High Risk of Renal Failure in Stage 3B Chronic Kidney Disease is Under-recognized in Standard Medical Screening

Ming-Ju Wu[1,2,3,4]*, Kuo-Hsiung Shu[1,3], Pi-Haw Liu[5], Po-Huang Chiang[6], Chi-Hung Cheng[1,3], Cheng-Hsu Chen[1], Dong-Ming Yu[1], Ya-Wen Chuang[1]

[1]Division of Nephrology, Department of Medicine and [5]Department of Family Medicine and Health Management, Taichung Veterans General Hospital, Taichung; [2]Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei; [3]School of Medicine, Chung-Shan Medical University, and [4]Graduate Institute of Biomedical Sciences, College of Life Sciences, National Chung Hsing University, Taichung; [6]Institute of Population Health Sciences, Center for Health Policy Research and Development, Miaoli, Taiwan, R.O.C.

Background: The objective of this study was to determine the risk of renal failure in patients with under-recognized chronic kidney disease (CKD) in the self-pay standard medical screening program of health management centers.

Methods: The abbreviated Modification of Diet in Renal Disease equation was used to calculate the estimated glomerular filtration rate (eGFR) of study subjects. Study subjects with eGFR less than 60 mL/min/1.73 m^2 but with normal results of routine assessment, including serum creatinine, blood urea nitrogen, urinalysis and kidney ultrasound, were defined as having under-recognized CKD. Episodes of renal failure requiring dialysis within 2 years in subjects with stage 3 to stage 5 CKD were evaluated.

Results: A total of 15,817 subjects were recruited and 28.4% of subjects were identified by routine assessments as having a kidney problem. The prevalences of CKD 3A, 3B, 4 and 5 were 8.3%, 1.9%, 0.3% and 0.2%, respectively. All subjects with stages 4 and 5 CKD had abnormal serum creatinine levels, but 48.7% of 1,507 subjects with stage 3 CKD (stage 3A, $n=713$; stage 3B, $n=21$) had normal routine assessments. Subjects with under-recognized stage 3B CKD had the highest risk (20%) of developing renal failure compared to subjects with stages 3–5 CKD and abnormal results of routine assessments.

Conclusion: Identifying subjects with CKD stage 3 by the eGFR equation, especially in stage 3B, is advantageous in detecting the risk of renal failure over the routine clinical assessment that is currently carried out by health management institutions in Taiwan. [*J Chin Med Assoc* 2010;73(10):515–522]

Key Words: chronic kidney disease, glomerular filtration rate, health management institution, MDRD equation, renal failure

Introduction

Chronic kidney disease (CKD) is currently recognized as a worldwide public health problem.[1–4] CKD is best treated early, before the onset of widespread fibrosis. This puts a great emphasis on the identification of patients with early and likely asymptomatic renal disease. The progression of CKD may be preventable by the avoidance of nephrotoxic drugs or procedures. Both the incidence and prevalence of end-stage renal disease in Taiwan are among the highest in the world.[4] The prevalence in Taiwan of CKD stages 3–5 is 6.9%. However, awareness rates for CKD are relatively low in Taiwan; they are 8.0% for individuals with stage 3, 25% for those with stage 4, and 71.4% for those with stage 5. The lower awareness rates of CKD are closely related to serum creatinine (Cr) levels. Patients with serum Cr levels higher than the upper normal limit are more likely to be informed that they have CKD.[4,5] Similar reports have shown that serum Cr levels are frequently normal

*Correspondence to: Dr Ming-Ju Wu, Division of Nephrology, Department of Medicine, Taichung Veterans General Hospital, 160, Section 3, Chung-Kang Road, Taichung 407, Taiwan, R.O.C.
E-mail: wmj530@gmail.com • Received: March 8, 2010 • Accepted: July 1, 2010

in people with a reduced glomerular filtration rate (GFR), especially in older and malnourished patients.[5–7] Several equations have been developed to estimate GFR.[8–11] The most commonly used is the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study, which was developed by applying linear regression analysis to data from enrollees in the MDRD study.[8] Calculation of an estimated GFR (eGFR) is widely accepted as the best method to measure renal function and define the stage of CKD; yet, in clinical practice beyond nephrology, it is not widely utilized.[12]

