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Review Article

Clinical Significance Of Serum And Urine Soluble Interleukin 2 Receptor, C-Reactive Protein, Cystatin C, and Serum and Urine Creatinine in Renal Transplant Patients

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Abstract

Cytokines play a major role in the inflammatory and allo-specific components of allograft rejection, and in the migration of cells into graft tissue. IL-2 binding of sIL-2R plays a major role in T cell activation. It is suggested that high urinary sIL-2R (U/sIL-2R) in the first 3-5 post-transplant days identified the patient sub-group at risk of developing acute rejection (RX). However, it was difficult to distinguish between RX and infection (INFX) as both of these factors can potentially affect serum sIL-2R (S/sIL-2R) and U/sIL-2R concentrations independent of actual production rates. The aims of this study were to validate and extend previous findings of the use of sIL-2R in renal transplantation, to investigate other protein markers currently used such as serum C-reactive protein (CRP), serum cystatin C (cys. C), and serum and urine creatinine (S/creat. and UCRE) and attempt to differentiate RX from INFX. SIL-2R ELISA kit was validated and used to establish reference ranges in healthy donors, transplant (TX) recipients, and renal disease controls. These values were compared with serial estimations of S/sIL-2R and U/sIL-2R of patients post-TX. Levels of serum CRP, cys. C, S/creat. and UCRE were also investigated in the renal disease control and 21 TX subjects to determine if a panel of investigation would have enhanced clinical diagnosis. RX and INFX were determined retrospectively on an "intention to treat" basis. Results show that sIL-2R levels in normal serum and urine subjects are lower than in disease controls, that CRP and cys C are good indicators of RX as well as U/sIL-2R and S/sIL-2R, that UCRE is not a good marker of differentiation, and that stratifying levels of these markers according to treatment differentiated RX from INFX.

Keywords: Cytokines; Renal transplant patients; Creatinine.

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Introduction

Renal transplantation (TX) is widely used as a definitive therapy for chronic, end-stage organ failure. Improved survival rate for transplanted kidneys has been attributed to better immune-suppression techniques [1].

Acute RX (cellular or vascular) frequently complicate graft survival. T cells are pivotal in RX [2], and RX is a process whereby donor tissue is recognized and destroyed by the host immune system [3].

The binding of IL-2 to the IL-2R on human T cells constitutes the key regulatory event in the initiation and maintenance of the immune response.

The receptor, IL-2R, is found in two forms: cellular and soluble. Both forms bind IL-2 efficiently, however, the soluble forms are expressed at only very low levels [4]. The structures responsible for RX are controlled by histocompatibility genes, namely class I and class II.

CD8+ cells are restricted to interact with class I molecules, and CD4+ cells are restricted to interact with class II molecules [5] HLA matching improves TX survival.

Significantly higher S/sIL-2R was seen in patients with renal diseases when compared with healthy subjects [6]. The elevation of S/sIL-2R acute-RX patients was shown to occur as early as 3-8 days before the elevation of S/create [7].

Further, it was shown that urinary IL-2 and U/sIL-2R rise approximately 2-4 days prior to the onset of clinical signs of RX, while plasma levels rise two days later [8] Urinary lymphokines are generated within the transplanted kidney, and this supports the concept that lymphokines that are associated with RX are produced within the transplanted organ, and that it appears in the plasma later on [9].

Further studies have shown that IL-2R and IL-2 were found in biopsied kidney tissues of the collecting tubules and occasionally in the lumen of the tubule [10]. Here I report the results of a prospective study on 21 renal transplant recipients, and show that sIL-2R is a good and earlier detection criterion, and that CRP, cys. C, S/creat. and UCRE help in the differentiation between RX, INFX, and normal transplant recipient (NTX) groups. Further, sIL-2R, CRP, and cys. C could differentiate INFX from RX when hospitalization periods prior to and after the onset of RX and INFX were stratified.

Materials and methods

Patient population and blood and urine collection

Venous blood was drawn from 5 consented categories:

1. 21 renal TX patients at the Sheffield Kidney Institute, six or more consecutive serum and urine samples were taken that included 1 pre-transplant serum sample.
2. From outpatient clinic, 30 samples /each category were drawn from subjects with glomerulonephritis (GN) and pyelonephritis (PY).
3. Subjects with lower urinary tract infection (UTI), 30 samples were collected from the Department of

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Clinical Microbiology (urine) and the Department of Clinical Biochemistry (serum).

4. 20-25 ml of urine sample from 37 normal healthy volunteers was collected in universal tubes.
5. 79 normal blood samples were collected from Blood Transfusion Services (BTS).

All blood samples were centrifuged, and serum was separated from cells. Samples were kept at 4 ˚C for next day sampling, or they were frozen at -20 ˚C until testing.

Urine samples were collected into a sterile universal tube either by the subject or by an attending nurse either normally or from catheters that were connected to TX patients.

S/creat. values were taken directly from TX recipient notes.

Renal TX recipients were divided into three groups based on "intention to treat". Patients in the RX group were treated with methyl-prednisolone and were culture negative at time of treatment.

