Kidney Res Clin Pract 34 (2015) 207–211

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Original Article

Comparison of estimated glomerular filtration rate equations at the time of hemodialysis initiation

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Article history:
Received 8 June 2015
Received in revised form
26 September 2015
Accepted 5 October 2015
Available online 12 November 2015

Keywords:
Corrected Cockcroft-Gault equation
End-stage renal disease
Estimated glomerular filtration rate
Hemodialysis

Abstract

Background: Estimated glomerular filtration rate (eGFR) is one of the most important guidelines in deciding the optimal timing of dialysis initiation. In the present study, we calculated the eGFR at the time of hemodialysis (HD) initiation using 5 commonly used equations to relate them with clinical and laboratory characteristics of the patients and to evaluate which of these equations best define the eGFR at HD initiation.

Methods: We retrospectively analyzed 409 end-stage renal disease patients who were newly started on HD treatment in our institution. The eGFR was calculated using the Cockcroft–Gault equation, the Cockcroft–Gault equation corrected for body surface area, the Modification of Diet in Renal Disease (MDRD) equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the Nankivell equation.

Results: The mean eGFRs at HD start were significantly different across the equations. The mean eGFR was 7.8 mL/min for the corrected Cockcroft–Gault equation, 7.7 mL/min for the Cockcroft–Gault equation, 6.2 mL/min/1.73 m^2 for the MDRD equation, and 5.6 mL/min/1.73 m^2 for the CKD-EPI equation. The corrected Cockcroft–Gault, the MDRD, and the CKD-EPI equations were well correlated with all CKD-specific complications including hypertension, anemia, hyperkalemia, metabolic acidosis, hypocalcemia, hyperphosphatemia, and hyperparathyroidism. The mean eGFR calculated by the corrected Cockcroft–Gault equation showed the lowest coefficient of variation among all the equations.

Conclusions: The eGFR at HD initiation are significantly different according to the used eGFR equations, and the corrected Cockcroft–Gault equation may be the best in defining the eGFR at HD initiation.

Introduction

Dialysis now offers life-sustaining treatment to approximately 2 million end-stage renal disease (ESRD) patients worldwide [1]. The guidelines across many regions in the world recommend the initiation of dialysis based on estimated glomerular filtration rate (eGFR). In fact, the guidelines of National Kidney Foundation Kidney Disease Outcomes

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http://dx.doi.org/10.1016/j.krcp.2015.10.002

Quality Initiative [2], European [3], Australian [4], and Canadian guidelines [5], recommend the initiation of dialysis when the eGFR is less than 10–15 mL/min. However, recent studies showed that the early dialysis initiation as recommended by these guidelines was not associated with an improvement in clinical outcomes, as compared to the late-start dialysis [6–9].

The Initiating Dialysis Early and Late (IDEAL) study is a prospective, multicenter, randomized, controlled trial to compare outcomes in patients starting dialysis with a higher versus lower eGFR, where the mean eGFR was 12.0 mL/min for the patients who started dialysis early and 9.8 mL/min for those who started dialysis late with the use of the corrected Cockcroft–Gault equation and 9.0 mL/min and 7.2 mL/min, respectively, with the use of the Modification of Diet in Renal Disease (MDRD) equation [6]. Interestingly, the differences between the early-start and the late-start groups (2.2 and 1.8 mL/min) were smaller than the differences created by the 2 equations within the group (3.0 and 2.6 mL/min), which indicates that the discrepancy of the mean eGFR between the 2 equations is too big for the equations to be used interchangeably.

In the present study, we calculated the eGFR at the time of hemodialysis (HD) initiation using 5 commonly used equations including the Cockcroft–Gault equation, the Cockcroft–Gault equation corrected for body surface area, the MDRD equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the Nankivell equation to relate them with clinical and laboratory characteristics of the patients and to evaluate which of these equations best define the eGFR at HD initiation.

