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Authors

Kalantar-Zadeh, Kamyar
Kovesdy, Csaba P
Streja, Elani
et al.

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Full Review

Transition of care from pre-dialysis prelude to renal replacement therapy: the blueprints of emerging research in advanced chronic kidney disease

Kamyar Kalantar-Zadeh[1,2,3,4], Csaba P. Kovesdy[5,6], Elani Streja[1,2], Connie M. Rhee[1,2], Melissa Soohoo[1], Joline L.T. Chen[2], Miklos Z. Molnar[5], Yoshitsugu Obi[1], Daniel Gillen[7], Danh V. Nguyen[8,9], Keith C. Norris[4], John J. Sim[10] and Steve S. Jacobsen[10]

[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, CA, USA, [2]VA Long Beach Healthcare System, Long Beach, CA, USA, [3]Los Angeles Biomedical Research Institute, Harbor-UCLA Med. Center, Torrance, CA, USA, [4]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA, [5]Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN, USA, [6]Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN, USA, [7]University of California Irvine Program for Public Health, Irvine, CA, USA, [8]General Internal Medicine, University of California Irvine Medical Center, Orange, CA, USA, [9]Biostatistics, Epidemiology and Research Design, University of California Irvine, Irvine, CA, USA and [10]Kaiser Permanente of Southern California, Pasadena, CA, USA

Correspondence and offprint requests to: Kamyar Kalantar-Zadeh; E-mail: kkz@uci.edu

ABSTRACT

In patients with advanced (estimated glomerular filtration rate <25 mL/min/1.73 m^2) non-dialysis-dependent chronic kidney disease (CKD) the optimal transition of care to renal replacement therapy (RRT), i.e. dialysis or transplantation, is not known. Mortality and hospitalization risk are extremely high upon transition and in the first months following the transition to dialysis. Major knowledge gaps persist pertaining to differential or individualized transitions across different demographics and clinical measures during the 'prelude' period prior to the transition, particularly in several key areas: (i) the best timing for RRT transition; (ii) the optimal RRT type (dialysis versus transplant), and in the case of dialysis, the best modality (hemodialysis versus peritoneal dialysis), format (in-center versus home), frequency (infrequent versus thrice-weekly versus more frequent) and vascular access preparation; (iii) the post-RRT impact of pre-RRT prelude conditions and events such as blood pressure and glycemic control, acute kidney injury episodes, and management of CKD-specific conditions such as anemia and mineral disorders; and (iv) the impact of the above prelude conditions on end-of-life care and RRT decision-making versus conservative management of CKD. Given the enormous changes occurring in the global CKD healthcare landscape, as well as the high costs of transitioning to dialysis therapy with persistently poor outcomes, there is an urgent need to answer these important questions. This review describes the key concepts and questions related to the emerging field of 'Transition of Care in CKD', systematically defines six main categories of CKD transition, and reviews approaches to data linkage and novel prelude analyses along with clinical applications of these studies.

Keywords: advanced chronic kidney disease, prelude, renal replacement therapy, transition, vintage

TRANSITION TO RENAL REPLACEMENT THERAPY

Each year over 100 000 Americans and a similar number of Europeans transition from advanced non-dialysis-dependent chronic kidney disease (CKD) to renal replacement therapy (RRT) [1, 2]. These patients usually have an estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2 at the time of

transition, among whom the majority embark on maintenance dialysis therapy, while <5% undergo pre-emptive kidney transplantation [2]. In most developed nations the transition of care in CKD is usually supported by the provision of universal coverage through the government, which ensures access to dialysis therapy to virtually all eligible patients. In the USA, the 1973 End-Stage Renal Disease (ESRD) legislation has assured Medicare coverage for maintenance dialysis therapy beyond 90 days even if patients are younger than 65 years, the otherwise threshold age for Medicare beneficiaries. In 2013 a total of 117 162 Americans transitioned to RRT in this 320 million-population nation, leading to an adjusted ESRD incidence rate of 352 per million population (PMP), the highest in the world, with remarkable racial and ethnic disparities (Whites: 286, African Americans: 865, Native Americans: 318 and Asian: 352 PMP) [2]. There were 661 648 prevalent ESRD patients in 2013 in the USA, the highest absolute number in any nation worldwide, including 466 607 dialysis patients and 193 262 kidney transplant recipients [2]. With an adjusted ESRD prevalence rate of 1981 Persons Per Million (PPM), the USA also leads all nations except for Japan and Taiwan, which have more dialysis patients per capita than the USA [3]. Transitioning such substantial numbers of patients to dialysis or transplantation in the USA has led to a total ESRD expenditure of $41.2 billion annually, including $30.9 billion by the Medicare ESRD program alone [2]. The annual total Medicare expenditures per person-year for hemodialysis, peritoneal dialysis and transplant patients are $85 000, $70 000 and $30 000, respectively.