Patients in the INFX group had culture positive at time of treatment with antibiotics. Patients in the NTX group had neither INFX (culture positive) nor RX episodes.

Commercial assays

1. Roche CRP, Art. No. 07 3665 1. Roche products Ltd., UK.
2. Dako Cystatin C PET Kit, Code No. 0071, Lot No. 117. Dako A/S, UK.
3. IDS Diaclone sIL-2R ELISA kit, Cat. No. 850.500.192. Immunodiagnostic System Ltd., UK.
4. Roche CREA Unimate 5, Art. No. 07 3665 1. Roche products Ltd., U. K.

Data analysis

Descriptive statistics were used for blood bank sera, normal urine, disease control groups, and for 21 prospective renal transplant recipient samples.

Geometric means (GM) were calculated for all skewed data, and it was achieved by Log10 transformation of each group of data. Student t-test was used to analyze data, and the significance level of p value was taken <0.05.

Results

Normal and renal disease control groups' markers levels

Results (Table 1) show that S/sIL-2R was significantly elevated in renal disease controls when compared with healthy subjects. U/sIL-2R and cys.

C levels were not significantly different between healthy and disease control groups ($p>0.05$). CRP was significantly increased in the UTI group ($p<0.0001$), and UCRE level was significantly lower in the UTI and the GN disease control groups than normal group ($p<0.05$ and $p<0.001$, respectively).

When markers levels were compared between the disease control groups (Table 2), S/sIL-2R and UCRE levels were not significantly different among all groups ($p>0.05$). U/sIL-2R level was significantly lower in the GN group ($p<0.05$), while CRP was significantly higher in the UTI group ($p<0.001$). Cys. C level was significantly higher in the GN than the PY group ($p<0.05$).

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Markers levels in RX, INFX, and NTX groups

All markers levels were significantly increased in the RX group when compared with the NTX group (p<0.01–p<0.0001, Table 3).

	Healthy	UTI n=30	PY n=30	GN n=30
S/sIL-2R (pg/ml)	3527 ± 468	8316 ± 2385	7015 ± 1835	8175 ± 1413
	n=79	p<0.0001	p<0.0001	p<0.0001
U/sIL-2R (pg/ml)	4450 ± 298	4980 ± 538	5416 ± 1431	4464 ± 410
	N=37	p>0.05	p>0.05	p>0.05
UCRE (mmol/L)	8050 ± 2053	6343 ± 1486	7664 ± 3036	5406 ± 1956
	n=37	p<0.05	p>0.05	p<0.001
CRP (mg/L)	6 ± 0.00	27 ± 32	6 ± 9	6 ± 12
	n=79	p<0.0001	p>0.05	p>0.05
Cys. C (mg/L)	1.51 ± 0.06	1.38 ± 0.32	1.29 ± 0.35	1.70 ± 0.41
	n=79	p>0.05	p>0.05	p>0.05

Table 1: Parametric analysis (Student t–test) of data between healthy subjects versus disease control groups, mean ± 1.96 SEM results are shown. *The significant p values shown are comparison of disease controls values of each group versus healthy subjects. *Values shown are GM ± 1.96 SEM results.

	U/sIL-2R	S/sIL-2R	CRP (mg/L)	Cys. C (mg/L)	UCRE (mmol/L)
GN vs PY	<0.05-S	>0.05-NS	>0.05-NS	<0.05-S	>0.05-NS
GN vs UTI	<0.05-S	>0.05-NS	<0.001-S	>0.05-NS	>0.05-NS
PY vs UTI	>0.05-NS	>0.05-NS	<0.001-S	>0.05-NS	>0.05-NS

Table 2: Student t-test analysis of markers between the three disease control groups. *p values are shown, S=significant, NS=Not Significant.

TX groups	U/sIL-2R (pg/ml)	S/sIL-2R (pg/ml)	CRP (mg/L)	Cys. C (mg/L)	S/Creat. (mmol/L)	UCRE (mmol/L)
RX n=5	9879 ± 2515	11427 ± 1400	20 ± 9	3.58 ± 0.57	404 ± 74	7509 ± 1019
	p<0.001	p<0.01	p<0.01	p<0.0001	p<0.0001	p<0.01
INFX n=3	6796 ± 605	6632 ± 569	35 ± 11	1.92 ± 0.41	322 ± 55	6561 ± 1589
	p>0.05	p<0.0001	p<0.0001	p<0.0001	p<0.01	p>0.05
NTX n=13	7026 ± 779	9111 ± 546	11 ± 3	1.48 ± 0.32	256 ± 49	6133 ± 931

Table 3: Parametric analysis of each protein marker in rejection (RX), infection (INFX), and normal transplant (N. TX) recipients. *GM ± 1.96 SEM results are shown. *p values shown are data comparisons between RX or INFX groups versus NTX group.

