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EARLY RISK ASSESSMENT OF RENAL IMPAIRMENT
USING THE BIOMARKER CYSTATIN C

RANDOX

Early Risk Assessment of Renal Impairment Using the Biomarker Cystatin C

1. BACKGROUND

Kidney disease is a huge global health crisis, increasing healthcare costs, mortality and morbidity rates. The global prevalence of CKD has continued to rise during a short lifespan. In 2016, 1 in 10, equivalent to 10% of the global population were identified with having chronic kidney disease (CKD) with the highest prevalence's reported in Europe, the Middle East, East Asia and Latin America, estimated at 12% and the lowest in South Asia, estimated at 7% (1).

The early risk assessment of renal function is vital. In 1990, CKD was ranked the 27th leading cause of death in the Global Burden of Disease study (2), rising to 18th (3) in 2010, 13th in 2013 (2) and 12th by 2015. From 2005-2015, the overall CKD mortality rate has risen by 31.7%, accounting for 1.1 million deaths globally in 2015 (4).

CKD years lost of life (YLL) has significantly increased between 2005 and 2015 in comparison to cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD). Within this timeframe, CKD YLL rose by 18.4%, whereas CVD and COPD fell by 10.2% and 3%, respectively (4).

The CKD burden can be attributed to obesity and diabetes. Globally, the prevalence of diabetic kidney disease rose by 39.5% between 2005 and 2015, coinciding with the increased CKD prevalence (4).

The prevalence, mortality and morbidity rates of CKD can be prohibited and progression halted or slowed with early diagnosis and treatment (3).

2. CKD CLASSIFICATION

The modern classification of kidney function is based on estimated GFR (eGFR), which classifies CKD into five stages (5).

In 2004, the National Institute for Health and Care Excellence (NICE) updated the classification of CKD to include the albumin:creatinine ratio (ACR) which indicates the level of proteinuria, aiding in the risk stratification of patients as testing based on eGFR alone can produce falsely low eGFR results in patients with near-normal function (6).

eGFR is classified as G1-G5 depending on the level of kidney function remaining and ACR is classified as A1-A3 depending on the level of proteinuria present (see figure 1) (5).

Figure 1: Classification of chronic kidney disease using GFR and ACR categories (5)

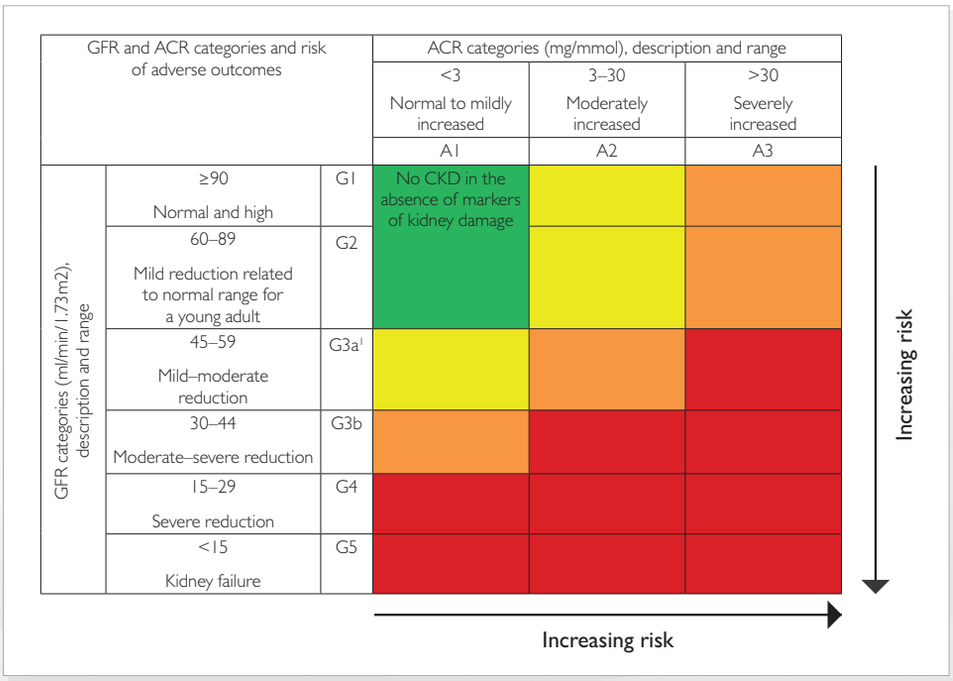

Figure 1 left indicates that the most severe stage of CKD is based on low levels of kidney function remaining (higher GFR category) combined with greater amounts of protein present in urine (higher ACR category). For example, a patient with an eGFR of 14 ml/min/1.73 m² and an ACR of 35 ml/mmol has CKD G5A3, meaning the stage of CKD is kidney failure and the level of proteinuria is severely increased (5) (6).

