



ARTICLE

# Evaluating estimated glomerular filtration rates of creatinine and cystatin C for male patients with chronic spinal cord injury

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## Abstract

**Study design** Retrospective study

**Objectives** To compare the accuracy of estimated serum creatinine (Cre)-based glomerular filtration rates (eGFRcre) and serum cystatin C (CysC)-based eGFR (eGFRcys) for determining renal function in patients with spinal cord injury (SCI).

**Setting** Department of Urology, Tohoku Rosai Hospital, Japan

**Methods** Male patients with SCI for longer than 5 years after injury were eligible for inclusion in this study. eGFRcre and eGFRcys were calculated using the following formulas:  $eGFR_{cre} = 194 \times Cre^{-1.094} \times age^{-0.287}$ ;  $eGFR_{cys} = (104 \times CysC^{-0.1019} \times 0.996^{age}) - 8$ . The eGFRcre/eGFRcys ratio between 0.8 and 1.2 was considered to be equal, and a relationship between them was investigated. Demographic data, degree of spinal cord damage, management of bladder emptying, post-injury period, and ambulatory status were evaluated.

**Results** A total of 115 male patients were included. eGFRcre overestimated renal function in 87 (76%) patients with SCI compared with eGFRcys. On univariate analysis, renal function by eGFRcre was overestimated in patients with an eGFRcre of more than  $60 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^2$  ( $P < 0.001$ ), in non-ambulatory patients ( $P < 0.001$ ) and, in patients with complete paralysis ( $P < 0.001$ ). On multivariate analysis, an eGFRcre of more than  $60 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^2$  ( $P < 0.001$ ), non-ambulatory status ( $P < 0.001$ ), complete paralysis ( $P = 0.17$ ), and age ( $P < 0.001$ ) were independent factors for overestimated renal function by eGFRcre.

**Conclusions** eGFRcre overestimates renal function compared with eGFRcys. eGFRcys is beneficial, particularly in patients with an eGFRcre of more than  $60 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^2$ , in non-ambulatory patients, and in older patients with SCI.

## Introduction

Estimated serum creatinine (Cre)-based glomerular filtration rates (eGFRcre) are commonly used to evaluate renal function [1, 2]. Cre production is dependent on muscle mass, and the concentration of Cre is influenced by renal handling and metabolism as well as by food intake [2, 3]. Patients with chronic spinal cord injury (SCI) exhibit decreased muscle mass. Therefore, Cre has been reported to

be an unreliable indicator of renal function in some patients with SCI [4].

Cystatin C (CysC) is a beneficial marker of glomerular filtration rate (GFR). CysC is a non-glycosylated low molecular weight protein. It is produced by all nucleated cells at a constant rate, freely filtered in the glomeruli, and reabsorbed and catabolized in the proximal tubular cells. The blood concentration of CysC depends almost entirely on the GFR and is not substantially affected by diet or nutritional status. CysC is independent of gender, age (>1 year), and muscle mass [5–7]. In SCI patients, it has been reported that CysC correlated better with GFR measured by <sup>51</sup>Cr-ethylenediaminetetraacetic acid (EDTA) clearance or 24-h creatinine clearance than did Cre [8, 9].

The objective of this study was to compare the accuracy of eGFRcre and serum cystatin C-based eGFR (eGFRcys) for determining renal function and to detect which SCI patients should be evaluated by CysC.

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## Methods

### Patients

In this retrospective study, 239 patients with SCI who had been under management of bladder emptying in our hospital were recruited from April 2011 to March 2016. Male patients with an SCI for longer than 5 years who were evaluated by both Cre and CysC on regular visits were included. Almost all SCI patients had Cre measured, and about half of the patients had CysC measured once a year. We used the blood sample on first regular visit during the study period. A total of 115 male patients were eligible for inclusion in this study.

