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ORIGINAL ARTICLE

Progression of stages 3b–5 chronic kidney disease—Preliminary results of Taiwan National Pre-ESRD Disease Management Program in Southern Taiwan

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KEYWORDS
chronic kidney disease;
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Background/Purpose: The outcomes and their predictors, and rates of estimated glomerular filtration rate (eGFR) changes among Taiwanese, an ethnic Chinese population, with chronic kidney disease (CKD) stages 3b–5, enrolled in a nationwide pre-end-stage renal disease (pre-ESRD) management program that have not been previously reported.
Methods: This study focused on a cohort of patients enrolled in the Taiwan's pre-ESRD disease management program from Southern Taiwan, including 4061 CKD 3b–5 patients who received more than 12 weeks of follow-up from 2007 to 2010. The decline rates of eGFR, outcomes, and the predictors of initiating dialysis were analyzed.
Results: The study participants consisted of patients who were 70.1 ± 12.3 years old, of whom 56.4% were male, 46.3% were diabetic, and 72.1% were hypertensive. The mean annual eGFR changes were 0.47 ± 0.42 mL/min/1.73 m^2/year, −1.27 ± 0.32 mL/min/1.73 m^2/year, and −2.69 ± 0.39 mL/min/1.73 m^2/year for stages 3b, 4, and 5, respectively; however, more rapid declines were noted in diabetic patients. The Kaplan–Meier analyses revealed that the probabilities of patients remaining alive and free of dialysis treatment for CKD stage 3b, 4, and 5 without or with diabetes were 89.46% versus 84.65%, 79.88% versus 55.68%, and 34.42% versus

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9.64%, respectively, during 42 months of follow-up. Male gender, diabetes, lower baseline eGFR, higher systolic blood pressure, lower hematocrit, and albumin levels were the significant risk factors for initiating dialysis.
Conclusion: Even though we cannot conclude with certainty that the Taiwan pre-ESRD disease management program is beneficial in slowing the progression of CKD stages 3b—5, our preliminary results seem to suggest this trend. Furthermore, the program may be improved by integrating it with other programs, such as those on diabetes and hypertension, thus making it a more patient-centered, multidisciplinary program.

Introduction

Treatments for end-stage renal disease (ESRD) are costly and represent a growing burden on healthcare systems; therefore, the adequate management of chronic kidney diseases (CKDs) to slow the incidence and progression of this condition is of considerable interest.[1–3] This is especially true in Taiwan, which has a universal health insurance system [Taiwan National Health Insurance (Taiwan NHI)] and the highest prevalence and incidence of ESRD in the world.[4] According to the Taiwan Bureau of National Health Insurance (TBNHI), the costs associated with ESRD amounted to US$1.17 billion in 2009, which is approximately 8% of the total annual health insurance expenditure.[5]

CKD is also associated with high mortality and morbidity, which are mainly associated with cardiovascular diseases (CVDs).[6] Slowing the progression of CKD can reduce complications and improve both survival and quality of life of patients,[7–9] and this might be achieved with the development and application of disease management programs.[10–16] Recently, Jia et al[17] showed the beneficial effects of a multidimensional education program held for 302 Chinese patients with CKD stages 3b—5. However, relatively few studies have reported the results of national disease management programs that focus on CKD.

Taiwan's pre-ESRD disease management program was established in November 2006 by the TBNHI,[18] and combines nephrology, nursing, and dietary counseling, along with—if necessary—counseling by professionals from other disciplines, such as cardiology. The content of the program was standardized in accordance with the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative guidelines. Wu et al[19] and Chen et al[20] reported that this program has managed to decrease the incidence of dialysis and reduce mortality, although both studies were based on small proportions of the patients enrolled in the program, and to date there remains limited knowledge about the results for large cohorts of patients enrolled in national pre-ESRD programs. It is worth noting that the risk factors for poor patient outcomes under a disease management program may not be the same as those for patients not enrolled in such a program. In this study, we obtained the relevant knowledge related to the progression from CKD to ESRD in the pre-ESRD disease management program from Taiwan's NHI database. The aims of this study are to investigate changes in the estimated glomerular filtration rate (eGFR) and the predictors of initiating dialysis therapy among patients with CKD stages 3b—5, enrolled in Taiwan's pre-ESRD disease management program.

Patients and methods

Taiwan pre-ESRD disease management program

The program's goals are to decrease the incidence of ESRD, as well as the morbidity and mortality of CKD. Specifically, the program aims to improve the early detection rate of CKD, to facilitate identification of patients at high risk of progressing to ESRD or pre-ESRD death, and to promote evidence-based interventions. In addition, the program also aims to help pre-ESRD patients to initiate dialysis and to reduce both the use of emergency care and hospitalization costs.[19–21] The program is provided by a multidisciplinary team, including nephrologists, renal nurses, and dieticians, to care for patients with different CKD stages, as measured by a specific function of the kidneys, known as the Modification of Diet in Renal Disease eGFR (calculated by the Modification of Diet in Renal Disease abbreviated equation).[22] This initiative includes the control of blood pressure (BP), sugar, and lipid by the use of counseling and medication, prescription of a low protein diet, selection of appropriate dialysis mode, early preparation of dialysis access, and outpatient dialysis treatment.

