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High Pre-Transplant Serum Levels of CXCL10 Predict Early Renal Allograft Failure

Background: The chemokine CXCL10 is a potent chemoattractant for activated lymphocytes and dendritic cells and mediates vascular injury by inducing intimal hyperplasia and inhibition of endothelial cell growth. Neutralisation of CXCL10 prolongs allograft survival and transplant knock-out models have shown that this chemokine is required for the initiation and development of graft failure due to both acute and chronic rejection. In the present study, we investigated whether pre-transplant CXCL10 serum levels may predict the recipient risk of graft rejection and transplant failure.

Methods: Pre-transplant sera of 299 cadaver kidney graft recipients were tested retrospectively for serum CXCL10 levels by a quantitative sandwich immunoassay.

Results: Kidney graft recipients with normally functioning grafts showed higher pre-transplant CXCL10 serum levels than healthy controls, but significantly lower than patients who experienced graft failure (133.47 ± 119.6 vs. 182.8 ± 155.01 pg/ml; $p < 0.05$). After the assignment of all patients to four groups at 25°, 50° and 75° centiles according to serum CXCL10 levels, the censored survival rates of grafts were 97.3%, 94%, 93.3%, 85.3% at 1-year. Accordingly, patients with the highest pre-transplant serum CXCL10 levels (75°-100°) centiles showed an increased frequency and severity of rejection episodes in the first month after transplantation.

Conclusions: The results of this study show that high pre-transplant serum CXCL10 levels represent an important predictive risk factor for the development of rejection and transplant failure, thus suggesting that measurement of pre-transplant serum CXCL10 levels might represent a clinically useful marker for the transplant outcome.

Key words:

renal transplantation, chemokines, allograft failure, allograft rejection, IP-10

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Hohe CXCL10-Serumspiegel vor Transplantation: Hinweis auf ein frühes Transplantatversagen nach Nierentransplantation

Hintergrund: Das Chemokin CXCL10, ein potenter chemotaktischer Faktor für aktivierte Lymphozyten und dendritische Zellen, vermittelt Gefäßschäden durch Induzieren von Intima-Hyperplasie und Hemmung des Endothelialzellwachstums. Das Überleben des Transplantates kann durch Neutralisation von CXCL10 verlängert werden, und Knock-out-Modelle haben gezeigt, dass dieses Che-

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mokin erforderlich ist für die Einleitung und Entwicklung eines Transplantatversagens infolge akuter als auch chronischer Abstoßung. In der vorliegenden Studie untersuchen wir, ob die vor Transplantation (vor Tx) gemessenen CXCL10-Serumspiegel das Risiko einer Transplantatabstoßung und eines Transplantatversagens beim Empfänger vorhersagen können.

Methoden: Seren (vor Tx) von 299 Empfängern von Leichennierentransplantaten wurden retrospektiv auf ihre CXCL10-Spiegel mittels quantitativem Sandwich-Immunoassay getestet.

Ergebnisse: Nierentransplantatempfänger mit normal funktionierenden Transplantaten wiesen höhere CXCL10-Serumspiegel vor Tx auf als gesunde Kontrollen, aber signifikant niedrigere Spiegel als Patienten, bei denen es zu einem Transplantatversagen kam ($133,47 \pm 119,6$ vs. $182,8 \pm 155,01$ pg/ml; $p < 0,05$).

Bei der Aufgliederung der Patienten in zwei Gruppen entsprechend ihren CXCL10-Spiegeln (über oder unter die 50°-Zentile) zeigte sich ein signifikanter Unterschied im 1-Jahres-Transplantatüberleben (89,3% vs. 96%; $p < 0,05$).

Das relative Risiko wurde für beide Gruppen mit signifikanten Ergebnissen errechnet (Gruppe mit hohem CXCL10: RR = 1.101, CI = 1.019-1.190 und Gruppe mit niedrigem CXCL10: RR = 0.404, CI = 0.191-0.852). Nach Einteilung aller Patienten in vier Gruppen nach 25°-, 50°- und 75°-Zentilen entsprechend der CXCL10-Spiegel im Serum lagen die geschätzten 1-Jahres-Überlebensraten der Transplantate bei 97,3%, 94%, 93,3% und 85,3%. Dementsprechend wiesen Patienten mit den höchsten CXCL10-Serumspiegeln vor Tx (75°-100° Zentile) eine größere Häufigkeit und Schwere der Abstoßungsepisoden im ersten Monat nach Tx auf. Es konnte bestätigt werden, dass der CXCL10-Serumspiegel eine entscheidende Rolle in der Vorhersage von Transplantatversagen ($p = 0,004$ in der multivariaten Analyse) und Abstoßungshäufigkeit im ersten Monat nach Tx ($p = 0,013$ in der multivariaten Analyse) spielt.

