LIVER TRANSPLANTATION 12:285-291, 2006

ORIGINAL ARTICLE

Cystatin C as a Marker of Renal Function Immediately after Liver Transplantation

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To verify whether cystatin C may be of some use as a renal function marker immediately after orthotopic liver transplantation (OLT), we compared serum cystatin C (S_{Cyst}), serum creatinine (S_{cr}), and creatinine clearance (C_{cr}) levels with the glomerular filtration rate (GFR). On postoperative days 1, 3, 5, and 7, S_{Cyst} and S_{cr} was measured in simultaneously drawn blood samples, whereas C_{cr} was calculated using a complete 24-hour urine collection. The GFR was determined on the same days by means of iohexol plasma clearance (I-GFR). The correlation between $1/S_{Cyst}$ and I-GFR was stronger than that of $1/S_{cr}$ or C_{cr} ($P < 0.01$). In the case of moderate reductions in I-GFR (80-60 mL/minute/1.73 m^2), S_{cr} remained within the normal range, whereas the increase in S_{cyst} was beyond its upper limit; for I-GFR reductions to lower levels (59-40 mL/minute/1.73 m^2), S_{cr} increased slightly, whereas S_{cyst} was twice its upper normal limit. When we isolated all of the I-GFR values on days 3, 5, and 7 that were ≥30% lower than that recorded on the first postoperative day, S_{Cyst} ($P < 0.0001$) and S_{cr} ($P < 0.01$) levels were increased, whereas C_{cr} remained unchanged ($P = 0.09$). Receiver operating characteristic (ROC) area-under-the-curve analysis showed that the diagnostic accuracy of S_{cyst} was better than that of S_{cr} and C_{cr}. S_{cyst} levels of 1.4, 1.7, and 2.2 mg/L respectively predicted I-GFR levels of 80, 60, and 40 mL/minute/1.73 m^2. In conclusion, cystatin C is a reliable marker of renal function during the immediate post-OLT period, especially when the goal is to identify moderate changes in GFR. *Liver Transpl 12:285-291, 2006.* © 2006 AASLD.

Received August 3, 2005; accepted September 28, 2005.

It has been widely demonstrated that acute renal failure can severely affect the postoperative course of a complex procedure such as orthotopic liver transplantation (OLT).[1,2] As renal function can be threatened for different reasons in the period immediately following OLT (i.e., hemodynamic disturbances, drug nephrotoxicity, acute surgical or infectious complications), it is very important for clinicians to have access to sensitive and reliable markers that can promptly identify renal dysfunction from its initial stage in order to allow them to adopt the necessary preventive and supportive measures for avoiding or containing the development of renal damage.

Although commonly used, the measurement of serum creatinine (S_{cr}) and the calculation of creatinine clearance (C_{cr}) are not very reliable in cirrhotic patients undergoing OLT because some of the peculiarities of the liver disease (reduced muscle mass, decreased creatinine biosynthesis, high blood bilirubin levels) can lead to false results.[3-5] Furthermore, it has been reported that making routine S_{cr} measurements is an insensitive way of assessing renal function in patients adminis-

Abbreviations: OLT, orthotopic liver transplantation; S_{Cyst}, serum cystatin C; S_{cr}, serum creatinine; C_{cr}, creatinine clearance; GFR, glomerular filtration rate; I-GFR, glomerular filtration rate measured by means of iohexol plasma clearance; ROC, receiver operating characteristic.

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DOI 10.1002/lt.20657
Published online in Wiley InterScience (www.interscience.wiley.com).

tered either cyclosporin A or tacrolimus.[6] On the other hand, assessing the glomerular filtration rate (GFR) by more accurate methods using exogenous markers or radioisotopes is expensive and hardly practical in the clinical management of critically ill and unstable patients. This situation has drawn attention to the use of an endogenous marker of GFR, such as cystatin C, a low-molecular-weight polypeptide (~13.3 kD) that is constantly produced by all nucleated cells, freely filtered by glomeruli, and reabsorbed and catabolized in kidney proximal tubular cells. Consequently, serum cystatin C (S_{cyst}) concentrations are determined by GFR regardless of age, gender, muscle mass, or the presence of inflammatory states.[7-11] It has already been shown that S_{cyst} is a reliable marker of GFR in cirrhotic patients[12-14] and after kidney transplantation.[15,16] In relation to OLT, cystatin C has so far been tested in the later postoperative phase,[8,9,17] and so the aim of this study was to verify whether S_{cyst} may be of some use also during such a delicate period as the immediate postoperative phase.