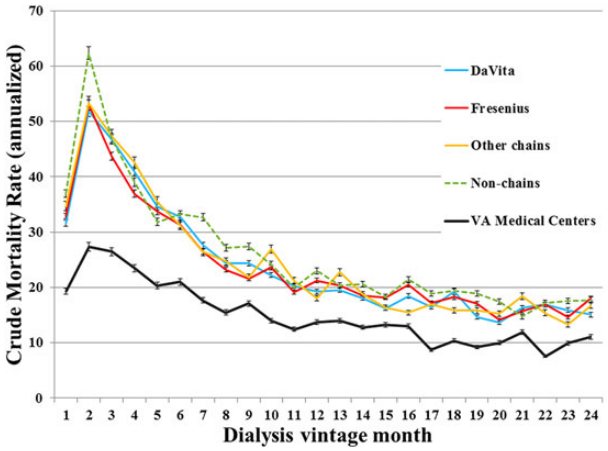

FIGURE 1: Higher mortality during the first several months of transition to maintenance dialysis therapy, reflected by the crude annualized mortality rates over the first 24 months after transition to maintenance dialysis treatment, stratified by dialysis provider, in 52 172 incident ESRD veterans from October 2007 to September 2011. The dialysis providers include the two major large dialysis organizations (Fresenius Medical Care and DaVita), other dialysis chains, independent dialysis centers (non-chains) and dialysis centers that are based in a Veterans Affairs (VA) medical center (adapted from the USRDS 2015 Annual Data Report, chapter on Transition of Care in CKD, Veterans Data, www.USRDS.org) [1].

IMPORTANCE OF STUDYING TRANSITIONS IN THE COURSE OF CKD

Whereas dialysis therapy is intended to be life-sustaining, ESRD patients have a 10-fold or higher risk of death compared with the general population [4], given the US annual dialysis patient mortality of close to 18% [2]. These patients also have markedly higher hospitalization rates and worse health-related quality of life [5, 6]. Ironically the first 3 to 6 months of dialysis therapy or transplantation is associated with an even higher risk of death compared with prevalent dialysis or transplant patients (Figure 1) [7], yet it is not clear whether the earlier transition to dialysis in the USA is a contributing cause of this high death rate. Some guidelines still advise that in the context of worsening clinical symptoms, transitioning to ESRD should occur earlier and at even higher eGFR levels than the arbitrary Stage 5 CKD definition of <15 mL/min/1.73 m^2 [8, 9], whereas in some countries such as Taiwan the average eGFR at dialysis transition is lower (<5 mL/min/1.73 m^2) [10]. In recent years, in the USA 30% and 15% of patients transition to dialysis with an eGFR of 10 to <15 and ≥15 mL/min/1.73 m^2, respectively [9]. However, very few if any patients ever transition to RRT with an eGFR >25 mL/min/1.73 m^2 (Figure 2) [11]. Although several studies have questioned the wisdom of premature dialysis initiation [12], it remains unknown as to when the best timing for ESRD transition should occur for individuals, i.e. across different age groups or comorbid conditions or race/ethnicities, in order to achieve the best ESRD survival and other outcomes. There are a number of key unanswered questions related to the transition of care in CKD [11, 13]. For instance, there is an urgent need to examine whether the transition to RRT and the type and modality of the transition should be selected based on pre-dialysis patient data. Unanswered questions also exist regarding the outcome-predictability of pre-ESRD conditions with selection of dialysis modality (hemodialysis versus peritoneal dialysis), format (in-center versus home), frequency (daily versus infrequent) and vascular access (pre-emptive arteriovenous fistula or peritoneal dialysis catheter placement versus no access placement until dialysis starts).