Further, the NTX group has significantly elevated S/sIL-2R (p<0.0001) when compared with the INFX group. CRP level was significantly elevated (p<0.0001) in the INFX group (35mg/L) when compared with the NTX group. S/sIL-2R, S/creat., and cys. C levels were significantly variable among the three TX groups (p<0.01-p<0.0001). UCRE

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level was significant between RX and N. TX groups only ($p<0.01$).

Except for CRP and UCRE levels ($p > 0.05$, Table 4), the levels of other markers were significantly increased ($p<0.01$ for U/sIL-2R, and $p<0.0001$ for the other serum markers) when RX and INFX groups were compared.

Stratification of time periods starting from treatment days

Table 5 shows the GM results of log10 transformed data of stratified values for renal TX recipients who were treated for RX or INFX. When RX markers levels were compared with INFX levels, S/sIL-2R mean stratified value significantly increased ($p<0.05$) above NTX range 9-11 days prior to RX treatment (10,874 pg/ml). Stratified mean S/sIL-2R levels decreased until 3-5 days prior to RX treatment where it increased, but this increase was within NTX ranges.

	U/sIL-2R (pg/ml)	S/sIL-2R (pg/ml)	CRP (mg/L)	Cys. C (mg/L)	S/creat. (mmol/L)	UCRE (mmol/L)
RX vs INFX	< 0.01–S	< 0.0001–S	> 0.05–NS	< 0.0001–S	< 0.0001–S	> 0.05–NS

Table 4: Student t-test analyses of markers between rejection and infection groups. *p values are shown, S=Significant, NS=Not Significant.

	RX	U/sIL-2R (pg/ml)	S/sIL-2R (pg/ml)	CRP (mg/L)	Cys C (mg/L)	S/creat (mmol/L)	UCRE (mmol/L)
↑	**A**	10225 ± 6187	21141 ± 596	45 ± 15	4.74 ± 1.34	1034 ± 183	11400 ± 0
	B	8602 ± 2476	10874 ± 3374	29 ± 8	2.63 ± 1.15	519 ± 134	5655 ± 2117
	C	6621 ± 567	8740 ± 1582	12 ± 8	3.62 ± 0.93	411 ± 107	6889 ± 4154
BE	**D**	8576 ± 1721	9503 ± 1478	24 ± 7	2.68 ± 0.99	307 ± 122	6494 ± 1116
	E	8449 ± 1431	9167 ± 1595	14 ± 5	3.49 ± 0.98	368 ± 140	9005 ± 1114
AF	**F**	10154 ± 2838	10552 ± 2148	20 ± 24	4.01 ± 0.87	381 ± 114	7917 ± 1593
↓	**G**	9843 ± 3165	10364 ± 2155	11 ± 12	3.56 ± 0.77	342 ± 93	7890 ± 951
	H	15158 ± 6154	14646 ± 2208	14 ± 9	3.55 ± 0.72	388 ± 62	7053 ± 1130
	I	15091 ± 9304	15727 ± 2984	20 ± 27	3.98 ± 0.78	470 ± 26	6747 ± 656
	J	-	21691 ± 1871	98 ± 55	5.70 ± 0.46	482 ± 25	-
	K	-	21548 ± 754	62 ± 12	5.21± 0.07	637 ± 73	-
	INFX						
↑	**A**	-	-	-	-	-	-
	B	8945 ± 1720	5685 ± 1235	37 ± 34	3.10 ± 0.30	427 ± 62	2551 ± 500
	C	6638 ± 759	7417 ± 1036	21 ± 17	3.80 ± 0.93	522 ± 106	5979 ± 2017
BE	**D**	5816 ± 480	6271 ± 495	37 ± 10	2.32 ± 0.30	381 ± 61	6910 ± 1233
	E	7990 ± 1216	6387 ± 527	49 ± 24	2.47 ± 0.47	352 ± 89	8527 ± 2503
AF	**F**	6566 ± 689	5937 ± 417	46 ± 23	2.34 ± 0.34	345 ± 73	7221 ± 2767
↓	**G**	7418 ± 796	5462 ± 756	31 ± 7	2.41 ± 0.62	420 ± 52	8835 ± 2423
	H	7048 ± 469	5711 ± 392	25 ± 6	1.63 ± 0.55	349 ± 60	7569 ± 1701
	I	7168 ± 0	8049 ± 1057	60 ± 7	0.79 ± 0.03	217 ± 9	4200 ± 0
	J	5148 ± 371	7896 ± 1687	40 ± 10	0.61 ± 0.04	120 ± 4	4209 ± 1048
	K	5765 ± 600	10637 ± 981	28 ± 8	0.59 ± 0.01	121 ± 3	2750 ± 50

Table 5: Stratified mean ± 1.96 SEM results of log10 transformed data starting from rejection or infection treatment day. *A=12-14 days prior to treatment, B=9-11 days prior to treatment, C=6-8 days prior to

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treatment, D=3-5 days prior to treatment, E=treatment day-2 days prior to treatment, I=10-12 days post treatment, J=13-15 days post treatment, K=16-21 days post treatment, F=1-3 days post treatment, G=4-6 days post treatment, H=7-9 days post treatment, Before treatment=BE, *After treatment=AF.