MATERIALS AND METHODS

The study involved a population of post-OLT cirrhotic patients in an intensive care unit who gave their consent to participate. The only exclusion criterion was the need for any extra-corporeal renal replacement therapy.

The renal function of all of the enrolled patients was monitored by measuring S_{cr}, S_{cyst}, and GFR, and by calculating C_{cr}, on postoperative days 1, 3, 5, and 7. Creatinine and cystatin C were measured in simultaneously drawn blood samples; C_{cr} was calculated using a complete 24-hour urine collection; GFR was measured by determining iohexol plasma clearance (I-GFR), and non-age-adjusted values of <80 mL/minute/1.73 m^2 were considered compatible with reduced renal function.[8,9]

Laboratory Methods

S_{cr} levels were determined by means of Jaffè's reaction; S_{cyst} concentrations were measured by means of latex-amplified nephelometry using the N Latex Cystatin C diagnostic kit (Dade Behring Diagnostic, Manheim, Germany) and the BN-II system (Dade Behring Diagnostic, Manheim, Germany). I-GFR was determined by intravenously administering 5 mL of an Omnipaque 300 solution (Nycomed, Oslo, Norway) containing 647 mg/mL of iohexol (corresponding to 300 mg/mL of iodine); the blood samples were taken immediately before (time 0) and 5, 15, 60, 90, 180, 240, and 300 minutes after the injection, as previously described.[18] If the level of S_{cr} was ≥2 mg/dL, 2 further blood samples were taken 360 and 420 minutes after the injection, and if it was ≥5 mg/dL, a final sample was drawn after 1,440 minutes. Plasma iohexol concentrations were determined in duplicate by means of high-pressure liquid chromatography (Waters Millipore, Milford, MA) on a Bondapak C_{18} inverse phase column (Waters, Milford, MA). The mobile phase consisted of a 96:4 solution of bi-distilled water and acetonitrile, pH 2.6. I-GFR was calculated using the formula I-GFR = injected iohexol dose/area under the plasma disappearance curve; the result was corrected by body surface area.[19,20] All of the samples for I-GFR determinations were processed in the same laboratory.

TABLE 1. Study Population Data

Study population, n	68
Males/females, n (%)	48 (69.7)/20 (30.3)
Age, (range)	50.3 ± 2 (35–61)
Primary liver disease, n (%)	
Post-viral infection cirrhosis	54 (79.5)
Alcoholic disease	1 (1.5)
Liver cancer	6 (8.8)
Acute liver failure	2 (2.9)
Other	5 (7.3)
Length of ICU stay, days	4.7 ± 4.6
ICU outcome, alive/dead, n (%)	67/1 (98.5/1.5)

Abbreviation: ICU, intensive care unit.

Concomitant Treatments

Standard perioperative anti-infective prophylaxis consisted of the administration of third-generation cephalosporins for 2 days after OLT. Postoperative pain was controlled by administering intramuscular morphine 1 mg/kg 40 minutes before the end of the procedure, followed by a continuous intravenous infusion of 20 to 40 mg/day, starting when the patients arrived in the intensive care unit. The immunosuppressive protocol included oral cyclosporin A (Sandimmun Neoral, Novartis Pharma S.A., Haningue, France) or tacrolimus (Prograf, Fujisawa, Milano, Italy), methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Puurs, Belgium), and basiliximab (Simulect, Novartis Pharma S.A., Haningue, France).