Examining transitions of care in advanced CKD patients has become an exceptionally important emerging front under the new Affordable Care Act and with the imminent establishment of Accountable Care Organizations [14–16], leading to an unprecedented urgency to move innovatively beyond the traditional CKD studies. Currently it is not clear what policies or standards should be adopted to ensure the most appropriate ESRD transition given enormous heterogeneity and diversity among CKD patients across varying demographics, racial/ethnic groups and comorbid conditions, as well as the complexity and costliness of dialysis and transplant care. Major cost-savings and improved outcomes and better patient-centered care can result from innovative approaches to examine transitions of care in advanced CKD based on data prior to the ESRD intercept such as the rate of progression of kidney disease and pre-ESRD comorbid conditions. Hence, there is an urgent need to examine the emerging field of 'Transition of Care in CKD,' and the task necessitates systematically defined nomenclature in order to better articulate these important questions

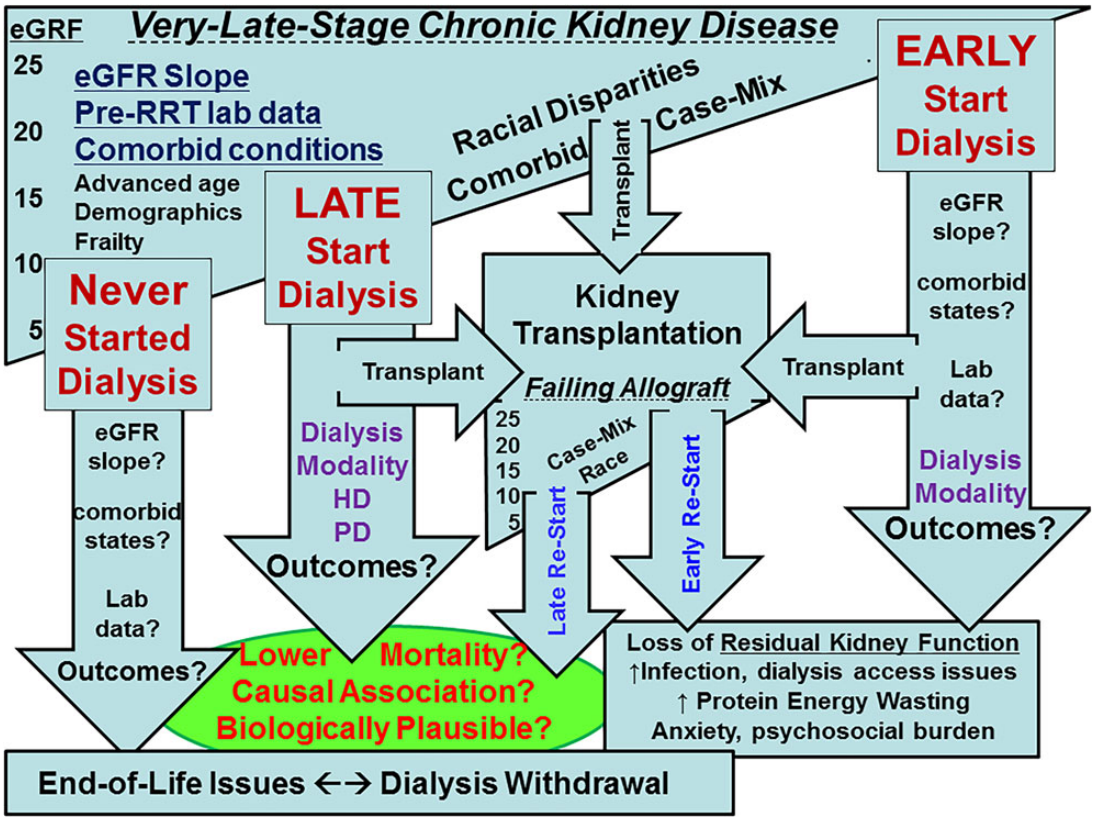

FIGURE 2: Common scenarios of transitions of care in patients with an advanced CKD (eGFR <25 mL/min/1.73 m^2 body surface area) to RRT, and potential challenges and pitfalls of examining these transitions in epidemiologic studies (see also Table 1 for different types of transition). HD, hemodialysis; PD, peritoneal dialysis.

and to more effectively conduct epidemiologic and translational research in the field, with the ultimate goal of improving CKD patient outcomes. Hence, we suggest the term "advanced CKD" for this level of eGFR, so that the transition of care from non-dialysis-dependent CKD to ESRD can be more pragmatically defined and studied. In advanced CKD eGFR is often <25 ml/min/1.73 m^2.

