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A Paradigm to Discover Biomarkers Associated With Chronic Kidney Disease Progression

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ABSTRACT: Biomarker discovery in the field of risk prediction in chronic kidney disease (CKD) embraces the prospect of improving our ability to risk stratify future adverse outcomes and thereby guide patient care in a new era of personalised medicine. However, many studies that report biomarkers predictive of CKD progression share a key methodological limitation: failure to characterise patients' renal progression precisely. This weakens any observable association between a biomarker and an outcome poorly defined by a patient's change in renal function over time. In this commentary, we discuss the need for a better approach in this research arena and describe a compelling strategy that has the advantage of offering robust and meaningful biomarker exploration relevant to CKD progression.

KEYWORDS: Chronic kidney disease, biomarkers, progression, methodology

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Introduction

Chronic kidney disease (CKD) is a global health problem given that reduced glomerular filtration rate (eGFR) increases the risk of progressive renal decline, multi-organ complications, major cardiovascular events and all-cause mortality.[1]

Accurately predicting which patients will experience deteriorating renal function is an important tenet to CKD care. Being able to determine the likely future eGFR trajectory would help to instigate timely treatment, potentially reduce the burden of adverse outcomes and optimise provision and planning for renal replacement therapy in patients at high-risk of progression. To meet the clinical need of better risk prediction tools, there has been significant interest in discovering novel biomarkers that could aid risk stratification, as well as provide new insights into unravelling CKD pathophysiology.[2]

A plethora of studies have investigated a wide range of biomarkers, including those derived from proteomics,[3–5] metabolomics[6] and genomics[7] that may help identify patients at risk of CKD progression. These studies, however, are heterogeneous in their study population, follow-up time and their definition of progression. Some define progression based on clinical endpoints such as progression to end-stage renal disease, whilst others characterise patients based on an eGFR trajectory: either stable non-progressors or those with varying rates of progression determined by the change in eGFR over time. Different biomarkers have been shown to be associated with different endpoints[8] and so it is important to make this distinction clear.

In studies where CKD progression is defined by a change in eGFR over time, efforts to accurately define rates of progression face a number of challenges. For instance, changes in renal function may reflect episodes of acute kidney injury as opposed to true progression, and it is recognised that deterioration can be non-linear and episodic, with phases of stability interrupted by periods of eGFR decline. In addition, various interventions such as initiation or up-titration of prognostically beneficial reno-protective agents that block the renin-angiotensin system can cause the eGFR to reduce acutely but this may equate to slower renal decline in the long-term.

Recognising these limitations, guidelines from Kidney Disease Improving Global Outcomes (KDIGO) suggest 2 strategies to define a rate of CKD progression based on clinical utility.[9] The first is to assess the absolute change in renal function, requiring a change in GFR category with at least a 25% drop in eGFR from baseline. Alternative endpoints of doubling of creatinine or ⩾30% decline in eGFR have also been proposed.[10] The second approach is to calculate the rate of eGFR change per year with a slope analysis. Both these methods, however, are still beset by 2 limiting factors: the number of available eGFR readings and the duration of a patient's follow-up. Indeed, some biomarker studies are prone to significant limitation by defining CKD progression based on only 2 eGFR measurements – 1 at baseline and 1 at follow-up.[11,12] This approach is limited by the problem of regression to the mean and raises 2 additional concerns: one, it assumes linear

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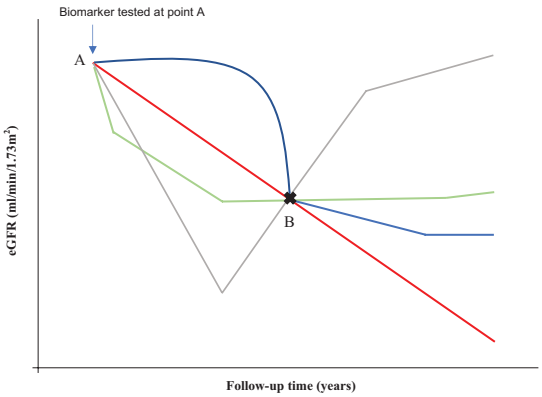

Figure 1. The limitation of biomarker testing to predict CKD progression using 2 eGFR samples (points A and B).

progression has occurred between 2 time points and, secondly, that if an acute change in eGFR has occurred, that it is non-reversible. It is conceivable that a biomarker discovered in this methodological construct may simply reflect an acute injury as opposed to being associated with genuine, long-term progressive decline (Figure 1).