Statistical Analysis

The data are expressed as mean values ± standard deviation unless otherwise specified. We compared I-GFR with C_{cr} and the reciprocal values of S_{cr}, and S_{cyst} (because S_{cr} and cystatin C are inversely related to GFR) by means of simple regression analyses and correlation coefficient estimates. The significance of the differences between the correlation coefficients was estimated using Fisher's z-transformation test. Receiver operating characteristic (ROC) analysis was used to identify the S_{cys} values that predicted different levels of renal dysfunction corresponding to I-GFR limits of 80, 60, and 40 mL/minute/1.73 m^2. The area under the ROC curve was used to evaluate the diagnostic accuracy of the studied markers. The t-test, the Wilcoxon's signed rank test, and the chi-square test were also used. The statistical analyses were performed using STATA software (release 7.0, Stata Corporation, College

TABLE 2. Markers of Renal Function During the Study

	POD 1	POD 3	POD 5	POD 7
Serum cystatin C (mg/L)	1.4 ± 0.8	1.7 ± 0.9	1.7 ± 1.1	1.6 ± 1.0
Serum creatinine (mg/dL)	1.0 ± 0.6	1.2 ± 1.3	1.2 ± 1.4	1.2 ± 1.5
Creatinine clearance (mL/minute)	108.6 ± 65.5	114.0 ± 63.7	100.4 ± 55.5	98.1 ± 50.6
I-GFR (mL/minute 1.73 m^2)	91.7 ± 43.5	97.1 ± 44.5	89.5 ± 38.4	86.9 ± 32.3

Abbreviations: I-GFR, glomerular filtration rate measured by means of iohexol clearance; POD, postoperative day.

Station, TX), and a probability of 5% was considered significant.

RESULTS

The study involved 68 patients who underwent OLT at the Liver Transplantation Centres of Pisa (48 patients) and Turin (20 patients) between August 2003 and March 2004. Some of the characteristics of the study population are given in Table 1.

The time-course of each renal function marker is shown in Table 2. The reciprocal of S_{Cyst} and S_{cr} and the values of C_{cr} were plotted against I-GFR: the coefficients of correlation between $1/S_{Cyst}$ and I-GFR on the 4 study days were 0.80, 0.90, 0.86, and 0.86, those between $1/S_{cr}$ and I-GFR were 0.78, 0.76, 0.51, and 0.61, and those between C_{cr} and I-GFR were 0.75, 0.81, 0.37, and 0.60 (Figs. 1-3). The difference in favor of $1/S_{Cyst}$ was significant in comparison with both $1/S_{cr}$ and C_{cr} ($P < 0.01$ in both cases).

In correspondence with slightly reduced I-GFR values (80-60 mL/minute/1.73 m^2), the levels of S_{cr} remained within normal limits, whereas those of S_{cyst} were already high (Table 3). At lower I-GFR levels (59-40 mL/minute/1.73 m^2), S_{cr} levels were slightly increased, whereas S_{cyst} levels were twice the upper normal limit (Table 3); in the case of severely reduced GFR levels (<40 mL/minute/1.73 m^2), also the levels of S_{cr} became clearly high (Table 3). Finally, the 100 I-GFR values ≤80 mL/minute/1.73 m^2 (36.7% of the total) measured during the study corresponded to 51 S_{cr} determinations within the normal range, but to no normal determinations of S_{cyst} ($P < 0.0001$) (Fig. 4). However, the same plot highlights that elevated S_{cyst} values may be found when GFR is within the normal range.