*Unlike the RX group, no values are seen in row A of INFX group because the maximum INFX treatment day for some members of this group was day 11. *Markers levels above NTX ranges before treatment are shown in bold.

U/sIL-2R levels decreased until 3-5 days prior to RX treatment where it increased above NTX ranges (8,576 pg/ml), but this increase was not significant ($p>0.05$) when levels were compared with INFX levels at the same time period. S/creat.

levels were increased outside the NTX ranges 12-14 days prior to RX treatment (1,034 µmol/L), and the levels decreased until 0-2 days prior to RX treatment when it increased (368 µmol/L). The INFX group showed significantly higher ($p<0.05$) S/creat. level 6-8 days prior to INFX treatment when levels were compared with the RX group (522 µmol/L).

CRP levels were always elevated outside the NTX range in the INFX group, but a significant increase ($p<0.05$) in the levels occurred 0-2 days prior to INFX treatment (49mg/L) when levels were compared with the RX group at the same time period. Cys. C levels were always outside the NTX ranges both in the RX and in the INFX groups, but levels were significant ($p<0.05$) 6-8 days prior to INFX treatment (3.80mg/L) when compared with the RX group.

UCRE increased outside the NTX ranges 0-2 days prior to RX and INFX treatments (9,005 µmol/L and 8,527 µmol/L, respectively), but there was no significance between their levels when both groups were compared.

Discussion

It has been demonstrated increased sIL-2R in the serum of disease controls in comparison with normal healthy subjects. Further, it has been also demonstrated that the levels of the same marker in the urine of healthy subjects were not significantly different from the levels of disease controls. This finding was in accordance with those elsewhere [6,11-14], which may demonstrate reduced marker excretion from the kidney and increased activation of T helper cell population [11,14]. Together with sIL-2R levels, subjects in the urinary tract infection group had also higher CRP levels than did healthy individuals or subjects in the other two disease controls. Infection of the urinary tract leads to local tissue injury and inflammation, and CRP levels elevate in response to the severity of the disease [15,16].

In other studies that explored advanced epithelial ovarian cancer and renal cell carcinoma, a strong association was found between high serum sIL-2R and CRP [17,18] Disease control subjects attended the outpatient clinics for diagnosis and treatment, and cases such as chronic pyelonephritis were already receiving therapy. This might explain the low CRP levels in this group since the acute episode has passed. Cystatin C level is a marker of glomerular filtration rate (GFR) [19-21] which

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is expressed as GFR=UV/P (U=urine concentration, V=urine volume, and P=concentration of the substance or protein in plasma) [22]. The slightly increased, but not significant compared to healthy subjects, levels of this marker in patients who were diagnosed clinically as having glomerulonephritis may indicate early problems with GFR. Lower cystatin C levels in this group, however, could be the result of therapy. Only patients in the pyelonephritis control group had significantly lower marker levels when compared with subjects in the glomerulonephritis group. The reason for this is not obvious.

Creatinine is excreted from serum to urine by the process of glomerular filtration, and some workers use its serum concentration level to predict renal function [23-25]. However, other underlying disease conditions, such as hypo- and hyperthyroidism, can cause alterations in muscle metabolism, which leads to alterations in creatinine production, and therefore, elevation or reduction of creatinine excretion in urine [26-28]. Urine creatinine was not clinically useful as a marker to differentiate two of the disease control groups from healthy subjects, probably as a result of interfering factors such as dialysis, and the level of this marker was not significant among the disease controls in this study.

Only glomerulonephritis disease controls had significantly lower urine creatinine when compared with healthy subjects. This may further be related to reduced GFR that could increase serum levels of this marker. Three out of four markers of study appear to have clinical utility in the diagnosis of rejection and infection in the post-transplant period. These markers include serum and urine sIL-2R, CRP, and cystatin C. Urine creatinine was not important as a marker of differentiation because this marker level was not significantly different among the disease control groups.

Urine sIL-2R and serum sIL-2R levels were significantly higher in the rejection group than infection and normal transplant recipient groups. The level of this soluble marker is dependent on the number of T cells being activated. The high urine sIL-2R in the rejection group, and the low levels of this marker in the infection and normal transplant groups are consistent with the results of Simpson et al. [8]. They concluded that the origin of elevated urine sIL-2R was from within the transplant, and that serum levels elevated two days later than the urine. This could be a clue that direct antigen presentation by renal cells was taking place in the rejecting group.

This may be the reason that the urinary tract infection group above had elevated serum and not urine sIL-2R following inflammation of lower urinary tract and supports the concept that serum sIL-2R is a secondary phenomenon reflecting T cell activation in the transplant. [8] This could be also one reason behind the lower levels of this marker in the urine and serum of the infection group of transplant recipients. However, unlike other previous results [29], the lower levels of this marker in the serum and urine of transplant infection cohort (compared with rejection and normal transplant groups) could be attributed to two reasons. The first reason could be the low number of patients in this group (n=3), and the second reason could

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be due to the normal renal transplant function [30]. The results of my study were different from that of Cassiraghi, et al. [31] in many ways. There were no disease control groups or transplant infection group in that study, Cellfree kits were used, and their results indicated no difference in serum sIL-2R levels between patients experiencing rejection and those who had stable graft. As one group concluded, an isolated value probably may not provide a clue to the condition of the graft [32], but as demonstrated here, serial daily values post-transplant is important [33].