Surprisingly, the eGFR equation is routinely used to identify CKD in people who participate in a self-pay standard medical screening program in health management centers in Taiwan. Since the primary purpose of such screening programs in health management centers is to detect illnesses while they are still in the early stages, the use of eGFR to identify patients with CKD during health assessment seems strongly justified. The routine assessment of kidney disease includes blood urea nitrogen (BUN) and serum Cr levels, urinalysis, and kidney ultrasound examination. This study aimed to determine the difference between routine assessment and the eGFR method in identifying patients with CKD in health management centers. Study subjects who had stages 3–5 CKD according to the abbreviated MDRD (aMDRD) eGFR equation but who had normal results from routine assessments were classified as the "under-recognized group". To identify the risk of renal failure in study subjects with normal results of routine assessment of kidney disease, episodes of renal failure that had occurred within 2 years of standard medical screening were evaluated in all study subjects with stages 3–5 CKD by eGFR.

Methods

All participants in the self-pay standard medical screening program in the health management center at Taichung Veterans General Hospital, Taiwan, between January 2003 and November 2006 were enrolled in the study. The health management center attracted paying participants from all over central Taiwan because of its known quality services. All subjects participated in a standard medical screening protocol, including a medical interview, comprehensive physical examination, chest X-ray, resting electrocardiography, echocardiography, abdominal ultrasound, upper gastrointestinal endoscopy, lower gastrointestinal endoscopy, urine and stool analysis, blood biochemistry, hematology analysis, thyroid hormone study, and tumor marker screening.

Abnormal BUN was defined as a BUN over the upper limit of normal (25 mg/dL). Abnormal Cr was defined as serum Cr over the upper limit of normal (1.4 mg/dL). The same cutoff values of serum Cr were used for males and females. Abnormal urinalysis was defined as the presence of proteinuria (protein +/– to ++++), hematuria (red blood cells > 2 per high-powered field), pyuria (white blood cells > 2 per high-powered field in males or > 5 per high-powered field in females), bacteriuria, occult blood, or glycosuria by spot urine microscopic and chemical examinations. Abnormal kidney ultrasound was defined as the presence of calcification or stones, cysts, nodules, hydronephrosis, increased echogenicity, abnormal kidney size (> 13 cm or < 10 cm) or a single kidney.

We used the aMDRD equation to estimate GFR as follows: $186.3 \times (\text{serum Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ for women).

The classification of CKD was based on clinical practice guidelines recommended by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation.[8] CKD stages were classified as follows: patients with a GFR less than 60 mL/min/1.73 m^2 were categorized as stages 3–5 CKD; those with a GFR of 30–59 mL/min/1.73 m^2 were classified as CKD stage 3; those with a GFR of 15–29 mL/min/1.73 m^2 as CKD stage 4; and those with a GFR less than 15 mL/min/1.73 m^2 as CKD stage 5. Stage 3 was further divided into stage 3A (GFR of 45–59 mL/min/1.73 m^2) and stage 3B (GFR of 30–44 mL/min/1.73 m^2).[8,12]

Study subjects who had an eGFR less than 60 mL/min/1.73 m^2 but with normal results from routine assessments were classified as "under-recognized CKD". Two methods were used to detect episodes of renal failure in study subjects with stages 3–5 CKD by eGFR. The first method was a review of the medical records and the second method was interviews by phone calls. An episode of renal failure was defined as renal failure requiring dialysis within 2 years after standard medical screening.

The prevalence of CKD in this study was minimally affected by missing data. Only 3 participants were excluded for missing records of medical interviews and physical examinations. Another 28 patients who had undergone regular dialysis or who were kidney transplant recipients were also excluded. All participants had provided signed consent for processing the data generated from medical screening. Ethics reviews were processed and approved by the Ethics Committee of Taichung Veterans General Hospital (IRB TCVGH No: C08052).

Participants' characteristics were summarized descriptively (using mean ± standard deviation for continuous variables and counts and percentages for categorical variables). Statistical analysis was performed with SPSS version 13 (SPSS Inc., Chicago, IL, USA). The cumulative renal survival curve was constructed by Kaplan-Meier analysis. Intergroup comparisons were presented with *p* values by the log-rank test. The multivariate Cox proportional hazard model was used to analyze the hazard ratio (HR) and 95% confidence interval (CI) of stage 3B with abnormal clinical routine assessment among the other 5 CKD groups. A p value < 0.05 was considered statistically significant.

