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Review

Utility of cystatin C-based equations in patients undergoing dialysis

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ABSTRACT

Serum cystatin C (CysC) measurement is regarded as a simple and practical alternative to measure residual renal function for dialysis patients. Recent studies have shown that CysC has better diagnostic accuracy or at least equivalence to creatinine in predicting the early stages of renal damage, and is closely related to clinical outcomes of dialysis patients. Thus, the applicability of CysC-derived equations in patients undergoing dialysis should be paid attention. Here, we review the role of CysC in diagnosis, renal function evaluation, and prognosis outcomes for dialysis patients, so as to provide them with useful suggestions on evaluating renal function and predicting adverse outcomes in clinical practice.

1. Introduction

In the past 10 years, chronic kidney disease (CKD) has received increased attention as a leading public health problem [1,2]. With the rapid rise in the incidence and prevalence of end-stage renal disease (ESRD) worldwide, the number of patients undergoing renal replacement therapy (RRT) continues to increase [3]. RRT is a lifesaving treatment including dialysis and renal transplantation for people with ESRD [4]. Hemodialysis (HD), the major RRT in China, accounts for 80%–85% of patients [5], with a prevalence increasing from 49 per million population in 2006 to 83 per million population in 2008 [6]. What's more, the cost of dialysis treatment alone for one patient would be about $14,300 per year in China [6], posing a substantial burden on patients. Therefore, it is of great importance to assess renal function for dialysis patients.

Residual renal function (RRF) contributes significantly to the overall health and well-being of chronic dialysis patients [7]. The mechanism of the association between RRF and the survival in dialysis patients is that RRF not only provides small solute clearance, but also has other important metabolic effects that may not be simply replaced by increasing the peritoneal small solute clearance [8], first reported in the mid 1990s [9]. In addition, preserving RRF has always been the primary clinical goal for every nephrologist managing patients with CKD. Indeed, there is now clear evidence that preserving RRF remains important after the commencement of dialysis. In clinical practice, RRF is usually determined as the arithmetic mean of creatinine and urine clearance requiring accurate 24-h urine collection and a blood draw. However, this process is cumbersome, timeconsuming, and difficult to monitor, therefore subjected to measurement error. Thus, a single surrogate marker able to reliably estimate glomerular filtration rate (GFR) values and could replace RRF measurement in clinical practice is desirable. Cystatin C (CysC) has been proposed in this regard. But there lacks specific benchmark so far to guide the dialysis patients to properly use the eGFR equations to assess their RRF.

In this article, we will focus on three areas: (i) the diagnostic performance of CysC against other renal markers; (ii) the published CysC-based estimated GFR (eGFR) equations especially developed in dialysis patients to evaluate RRF; and (iii) the relationship between CysC and prognosis outcomes in patients on dialysis.

2. Characteristics of CysC

CysC is a low molecular weight protein (13.2 kDa) that was first described in cerebrospinal fluid and in urine from patients with tubular disease [10]. CysC belongs to the family of cysteine proteinase inhibitors [11], is encoded by a “housekeeping” gene expressed in all nucleated cells and is produced at a constant rate [8]. Due to the small size and basic pI (~9.0), CysC is freely filtered by the glomerulus. CysC is not secreted, but reabsorbed by tubular epithelial cells and subsequently catabolized, thus, it does not return to the blood flow [8]. In

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addition, CysC is readily measured from a single blood sample by using reliable and reproducible assays [12]. These unique characteristics make CysC potentially an ideal endogenous marker for assessment of renal function.

Factors influencing CysC levels include renal function, thyroid disorders [13], tobacco consumption [14,15], viral load in Human Immunodeficiency Virus [16], obesity [17], high doses of steroid therapy [18], and inflammation [14,19]. When compared with serum creatinine (Scr), the most important feature of CysC is the constant production, independent of muscle mass, age, or sex, and lacking renal secretion or resorption back into the bloodstream [8]. Since the volume of distribution of Scr is about three times greater than that for CysC, the half-life of Scr will be approximately three times longer. Thus, the time for CysC to attain a new steady state will be about a third of that for Scr and changes in GFR detected earlier [20]. Owing to the unique properties of CysC, it serves as a marker of mild renal damage in most studies.

3. CysC as a renal marker

Currently, multiple studies suggest that the CysC improved utility or at least equivalence to Scr in settings prone to acute kidney injury (AKI), CKD, renal damage including renal transplant and tubular impairment, dialysis [21], and so on.

3.1. Patients with early stages of AKI

CysC could predict the early stages of AKI sensitively. A study enrolling 85 patients at high risk to develop AKI revealed that a 50% increase in CysC predicted AKI 1–2 days before the Scr rising, with an area under the curve (AUC) of 0.97 and 0.82, respectively [22]. Villa et al. [23] analyzed 50 critically ill patients without CKD but were at risk for developing renal dysfunction, confirming that CysC was more accurate to evaluate subtle changes in GFR than Scr. Another research [24] including 350 consecutive patients undergoing peripheral arterial angiography noticed that a CysC increase $\geq 5\%$ at 24 h was associated with higher probability of major adverse events, whereas a Scr increase $\geq 25\%$ was not. This demonstrated that CysC had better predictive power than Scr and could act as a convenient diagnostic tool in the evaluation of contrast-induced acute kidney injury (CI-AKI).

