The Efficacy of Serum Cystatin C and Creatinine to Diagnose Impaired Renal Function in Cancer Patients Under Treatment with Cisplatin

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ABSTRACT

Renal function can be impaired in cancer patients treated with cisplatin. Currently, serum creatinine is used to diagnose renal dysfunction. This study aims to determine the efficacy of serum cyatatin C and ceratinine in contrast to the 24-hour urine creatinine clearance [CrCl] as the gold standard method in diagnosis of renal dysfunction in cancer patients under treatment with cisplatin. Seventy patients under treatment with cisplatin included. Serum cystatin C and creatinine were measured. CrCl in 24-hour urine was calculated. Measurements were done two times; before initiation of chemotherapy and before the fourth cycle of the chemotherapy. Then, using Receive Operating Curve [ROC] curve and at different cut-off points, sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV] of both cystatin C and creatinine to detect renal dysfunction were calculated. 24-hour urine CrCl was the gold standard method to define renal dysfunction. Sensitivity and specificity values of cystatin C of > 1.28 mg/L to predict CrCl< 78 mL/min were 77% and 95%, respectively. PPV and NPV of cystatin C were 95% and 79%, respectively with a diagnostic accuracy of 86%. On the other hand, sensitivity and specificity of creatinine were 64% and 47%, respectively. Serum cystatin C concentration had better sensitivity, specificity, PPV, and NPV compared to creatinine in detection of early stages of renal dysfunction in cancer patients under treatment with cisplatin. This marker can be used as an effective screening method in such patients to find renal dysfunction at its early stages.

Keywords: Cystatin C, Creatinine, Creatinine clearance, Cisplatin, Chemotherapy

ÖZET

Sisplatin ile Tedavi Edilen Kanser Hastalarında Bozulmuş Böbrek Fonksiyonunu Belirlemede Serum Cystatin C ve Kreatinin-in Etkinliği

Sisplatin ile tedavi edilen kanser hastalarında böbrek fonksiyonları bozulabilir. Günümüzde böbrek disfonksiyonlarını belirlemede kreatinin kullanılmaktadır. Bu çalışmada sisplatin ile tedavi edilen kanser hastalarında serum cystatin C ve kreatinin etkinliğinin böbrek disfonksiyonlarını belirlemede altın standart olarak kabul edilen 24 saatlik idrar kreatinin klerensi [CrCl] ile karşılaştırmayı amaç edinilmiştir.

Sisplatin ile tedavi edilmiş yetmiş hasta çalışmaya dahil edildi. Serum cystatin C ve kreatinin düzeyleri ölçüldü. 24 saatlik idrar ile CrCl değerleri hesaplandı. Ölçümler kemoterapi başlamadan önce ve dördüncü kür öncesi olmak üzere iki kez yapıldı. Sonrasında cystatin C ve kreatinin için Receive Operating Curve [ROC] eğrisi kullanılarak farklı eşik değerler, sensitivite, spesifisite, pozitif prediktif değer [PPV], negatif prediktif değer [NPV] hesaplandı. Böbrek disfonksiyonunu belirlemede 24 saatlik idrar CrCl altın standart olarak kabul edildi.

CrCl < 78 mL/dakika tahmin edebilmek için cystatin C serum 1.28 mg/L sensitivite ve spesifisite değerleri sırası ile %77 ve %95 idi. Cystatin C için PPV ve NPV değerler %95 ve %79 idi. Tanısal doğruluk oranı ise %86 idi. Ancak kreatinin için sensitivite ve spesifisite değerleri sırası ile %64 ve %47 idi.