Methods

Patients

We retrospectively analyzed ESRD patients who were newly started on HD between January 2010 and December 2012 in our institution. Patients were included if they were 18 years or older and started HD for the first time. Data regarding clinical and demographic characteristics including age, gender, height, weight, systolic and diastolic blood pressures, causes of ESRD, and comorbidities including diabetes mellitus (DM), hypertension, cardiovascular disease (CVD), and congestive heart failure (CHF) were collected from the medical records. DM was defined based on the presence of documented or self-reported history of diabetes or diabetic retinopathy or the presence of diabetic medications in patients' prescription records. Hypertension was defined in the same way as in DM. This study was approved by the Institutional Review Board of our institution.

Laboratory data

Blood urea nitrogen, creatinine (Cr), bone mineral markers (intact parathyroid hormone, phosphorus, and total calcium), a nutritional marker (albumin), metabolic acidosis markers (bicarbonate), and anemia markers (hemoglobin) were recorded. All laboratory data except intact parathyroid hormone levels were obtained within 1 day before the start of HD. Intact parathyroid hormone levels were obtained within 3 months before the start of HD or within 3 days after the start of HD.

Estimated glomerular filtration rate

For eGFR, we used 5 equations as follows: Cockcroft–Gault equation [10], [140 − age (years)] × [weight (kg)] × (0.85 if female)/[72 × serum Cr (sCr, mg/dL)]; Cockcroft–Gault equation corrected for body surface area, [140 − age (years)] × [weight (kg)] × (0.85 if female)/[72 × sCr (mg/dL)] × 1.73/body surface area (m^2); MDRD equation [11], 186.3 × [sCr (mg/dL)]$^{-1.154}$ × [age (years)]$^{-0.203}$ × (0.742 if female); CKD-EPI equation [12], 141 × min [Scr (mg/dL)/κ,1]$^{\alpha}$ × max [Scr (mg/dL)/κ,1]$^{-1.209}$ × 0.993$^{\text{age (years)}}$ × 1.018 (if female) × 1.159 (if black), where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1; Nankivell equation [13], [6.7/sCr (mmol/L)] + [weight (kg)/4] − [serum urea (mmol/L)/2] − [100/height $(m)^2$] + (35 if males and 25 if females).

Statistical analysis

Continuous variables are described as means with standard deviation and categorical variables as proportions. Differences between the subgroups were assessed using chi-square tests for categorical variables and Student's *t* tests for continuous variables. The coefficient of variation (CV) was calculated as the percent ratio of the standard deviation to the mean. Correlations between variables were assessed by Pearson's correlation tests. Values of $P < 0.05$ were considered statistically significant. The analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows 18.0, SPSS Inc., Chicago, IL, USA).

Results

Between January 2010 and December 2012, 1,369 patients who were new to our HD unit were reviewed, and of these, 660 patients were excluded because they had started HD previously in other centers. Other excluded patients were 249 who received HD for acute kidney injury, 17 who received pre-emptive HD for kidney transplantation, 11 who returned to HD after renal allograft failure, and 23 who switched to HD from peritoneal dialysis. Finally, 409 patients who started maintenance HD for ESRD were included in the present analysis. Table 1 summarized the patients' demographics and the causes of ESRD. The mean age was 58 years, and 52.6% of the patients were men. Comorbidities were common, particularly hypertension (81.9%) and DM (52.8%). The most common causes of ESRD were diabetic nephropathy (48.7%), followed by biopsy-proven glomerulonephritis (11.7%). The mean eGFR at the start of HD was significantly different across the different equations (Table 2). The highest mean eGFR was derived from the corrected Cockcroft–Gault equation (7.8 ± 3.6 mL/min/1.73 m^2) followed by the Cockcroft–Gault (7.7 ± 3.8 mL/min), MDRD (6.2 ± 3.4 mL/min/1.73 m^2), CKD-EPI (5.6 ± 3.2 mL/min/1.73 m^2), and finally the Nankivell equation (0.10 ± 12.74 mL/min/1.73 m^2; Table 2). CV of each eGFR was used to evaluate the extent of variability in relation to the mean eGFR. The results showed that the CV of the corrected Cockcroft–Gault equation (46.0%) was the smallest among the included equations, whereas the Nankivell equation showed the biggest CV (127.4%) despite its lowest eGFR value (Table 2).