TRANSITION AMONG ELDERLY AND MULTI-MORBID CKD PATIENTS

The number of elderly in the USA and Europe has shown 20% growth over the past two to three decades [17, 18]. Consequently, the prevalence and incidence of chronic diseases including CKD have risen substantially [19, 20]. In 1990, 2000 and 2010, 39, 43 and 44% of all prevalent dialysis patients, and 4, 10 and 20% of all kidney transplant recipients, respectively, were over 65 years. It is not clear whether the poor outcomes of ESRD justify these expensive therapies in the elderly, especially since mortality remains unchanged [19], while functional status may deteriorate [21]. Indeed it is far from clear whether deferring, interrupting or avoiding dialysis is associated with unfavorable outcomes in certain age or comorbid groups as compared with dialysis transition, which may worsen frailty and lead to an unknown or even worse survival [22]. End-of-life issues in people with advanced CKD (eGFR <25 mL/min/1.73 m^2) have not been well studied, particularly in the elderly and multimorbid individuals, especially among those undergoing dialysis therapy and with a gradually failing kidney transplant [9]. There is an urgent need to answer these important questions related to transitions of care in advanced CKD given the high costs of dialysis therapy and its poor outcomes.

TYPES OF TRANSITION OF CARE IN CKD

We have identified six major categories of transitions of care during advanced CKD as shown in Table 1 [23]: (1) transition from non-dialysis-dependent CKD to *de novo* dialysis therapy with different subtypes according to dialysis modality (hemodialysis versus peritoneal dialysis), dialysis format (in-center versus home) and dialysis treatment frequency [infrequent (e.g. once to twice-weekly hemodialysis) [24], conventional (thrice-weekly hemodialysis) and frequent (four or more times per week hemodialysis)] [25]; (2) transition from non-dialysis-dependent CKD to pre-emptive transplantation; (3) transition among or across dialysis modalities, formats and frequency (hemodialysis to peritoneal dialysis or vice versa, in-center to home, and less to more frequent, also known as incremental or progressive dialysis therapy [26]); (4) transition from dialysis therapy to kidney transplantation; (5) transition from a gradually failing kidney transplantation back to dialysis therapy; and (6) transition from any of the above stages to partial or full

Table 1. Different categories and subtypes of the transition of care from advanced CKD (eGFR <25 mL/min/1.73 m^2) to renal replacement therapy

Category	Description and subcategories
1	Transition from advanced NDD-CKD to dialysis therapy with different subtypes: 1.a. Dialysis modality (hemodialysis versus peritoneal dialysis) 1.b. Format (in-center versus home) 1.c. Frequency (infrequent, conventional and frequent)[a]
2	Transition from advanced NDD-CKD to pre-emptive transplantation: 2.a. Kidney alone 2.b. Kidney and additional organ (e.g. pancreas or liver)
3	Transition across dialysis modalities, formats and frequency: 2.a. HD to PD or vice versa 2.b. In-center to home, and vice versa 2.c. Less to more frequent care (incremental dialysis)
4	Transition from maintenance dialysis to renal transplantation 4.a. Kidney alone 4.b. Kidney and additional organ (e.g. pancreas or liver)
5	Transition from gradually failing kidney transplantation back to dialysis therapy: 5.a. Dialysis modality (HD versus PD) 5.b. Format (in-center versus home) 5.c. Frequency (infrequent, conventional and frequent)[a]
6	Transition from any of the above conditions to withdrawal of renal replacement care: 6.a. Partial withdrawal, e.g. hospice 6.b. Full withdrawal of care 6.c. Regain partial or total kidney function[b]
0 (null)	No transition to renal replacement therapy 0.a. Nutritional and other interventions to control uremia (conservative therapy) 0.b. Partial to full withdrawal of CKD care

