Biomarkers, 2012; 17(5): 477–481

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.3109/1354750X.2012.685953

informa
healthcare

TECHNICAL BRIEF

Decisional procalcitonin thresholds are not adapted to elderly patients admitted to the emergency room

Camille Chenevier-Gobeaux[1], Eloise Trabattoni[2,3], Yaelle Elfassy[1], Camille Picard[1], Sylvie Guérin[1], Didier Borderie[1,4], and Yann-Erick Claessens[2,3,5]

[1]Groupe hospitalier Cochin-Broca-Hôtel Dieu, APHP, Department of Biochemistry, Paris, France, [2]Groupe Hospitalier Cochin-Broca-Hôtel Dieu, APHP, Department of Emergency Medicine, Paris, France, [3]Université Paris Descartes, Faculté de Médecine, Paris, France, [4]EA4466, Université Paris Descartes, Sorbonne Paris Cité, Faculté de Pharmacie, Paris, France, and [5]Centre Hospitalier Princesse Grace, Department of Emergency Medicine, Monaco, France

Abstract

Context: Diagnosis of sepsis in elderly is challenging.

Objectives: We investigated whether procalcitonin concentrations in elderly differed from values for the general population.

Methods: Procalcitonin measurement was assessed prospectively in 307 apyretic patients ≥75 years visiting the emergency department.

Results: Median age was 86 years [IQR81–90] and 222 (72%) were female. Procalcitonin concentration was 0.057 µg/L [0.040–0.092]; 99th percentile was 0.661 µg/L. Patients with procalcitonin concentrations above decisional thresholds had lower glomerular filtration rate and higher C-reactive protein concentrations. *Conclusions:* Baseline procalcitonin levels are increased in elderly. Elevated values are common and associated to low-grade inflammation and lower eGFR.

Keywords: Procalcitonin, reference values, infection, elderly, immune senescence, emergency medicine

Introduction

Making a diagnosis of infection in the emergency department (ED) is a challenge in elderly since these patients often present with atypical and incomplete signs or symptoms (Htwe et al., 2007). Moreover, time to diagnosis is deleterious as it delays adequate treatment (Claessens, 2007). Common inflammatory biomarkers such as C-reactive protein (CRP) and IL-6 might be of impaired usefulness because of the low-grade elevation observed in elderly, in relation to a number of chronic conditions of aging (Singh & Newman, 2011). Therefore developing tools that help physician improving assessment of diagnosis and triage at bedside is mandatory in this context.

The clinical use of procalcitonin has been developed to improve diagnosis of bacterial infection in various patients' groups, including patients with suspected low tract respiratory infection. In adults, high quality studies have suggested that procalcitonin could relieve uncertainty in suspected bacterial infection (Boussekey et al., 2005) and help physicians in decision to start and stop antimicrobial therapy (Christ-Crain et al., 2004). If reference values of procalcitonin have been derived from assessment in neonates and healthy young volunteers (Morgenthaler et al., 2002), the currently accepted clinical thresholds are derived from observational studies in lower respiratory tract infections (Christ-Crain et al., 2004; Schuetz et al., 2009). As ageing is associated to changes in several biochemical parameters including inflammation proteins (Cohen et al., 2003; Singh, 2011), we aimed to investigate whether procalcitonin

Address for Correspondence: Camille Chenevier-Gobeaux, Groupe hospitalier Cochin-Broca-Hôtel Dieu, APHP, Department of Biochemistry, 27 rue du faubourg Saint-Jacques 75014 Paris, France. Tel: +33 1 58 41 15 91. Fax: +33 1 58 41 15 85.
E-mail: camille.gobeaux@cch.aphp.fr

(Received 27 February 2012; revised 10 April 2012; accepted 13 April 2012)

concentrations in elderly patients differed from values commonly accepted for the general population, and to evaluate the impact of such possible difference on thresholds. For this purpose, considering that strategies based upon the use of biomarkers require determination of baseline concentrations in target populations, we measured procalcitonin concentrations in patients ≥75 years visiting the ED for non-infectious disorder/acute illness.