### Procedure

We reviewed the medical records of the patients. Renal function in all patients was assessed using eGFR<sub>cre</sub> and eGFR<sub>cys</sub>. Cre and CysC were measured using an enzymatic method and colloidal gold agglutination, respectively. eGFR<sub>cre</sub> and eGFR<sub>cys</sub> were calculated using the following formulas, as defined by the Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease (CKD) 2012 in Japan:  $eGFR_{cre} = 194 \times Cre^{-1.094} \times age^{-0.287}$ ;  $eGFR_{cys} = (104 \times CysC^{-0.1019} \times 0.996^{age}) - 8$  [10]. We considered eGFR<sub>cre</sub> and eGFR<sub>cys</sub> to be equal when the eGFR<sub>cre</sub>/eGFR<sub>cys</sub> ratio was between 0.8 and 1.2. When the ratio was <0.8, renal function was underestimated by eGFR<sub>cre</sub>, and when the ratio was >1.2, it was overestimated by eGFR<sub>cre</sub>. We investigated the overestimation rate by stratification of the eGFR<sub>cre</sub> ranges (<30, 30–59, 60–89, 90–119, 120–149, and 150+). We evaluated the number of patients with an eGFR<sub>cys</sub> <60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> in each GFR category using the eGFR<sub>cre</sub>. Similarly, we evaluated the number of patients with eGFR<sub>cys</sub> <45 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> in each GFR category using the eGFR<sub>cre</sub>. GFR categories were defined by the Kidney Disease Improving Global Outcomes (KDIGO) 2012 CKD Guideline [11]. Observational data included the following: (1) demographic data (age, gender, years from injury); (2) location of spinal cord damage (cervical, thoracic, or lumbosacral); (3) paralysis status (complete or incomplete); (4) management of bladder emptying at the time of study (spontaneous micturition, self-catheterization, or indwelling catheterization; indwelling catheterization included urethral and suprapubic catheterization); (5) ambulatory status (ambulatory status included patients who could walk, and non-ambulatory status included wheelchair users and bedridden patients).

### Statistical analyses

Categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were

compared using Student's *t*-test. Clinical factors and their associated clinical outcomes were assessed by multivariate analysis with logistic regression analysis.

Data were expressed as the median (IQR) or the mean (SD). We considered a *P*-value <0.05 to be significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) which is a graphical user interface for R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) [12]. The ethical committee at Tohoku Rosai Hospital approved this study protocol.

## Results

A total of 115 male patients (median age, 66 years; age range, 30–84 years; interquartile range, 58–72) were followed for a median of 23.3 years (range, 6.8–54.3 years; interquartile range, 14.2–39.1) after SCI. Among all patients (57 with cervical injury and, 58 with thoracic or lumbosacral injury), 76 (66%) had complete paralysis at the time of study initiation. Sixteen patients had spontaneous micturition, while 50 required self-catheterization, and 49 required indwelling catheterization at that time. Mean (SD) Cre and CysC were 0.58 (0.29) mg dl<sup>-1</sup> and 1.07 (0.44) mg l<sup>-1</sup>, respectively, eGFR<sub>cre</sub> and eGFR<sub>cys</sub> were 130.6 (54.7) and 79.2 (24.4) ml min<sup>-1</sup> per 1.73 m<sup>2</sup>, respectively. Based on eGFR<sub>cre</sub>/eGFR<sub>cys</sub> ratios, eGFR<sub>cre</sub> overestimated renal function in 87 (76%) patients with chronic SCI. eGFR<sub>cre</sub> was almost equivalent (90%) to eGFR<sub>cys</sub> in ambulatory patients with chronic SCI. There were no patients whose renal function was underestimated by the eGFR<sub>cre</sub> (Table 1, Fig. 1).