Figure 1 illustrates 4 different patients' modes of progression from point A to point B and beyond. The red line is indicative of progressive linear decline. The blue line highlights that point B was reached following an acute decline and thereafter the renal trajectory is one of a slower rate of decline. The green line shows different rates of decline between points A and B, followed by a phase of stability. The grey line shows an initial acute decline but renal function is recovering when point B is reached and continues to do so beyond this point.

If a biomarker is tested at point A for all 4 patients and a repeat eGFR was performed at point B, the biomarker signal at point A may be perceived to be associated with true CKD progression. However, it cannot accurately characterise changes in renal trajectory between points A and B and equally fails to take account of future CKD progression, limiting its clinical utility.

It is therefore important that efforts invested in biomarker profiling are matched equally by a rigorous approach to determining patients' phenotypic pattern of progression beforehand. Herein, we propose a new paradigm that overcomes methodological limitations in biomarker studies concerned with CKD progression (Figure 2). This paradigm relies upon harnessing data from established CKD cohorts, which provide an invaluable resource to identify patients in whom the pattern and rate of CKD progression can be accurately characterised using validated techniques, and which provides the means to undertake biomarker analysis in bio-banked samples during the course of patients' CKD progression.

Towards a better paradigm

Rates and patterns of CKD progression

Large, prospective CKD cohorts around the world (such as the Salford Kidney Study,[13] the German CKD Study[14] or the Chronic Renal Insufficiency Cohort Study[15]) afford access to patients who have already undergone multiple eGFR measurements over many years of follow-up. This permits a retrospective assessment of detecting true CKD progression: the greater the number of measurements over a longer period of time, the greater the ability to define patients' eGFR trajectories. Although current recommendations suggest acquiring 4 eGFR measurements over 2 years,[10] our own experience would advocate for a greater number of measurements over a longer period of time. Quantifying the rate of progression accurately is then achieved by applying validated analytic methods to define the rate of eGFR change over time (ΔeGFR, ml/min/1.73 m^2/yr). Some studies have relied upon an absolute change in eGFR or the percentage change in eGFR over time,[5] but these methods assume linearity in kidney function. Indeed, previous studies have highlighted that patients progress in a variety of different patterns and trajectories.[16-18] For instance, O'Hare et al[18] showed 4 unique patterns of CKD progression in 5606 patients in the 2 years prior to initiation of dialysis, including slowly progressive patients with persistently low eGFR of <30ml/min/1.73m^2, progressive loss of eGFR from approximately 30-59ml/min/1.73m^2, accelerated eGFR decline in those with eGFR >60ml/min/1.73m^2, and those with catastrophic loss in function ⩽6 months from eGFR levels >60ml/min/1.73m^2. Given renal trajectory can be heterogeneous, more sophisticated methods of characterising CKD trajectory ought to be employed including generalised estimation equations or linear mixed regression models, which can better handle non-linear trajectories, by taking account of the variability in the eGFR values, and the variable number of eGFR measurements and follow-up duration patients have.[19,20]

Nonetheless, work by Weldegiorgis et al,[21] who analysed data from 6 randomised controlled trials that included diabetic and non-diabetic patients with CKD, showed that the majority of the 3523 pooled patients in fact followed a linear pattern of eGFR decline. If patients with a linear pattern of progression are the focus of interest, especially given biomarker signals in these patients may have a stronger and more accurate association with progression than in patients with non-linear progression, then a more systematic approach to determine eGFR trajectory may be required. In such cases, ordinary least squares linear regression can be first applied to all measured eGFR values for a patient to quantify the ΔeGFR. This should then be allied with a visual inspection of the eGFR-time graphs to help unmask those with non-linear progression. This latter step can be supplemented further by determining the 95% confidence interval (CI) of the ΔeGFR calculation, which can help indicate linearity – the smaller the CI, by definition, the greater the degree of linearity.[22]