Anahtar Kelimeler: Sistatin C, Kreatinin, Kreatinin klerensi, Sisplatin, Kemoterapi

INTRODUCTION

One of the concerns encountered in treatment of cancer patients with chemotherapy agents like cisplatin is the early diagnosis of renal function disorder.[1-3] In 1974, renal function disorder following treatment with cisplatin was reported for the first time.[2]

Currently, serum creatinine is used to diagnose renal function disorder. However, this laboratory test cannot diagnose the early stages of renal dysfunction. And until the time when the creatinine clearance [CrCl] reaches < 70 ml/min, we cannot see remarkable changes in serum creatinine level. On the other hand, serum creatinine level is affected by various factors including age, gender, the amount of protein consumption, muscular mass, inflammation, and some medications such as cimetidine, trimethoprim, etc.[1,3,4]

If renal dysfunction is not diagnosed at early stages and treatment with cisplatin continues, it can result in renal failure and ultimately death of patient may occur.[3,5-7] One of the laboratory markers proposed for early diagnosis of renal dysfunction is serum cystatin C level. Regarding this fact that this marker is not secreted by the kidney and is not reabsorbed to the blood stream after complete glomerular filtration, this marker is close to the ideal endogenous marker and also it is not changed by external factors.[3,4,8] For the first time, cystatin C and its application was reported by Stabuc et al. in patients who were treated by cisplatin and it was reported that it has a higher efficacy compared to serum creatinine.[3] In our country, this method has not been studied yet.

Regarding the high prevalence of patients who are receiving cisplatin chemotherapy, this study was carried out with the objective of determining the efficacy of cystatin C and serum ceratinine compared to the standard renal function assessment (i.e., 24-hour urine CrCl) in the diagnosis of renal dysfunction.

MATERIALS AND METHODS

In this diagnostic clinical trial, all patients whose cancer diagnosis had been confirmed by histopathology examination and chemotherapy with cisplatin was indicated and met the inclusion criteria were entered into the study. The study was done in the Radiotherapy-Oncology Department of Imam Hussein Hospital between 2006 and 2007.

Inclusion criteria consisted of cancer patients who were candidate for chemotherapy with cisplatin (alone or in combination chemotherapy) with a dosage of 50-100 mg/m^2 and who aged 25-65 years and had normal serum creatinine, blood urea nitrogen [BUN], and cystatin C. Exclusion criteria were age> 65 years, renal failure (i.e., CrCl ≤ 60 cc/min), taking medications including diuretics, cimetidine, trimethoprim, triamteren, combination chemotherapy of cisplatin with other nephrotoxic chemotherapeutic agents, prior kidney radiotherapy, or metastatic cancer.

In all patients (70 patients) in two time points (before initiation of chemotherapy and before the fourth cycle of the chemotherapy), serum creatinine and cystatin C were measured and 24-hour urine CrCl was calculated. The patient poured out, in the morning of the first day, the first urine sample and then started to collect his/her urine for 24 hours until the morning of the next day. In the morning of the second day, while in the fasting state, five cc of clotted blood was obtained to determine serum concentration of creatinine and cystatin C. The blood sample was then sent to the laboratory under standard conditions. Serum creatinine was measured with Pars Azmoon kit using Cobasmira RI 1000 instrument. Cystatin C was measured by Dako cystatin C PET kit with turbidimetry method [PETIA].

24-hour urine CrCl was calculated using the following formula:

$$\frac{\text{Urine creatinine (mg/dL)} \times \text{24-hours urine volume (ml/min)}}{\text{Serum creatinine (mg/dl)}} \times \frac{1.73\ \text{m}^2}{\text{Body surface area m}^2}$$

Since serum concentrations of creatinine and cystatin C have inverse relations with glomerular filtration rate [GFR] (i.e., CrCl), to determine the efficacy of these markers the patients were divided, according to their GFR, into good renal function (CrCl ≥ 78 cc/min) and reduced renal function (CrCl< 78 cc/min).