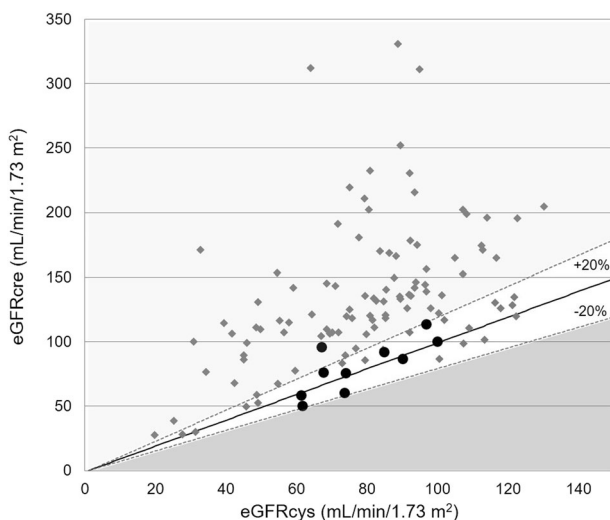
In patients with chronic SCI, a higher eGFR<sub>cre</sub> increased the overestimation rate of eGFR. However, only 22% of patients (2 of 9) with an eGFR<sub>cre</sub> <60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> (GFR category G3a–G5) were overestimated (Fig. 2). In addition, 78% (7 of 9) patients in GFR<sub>cre</sub> category G3a–G5 had a result <60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> by eGFR<sub>cys</sub> (Fig. 3). All four patients with an eGFR<sub>cre</sub> <45 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> (GFR category G3b–G5) also had a result <45 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> by eGFR<sub>cys</sub> (Fig. 4). On the other hand, there were 30 patients with an eGFR<sub>cre</sub> of >150 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>, and 28 of 30 (93%) patients had an eGFR<sub>cys</sub> >60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>. When we used eGFR<sub>cre</sub> 60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> as a cutoff value of renal deterioration which defined by eGFR<sub>cys</sub> <60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>, the sensitivity was 78% and the specificity was 82%.

On univariate analysis, renal function by eGFR<sub>cre</sub> was significantly overestimated when compared with eGFR<sub>cys</sub> in patients with an eGFR<sub>cre</sub> of >60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> (*P* <0.001), in non-ambulatory patients (*P* <0.001) and in

**Table 1** Characteristics of patients with spinal cord injuries (median (IQR) or mean (SD)) and factors associated with eGFRcys/eGFRcre ratio difference

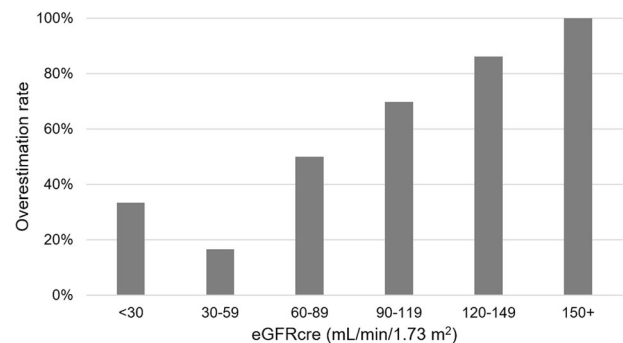
	Total	0.8–1.2	>1.2	<i>P</i> -value
eGFRcre/eGFRcys ratio				
No. of patients	115	28	87	
Median age (IQR)	66 (58–72)	61.5 (52–73.3)	67 (60.5–72)	0.108
Median years since injury (IQR)	23.3 (14.2–39.1)	18.5 (13.3–27.0)	26.6 (14.9–40.8)	0.029
Cre (mg dl <sup>-1</sup> )	0.58 ± 0.29	0.81 ± 0.34	0.50 ± 0.22	<0.001
eGFRcre (ml min <sup>-1</sup> per 1.73 m <sup>2</sup> )	130.6 ± 54.9	87.8 ± 30.3	144.4 ± 54.0	<0.001
CysC (mg l <sup>-1</sup> )	1.07 ± 0.44	1.05 ± 0.48	1.08 ± 0.43	0.831
eGFRcys (ml min <sup>-1</sup> per 1.73 m <sup>2</sup> )	79.2 ± 24.4	84.7 ± 28.0	77.5 ± 23.0	0.171
No. of patients with eGFRcre < 60	9	7 (78%)	2	<0.001
No. of patients with eGFRcys < 60	26	5 (19%)	21	0.608
Ambulation (AIS)				<0.001
Non-ambulatory	105	19 (18%)	86	
Ambulatory (non A-B)	10	9 (90%)	1	
Paralysis (AIS)				<0.001
Complete SCI (A)	76	10 (13%)	66	
Incomplete SCI (B-D)	39	18 (46%)	21	
Bladder management				0.052
Indwelling catheters	64	11 (17%)	53	
Spontaneous voiding /CIC	51	17 (33%)	34	
Level of injury				0.278
Cervical	57	11 (19%)	46	
Thoracic/lumbosacral	58	17 (29%)	41	

*IQR* interquartile range, *AIS* American Spinal Injury Association Impairment Scale, *eGFR* estimated serum creatinine glomerular filtration rates, *Cre* creatinine, *CysC* cystatin C, *SCI* spinal cord injury, *CIC* clean intermittent catheterization