Only then it can see changes in the levels of sIL-2R. Finally, excess creatinine is removed by dialysis, and creatinine correction of urine or serum sIL-2R is affected by it. Some workers did not take this point into consideration when performing creatinine correction on urinary sIL-2R values [34].

CRP level was significantly higher in the infection and in the rejection groups when compared with the normal transplant recipients, but it was not significantly different when the rejection group was compared with the infection group. Because CRP is an acute phase protein, usage of CRP as a marker of rejection or infection should have limitations because the presence of any inflammation leads to the elevation of this marker. In other words, this marker can be used to determine the severity of the inflammation, not its cause [35]. The elevation of this marker as a result of surgery subsides, but a further rise could be an early sign of complications that may be related to either rejection or infection. One study showed similar results to mine in that rejection and infection produced similar patterns of C-reactive protein increase post-transplant. They concluded that C-reactive protein was unable to discriminate the causes of renal graft dysfunction [36].

Cystatin C level was significantly higher in the rejection group when compared with infection and normal transplant groups. As a low molecular weight marker of kidney damage and reduced GFR, cystatin C level rises in rejection and its level will not be affected by dialysis [37]. Further, the low level of this marker in the infection group indicates that this protein is unaltered in inflammatory conditions. The same result was achieved by other workers [38,39]. Unlike creatinine, Cystatin C has the advantage of being independent of gender and muscle mass [40]. In one study with renal transplant patients, cystatin C, in terms of positive predictive value, had a similar diagnostic value as creatinine clearance. However, it was superior to serum creatinine due to the better ability of cystatin C to reflect changes in mildly impaired GFR that is critical for early detection of rejection and other function impairment [41].

Serum creatinine level is the marker commonly used as a predictor of GFR in chronic renal disease [42]. Serum creatinine level was important in daily renal assessment, but Increased creatinine in serum is a sign of impaired kidney function (GFR), and rejecting patients are placed back on dialysis to remove the excess creatinine. However, some workers fail to take this factor into consideration when they carry out creatinine corrections of markers [43,44]. Even though serum creatinine levels are important on a

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daily basis and in daily individual assessment, this marker could not show whether low GFR was due to rejection or infection, and its level is affected by dialysis. Results of this study also indicated that urine creatinine level was not significant between infection, rejection, or normal transplant groups, and, therefore, it could not be used as a marker of differentiation. Therefore, it is concluded that the levels of urine sIL-2R, serum sIL-2R, CRP, cystatin C, and serum creatinine could be used to differentiate rejection from infection and from normal transplant groups, and that dialysis will interfere with the usefulness of creatinine correction of values.

The prognostic and predictive values of these markers post-transplant was explored to see if they can predict the onset period of rejection, and if they can differentiate rejection from infection in any time period. Urine sIL-2R, serum sIL-2R, CRP, and cystatin C levels increased 3-5 days prior to rejection (or 7-9 days post-transplant). CRP levels increase 0-2 days prior to infection treatment. Other workers found that serum and urine sIL-2R increased 4 days to rejection day, which is a similar time course to this study (3-5 days) [44,34] Another group reported increases in serum sIL-2R 3-8 days before elevation of serum creatinine [7]. In this study, elevation of sIL-2R occurred 9-11 days prior to diagnosis of rejection, and 7-9 days prior to serum creatinine levels increase.

The collection method of urine for urine sIL-2R measurement in other studies was by taking weekly 24-hour samples, 36 instead of daily 20 ml urine samples as in this study. The estimated sIL-2R level increase was within 5 to 6-day period [7,34], and mine was within 3-day period. Elevation in the mean or median level of a marker within a short time frame is more significant than its increase over a larger time range.

Further, there were no comparisons with transplant recipients who had infection. Variations in the levels of a single marker may lead to increased misdiagnosis than using a panel of markers [45,46]. Even though statistically not significant, the increase of cystatin C levels in the GN group reflect reduced glomerular filtration rate (GFR) [19]. A reduced GFR may contribute to increased S/sIL-2R in renal disease [13]. On the basis of CRP, patients with UTI could be differentiated from the other two disease control groups and healthy subjects. High CRP levels in the UTI disease control group probably reflect an inflammatory response. Parametric analysis indicates that S/sIL-2R, CRP, and cystatin C levels could be used to differentiate renal disease controls from healthy subjects as well as differentiating the three disease control groups. Statistical analyses also indicate, at least for U/sIL-2R and UCRE, that serum markers are more significant in differentiating between healthy subjects and disease control groups than urine markers.

