (2). Diabetic nephropathy affects 20% to 40% of patients with diabetes mellitus (DM), both types 1 and 2. If left untreated, this condition can progress to end-stage renal disease (ESRD). (3).

Diabetic nephropathy is defined as the elevation of albuminuria (>300 mg/24 hours or 200 mcg/min) in patients with diabetes mellitus, who typically also have retinopathy, high blood pressure, and declining glomerular function. (4). This condition occurs when there is no clinical or laboratory evidence of other kidney or renal tract disease. Thus, mortality from DM nephropathy can be reduced with early identification (5). Currently, assessing GFR, serum creatinine, and creatinine clearance are additional steps in the screening procedure for diabetic nephropathy, along with monitoring the patient for the start of microalbuminuria (6). Albuminuria has represents glomerular injury and increased glomerular permeability to macromolecules. It has been one of the biomarkers used to screen renal function, but it might not be apparent in the beginning. (3). The albumin creatinine ratio is a useful diagnostic test for diabetic nephropathy; however, when used in conjunction with other variables including menstruation, UTIs, and high activity, it may yield false-positive results. (7). Serum creatinine often used test for renal function; but its levels vary with age, sex, muscle mass, medication, and level of hydration, however, does not change until approximately 50% of renal function is lost. (8). Biomarkers are indicators, such as proteins, lipids and cells that may be detected by urine and blood examination. (9). Diabetic patients have the potential to can increase their lifespan if an early biomarker allows for earlier identification and intervention, reduces the occurrence of diabetes, and decelerates the advancement of the condition (10), (5). Cystatin C is a 13 kDa cysteine protease inhibitor, a tiny protein that is freely filtered by the renal glomeruli. Cystatin C has been linked to eGFR decline and factors that indicate how type 2 DN may advance. (11).

2. Materials and Methods

Researching in PubMed, Google Scholar, EMBASE, Scopus and web of science the data were collected. The search words were Serum Cystatin C, diabetic nephropathy, Diabetes kidney disease, biomarker, early diagnosis and "type 2 diabetes mellitus.

The researchers tested the bias risk of included studies according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).

Included studies: full text studies which involved serum cystatin C measured in diabetic patients and diabetic patients with nephropathy and published in the period from 2029 to 2023.

Exclusion criteria
Case reports, reviews, letters, conference abstracts, or animal studies, inadequate data to extract four-cell table data

and duplicate data are the excluded criteria. **Sample size**: 10 studies carried out from 2019-2023, were included in this study.

Data extraction

Data was independently extracted for measured values for serum cystatin C in DM and DM with nephropathy, cut-off value, specificity, sensitivity, and the Area under the curve (AUC) and Receiver operating characteristic curve (ROC) were calculated.

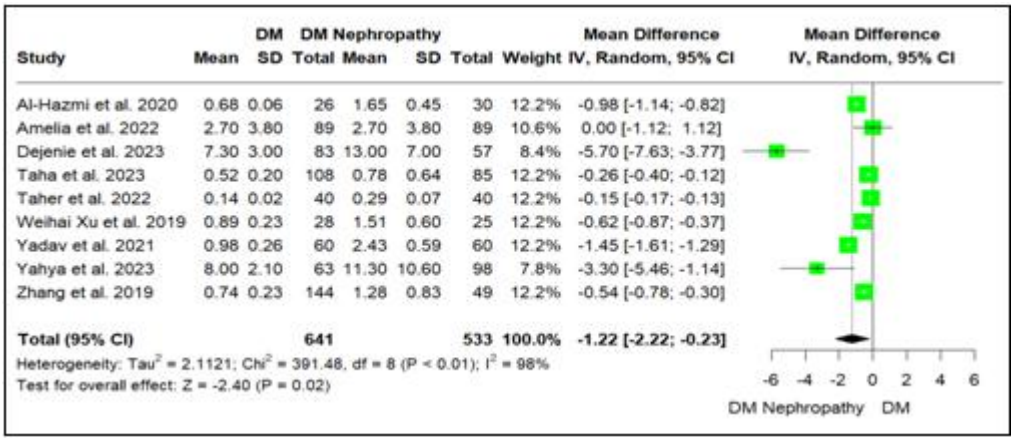
Statistical analysis approach:

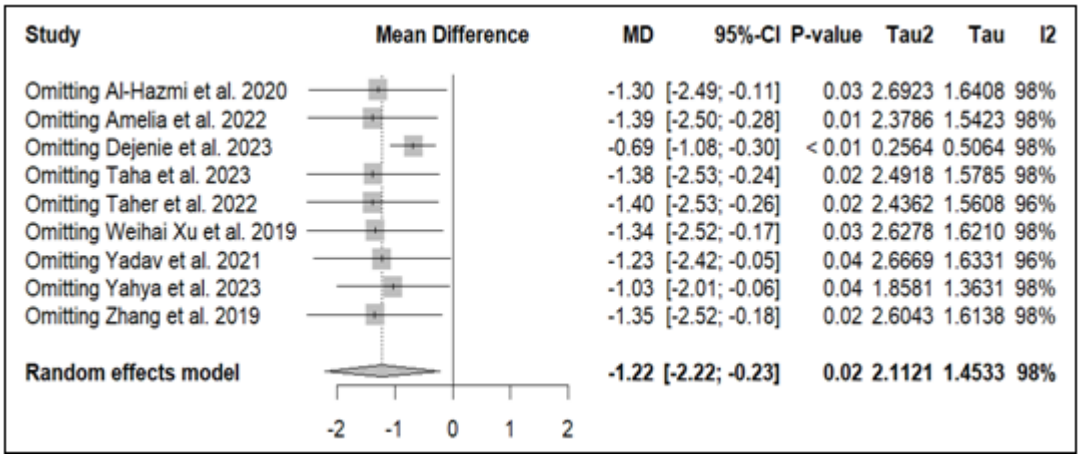
We extracted data in the form of mean and standard deviation to compare between serum level of cystatin C in diabetic patients and diabetic patients with nephropathy. All values of cystatin C transformed to mg/L. These data were pooled in mean difference and 95% confidence interval (CI). sensitivity and specificity were calculated using Rev Man calculator to calculate the pooled sensitivity, specificity, diagnostic odds ratio (DOR) and optimal cutoff value that give best sensitivity and specificity. The optimum cutoff value was calculated using the common random intercept method (CI). All analysis was done using "meta", "metasens" and "diagmeta" packages. R version 4.2.2 (2022-10-31) and R Studio version 2022.07.2 (2009-2022) R Studio, Inc.) were used in the analysis.

3. Results

1) Serum level of Cystatin C in DM and DM with nephropathy

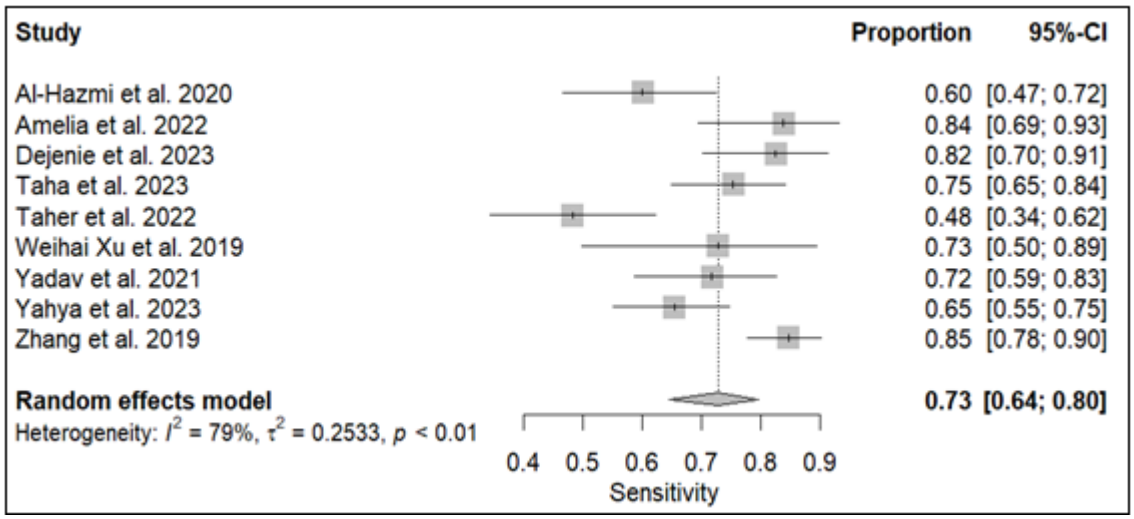
Table 1: showed that the level of cystatin C was significantly higher in DM with nephropathy group [MD = 1.22, 95% CI (-2.22,-0.23), p-value = 0.02]. The pooled data was heterogeneous (I^2 = 98%, p-value < 0.01). As illustrated below.