In order to evaluate the ability of cystatin C to reveal moderate variations in GFR, we compared the behavior of the studied markers after having isolated all of the I-GFR values recorded on days 3, 5, and 7 that were ≥30% lower than that recorded on the first postoperative day (baseline). Such reductions were observed in 30 subjects (44.1% of the total), where I-GFR passed from 112.7 ± 41.1 to 69.8 ± 28.6 mL/minute/1.73 m^2 ($P < 0.001$). In the 49 corresponding data sets, S_{Cyst} increased from 1.1 ± 0.6 to 1.9 ± 0.9 mg/L ($P < 0.0001$) and S_{cr} from 0.9 ± 0.6 to 1.3 ± 0.8 mg/dL ($P < 0.01$), with no change in C_{cr} (from 116.1 ± 53.2 to 94.8 ± 56.1 mL/min; $P = 0.09$). However, in these patients, 33 (67.3%) of the creatinine values were within the normal

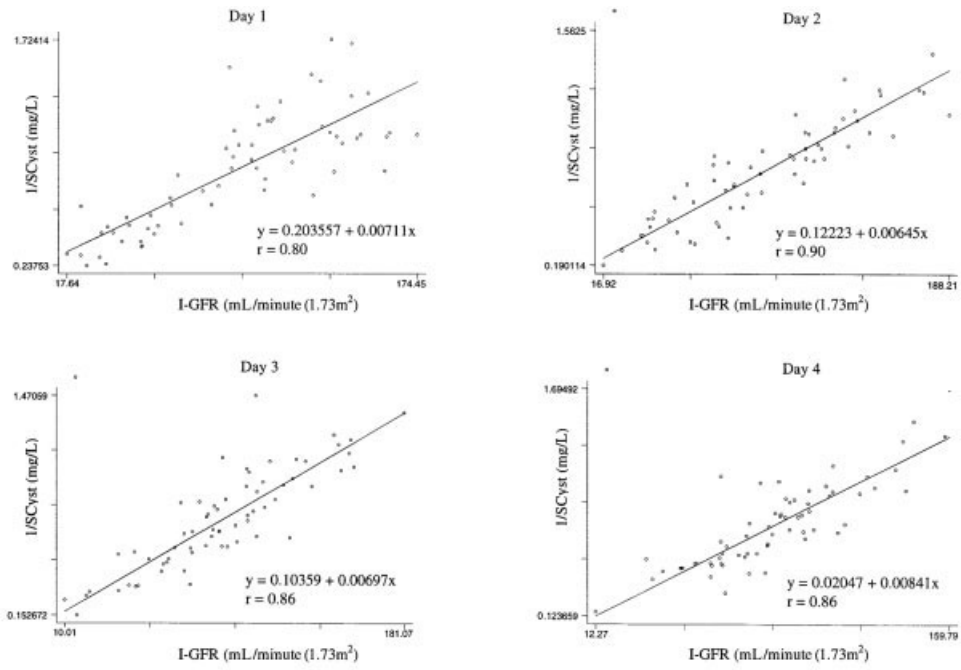

Figure 1. Correlations between S_{Cyst} and I-GFR. I-GFR = GFR measured by means of iohexol clearance.