It should be noted that all parameters were not creatinine corrected. Many laboratories use this on kidney disease or transplant patients without taking into consideration that some of their study cohorts are on dialysis. Placing patients on hemodialysis remove creatinine but not sIL-2R or cystatin C. Thus, the usability of creatinine correction in renal impairment is debatable. This study also shows variability and overlaps in UCRE

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levels in renal control groups and transplant groups that rarely reach statistical significance.

The rejection group could be differentiated from the other two groups by higher levels of five protein markers levels other than CRP. Rejection led to reduced GFR, which leads to the increased markers levels in the rejection group. Increased CRP level could be used to differentiate the infection group from rejection and normal transplant groups. This study strongly points to 4 highly significant markers (S/sIL-2R, U/sIL-2R, CRP, and cystatin C), and to a lesser extent serum creatinine that should be used in differentiating the three transplant recipient groups. Even though serum creatinine is a good marker on daily basis, its level could not be used as a marker of differentiation as it fluctuates with dialysis. UCRE level measurement was not useful. Stratification according to treatment of rejection or infection day can predict rejection, and can differentiate rejection from infection and normal transplant [34]. By stratifying from the day of treatment, and by comparing rejection and infection results with normal transplant ranges, U/sIL-2R and S/sIL-2R show higher levels in the rejection group. CRP levels, on the other hand, were higher in the infection group than in the rejection group. Further, CRP levels increase 0-2 days before treatment of infection. U/sIL-2R and S/sIL-2R levels increase as early as 3-5 days prior to rejection treatment. Others showed that an increase in U/sIL-2R and S/sIL-2R levels was found to occur the week prior clinical diagnosis of acute rejection [47]. Cystatin C and serum creatinine levels were much higher in the rejection group when compared to the infection group.

Conclusion

This study has shown that S/sIL-2R, CRP, and cystatin C levels could be used to differentiate renal disease controls from healthy subjects. Further, the levels of U/sIL-2R, S/sIL-2R, CRP, and cystatin C differentiated rejection from infection and from normal transplant groups. Finally, the prognostic and predictive values of using these markers in stratified periods post-transplant shows that U/sIL-2R, S/sIL-2R, and cystatin C levels increase 3-5 days prior to rejection treatment, and CRP levels increase 0-2 days prior to infection treatment.

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References

1. Wolner E, Laczkovics A, Havel M. New trends in heart transplantation. S Krager, AG, Basel. 1988:1-9.
2. Roitt I, Brostoff J, Male D. Immunology. 4th Ed. Mosby, London. 1996:26.1-26.13.
3. Danovitch GM. Handbook of kidney transport. Little, Brown and Co., Boston. 1992:19-42.
4. Hakimi J, Seals C, Anderson LE, Podlaski FJ, Lin P, Danho W, et al. Biochemical and Functional Analysis of Soluble Human Interleukin-2 Receptor Produced in Rodent Cells. Solid-Phase Reconstitution of a Receptor-Ligand Binding Reaction. J Biol Chem. 1987;262(36):17336-41. PubMed | CrossRef

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DOI: https://doi.orG/10.37191/Mapsci-2582-6549-3(2)-035