Fundamentally, having the ΔeGFR calculated using a robust methodological approach provides the foundations to meaningfully evaluate whether or not a distinct biomarker pattern exists in specific forms of CKD progression, and such

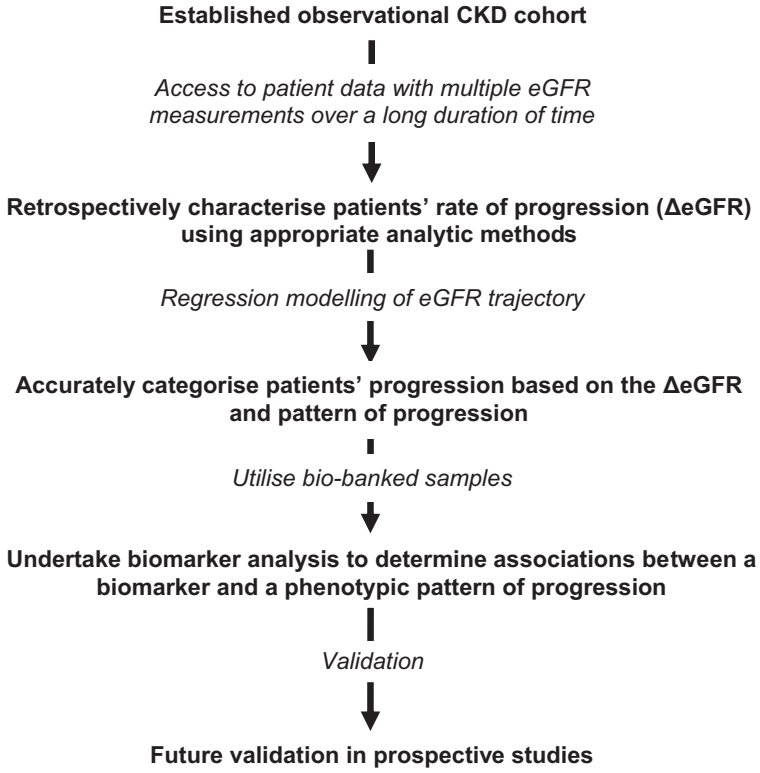

Figure 2. A paradigm for discovering biomarkers associated with CKD progression.

information may provide insight into pathophysiological mechanisms driving progression. Patterns of progression could be defined by a combination of descriptive terms such as linear or non-linear, slow progressive or exponential decline (in parallel with patterns described by O'Hare et al) or simply rapid progressors, stable non-progressors or those with positively improving eGFR.[23] Categorisation of patients as a rapid progressor or a stable patient is based on pre-defined ΔeGFR cut-off values. KDIGO recommend defining rapid progression as those with a ΔeGFR of <-5ml/min/1.73m^2/yr (ie, losing more than 5ml/min/1.73m^2/yr)[9], but adverse clinical outcomes have been shown to be associated with rates of <-3ml/min/1.73m^2/yr[24, 25] and this ought to be the lowest threshold for ΔeGFR to define rapid progression. A ΔeGFR of −0.5 to +0.5ml/min/1.73m^2/yr can define stable patients, where stability is reflected in a ΔeGFR that centres on zero (ie, no change in eGFR over time). More positive ΔeGFR values (for instance, a ΔeGFR $>+0.5$ml/min/1.73m^2/yr) could define those with improving renal function.