Statistical Analysis

To describe data we used frequency (percent), mean ±SD (standard deviation), 95% confidence interval, median, and range. To evaluate the difference between the two groups at baseline we used the Chi-squared and t-test. Any change was evaluated by the paired t-test. To evaluate the performance of cystatin C and creatinine in predicting the CrCl< 78 cc/min, we used Receive Operating Curve [ROC]. Then best cutoff point obtained by Youden index from this curve and we evaluate the sensitivity, specificity, positive predicted value [PPV], negative predicted value [NPV], likelihood ratio, diagnostic accuracy, diagnostic odds, and the Cohen's kappa index with their 95% confidence intervals for this cutoff point. P-value less than 0.05 was considered as statistically significant. At the last step, we evaluated the ability of the selected cutoff point in predicting the change in CrCl category (less than or more than 78 cc/min) before and after chemotherapy by the mentioned indexes and the Mac-Nemar test was applied to evaluate this ability. All statistical analyses were performed by the SPSS software (Version 17.0, SPSS Inc., and Chicago, IL)

The proposal of this study was approved by the Ethics Committee for Research of our medical university.

RESULTS

Totally, 70 patients participated in this study with a mean (±SD) age of 51 (±11) (median= 54, range= 25 to 65) years. Among them, 38 patients were male (54%). Thirty-five patients had CrCl of 60-

Table 1. Baseline characteristics of patients by their creatinine clearance status

			Baseline Creatinine Clearance		p
		Total	**<78**	**≥ 78**	
Age		51 ± 11	54 ± 10	49 ± 11	0.076*
		54 (25 to 65)	55 (25 to 65)	50 (30 to 65)	
Sex	Male	32 (46)	16 (46)	16 (46)	1*
	Female	38 (54)	19 (54)	19 (54)	
Treatment	Weekly	33 (48)	15 (44)	18 (51)	0.543*
	Each 3 week	36 (52)	19 (56)	17 (49)	
Height		161 ± 9	161 ± 9	161 ± 9	0.905**
		159 (146 to 185)	158 (148 to 185)	160 (146 to 178)	
Weight		64 ± 12	62 ± 11	65 ± 13	0.358**
		64 (41 to 100)	61 (41 to 86)	64 (43 to 100)	
BMI. Pre		24.7 ± 5.5	24.2 ± 4.7	25.3 ± 6.3	0.394**
		23.4 (15.6 to 42.2)	22.4 (18 to 35.5)	23.6 (15.6 to 42.2)	
Creatinin Pre		0.9 ± 0.2	1 ± 0.2	0.9 ± 0.2	
		0.9 (0.4 to 1.4)	0.9 (0.6 to 1.4)	0.9 (0.4 to 1.3)	0.165**
Cystatin C Pre		1.15 ± 0.33 1.16 (0.39 to 1.92)	1.37 ± 0.25 1.39 (0.8 to 1.92)	0.94 ± 0.23 0.94 (0.39 to 1.32)	<0.001**

* Based on t-test; ** Based on Chi-Square test

BMI= body mass index; Pre= before starting chemotherapy

Table 2. Change of the parameters before and after the chemotherapy

	Pre	Post	Change	Change %	95% CI	P*
Weight	64 ± 12	59 ± 10	3 ± 4	5 ± 7	2 to 5	<0.001
	64 (41 to 100)	60 (40 to 80)	3 (-10 to 15)	6 (-20 to 18)		
BMI	24.7 ± 5.5	22.8 ± 4.7	1.3 ± 1.8	5 ± 7	0.8 to 1.8	<0.001
	23.4 (15.6 to 42.2)	22.6 (15.6 to 34.6)	1.3 (-4.3 to 6.2)	6 (-20 to 18)		
Crcl	81 ± 22	77 ± 19	4 ± 13	3 ± 15	1 to 7	0.014
	78 (60 to 190)	75 (45 to 150)	3 (-33 to 51)	3 (-49 to 46)		
Creatinine	0.9 ± 0.2	0.9 ± 0.2	0 ± 0.2	0 ± 25	-0.02 to 0.07	0.315
	0.9 (0.4 to 1.4)	0.9 (0.5 to 1.6)	0 (-0.5 to 0.4)	0 (-125 to 44)		
Cystatin C	1.15 ± 0.33	1.21 ± 0.28	-0.06 ± 0.22	-9 ± 26	-0.11 to -0.004	0.033
	1.15 (0.39 to 1.92)	1.23 (0.12 to 1.97)	-0.06 (-0.64 to 0.83)	-5 (-105 to 87)		

* Based on Paired t-test

Crcl= creatinine clearance; BMI= body mass index; pre= before starting chemotherapy; Post= before the fourth cycle of chemotherapy

77cc/min and 35 patients had CrCl ≥ 78 cc/min. The baseline characteristics of the patients by their creatinine clearance status are demonstrated in Table 1.