Patients were enrolled in the pre-ESRD disease management program if they met the entry criteria and were willing to participate. At the initial visits, the nephrologists developed a patient care plan according to the Kidney Disease Outcomes Quality Initiative guidelines,[23] performed renal function tests, and provided basic knowledge about CKD and its treatment. The diagnosis of CKD was confirmed by at least two eGFR determinations, the interval between two data must be $\geq$28 days, and the care nephrologists were responsible for excluding patients with acute kidney injury (AKI) prior to registering. Specific counseling was performed when registering the patient and at the subsequent visits, based on the needs of individual patients during the follow-up period. Generally, patients with stages 3b, 4, and 5 CKD were followed up every 12 weeks, 8 weeks, and 4 weeks, respectively, or when necessary. The blood tests were performed every 12 weeks or when necessary. Enrolled patients were followed up until death, or initialing long-term dialysis, or loss of follow-up. Clinical characteristics, such as age, sex, underlying diseases, comorbidities, BP, and laboratory data [including serum albumin, creatinine, and hematocrit (Hct) levels, and eGFR], were submitted to the TBNHI via a secure virtual private network every 12 weeks. The patients' fasting blood lipid, uric acid, sodium, potassium, calcium, phosphate, sugar, and

hemoglobin A1C levels were checked when registering and at least once every year. It should be noted that these data were used for patient care and counseling, but not submitted to the TBNHI. Every patient whose information was submitted successfully to the TBNHI and satisfied the related requirements was reimbursed for this program. In addition, the patients' details when reaching the endpoint of the program were also submitted to the TBNHI. With regard to individual patients, the interval between every reimbursement should be more than 77 days, except for the reimbursement on reaching the endpoint.

Study patients and data extraction

The study patients were drawn from a multicenter cohort drawn from 27 predialysis clinics (i.e., nephrologists) or general/university-affiliated hospitals contracted with the TBNHI from 2007 to 2010 in Southern Taiwan, which contains two cities and two counties, and covers 3.2 million residents. Demographic and laboratory data were collected from the patients' data submitted to the TBNHI via a secure virtual private network. CKD stage was determined following the method used by the National Kidney Foundation of the United States. At the time of entry, eGFRs of 30–45 mL/min/1.73 m^2, 29–15 mL/min/1.73 m^2, and <15 mL/min/1.73 m^2 were classified as CKD stages 3b, 4, and 5, respectively. The observation period for each patient was defined as starting immediately after the registered measurement of eGFR satisfying the above criteria (designated as the index date), and until ESRD, or predialysis death, or loss of follow-up. As there is no consistent definition for "loss of follow-up" with regard to the Taiwan pre-ESRD program during the study period, we arbitrarily defined this as not uploading data more than 1 year prior to the end of the current study period (December 30, 2010) in patients who did not develop ESRD or suffer a pre-ESRD death.

Patients who had enrolled in a pre-ESRD program were identified as those who had submitted medical claims that included at least one of the following procedure payment codes, namely, P3402C, P3403C, P3404C, and P3405C, during the period from 2007 to 2010. ESRD was defined as initiation of renal replacement therapy, that is, chronic dialysis or kidney transplantation. However, none of the enrolled patients received preemptive kidney transplantation in Southern Taiwan during the study period. The timing to initiate renal replacement therapy follows the regulations set by the TBNHI, including creatinine clearance <15 mL/min or serum Cr >6 mg/dl, plus any of the following conditions: (1) blood urea nitrogen >100 mg/dl; (2) refractory heart failure, lung edema, metabolic acidosis, or hyperkalemia; (3) pericarditis; (4) bleeding tendency; (5) uremic encephalopathy or neuropathy; or (6) uncontrolled nausea, vomiting, or cachexia. Using the TBNHI's pre-ESRD database enabled this study to obtain data on all the patients who were enrolled in the pre-ESRD program and had an estimated GFR of <45 mL/min/1.73 m^2 in Southern Taiwan. Fig. 1 shows the derivation of the cohort based on the available records. Generally, a registered eGFR <45 mL/min/1.73 m^2 per patient was considered the index result from which we started the follow-up analysis. To ensure the appropriate inclusion of CKD patients with adequate follow-up for the analysis of interest, we excluded patients who had less than two eGFR results after the first registration (n = 752). Patients with a second set of eGFR data submitted to the TBNHI should have received multidisciplinary care from this program for at least 12 weeks. When establishing the study cohort, those patients with possible AKI, who were arbitrarily defined as patients who had differences between the second eGFR data and registered eGFR data (obtained with an interval that ranged from 12 weeks to 24 weeks) of more than 25%, or 50% of the registered eGFR every 12 weeks {calculated by the equation: [12× change of eGFR (%)]/the interval between the second eGFR and registered eGFR (weeks)}, in patients enrolled with CKD stage 3b or stages 4–5, or patients who commenced chronic hemodialysis therapy within 12 weeks after enrollment, were also excluded to avoid the confounding of AKI when enrolled (n = 51). Although some of these 51 patients may have been CKD patients with rapid progression, this would not significantly change the results of the present study because of the small number of affected patients. In addition, patients whose second visit and eGFR data were more than 24 weeks after the registration were arbitrarily defined as possibly noncompliant patients, and were also excluded from the final analyses (n = 95). The baseline demographic data and clinical characteristics of the excluded patients were compared with those included in the follow-up group according to CKD stages, and no significant differences were found. Finally, during a cumulative follow-up of 7213 patient-years in this cohort, there were 558 dialysis initiations (484 hemodialysis and 74 peritoneal dialysis), 94 deaths, and 795 loss of follow-up (Fig. 1). The variables used in the analyses for initiating dialysis included demographics, such as age and sex, as well as various laboratory variables, such as Hct, serum albumin and creatinine, BP, and comorbidities, such as diabetes, CVD, and hypertension. Urine protein loss data were not recorded in the early phase (from year 2007 to 2010) of this program.