Table 1. Baseline characteristics of the patients ($N = 409$)

Characteristics	Mean ± SD
Age (y)	58.6 ± 14.6
Male gender, *n* (%)	215 (52.6)
Weight (kg)	63.2 ± 12.7
BMI (kg/m^2)	24.3 ± 9.1
Systolic BP (mmHg)	153.2 ± 25.4
Diastolic BP (mmHg)	81.6 ± 16.2
Hypertension, *n* (%)	335 (81.9)
CVD/CHF, *n* (%)	79 (19.3)
Causes of renal failure, *n* (%)	
Diabetic nephropathy	197 (48.2)
Chronic glomerulonephritis*	48 (11.7)
Polycystic kidney disease	13 (3.2)
Unknown†	130 (31.7)
Miscellaneous	21 (5.1)
Hemoglobin (g/dL)	8.5 ± 1.7
BUN (mg/dL)	97.4 ± 67.7
Creatinine (mg/dL)	10.3 ± 5.1
Sodium (mmol/L)	136.7 ± 5.5
Potassium (mmol/L)	5.1 ± 1.1
Bicarbonate (mmol/L)	15.8 ± 4.6
Calcium (mg/dL)	7.5 ± 1.3
Phosphorus (mg/dL)	6.4 ± 2.2
Albumin (g/dL)	3.5 ± 0.6
iPTH (pg/dL)‡	237.9 ± 173.6

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CHF, congestive heart failure; CVD, cardiovascular disease; iPTH, intact parathyroid hormone; SD, standard deviation.

* Included are biopsy-proven glomerulonephritis.

† Included are clinically suspected chronic glomerulonephritis without biopsy.

‡ $N = 268$.

We also evaluated the correlation between each eGFR and CKD-specific complications including hypertension, anemia, hyperkalemia, metabolic acidosis, hypocalcemia, hyperphosphatemia, and hyperparathyroidism. We found that the corrected Cockcroft–Gault, the MDRD, and the CKD-EPI equations showed significant correlations with all categories of CKD complications, suggesting that these equations are better than the others in reflecting the clinical status of the patients (Table 3). In contrast, the eGFR from the Nankivell equation showed a paradoxical relationship with hypertension and with serum calcium levels (Table 3), suggesting that this equation, derived from kidney transplant recipients, poorly reflects the clinical status of the advanced CKD patients.

The reasons to start HD were uremia (progressive azotemia, anorexia, nausea, fatigue, pericarditis, and mental change; 54.7%), fluid overload (38.4%), hyperkalemia (3.9%), and metabolic acidosis (2.9%).

In addition, we analyzed the data according to the presence of DM that accounted for 52.8% of the patients. DM patients were significantly older and had a higher incidence of CVDs/CHF than non-DM patients (Table 4). DM patients started HD at significantly higher eGFR levels than non-DM patients; however, DM patients were significantly better in metabolic acidosis, hyperphosphatemia, and hyperparathyroidism (Table 4). Among the reasons for HD, uremia accounted for 48.1% in DM and 61.6% in non-DM patients, whereas fluid overload accounted for 44.9% in DM and 31.4% in non-DM patients, indicative of a higher incidence of fluid overload in DM patients (Table 4).

Finally, we analyzed the data after subgrouping the patients into the outpatient clinic group and the emergency room (ER) group according to the places where the decisions on HD were made. Of all the patients, 59.2% started HD through clinic visits and the remaining 40.8% started HD in the ER. Contrary to our expectation, both groups were comparable in eGFR; however, they had differing reasons to start HD. The most common cause for the ER group was fluid overload (48.5%) in contrast to uremia (66.5%) for the clinic group (Table 5). Hyperkalemia and metabolic acidosis were significantly more severe in the ER group, as compared with the clinic group (Table 5).