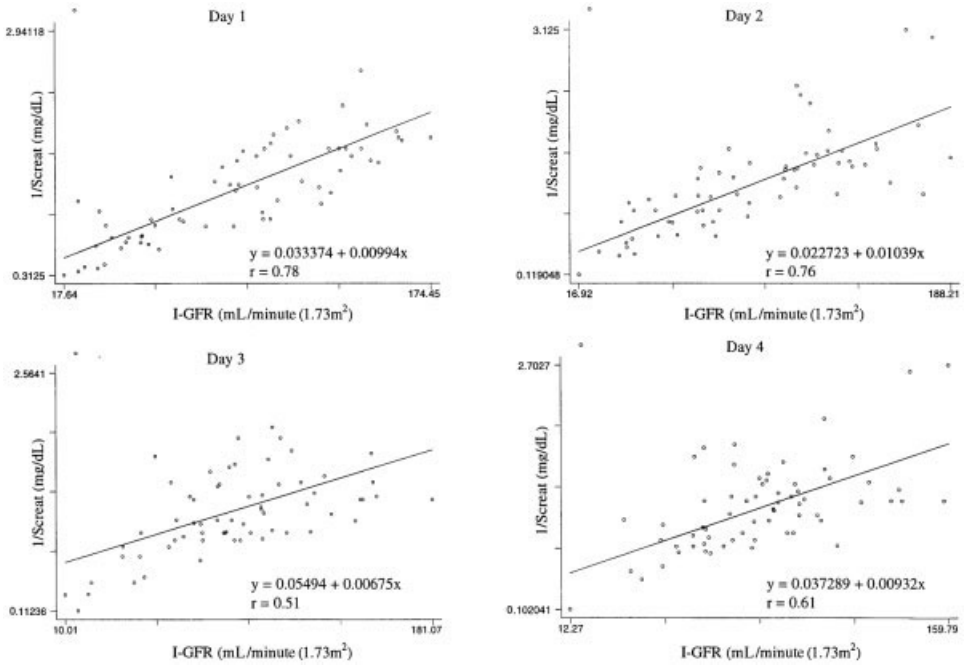

Figure 2. Correlations between creatinine and I-GFR. I-GFR = GFR measured by means of iohexol clearance; SCreat = S_{cr}.

range, compared to none of the cystatin C values ($P <$ 0.0001). The patients experiencing a reduction in GFR of ≥30% in comparison with the first day baseline value were further subdivided on the basis of their initial I-GFR values (>80 and ≤80 mL/minute/1.73 m^2). In the group with initially normal renal function (n = 40), the levels of I-GFR decreased from 130.04 ± 25.4 to 80.95 ± 21.3 mL/minute/1.73 m^2 ($P < 0.0001$), S_{Cys} increased from 1.06 ± 0.55 to 1.86 ± 0.99 mg/L ($P <$ 0.0001), S_{Cr} passed from 0.71 ± 0.22 to 1.09 ± 0.42 mg/dL ($P < 0.0001$), and C_{Cr} did not change (117.3 ± 13.3 vs. 116.6 ± 35.7 mL/minute; $P = 0.9$). In the subjects with initial I-GFR values of <80 mL/minute/1.73 m^2 (n = 10), I-GFR decreased from 48.0 ± 22.4 to 30.0 ± 18.4 mL/minute/1.73 m^2, S_{Cys} increased from 1.5 ± 1.0 to 2.5 ± 1.47 mg/L ($P < 0.01$), and S_{Cr} from 1.7 ± 0.9 to 3.1 ± 2.6 mg/mL ($P = 0.05$), whereas, once again, there was no statistically significant change in C_{Cr} (111.3 ± 52.0 vs. 91.7 ± 57.4 mL/minute; $P =$ 0.09).

The results of the ROC area-under-the-curve analysis testing the studied markers for their diagnostic accu-