5. Shearer WT and Fleisher TA. Immunology and allergy clinics of North America: Organ and bone marrow transplantation. WB Saunders Company. Philadelphia. 1996:221-331.
6. Sugimoto H, Hashimoto N, Suzuki S, Gejyo F. Serum Levels of Soluble Interleukin-2 Receptor in Patients with Various Renal Diseases. Tohoku J Exp Med. 1998;184(4):311-6. PubMed | CrossRef
7. Lu J, Tian J, Zhang J. A Study on Serum Soluble Interleukin-2 Receptor Level in the Diagnosis of Acute Rejection in Renal Transplantation. Zhonghua Nei Ke Za Zhi. 1995;34(6):371-3. PubMed
8. Simpson MA, Madras PN, Cornaby AJ, Dempsey RA, Monaco AP. Origin of Elevated IL-2 And IL-2R in the Urine of Rejecting Renal Allograft Recipients. Transplant Proc. 1989;21(1):299-300. PubMed
9. Beksaç M, Dalva K, Gönenç F, Dalva I, GARIBOGLU S, Batur N. Soluble CD23 and Interleukin-2 Receptor Levels in Renal Allograft Recipients. Transplant Proc. 1993;25(2):2145-47. PubMed
10. Pollak R, Fabrega Aj, Vasquez E, Sanchez J, Mulero Cb, Williams Rh. Measurement of Serum-Soluble Interleukin 2 Receptor Levels Following Renal Transplantation. Transplantation. 1995;59(6):926. PubMed | CrossRef
11. Morris K, Mohan C, Wahi PL, Anand IS, Ganguly NK. Enhancement Of IL-1, IL-2 Production And IL-2 Receptor Generation in Patients with Acute Rheumatic Fever and Active Rheumatic Heart Disease; A Prospective Study. Clin Exp Immunol. 1993;91(3):429-36. PubMed | CrossRef
12. Bock GH, Ongkingco JR, Patterson LT, Ruley J, Schroepfer LR, Nelson DL. Serum and Urine Soluble Interleukin-2 Receptor in Idiopathic Nephrotic Syndrome. Pediatr Nephrol. 1993;7(5):523-8. PubMed | CrossRef
13. Chen HS, Wu MS, Yen TS, Chen WY. Soluble Interleukin-2 Receptor in Patients with Glomerular Diseases. Postgrad Med J. 1995;71(840):617-22. PubMed | CrossRef
14. Balbay D, Bakkaloglu M, Özen H, Tasar C, Özkardes H, Remzi D, et al. Detection of Urinary Interleukin-2, Interleukin-2 Receptor, And Tumor Necrosis Factor Levels in Patients with Superficial Bladder Tumors After Intravesical BCG Immunotherapy. Urology. 1994;43(2):187-90. PubMed | CrossRef
15. Harris KR, Digard NJ, Slapak M, Lee HA. Serum C-Reactive Protein: A Useful, Economical Marker of Immune Activation in Cadaveric Renal Transplantation. Transplant Proc. 1995;27(1):1046-47. PubMed | CrossRef
16. Steinhoff J. Differential Diagnosis of Rejection After Kidney Transplantation. Noninvasive Rapid Diagnosis by Determining Special Urinary Proteins. Fortschr Med. 1995;113(35-36):507-9. PubMed
17. Macciò A, Lai P, Santona MC, Pagliara L, Melis GB, Mantovani G. High Serum Levels of Soluble IL-2 Receptor, Cytokines, and C Reactive Protein Correlate with Impairment of T Cell Response in Patients with Advanced Epithelial Ovarian Cancer. Gynecol Oncol. 1998;69(3):248-52. PubMed | CrossRef
18. Matsumoto T, Furukawa A, Sumiyoshi Y, Akiyama KY, Kanayama HO, Kagawa S. Serum Levels of Soluble Interleukin-2 Receptor in Renal Cell Carcinoma. Urology. 1998;51(1):145-9. PubMed | CrossRef
19. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO, et al. Serum Cystatin C: A Replacement for Creatinine as a Biochemical Marker of GFR. Kidney Int Suppl. Supplement. 1994;47:S20-1. PubMed
20. Keevil BG, Kilpatrick ES, Nichols SP, Maylor PW. Biological Variation of Cystatin C: Implications for the Assessment of Glomerular Filtration Rate. Clin Chem. 1998;44(7):1535-9. PubMed | CrossRef
21. Plebani M, Amico RD, Mussap M, Montini G, Ruzzante N, Marsilio R, et al. is Serum Cystatin C A Sensitive Marker of Glomerular Filtration Rate (GFR)? A Preliminary Study on Renal Transplant Patients. Ren Fail. 1998;20(2):303-9. PubMed | CrossRef
22. Dunnick NR, Sandler CM. Textbook of Uroradiology. Lippincott Williams & Wilkins; 1997. CrossRef
23. Woronik V, Freitas IF, Saldanha LB, Sabbaga E, Marcondes M. Glycosuria in Glomerular Diseases: Histopathology and Clinical Correlations. Braz J Med Biol Res. 1998;31:633-7. PubMed | CrossRef
24. Mendelssohn DC, Barrett BJ, Brownscombe LM, Ethier J, Greenberg DE, Kanani SD, et al. Elevated Levels of Serum Creatinine: Recommendations for Management and Referral. CMAJ. 1999;161(4):413-7. PubMed
25. Schück O, Stribrna J, Teplan V, Vitko S, Matl I, Skibova J, et al. Long-Term Follow-Up of the Tubular Secretion of Creatinine in Renal Graft Recipients. Physiol Res. 1998;47(6):419-26. PubMed
26. Lafayette RA, Costa ME, King AJ. Increased Serum creatinine in the Absence of Renal Failure in Profound Hypothyroidism. Am J Med. 1994;96(3):298-9. PubMed | CrossRef
27. Katz AI, Emmanouel DS, Lindheimer MD. Thyroid Hormone and the Kidney. Nephron. 1975;15(3-5):223-49. PubMed | CrossRef
28. Kuhlback B. Creatine and Creatinine Metabolism in Thyrotoxicosis and Hypothyroidism; A Clinical Study. Acta Med Scand Suppl. 1957;331:1-70. PubMed | CrossRef

Citation: Kazim K. Clinical Significance of Serum and Urine Soluble Interleukin 2 Receptor, C-Reactive Protein, Cystatin C, and Serum and Urine Creatinine in Renal Transplant Patients. J Immuno Allerg. 2022;3(2):1-12.
DOI: https://doi.orG/10.37191/Mapsci-2582-6549-3(2)-035