Table 2. Comparisons of mean eGFR derived from different equations

	Mean ± SD	CV, %	Range	*P*				
				C-G	Corrected C-G	MDRD	CKD-EPI	Nankivell
C-G (mL/min)	7.7 ± 3.8	49.5	1.9–29.1		0.002	<0.001	<0.001	<0.001
Corrected C-G (mL/min/1.73 m^2)	7.8 ± 3.6	46.0	1.9–30.6			<0.001	<0.001	<0.001
MDRD (mL/min/1.73 m^2)	6.2 ± 3.4	54.5	1.4–23.4				<0.001	<0.001
CKD-EPI (mL/min/1.73 m^2)	5.6 ± 3.2	56.5	1.1–23.9					<0.001
Nankivell (mL/min/1.73 m^2)	0.10 ± 12.74	127.4	−54.1–33.0					

C-G, Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SD, standard deviation.

Table 3. Relationships between eGFR- and CKD-specific complications

	SBP	DBP	Hb	K	HCO_3	Ca	P	iPTH
C-G	−0.073	−0.070	0.161**	−0.161**	0.300**	0.135**	−0.399**	−0.203**
Corrected C-G	−0.115*	−0.110*	0.179**	−0.182**	0.343**	0.187**	−0.461**	−0.221**
MDRD	−0.133**	−0.201**	0.204**	−0.203**	0.375**	0.242**	−0.549**	−0.272**
CKD-EPI	−0.133**	−0.178**	0.198**	−0.206**	0.375**	0.232**	−0.532**	−0.259**
Nankivell	0.091	0.039	0.161**	−0.095	0.241**	−0.014	−0.368**	−0.188**

Pearson's correlation coefficient, *$P < 0.05$, **$P < 0.01$.

Ca, serum total calcium; C-G, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HCO_3, bicarbonate; iPTH, intact parathyroid hormone; K, potassium; MDRD, Modification of Diet in Renal Disease; P, inorganic phosphate; SBP, systolic blood pressure.

Table 4. Comparisons of clinical and laboratory characteristics according to the presence of DM

Characteristics	DM ($N = 216$)	Non-DM ($N = 193$)	P
Age (y)	61.1 ± 11.5	55.7 ± 17.0	<0.001
Male gender, *n* (%)	109 (50.5)	105 (55.0)	0.363
Weight (kg)	63.8 ± 11.1	62.3 ± 14.2	0.237
BMI (kg/m^2)	25.1 ± 11.9	23.4 ± 4.0	0.067
Systolic BP (mmHg)	154.2 ± 24.1	151.9 ± 30.0	0.347
Diastolic BP (mmHg)	78.2 ± 15.0	85.4 ± 16.8	<0.001
CVD/CHF, *n* (%)	58 (26.9)	21 (10.88)	<0.001
Hemoglobin (g/dL)	8.6 ± 1.6	8.5 ± 1.8	0.756
BUN (mg/dL)	93.0 ± 84.0	102.8 ± 42.3	0.147
Creatinine (mg/dL)	9.0 ± 3.71	11.9 ± 5.9	<0.001
Sodium (mmol/L)	136.6 ± 5.1	136.7 ± 5.9	0.626
Potassium (mmol/L)	5.1 ± 1.1	5.1 ± 1.1	0.913
Bicarbonate (mmol/L)	16.4 ± 4.4	15.2 ± 5.1	0.018
Calcium (mg/dL)	7.5 ± 1.1	7.6 ± 1.5	0.496
Phosphorus (mg/dL)	6.0 ± 1.9	6.7 ± 2.4	0.002
Albumin (g/dL)	3.4 ± 0.5	3.6 ± 0.6	<0.001
iPTH (pg/dL)	216.9 ± 157.5	260.2 ± 188.1	0.042
eGFR			
C-G	8.5 ± 4.2	6.7 ± 3.0	<0.001
Corrected C-G	8.6 ± 4.0	6.9 ± 2.8	<0.001
MDRD	6.9 ± 3.6	5.4 ± 2.9	<0.001
CKD-EPI	6.2 ± 3.5	4.8 ± 2.6	<0.001
Nankivell	2.0 ± 11.9	−2.2 ± 13.3	0.001
Reasons to start HD, *n* (%)			0.031
Fluid overload	97 (44.9)	60 (31.4)	
Uremia	104 (48.1)	119 (61.6)	
Hyperkalemia	11 (5.1)	5 (2.6)	
Metabolic acidosis	4 (1.9)	7 (3.7)	

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; C-G, Cockcroft–Gault; CHF, congestive heart failure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HD, hemodialysis; iPTH, intact parathyroid hormone; MDRD, Modification of Diet in Renal Disease.

