Table 1. Participant Characteristics

	Development Data Set	Validation Data Set
No. of participants (men/women)	413 (262/151)	350 (203/147)
Age (y)	51.4 ± 16.5 (18-88)	53.9 ± 17.5 (19-91)
Serum creatinine (mg/dL)	1.62 ± 1.59 (0.41-10.75)	1.57 ± 1.38 (0.34-10.28)
Albumin (g/dL)	3.80 ± 0.64 (1.70-5.20)	3.91 ± 0.56 (1.70-5.10)
Serum urea nitrogen (mg/dL)	22.0 ± 15.5 (5.0-107.3)	22.4 ± 14.2 (6.1-81.2)
GFR (mL/min/1.73 m^2)	59.1 ± 35.4 (3.0-199.3)	57.2 ± 34.7 (2.6-228.7)
0-29	108 (26%)	93 (27%)
30-59	115 (28%)	113 (32%)
60-89	102 (25%)	73 (21%)
>90	88 (21%)	71 (20%)
Creatinine clearance (mL/min/1.73 m^2)	81.2 ± 47.2 (3.1-274.1)	79.7 ± 44.9 (5.3-268.5)
Height (cm)	163.3 ± 8.8	161.6 ± 9.5
Weight (kg)	61.0 ± 12.9	60.4 ± 12.7
Body surface area (m^2)	1.65 ± 0.19	1.63 ± 0.19
Diagnosis		
Chronic glomerulonephritis	219	173
Acute glomerulonephritis	4	3
RPGN	10	4
Interstitial nephritis	6	3
Diabetes mellitus	46	44
Polycystic kidney disease	2	0
Nephrosclerosis	25	30
Lupus	10	3
Kidney donor	1	10
Kidney recipient	9	2
Hereditary nephritis	3	1
Hypoplasia	3	0
Unilateral nephrectomy	6	3
Miscellaneous	69	74

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; urinary albumin in g/dL to g/L, ×10; serum urea nitrogen in mg/dL to mmol/L, ×0.357; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: GFR, glomerular filtration rate; RPGN, .

Hitachi creatinine auto-analyzer, model 7170 (Hitachi, Tokyo, Japan) and enzyme solution (Preauto-SCrE-N; Daiichi Pure Chemicals Co, Tokyo, Japan). SCr values obtained in the central laboratory were compared with those of the Cleveland Clinic (Cleveland, OH) by using a calibration panel of 40 samples, provided by Dr Frederick Van Lente, Cleveland Clinic.

Comparison of Measured Versus Expected Creatinine Excretion

Creatinine excretion was measured in 90-minute urine samples obtained during Cin measurements and predicted based on previously published formulas.

Creatinine excretion rates were based on published equations for Japenese[20] and whites[21] and are given in the notes to Table 2.

Development of the Correction Coefficient for the IDMS–MDRD Study Equation

The new Japanese coefficient to modify the IDMS–MDRD Study equation[7] for Japanese was calculated from the development data set of 413 participants. The coefficient was derived by minimizing the root mean squared error (RMSE) of the estimate calculated as the square root of (sum of squared errors of the estimate/[N]).

Development of the New Equations for Japanese

The new 3- and 5-variable Japanese equations were derived in the development data set by using a multiple linear regression model and the variables age, sex, and SCr, SUN, and serum albumin levels in relation to measured GFR (mGFR). All variables were log transformed.

Development of the Correction Coefficient for the CG Equation

The CG equation was modified by a Japanese CG coefficient that was calculated in the development data set. The correction coefficient was determined by minimizing the RMSEs of the estimate.

Validation of Equations

GFR was estimated by using all equations and compared with mGFR in the development and validation data

Table 2. Participant Characteristics

	Men (n = 462)	Women (n = 296)
Age (y)	53.7 ± 17.1	50.8 ± 16.8
Height (cm)	167.4 ± 7.1	154.9 ± 6.3
Weight (kg)	65.7 ± 11.9	52.7 ± 9.5
Body surface area (m^2)	1.74 ± 0.16	1.49 ± 0.13
Body mass index (kg/m^2)	23.4 ± 3.7	22.0 ± 3.8
Measured creatinine excretion (mg/kg/d)	20.2 ± 0.8	16.7 ± 4.6
Estimated creatinine excretion (for Japanese)	18.4 ± 1.2	14.3 ± 1.0
Estimated creatinine excretion (for whites)	19.0 ± 2.9	16.1 ± 1.9

Note: Data expressed as mean ± SD. Measured creatinine excretion was obtained during the measurement of inulin clearance. Expected creatinine excretion for Japanese was calculated by using the following equations: Creatinine excretion rate (mg/kg/d) = 22.1 − 0.068 × Age (in men) or 17.2 − 0.057 × Age (in women). Estimated creatinine excretion for whites was calculated by the following equations: Creatinine excretion rate (mg/kg/d) = 28.2 − 0.172 × Age (in men) or 21.9 − 0.115 × Age (in women).

sets. We compared all equations, but specifically focused on the comparison in the validation data set of the IDMS–MDRD Study equations modified by the previously published JSN Chronic Kidney Disease Initiative (JSN-CKDI) coefficient and the new Japanese coefficient, as well as the JSN-CKDI equation and new Japanese equations. Metrics for comparison were RMSE, bias, accuracy, and r^2. The RMSE of GFR estimated by using the equation was calculated as the square root of (sum of squared errors of the estimate/[N]). Bias of the equations was expressed as the mean difference between eGFR and mGFR (eGFR − mGFR). Accuracy was expressed as percentage of participants with eGFR less than 15% and 30% from mGFR. RMSE and correlation coefficients were computed on the raw scale. Data sets were combined for correlation between eGFR and mGFR. Intercepts and slopes were evaluated in a linear regression model.

Statistical Analysis

Data are expressed as mean ± SD. Measured versus predicted creatinine excretion was compared by using Student *t*-test. Creatinine values were calibrated by using the calibration panel and evaluated by means of linear regression. Differences in accuracy of eGFR were evaluated between equations by means of χ^2 tests. Differences in bias of eGFR were evaluated between equations by using Student *t*-test. A difference with *P* less than 0.05 was considered statistically significant. Statview, version 4.02 (SAS Institute, Cary, NC), and JMP, version 6.02 (SAS Institute), were used for statistical analysis and calculation of correction factors and confidence intervals (CIs).

RESULTS

Patient Characteristics in the Development and Validation Populations

Characteristics of the development population (n = 413) and validation population (n = 350) are listed in Table 1. Distributions of participant numbers by cause of kidney disease and mean age, SCr level, albumin level, SUN level, height, weight, and body surface area were similar between the 2 populations. Mean Cin was also similar between them at 59.1 ± 35.4 mL/min/1.73 m^2 in the development population and 57.2 ± 34.7 mL/min/1.73 m^2 in the validation population. Proportions of participants with mGFR less than 60 mL/min/1.73 m^2 were 54% in the development population and 60% in the validation population.

Body Size and Creatinine Excretion

Body size and creatinine excretion in the combined development and validation data sets are listed separately for men and women in Table 2. The creatinine excretion rate was greater in men than women (20.2 versus 16.7 mg/kg/d). Measured values were significantly, but not substantially, greater than expected values for both Japanese ($P < 0.001$) and whites ($P < 0.001$).

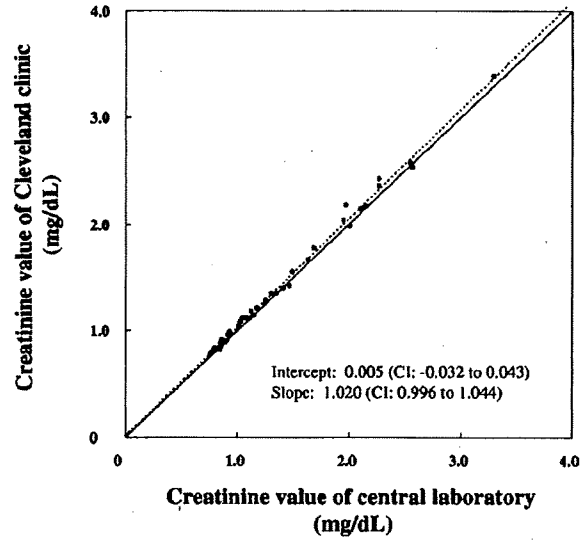

Figure 1. Correlation between creatinine values of the Cleveland Clinic and a central laboratory. Y = X (solid line), and regression line (dotted line). Abbreviation: CI, confidence interval.