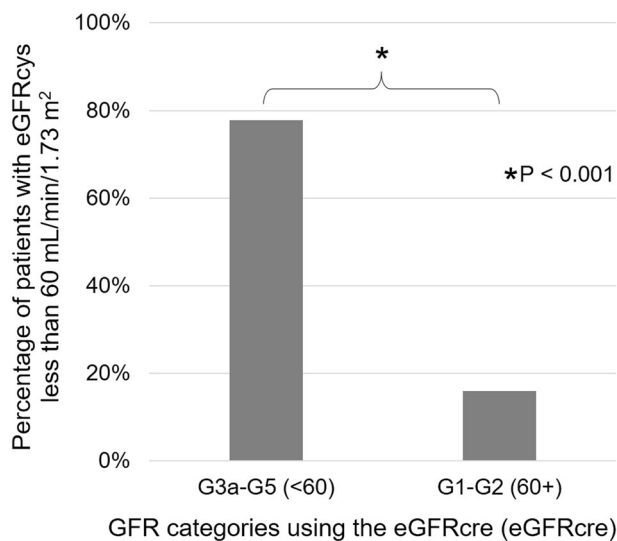
**Fig. 1** Relationship between eGFRcre and eGFRcys. Points between dotted lines are equivalent and points above an upper dotted line are overestimated by eGFRcre when compared with eGFRcys. ● ambulatory patients ( $n = 10$ ); ◆ non-ambulatory patients ( $n = 105$ )

patients with complete paralysis ( $P < 0.001$ ). Number of years after spinal cord injury was also a factor in overestimation of renal function by eGFRcre ( $P = 0.029$ ).

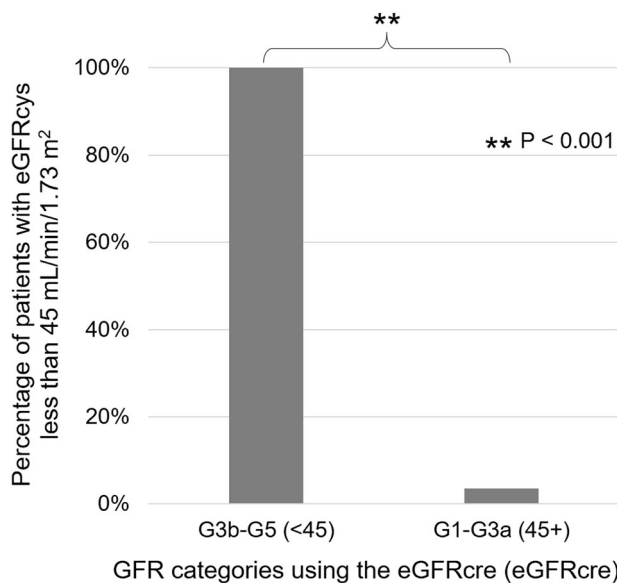


**Fig. 2** Percentage of patients with renal function overestimated by eGFRcre when compared with eGFRcys according to the level of eGFRcre

Management of bladder emptying and cervical injury or injury at another site were not independent factors that impacted overestimation of eGFR ( $P = 0.052$ ,  $P = 0.301$ , respectively) (Table 1). On multivariate analysis, renal function by eGFRcre was significantly overestimated when compared with eGFRcys in patients with an eGFRcre of  $>60$  ml min<sup>-1</sup> per 1.73 m<sup>2</sup> ( $P < 0.001$ ), in non-ambulatory patients ( $P = 0.002$ ), in patients with complete paralysis



**Fig. 3** Percentage of patients with eGFRcys  $<60 \text{ ml min}^{-1}$  per  $1.73 \text{ m}^2$ . Categories G3a-G5 had a result  $<60 \text{ ml min}^{-1}$  per  $1.73 \text{ m}^2$  by eGFRcre. Categories G1-G2 had a result  $>60$  and  $60 \text{ ml min}^{-1}$  per  $1.73 \text{ m}^2$  by eGFRcre. A significant difference was found between groups ( $*P < 0.001$ )



**Fig. 4** Rate of patients with eGFRcys  $<45 \text{ ml min}^{-1}$  per  $1.73 \text{ m}^2$ . Categories G3b-G5 had a result  $<45 \text{ ml min}^{-1}$  per  $1.73 \text{ m}^2$  by eGFRcre. Categories G1-G3a had a result  $>45$  and  $45 \text{ ml min}^{-1}$  per  $1.73 \text{ m}^2$  by eGFRcre. A significant difference was found between groups ( $**P < 0.001$ )

( $P = 0.017$ ) and in older patients ( $P < 0.001$ ) (Table 2). When stratified by SCI level, eGFRcre in patients with cervical injury was equal to that of those with thoracic injury but was overestimated when compared with those with lumbosacral injury (Table 3).