29. Kaden J, Schütze B, May G. A Critical Analysis of Soluble Interleukin-2 Receptor Levels in Kidney Allograft Recipients. Transpl Int. 1996;9:S63-7. PubMed | CrossRef
30. Nässberger L, Sturfelt G, Thysell H. Serum Levels of the Soluble lnterleukin-2 Receptor Are Dependent on the Kidney Function. Am J Nephrol. 1992;12(6):401-5. PubMed | CrossRef
31. Casiraghi F, Ruggenenti P, Noris M, Locatelli G, Perico N, Perna A, et al. Sequential Monitoring of Urine-Soluble Interleukin 2 Receptor and Interleukin 6 Predicts Acute Rejection of Human Renal Allografts Before Clinical or Laboratory Signs of Renal Dysfunction. Transplantation. 1997;63(10):1508-14. PubMed | CrossRef
32. Trochu JN, Denis M, Auget JL, Giral M, Jacques Y, Soulillou JP, et al. Soluble Interleukin 2 Receptor (Tac chain) is Not a Reliable Marker in Kidney Transplant Recipient Monitoring. Transpl Int. 1992;5(3):145-50. PubMed | CrossRef
33. Bock GH, Neu L, Long C, Patterson LT, Korb S, Gelpi J, et al. An Assessment of Serum and Urine Soluble Interleukin-2 Receptor Concentrations During Renal Transplant Rejection. Am J Kidney dis. 1994;23(3):421-6. PubMed | CrossRef
34. Teppo A, Honkanen E, Ahonen J, Grönhagen-Riska C. Urinary markers of renal graft rejection. Transplant proc. 2001;(33):2485-2486. PubMed | CrossRef
35. Steinhoff J, Bühner U, Feddersen A, Wood WG, Wiedemann G. Anallysis of C-reactive protein in urine as an aid in the clinical diagnosis of disturbed renal transplant function. Transplant proc. 1992;24(6):2735-2737. PubMed
36. Reek C, Conrad S, Huland H. The Role of C-Reactive Protein in Graft Dysfunction After Renal Transplantation. J urol. 1999;161(5):1463-6. PubMed | CrossRef
37. Tian S, Kusano E, Ohara T, Tabei K, Itoh Y, Kawai T, et al. Cystatin C Measurement and its Practical Use in Patients with Various Renal Diseases. Clin Nephrol. 1997;48(2):104-8. PubMed
38. Grubb A, Simonsen O, Sturfelt G, Truedsson L, Thysell H. Serum Concentration of Cystatin C, Factor D and β2-Microglobulin as a Measure of Glomerular Filtration Rate. Acta Med Scand. 1985;218(5):499-503. PubMed | CrossRef
39. Grubb A. Diagnostic Value of Analysis of Cystatin C and Protein HC in Biological Fluids. Clin nephrol. 1992;38:S20-7. PubMed
40. Randers E, Kristensen H, Erlandsen EJ, Danielsen S. Serum Cystatin C as a Marker of the Renal Function. Scand J Clin Lab Invest. 1998;58(7):585-92. PubMed | CrossRef
41. Risch L, Blumberg A, Huber A. Rapid and Accurate Assessment of Glomerular Filtration Rate in Patients with Renal Transplants Using Serum Cystatin C. Nephrol Dial Transplant. 1999;14(8):1991-6. PubMed | CrossRef
42. Walser M, Drew HH, Guldan JL. Prediction of Glomerular Filtration Rate from Serum Creatinine Concentration in Advanced Chronic Renal Failure. Kidney Int. 1993;44(5):1145-8. PubMed | CrossRef
43. Sumrani N, Hong J, Miles A, Markell M, Distant D. Posttransplant Serum Creatinine Area Under the Curve Predicts Renal Allograft Outcome. Transplant proc. 1996;28(1)p356-357. PubMed
44. Lee PH, Chung YC, Hu RH, Huang MT, Chao SH, Lee CJ, et al. Serum Interleukin-2 and Soluble Interleukin-2 Receptor in Renal Transplant Recipients. J Formos Med Assoc. 1992;91(9):844-8. PubMed
45. Montagnino G, Tarantino A, Grignani S, Braga M, Ponticelli C. Soluble Interleukin-2 Receptor (sIL-2R) Levels in Renal Transplantation: Comparison Between Clinical and Laboratory Analysis. Clin Transplant. 1995;9(1):25-30. PubMed
46. Zucchelli GC, Clerico A, De Maria R, Carmellini M, Di Stefano R, Masini S, et al. Increased Circulating Concentrations of Interleukin 2 Receptor During Rejection Episodes in Heart-or Kidney-Transplant Recipients. Clin Chem. 1990;36(12):2106-9. PubMed
47. Ribeiro-David DS, David-Neto E, Castro MC, Souza NA, Reis MM, Saldanha LB, et al. Contribution of the Expression of ICAM-1, HLA-DR and IL-2R to the Diagnosis of Acute Rejection in Renal Allograft Aspirative Cytology. Transpl Int. 1998:S19-25. PubMed | CrossRef

Citation: Kazim K. Clinical Significance of Serum and Urine Soluble Interleukin 2 Receptor, C-Reactive Protein, Cystatin C, and Serum and Urine Creatinine in Renal Transplant Patients. J Immuno Allerg. 2022;3(2):1-12.
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