There are six main categories. Note that category 0, reflecting no transition to renal replacement therapy, i.e. conservative management of CKD, is also included here for the sake of completeness to cover all possible scenarios.
NDD-CKD, non-dialysis-dependent CKD; HD, hemodialysis; PD, peritoneal dialysis.
[a]Conventional HD frequency pertains to thrice-weekly HD treatment. Conventional PD frequency pertains to daily PD with at least four exchanges per 24 h. Infrequent HD is often twice-weekly but may be even less frequent.
[b]Dialysis patients who 'regain function' after several weeks of outpatient dialysis therapy may be categorized under this class, although most such cases likely have had protracted acute kidney injury (AKI) or AKI on CKD.

withdrawal of care. There appears to be major knowledge gaps surrounding the indications for or selection of these six categories of transition as well as their timing. Similarly, the choice of no transition from CKD to RRT (e.g. conservative management of CKD) is less than clear, and its outcomes should be compared with those of other six transition categories (Table 1).

METHODOLOGICAL CHALLENGES IN EPIDEMIOLOGIC STUDIES OF CKD TRANSITIONS: CKD DATABASE LINKAGE

Since there are often separate cohorts and databases related to different periods of RRT lacking data prior to the transition to RRT, a major challenge of epidemiologic studies of CKD transitions is ensuring effective, efficient and accurate data linkages, for instance, by linking pre-ESRD databases to the data from national or regional dialysis patient cohorts. A recent example is the linkage of the US Veterans Health Administration (VHA) database with the entire US national dialysis database, also known as the United States Renal Data System (USRDS) [27–29]. This innovative linkage has enabled researchers and care providers for the first time to examine the first two categories of transitions (from non-dialysis CKD to *de novo* RRT, see Table 1) including the impact of pre-ESRD conditions during the prelude period (see below) on early ESRD outcomes [27–29]. Transition categories 3 and 4 (inter-modality transitions) can also be examined via these data linkages during the first several months of dialysis therapy, where the impact of pre-dialysis conditions on dialysis outcomes is still likely substantial. Category 5 transition (returning from a failing kidney transplant back to dialysis) can be examined if pre-dialysis data during the gradually failing kidney transplant are available as recently presented in a study by Molnar *et al.* [30]. Additionally, the impact of pre-ESRD conditions on transition category 6 (withdrawal and end-of-life pathways) can be examined more effectively using USRDS data linkages with hospice data. To compare the outcomes of *de novo* ESRD transitions with the conservative management of CKD without dialysis therapy, more sophisticated methods including propensity score matching may be used [31, 32].

Merging data from distinct databases in order to create opportunities for even larger datasets to study transitions is currently also hampered by stringent information security and data privacy laws in the USA and elsewhere, which prohibits the disclosure of individual identifiers needed for matching of data for the same individual from different databases. As shown by our recent merging of data from the dialysis databases with data from the Scientific Registry of Transplant Recipients (SRTR) [33–35], one possible—albeit imperfect—solution for this problem is to perform probabilistic matching, i.e. by combining individual characteristics that do not qualify individually as protected health information, yet allow the matching of data from the same individual with reasonable accuracy. Similar and other innovative approaches will be needed in order to better utilize the ever growing 'big data' from various healthcare systems and data repositories towards the studying of transition of care.

THE CONCEPT OF PRELUDE

A major methodologic challenge in studying the first transition to RRT and the impact of pre-ESRD care on early dialysis outcome is the dearth of systematic and quantitative definitions of pre- and post-ESRD periods, including distinct points in time and directions. As a pragmatic solution we have defined the term 'prelude' as the period prior to the ESRD transition intercept, as opposed to 'vintage', which refers to the time after transition to RRT (Figure 3). Prelude is a negative count since it goes backward in time, e.g. −6 (minus six) months prior to ESRD transition, whereas vintage is a positive count, e.g. +3 months since dialysis initiation.