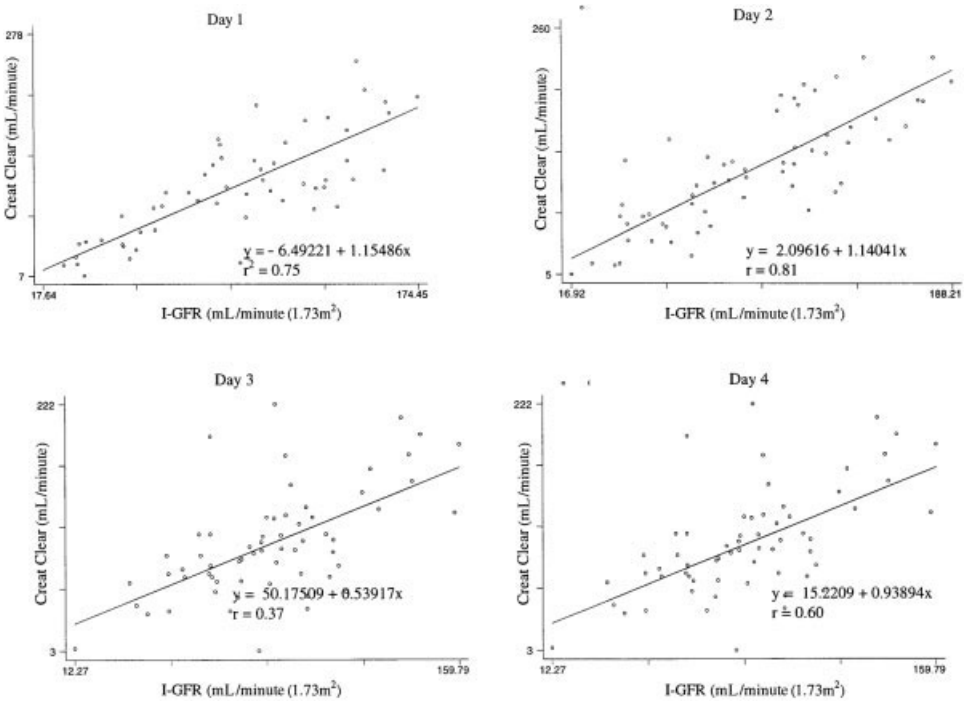

Figure 3. Relationships between I-GFR and C_{cr}. I-GFR = GFR measured by means of iohexol clearance; Creat Clear = C_{cr}.

TABLE 3. Variations in Renal Function Markers by I-GFR Ranges

	I-GFR (mL/minute/1.73 m^2)	S_{Cr} (mg/dL)	S_{Cyst} (mg/L)	C_{Cr} (mL/minute)
I-GFR >80 mL/minute/1.73m^2 (174 measurements)	116.0 ± 26.2	0.7 ± 0.2	1.1 ± 0.3	124.8 ± 51.1
I-GFR = 79 − 60 mL/minute/1.73m^2 (50 measurements)	69.7 ± 6.4	1.0 ± 0.2	1.8 ± 0.5	80.4 ± 49.5
I-GFR = 59 − 40 mL/minute/1.73m^2 (38 measurements)	50.8 ± 6.7	1.4 ± 0.4	2.3 ± 0.4	61.9 ± 24.1
I-GFR < 40 mL/minute/1.73m^2 (18 measurements)	30.7 ± 7.2	2.2 ± 1.7	2.9 ± 0.9	32.4 ± 23.6

NOTE: Normal ranges: S_{Cr} = 0.6–1.3 mg/dL; S_{Cyst} = 0.5–0.95 mg/L; C_{Cr} = 65–135 ml/minute.
Abbreviations: I-GFR, glomerular filtration rate measured by means of iohexol clearance; S_{Cr}, serum creatinine; S_{Cyst}, serum cystatin C; C_{Cr}, creatinine clearance.