[1]Consider using eGFR Cystatin C for people with CKD G3aA1

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

3. INADEQUACIES OF TRADITIONAL CKD BIOMARKERS

The most commonly used screening test for renal impairment is Creatinine. When testing for CKD using Creatinine, certain factors must be taken into consideration, including: age, gender, ethnicity, and muscle mass. As such, black men and women will present with higher Creatinine levels compared to white men and women respectively (7).

Serum Creatinine is not an adequate screening test for renal impairment in the elderly (65 years of age and over) due to their decreased muscle mass. As such, patients are misdiagnosed, thus, patients with severe renal failure are receiving suboptimal care (8).

A review of CKD biomarkers (2011) found that proteinuria is the most sensitive marker of CKD progression, especially when used with eGFR, however an earlier and more sensitive biomarker is required (9).

The main disadvantage of using Creatinine to screen for renal impairment is that up to 50% of renal function can be lost before significant Creatinine levels become detectable as Creatinine is insensitive to small changes in GFR. Consequently, treatment is not provided at the appropriate time which can be fatal, thus, an earlier and more sensitive biomarker for renal function is vital (10)

4. CYSTATIN C AND ITS APPLICATION TO CKD

A. CLINICAL SIGNIFICANCE

Cystatin C is a small (13 kDa) cysteine proteinase inhibitor, produced by all nucleated cells at a constant rate. Cystatin C travels through the bloodstream to the kidneys where it is freely filtered by the glomerular membrane, resorbed and fully catabolised by the proximal renal tubes. Consequently, Cystatin C is the ideal biomarker of GFR function (11).

B. APPLICATION TO CKD

1. Clinical evaluation of serum Cystatin C and Creatinine in patients with chronic kidney disease: a meta-analysis (2013) (12)

   The meta-analysis study searched numerous sites, including, China National Knowledge Infrastructure databases, PubMed®, Google Scholar, and Cochrane Library to identify randomised controlled trials that determines the diagnostic value of Cystatin C and Creatinine, for estimating GFR in patients with chronic kidney disease. Seventeen studies met this inclusion criteria totalling 2521 patients with CKD. The meta-analysis study found that Cystatin C was more specific than Creatinine in estimating GFR.

2. Serum Cystatin C as a marker of renal function in detection of early acute kidney injury (2013) (13)

   This study assessed 200 healthy subjects and 130 subjects with acute kidney injury (AKI). The study examined serum Creatinine and serum Cystatin C levels in the AKI subjects to establish the relevance of both Creatinine and Cystatin C in the early stages of AKI. The study found that 56.2% of the AKI subjects have normal Creatinine levels, however, Cystatin C levels were elevated, which is referred to as the 'Creatinine blind range'. Therefore, Cystatin C levels are elevated long before Creatinine levels begin to rise. As such, Cystatin C is a more sensitive marker for AKI compared to Creatinine and Cystatin C does not have a blind area.

3. Chronic kidney disease in adults: assessment and management (2015) (14)

   NICE have updated their chronic kidney disease in adults: assessment and management guidelines, recommending Cystatin C testing due to its higher specificity for significant disease outcomes than those based on creatinine. As such, eGFR Cystatin C measurements will also significantly reduce the number of patients being misdiagnosed as having renal disease, thus reducing the overall CKD burden. NICE also recommend using eGFR Cystatin C when a patient has an eGFR Creatinine of 45 - 53 ml/min/1.73 m2, sustained for a minimum of 90 days and no proteinuria or other marker of kidney disease is present.

4. Cystatin C is Indispensable for Evaluation of Kidney Disease (2017) (15)

   A systematic literature search found 3,500 investigations into Cystatin C as a marker of GFR. These investigations concluded that Cystatin C should be an integral part of the analysis spectrum for the optimal evaluation of CKD as Cystatin C is not dependent on body composition, unlike Creatinine where muscle mass is a strong influencer. The studies concluded that eGFR Cystatin C was significantly more superior than eGFR Creatinine, however, using both improves GFR estimations.