Table 3. Intercepts and Coefficients for GFR-Estimating Equations in the Development Population

Equation	Exponent-Transformed Intercept (95% CI)	Coefficient of Continuous Parameters (95% CI)				Exponent-Transformed Coefficient Of Dichotomous Variables (95% CI)
		SCr	Age	SUN	Alb	
IDMS–MDRD Study	175	−1.154	−0.203	–	–	0.742 if female 1.01 if white 1.212 if black
1	175	−1.154	−0.203	–	–	0.742 if female 0.741 if Japanese
2	171	−1.004	−0.287	–	–	0.782 if female
3	175	−1.154	−0.203	–	–	0.742 if female 0.808 if Japanese (0.728 to 0.829)
4	194 (143 to 262)	−1.094 (−1.139 to −1.048)	−0.287 (−0.366 to −0.208)	–	–	0.739 if female (0.695 to 0.786)
5	142 (93 to 217)	−0.923 (−0.997 to −0.849)	−0.185 (−0.263 to −0.108)	−0.233 (−0.319 to −0.148)	0.414 (0.272 to 0.557)	0.772 if female (0.728 to 0.818)
6	–	–	–	–	–	0.85 if female (0.769 to 0.810)

Equation 1: IDMS–MDRD Study equation with previously reported JSN-CKDI coefficient: $eGFR = 0.741 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female).

Equation 2: Previously reported JSN-CKDI equation: $eGFR = 171 \times SCr^{-1.004} \times Age^{-0.287} \times 0.782$ (if female).

Equation 3: IDMS–MDRD Study equation with new Japanese coefficient: $eGFR = 0.808 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female).

Equation 4: New 3-variable Japanese equation: $eGFR = 194 \times SCr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female).

Equation 5: New 5-variable Japanese equation: $eGFR = 142 \times SCr^{-0.923} \times Age^{-0.185} \times Alb^{0.414} \times SUN^{-0.233} \times 0.772$ (if female).

Equation 6: 0.789 × CG equation: $eGFR = 0.789 \times (140 - Age) \times BW/SCr/72 \times 1.73/BSA \times 0.85$ (if female).

Abbreviations: Alb, albumin; BSA, body surface area; BW, body weight; CG, Cockcroft-Gault; CI, confidence interval; CKDI, Chronic Kidney Disease Initiative; eGFR, estimated glomerular filtration rate; IDMS, isotope dilution mass spectrometry; JSN, Japanese Society of Nephrology; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; SUN, serum urea nitrogen.

Calibration of Creatinine Assays

Creatinine values for the calibration panel assigned in our laboratory were compared with values assigned by Cleveland Clinic Laboratory (Fig 1). Mean SCr level was 1.415 ± 0.100 (SEM) versus 1.449 ± 0.102 mg/dL. Creatinine values correlated highly with values assigned by the Cleveland Clinic as judged by the intercept of 0.005 (95% CI, −0.0032 to 0.043), close to zero, and the slope of 1.020 (95% CI, 0.996 to 1.044), close to 1.0. Because there was no significant systemic bias, creatinine values were not adjusted in the present study.

Cin and Ccr

Cin and Ccr were measured simultaneously in 757 patients. Mean serum inulin concentrations were 18.4 ± 4.9, 18.3 ± 5.1, and 19.3 ± 5.9 mg/dL at 45, 75, and 105 minutes, respectively. The median coefficient of variation for Cin was 10.9% (95% CI, 5.8 to 20.4) during the 90-minute renal Cin test. The median coefficient of variation for Ccr was 13.3%. Cin and Ccr significantly correlated ($r = 0.889$; $r^2 = 0.790$). The slope was 0.698 (95% CI, 0.672 to 0.724) and the intercept was 2.339 (95% CI, 0.143 to 4.622). Ccr was significantly greater than Cin, and the correction coefficient for the bias was determined to be 0.715 (95% CI, 0.703 to 0.726).

eGFR Equations

All equations are listed in the notes to Table 3.

The new Japanese correction coefficient calculated for modification of the IDMS–MDRD Study equation was 0.808 (95% CI, 0.728 to 0.829; equation 3) in the development population, whereas the previously reported coefficient was 0.741 (equation 1), as listed in Table 3.

Using the development data set, we derived a new 3-variable Japanese equation (equation 4) and a new 5-variable Japanese equation (equation 5; Table 3).

Table 4. Performance of GFR-Estimating Equations in the Development Population

Equation	RMSE (mL/min/1.73 m²)	Accuracy	
		Within 15% of mGFR (95% CI)	Within 30% of mGFR (95% CI)
IDMS–MDRD Study equation	23.6	36 (32-41)	59 (55-64)
Equation 1	18.4	38 (34-43)	73 (69-77)
Equation 2	19.2	39 (35-44)	73 (68-77)
Equation 3	17.6	44 (39-48)	77 (72-81)
Equation 4	17.3	44 (39-48)	78 (74-82)
Equation 5	16.4	52 (47-57)	83 (79-86)
Equation 6	17.7	44 (39-49)	76 (72-80)

P

15% Accuracy Level							30% Accuracy Level						
	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5		IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS							IDMS						
Eq 1	0.6						Eq 1	<0.001					
Eq 2	0.4	0.7					Eq 2	<0.001	0.9				
Eq 3	0.03	0.1	0.2				Eq 3	<0.001	0.2	0.2			
Eq 4	0.03	0.1	0.2	0.9			Eq 4	<0.001	0.09	0.06	0.6		
Eq 5	<0.001	<0.001	<0.001	0.01	0.01		Eq 5	<0.001	<0.001	<0.001	0.03	0.1	
Eq 6	0.03	0.1	0.2	0.9	0.9	0.02	Eq 6	<0.001	0.3	0.3	0.8	0.5	0.02

Note: Accuracy given as percentage of participants whose estimated GFR was within 15% or 30% of measured GFR.

Abbreviations: CI, confidence interval; Eq, equation; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; RMSE, root mean squared error.

The CG equation was modified with a correction coefficient. The Japanese coefficient of 0.789 (95% CI, 0.769 to 0.810) was obtained from the development data set and is provided as equation 6 in Table 3.

Comparison of Performance of the Equations

Performance in GFR estimation was evaluated among equations by using the development and validation data sets based on RMSE, bias, and accuracy of eGFR in reference to mGFR.

Accuracy in the Development Data Set

Performance of each derived equation was evaluated by using the development data set, as listed in Table 4. Bias is not compared because it is expected to be approximately zero for equations developed in the development data set. There were no significant differences in accuracy within 15% or 30% between equations 3 and 1 or between equations 4 and 2, reflecting no significant different in precision.

Bias and Accuracy in the Validation Data Set

Performance of each derived equation was evaluated by using the validation data set, as listed in Table 5. Bias was significantly less in equation 3 than in equation 1 ($P = 0.002$) and in equation 4 than in equation 2 ($P < 0.001$). Equation 3 provided GFR with significantly better accuracy within 15% than equation 1 ($P = 0.02$), but no significant difference in accuracy within 30% deviation ($P = 0.6$) between the 2 equations. There was a trend toward improved accuracy within 15% and 30% between equations 4 and 2 ($P = 0.06$). Equation 5 performed similarly to equation 4.

Correlation Between eGFR and mGFR

The correlation between eGFR and mGFR was evaluated in the combined population as shown for each equation in Fig 2. Intercepts and slopes for equations are listed in Table 6.