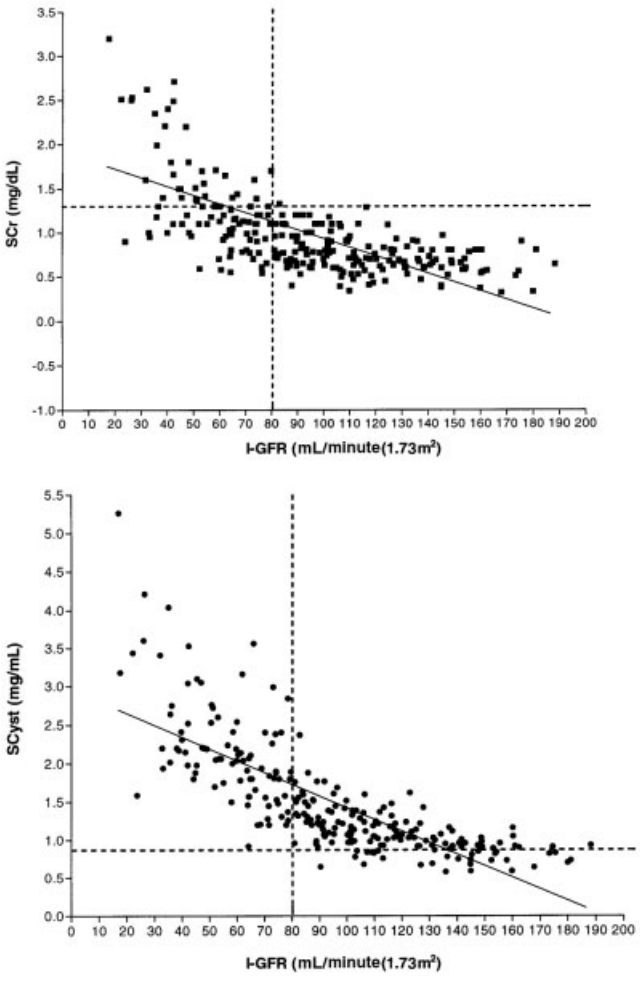

Figure 4. Total relationships between S_{cr} , S_{cyst}, and I-GFR. The broken vertical lines indicate the lower limit of normal GFR (80 mL/minute/1.73 m^2), and the broken horizontal lines the upper limit of normal S_{cyst} (0.9 mg/L) and S_{cr} (1.3 mg/dL) levels in our laboratory.

racy are given in Table 4. Finally, ROC analysis revealed the S_{cyst} levels that predicted reduced I-GFR values: the levels maximizing the sensitivity/specificity ratio were 1.4 mg/L (sensitivity, 90.6%; specificity, 85.2%) for I-GFR values of <80 mL/minute/1.73 m^2, 1.7 mg/L (sensitivity, 96.7%; specificity, 85%) for I-GFR values of <60 mL/minute/1.73 m^2, and 2.2 mg/L (sensitivity, 85.7%; specificity, 88.3%) for I-GFR values of <40 mL/minute/1.73 m^2.

DISCUSSION

Cystatin C has been found to be useful in cirrhotic patients with renal dysfunction[10,11,21] and in OLT subjects some time after they have undergone surgery.[8,9,17] Now our study highlights its potential in the immediate post-OLT phase, when hemodynamic or metabolic disturbances, technical and/or infectious complications, and the need to keep high blood levels of the immunosuppressive drugs may cause insidious variations in GFR. Our results show a better relationship between S_{cyst} and I-GFR than between I-GFR and S_{Cr} or C_{Cr} throughout the study period, with significantly higher correlation coefficients. Furthermore, cystatin C accurately and reliably identified moderate reductions in the GFR. Some of the other characteristics of cystatin C also make it particularly interesting as a renal function marker in the immediate post-OLT phase. In fact, in addition to being independent of muscle mass, gender, blood bilirubin levels, and age, S_{cyst} is unaffected by events that may be frequent after OLT, such as inflammatory or septic states and/or pharmacological or biochemical interferences, unlike other markers, such as β2-microglobulin, retinal-binding protein, and β trace protein.[10-12,21,23] Cystatin C is also interesting as a means of monitoring immediate post-OLT renal function because of the reported drawbacks of using C_{cr} and S_{cr} in cirrhotic patients, making these markers not very sensitive in revealing slight renal damages.[3-6] Furthermore, the reliability of S_{cr} is undermined by the fact that it increases only a relatively long time after a reduction in GFR, which may even need to be as much as 75% before abnormal values can be seen.[22] Finally, the calculation of C_{cr} can be unreliable soon after OLT, as it has been found to overestimate GFR by as much as 50[4] or 100%[6] in

TABLE 4. ROC-AUC Analysis at Different I-GFR Cut-off Points

I-GFR	ROC-AUC POD 1 (95% CI)	ROC-AUC POD 3 (95% CI)	ROC-AUC POD 5 (95% CI)	ROC-AUC POD 7 (95% CI)
80 mL/minute/1.73m^2				
1/SCreat	0.96 (0.91–1)	0.92 (0.83–1)	0.81 (0.69–0.93)	0.76 (0.61–0.90)
1/SCyst	0.98 (0.97–1)	0.90 (0.8–0.99)	0.94 (0.88–1)	0.92 (0.84–1)
CreatClear	0.92 (0.85–0.99)	0.89 (0.79–0.99)	0.68 (0.54–0.83)	0.79 (0.67–0.91)0
P	0.08	0.06	<0.0001	<0.001
60 mL/minute/1.73m^2				
1/SCreat	0.98 (0.95–1)	0.93 (0.88–0.99)	0.84 (0.66–1)	0.91 (0.82–0.99)
1/SCyst	1	0.95 (0.90–1)	0.97 (0.94–1)	0.92 (0.86–0.99)
CreatClear	0.96 (0.91–1)	0.91 (0.83–0.99)	0.77 (0.62–0.91)	0.80 (0.66–0.93)
P	0.13	0.08	<0.05	<0.05
40 mL/minute/1.73m^2				
1/SCreat	0.91 (0.79–1)	0.92 (0.82–1)	0.98 (0.95–1)	0.86 (0.61–1)
1/SCyst	0.95 (0.89–1)	0.95 (0.90–1)	0.95 (0.85–1)	0.92 (0.77–1)
CreatClear	0.95 (0.88–1)	0.93 (0.83–1)	0.74 (0.44–1)	0.90 (0.80–1)
P	0.5	0.2	0.4	0.3