Results

The characteristics of all study subjects are summarized in Table 1. Of the total cohort, 909 subjects (5.7%) had a history of diabetes mellitus and 3,372 (21.3%) a history of hypertension; 489 (3.1%) had abnormal serum Cr levels and 317 (2.0%) had abnormal BUN levels. Abnormal kidney ultrasound results were found in 2,626 (16.6%), while 3,698 (23.4%) had at least 1 abnormal urine analysis result. A total of 1,060 (6.7%) subjects had proteinuria over 30 mg (1+) and 664 (4.2%) had trace proteinuria (+/−), 2,521 (15.9%) subjects had hematuria, 3,580 (22.6%) subjects had pyuria, and 221 (1.4%) subjects had glycosuria. Compared to males, females had significantly more hematuria (23.1% *vs.* 10.9%, $p = 0.024$) and pyuria (38% *vs.* 11.8%, $p < 0.001$). Among subjects with abnormal serum Cr or BUN levels, 139 of 537 subjects (25.9%) had normal urine analysis results. In total, 28.4% of study subjects were identified as having a kidney problem by routine clinical assessment and were referred to nephrologists.

Using the aMDRD equation to estimate GFR, 1,319 (8.3%) subjects had stage 3A CKD and 188 (1.9%) subjects had stage 3B CKD (Table 2). Another 54 (0.3%) subjects had stage 4 CKD and 32 (0.2%) subjects had stage 5 CKD. Overall, 1,593 (10.7%) study subjects including 1,002 (10.8%) males and 591 (9%) females, were diagnosed as stages 3–5 CKD. The overall prevalence of stages 3–5 CKD among study subjects older than 60 years was 29.3% (Figure 1). The prevalence of stages 3–5 CKD increased with age. Table 2 shows the range, mean, and mode of serum Cr in all subjects with stages 3–5 CKD. Female subjects had lower levels of the range, mean, and mode of serum Cr than males. All 86 patients who were identified as stage 4 or 5 CKD via the aMDRD equation had serum Cr levels higher than 1.4 mg/dL, and were found to have kidney disease via the standard medical screening program. The serum Cr level of all subjects with stage 3 CKD was 1.0–2.6 mg/dL. All female

Table 1. Characteristics of study subjects in the standard medical screening program*

	Total	Male	Female
Study subjects	15,817 (100)	9,264 (58.6)	6,553 (41.4)
Age (yr)	51.5 ± 12.4 (15–90)	51.5 ± 12.5 (16–90)	51.1 ± 12.3 (15–86)
≥ 80	138 (0.9)	114 (1.2)	24 (0.4)
70–79	1,190 (7.5)	748 (8.1)	442 (6.7)
60–69	2,613 (16.5)	1,445 (15.6)	1,168 (17.8)
50–59	4,772 (30.2)	2,824 (30.5)	1,948 (29.7)
40–49	4,580 (29.0)	2,828 (30.5)	1,752 (26.7)
< 40	2,524 (15.9)	1,321 (14.3)	1,203 (18.4)
Stages 3–5 CKD	1,593 (10.1)	1,002 (10.8)	591 (9.0)
Diabetes mellitus	909 (5.7)	602 (6.5)	307 (4.7)
Hypertension	3,372 (21.3)	2,009 (21.7)	1,363 (20.8)
Abnormal serum Cr (> 1.4 mg/dL)	489 (3.1)	329 (3.6)	160 (2.4)
Abnormal BUN (> 25 mg/dL)	317 (2.0)	167 (1.8)	150 (2.3)
Abnormal urinalysis†	3,698 (23.4)	1,133 (12.2)	2,565 (39.1)
Abnormal kidney ultrasound‡	2,626 (16.6)	1,608 (17.4)	1,018 (15.5)

**Data are presented as n (%) or mean ± standard deviation (range); †abnormal urinalysis is defined as the presence of proteinuria, hematuria, pyuria, bacteriuria, occult blood, or glycosuria by spot urine microscopic and chemical examinations; ‡abnormal kidney ultrasound is defined as the presence of calcification or stones, cysts, nodules, hydronephrosis, increased echogenicity, abnormal kidney size (> 13 cm or < 10 cm), or a single kidney. CKD = chronic kidney disease; Cr = creatinine; BUN = blood urea nitrogen.*

Table 2. Serum creatinine levels of 1,593 study subjects with stages 3–5 chronic kidney disease identified by the abbreviated Modification of Diet in Renal Disease equation