Methods

We conducted a monocentric, prospective, observational study in the ED of a tertiary teaching hospital. Study protocol and procedures complied with the principles of the declaration of Helsinki. The institutional review board for the protection of human subjects of our institution approved the study protocol and patient information procedures.

From June to December 2011, we enrolled all consecutive consenting patients ≥75 years that required blood sampling for non-infectious disorder/acute illness such as extrinsic falls with minor trauma and fracture, progression of dementia and chronic neurodegenerative disorders, malaise and fatigue without evidence for organic origin, and social or organizational considerations. Exclusion criteria included the presence of acute infection or any acute or unstable disorder, hyperthermia, previously recognized end-stage kidney failure, and patients with post-trauma intracranial haemorrhage. Baseline data consisted in demographics, coexisting illnesses, results of white blood cell count (WBC) and values of ultra-sensitive CRP, when available.

Blood samples were collected in sodium heparin-treated tubes, centrifuged, and stored at –40°C until completion of the study. Procalcitonin concentrations were analyzed using an electrochemiluminescent immunoassay (ELECSYS BRAHMS procalcitonin, Hennigsdorf, Germany), performed on a cobas e601 analyzer (Roche Diagnostics, Meylan, France). The limit of detection of the method is 0.020 μg/L; values below this limit were considered as 0.020 μg/L. The functional sensitivity (20% CV) is 0.060 μg/L. In our laboratory, coefficients of variation for procalcitonin were <4% at two concentrations during the study period. The upper reference limit (URL) announced by the manufacturer was 0.046 μg/L (Morgenthaler et al., 2002). WBC were counted on a LH750 analyzer (Beckman Coulter, Villepinte, France). CRP concentrations were measured using the Tina-quant CRP-Gen3 immunoturbidimetric assay (limit of detection: 0.1 mg/L), and creatinine concentrations using the standardized rate-blanked Jaffe method; both parameters were analyzed on a Modular PP analyzer (Roche Diagnostics Meylan, France). Estimated glomerular filtration rates (eGFR, in ml/min/1.73 m^2) were calculated using the revised Modification of Diet in Renal Disease (Levey et al., 2007).

Results were expressed as medians [interquartile range, IQR] for continuous variables, and numbers (percentage) for discrete variables. Data were compared using the Kruskal–Wallis test for continuous variables, and the χ^2 for differences in frequencies. Percentiles were calculated following the NCCLS procedure using a non-parametric percentile method. Procalcitonin correlation with other variables was assessed using Pearson's coefficient. The results were analyzed using Med Calc 3.4.2.0 for Windows (MedCalc Software, Mariakerke, Belgium). p values were two-tailed. A p value <0.05 was considered to be statistically significant.

Results

Baseline characteristics of patients

Among 408 patients ≥75 years visiting the ED, 326 corresponded to entry criteria and 19 were not included because clinical or biological data were lacking. Finally, 307 patients were enrolled in the study. Median age was 86 years [IQR 81–90], 222 (72%) were female (Table 1). No patient had temperature above 37.7°C, arterial blood pressure and pulse oxymetry were normal. Main complaint for ED visit were fall of extrinsic cause in 206 (67%) including 143 fractures (47%). Neurodegenerative disorder was the main underlying disorder (n = 80, 26%). Active cancer represented 20 (7%). Of note, none of the patients had medullary thyroid tumor nor lung small cell carcinoma.

Baseline concentrations of procalcitonin

Procalcitonin concentrations ranged from 0.02 to 1.02 μg/L, and median value was 0.057 μg/L [0.040–0.092]. Procalcitonin values were similar in men and women (0.059 [0.040–0.090] versus 0.056 μg/L [0.040–0.094], p = 0.545). Median procalcitonin concentrations did not differ from patients who fell (n = 206) versus others (0.059 [0.040–0.099] vs. 0.053 μg/L [0.040–0.075], p = 0.080). In patients who fell, PCT did not differ between patients with fracture (n = 143) versus patients without fracture (0.054 [0.038–0.092] versus 0.069 μg/L [0.048–0.139], p = 0.854). In addition, procalcitonin values were not influenced by any of the co-morbidities listed in Table 1.