Table 5. Comparisons of clinical and laboratory characteristics according to the urgency for hemodialysis

Characteristics	Clinic ($N = 242$)	ER ($N = 167$)	P
Age (y)	56.7 ± 14.3	61.3 ± 14.6	0.002
Male gender, *n* (%)	123 (50.8)	92 (55.1)	0.396
Weight (kg)	62.8 ± 11.5	63.9 ± 14.2	0.405
BMI (kg/m^2)	24.4 ± 11.2	24.1 ± 4.5	0.767
DM, *n* (%)	120 (49.8)	96 (57.8)	0.110
Systolic BP (mmHg)	151.1 ± 24.4	156.3 ± 26.6	0.043
Diastolic BP (mmHg)	81.8 ± 15.7	81.3 ± 17.0	0.758
CVD/CHF, *n* (%)	34 (14.0)	45 (26.9)	0.001
Hemoglobin (g/dL)	8.6 ± 1.6	8.4 ± 1.7	0.335
BUN (mg/dL)	92.5 ± 32.3	104.5 ± 98.3	0.131
Creatinine (mg/dL)	10.3 ± 4.7	10.4 ± 5.6	0.874
Sodium (mmol/L)	137.2 ± 5.2	136.1 ± 5.9	0.054
Potassium (mmol/L)	5.0 ± 0.9	5.3 ± 1.2	0.014
Bicarbonate (mmol/L)	16.8 ± 4.2	14.4 ± 5.2	<0.001
Calcium (mg/dL)	7.5 ± 1.1	7.3 ± 1.5	0.897
Phosphorus (mg/dL)	6.3 ± 2.0	6.4 ± 2.5	0.499
Albumin (g/dL)	3.6 ± 0.6	3.5 ± 0.5	0.472
iPTH (pg/dL)	239.7 ± 178.5	235.5 ± 167.8	0.845
eGFR			
C-G	7.7 ± 3.9	7.6 ± 3.7	0.728
Corrected C-G	7.9 ± 3.7	7.7 ± 3.4	0.538
MDRD	6.2 ± 3.4	6.3 ± 3.4	0.640
CKD-EPI	5.6 ± 3.2	5.6 ± 3.1	0.880
Nankivell	0.13 ± 12.19	0.06 ± 13.57	0.956
Reasons to start HD, *n* (%)			<0.001
Fluid overload	76 (31.4)	81 (48.5)	
Uremic symptoms	161 (66.5)	63 (37.7)	
Hyperkalemia	3 (1.2)	13 (7.8)	
Metabolic acidosis	2 (0.8)	10 (6.0)	

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; C-G, Cockcroft–Gault; CHF, congestive heart failure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ER, emergency room; HD, hemodialysis; iPTH, intact parathyroid hormone; MDRD, Modification of Diet in Renal Disease.

Discussion

In the IDEAL study, dialysis was planned at an eGFR of 5–7 mL/min in the late-start group; however, three-fourth of the patients could not delay the dialysis until this level because of various symptoms including uremia (72.7%), fluid overload (8.7%), malnutrition (1.6%), and hyperkalemia (1.2%), which results in dialysis initiation at a higher eGFR of 9.8 mL/min by the corrected Cockcroft–Gault equation and 7.2 mL/min by the MDRD equation [6]. Because most of our patients started HD based on uremic symptoms and fluid and electrolyte disturbances, it is reasonable to compare them with this late-start group in the IDEAL study. We found that our patients started dialysis at an eGFR of 7.8 mL/min by the corrected Cockcroft–Gault equation and 6.2 mL/min by the MDRD equation, which are lower than the corresponding eGFR in the IDEAL study by 2 mL/min. To exclude cases of early planned HD initiation completely, we separately evaluated the patients who started HD urgently in the ER. The eGFR of these patients were 7.7 mL/min by the corrected Cockcroft–Gault equation and 6.3 mL/min by the MDRD equation, which was similar to the eGFRs of the total patients. The difference of eGFR between our patients and the IDEAL patients may indicate that either our patients develop symptoms at a lower GFR or report symptoms later, as compared with patients in the West.