DISCUSSION

We previously reported that eGFR calculated using either the IDMS–MDRD Study equation modified by using the JSN–CKDI coefficient (0.741; equation 1) or the JSN–CKDI equation (equation 2) was more accurate than the unmodified MDRD Study equation in Japanese individu-

Table 5. Performance of GFR-Estimating Equations in the Validation Population

Equations	RMSE (mL/min/1.73 m²)	Bias (mL/min/1.73 m²)	Accuracy	
			Within 15% of mGFR (95% CI)	Within 30% of mGFR (95% CI)
IDMS–MDRD Study equation	25.2	12.0 ± 22.2	39 (34-45)	59 (54-64)
Equation 1	19.9	−5.9 ± 19.0	34 (29-39)	72 (67-76)
Equation 2	20.3	−7.9 ± 18.7	36 (31-41)	73 (69-78)
Equation 3	19.4	−1.3 ± 19.4*	43 (38-48)	73 (59-78)
Equation 4	19.1	−2.1 ± 19.0†	43 (38-48)	75 (70-79)
Equation 5	17.7	−1.2 ± 17.6	49 (44-54)	79 (75-83)
Equation 6	19.4	−1.7 ± 19.6	45 (40-50)	75 (70-79)

P

	15% Accuracy Level						30% Accuracy Level					
	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS							IDMS					
Eq 1	0.1						Eq 1	<0.001				
Eq 2	0.4	0.5					Eq 2	<0.001	0.6			
Eq 3	0.4	0.02	0.08				Eq 3	<0.001	0.6	0.9		
Eq 4	0.3	0.01	0.06	0.9			Eq 4	<0.001	0.3	0.06	0.6	
Eq 5	0.01	<0.001	<0.001	0.1	0.1		Eq 5	<0.001	0.02	0.08	0.08	0.2
Eq 6	0.1	0.003	0.02	0.5	0.6	0.3	Eq 6	<0.001	0.3	0.7	0.7	0.9	0.2

Note: Accuracy given as percentage of participants whose estimated GFR was within 15% or 30% of measured GFR.

Abbreviations: CI, confidence interval; Eq, equation; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; RMSE, root mean squared error.

als.[19] The present study verifies our previous results, and accuracy of GFR estimation is improved further by means of newly derived equations, the modified IDMS–MDRD Study equation with the new Japanese coefficient (0.808; 95% CI, 0.728 to 0.829; equation 3) and the new 3-variable equation (equation 4). Bias was significantly reduced in equation 3 and 4 from that in equations 1 and 2 in the validation population. We also developed a 5-variable equation (equation 5). The new Japanese equations and the new Japanese coefficient for the IDMS–MDRD Study equation provided more reliable eGFRs in Japanese individuals. The present study had a larger number of participants than the previous study, and all samples were assayed for inulin and creatinine in a central laboratory.

In both the previous[18,19] and present studies, the original IDMS–MDRD Study equation overestimated GFR in comparison to mGFR by using Cin in Japanese patients with CKD (Fig 2). The correction coefficient less than 1.0 indicates lower SCr levels in Japanese than in whites in the MDRD Study for equivalent levels of GFR.

SCr level is affected by 3 major factors: level of kidney function, skeletal muscle mass,[2] and amount of protein intake.[22] In the steady state, creatinine excretion is a measure of creatinine generation from muscle or protein intake. Our data suggest that creatinine excretion was slightly greater than expected per kilogram of body weight, but less than observed in the MDRD Study because of lower body weight. Mean creatinine excretion values were 20.2 and 16.7 mg/kg/d in men and women in our study compared with 19.2 and 15.8 mg/kg/d in the MDRD Study, respectively.[23] Mean body weight was 60 kg in our study compared with 79 kg in the MDRD Study. Mean body mass index (BMI) was 23 kg/m² in the present study and 27 kg/m² in the MDRD Study.[23]

Differences in creatinine excretion, body weight, and BMI between participants in our study and the MDRD Study are consistent with studies that have shown a mean skeletal muscle mass assessed by means of magnetic resonance imaging data significantly less in Japanese (men, 24.8 ± 3.5 kg; women, 14.7 ± 2.3 kg)[24] than in North Americans (men, 33.0 ± 5.3 kg; women,

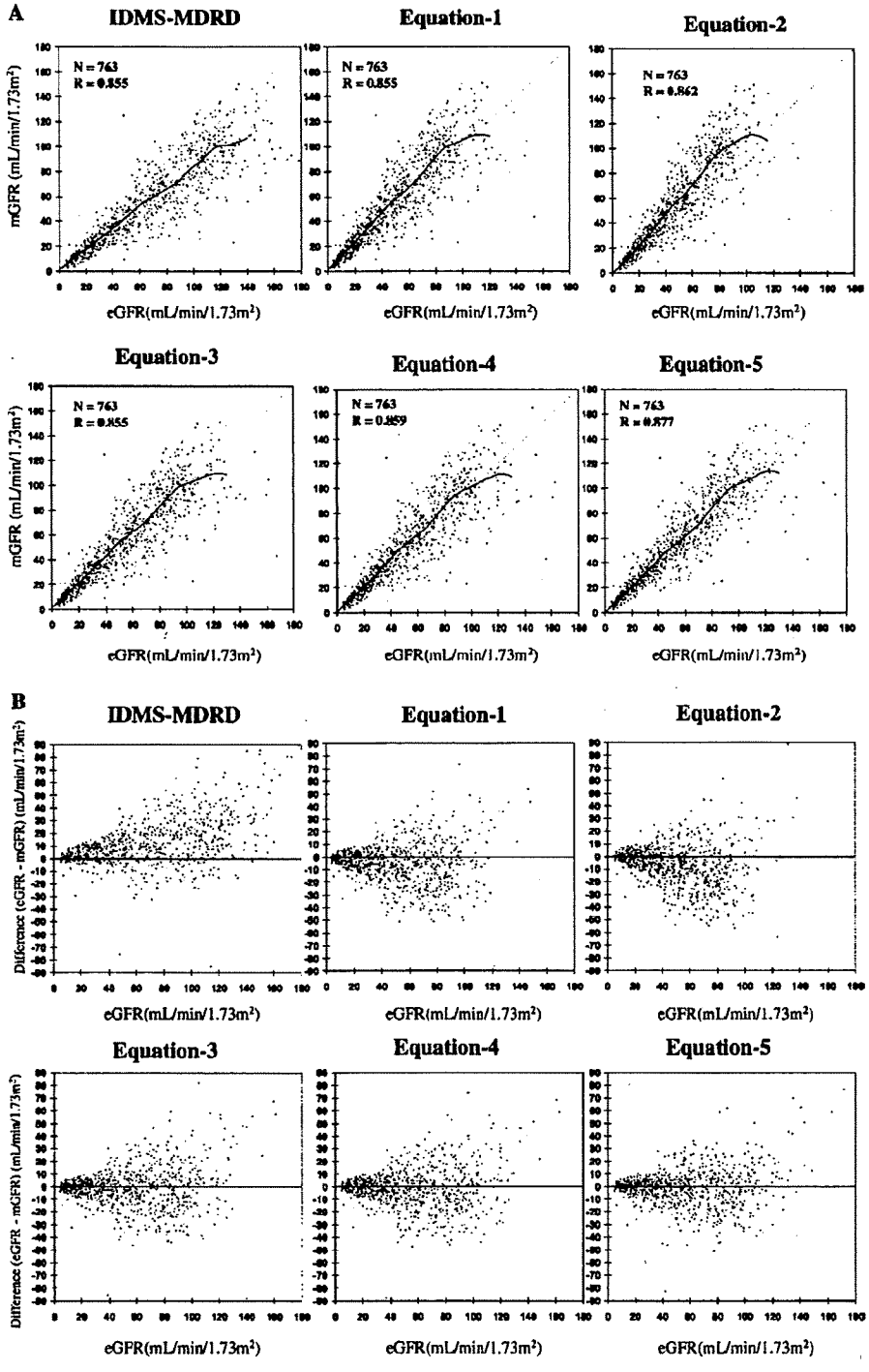

Figure 2. Correlation between estimated glomerular filtration rate (eGFR) using each equation and measured GFR (mGFR) in the combined population. (A) mGFR versus eGFR and (B) eGFR minus mGFR versus eGFR. Smoothed lines show the fit of the data. Abbreviations: IDMS-MDRD, isotope dilution mass spectrometry Modification of Diet in Renal Disease.