The 95th, 97.5th and 99th percentiles of procalcitonin were: 0.354 μg/L[0.249-0.485], 0.488 μg/L [0.400–0.668] and 0.661 μg/L [0.581–1.020], respectively.

Procalcitonin concentrations weakly correlated to WBC (r^2 = 0.014, p = 0.043), and inversely correlated to eGFR (r^2 = 0.017, p = 0.023) (Figure 1). In patients with CRP measurement (n = 89, 29%), PCT was significantly correlated to CRP (r^2 = 0.213; p < 0.0001).

Characteristics of patients according to procalcitonin values

A procalcitonin value ≥0.046 μg/L (manufacturer's URL) was registered in 197 (64%) participants.

Moreover, a procalcitonin value above the clinical thresholds (≥0.100 μg/L and ≥0.250 μg/L) was observed in 73 (24%) and 25 (8%) participants, respectively (see Table 1 for baseline characteristics). These patients were comparable to those with lower procalcitonin, except for CRP and renal status: they presented lower

Table 1. Baseline characteristics of the studied population.

Parameters	All patients	Patients with PCT values <0.100 µg/L	Patients with elevated PCT ≥0.100 µg/L	Patients with elevated PCT ≥0.250 µg/L
n	307	234	73	25
Women, *n* (%)	222 (72)	168 (72)	54 (74)	19 (76)
Men, *n* (%)	85 (28)	66 (28)	19 (26)	6 (24)
Age, years	86 [81–90]	86 [81–90]	86 [80–89]	88 [83–90]
Heart rate, bpm	78 [70–93]	77 [68–90]	83 [75–96]	83 [74–97]
Systolic arterial BP, mm Hg	145 [127–159]	147 [130–144]	132 [117–146] £	136 [127–149]
Diastolic arterial BP, mm Hg	77 [69–85]	78 [70–86]	76 [64–84]	76 [68–83]
Pulse oxymetry, %	97 [95–98]	97 [95–98]	96 [94–98]	96 [94–97] £
Temperature, °C	36.8 [36.4–37.1]	36.8 [36.4–37.0]	37.0 [36.5–37.4]	37.0 [36.4–37.4]
White blood cells, per $mm^3 \times 10^3$	9.7 [7.4–12.1]	9.2 [7.3–11.8]	10.5 [7.9–13.0]	10.7 [8.6–12.1]
CRP**, mg/L	7.4 [1.8–21]	4.8 [1.3–12.5]	34 [11–75] £	62 [46–89] £
eGFR, mL/min/1.73m^2	67 [50–83]	71 [55–86]	50 [41–69] £	48 [37–66] £
Main complaint for ED visit, *n* (%)				
Fall of extrinsic cause	206 (67)	151 (65)	55 (75)	19 (76)
including fractures	143 (47)	111 (47)	32 (44)	11 (44)
Progression of NDD*	32 (10)	27 (12)	5 (7)	3 (12)
Fatigue with no organic origin	25 (8)	18 (8)	7 (10)	2 (8)
Malaise with no organic origin	11 (4)	9 (4)	2 (3)	0 (0)
Urine retention	8 (3)	8 (3)	0 (0)	0 (0)
Social/organizational purpose	6 (2)	6 (2)	0 (0)	0 (0)
Miscellaneous	19 (6)	17 (7)	2 (3)	1 (4)
Co-morbidities, *n* (%)				
Neurodegenerative disorder	80 (26)	59 (25)	21 (29)	6 (24)
Neurovascular disorder	29 (9)	21 (9)	8 (11)	3 (12)
Diabetes	27 (9)	18 (8)	9 (12)	2 (8)
Active cancer (<6 months)***	20 (7)	14 (6)	6 (8)	3 (12)
Previous CHF	20 (7)	17 (7)	3 (4)	1 (4)
Chronic respiratory disease	19 (6)	17 (7)	2 (3)	1 (4)
Arthritis	12 (4)	8 (3)	4 (5)	1 (4)
Hospital admission, *n* (%)	190 (62)	139 (59)	51 (70)	18 (72)