Stage	Subjects*			Range of serum Cr (mg/dL)			Mean serum Cr (mg/dL)			Mode of serum Cr (mg/dL)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
3A	1,319 (8.3)	853 (9.2)	466 (7.1)	1.0–1.7	1.3–1.7	1.0–1.2	1.3±0.2	1.4±0.1	1.1±0.1	1.4	1.4	1.0
3B	188 (1.9)	111 (1.2)	77 (1.2)	1.3–2.6	1.7–2.6	1.3–1.7	1.7±0.3	1.8±0.2	1.5±0.1	1.7	1.8	1.3
4	54 (0.3)	28 (0.3)	26 (0.4)	1.8–4.0	2.3–4.0	1.8–2.9	2.6±0.6	3.0±0.5	2.2±0.4	2.4	2.4	1.8
5	32 (0.2)	10 (0.1)	22 (0.3)	3.4–17.8	5.6–17.8	3.4–11.8	7.2±3.7	10.0±4.3	6.0±2.5	5.8	7.6	4.0

**Data are presented as n (%) of 15,817 study subjects by sex or total. Cr = creatinine.*

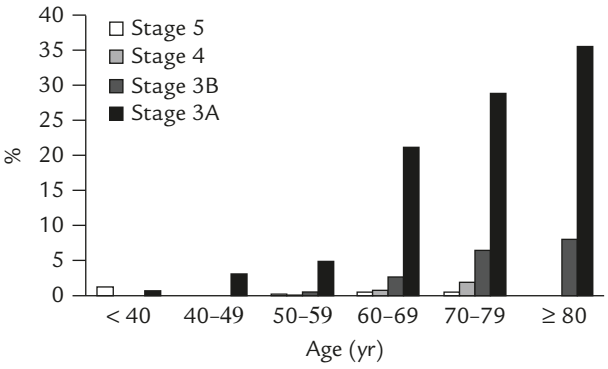


Figure 1. Prevalence of stages 3–5 chronic kidney disease by age group.

subjects with stage 3A CKD had normal serum Cr level of 1.0–1.2 mg/dL. Male participants had a higher percentage of stage 3 CKD, but a lower percentage of stages 4 and 5 CKD compared to females (Table 3).

Among subjects with stages 3–5 CKD, 921 (57.8%) subjects (69.7% males, 37.7% females) had normal urinalysis results. Since all subjects with stages 4 and 5 CKD had abnormal serum Cr levels, we evaluated the results of routine assessments in subjects with stage 3 CKD. In 188 subjects with stage 3B CKD, 78 (41.5%) subjects (46.7% males, 32.4% females) had normal urinalysis results. Of 1,507 subjects with stage 3 CKD identified by the aMDRD equation, 470 subjects had abnormal serum Cr levels with or without abnormal BUN levels, while 734 (48.7%) had normal results for serum Cr and BUN levels, urinalysis and kidney ultrasound (Table 4). These 734 (4.6%) study subjects out of the total of 15,817 were then classified as under-recognized.

All 1,593 study subjects with stages 3–5 CKD identified by the aMDRD equation were evaluated via medical records and interviews. Eighteen subjects were lost at this cross-sectional follow-up. In total, 32 episodes of renal failure requiring dialysis within 2 years after standard medical screening were found in the remaining 1,575 study subjects. Table 5 demonstrates the episodes of renal failure in all subjects with stages 3–5 CKD by eGFR. Six (18.8%) subjects with stage 5 CKD developed renal failure. Two (3.7%) subjects with stage 4 CKD developed renal failure. Figure 2 shows the cumulative renal survival of different CKD groups. The group of stage 3B with normal routine clinical assessment had the lowest renal survival and the group of stage 5 CKD had the second lowest renal survival. There was no significant difference in survival between these 2 groups. Compared with stage 3B with normal routine clinical assessment

and stage 5 CKD, the other 4 groups had significantly higher renal survival ($p<0.05$) and the between-group comparisons were not significant.

Univariate logistic regression showed that being older (HR, 1.09; 95% CI, 1.05–1.11), having diabetes mellitus (HR, 1.39; 95% CI, 1.28–1.55), and lower baseline GFR (HR, 0.82; 95% CI, 0.72–0.94) were associated with a higher risk of renal failure within 2 years (Table 4). By age-adjusted multivariate Cox proportional survival analysis, having diabetes mellitus (HR, 1.44; 95% CI, 1.21–1.66) and lower baseline GFR (HR, 0.82; 95% CI, 0.72–0.94) remained independent predictors of renal failure within 2 years.