21.0 ± 3.8 kg; study population included whites [67%], blacks [17%], Asians [8%], and Hispanics [7%]).[25]

These differences in muscle mass are reflected as differences in SCr levels between Japanese and North American populations. Muscle mass significantly decreases with aging in Japanese men,[24] but does not significantly change in North American men.[25] SCr values were lower and remained constant until age 70 years in Japanese for both men and women,[26] whereas values were greater and increased after age 40 years in whites and blacks[27]: 0.831 mg/dL at age 20 to 39 years, 0.822 mg/dL at age 40 to 59 years, and 0.868 mg/dL at age 60 to 79 years in Japanese men versus 0.865 mg/dL at age 20 to 39 years, 0.883

Table 6. Intercepts and Slopes for GFR-Estimating Equations

Equations	Intercept (95% CI)	Slope (95% CI)	*R2*
IDMS–MDRD Study equation	6.1 (3.5 to 8.6)	0.740 (0.708 to 0.771)	0.731
Equation 1	6.1 (3.5 to 8.6)	0.998 (0.955 to 1.041)	0.731
Equation 2	1.8 (−0.9 to 4.5)	1.123 (1.076 to 1.170)	0.743
Equation 3	6.1 (3.5 to 8.6)	0.915 (0.876 to 0.955)	0.731
Equation 4	5.1 (2.5 to 7.7)	0.943 (0.903 to 0.983)	0.738
Equation 5	4.5 (2.1 to 6.9)	0.944 (0.907 to 0.980)	0.770
Equation 6	6.7 (4.1 to 9.3)	0.908 (0.869 to 0.948)	0.730

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease.

mg/dL at age 40 to 59 years, and 0.998 mg/dL at 60 years and older as calibrated to IDMS-traceable creatinine in white men. Mean noncalibrated SCr values in the Third National Health and Nutrition Examination Survey (NHANES III) were 1.14 mg/dL at age 20 to 39 years, 1.16 mg/dL at age 40 to 59 years, and 1.28 mg/dL at 60 years and older[28] in white men (calibrated SCr = [SCr − 0.23] × 0.95).[29,30] After age 50 years, urinary creatinine excretion decreases as body weight decreases in Japanese men. However, in whites body weight is not as good a marker to estimate urinary creatinine excretion as muscle mass. Lean body mass, not body weight, correlates with urinary creatinine excretion and muscle mass in whites.[31]

Differences in muscle mass are parallel to differences in obesity. The obese population (BMI > 25 kg/m^2) increases with age in white Americans: 61% at age 20 to 39 years, 70% at age 40 to 59 years, and 74% at 60 years and older.[32] However, obesity decreases after age 50 years in Japanese men: BMI greater than 25 kg/m^2 is 20% at age 20 to 29 years, 28.9% at age 30 to 39 years, 32.7% at age 40 to 49 years, 30.8% at age 50 to 59 years, 29.7% at age 60 to 69 years, and 26% at 70 years and older (Japanese Ministry of Health, Labor, and Welfare). It was reported that an increase of 5 kg/m^2 in BMI resulted in increase of 1.1% in SCr level.[33] With aging, skeletal muscle mass and protein intake decrease at a greater rate in Japanese than in whites, whereas the prevalence of obesity increases in whites, but not Japanese.

Altogether, these data are consistent with a correction coefficient less than 1.0 for modification of the MDRD Study equation for Japanese. In contrast, the correction coefficient for Chinese is 1.233. Possible explanations for the large difference in correction coefficients between Japanese and Chinese studies may be differences in muscle mass in the study populations, creatinine assays, or GFR measurement methods. Additional study is required to understand the difference in GFR-estimating equations between Chinese and Japanese.

In the present study, no significant systemic bias was observed in SCr values used for the development of new equations by the panel of the Cleveland Clinic Laboratory. SCr values assayed using the enzymatic method were more accurate and had greater precision than other methods.[2] Although 95% of laboratories in Japan have switched to the enzymatic method from the Jaffé method, creatinine values must be standardized for use of the new equations.

Limitations of the present study are as follows. (1) The new Japanese GFR-estimating equations may not be applicable to the healthy population because they were derived mostly from patients with chronic kidney disease. Rule et al[10] also suggested that the MDRD Study equation might systematically underestimate GFR in the normal healthy population. (2) Equations were derived from data for inpatients and outpatients. Some participants were hospitalized for renal biopsy as is customary practice in Japan, although some inpatient participants may have had clinical conditions related to creatinine metabolism.[14] (3) About 15% of patients had diabetes, and GFR was estimated accurately for patients with diabetes with our new equations. However, GFRs calculated by using the MDRD Study equation and CG equations were underestimated in patients with diabetes over the range of eGFR of 90 mL/min/1.73 m^2 or greater.[34] We must further

study the accuracy of eGFR in Japanese patients with diabetes.

In conclusion, according to Cin data, the newly derived creatinine-based GFR-estimating equations accurately estimate GFR for Japanese. Although the 5-variable Japanese equation estimates GFR more accurately than other equations, SUN and albumin are not routinely measured in Japan. Because the new 3-variable Japanese equation provided reasonably accurate eGFRs, we recommend using the new 3-variable Japanese equation for GFR estimation from SCr level and age in clinical practice and for epidemiological study.

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ORIGINAL ARTICLE

Report of the Asian Forum of Chronic Kidney Disease Initiative (AFCKDI) 2007. "Current status and perspective of CKD in Asia": diversity and specificity among Asian countries

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Abstract The Japanese Society of Nephrology (JSN) sponsored the Asian Forum of CKD Initiative (AFCKDI) 2007 with the support of the International Society of Nephrology-Commission for Global Advancement in Nephrology (ISN-COMGAN), Asian Pacific Society of Nephrology (APSN), the Kidney Disease: Improving Global Outcome (KDIGO) and other national societies of nephrology in the Asian Pacific region on 27–28 May 2007 in Hamamatsu City, Japan. An international organising committee was established by leading experts of the CKD initiative. The main objective of this forum was to clarify the current status and perspectives of CKD and to promote coordination, collaboration and integration of initiatives in the Asian Pacific region. The forum received 56 papers

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from 16 countries; it began with the symposium "A Challenge to CKD in the world" and was followed by the ISN-COMGAN affiliated workshop "Current status and perspective of CKD in Asia". The second day was dedicated to discussion on the evaluation, surveillance and intervention in CKD in this area. At the end of the forum, we decided on the future plan as follows: (1) The AFCKDI will provide opportunities annually or biannually for every person who promotes CKD initiatives in the Asian Pacific region to join together and build consensus for action; (2) the second forum will be held in Kuala Lumpur on 4 May 2008 at the time of the 11th Asian Pacific Congress of Nephrology (APCN). Zaki Morad, President of the 11th APCN, will host the second forum; (3) the International Organising Committee (IOC) of the 1st AFCKDI will continue its function by adding other experts, including the organisers of the APCN; (4) the AFCKDI is not an organisation by itself, nor does it belong to any society, but is organised by each host national society of nephrology. The IOC will assist the domestic committee for the success of the forum and will assure the continuation of the mission; (5) in order to organise the forum and promote CKD initiatives in the Asia Pacific region, the AFCKDI will look for support by both national and international societies. The AFCKDI will keep an intimate and mutual relation with the ISN, APSN and KDIGO.

Keywords Chronic kidney disease · AFCKDI · Asia · APSN · KDIGO · ISN COMGAN · Japan

Introduction

Nearly 50% of the global population lives in the Asian Pacific region, including the world's two large and most populous countries, China and India, which together account for over 35%, and are the two countries with the highest incidence and prevalence of chronic kidney disease (CKD) dialysis patients (CKD 5-D). Recognising the need for a coordinated regional approach, the Japanese Society of Nephrology, as part of its 50th anniversary celebrations, established the Asian Forum on Chronic Kidney Disease Initiative (AFCKDI) in 2007. Aided by the International Society of Nephrology (ISN), Kidney Disease: Improving Global Outcomes (KDIGO), the Asian Pacific Society of Nephrology, the Australian and New Zealand Society of Nephrology and the Malaysian Society of Nephrology, two regional meetings have now been held: in Hamamatsu, Japan, in 2007 and in Kuala Lumpur, Malaysia, in 2008. The tasks facing AFCKDI are formidable, with enormous economic, cultural and geographic differences characterising the region. However, regional and international interest and support have been overwhelming. At very short notice, in Hamamatsu 16 countries submitted 56 abstracts, from which many were chosen to supplement the invited speakers, allowing representation of a very wide range of nations.

In Hamamatsu the agreed aims were to clarify the current state of CKD in the Asian Pacific region and to promote coordination, collaboration and integration of initiatives to combat this disease burden. As host chair, Dr. Seichi Matsuo introduced the three main topics for discussion: (1) CKD screening and early detection, (2) clinical practice guidelines (CPGs) and their implementation, and (3) education, implementation and international and regional cooperation and support.

Screening for CKD

Japan (S. Matsuo)

Statutory urinalysis has been carried out on industrial workers since 1972, school children since 1973 and persons aged over 40 years since 1982 [1]. Despite this, Japan unfortunately still ranks among the highest in the world for CKD-5D prevalence and incidence, with particularly a rising incidence of diabetic patients [2]. Clearly screening alone has made little impact, hence the Japanese Association of CKD has now been established and government funded to pursue a strategic research project aimed at prevention of CKD, or reducing CKD-5D.