**Table 2** Factors associated with overestimation of renal function using eGFRcre by multivariate analysis

	Odds ratio	95% CI	P-value
eGFRcre $> 60 \text{ ml min}^{-1}$ per $1.73 \text{ m}^2$	83.3	8.74–794	$<0.001$
Non-ambulatory	45.5	4.05–511	0.002
Age	1.11	1.04–1.16	$<0.001$
Complete paralysis	4.79	1.32–17.4	0.017

CI confidence interval

## Discussion

In this study, we estimated renal function in patients with SCI investigating with the eGFRcre/eGFRcys ratio. Our results indicated that we might have overestimated many of those patients' renal function when using the Cre method. Erlandsen et al. [13] reported that eGFR using the Cre method matched only 50% of SCI patients compared with GFR measured by  $^{51}\text{Cr}$ -EDTA clearance. They considered a ratio of eGFRcre to measured GFR between 0.7 and 1.3 to be equal, and this result was similar to our study. Evaluating renal function precisely leads to early detection of CKD, which is defined as a GFR less than  $60 \text{ ml min}^{-1}$  per  $1.73 \text{ m}^2$ . CKD is associated with an increased risk of adverse outcomes including cardiovascular events, development of end-stage renal disease, and death [14].

It has been reported that patients with SCI may be more likely to develop CKD because they have risk factors for CKD such as high-pressure voiding, vesicoureteral reflux, urinary tract infection, and renal calculi [4]. Moreover, CKD has been shown to be a strong predictor of mortality in adults with SCI [15]. Therefore, it is important to detect early-stage CKD in these patients.

To our knowledge, renal function is evaluated by serum Cre in general practice because of its convenience and low cost. However, previous studies have found that serum Cre is not able to detect the early deterioration of renal function [4, 8]. CysC is a sensitive marker for detecting a reduced GFR and improves the detection of patients with CKD at an earlier stage. It has been established that CysC is superior to serum Cre for eGFR, but CysC is not the gold standard. Reference methods include inulin clearance and isotopic methods. Serum CysC-based equations have been proposed and validated, such as the Chronic Kidney Disease

**Table 3** Odds ratio stratified by level of injury

Level of injury	No.	0.8–1.2	$>1.2$	Odds ratio	95% CI	P-value
Cervical	57	11	46	—	—	—
Thoracic	44	10	34	0.81	0.28–2.41	0.81
Lumbosacral	14	7	7	0.25	0.059–1.00	0.035

Epidemiology Collaboration (CKD-EPI) creatinine/cystatin C combined equation, and the CKD-EPI cystatin C equation [16]. In general population cohorts, CysC is a stronger predictor for cardiovascular disease and risk of death than Cre [17, 18]. Mingat et al. [19] reported that an equation using cystatin C was the most precise method of renal function evaluation in patients with various causes of neurogenic bladder including multiple sclerosis, spinal cord injury, spina bifida, etc. Serum CysC is also a better index of renal function than Cre in patients with SCI [8, 9, 13]. Therefore, we compared Cre with CysC, considering CysC as a reference.

However, there is a disadvantage associated with CysC in the follow-up of patients with established renal disease such as IgA nephropathy, diabetic nephropathy, and glomerulonephritis because the rise in CysC is blunted compared with Cre at a lower GFR [20, 21]. Thus, Cre is still the better assay for following sequential changes in an individual with confirmed renal disease and this would be the same for patients with SCI.