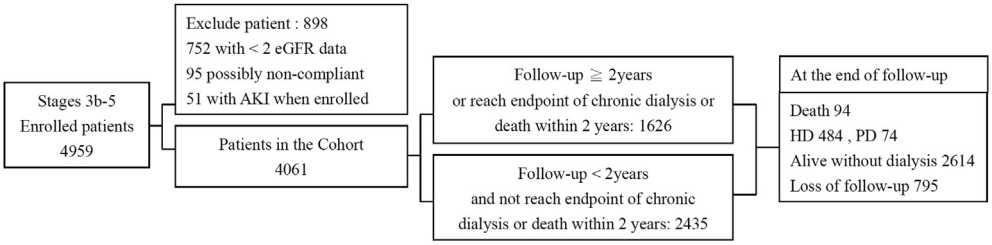

Figure 1 Flow chart of the derivation of study cohort. HD = hemodialysis; PD = peritoneal dialysis.

Table 1 Patient characteristics by baseline stage of CKD.[a]

Variables	All	Stage 3b	Stage 4	Stage 5	*p*
	n = 4061	*n* = 1040	*n* = 1773	*n* = 1248	
		(26%)	(44%)	(30%)	
Age (y)	70.1 ± 12.3	70.5 ± 12.0	70.9 ± 12.3	68.8 ± 12.5	0.001
Sex					
Male	56.4	71.3	56.7	43.9	<0.001
Past medical history					
Diabetes	46.3	42.0	50.1	44.6	<0.001
Hypertension	72.1	69.2	73.0	73.2	0.006
Cardiovascular diseases	12.7	12.9	13.4	11.5	0.316
Systolic BP (mmHg)	137.7 ± 20.4	135.5 ± 20.0	137.3 ± 20.3	139.9 ± 20.7	<0.001
Diastolic BP (mmHg)	76.2 ± 12.2	76.7 ± 12.5	75.9 ± 12.2	76.2 ± 12.0	0.462
Hematocrit	32.9 ± 6.1	37.7 ± 5.5	33.17 ± 5.2	28.4 ± 4.7	<0.001
Serum albumin (g/dL)	3.9 ± 0.6	4.0 ± 0.5	3.8 ± 0.6	3.8 ± 0.6	<0.001
Serum creatinine (mg/dL)	3.4 ± 2.0	1.8 ± 0.3	2.8 ± 0.9	5.7 ± 1.9	<0.001
eGFR (mL/min/1.73 m^2)	22.4 ± 11.0	37.3 ± 4.4	22.5 ± 4.3	10.1 ± 2.9	<0.001
Follow-up (mo)	15.0 ± 10.9	12.5 ± 7.5	17.9 ± 12.1	13.0 ± 10.5	<0.01

Data are expressed as mean ± standard deviation or %, unless otherwise indicated.
ANOVA = analysis of variance; BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
[a] Statistical tests are done by Chi-square test and one-way ANOVA to examine categorical and continuous variables, respectively, with $p < 0.05$ indicating statistical significance.

Statistical analyses

Data were expressed as means (±SD or SE) or percentages (*n*). We tested for differences using Chi-square tests and one-way analysis of variance to examine the categorical and continuous variables, respectively, with $p < 0.05$ indicating statistical significance. The associations of presumed risk factors with initiating dialysis were analyzed by the Cox proportional hazards model. The proportional hazards assumption was checked using log-minus-log plots, and accepted as not violated. To calculate the rate of eGFR decline, the first registered and latest available serum creatinine data were used. Statistical analysis was conducted using the JMP Base, version 9.0.0 (SAS Campus Drive, Cary, NC, USA).

Results

Baseline demographic characteristics

A total of 4061 patients with a mean age of 70.1 were enrolled in the program and were available for analysis. The median follow-up was 12 months (25^{th}–75^{th} percentile, 6–20 months). Table 1 gives the baseline characteristics of the population cohort. At the start of the study, 1040 (26%) patients were at stage 3b, 1773 (44%) patients were at stage 4, and 1248 (31%) patients were at stage 5. There were slightly more male patients than female ones (56.4%). Of the total patients, 46.3% had diabetes, 72.1% had hypertension, and 12.7% had CVD. More male patients were at stage 3b, but the percentages become more balanced at stages 4–5. Although statistically significant, there was no substantial difference in the prevalence of hypertension across the three CKD stages. Patients with stage 3b had significantly lower systolic BP, and higher Hct and serum albumin levels when compared with patients with stages 4 and 5 CKD.

Patient's outcomes during follow-up

Among the 4061 patients, 1626 patients received follow-up ≥2 years or reached endpoints of ESRD or predialysis death within 2 years. There were no significant differences in the baseline characteristics between these 1626 patients and the rest of those in each subgroup of the cohort (Table S1 in the supplementary material online). Fig. 2A shows the 2-year cumulative outcomes of the cohort ($n = 1626$). It can be seen that 0.2%, 17.5%, and 64.7% of the patients progressed to ESRD, necessitating dialysis treatment for those with baseline CKD stages 3b, 4, and 5, respectively. The percentages of patients who had improved CKD staging or stayed at the baseline stage were 75.1%, 54.5%, and 29.4% for stages CKD 3b, 4, and 5, respectively. Fig. 2B demonstrates the patient outcomes of the whole cohort by months and grouped by baseline stages of CKD ($n = 4061$).