Hong Kong (P. KT. Li)

In 2004 the ISN held a Consensus Workshop on Prevention of Progression of Renal Disease in Hong Kong [3]. The consensus was that screening for CKD was worthwhile in diabetic and hypertensive patients and in the relatives of patients with CKD due to diabetes, hypertension and glomerulonephritis, and that CKD was more common in individuals over 60–65. This consensus meeting published recommendations for prevention of progression once CKD was detected [4].

Clinical practice guidelines and international collaboration

KDIGO (N. Lameire)

A non-profit foundation governed by an international board of directors (six currently from our region), KDIGO aims to improve global CKD care by promoting, integrating and

aiding implementation of CPGs [5], [6]. KDIGO has published a revision of the definition and classification of CKD [7], reviewed definition, evaluation and classifications in CKD mineral and bone disorders [8], and is in the process of preparing CPGs on hepatitis C in CKD [9]. KDIGO aims to provide reviews of the evidence behind clinical care and CPGs, allowing local carers to construct the own CPGs without the resource burden of this task. It also hopes to coordinate CPG development to prevent redundancy of effort and stimulate consensus (http://www.kdigo.org/).

CARI (R. Walker)

CARI is the only Asia Pacific regional group currently producing English language CPGs available on the web. The key aspects are an absolute need for a good evidence base to construct CPGs and the recognition that implementation must be inherent in the process [10].

ISN (W. Couser)

The ISN Commission on Global Advancement of Nephrology (ISN-COMGAN) pointed out the focus shifting from emphasis on renal replacement therapy to the "new nephrology"—the early detection and prevention of kidney disease and its cardiovascular consequences [4]. Core outreach programmes are encompassed under COMGAN [11]. The ISN Fellowship programme now emphasises training in clinical epidemiology and outcomes research. The ISN Continuing Nephrology Education (CNE) programme supports over 50 educational events each year, reaching over 10,000 health-care workers, with an emphasis on early detection and treatment of CKD. The restructured ISN Sister Centre programme supports 40 centre relationships worldwide aimed at progressing the developing centre through to becoming a regional, independent focus for promotion of all aspects of renal health care. The ISN Research and Prevention Committee has developed the programme for detection and management of CKD, hypertension, diabetes and cardiovascular diseases.

Diversity and specificity of CKD in Asia

Speakers dealt with CKD in the COMGAN regions, first from the two most populous countries, China and India, then a mix of developing and developed countries of differing sizes and economies. Highlighted was the urgent need to develop strategies to combat CKD, given the huge population of Asia, the high prevalence of CKD and the poor economic state of much of the region.

China (W. Chen)

A randomly selected population-based screening study in southern China (both rural and urban) showed 10.6% had proteinuria, haematuria or reduced estimated GFR. Independent risk factors were age, hypertension and diabetes.

India (V. Jha)

CKD, diabetes and hypertension have been identified as increasing in prevalence in several small surveys. Diabetes is the commonest cause of end-stage renal diseases (ESRD); 73% of ESRD patients present less than 3 months before diagnosis [12].

Korea (H. J. Chin)

A nationwide survey from health checks in 39 hospitals indicated a prevalence of CKD stages 1, 2, 3 or more of 1.39, 3.64 and 2.67%, respectively, with very similar risk factors to Western countries, and a particularly high prevalence in the elderly.

Nepal (S. K. Sharma)

In this country, where renal replacement therapy (RRT) cannot be afforded, a door-to-door screening and intervention programme was conducted. Of 3,218 people over 20, CKD was detected in 10.6%. Age and diabetes were particularly predictive. When hyperglycaemia and hypertension were controlled, regression or stabilisation of proteinuria was seen in 52%.

Japan (K. Iseki)

In 2005 Japan had the world's highest prevalence of CKD-5 patients, 2,018 per million population (pmp) [13]. Sleep apnoea has recently been shown to be particularly common in Japanese CKD-5 patients, 30.5% compared with a non-CKD-5 population prevalence of 15.1% [14].

Australia (D. Harris)

The AUSDIAB study [15] has indicated a population prevalence of CKD similar to other developed countries. Automatic reporting of estimated GFR (eGFR, modified MDRD formula) by laboratories, general practitioner education and screening/intervention studies are underway. A particularly important issue is "How can developed countries help developing nations?" Screening and intervention programmes in Indonesia and Brunei are being assisted by Australian centres.

Screening, risk factors, evaluation, comorbidity and intervention in CKD in Asia

Many important issues were discussed, including: (1) Who should be screened? Cost effectiveness suggests a targeted approach. (2) What is the high-risk population? Is it similar to those in North America and Europe or different in Asia? (3) Is it necessary to study selected populations using epidemiological designs to collect regional data? (4) Is it necessary to have a common language about criteria for eGFR and urinary protein/albumin estimation in Asia? Is haematuria particularly relevant in Asia with the prevalence of glomerulonephritis, especially IgA disease? (5) Should we intervene in high-risk populations? Which subgroups would benefit most? What would be most cost-effective?

Estimating GFR in Asian populations

Standardised methods for estimating GFR are essential for detection and classification of CKD. The MDRD formula was not developed in Asian subjects, hence eGFR formulae need to be developed.

China (L. Zuo)

The broad issues for proper selection of eGFR formulae were introduced [16, 17, 18]. Methods for developing estimating equations were reviewed, including the inherent problems involved in regression, linear assumption and calibration of plasma creatinine or other measurements. Variations can lead to systemic differences in eGFR results. The recommendation was that eGFR should be developed based on both the ethnic group and the method and calibration of plasma creatinine or other measurements.

Japan (M. Horio)

The Japanese CKD Initiative has on-going studies to refine a Japanese eGFR equation [19–21]. eGFR by the MDRD formula was compared with inulin renal clearance in 247 Japanese CKD patients. Serum creatinine was measured by an enzymatic method in a central laboratory, which gave results virtually equivalent to standardised creatinine values. A tendency for eGFR MDRD to overestimate GFR was adjusted by introducing an ethnic coefficient (X 0.808) for Japanese, calculated by minimising the sum of squared errors between eGFR MDRD and inulin clearances in patients with GFR <90 ml/min/1.73 m^2.

China (Y.-C. Ma)

The Chinese eGFR Collaboration Group has produced a modified EGFR for Chinese (eGFR = $175 \times Pcr^{-1.234} \times age^{-0.179} \times 0.79$ for females). Changes in eGFR with ageing were studied in 747 apparently healthy Chinese subjects [22]. Jaffe's method was used in a central laboratory to measure serum creatinine. eGFR decrease per 10 tears was 4.3 ml/min/1.73 m^2, and about one-third of subjects 70 years or over had eGFR less than 60 ml/min/1.73 m^2. Overestimation of renal disease was a risk in the elderly. The utility of single or repeated spot urine albumin/creatinine ratios was studied in 659 Beijing residents (F. Wang). While microalbuminuria was present in 10.2% initially, this declined to 6.4% when repeated 4 months later, indicating that repeated measurements are needed to confirm CKD.

Prevalence, risk factors and comorbidity of CKD in Asia

Table 1 summarises the prevalence of CKD and prevalence/incidence of ESRD (RRT) reported in this meeting. Data were presented from 8 countries—Bangladesh, China, Malaysia, Mongolia, Sri Lanka, Singapore, Taiwan and Vietnam—as well as 19 further posters, indicating CKD is a major problem in all these countries, with some unique regional differences. These contained recurrent themes of increasing incidences of diabetes as a cause of ESKD and the need for early intervention schemes to combat the epidemic of ESKD in Asia, rather than the unaffordable alternative of RRT. All abstracts are available on the AFCKDI web site (http://www.jsn.or.jp/AFCKDI2007/), or as published papers [23–25, 26, 27, 28, 29].

Southern China (U. Kuok)

In Macau, preliminary analysis from over 1,000 people indicates some evidence of CKD in over 20%, but only 3–5% have stages 3–5. However, in persons aged 65 years or over, this rises to more than 20%.

Southern Taiwan (H. C. Chen)

Screening of family members of nearly 200 haemodialysis patients showed a 13% prevalence of eGFR 60 ml/min/1.73 m^2 and 17% prevalence of albuminuria. Only 15% showed awareness of CKD, indicating the need for more screening and education of family members [30, 31].

Bangladesh (H. U. Rashid)

A rural survey has indicated a prevalence of CKD of 17% in this country where RRT cannot be afforded. The need for primary care of CKD patients was highlighted [2].