Table 3. Clinical manifestation of study subjects with normal serum creatinine levels and stage 3 chronic kidney disease identified by the abbreviated Modification of Diet in Renal Disease equation

	CKD stage	
	3A* (*n*)	3B† (*n*)
Total subjects	1,319	188
Classified as normal by serum Cr, BUN, and routine assessment	713	21
Subjects with serum Cr > 1.4 mg/dL	295	141
Subjects with serum BUN > 25 mg/dL	101	106
Subjects with abnormal urinalysis	427	20
Subjects with abnormal kidney ultrasound	302	15

**Glomerular filtration rate of 45–59 mL/min/1.73 m^2; †glomerular filtration rate of 30–44 mL/min/1.73 m^2. CKD = chronic kidney disease; Cr = creatinine; BUN = blood urea nitrogen.*

Stage 5 CKD and stage 3B CKD with normal routine clinical assessment had a similar risk of renal failure and this risk was significantly higher than that for the other CKD groups (Table 5).

Discussion

In the past 2 decades, the kidney disease screening program has changed in Japan and many countries.[4,13] The program started with urinalysis and measurements of serum Cr and estimation of GFR by equation were added later. Currently, formulaic estimations of GFR are widely used by nephrologists, but these estimations have many pitfalls. Although eGFR reporting could promote identification of more cases of CKD, it is also possible that attention and resources could be directed towards patients falsely identified as having CKD or with early CKD. Application of eGFR without adjustment for the effects of racial disparity, age and sex may also result in over-diagnosis of CKD.[14,15] Although increasing the rate of patient referral to nephrologists on the basis of eGFR could increase costs and use of medical resources, nephrologists obtain better blood pressure control and slower progression of renal function than non-nephrologists.[16,17] Moreover, the purpose of self-pay standard medical screening programs in health management centers is to evaluate how healthy a person is and help minimize the barriers to health care. The routine health assessment tools for identifying kidney disease in most management centers in

Table 4. Univariate analysis of baseline variables in association with risk of renal failure in 2 years of follow-up ($n = 1,575$ patients with available data)

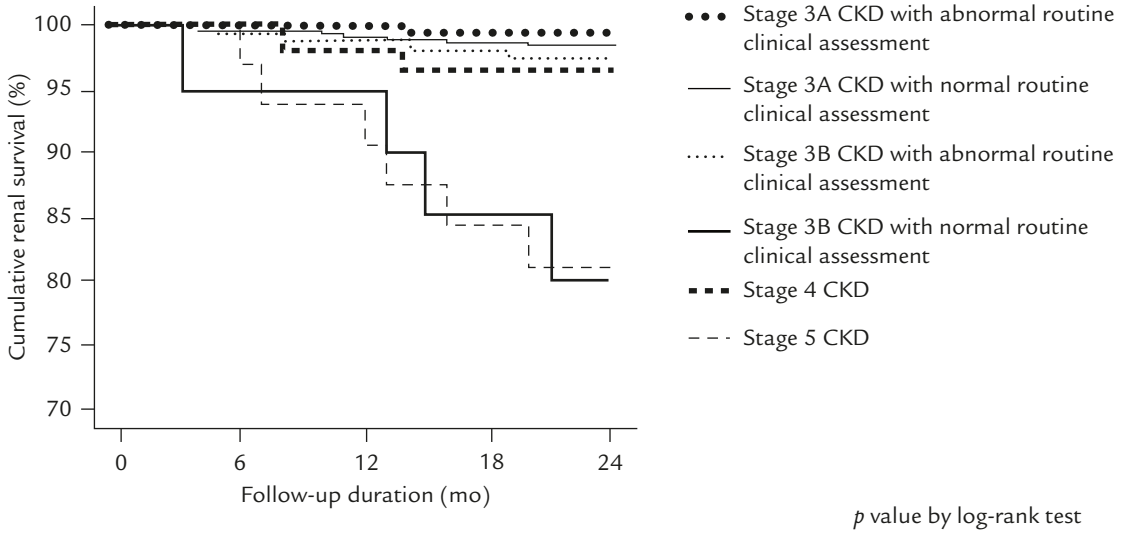
Variable	HR	95% CI	*p*
Age (per 10 yr)	1.09	1.05–1.11	< 0.001
Male sex	1.01	0.92–1.09	0.437
Diabetes mellitus	1.39	1.28–1.55	< 0.001
Hypertension	1.27	0.89–1.91	0.209
Serum albumin (g/dL)	0.89	0.79–1.12	0.303
Hemoglobin (g/dL)	1.05	0.94–1.21	0.178
Abnormal urinalysis	1.06	0.94–1.19	0.292
Abnormal kidney ultrasound	0.99	0.95–1.04	0.195
eGFR (mL/min/1.73 m^2)	0.82	0.72–0.91	< 0.001
Stage 5 CKD	Reference		
Stage 4 CKD	0.86	0.71–0.94	0.005
Stage 3B* CKD with normal routine clinical assessment	1.06	0.98–1.15	0.263
Stage 3B* CKD with abnormal routine clinical assessment	0.71	0.25–0.93	0.001
Stage 3A† CKD with normal routine clinical assessment	0.55	0.41–0.69	< 0.001
Stage 3A† CKD with abnormal routine clinical assessment	0.42	0.33–0.58	< 0.001