In Table 2, changes of body mass index [BMI], CrCL, serum creatinine, and serum cystatin C concentrations before and after chemotherapy are presented. As shown, except for serum creatinine, a significant change was seen in other factors.

Figure 1 presents the status of CrCl after chemotherapy. CrCl in 8 patients (23%) of those with baseline CrCl of 60-77 cc/min decreased to less than 60 cc/min. However, in those with baseline CrCl of ≥ 78 cc/min, only one patient showed CrCl of less than 60 cc/min after chemotherapy.

Figure 2 depicts the scatter plot which demonstrates the inverse linear relationship between serum cystatin C level and CrCl. However this relation was weak (r=–0.447, p< 0.001).

Figure 3 shows the inverse linear relationship between serum creatinine and CrCl values.

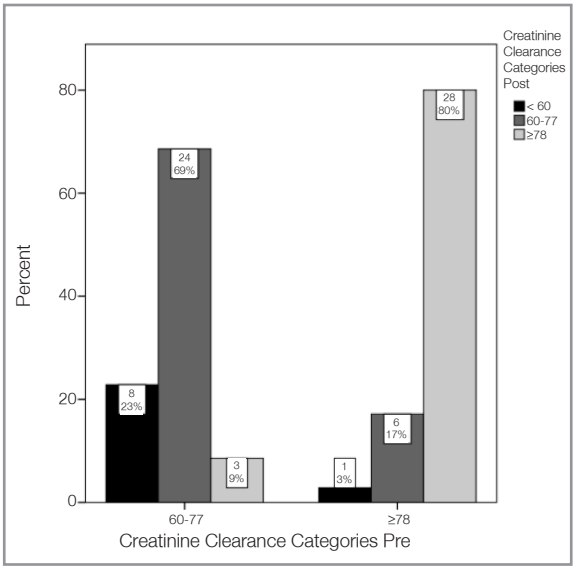

Figure 1. As demonstrated there were 35 patients who had creatinine clearance ranging from 60 to 78 in the baseline. Among them 8 (23%) had creatinine clearance < 60 after chemotherapy. Also, 35 patients creatinine clearance ≥ 78 who 1 (3%) of them had creatinine clearance < 60 after chemotherapy.

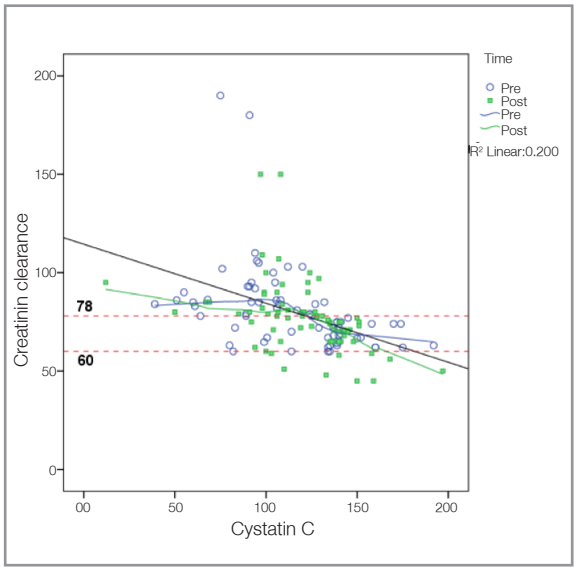

Figure 2. The scatter plot demonstrating the inverse linear relation between cystatin C and creatinine clearance value. However this relation was weak (r=–0.447, p< 0.001).