Table 1 Prevalence of CKD and prevalence/incidence of ESRD (RRT)

Area	CKD prevalence (stages)	GFR equation[c]	Study population	Study year	ESRD (incidence)	RRT (prevalence)	Author
Guangzou/Zhuhai	10.6% (I–V)	Classic MDRD	4,642	2007	NA	NA	W. Chen
Korea	1.39% (I), 3.64% (II), 2.67% (III–V)	Classic MDRD	329,581	2005	185 pmp[a]	942 pmp[a]	H. J. Chin
Nepal	10.6% (I–V)	Classic MDRD	3,218	2006	Very few	Very few	S. K. Sharma
Japan	9.2% (III–V)	0.808XMDRD[d]	574,023	2006	275 pmp[a]	1,956 pmp[a]	E. Imai
Macau	18.0% (I–II), 3.3% (III–V)	Classic MDRD	1,047	2006	NA	933 pmp	U. Kuo
Taiwan	6.9% (III–V)	Classic MDRD	6,001	2006	418 pmp[a]	2,226 pmp[a]	C.C. Hsu
Bangladesh	17% in rural area	CG			9 pmp[a]	92 pmp[a]	H. U. Rashid,
Mongolia	NA	NA	NA	2005	(196 pmp)[b]	36 pmp	K. Gelegjamts
Singapore	4.45% (III–V)	Classic MDRD	2,112		NA	NA	B. W. Teo
Vietnam	3.9% (III–V)	Classic MDRD	8,509		NA	NA	J. Ito
Beijing	9.3% (I–V), 1.7% (III–V)	1,23XMDRD[d]	13,925		NA	NA	L. Zhang
Bhopal	3.2% (age >60, DM 58.4%)	Classic MDRD	572,029	2001	NA	152 pmp	V. Jha
Indonesia	5.8% (I), 7.0% (II) 5.2% (III–V)	CG	6,040	2006	NA	NA	Dharmeizar
Australia	NA	NA		2006	115 pmp[a]	778 pmp[a]	USRDS
Malaysia	NA	NA		2006	119 pmp[a]	615 pmp[a]	Z. Morard
Thailand	NA	NA		2006	139 pmp[a]	286 pmp[a]	K. Praditpornsilpa
HongKong	NA	NA		2006	140 pmp[a]	994 pmp[a]	USRDS
Shanghai	NA	NA		2006	282 pmp[a]	447 pmp[a]	USRDS

Results in this table were obtained from the reports of this conference and published studies. Some of the data may be different from the data published later

NA not available, *CG* Cockcroft–Gault, *pmp* per million people, *CKD* chronic kidney disease, *ESRD* end-stage renal diseases

[a] Data were obtained from the USRDS database 2006 (http://www.usrds.org/)

[b] Renal replacement therapy (RRT) was not applied to every patient

[c] Classic MDRD used an ethnic cofactor for non-black without creatinine standardisation

[d] Only Chinese and Japanese data used an ethnic cofactor (1.23 and 0.808, respectively) for the MDRD equation with creatinine standardisation

Mongolia (K. Gelegjamts)

There are unique local issues in this isolated country. A survey of hospitalised patients from 2002–2005 showed a high incidence of CKD because of nephrolithiasis, particularly in children and women. Kidney and urinary tract infection was the third commonest cause of illness in the general community, and the commonest cause of hospital morbidity. Chronic pyelonephritis and glomerulonephritis are the main causes of ESRD, contributed to by the harsh climate, high fertility rate and poverty.

Sri Lanka (G. Priyadarshana)

In the north-central and western provinces (Polonnaruwa and Anuradhapura), there is a very high prevalence of a chronic interstitial disease of unknown cause. In Anuradhapura, CKD is the leading cause of in-hospital mortality. Environmental toxins are suspected, but have not been identified. Elsewhere in Sri Lanka, the causes of ESRD are similar to other counties.

Singapore (B. W. Teo)

Of over 200 persons presenting to one academic hospital for voluntary health screening, only 1.6% had a serum creatinine above the normal range, but 4.5% had CKD stage 3–5 when eGFR was calculated.

Malaysia (Z. Morad)

Malaysia has seen a rapid rise in ESRD because of diabetes in the last 2 decades, such that by 2006 it was the cause of 57% of ESRD, the highest in the world, mirroring the high (11.50%) community incidence of diabetes. Glomerulonephritis and stone disease are falling as causes of ESRD.

Vietnam (J. Ito)

Japan has collaborated with Vietnam to find a prevalence of CKD stages 3–5 in 4% and hypertension >30% in 8,500 subjects aged >40 years in one region [32].

Intervention in CKD in Asia

Various attempts to improve care in CKD were presented

Taiwan (S. L. Wang)

The Kaohsiung Medical University Hospital led a national care project starting in 2003. About 1,400 patients with CKD stage 3–5 have been enrolled. The investigators goals were for more CKD patients to choose home peritoneal dialysis over centre haemodialysis (result, marginal fall), an increase in patients on rHuEPO (result, 68.8–83.0%) and permanent vascular access (result, 38.5–63.0%), higher hematocrits (result 23.9–25.2%) and reduced hospitalisation rates before initiation of dialysis. The programme was successful for most of the goals, though the proportion of patients choosing PD as the primary treatment modality fell marginally. The authors concluded that an integrated CKD care programme is effective in improving the dialysis-preparedness and clinical profile of CKD patients. The message was in addition to steps needed to slow disease progression; CKD care should also include preparing patients for renal replacement therapy.

Indonesia (Dharmeizar)

The utility of a questionnaire-based screen for CKD risk factors with blood pressure and urinalysis was assessed in four rural areas of Indonesia. Of 6,040 subjects with a mean age 41 years, 41% had obesity, 14% hypertension, 22% diabetes and 3.6% proteinuria; 1,100 had serum creatinine measured, resulting in a 5.7% prevalence of CKD. The high incidence of obesity was a surprise, and in general the results suggest that this approach needs to be viewed with caution, since most measurements were performed only once.

Japan (S. Matsuo)

The outcomes from the Japanese Governmental Programme of Urinalysis commenced in 1973 were reported [28, 29]. Urinalysis is carried out in population groups, particularly school children, employees and all citizens over 40 years of age. It is mandatory in the first two groups, and about 44% of the last group have been tested. Urinary abnormalities were noted in 2.7, 6.8, 4.9, 6.3 and 18.4% of elementary school students, junior high school students, high school students, industry workers and citizens over 40 years of age, respectively. Despite a decline in the contribution of glomerulonephritis (GN) to ESRD, the overall prevalence of ESRD in Japan has been relentless, and the numbers have been constantly increasing. The mean age of new Japanese ESRD patients with GN showed a significantly faster increase than in US patients, whereas those of patients with diabetes or nephrosclerosis increased at the same rate. It appears that while the urine testing programme has made a positive difference in GN, it has had little impact on the overall growth of ESRD, possibly because the new lifestyle diseases and population age more than compensated for the decline in GN cases. Nevertheless, the database that has been accumulated as a result of the screenings is a fantastic one and can be mined to get valuable data of a type probably not available anywhere else in the world [1].

Mission and future action plan

The burden of CKD is high and unique in each of our neighbours. There is a clear need for coordination, collaboration and integration of initiatives to fight the epidemic of CKD in the Asian Pacific region; however, there is a considerable amount of variability in the resource availability among different countries or regions. Access to global information and evidence databases is also limited in some. To overcome these limitations, it was agreed that AFCKDI could play a very valuable role in harmony with ISN (especially COMGAN activity) and APSN activity, and we should continue to embrace the opportunity in the form of this meeting further in the future. There is no question that this is also a very good opportunity to give strength to networks and friendship of nephrologists in our region.

Few countries have developed local evidence-based clinical practice guidelines (CPGs) for CKD. Fortunately, global CKD guideline development is now in progress, and the definition and classification system introduced by KDIGO has been well accepted in this area. However, several local issues need to be addressed.

These include (1) estimated GFR equation(s) based on standardised creatinine estimation, which most efficiently reflect the Asian ethnicities, (2) efficient screening methods, which reflect the common pathogenesis of CKD in Asian countries, and (3) short-term strategies for intervention.

The ISN-KHDC programme for delaying progression could be applied in most of Asia areas regardless of economic status. Availability of interventions in other co-morbidities and complications of CKD, such as renal anaemia and CKD-MBD (mineral bone disease), varies among countries and regions because of economic status and/or public health policy.