Results are expressed in numbers (percentage) or in median [IQR].
BP, blood pressure; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; PCT, procalcitonin.
*Neurodegenerative disorder. **measured in *n* = 89 (29%), including 24 patients with procalcitonin value ≥0.100 µg/L and 9 patients with procalcitonin value ≥0.250 µg/L. ***, including: breast cancer (*n* = 6), prostatic cancer (*n* = 5), colonic cancer (*n* = 2), sarcomas (*n* = 2), bronchopulmonary cancer (*n* = 2), lymphoproliferative cancer(*n* = 2), myeloproliferative cancer (*n* = 1).
£, $p < 0.001$ vs patients below the threshold.

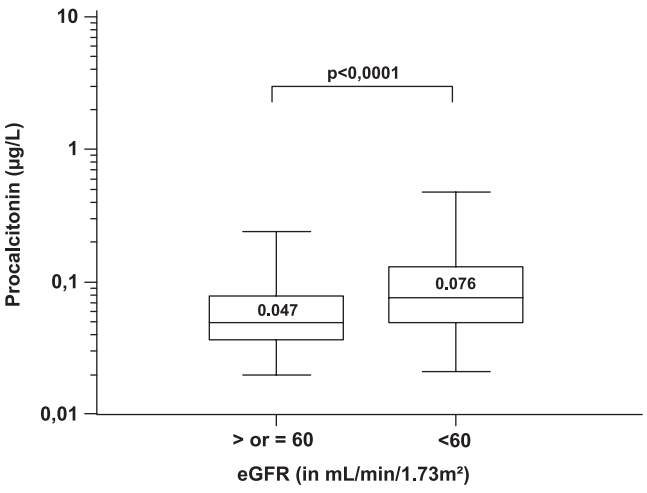

Figure 1. Box-plot for procalcitonin concentrations according to eGFR categories. Patients with eGFR<60 ml/min/1.73 m^2: *n* = 115 (37%); patients with eGFR ≥60 ml/min/1.73 m^2: *n* = 192 (63%). Values in the box-plot indicate the median value. eGFR, estimated glomerular filtration rate.

systolic blood pressure, higher CRP concentrations and lower eGFR (Table 1).

Discussion

We report here that baseline levels of procalcitonin are increased in ≥75 years patients visiting the ED. Values above the usual thresholds are common in elderly, and associated to low-grade elderly inflammation and low eGFR.

Reference values have been proposed for procalcitonin may present some limits in terms of age range. In 410 healthy adults (range 18–62 years), 97.5th percentile was determined at 0.047 µg/L (Morgenthaler et al., 2002). In 12,485 newborns, median procalcitonin measurement was 0.160 µg/L in healthy participants, and threshold to predict infection was 0.600 µg/L (Joram et al., 2006).

It is not easy to define a control group of non-infected individuals to assess a procalcitonin threshold. On one hand, recurrent data indicate that patients with documented infection may have no elevation of procalcitonin

concentrations (Schuetz et al., 2011). On the other hand, several non-infection clinical situations have shown to increase procalcitonin concentration, such as trauma. However, our results indicated that procalcitonin values were similar in patients who fell versus those who did not, and in patients with fracture versus patients without fracture. Furthermore, none of the co-morbidities observed in our population influenced procalcitonin values.

Inflammation is tightly amplified and regulated to generate an intricately related network that participates to the adequate response against primary insult (Opal & Esmon, 2003). During ageing, these mechanisms can be deregulated. This results in increased baseline levels of pro-inflammatory factors (Singh, 2011). An association also exists between inflammatory markers and frailty in elderly, even in the absence of obvious comorbidity (Cohen, 2003). Our results are in accordance with the literature (Cohen, 2003; Singh, 2011), as we found moderate elevations of CRP.