Table 2 summarizes the annual rate of change in annual eGFR (mL/min/1.73 m^2/year) and clinical outcomes for the 4061 patients by baseline CKD stages. The mean annual changes in eGFR were 0.47 mL/min/1.73 m^2, −1.27 mL/min/1.73 m^2, and −2.69 mL/min/1.73 m^2 for stages 3b, 4, and 5, respectively. The eGFR changes were greater for patients with diabetes compared to those without diabetes among CKD stages 3b, 4, and 5, being −2.06 mL/min/1.73 m^2 versus 2.29 mL/min/1.73 m^2, −2.45 mL/min/1.73 m^2 versus −0.11 mL/min/1.73 m^2, and −3.77 mL/min/1.73 m^2 versus −1.70 mL/min/1.73 m^2/year, respectively.

Fig. 3 shows the mean rate of decline in annual eGFR. The annual eGFRs skewed to the left, with a fast declining slope for patients with diabetes. In addition, the cohort with diabetes had a mean eGFR rate of decline of −1.91 mL/min/1.73 m^2/year, with a median of −2 mL/min/1.73 m^2/year, and the 25^{th}–75^{th} percentile declined from −5.0 to 0. By comparison, the patients without diabetes had a mean eGFR rate of decline of −0.31 mL/min/1.73 m^2/year, with a

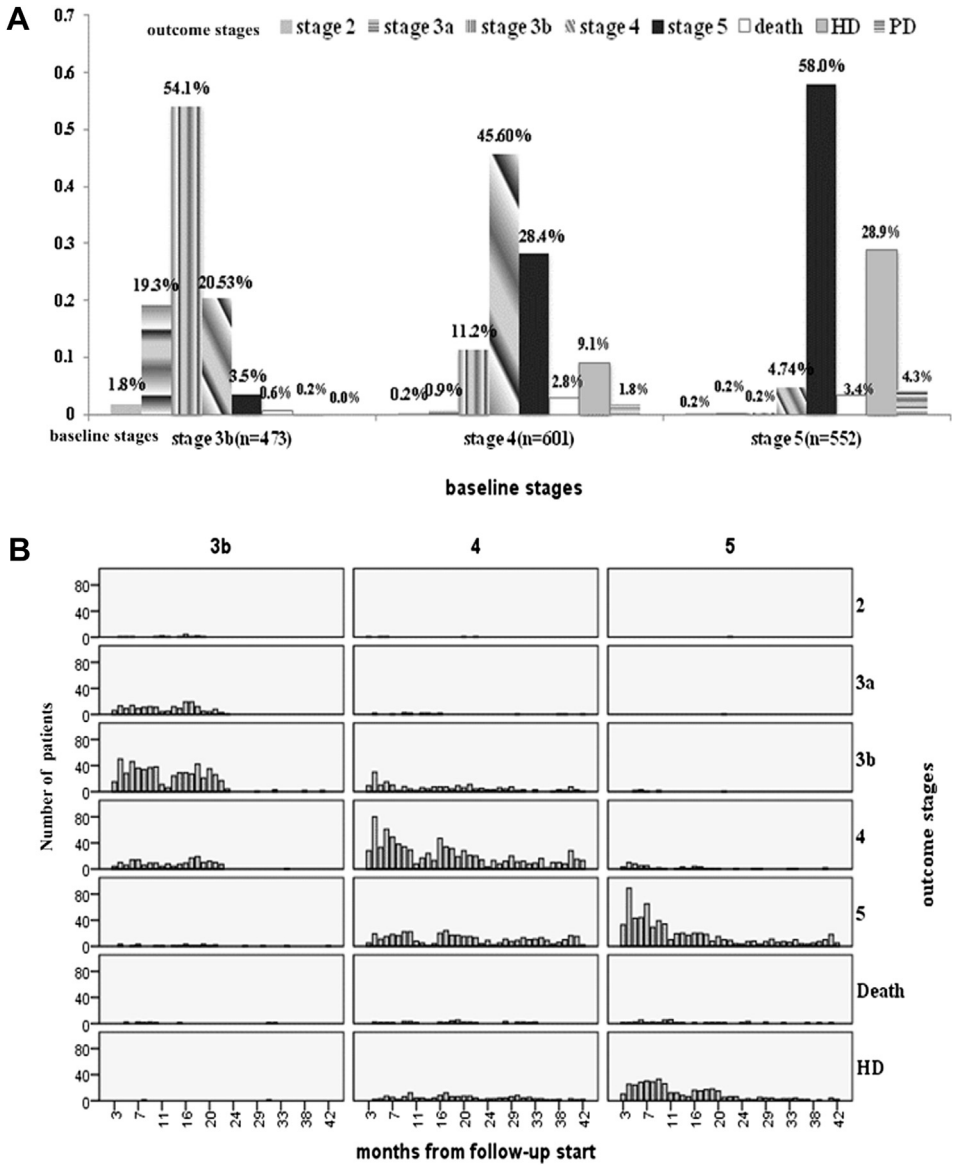

Figure 2 (A) Two-year cumulative outcomes grouped by baseline stages of CKD (n = 1626) and (B) the patient outcomes of the whole cohort by months and grouped by baseline stages of (n = 4061). CKD = chronic kidney disease; HD = hemodialysis; PD = peritoneal dialysis.

median of −1 mL/min/1.73 m^2/year, and the 25^{th}–75^{th} percentile declined from −3.0 mL/min/1.73 m^2 to 1 mL/min/1.73 m^2/year.