Existing cohorts offer a potential treasure trove for biomarker discovery

The paradigm relies on a retrospective method to select patients for future biomarker work, which specifically has 2 key advantages. Firstly, biomarkers can be tested in bio-banked samples in appropriately selected patients whose functional outcome is already known, enabling the question of whether the biomarker is associated with a specific pattern of CKD progression to be answered more confidently. Secondly, bio-banked samples also create enhanced opportunities for biomarker research, such as the serial testing of a biomarker, especially at points of renal decline, where possible. This would overcome the limitation of attempting to attribute significance to biomarkers measured at baseline being associated with patients who have variable, non-linear progression. This approach therefore provides the means for further exploratory research: firstly, in assessing whether repeated biomarker measurements remain consistently present in those with linear forms of progression; secondly, whether a biomarker quantitatively changes with worsening renal function in those with rapid progression; and thirdly, in assessing if biomarker signals change when a patient experiences a change in renal trajectory. Biomarkers discovered in this retrospective manner would then ideally be validated by examining them in patients in future prospective studies to ascertain whether they are able to predict different rates of CKD progression.

Whilst there may be specific biomarkers that cannot be measured in this retrospective manner, and which may require evaluation with new studies, we would advocate for collaborative efforts to harness and uncover the potential treasure trove of biomarker discovery from the analysis of stored samples in existing cohorts. As a corollary, we would recommend for the

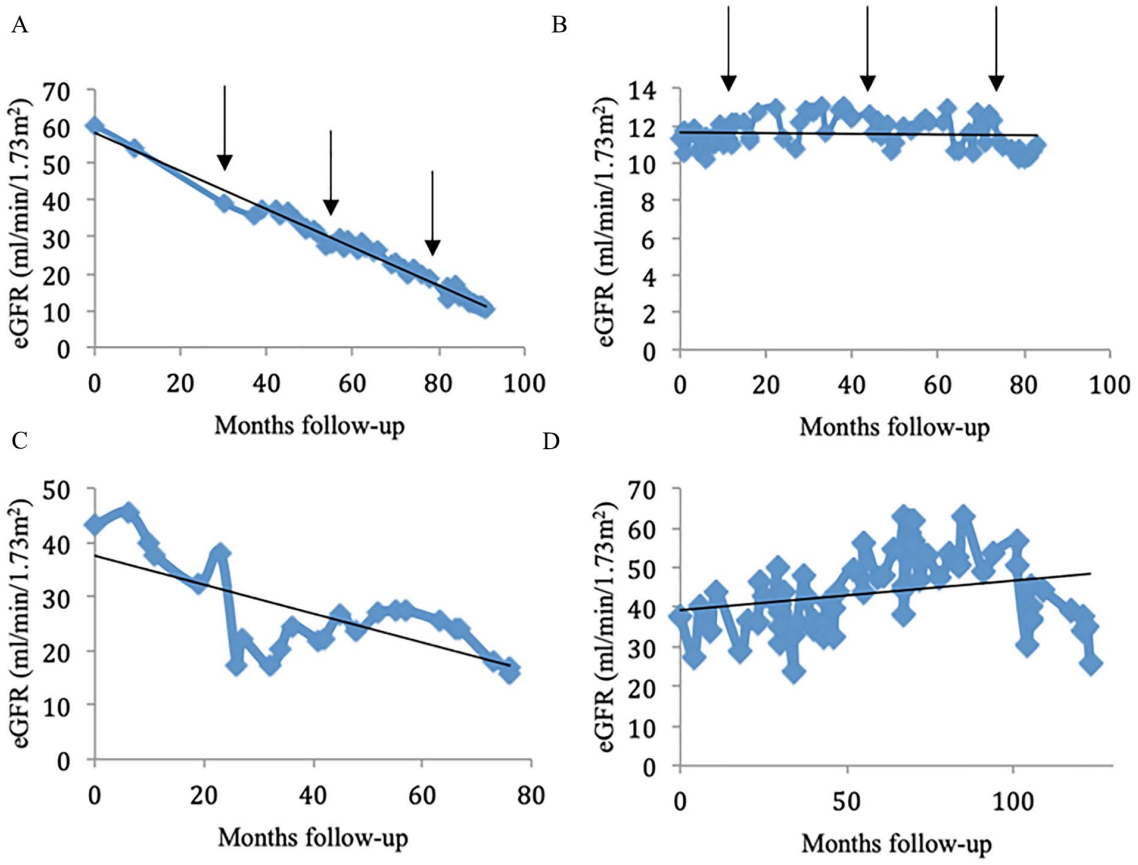

Figure 3. Illustrative eGFR-time graphs of individual patients to demonstrate the selection of patients with linear CKD progression into biomarker studies. Panels (A) to (D) highlight the eGFR-time graphs for 4 individual patients in the Salford Kidney Study.