**Glomerular filtration rate of 30–44 mL/min/1.73 m^2; †glomerular filtration rate of 45–59 mL/min/1.73 m^2. HR = hazard ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease.*

Table 5. Age-adjusted multivariate Cox proportional model for the effect of baseline variables on the risk of renal failure ($n = 1,575$ patients with available data)

Variable	HR	95% CI	*p*
Diabetes mellitus	1.44	1.21–1.66	0.005
eGFR (mL/min/1.73 m^2)	0.86	0.67–0.98	0.001
Stage 5 CKD	Reference		
Stage 4 CKD	0.89	0.61–0.96	0.01
Stage 3B* CKD with normal routine clinical assessment	1.02	0.94–1.18	0.346
Stage 3B* CKD with abnormal routine clinical assessment	0.77	0.45–0.93	0.01
Stage 3A† CKD with normal routine clinical assessment	0.59	0.46–0.73	< 0.001
Stage 3A† CKD with abnormal routine clinical assessment	0.33	0.23–0.64	< 0.001

**Glomerular filtration rate of 30–44 mL/min/1.73 m^2; †glomerular filtration rate of 45–59 mL/min/1.73 m^2. HR = hazard ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease.*



	p value by log-rank test
Stage 3B with normal routine assessment *vs.* stage 3A with normal routine assessment	< 0.001
Stage 3B with normal routine assessment *vs.* stage 3A with abnormal routine assessment	< 0.001
Stage 3B with normal routine assessment *vs.* stage 3B with abnormal routine assessment	< 0.001
Stage 3B with normal routine assessment *vs.* stage 4	0.022
Stage 3B with normal routine assessment *vs.* stage 5	0.931
Stage 3A with normal routine assessment *vs.* stage 3A with abnormal routine assessment	0.025
Stage 3A with normal routine assessment *vs.* stage 3B with abnormal routine assessment	0.462
Stage 3A with normal routine assessment *vs.* stage 4	0.244
Stage 3A with normal routine assessment *vs.* stage 5	< 0.001
Stage 4 *vs.* stage 5	0.020

Figure 2. Two-year cumulative renal survival in study subjects with an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 by Kaplan-Meier analysis. The *p* values for comparison between groups are presented by log-rank test. CKD = chronic kidney disease.

Taiwan are serum Cr and BUN levels, urinalysis, and kidney ultrasound. The eGFR equation is not included. In our cohort, 28.4% of study subjects were identified as having a kidney problem by the above routine assessment tools and were referred to nephrologists. However, only a small percentage of subjects had abnormal results for serum Cr levels (3.1%) and BUN levels (2.0%), and proteinuria over 30 mg (6.7%). The percentage of proteinuria in our study is similar to a previous report from a nationally representative survey in Taiwan.[4] Although 22.6% of subjects had pyuria and 15.9% had hematuria, it is not surprising that female subjects had significantly higher percentages of hematuria and pyuria than male subjects. The use of urinalysis is not sufficient to screen for kidney disease. A significant proportion of subjects with either stages 3–5 CKD or abnormal serum Cr/BUN levels had normal urinalysis results. On the other hand, many subjects with

stages 3–5 CKD or abnormal serum Cr/BUN levels had normal kidney ultrasound results. Some kidney ultrasound findings, such as renal stones or cysts, may not directly predict a risk of developing renal failure.