With regard to the 95 patients with possible noncompliance, "loss of follow-up" was noted in 50 (52.6%) patients, which was a greater proportion than that seen in the overall study population (19.6%, 795 among 4061 patients), suggesting poor adherence to the program in these patients. The baseline characteristics of these patients are shown in Table S2 (see the supplementary material online), and it can be seen that there were no statistically significant differences when comparing the rates of eGFR changes of these patients with those of the corresponding groups in the study population (Table S3 in the supplementary material online), although the decline rate of eGFR for the stage 4 possibly noncompliant patients tended to be more rapid.

Fig. 4 shows the Kaplan–Meier curves for nondialysis treatment and being alive in patients among CKD stages 3b–5 with and without diabetes. The probabilities of patients remaining alive and free of dialysis treatment for CKD stages 3b, 4, and 5 without or with diabetes were 89.46% versus 84.65%, 79.88% versus 55.68%, 34.42% versus 9.64%, respectively, during 42 months of follow-up (all $p < 0.05$ except for patients with CKD stage3b). Furthermore, the probability of patients remaining alive and free of dialysis was significantly different only between CKD stage 4 patients with or without hypertension (Fig. 5). The Kaplan–Meier results analyzing the effects of the presence of diabetes or hypertension on the outcome of either nonpredialysis death or not reaching ESRD are shown in Figs. S1–4 (see the supplementary material online). It can be seen that diabetes or hypertension had no significant impacts on the outcome of pre-ESRD death, which might be

Table 2 Clinical outcomes of patients by baseline CKD stages.[a]

Variables	All	Stage 3b	Stage 4	Stage 5	*p*
	n = 4061	*n* = 1040	*n* = 1773	*n* = 1248	
	100%	25%	44%	31%	
eGFR change (mL/min/1.73 m^2/y)					
With diabetes		−2.06 ± 0.73	−2.45 ± 0.51	−3.77 ± 0.65	0.158
Without diabetes		2.29 ± 0.49	−0.11 ± 0.4	−1.70 ± 0.46	<0.001
All		0.47 ± 0.42	−1.27 ± 0.32	−2.69 ± 0.39	<0.001
Dialysis treatment	13.7 (558)	0.2 (2)	8.9 (158)	31.9 (398)	<0.001
Dialysis/per 100 patient-years	7.94	0.13	4.53	20.31	<0.001
Death	2 (94)	1 (11)	2 (41)	3 (42)	<0.001
Death/per 100 patient-years	1.34	0.70	1.18	2.14	<0.001

Data are expressed as means ± standard error or % (*n*).
ANOVA = analysis if variance; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
[a] Statistical tests are done by Chi-square test and one-way ANOVA to examine categorical and continuous variables, respectively, with $p < 0.05$ indicating statistical significance.

because only a small proportion of the patients had pre-ESRD death in this cohort.

Estimate the proportion of patients with CKD stages 3b−5 participating in the pre-ESRD program

Table S4 in the supplementary material online shows the estimated number (proportion) of CKD stages 3b−5 patients participating in the pre-ESRD program in Southern Taiwan. From January 2012 to December 2012, the number (proportion) of incident dialysis patients in Southern Taiwan were 8519 patients, among whom 3563 (42%) had joined and had ≥2 visits to the pre-ESRD program prior to initiating chronic dialysis (in-house analysis of the TBNHI database).

Predictors for dialysis treatment

The outcome of interest in Table 3 is ESRD, which is defined as initiation of dialysis, with the time intervals of follow-up being censored when patients had pre-ESRD mortality or a loss of follow-up prior to ESRD. Table 3 shows the baseline characteristics that are significantly associated with the risk for initiating dialysis treatment, as obtained by the multivariate Cox proportional analysis. Lower baseline eGFR, male gender, higher systolic BP, lower Hct, and lower albumin levels, and having diabetes were all independent and significant risk factors for reaching dialysis treatment in CKD stages 3b−5 patients. However, diastolic BP and the presence of CVD were not significantly associated with the risk of dialysis. When multivariate Cox analyses were performed for different baseline CKD stages, the above risk factors were still independently associated with reaching ESRD in stages 4 and 5 patients, but not in patients with CKD stage 3b, except for albumin, which may be because only a small proportion of CKD stage 3b patients progressed to ESRD in the current study.

Discussion

This study analyzed the status of CKD progression in a multicenter cohort who enrolled in a pre-ESRD disease

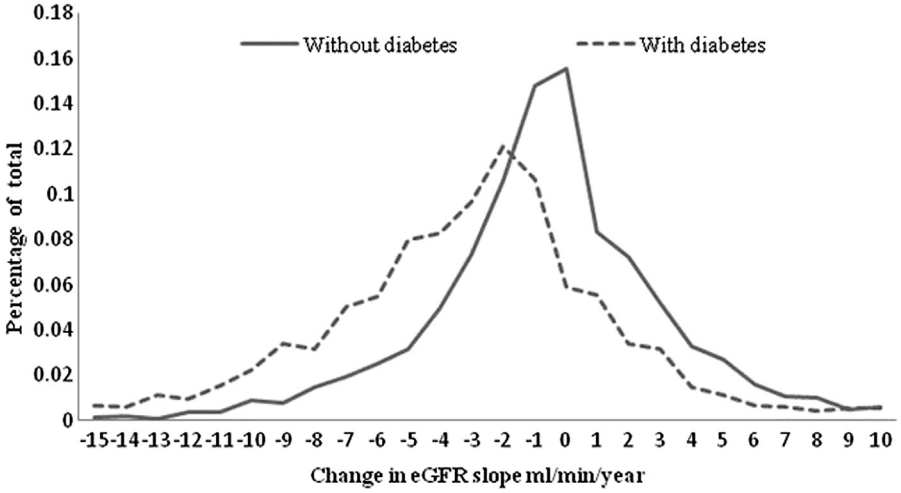

Figure 3 The distribution of annual estimated glomerular filtration rate (eGFR) changes for patients with and without diabetes. The eGFR decline rate is more rapid in patients with diabetes, and patients with diabetes have higher percentages of rapid eGFR decline rates.