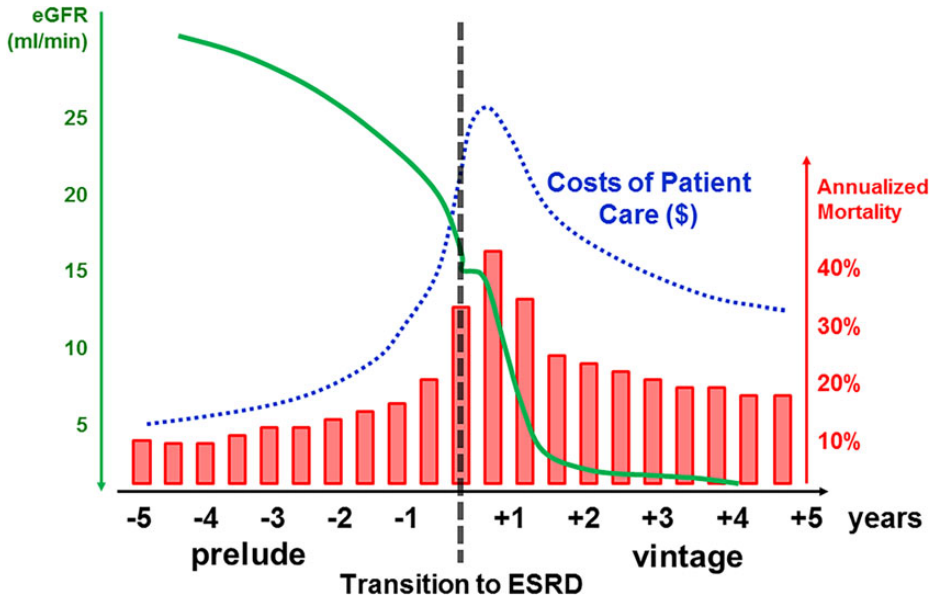

FIGURE 3: Schematic illustrations of the concepts of 'prelude' and 'vintage' periods in examining the transition of care from advanced CKD (eGFR <25 mL/min/1.73 m^2 body surface area) to renal replacement therapy, along with the trends in residual kidney function (eGFR) (solid line) and variations in patient mortality (vertical bars) and costs of CKD patient care (dotted line) at different points in time relative to the transition intercept.

This systemic definition of prelude has enabled a more efficient and commensurate analysis of pre-ESRD conditions and their impact on outcomes during RRT, as we have recently reported [27, 28]. The concept of prelude has particularly facilitated the study of ESRD transition decisions, including timing and modality selection, associated with the best outcomes. This approach is innovative and analogous to a similar model that we have pioneered in examining the association of pre-transplant data on post-transplant patient and allograft survival by linking the USRDS database, to better acquire and verify comorbidity and death data, and the SRTR, to obtain post-transplant outcome data [33–35]. A pragmatic approach in summarizing large quantities of repeated measures data has been to create quarterly averaged values of all laboratory data during the −12 months to −5 years of prelude time prior to ESRD transition to assess differences in longitudinal changes with advancing CKD during prelude periods and their impact on transition and ESRD outcomes.

LIMITATIONS OF THE LARGE NATIONAL DIALYSIS DATABASES

As a rich and comprehensive database of almost all dialysis and transplant patients in the USA, the USRDS dataset has contributed immensely to important research with regard to ESRD patient outcomes. However, there are some inherent limitations in the USRDS dataset, in particular the lack of key pre-ESRD care data; hence, there is an urgent need for innovative linkage approaches to address this shortcoming. Similarly, whereas over the past decade some important contributions related to dialysis patient studies and outcomes have emerged as a result of epidemiologic analyses of large national dialysis databases in the USA such as those from the clinical care of Fresenius [36] and DaVita patients [37], these databases often lack pre-ESRD data. Hence, linking the pre-transition or prelude data to large national ESRD databases and analyzing the prelude variables as predictors of early ESRD outcomes enables better examination of the impact of pre-ESRD care on outcomes during the RRT.

CHALLENGING THE CURRENT PARADIGMS

A core hypothesis of the CKD transition concept implies that different CKD patients benefit from different approaches to transition of care in CKD. The key concept challenges the quintessential aspects of the current paradigm that RRT should be provided uniformly to all advanced CKD patients using the same approach. To expand and innovate beyond the standard of care, we hypothesize that a differential or individualized transition in CKD is associated with more favorable outcomes including greater survival and more cost-savings, if the decisions are based on key pre-ESRD prelude data such as CKD progression rates, quality of pre-transition care and laboratory data, and comorbidities. We suggest that a comprehensive scoring system be derived from the prelude data to determine the best timing, preparation, and modality, and to achieve the best outcomes for each individual patient with advanced CKD. Similar prognostic scores have been successfully created and validated including the Malnutrition-Inflammation Score [38–40], which is annually assessed as the standard of care across approximately 150 000 US dialysis patients in order to prognosticate nutritional status and outcomes of ESRD care [41–54].