routine ongoing collection and storage of bio-banked samples in ongoing studies to afford the means to accomplish future research using this paradigm.

We illustrate aspects of the paradigm concepts using illustrative examples of eGFR-time graphs in Figure 3. Each eGFR-time graph shows the changes in renal function over time for an individual patient within the Salford Kidney Study (SKS). The SKS is a prospective observational cohort study that has been recruiting non-dialysis dependent CKD patients since 2002. Any patient referred to the renal services at Salford Royal NHS Foundation Trust (a tertiary renal centre in the United Kingdom with a catchment population of 1.55 million) and is over 18 years old with an eGFR of <60ml/min/1.73m^2 is eligible for recruitment. Blood and urine sampling for routine clinical tests is performed at baseline and at subsequent clinic visits and is available throughout the patient journey via laboratory linkage to the electronic patient record. Further samples including EDTA whole blood, serum and citrate plasma are collected, centrifuged and bio-banked at −80°C for future research. We present cases in Figure 3 where a consistent linear pattern of progression is sought in patients and how bio-banked samples at various time-points in these patients' follow-up allow important biomarker evaluation to be undertaken.

In each case, the ΔeGFR has been calculated with linear regression with the specific aim of identifying patients with a linear, consistent pattern of progression, be it either stable or rapid (defined in this instance as a ΔeGFR of <−4ml/min/1.73m^2/yr) in nature. A linear regression line has been applied to all graphs. (A) The linear ΔeGFR is −6.5ml/min/1.73 m^2/yr (95% CI −6.7 to −6.2). Linear progression is clearly seen on the eGFR-time graph. Note also the small CI of 0.5 ml/min/1.73m^2/yr, reflecting a strong degree of linearity of the eGFR values. (B) The linear ΔeGFR is −0.2ml/min/1.73m^2/yr (95% CI −0.3 to −0.1) and stability is seen throughout follow-up. This patient could be defined as a 'stable patient'. Bio-banked samples in both patients A and patient B at various times (highlighted by arrows) would provide the means to evaluate the differences in biomarkers between these 2 patients. Additionally, the opportunity to undertake longitudinal assessment of biomarkers within each patient (at each arrow) would provide valuable insight into whether changes occur to biomarkers over time. (C) The linear ΔeGFR for this patient was −3.2ml/min/1.73m^2/yr (95% CI −4.6 to −1.8) but the graph reveals a fluctuating course in renal function. This patient would not be suitable for a study focused on linear progression specifically. (D) The ΔeGFR is +0.15ml/min/1.72m^2/yr (95% CI

−1.2 to +1.5), but similar to graph C, the eGFR varies widely over the follow-up period. Thus, the panels show how eGFR-time graphs can help visually substantiate the linear ΔeGFR or unmask non-linear progression.

Conclusion

Studies involved in CKD progression that define their outcome based on a change in renal function share a number of important limitations, especially a weak and imprecise characterisation of eGFR trajectory. There is a pressing need for more robust work with improved patient phenotype identification to help determine whether biomarkers offer clinical value. To that end, we recommend utilisation of currently established CKD cohorts that not only provides a means to accurately characterise a patient's eGFR trajectory but also offer new avenues in biomarker research using bio-banked samples at different points in a patient's CKD progression timeline.

Author contributions

IA and PAK conceived the idea. IA undertook data analysis and prepared the initial draft. RC and STI supported in data analysis. DG, MT, TDW and PAK critically revised the article for important intellectual content. All authors approved the final version.

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