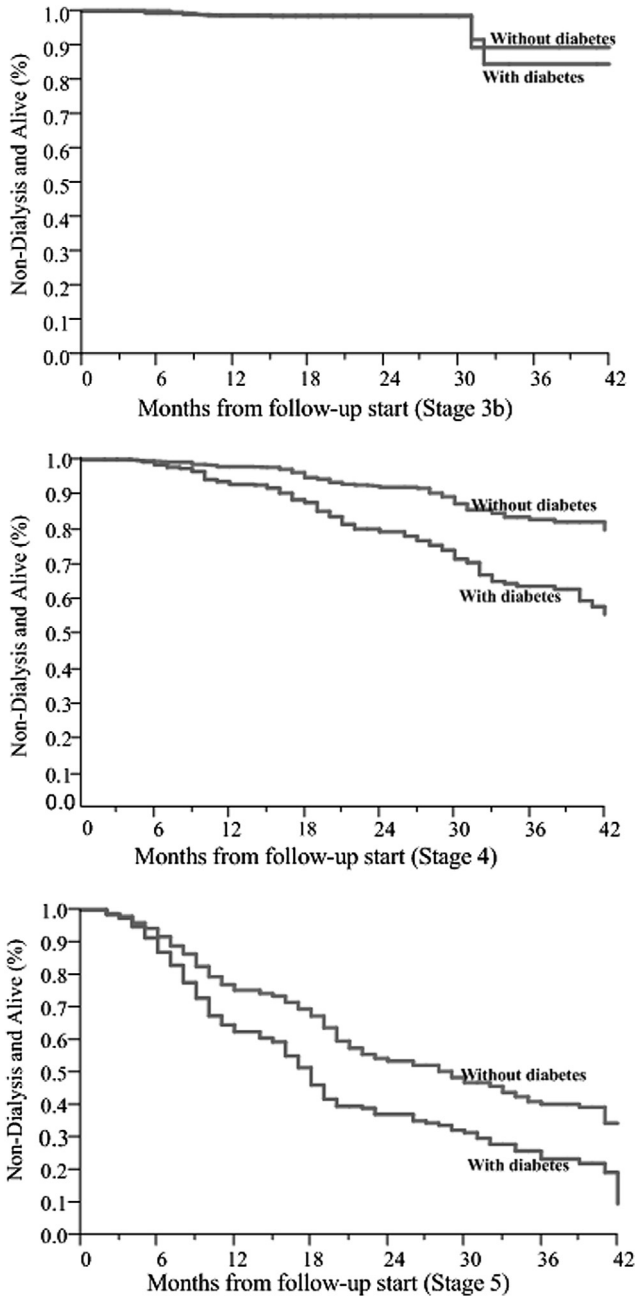

Figure 4 The Kaplan–Meier curves show the probability of non-dialysis and being alive for chronic kidney disease (CKD) patients with or without diabetes in CKD stage 3b (log-rank test indicates $p = 0.92$ between the two groups, $n = 1040$; upper panel), in CKD stage 4 (log-rank test indicates $p < 0.001$ between the two groups, $n = 1773$; middle panel), and in CKD stage 5 (log-rank test indicates $p < 0.001$ between the two groups, $n = 1248$; lower panel).