Procalcitonin has good specificity for bacterial systemic invasion (Guinard-Barbier et al., 2011). However, thresholds have been determined from interventional studies in lower respiratory tract infections, in patients aged from 62.8 to 73 years (Christ-Crain et al., 2004; Schuetz et al., 2009). Antimicrobial therapy was (strongly) discouraged if procalcitonin levels were below (0.100) 0.250 μg/L, and encouraged if levels were ≥0.250 μg/L. These trials selected high probability community-acquired pneumonia patients. In this circumstance of high level of certainty for bacterial infection, procalcitonin had little use. To note, likelihood ratios for procalcitonin were inconsistent with clinical assessment in a study comparing 30 controls to 14 bacteraemic elderly patients (Caterino et al., 2004). Therefore, translating usual procalcitonin classes for diagnosis can be interrogated in ≥75 years patients, as baseline values may differ from usually admitted thresholds. In our study, 8% of our patients had procalcitonin concentrations ≥0.250 μg/L. Usual thresholds to "rule in" patients for antibiotics strategies in the emergency room might have been inappropriate for at least 8% of our population because of a clear overlap of baseline values with decisional thresholds, and unnecessary antimicrobial treatment might have been spared in elderly. Furthermore, during the follow-up of these non-infected patients receiving therapy, because of non-modification of values, antibiotics might be continued or changed, leading to an increased antibiotic exposition – and its consequences. We believe that this proportion is not negligible, and that currently decisional thresholds are not optimal in elderly patients. Procalcitonin changes are not strictly specific to bacterial invasion and may correspond to inflammation without infection. Levels were elevated in 32% to 59% patients after aseptic surgery (Müller et al., 2000), and non-infectious systemic inflammatory syndrome (SIRS) was associated to procalcitonin elevation (Morgenthaler et al., 2005). This suggested that non infectious insult may increase procalcitonin concentrations. Therefore, aspecific inflammation related to ageing may alter baseline levels of procalcitonin as well as CRP, as suggested by our results.

We further found that concentrations of procalcitonin weakly but significantly correlated to eGFR. Furthermore, eGFR values were significantly lower in participants that presented elevated procalcitonin concentrations. This observation was forecasted as one third procalcitonin is eliminated by kidney. Indeed, procalcitonin levels increased in non-septic uremic patients (Dahaba et al, 2003), and also with renal impairment in 280 patients with mean age below 60 years (Herget-Rosenthal et al., 2005). In addition, procalcitonin levels were higher in patients with impaired kidney function in both post-operative infected patients and controls, in the setting of vascular surgery (Amour et al., 2008). Prevalence of chronic kidney disease is increased in elderly (Stevens et al, 2010). Renal dysfunction associated to ageing is known to be associated to glomerulosclerosis, but it is also characterized by vascular dysautonomia, altered tubular handling of creatinine, reduction in sodium reabsorption and potassium secretion, and diminished renal reserve (Musso & Oreopoulos, 2011). Thus, the renal retention of procalcitonin (a 12.7 kDa protein) in elderly might be multifactorial.

We acknowledge that our study suffers from limitations of monocentric studies, regarding bias for patients' recruitment and external validity. Consequently it is disputable that our results can be translated in general elderly population. However, distribution of underlying disorders corresponds to usual findings in such population. We included elderly patients experiencing falls and requiring organizational assistance. As these are symptoms of frailty, it can be assumed that most patients enrolled in this study could have been considered as frail persons. Furthermore, our data are not sufficient to establish decisional thresholds. Further interventional studies including septic patients are needed to validate decisional thresholds in elderly. Finally, eGFR calculation using a single value of creatinine could not indicate if renal status was stable or not, in the setting of emergency.

Conclusions

Baseline levels of procalcitonin are increased in ≥75 years patients without active acute infectious disorder visiting the ED. Values above the decisional thresholds are common, and are associated to moderated elevations of CRP and low eGFR. Therefore interpretation of procalcitonin might be altered in elderly patients if decisional thresholds are employed. These findings highlight the need of improvement of antibiotic guidance on the basis of established higher thresholds for elderly patients.

Acknowledgments

We thank Thermo Fisher Scientific for supplying the reagents and kits for the procalcitonin assay, free of charge.