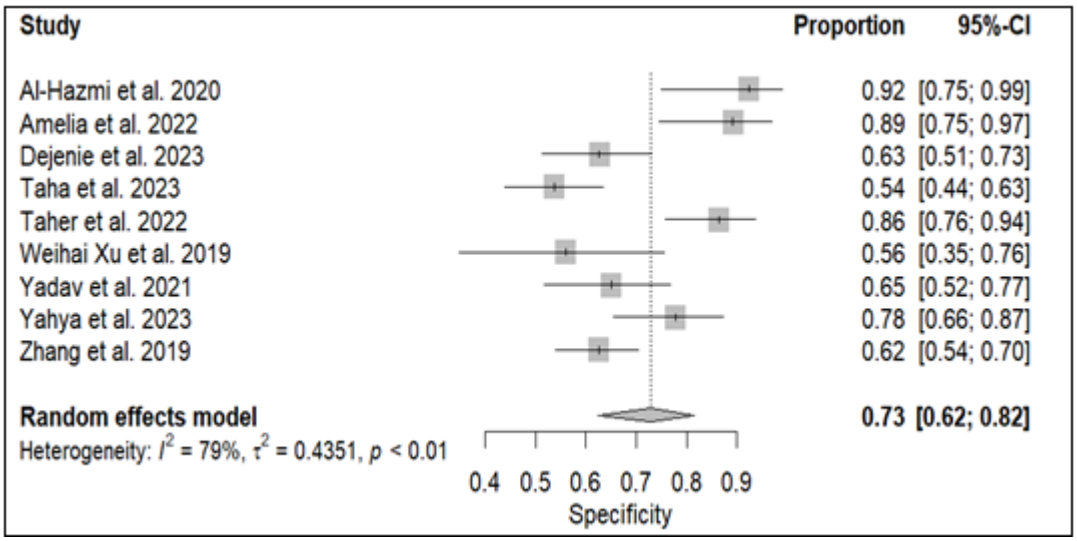




2) Sensitivity and specificity of serum Cystatin C Level

The pooled sensitivity of cystatin C level was [73%, 95% CI (64%, 80%)]. The pooled analysis was heterogeneous (I^2 = 79%, p-value < 0.01). As illustrated below.

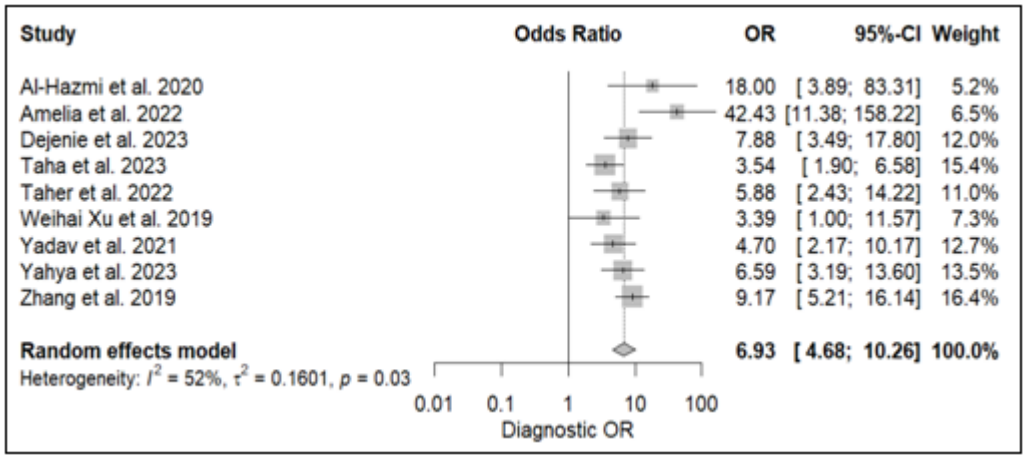




The pooled specificity of cystatin C level was [73%, 95% CI (62%, 82%)]. The pooled analysis was heterogeneous (I^2 = 79%, p-value < 0.01).