Using the aMDRD eGFR equation, we found that 10.1% of study subjects had stages 3–5 CKD. We found that 734 (48.7%) subjects with stage 3 CKD had normal results for serum Cr and BUN, urinalysis and kidney ultrasound. Moreover, significant episodes of renal failure requiring dialysis were found among the 4.6% of subjects who were classified as under-recognized. Taiwan has the largest end-stage renal disease population in the world, and therefore, early identification of CKD (e.g. via the application of the aMDRD eGFR equation) is very important.[4] A nationally representative survey from Taiwan in 2002 showed that the prevalence of stages 3–5 CKD in Taiwan was 6.9%.[4] However, the awareness rates for CKD in Taiwan were very low, being only 8% in stage 3 CKD. The low awareness rate was closely related to serum Cr levels. Subjects with serum Cr levels greater than 1.6 mg/dL (> 141 μmol/L) were more likely to be informed that they have kidney disease.[4] Another large-scale prospective cohort study based on 462,293 adults in Taiwan also reported a high prevalence of CKD and its associated all-cause mortality.[5] It also reported a significant lack of awareness of CKD among the study subjects in a standard medical screening program run by a private health management institution in Taiwan.

We found that all subjects with stages 4 and 5 CKD identified via the aMDRD equation had abnormal serum Cr levels and were identified as having kidney disease. For subjects with stage 4 or 5 CKD, many nonnephrologists may underestimate the disease status of CKD and fail to prevent the episode of acute or chronic renal disease. The low-limit values of serum Cr in subjects with stage 3 CKD for males and females were 1.3 mg/dL and 1.0 mg/dL, respectively. Both values overlapped the upper limit of normal for serum Cr level, which is 1.4 mg/dL. This finding challenges the traditional upper normal limit value for serum Cr. Further studies by separate gold standards such as iothalamate clearance or inulin clearance may help to adjust the normal range for serum Cr in Taiwanese.

Even if the routine clinical assessment tools for kidney disease are combined, a significant percentage of under-recognized CKD and a risk of renal failure were still reported in the current study. Episodes of renal failure within 2 years after standard medical screening may not be the best way to evaluate the accuracy of the eGFR equation or the routine assessment in health management centers. Although we failed to evaluate changes in serum Cr or eGFR in this large cohort, episodes of renal failure vary in different stages of CKD. Subjects with stage 3 CKD and normal routine clinical assessments had a higher risk of developing renal failure requiring dialysis compared with subjects with at least 1 abnormal routine clinical assessment. In particular, subjects with stage 3B CKD and normal routine clinical assessments may have the highest risk of developing renal failure requiring dialysis within 2 years. One possible explanation is that most clinicians may neglect the risk of renal injury induced by nephrotoxic drugs or procedures in patients with stage 3 CKD when they have had a normal renal function survey by serum Cr and BUN, urinalysis, and kidney ultrasound. There is growing evidence to suggest that patients with stage 3B have a higher risk of cardiovascular disease and rapid renal function progression compared with stage 3A patients.[18–22]

Some limitations of this study should be noted. First, the relatively very small number of subjects with stage 3B CKD with normal routine clinical assessment may have had an impact on episodes of renal failure. Second, the definition of renal failure requiring dialysis was based on episodes of both acute and chronic renal failure requiring dialysis within 2 years after standard medical screening by review of medical records and interviews by phone. Potential errors from the phone interviews may also have limited the generalizability of the results.

The eGFR equation is not widely used in most clinical practices beyond nephrology in Taiwan, including most standard medical screening programs of health management centers. Our findings provide strong evidence for using the aMDRD eGFR equation as a routine assessment for CKD. In agreement with increasingly more international organizations, we have established an automatic eGFR reporting system by clinical laboratory in our hospital whenever serum Cr is measured to facilitate early recognition of CKD and to reduce the potential risk of nephrotoxic drugs or procedures.[23–25]

There remains a lack of clarity in the definition of abnormal routine clinical assessment and its clinical significance in CKD classification for stages 3, 3A and 3B. In particular, abnormal laboratory findings are mainly due to non-renal problems, such as hematuria due to extra-renal origin, pyuria due to lower urinary tract infection and occult blood due to pigmenturia (hemoglobin or myoglobin), as well as renal cysts, stones, nodules or calcification, and change in kidney size with interference with kidney function. However, we failed to further reanalyze these factors in stage 3 CKD.

Accordingly, patients with stage 3 CKD were arbitrarily classified into only 2 groups (with or without

normal routine clinical assessment), and this could have led to overestimating patient numbers in the 2 subgroups, in terms of stages 3A ($n=606$) and 3B ($n=167$) CKD with abnormal routine clinical assessment. Therefore, the crude rate of renal failure necessary for dialysis could have been exaggerated in stages 3A (1.7%) and 3B (20%) CKD with normal routine clinical assessment. We also failed to reclassify the subgroups in stages 3A and 3B CKD patients and reanalyze the crude rate of renal failure progression.