C. IMPLEMENTATION CHALLENGES

It is likely that primary care teams are unsure of when to request the Cystatin C test as Cystatin C testing is a new recommendation. As such, the Cystatin C test may not be available within all territories. The financial impact has also caused concern for using Cystatin C as an additional test as some laboratories may need to invest in training (14). However, the clinical implications of Cystatin C becoming widely available can be extremely valuable for clinicians as:

- Cystatin C testing is generally only required once per person which is not impacted by race, sex, age or muscle mass (15).
- Unlike Creatinine, Cystatin C does not have a 'blind area', allowing for earlier diagnosis of CKD (13).
- Cystatin C is a more superior test than Creatinine as acute changes in kidney function are not immediately apparent when testing with Creatinine (16).
- In kidney transplant patients, it was reported that Cystatin C is more sensitive for detecting reductions in GFR and delayed graft function compared to Creatinine, enabling the opportunity for timely interventions (16).
- Some patient groups will greatly benefit from the early detection of renal function including patients with mild to modern renal disease, liver cirrhosis, kidney transplants, spinal injuries, diabetes, and the elderly (17)

When the risk of renal disease has been identified using Cystatin C measurements, lifestyle modifications are recommended as the first line of response to prevent the further decline of renal function (18).

5. METHODS USED TO MEASURE CYSTATIN C

Previously, the only method available to measure Cystatin C levels was the ELISA assay technique. Today, automated methods are available, offering numerous benefits for the laboratory.

EFFICIENCIES

In a laboratory, using the ELISA method for clinical testing is notably time and personnel consuming, with heavy resources used on manual interaction. Moving from this method to an automated method is considerably more time efficient. The significance of ensuring quality in testing practices and confidence in patient results, is a key consideration for running automated biochemistry tests over manual ELISA techniques. The risk of errors and contamination on samples, thereby compromising patient results is greatly reduced using automated methods as opposed to manual methods.

EXPANSION

Automated biochemistry methods enable laboratories to expand their test menu with ease, allowing the inclusion of Cystatin C into routine testing panels due to reduced manual work. Automated biochemistry assays increase testing ranges, allowing for detailed patient testing profiles, without the manual restrictions placed by running ELISA techniques.

Randox is currently one of the only diagnostic manufacturers who offer an automated biochemistry test for Cystatin C measurement, worldwide.

6. RANDOX AUTOMATED CYSTATIN C ASSAY

Randox Cystatin C is a Latex Enhanced Immunoturbidimetric Assay offering numerous key features:

- A niche product from Randox meaning that we are one of the only manufacturers to provide the Cystatin C test in an automated biochemistry format
- Automated assay which removes the inconvenience and time consumption associated with traditional ELISA testing
- Applications are available for a wide range of automated biochemistry analysers ensuring ease of programming and confidence in results
- Liquid ready-to-use reagents for convenience and ease-of-use
- Latex Enhanced Immunoturbidimetric method delivering high performance
- Extensive measuring range for measurement of clinically important results
- Complementary controls and calibrators available offering a complete testing package
- Limited interference from Bilirubin, Haemoglobin, Intralipid® and Triglycerides
- Cystatin C does not suffer from a 'blind area' like Creatinine due to Cystatin C's sensitivity to small changes in GFR enabling the early detection of renal impairment
- A correlation coefficient of r=1.00 when compared against standard methods

The Randox automated Latex Enhanced Immunoturbidimetric Cystatin C test offers an improved method for assessing renal function combined with a convenient format for routine clinical use, enabling physicians to accurately evaluate at-risk patients.

7. CONCLUSIONS

Chronic kidney disease has become a global health burden. In middle-income countries, the CKD burden is creating a huge financial burden. In 112 countries, there has been over 1 million deaths annually as these individuals could not afford to pay for treatment (3).

The early risk assessment of CKD is vital, not only because of the health implications associated with CKD, but also due to the financial burden of treatment to patients with CKD, their families, and to healthcare systems and national economies due to the direct medical costs and loss of work and wages (3).

Given the limitations of the traditional CKD risk assessment, it is evident that an improved method for assessing this risk, combined with a convenient format for routine clinical use, will enable physicians to accurately assess and evaluate more patients.

Cystatin C testing is not yet a routinely run test in most laboratories worldwide, and so it is not available for many clinicians to request. Although, the clinical implications of this test becoming widely available could be extremely beneficial, enabling the early detection of renal impairment.

The Randox automated Latex Enhanced Immunoturbidimetric Cystatin C tests offers an improved method for assessing CKD risk, combined with a convenient format for routine clinical use, for the early assessment of at risk patients. Randox is currently one of the only diagnostic manufacturers who offer an automated biochemistry test for Cystatin C measurement, worldwide.

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