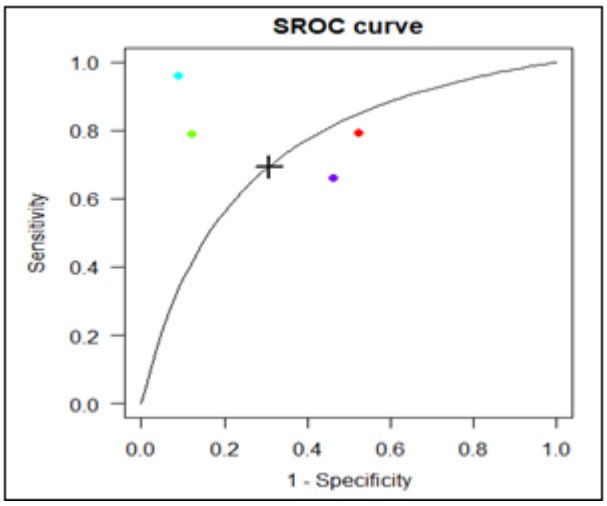
3) Diagnostic odds ratio (DOR) of cystatin C level

The pooled DOR of cystatin C was [69.9, 95% CI (4.68, 10.26)]. The pooled analysis was heterogeneous (I^2 = 52%, p-value = 0.03) as illustrated below.



4) The optimum cutoff that give the best sensitivity and specificity:

The SROC summary receiver operating characteristic curve showed that the optimal cutoff point that gives the best sensitivity and specificity was 7.204. Sensitivity and specificity at optimal cutoff point was [0.6932, 95% CI (0.2050; 0.9519)], [0.6932, 95% CI (0.1741; 0.9604)]; respectively. The Area under the curve (AUC) was 0.7498. As illustrated below.



4. Discussion

Assessment of kidney function is essential in diabetics because decreases in kidney function result in reduce in glomerular filtration rate and a proportionate increase in microalbuminuria in such patients. Many assessment methods are considered useful, but it insensitive and give negative results, till the Glomerular filtration rate is moderately decreased (12).

In this meta-analysis ten studies carried out from 2019-2023 were included ((13), (14), (15), (4), (16), (17), (18), (19), (7). to evaluate value of serum Cystatin C as an early biomarker for detecting of chronic kidney disease in diabetic patients.

The results of the study revealed a significant increase in the level of cystatin C among patients with diabetic nephropathy compared to those without nephropathy, this similar to many studies. (20), (21), (22), (23). The mean difference (MD) in cystatin C levels between the DM with nephropathy group and the control group was 1.22 (95% CI: -2.22, -0.23), with a p-value of 0.02. According to the findings serum cystatin C can predict diabetic nephropathy with a pooled sensitivity 0.73 and pooled specificity.0.73 and (p-value = 0.03). The summary receiver operating characteristic curve (SROC) is considered as general assessment of value of the diagnostic procedure. the Area under the curve (AUC) was calculated to be 0.7498.

The pooled diagnostic odd ratio (DOR) of cystatin C was [69.9, 95% CI (4.68, 10.26)]. The pooled analysis was heterogeneous (I^2 = 52%, p-value = 0.03). The study explain serum Cystatin C may used as possible indicator for diabetic nephropathy among patients with type 2 diabetes mellitus and its level rise as the condition worsened and prolonged.

5. Conclusion

In conclusion, this meta-analysis study demonstrated that cystatin C is a potential early biomarker for predicting diabetic nephropathy. Further research is needed to validate these findings and establish the clinical utility of cystatin C as a prognostic or diagnostic tool in diabetic nephropathy.

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