Schlussfolgerungen: Die Ergebnisse dieser Studie zeigen, dass hohe CXCL10-Serumspiegel vor Tx einen wichtigen prädiktiven Risikofaktor für die Entstehung von Abstoßungen und Transplantatversagen darstellen. Die Bestimmung der CXCL10-Serumspiegel im Vorfeld einer Transplantation könnte folglich einen klinisch hilfreichen Marker für das Transplantatsergebnis liefern.

Schlüsselwörter:

Nierentransplantation, Chemokine, Transplantatversagen, Transplantatabstoßung, IP-10

Introduction

Chemokines are a large family of cytokines that direct normal leukocyte migration and have been implicated in the regulation of leukocyte development, angiogenesis, tumor growth and metastasis (1). The chemokine CXCL10/IP-10 is a potent chemoattractant for activated type-1 T helper (Th1) cells (2), NK cells (3), macrophage (4), dendritic cells (5) and $\gamma\delta$ T cells (6), because of its interaction with the specific receptor CXC-chemokine receptor 3 (CXCR3) (3) and critically participates in several diseases.

Several studies demonstrated increased expression of this chemokine in biopsies from subjects affected by proliferative glomerulonephritis (7) and acute and chronic allograft rejection (8-10). Our group too observed high expression of CXCR3 and of chemokines interferon (IFN)- γ inducible protein of 10kD (IP-10/CXCL10) and the monokine induced by IFN- γ (Mig/CXCL9) was found by using in situ hybridisation and immunohistochemistry in kidney biopsy specimens of patients affected by acute or chronic allograft rejection.

Furthermore neutralisation of CXCL10 with monoclonal antibodies prolongs allograft survival (11-12). More importantly, in knockout transplant models, CXCL10/IP10 and its receptor CXCR3 are required for initiation and development of both acute and chronic rejection (12-13). These results indicate a critical biological role for the CXCL10-CXCR3 interaction in the pathogenesis of graft failure due to rejection.

Despite the administration of immunosuppressant, allograft rejection remains the primary cause of human renal transplant failure. Acute rejection (AR) is particularly frequent in the early post-transplant period and, despite the graft loss in only a small percentage of subjects, represents a leading cause of morbidity and hospitalisation, and predisposes renal allografts to the development of chronic rejection (CR) (14). Pre-transplant determination of a recipient risk of graft failure is an important clinical target because the identification of high immunological responders is desirable for the selection of appropriate immunosuppressive regimens. Indeed in current clinical practice, panel reactive antibodies (PRA) is the only

established immunological parameter that provides clinically useful information concerning the responder status of a recipient.

Recently, soluble CD30 serum levels were proposed as a useful pre-transplant predictive marker of graft failure (15,16). High sCD30 levels represent a marker of activation of the immune system (17), but the role of CD30+ T cells contribution to the pathogenesis of acute or chronic rejection wasn't established.

Similarly has been documented that patients lacking the receptor CCR5 due to genomic alteration have a significantly longer graft survival with respect to normal population (18).

Otherwise, CXCL10 is an interferon-inducible chemokine, whose expression is associated with Th1-type immune responses (2). End-stage renal disease (ESRD) is associated with severe alterations of the immune system, including defective antigen presentation, insufficient generation of Th2-type responses, and constantly presence Th1-type-cytokine-mediated chronic inflammation (19-20), thus explaining why a relevant percentage of dialysis patients displays increased serum CXCL10 levels.

CXCL10 high serum expression has been found in several diseases as surgically induced peritoneal injury (21), type 1 diabetes mellitus (22), Grave's disease (23), multiple sclerosis (24) and in children affected by chronic allograft nephropathy (25).

Due to the above mentioned considerations, aim of the present study was to investigate whether pretransplant determination of CXCL10 serum levels may predict the recipient's risk of graft rejection and transplant failure.