CALCULATING eGFR SLOPE DURING PRELUDE

In a recent study examining the data of CKD patients in Southern California [55], the rate of change in eGFR (mL/min/1.73 m^2/year)

was determined by the ordinary least squares regression line for each participant, based on which participants were stratified into higher and lower risk of ESRD. Higher risk participants were designated as those with projected kidney failure based on a predicted eGFR <15 mL/min/1.73 m^2 within a specified time. Time frames of 1, 3 and 5 years after participants' entry eGFR levels were examined, as well as the time frame of the study period, which ended on 31 December 2009. By examining mortality in the subgroup with projected kidney failure within the study period, greater understanding of the influence of the competing risk of death on disparities in ESRD incidence was acquired [55]. These and other methods can be used to estimate the slope of eGFR during the prelude time and its changes upon a given procedure such as placement of arteriovenous fistulas [29].

Two important challenges in this approach have been establishing steady-state eGFR and differentiating between eGFR changes versus acute kidney injury (AKI) events; it is important to note that two eGFRs within a narrow range of each other should not be indicative of distinct kidney function. To operationalize this concept, a second eGFR can be viewed within ±10% of the first eGFR as indicating no change in renal function. Serum creatinine levels ≥30 days apart can be used to estimate GFR in order to avoid attributing a 'stable GFR' during AKI events that are superimposed upon and confound a CKD progression course [29, 55].

USE OF PROPENSITY SCORES AND INVERSE PROBABILITY WEIGHTS IN PRELUDE ANALYSES

In addition to conventional multivariate methods, propensity score (PS)-matched analyses can be used to compare increments (e.g. tertiles) of eGFR slope groups using Kaplan–Meier curves and unadjusted conditional Cox regression models. For each PS-matched analysis, several 'doubly robust' adjustment levels can be examined including minimally adjusted and case-mix adjusted models, as well as more comprehensive adjustment such as inclusion of laboratory and comorbidity status, as we have done in our recent studies [33, 56–63]. The PS method can primarily be used to account for confounding effects arising from differences in clinical characteristics of patients in whom transition to RRT occurs at different levels of eGFR.

Using logistic regression models we can also construct different PS levels to represent the likelihood of transition to RRT at higher eGFR or at lower eGFR slopes consistent with biological plausibility of the CKD-to-ESRD transition model [64, 65]. Investigators need to weight comparison patients by their estimated odds of being transitioned [66]. This weighting aligns the distribution in the linked cohorts of the variables used in the treatment-probability model to match the distribution across different eGFR slopes. These weights can then be used in an outcome-regression model to obtain doubly robust (DR) estimates of effect [67]. DR estimation builds on the PS approach as used by Rosenbaum and Rubin [68] and the inverse probability of weighting (IPW) approach of Robins that is used in marginal structural models (MSM) [69, 70]. DR estimation combines IPW by a PS with regression modeling of the relationship between covariates and outcome for each treatment in such a way that, as long as either the PS model or the outcome regression models are correctly specified, the effect of the exposure on the outcome will be correctly estimated, assuming that there are no unmeasured confounders [71, 72].

CONCLUSION

The transition of care in CKD is a rapidly emerging field and based on the core concept that the status of a patient and his/her clinical and laboratory data prior to ESRD transition, i.e. during the so-called prelude era, can be modeled to not only predict early and late ESRD outcomes but to also individualize the recommendations and decisions pertaining to the best transition format and modality. Linkages among large regional and national databases are essential to examine the impact of prelude conditions on ESRD outcomes, including exceptionally high mortality rates in the first several months following the transition to dialysis therapy. Sophisticated methodologies and innovative modeling and scoring systems will allow investigators, clinicians and health policy experts to advance more efficient and optimal approaches to transitions of care in CKD.

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CONFLICT OF INTEREST STATEMENT

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