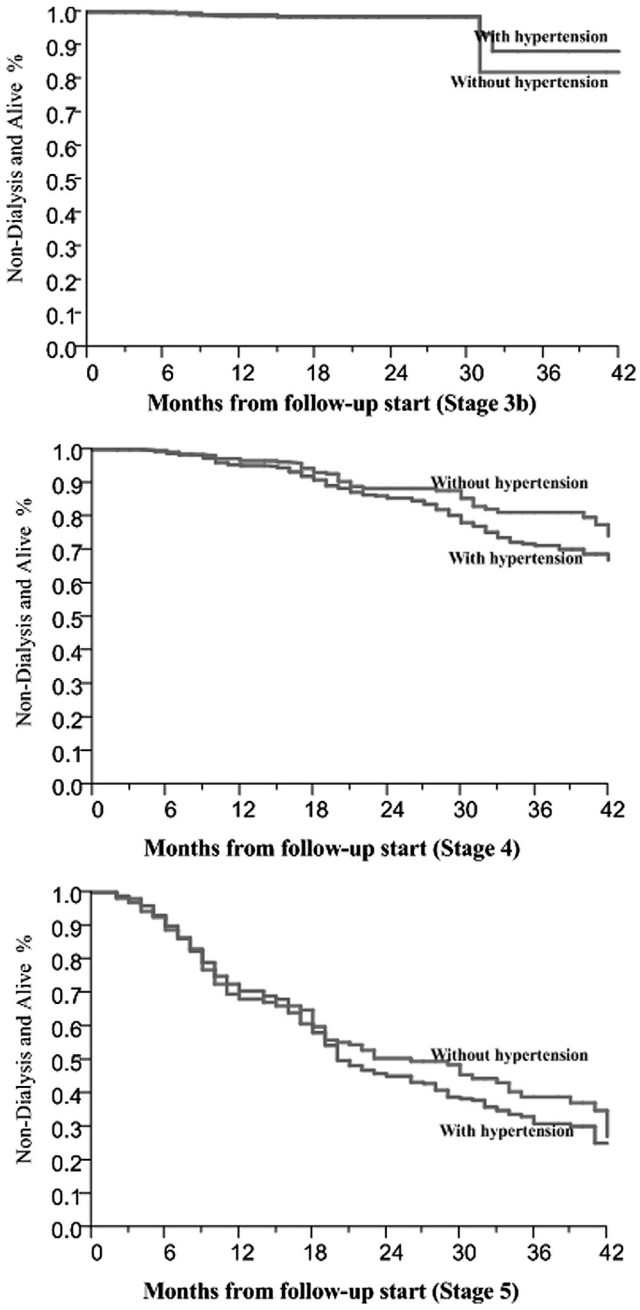

Figure 5 The Kaplan–Meier curves show the probability of nondialysis and being alive of chronic kidney disease (CKD) patients with or without hypertension in CKD stage 3b (log-rank test indicates $p = 0.846$ between the two groups, $n = 1040$; upper panel), in CKD stage 4 (log-rank test indicates $p = 0.014$ between the two groups, $n = 1773$; middle panel), and in CKD stage 5 (log-rank test indicates $p = 0.376$ between the two groups, $n = 1248$; lower panel).

management program in Southern Taiwan over a period of 4 years, with a median follow-up of 12 months. The mean rates of eGFR change were 2.29 mL/min/1.73 m^2/year, −0.11 mL/min/1.73 m^2/year, and −1.70 mL/min/1.73 m^2/year for nondiabetic patients with CKD stages 3b, 4, and 5, respectively, and were −2.06 mL/min/1.73 m^2/year, −2.45 mL/min/1.73 m^2/year, and −3.77 mL/min/1.73 m^2/year for diabetic patients. Because the Taiwan pre-ESRD disease management program is a nationwide policy, rather than a research project, it was unethical to enroll patients as part of a control group to study the beneficial effects of this program. However, Chiu et al[24] recruited 433 Taiwanese with CKD from a medical center prior to when this pre-ESRD disease management program was initiated, and the results

Table 3 Multivariable Cox regression model for the effects of the baseline variables on the risk of dialysis treatment ($n = 4061$).[a]

Variables	Stages 3b–5 ($n = 4061$)			Stage 3b ($n = 1040$)			Stage 4 ($n = 1773$)			Stage 5 ($n = 1248$)		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Baseline eGFR (mL/min/1.73 m^2)	0.88	0.86–0.89	<0.001	1.06	0.93–1.21	0.39	0.93	0.89–0.96	<0.001	0.85	0.82–0.88	<0.001
Age, per year increase	0.99	0.98–0.99	0.026	1.05	0.99–1.11	0.1	0.98	0.97–0.99	<0.001	0.99	0.99–1.01	0.86
Sex, male vs. female	1.69	1.44–1.99	<0.001	0.91	0.23–4.16	0.9	1.75	1.30–2.34	<0.001	1.73	1.42–2.11	<0.001
Systolic BP, per mmHg increase	1.01	1.01–1.02	<0.001	1.01	0.98–1.04	0.43	1.02	1.01–1.02	<0.001	1.01	1.00–1.01	0.009
Hematocrit (Hct), per %	0.96	0.94–0.97	<0.001	1.06	0.95–1.20	0.27	0.93	0.91–0.96	<0.001	0.97	0.95–0.99	0.005
Albumin, per g/dL	0.53	0.46–0.60	<0.001	0.13	0.05–0.35	<0.001	0.4	0.32–0.50	<0.001	0.63	0.53–0.74	<0.001
Diabetes, with vs. without	1.7	1.45–2.01	<0.001	1.42	0.39–4.95	0.58	1.98	1.47–2.69	<0.001	1.65	1.36–2.01	<0.001

BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio.

[a] Statistical tests are done by multivariable Cox regression to examine variables, respectively, with $p < 0.05$ indicating statistical significance. Diastolic BP, and the presence of CVD are not significantly associated the risk of dialysis.

showed an annual eGFR change of −2.05 mL/min/1.73 m^2/year, −3.77 mL/min/1.73 m^2/year, and −2.83 mL/min/1.73 m^2/year in Taiwanese participants without diabetes with CKD stages 3b, 4 and 5, respectively, and of −5.38 mL/min/1.73 m^2/year, −4.98 mL/min/1.73 m^2/year, and −5.10 mL/min/1.73 m^2/year for patients with diabetes. In addition, Hou et al[25] showed an annual GFR decline of −3.2 mL/min to −5 mL/min in Chinese patients without diabetes with stage 4 CKD. The eGFR declining rates for our study cohort were slower than those reported by Chiu et al[24] and Hou et al[25]; furthermore, the 2-year cumulative rate of reaching ESRD or pre-ESRD death was also lower (Fig. 2) than that seen for the patients in Chiu et al's[24] study. Although it would difficult to conclude that rates are slower with the program without making any direct comparisons with a historical or control cohort, our data suggest that there are some beneficial effects related to the Taiwan pre-ESRD disease management program with regard to the progression of patients with stages 3b–5 CKD. This tentative conclusion is consistent with the results of recent studies by Wu et al[19] and Chen et al,[20] which showed that the Taiwan pre-ESRD disease management program can decrease the incidence of dialysis and reduce mortality, by comparing selected patients enrolled in the program with those who were not enrolled in it. Furthermore, based on Fig. 2A, there were significant proportions of stage reversal—for example, from stage 3b to stage 3a (19.3%) and from stage 4 to stage 3b (11.2%)—in the current study. Because we excluded patients with possible AKI when enrolling, it is unlikely that the stage reversal could be explained by this cohort being contaminated by AKI patients. The findings that referral to a nephrology clinic with multidisciplinary care led not only to arresting or slowing the progression of CKD, but also to regression and improvement in a certain proportion of patients in the current study, are consistent with the results of previous studies conducted by Taskapan et al,[26] Jones et al,[2] and Zhang et al.[27] The reasons for these beneficial effects could be multifactorial, such as changes in lifestyle, avoiding nephrotoxins,[28] improving dietary habits, and having a positive attitude and greater compliance with medication regimens. To improve the allocation of limited healthcare resources, different strategies are required for each patient's follow-up based on the probability of progression. The risk factors associated with the need for dialysis therapy in our cohort were male gender, lower baseline eGFR, higher systolic BP, having diabetes, and lower Hct levels. Aging was protective of dialysis therapy in the current study, consistent with the data reported in the literature.[29,30] We speculate that this might be because aging patients were more compliant with regard to the suggestions of this program. Nevertheless, the risk factors identified in the current study should be taken into account when developing "the probability of reaching the ESRD score" to identify the patients in the CKD population who are at high risk of accelerated renal function loss, thus enabling the integration of a risk prediction tool as an intelligent clinical decision support to aid in outpatient renal care.[16,30,31]