Patients and Methods

Pretransplantation sera of 299 cadaver kidney graft recipients, transplanted in our centre, were tested retrospectively for serum CXCL10 levels by a quantitative sandwich immunoassay using a commercially available kit (R&D Systems, Minneapolis, USA), as previously described (23). The intra and interassay coefficient of variation were 3% and 6.9%. In addition, 48 adult healthy controls that had a similar age and gender distribution as adult kidney recipi-

Tab. 1: Patients Disposition

Number	299
Age (years)	46.23 ± 11.8
Gender M/F	203/96
Dialytic age (months)	38.4 ± 36.2
Donor age (years)	45.23 ± 16.7
Cold ischemia time (hours)	19.9 ± 6.3
Original disease (%)	
• Glomerulonephritis	43.3%
• ADPKD	21.5%
• Interstitial nephritis	12%
• Nephroangiosclerosis	11.5%
• Others	11.7%

ents were tested. All the recipients were Caucasian. The demographic characteristics of the recipients are summarised in tab. 1. 93% of the patients received cyclosporine based immunosuppression, while the remaining 7% received an FK based immunosuppression. Patients with PRA ≥ 5% represented the 7.7% of the subjects. Because of this fact we didn't perform any stratification according to the sensitisation degree. Graft function and patient survival rates were documented at 1,3 and 6 months and at 1,2,3,4,5 years.

Only biopsy proven acute rejections were used for statistical analysis. Acute rejections were classified according to Banff classification (26) and treated with steroids. Steroid resistant acute rejections were treated with ATG (rabbit anti-human thymocyte globulin).

Statistical analyses were performed using SSPS software (SPSS, Inc., Evanston, IL). Due to non-parametric distribution, comparisons of serum CXCL10 levels amongst different groups were performed by Mann Whitney *U*-test for unpaired data. Linear regression analysis and Spearman's correlation test as appropriate ascertained correlation between two variables. To test the effect of CXCL10 serum levels independently of a covariate on kidney allograft survival and rejection episodes, multivariate Cox regression analysis was used. The Kaplan-Meier method was used to estimate the disease free survival and differences among groups were assessed by log-rank test. Frequencies of allograft failure and rejection episodes were compared among groups by χ^2 test. A p-value < 0.05 was considered statistically significant.

Results

Pretransplant serum levels of CXCL10 were assayed in 299 adult kidney graft recipients by an appropriate ELISA method. Kidney graft recipients had significantly higher pretransplant serum CXCL10 levels before transplantation than 48 adult healthy controls (137.6±123.5 versus 80.4±33.6 pg/ml; $p < 0.005$). However, the assignment of all patients to two groups based on subsequent graft outcome, revealed important differences. Indeed, patients with normally functioning grafts showed lower pre-transplant CXCL10 serum levels than patients who experienced graft failure (133.47±119.6 versus 182.8±155.01 pg/ml; $p < 0.05$) (fig. 1). Such difference was even more significant in patients who lost the graft within 1 year after transplantation (133.47±119.6 versus 205.6±160.7 pg/ml; $p < 0.01$) (Fig.2). By contrast, no difference of serum pre-transplant CXCL10 levels with regard to age, gender, year of transplantation, original disease, transplant number, type or dialytic age were observed.

Stratification of patients in two groups according to CXCL10 levels (above or below the 50° centile) showed significant difference in one-year graft survival rates (89.3% versus 96%; $p < 0.05$).

Relative risk was calculated for both groups with significant findings (high CXCL10 group: R.R. 1.101, C.I. 1.019-1.190 and low CXCL10 group: R.R. 0.404, C.I. 0.191-0.852).

All patients were assigned to four groups according to the 0-25° (<65 pg/ml, n=75), 25°-50° (>65 and < 97 pg/ml, n=75), 50°-75° (>97 and < 157 pg/ml, n=75) and 75°-100° (>157