Declaration of interest

The authors report no declarations of interest.

References

Amour J, Birenbaum A, Langeron O, Le Manach Y, Bertrand M, Coriat P, Riou B, Bernard M, Hausfater P. (2008). Influence of renal dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after vascular surgery. *Crit Care Med* 36:1147–1154.

Boussekey N, Leroy O, Georges H, Devos P, d'Escrivan T, Guery B. (2005). Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. *Infection* 33:257–263.

Caterino JM, Scheatzle MD, Forbes ML, D'Antonio JA. (2004). Bacteremic elder emergency department patients: procalcitonin and white count. *Acad Emerg Med* 11:393–396.

Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Müller B. (2004). Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 363:600–607.

Claessens YE, Dhainaut JF. (2007). Diagnosis and treatment of severe sepsis. *Crit Care* 11 Suppl 5:S2.

Cohen HJ, Harris T, Pieper CF. (2003). Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *Am J Med* 114:180–187.

Dahaba AA, Rehak PH, List WF. (2003). Procalcitonin and C-reactive protein plasma concentrations in nonseptic uremic patients undergoing hemodialysis. *Intensive Care Med* 29:579–583.

Guinard-Barbier S, Grabar S, Chenevier-Gobeaux C, Quinquis L, Schmidt J, Kierzek G, Guérin S, Hausfater P, Bernot B, Brun P, Gayet A, Casalino E, Andreotti C, Renaud B, Claessens YE. (2011). Is mid-regional pro-atrial natriuretic peptide (MRproANP) an accurate marker of bacteremia in pyelonephritis? *Biomarkers* 16:355–363.

Herget-Rosenthal S, Klein T, Marggraf G, Hirsch T, Jakob HG, Philipp T, Kribben A. (2005). Modulation and source of procalcitonin in reduced renal function and renal replacement therapy. *Scand J Immunol* 61:180–186.

Htwe TH, Mushtaq A, Robinson SB, Rosher RB, Khardori N. (2007). Infection in the elderly. *Infect Dis Clin North Am* 21:711–43, ix.

Joram N, Boscher C, Denizot S, Loubersac V, Winer N, Roze JC, Gras-Le Guen C. (2006). Umbilical cord blood procalcitonin and C reactive protein concentrations as markers for early diagnosis of very early onset neonatal infection. *Arch Dis Child Fetal Neonatal Ed* 91:F65–F66.

Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. (2007). Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 53:766–772.

Morgenthaler NG, Struck J, Christ-Crain M, Bergmann A, Müller B. (2005). Pro-atrial natriuretic peptide is a prognostic marker in sepsis, similar to the APACHE II score: an observational study. *Crit Care* 9:R37–R45.

Morgenthaler NG, Struck J, Fischer-Schulz C, Seidel-Mueller E, Beier W, Bergmann A. (2002). Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. *Clin Lab* 48:263–270.

Müller B, Becker KL, Schächinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R. (2000). Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med* 28:977–983.

Musso CG, Oreopoulos DG. (2011). Aging and physiological changes of the kidneys including changes in glomerular filtration rate. *Nephron Physiol* 119 Suppl 1:p1–p5.

Opal SM, Esmon C. (2003). Functional relationships between coagulation and the innate immune response and their respective roles in the pathogenesis of sepsis. *Crit Care* 7:23–38.

Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C, Schild U, Regez K, Schoenenberger R, Henzen C, Bregenzer T, Hoess C, Krause M, Bucher HC, Zimmerli W, Mueller B; ProHOSP Study Group. (2009). Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 302:1059–1066.

Schuetz P, Albrich W, Mueller B. (2011). Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. *BMC Med* 9:107.

Singh T, Newman AB. (2011). Inflammatory markers in population studies of aging. *Ageing Res Rev* 10:319–329.

Stevens LA, Viswanathan G, Weiner DE. (2010). Chronic kidney disease and end-stage renal disease in the elderly population: current prevalence, future projections, and clinical significance. *Adv Chronic Kidney Dis* 17:293–301.