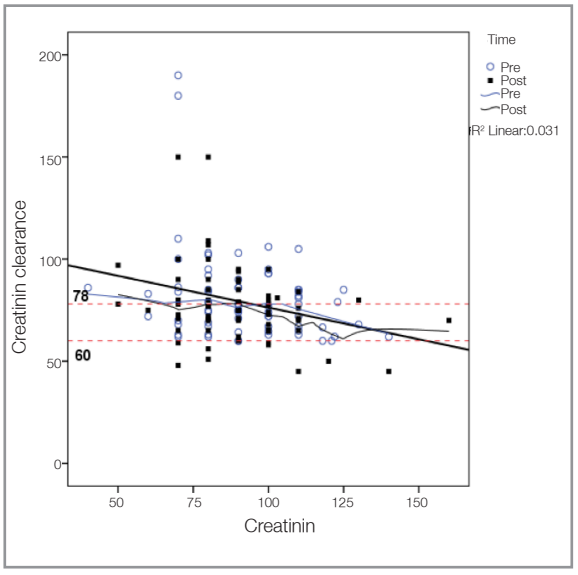

Figure 3. The scatter plot demonstrating the inverse linear relation between Cr and creatinine clearance value.

In Figure 4, ROC curve which demonstrates the sensitivity and specificity of cystatin C and creatinine in predicting the creatinine clearance < 78 at different cutoff points is presented. The area under the curve for cystatin C was 0.891 (95% CI= 0.837 to 0.946) and for creatinine it was 0.590 (95% CI= 0.496 to 0.684).

Table 3 shows the diagnostic accuracy of cystatin C in prediction of CrCl< 78 mL/min. The cut-off points were derived from the ROC based on both pre- and post-chemotherapy results. Sensitivity and specificity of cystatin C were 77% and 95%, respectively to predict CrCl< 78 mL/min. PPV and NPV were 95% and 79%, respectively. Sensitivity and specificity of creatinine were 64% and 47% respectively, and PPV & NPV were 56% and 55%, respectively.

Totally CrCl in 7 (10%) patients changed from "≥ 78 cc/min" into "< 78 cc/min". On the other hand, based on the serum creatinine, 9 (13%) patients showed unsatisfied changes and based on serum cystatin C 3 (4%) patients showed this renal function deterioration (i.e., CrCl< 78 cc/min). The accuracy of serum creatinine and cystatin C in the diagnosis of CrCl changes are shown in Table 4,5.

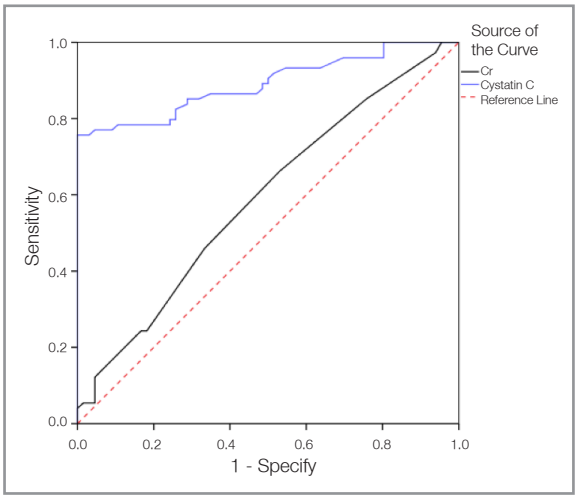

Figure 4. ROC Curve

DISCUSSION

According to the obtained result, PPV of serum creatinine was 56% and NPV was 55%. For serum cystatin C, PPV and NPV were 95% and 79%, respectively. Stabuc et al. 3 in 2000 studied 60 patients with combined chemotherapy with cisplatin to predict CrCl reduction. Serum cystatin C, creatinine, and 24-hour urine CrCl were measured before chemotherapy and also before the fourth cycle of the chemotherapy. They reported that compared to creatinine, cystatin C showed a better significant association with GFR (r= 0.84 vs. 0.74; P= 0.01).