We also need to facilitate collaboration, coordination and integration of locally developed CPGs, aiming to resolve the gaps in clinical practice. There is substantial

room for cooperation in implementing CPGs in the regions where resources are limited.

There are good examples of corporation between developed and developing countries. We need to expand this effort not just between two countries, but also among multiple relationships in our area by utilising the available resources of developed nations.

ESRD is a very visible outcome of CKD, and the availability of RRT is drastically different among countries and regions in the Asian Pacific area. Many lives are still lost because of lack of access to RRT. An international registry of patients on RRT among multiple countries in our area would be valuable.

Care of dialysis and renal transplant recipients can also be improved by implementing locally applicable global CPGs. More attention should be paid to previous live donors for renal transplantation because of the possible risk of future CKD.

The future plan for AFCKDI was decided as follows: (1) The AFCKDI will provide opportunity annually or biannually for every person who promotes CKD initiatives in the Asian Pacific region to join together and build consensus for action. (2) The second meeting was held at Kuala Lumpur in 2008, hosted at the 11th Asian Pacific Congress of Nephrology (APCN) by Zaki Morad, President of the 11th APCN. (3) The International Organising Committee (IOC) of the AFCKDI will continue its function by adding other experts, including the organiser of the next meeting. (4) The AFCKDI is not an organisation by itself nor does it belong to any society. Meetings will be organised by each host national society of nephrology. The IOC will assist the domestic committee for the success of the forum and will assure the continuation of the mission. (5) In order to organise the forum and promote CKD initiatives in the Asian Pacific region, the AFCKDI will look for support by both national and international societies. The AFCKDI will keep an intimate and mutual relation with the ISN, APSN and KDIGO.

Finally, we have reached the following consensus as the mission of the AFCKDI and decided on the continuation of this effort in the future: (1) to develop a consensus as a protocol of CKD detection in our region; (2) to analyse risk factors and cost-effective evaluation of the intervention; (3) to establish a network on the CKD Initiative in our region; (4) to contribute to the global initiative by using resources in our region.

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Appendix

Organization

President: Akira Hishida (President, JSN).
Secretary General: Yusuke Tsukamoto, Secretary: Yoshinari Yasuda.
International Organizing Committee.

Haiyan Wang (Co-chair), Yusuke Tsukamoto (Co-chair), Gavin Becker, Evan Lee Jon Choon, Hung-Chun Chen, Dae-Suk Han, Vivekanand Jha, Philip KT Li, Kriang Tungsanga, and Rowan Walker.

Domestic Organizing Committee:

Seiichi Matsuo (Chair), Kunitoshi Iseki (Co-chair), Tadao Akizawa, Yasuhiro Ando, Masafumi Fukagawa, Yasuhiko IIno, Takashi Igarashi, Hiroyasu Iso, Iekuni Ichikawa, Sadayoshi Ito, Yuhei Ito, Daijo Inaguma, Enyu Imai, Hirokazu Imai, Shunya Uchida, Nobuyuki Ura, Masayuki Endo, Kazo Kaizu, Naoki Kashihara, Yutaka Kiyohara, Yasuhiko Tomino, Ichiei Narita, Kosaku Nitta, Masakazu Haneda, Shigeko Hara, Hideki Hirakata, Masaru Horio, Hirofumi Makino, Takeshi Matsuyama, Toshio Miyata, Toshiki Moriyama, Kunihiro Yamagata, Kenji Wakai, Tsuyoshi Watanabe.

Hosted by the Japanese Society of Nephrology.
Affiliated by the Asian Pacific Society of Nephrology, the International Society of Nephrology-COMGAN, the KDIGO/Kidney Disease: Improving Global Outcomes.

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特集：血液浄化法

透析導入期データと生命予後

山縣邦弘　佐藤ちひろ

はじめに

わが国の透析導入においては，1992年度厚生科学研究腎不全医療研究事業研究報告書で示された慢性維持透析療法の導入基準が一つの目安として使用されてきた。しかしながら，透析導入患者の平均年齢は年々増加し，さらに透析導入の原疾患も，1983年には60％以上を占めていた慢性糸球体腎炎が年々減少し，1998年からは糖尿病性腎症が原疾患として1位となるなど，大きく変貌を遂げている。本稿では，このように透析導入原疾患や透析導入時年齢が変化する状況において，透析導入期の臨床検査値，特に残腎機能と透析導入後の生命予後との関連について，内外の報告ならびに日本透析医学会統計調査委員会の透析導入時調査の臨床検査データを中心に概説する。

わが国の透析導入の現況

日本透析医学会の調査による2008年度の新規透析導入患者数は37,671人で，年々増加の一途をたどっている。性別では，男性が女性の1.88倍と圧倒的に男性の割合が高い。さらに男女別の年齢分布は図**1**に示す通りであり，ピークは男性70～75歳，女性75～80歳に位置している。また主要な導入疾患別の平均年齢は，糖尿病性腎症が65.62歳(前年＋0.2歳)，慢性糸球体腎炎が66.86歳(＋0.5歳)，腎硬化症で73.99歳(＋0.4歳)と腎硬化症が特に高齢であるが，どの疾患でも導入時の高齢化が認められている。

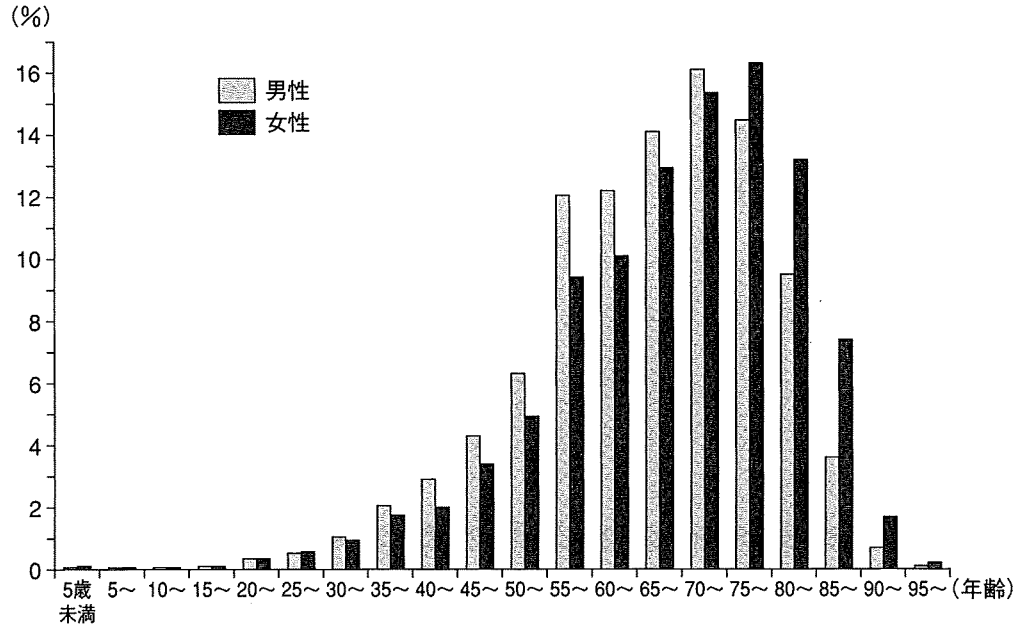

図 1　導入患者の性別年齢(文献1より引用)

Effect of residual renal function and other laboratory values on survival after initiation of dialysis therapy

筑波大学大学院人間総合科学研究科 疾患制御医学専攻腎臓病態医学分野

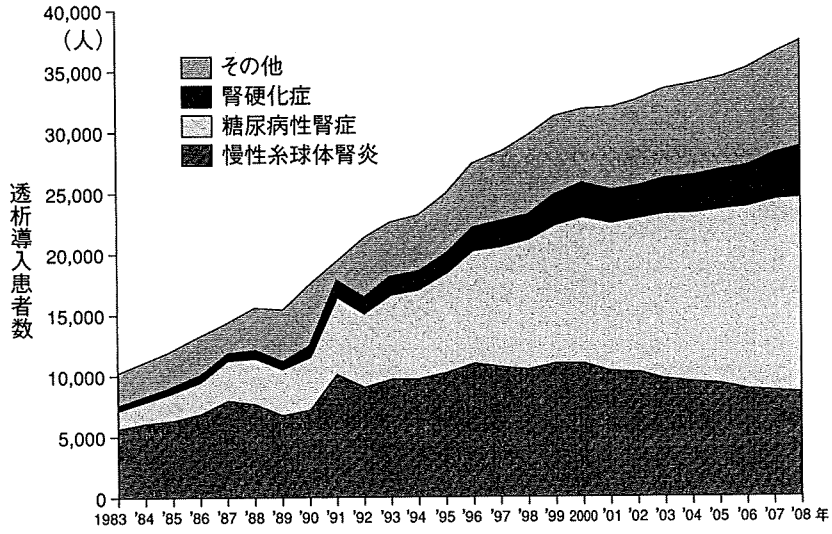

図 2 透析導入患者数と透析導入原疾患の推移(文献 1 より引用)