In conclusion, in the current large-cohort study, we found an apparent disagreement in identifying stage 3 CKD between routine clinical assessment tools and the aMDRD eGFR equation in a standard medical screening program. The significantly higher risk of renal failure in under-recognized stage 3B CKD suggests the value of using the eGFR equation in a health management institution and general clinical practice, especially in countries with a high prevalence of CKD such as Taiwan.

Acknowledgments

The authors wish to thank the Biostatistics Task Force of Taichung Veterans General Hospital for statistical analysis and Miss Chia-Fang Hung for her excellent assistance in chart review and interviews. This work was supported by a grant (TCVGH 993604C) from Taichung Veterans General Hospital.

References

1. Xue JL, Ma JZ, Louis TA, Collins AJ. Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. *J Am Soc Nephrol* 2001;12:2753–8.
2. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038–47.
3. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. *J Am Soc Nephrol* 2003;14(Suppl):S131–8.
4. Hsu CC, Hwang SJ, Wen CP, Chang HY, Chen T, Shiu RS, Horng SS, et al. High prevalence and low awareness of CKD in Taiwan: a study on the relationship between serum creatinine and awareness from a nationally representative survey. *Am J Kidney Dis* 2006;48:727–38.
5. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, Chiang PH, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462,293 adults in Taiwan. *Lancet* 2008;371:2173–82.
6. Lindeman RD. Assessment of renal function in the old: special considerations. *Clin Lab Med* 1993;13:6269–77.
7. Garg AX, Blake PG, Clark WF, Clase CM, Haynes RB, Moist LM. Association between renal insufficiency and malnutrition in older adults: results from NHANES III. *Kidney Int* 2001;60:1867–74.
8. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1–266.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
10. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol* 2002;13:2140–4.
11. Garg AX, Papaioannou A, Ferko N, Campbell GK, Clarke JA, Ray JG. Estimating the prevalence of renal insufficiency in seniors requiring long-term care. *Kidney Int* 2004;65:649–53.
12. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *New Engl J Med* 2006;345:2473–83.
13. Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkino H, Hishida A, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. *Clin J Am Soc Nephrol* 2007;2:1360–6.
14. Glassock RJ. Estimated glomerular filtration rate: time for a performance review? *Kidney Int* 2009;75:1001–3.
15. Gao SW, Oliver DK, Das N, Hurst FP, Lentine KL, Agodoa LY, Sawyers ES, et al. Assessment of racial disparities in chronic kidney disease stage 3 and 4 care in the department of defense health system. *Clin J Am Soc Nephrol* 2008;3:442–9.
16. Patwardhan MB, Samsa GP, Matchar DB, Haley WE. Advanced chronic kidney disease practice patterns among nephrologists and non-nephrologists: a database analysis. *Clin J Am Soc Nephrol* 2007;2:277–83.
17. Martínez-Ramírez HR, Jalomo-Martínez B, Cortés-Sanabria L, Rojas-Campos E, Barragán G, Alfaro G, Cueto-Manzano AM. Renal function preservation in type 2 diabetes mellitus patients with early nephropathy: a comparative prospective cohort study between primary health care doctors and a nephrologist. *Am J Kidney Dis* 2006;47:78–87.
18. Parikh NI, Hwang SJ, Larson MG, Levy D, Fox CS. Chronic kidney disease as a predictor of cardiovascular disease (from the Framingham Heart Study). *Am J Cardiol* 2008;102:47–53.
19. Abutaleb N. Why we should sub-divide CKD stage 3 into early (3a) and late (3b) components. *Nephrol Dial Transplant* 2007;22:2728–9.
20. Kirsztajn GM, Suassuna JH, Bastos MG. Dividing stage 3 of chronic kidney disease (CKD): 3A and 3B. *Kidney Int* 2009; 76:462–3.
21. Schena FP, Pascoe MD, Alberu J, Carmen Rial M, Oberbauer R, Brennan DC, Campistol JM, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation* 2009;87:233–42.
22. Wu MJ, Shu KH, Cheng CH, Chen CH. Sirolimus in chronic allograft nephropathy. *Transplant Proc* 2004;36:2053–5.
23. Levey AS, Stevens LA, Hostetter T. Automatic reporting of estimated glomerular filtration rate: just what the doctor ordered. *Clin Chem* 2006;52:2188–93.
24. The Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Clin Biochem Rev* 2005; 26;81–6.
25. Tarng DC. Cardiorenal anemia syndrome in chronic kidney disease. *J Chin Med Assoc* 2009;70:424–9.