Abbreviations: SCreat, serum creatinine; SCysta, serum cystatin C; CreatClear, creatinine clearance; I-GFR, glomerular filtration rate calculated by means of iohexol clearance; POD, postoperative day; ROC-AUC, receiver operator characteristic area under the curve.

cirrhotic patients with renal dysfunction, and the same happens when it is estimated using the Cockcroft-Gault formula.[10] Nevertheless, we do not believe that creatinine and cystatin C have to be considered competing markers of renal function in OLT recipients because our data also confirm the specificity of S_{cr} and its ability to reveal particularly substantial changes in GFR. Therefore, measuring S_{Cyst} could be used after OLT, especially in the more severely cirrhotic subjects, where S_{cr} can be of little help and where even a moderate change in GFR may be clinically and prognostically important.[11] However, despite these considerations, some data indicate the need to more deeply investigate the behavior of cystatin C in transplant patients. In fact, it has been reported that the use of steroids and cyclosporin A can negatively affect the measurement of cystatin C in kidney transplant recipients, thus suggesting that immunosuppression may lead to an overestimate of GFR.[24] Moreover, a study of a small population of pediatric organ transplant recipients has found greater intraindividual variations in S_{Cyst} than in S_{Cr}[26]; finally, a polymorphism of the gene responsible for the synthesis of cystatin C has been identified that leads to a genotype-dependent variation in its blood levels.[27] Nevertheless, it must also be considered that these findings require confirmation in adult and cirrhotic patients, and that all of the studies of cystatin C as an index of renal function in transplant patients have so far always demonstrated that it is by far the most sensitive, accurate, and reliable method of detecting slight changes in GFR,[8,9,14-17,25] and especially in more critically ill patients, this justifies its use despite its higher cost, which, in our case, was Euro1.9 vs. 0.4/test ($2.2 vs. 0.5).

As cystatin C is still little known and not yet widely used by transplant clinicians, we used ROC analysis to identify the S_{Cyst} values that, in our experience, indicated different levels of GFR, and found that values of 1.4, 1.7, and 2.2 mg/dL were reliable "alarm bells" for cutoff points of respectively <80, 60, and 40 mL/minute/1.73 m^2. However, in critically ill patients, it must always be remembered that it is important to evaluate biological markers in terms of their variations over time, because considering only the absolute values could be sometimes misleading due to possible false positives and/or negatives.

In conclusion, as the development of acute renal failure after liver transplantation is still associated with considerable mortality and morbidity, it is extremely important to be able to make use of highly sensitive indicators of GFR in order to identify renal dysfunction early, assess its severity, evaluate the efficacy of interventions, or adjust the dose of kidney-eliminated drugs. In this regard, our results show that cystatin C is an interesting marker of renal function in the immediate post-OLT period, also when it is necessary to identify moderate changes in GFR. However, it would be useful if expert leaders in the field drew up recommendations concerning the use of the different renal function biochemical markers in order to guide clinicians and laboratory staff in choosing, in everyday practice, the most appropriate index according to the different patients and clinical situations.

ACKNOWLEDGMENT

We thank Prof. Giorgio Della Rocca, Udine University School of Medicine, for his useful criticisms in reviewing the manuscript.

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