It is unclear in which SCI patients CysC measurement should be used, i.e., presence or absence of cervical injury, complete or incomplete paralysis, ambulatory or not, age, time from injury, etc. In the present study, we identified patients whose renal function should be evaluated by CysC. According to our results on univariate analysis, CysC was effective for patients with an eGFR<sub>cre</sub> of more than  $60 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$ , non-ambulatory status, and complete paralysis. Only when compared with lumbosacral injury patients, CysC was effective for cervical injury patients. The main reason is the dramatic loss of muscle mass below the level of the injury lesion after SCI. Leg and trunk lean masses were significantly lower than arm lean mass [22]. We should use CysC to detect early-stage CKD for patients with such muscle loss. On the other hand, eGFR<sub>cre</sub> was equivalent to eGFR<sub>cys</sub> in 90% of ambulatory patients. Mingat et al. evaluated renal function of patients with neurogenic bladder and investigated mobility status, i.e., ambulatory or wheelchair. They reported that the CysC equation was the most precise method. However, when using the Cre equation, the bias was small in ambulatory patients. This result supports our study [18].

On multivariate analysis, age was also one of the factors related to overestimation of renal function using eGFR<sub>cre</sub>. Some reports describe that serum Cre decreases over time in SCI patients, despite an increasing risk of developing renal insufficiency [23]. Extensive loss of muscle mass with increasing age in SCI patients is thought to be the biggest reason for the decrease in serum Cre.

As mentioned, a higher eGFR<sub>cre</sub> increases the possibility of overestimation of renal function. On the other hand, our data show that the discrepancy between eGFR<sub>cre</sub> and eGFR<sub>cys</sub> could be smaller in SCI patients with a

lower eGFR<sub>cre</sub>. About 80% of patients with an eGFR<sub>cre</sub>  $<60 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$  also had an eGFR<sub>cys</sub>  $<60 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$ . We suggest that Cre could be used to evaluate renal function in SCI patients with an eGFR<sub>cre</sub>  $<60 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$ . CysC would be beneficial for the detection of early-stage CKD, especially for patients with an eGFR<sub>cre</sub>  $>60 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$ . Among the patients who seem to be normal when evaluated by Cre, patients with CKD accounted for 20%. Therefore, they need to be evaluated by CysC. More than 90% of patients with an eGFR<sub>cre</sub>  $>150 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$  had an eGFR<sub>cys</sub>  $>60 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$ . Those patients might have normal renal function; however, we should pay attention to the fact that all of them were overestimated.

Zhang et al. [24] has reported that indwelling catheterization was a predictor of upper urinary tract deterioration in SCI patients. However, there was no difference in renal function based on the type of bladder emptying management in our study. Renal function of our patients had been maintained. Therefore, Cre did not overestimate renal function when compared with eGFR<sub>cys</sub> in patients with an indwelling catheter.

Limitations of this study included its observational and retrospective nature. The patients were all men. These results were determined based on a sample of 115 male veterans at a single hospital; therefore, its accuracy and generalizability are uncertain. Another limitation of our study is the lack of a comparison with gold standard methods using inulin or a radioactive marked tracer. This study was retrospective and based on data collected from clinical records. The inulin or radioactive marker methods are not used in clinical practice and they are not covered by medical insurance in Japan.

A recent study has shown that calculation of the eGFR with a combination of Cre and CysC more accurately reflects measured GFR than either marker alone [15]. Moreover, in SCI patients, newer SCI equations that lead to more accurate estimation of GFR have been developed [25, 26]. However, these have not been used in general practice. Longitudinal research studies are needed to examine the estimation of renal function of SCI patients to more accurately predict intermediate and long-term clinical outcomes.

## Conclusions

In our study, we revealed that renal function evaluated by eGFR<sub>cre</sub> is often overestimated when compared with eGFR<sub>cys</sub>, and eGFR<sub>cys</sub> should be recommended for SCI patients, especially in patients with an eGFR<sub>cre</sub>  $>60 \text{ min}^{-1} \text{ per } 1.73 \text{ m}^2$ , patients with non-ambulatory status, patients with complete paralysis, and older patients. Cre is not recommended for, and CysC is useful in, the detection



of early-stage CKD for SCI patients with an eGFR<sub>cre</sub> of  $>60 \text{ min}^{-1}$  per  $1.73 \text{ m}^2$ . For patients with an eGFR<sub>cre</sub>  $<60 \text{ min}^{-1}$  per  $1.73 \text{ m}^2$ , we can continue to use Cr<sub>e</sub>, which may still be useful to follow high-grade CKD in SCI patients.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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