Table 3. Diagnostic accuracy specification of cystatin C and creatinine in prediction of Crcl< 78 the cut off were derived from the Roc Curve based on both pre and post results

	Cystatin C > 1.28	Creatinine > 0.85
True Positive (TP)	57	49
True Negative (TN)	63	31
False Positive (FP)	3	35
False Negative (FN)	17	25
Sensitivity	77 (66, 85)	64 (53, 75)
Specificity	95 (87, 98)	47 (35, 59)
Positive Predictive Value	95 (86, 98)	56 (45, 67)
Negative Predictive Value	79 (69, 86)	55 (42, 68)
Diagnostic Accuracy	86 (79, 91)	56 (47, 64)
Likelihood ratio of a Positive Test	17 (9 - 33)	1.2 (1.1 - 1.3)
Likelihood ratio of a Negative Test	0.24 (0.21 - 0.27)	0.76 (0.65 - 0.88)
Diagnostic Odds	70.4 (19.6 - 252.9)	1.6 (0.8 - 3.2)
Cohen's kappa (Unweighted)	0.72 (0.55 - 0.88)	0.11 (-0.05 - 0.28)

Results are presented as frequency or value (95% confidence Interval).

Crcl= creatinine clearance; ROC= Receive Operating Curve

And according to ROC analysis, sensitivity of cystatin C was higher than that of creatinine (87% vs. 61%). According to their results, serum cystatin C for prediction of CrCl< 78 mL · min^{-1} · 1.73 m^{-2} was more efficacious compared to creatinine. The limitation of this study is that they did not report other chemotherapeutic agents used with cisplatin which may be nephrotoxic.

Macisaac et al.[8] investigated the accuracy of serum cystatin C and creatinine for diagnosing mild/moderate chronic renal disease in 251 diabetics was studied. They used TC^{99} DTPA as the standard method of renal function assessment. They reported that in mild chronic renal disease (CrCl< 90 mL/min), serum cystatin C had a higher diagnostic accuracy compared to creatinine. They concluded that for screening purposes in mild renal dysfunction in diabetic patients, serum cystatin C can be used. Since they used TC^{99} DTPA as the standard method for renal function assessment their study is high valid enough, but this method is costly. Narvaez et al.[9] in 2008 studied serum cystatin C with the objective of substituting this marker instead of serum creatinine to diagnose and monitor renal function in children; 109 children who aged < 18 years to estimate GFR with two methods of serum creatinine and cystatin C compared to standard method (TC 99 DTPA). They noted that to predict GFR < 70 m/min, serum cystatin C had a sensitivity of 100% and specificity was 48%. But serum creatinine had a sensitivity of 77% and specificity of 91%. They concluded that serum creatinine can be replaced by cystatin C to monitor renal function in pediatric patients.

Various studies have been done to determine an ideal method to estimate GFR and various standard renal function assessment methods were used in these studies including 24-hour urine CrCl, inulin, and TC^{99} and the association of serum cereatinine and cystatin C with the standard methods was evaluated. In all studies, cystatin C was superior to serum creatinine at estimation of early stages of renal dysfunction.[10-17] In contrast to what we observed here, in a study to determine the correlation

Table 4. Diagnostic accuracy of creatinine and cystatin C in detection of CrCl change to Crcl<78 category

	Cystatin C > 1.28	Creatinine > 0.85
True Positive (TP)	2	1
True Negative (TN)	62	55
False Positive (FP)	1	8
False Negative (FN)	5	6
Sensitivity	29 (8, 64)	14 (3, 51)
Specificity	98 (92, 100)	87 (77, 93)
Positive Predictive Value	67 (21, 94)	11 (2, 44)
Negative Predictive Value	93 (84, 97)	90 (80, 95)
Diagnostic Accuracy	91 (82, 96)	80 (69, 88)
Likelihood ratio of a Positive Test	18 (0.2 - 1481)	1.125 (0.0 - 184000)
Likelihood ratio of a Negative Test	0.73 (0.49 - 1.08)	0.98 (0.70 - 1.37)
Diagnostic Odds	24.8 (1.9 - 323.3)	1.2 (0.12 - 10.8)
Cohen's kappa (Unweighted)	0.36 (0.15 - 0.57)	0.01 (-0.22 - 0.25)
P*	0.791	0.219

Results are presented as frequency or value (95% confidence Interval).