Fluid overload accounted for 38.4% of HD initiation, as compared with 8.7% in the IDEAL study. This suggests that sodium intake of our patients may be higher than that of Western patients because of a higher content of sodium in Korean food.

In addition, we evaluated the eGFR according to different clinical situations: patients with DM versus without DM and outpatient clinic patients versus ER patients. DM patients started HD at a significantly higher eGFR than non-DM patients, which may be due to the higher proportion of fluid overload in DM (44.9%) than that in non-DM patients (31.4%). In our experience, it is more difficult to tolerate fluid overload than uremic symptoms. It is possible that the higher eGFR in DM patients should contribute to the less-severe metabolic acidosis, hyperphosphatemia, and hyperparathyroidism in these patients. Accordingly, the United States Renal Data System (USRDS) data showed that the early initiation of dialysis is associated with the presence of DM [14].

The patients who present to the ER are usually in more urgent need of HD than clinic patients. Therefore, it is conceivable that ER patients may have lower eGFR than the clinic patients. However, we found that both groups were comparable in eGFR. ER patients were older and had more disturbances of fluid balance, serum potassium, and serum bicarbonate levels, as compared to clinic patients, which might explain the more urgent need for dialysis in ER patients. The higher incidence of CVDs/CHF in DM and ER groups should have contributed to the higher proportion of volume overload as a reason for dialysis start in these groups.

Regarding the equation that best defines the eGFR value at HD initiation, our finding suggests that the corrected Cockcroft–Gault equation, which was adopted in the IDEAL study, may best fit the purpose because of its good correlations with CKD-specific complications and the smallest dispersion (coefficient variation). In addition, our data indicate that the Nankivell equations that were originally developed for kidney transplants should not be used in CKD patients given its high dispersion and irrelevance to CKD-specific complications. The poor performance of the Nankivell equation may be explained by its development from the transplant population and the inclusion of blood urea nitrogen as one of the variables unlike the other equations [13].

A limitation of this study is that we were not successful in defining the best eGFR in the subgroups such as DM or ER groups because the reduced sample sizes of the subgroups were not big enough to make the statistical analysis adequately powered. Another limitation is that we do not have data on GFR using 24-hour urine Cr clearance or radioisotope renal scans to compare with each eGFR. A larger prospective study with the actual measurement of GFR is required to better evaluate the utility of various eGFRs at the time of HD initiation.

In summary, we showed that the mean eGFR at HD start was significantly different across the equations. The mean eGFR ranged between 5.6 and 7.8 mL/min according to the 4 eGFR equations, excluding the Nankivell equation. The Nankivell equation was not suitable for CKD patients. The corrected Cockcroft–Gault, the MDRD, and the CKD-EPI equations were well correlated with all CKD-specific complications. The mean eGFR by the corrected Cockcroft–Gault equation showed the lowest dispersion among all equations. DM patients started HD at a higher eGFR than non-DM patients, and the patients who underwent emergent HD in ER did not differ in eGFR, as compared with the nonemergent patients. This study was not designed to evaluate the optimal timing of dialysis initiation; hence, the eGFR in this study is not an indication for the initiation of dialysis.

This study is potentially a valuable reference in the management of CKD patients and in the design of the future studies for the optimal timing of dialysis initiation.

Conflicts of interest

All authors have no conflicts of interest to declare.

Author contributions

Dr. Shin had full access to the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis were done by Drs. Shin and Lee; critical revision of the manuscript for important intellectual content was carried out by all authors and administrative, technical, and material support was also provided by everyone. Study supervision was done by Drs. Shin and Kim (KHS). All authors have contributed to the paper.

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