導入時年齢の高齢化，糖尿病性腎症の増加はともに透析導入患者の粗死亡率増加を懸念させるが，今のところ透析患者全体の粗死亡率は 1992 年以来 9.2〜9.7 %の範囲で推移しており，特定の傾向は示していない。

新規透析導入患者の原疾患としては，糖尿病性腎症が最多を占めるのは 1998 年以降不変で，糖尿病性腎症による透析導入患者数は増加しているものの，その割合は 2007 年度と比して 2008 年度は減少に転じ，頭打ちの傾向を示している。その他透析導入患者の高齢化とほぼ一致して，腎硬化症の割合が増加傾向を示している(**図 2**)。

透析導入のタイミング：導入時残腎機能の観点から

従来の救命が主とした目的であった透析導入では，透析導入のタイミングは，腎不全が進行し，さまざまな尿毒症症状の出現のため，そのままでは日常生活を行うのが困難と考えられるときであった。しかしながら，ESRD 患者の長期生存が当たり前のこととなると，透析導入のタイミングは透析導入後の生命予後を意識したものに変わってきた。尿毒症病態が長期的に持続することが生命予後に影響を与えることが危惧され，残腎機能の十分にある時期の透析導入のほうが生命予後が良いのではと期待されるようになってきた。Bonomini らは，透析導入時平均 Ccr 12.9 mL/min の早期導入群と 2.1 mL/min の遅れて導入した患者群の透析導入後 12 年での生存率を比較し，早期導入群 77 %に対し，遅れて導入した群では 51 %であったと報告している[2]。さらに，CANUSA study における CAPD 患者のクリアランスデータと生命予後の関係が残腎機能との関連で強く注目されるようになった。すなわち，残腎機能を含めた全透析量として，週当たり Ccr が 5 L/week/1.73 m^2 (6.94 mL/min/1.73 m^2) 増えるごとに，透析導入後 2 年以内の死亡の相対危険度が 0.95 ずつ減少するとされたことである[3]。このような残腎機能の余裕のあるうちに透析導入を行うことが，患者生命予後改善のために有効と考えられるようになった。

なお，現在用いられている透析導入の各国ガイドラインで，導入基準となる eGFR 値は，NKF-K/DOQI[4]2006：eGFR＜15 mL/min/1.73 m^2，カナダ[5]：eGFR＜18 mL/min/1.73 m^2，ヨーロッパ[6]：eGFR＜15 mL/min/1.73 m^2となっている。表に各国の透析導入ガイドラインをまとめた。表に示したごとく，これらの数値はあくまでもこの数値を満たしたうえで，尿毒症などの症状出現時に透析導入を行うとするものである。

ここで NKF/DOQI 1997 年度版では透析導入基準を eGFR＜10 mL/min/1.73 m^2としていたが，2006 年度版では＜15 mL/min/1.73 m^2と引き上げている。この理由としては，合併症の多くが eGFR＞15 mL/min/1.73 m^2の CKD ステージ 4 の時期から出現することや，透析導入時の腎機能が悪い群で生命予後が不良であるとする研究が引用されているが，一方で，残腎機能を eGFR のみで代用することの限界や，また透析導入時期による生命予後の差は，lead time bias を考慮すると統計的な有意差はないとする研究も紹介されている[7]。特に透析導入患者の観察研究から得ら

表　諸外国の主な透析導入ガイドラインの概略

souce	国・地域	公表年	GFR*		その他の条件
K/DOQI	米国	2006	＜15 mL/min/1.73 m^2	＋	腎機能で栄養不良，蛋白異化亢進，尿毒症症状出現時
ASN	米国	1999	＜12 mL/min/1.73 m^2	＋	尿毒症症状出現，蛋白摂取量＜0.8 g/kg/day に低下，栄養不良出現
			＜6 mL/min/1.73 m^2		
EBPG	ヨーロッパ	2005	＜15 mL/min/1.73 m^2	＋	尿毒症症状出現，血圧，水バランスのコントロール不能時 GFR＜6 mL/min/1.73 m^{2}に なるまで待たず GFR 8～10 mL/min/1.73 m^{2}で導入
			＜6 mL/min/1.73 m^2		
厚生労働省研究班	日本	1992	＜10 mL/min (Scre**＞8 mg/dL)	＋	尿毒症症状，日常生活度などや年齢も加味して点数化
			10～20 mL/min (Scre 5～8 mg/dL)	＋	
			20～30 mL/min (Scre 3～5 mg/dL)	＋	

*：日本はクレアチニンクリアランス値，**Scre：血清クレアチニン

れる結果については，残腎機能が十分にある早期透析導入は，生命予後不良であるとする報告が多くみられる[8～10]。それでも米国では新規透析導入患者の残腎機能が，1996年は eGFR＞10 mL/min/1.73 m^{2}で導入された患者は全体の25％であったのに対して，2005年には54％にまで増加しており，eGFR の比較的高い段階で導入する傾向が示されている。

しかしながら，残腎機能がまだ十分に保持されている状態でありながら，他の溢水などの合併症で早期に導入せざるをえない症例も日常の診療上では多く経験するところである。わが国の透析導入調査においても，透析時 eGFR が低いほど導入後の生命予後は良いとする結果が得られているが，真の生命予後を反映しているというよりは，感染，溢水，心不全などの重篤な合併症の有無を交絡因子としてみている可能性を否定できない[11,12]。そこで，2007年の透析導入患者調査では，さまざまな疾患による入院患者の1年後の生命予後予測が可能とされる Charlson comorbidity index を用いて[13]，透析導入時の併発症をカールソンスコアで補正前後の eGFR 別生命予後を示したのが**図3**である。カールソンスコアを共変量としてモデルに追加する前では，USRDS データを用いた米国の報告と同様[10]で，残腎機能の多い患者ほど生命予後が不良であった。しかしながら，カールソンスコアによる補正を追加することにより，さまざまな合併症，併発症状のために透析導入をせざるをえなかった状況が平均化されるため，透析導入後1年間の死亡のリスクが，補正前よりも残腎機能が多く残る群で改善し，残腎機能が少ない群では，死亡リスクが上昇，特に eGFR ＜2 mL/min/1.73 m^{2}では，4～6 mL/min/1.73 m^{2}よりも有意に死亡リスクが高くなり，少なくとも残腎機能の点からも，＜2 mL/min/1.73 m^{2}で透析導入すると，生命予後は不良となることが明らかである(図3)。

残腎機能以外の透析導入後生命予後に影響を与える透析導入時のパラメータ

透析導入時の残腎機能以外に生命予後に影響を与える因子として，体重，血清アルブミン(Alb)値に代表される栄養指標，炎症所見，貧血，腎透析専門医への late referral について，主に2006年，2007年に日本透析医学会において実施された透析導入患者調査の結果[1,11]を基に検討する。

1．栄養指標

従来から，BMI 低値，体重減少は透析導入時の予後不良因子とされてきた。また，血清 Alb 値も強力な予後不良因子として知られる。血清 Alb については 3.5 g/dL 以上に維持すれば，3.0～3.5 g/dL よりも 1.57 倍死亡のリスクは低下し，3.0 g/dL 未満では 3.3 倍に死亡リスクが跳ね上がる[1]。Canusa study の結果でも，血清 Alb 3.5 g/dL 以上での2年生存率 85％，3～3.5 g/dL で 75％，3.0 g/dL 未満で 64％である[3]。Ikizler らは Ccr 35 mL/min の患者 90 例をカリウム制限以外の栄養制限を一切行わず平均 16.5 カ月の経過観察を行ったところ，蛋白摂取量の進行性の低下を認め，Ccr 10 mL/min 未満では，蛋白摂取量 0.54 g/kg/day となって