* Based on MacNemar test.

Crcl= creatinine clearance; P= P value

of serum cystatin C levels with the serum creatinine levels and GFR and to examine potential use of cystatin C for prediction of the renal function changes in patients who received cisplatin-based chemotherapy, the authors reported that although there was a statistically significant correlation between the serum levels of cystatin C and creatinine before initiating chemotherapy, no correlation was found between level of cystatin C subsequent to the cisplatin infusion and serum creatinine level following the third course of chemotherapy.[18]

In patients with minor reduction in renal function, since cystatin C is not secreted by the kidney after glomerular filtration and is not reabsorbed to the blood stream is close to endogenous ideal marker and provides more information than serum creatinine.[3,4] Also, creatinine is affected by non-renal-related factors but cystatin C is not affected by external factors such as age, gender, muscular mass, diet, and inflammation.[1,3,5]

The concept of application of cystatin C in chemotherapy patients may not necessarily be generalizable to other chemotherapeutic agents. For instance, in a study on patients with ovarian cancer who received paclitaxel plus cisplatin, it was reported that cystatin C is not a reliable marker of the GFR in ovarian cancer patients.19 Kume et al.[20] in their study on esophageal cancer patients who received cisplatin reported that concentration fluctuations in serum cystatin C concentrations are unlikely to correlate with platinum elimination from the plasma. Therefore, renal function estimates according to measurement of serum cystatin C may be underestimated during perioperative cisplatin-based chemotherapy for esophageal cancer.

The limitations we encountered were low sample size and not considering some other factors like diet which can affect CrCl. We also were not able to follow the cases for a longer time to examine the long term effects of cisplatin. We recommend

Table 5. Diagnostic accuracy specification of cystatin C and creatinine in prediction of Crcl < 78 the cut off were derived from the Roc Curve based on both pre and post results

	Cystatin C > 1.28	Creatinine > 0.85	Cr > 1.3
True Positive (TP)	57	49	
True Negative (TN)	63	31	
False Positive (FP)	3	35	
False Negative (FN)	17	25	
Sensitivity	77 (66, 85)	64 (53, 75)	5 (2, 13)
Specificity	95 (87, 98)	47 (35, 59)	97 (90, 99)
Positive Predictive Value	95 (86, 98)	56 (45, 67)	67 (30, 90)
Negative Predictive Value	79 (69, 86)	55 (42, 68)	48 (39, 56)
Diagnostic Accuracy	86 (79, 91)	56 (47, 64)	49 (40, 57)
Likelihood ratio of a Positive Test	17 (9 - 33)	1.2 (1.1 - 1.3)	1.78 (0.00 - 25180)
Likelihood ratio of a Negative Test	0.24 (0.21 - 0.27)	0.76 (0.65 - 0.88)	0.97 (0.95 - 1.00)
Diagnostic Odds	70.4 (19.6 - 252.9)	1.6 (0.8 - 3.2)	1.8 (0.3 - 10.3)
Cohen's kappa (Unweighted)	0.72 (0.55 - 0.88)	0.11 (-0.05 - 0.28)	0.02 (-0.04 - 0.09)

Results are presented as frequency or value (95% confidence Interval).

Crcl= creatinine clearance

that in future studies, these issues should be considered for a better clarification of cystatin C role in defining renal dysfunction in patients treated by cisplatin.

It seems, according to our results, that serum cystatin C concentration can be applied to diagnose early stages of reduced renal function but serum creatinine cannot be used. Regarding difficulties in collection of urine in the method of 24-hour urine CrCl, serum cystatin C concentration can be used as a screening method for detection of reduced renal function before chemotherapy with nephrotoxic agents such as cisplatin and its dose modification as a substitute for CrCl.

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