3.2. Patients with CKD

CysC is also a crucial indicator to evaluate kidney damage in CKD. A meta-analysis [25] including 54 datasets reported that the receiver operating characteristic (ROC)-plot AUC values for 1/CysC had greater identity with the reference test for GFR (mean ROC-plot AUC for CysC, 0.926; 95% confidence interval [CI] 0.892–0.960) than ROC-plot AUC values for 1/Scr (mean ROC-plot AUC for Scr, 0.837; 95% CI 0.796–0.878; $p < 0.001$), showing CysC was clearly superior to Scr as a marker to reflect kidney damage by correlation or diagnostic accuracy. Hojs et al. [26] studied 252 patients with CKD and GFR < 90 mL/min/1.73 m^2, and found a statistically significant correlation between ^{51}Cr-EDTA clearance with Scr ($r = -0.880$; $p < 0.0001$), CysC ($r = -0.896$; $p < 0.0001$), 1/Scr ($r = 0.855$; $p < 0.0001$), 1/CysC ($r = 0.898$; $p < 0.0001$), and also with calculated creatinine clearance by Cockcroft-Gault (C-G) ($r = 0.811$; $p < 0.0001$), indicating that CysC was a more reliable marker of GFR than Scr in CKD population. A research [27] evaluating 123 patients with type 1 or 2 diabetes found that CysC correlated significantly stronger than Scr with measured GFR (0.817 vs. 0.678), revealing that CysC had better diagnostic accuracy to detect mild nephropathy as compared to Scr.

3.3. Kidney transplantation patients

For kidney transplantation patients, CysC plays a key role in the early detection of renal damage, leading to more effective intervention to reduce the risk of acute transplanted kidney damage from rejection or drug toxicity. A research [28] including 42 renal transplant patients found that the CysC increased significantly when GFR dropped to 88 mL/min/1.73 m^2, whereas Scr began to rise until GFR dropped to 75 mL/min/1.73 m^2. Xu et al. [29] recruited 39 renal transplant patients for determination of CysC and Scr before operation, at 7 and 28 days after operation, showing that CysC was significant correlated with Scr and creatinine clearance rate (Ccr). At the Ccr level of 50–80 mL/min/1.73 m^2, the correlation between CysC and Ccr was significantly better than that between Scr and Ccr (0.778 vs. 0.553). This indicated that CysC could detect early and moderate deterioration of GFR in adult renal transplant recipients more sensitively than Scr, although the concentration was slightly influenced by medications.

3.4. Patients with tubular impairment

In addition, an increase in urinary CysC is seen in patients with functional and structural tubular impairment with high stability and independence. Herget-Rosenthal et al. [30] observed 73 consecutive patients with initially nonoliguric acute tubular necrosis (ATN), finding that urinary excretion of CysC had the highest diagnostic accuracy in identifying patients requiring RRF as indicated by the largest areas under the ROC curves of 0.92.

3.5. Patients on dialysis

Dialysis is based on the principle of diffusion, separating small molecules and biological macromolecules, then excreting components (solute or moisture) in body fluids through the semipermeable membrane [8]. HD and peritoneal dialysis (PD) are two commonly used dialysis methods [3] with a similar principle [31]. As a low molecular weight protein, CysC could be easily dialyzable with the high flux polysulphone membrane used by the HD patients and the natural peritoneum in the PD population. A cross-sectional study [12] including 119 PD patients showed that serum CysC concentrations reflected predominantly renal clearance instead of peritoneal clearance. Another study [7] including 322 HD and 143 chronic ambulatory PD (CAPD) patients also indicated that serum CysC could give a good estimate of GFR in dialysis patients. Recently, Balik et al. [32] reported a research of 33 mechanically ventilated patients suffering from renal failure investigating CysC as a marker of RRF during continuous haemodiafiltration. Thus, serum CysC measurement has been regarded as a simple and practical alternative to measure RRF for patients undergoing HD and PD in clinical practice.

However, the disadvantages of CysC include the higher cost of the immunoassay compared with that for Scr and the intraindividual variability which is suggested to be too high to support early detection of renal damage [20,31,33]. These issues need to be addressed clearly by future studies. And the observations that CysC may underestimate clearance in transplant patients and that CysC may be increased in cancer patients require additional studies to determine the effect of increased cell turnover/death on values of this protein that is present in each nucleated cell. Hence, whether CysC could become more routinely used will ultimately depend on the results of outcome-based studies and consideration of some of the possible disadvantages of CysC mentioned above [21].

4. CysC-derived equations

Using CysC to estimate GFR is based on the same logic as the use of Scr and blood urea nitrogen, but because it does not return to the bloodstream and is not secreted by renal tubules, it has been considered to be closer to the ideal endogenous marker [21].