In this cohort, patients with diabetes had an estimated 1.70-fold greater chance of requiring dialysis treatment compared to those without diabetes. The probability of patients remaining alive and not requiring dialysis treatment for CKD stages 4 and 5 was also higher for those without diabetes than those with it. Many countries have identified diabetes as an independent risk factor for dialysis treatment.[4,32] Because progression of CKD to ESRD is a continuous process, a loss in renal function in CKD patients with diabetes is a significant cause of accelerated declines in eGFR,[24] and of the increased prevalence of ESRD in Taiwan. Diabetes affects 6.2–8% of the Taiwanese population aged over 40 years, and with the aid of NHI coverage such individuals have access to healthcare, thus increasing of the incidence of diabetic nephropathy,[33] with fewer such patients dying from other complications.[34] Among CKD stages 3b–5, patients with diabetes thus serve as a pointed reminder of the importance of the aggressive management of diabetes,[35,36] its complications, and the associated risk

factors for progressive loss of eGFR, and the eventual need for dialysis.[37] The results also reinforce the importance of and need for the greater involvement of endocrinologists and diabetes nurses in the care of patients with CKD stages 4 and 5 who have diabetes, rather than leaving such work to nephrologists, who may or may not be providing complete care.[38–40]

The enrollment rate and adherence of the pre-ESRD program are also important issues. From January 2012 to December 2012, the proportion of incident dialysis patients who received care under the pre-ESRD program prior to the initiation of chronic dialysis therapy was 42%. The estimated enrollment rate was 48% for CKD stage 5 patients in Southern Taiwan from 2007 to 2010, suggesting that there has been no significant improvement in enrollment in recent years. Furthermore, during the study period, 752 patients in this program had only one set of eGFR data, and 795 of the 4061 patients in the study cohort had loss of follow-up. These data underline the importance of developing strategies to increase the enrollment and adherence of CKD patients.

The strengths of our study include its large sample population of patients in CKD stages 3b–5 who were enrolled in the program, receiving routine care by nephrology teams and multicenter clinics/hospitals in a nonclinical trial setting. The data from these real cases can thus help health policymakers better understand the progression among patients with CKD stages 3b–5, and thus leverage the pre-ESRD disease management claims data to control the risk factors associated with accelerated declines of eGFR (i.e., with the aim of preventing diabetes and hypertension), in order to reduce the incidence of ESRD in this program.

There are a number of practical and ethical restrictions that preclude the use of randomized controlled trials in evaluating the effectiveness of disease management programs. As a consequence, the findings of this observational study need to be considered in the light of several limitations. First, a potential selection bias might exist in this cohort, because patients voluntarily enrolled in the pre-ESRD disease management program and there was no control group. This might have caused the patients to more closely follow the nephrologists' predialysis instructions, and lead to a slower rate of decline in eGFR than would have been seen in patients who were not enrolled in such a program. Second, the progression of the decline and stabilization of eGFR shown in this work could be influenced by different serum creatinine testing practices adopted by the multicenter laboratories, although they all met the standards of the Taiwan Laboratory for Healthcare Quality Regulation Policy. This may also have led to the possibility of small errors in the eGFR calculation, and misclassification of cases into different stages of CKD. Third, this study did not gather data related to some important variables, such as daily urine protein loss (or urine protein/creatinine ratio), smoking habits, dyslipidemia, serum calcium, phosphate, sodium, and potassium levels, hemoglobin A1c data, and type of antihypertensive agents used. Therefore, it can be argued that the results presented in this work are potentially biased by some confounding factors. These variables should thus be collected regularly for the program in future studies to more comprehensively explore the risk factors of poor outcomes, and more accurately identify high-risk patients who are enrolled in the pre-ESRD program. However, despite these limitations, the findings of this study remain important and useful for developing a prevention policy for ESRD and predialysis mortality.

In summary, despite the progressive eGFR decline in patients with CKD stages 3b–5, especially in diabetic CKD, our preliminary results suggest a lower eGFR declining rate in patients enrolled in the Taiwan pre-ESRD disease management program. This study also identified the varying probabilities and risk factors of CKD progressing to ESRD in this program, suggesting that a more effective pre-ESRD disease management program would be more than just a renal program, and should instead utilize the integrated efforts of various health professionals, such as diabetologists and cardiologists, to provide a more patient-centered multidisciplinary program.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2013.10.021.

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