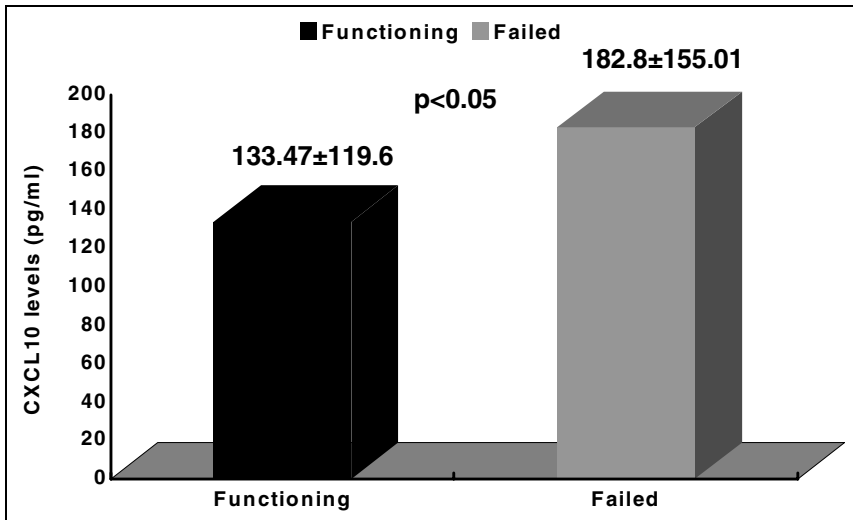


Fig. 1: Serum pre-transplant CXCL10 levels in transplant patients: functioning versus failed grafts

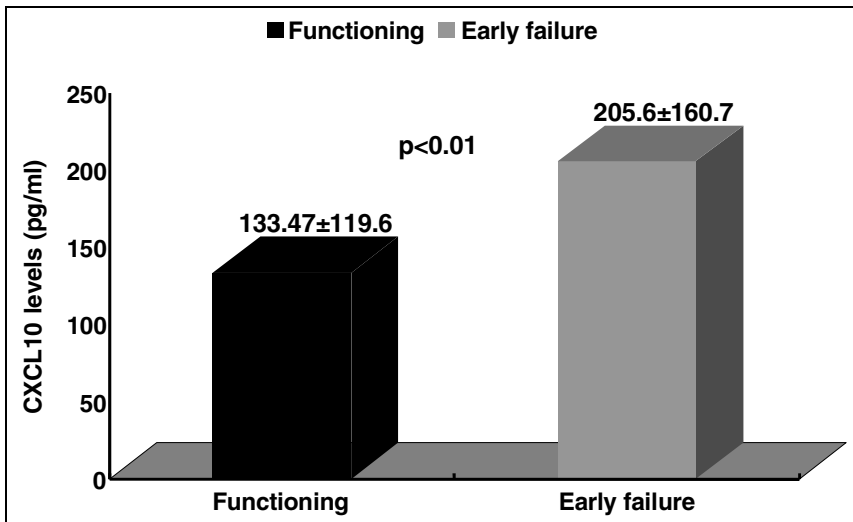


Fig. 2: Serum pre-transplant CXCL10 levels in transplant patients : functioning versus early failure

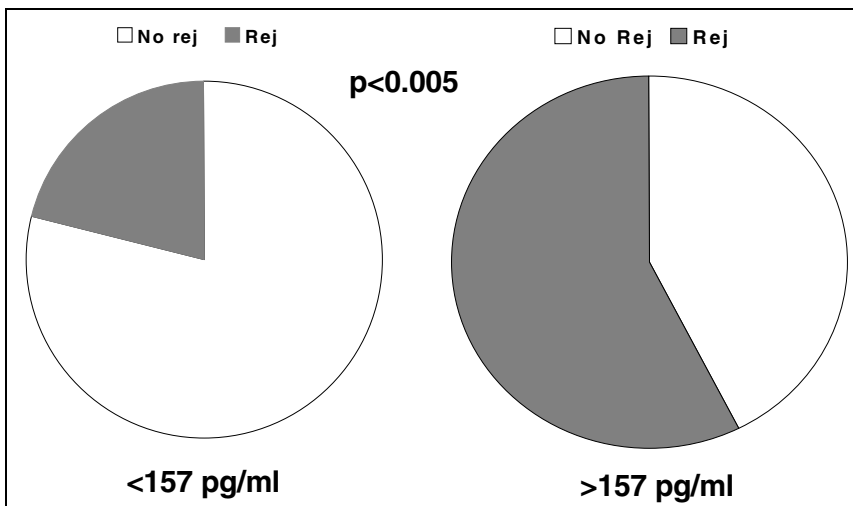


Fig. 3: Increased frequencies of rejection during the first month after transplantation in patients with very high pre-transplant CXCL10 serum levels

pg/ml, n=74) percentiles accordingly to serum CXCL10 levels.

Stratification of patients in 4 groups according to CXCL10 levels showed significant difference in 1-year graft survival rates. The 1-year graft survival rates were particularly different in the two extreme percentiles. Accordingly, the frequency of rejection episodes in the first month after transplant was strikingly increased in the group with pretransplant serum CXCL10 levels above 75° centile (57.4% versus 31.2%; $p < 0.005$) (fig.3).

The 5-year graft survival rates confirmed the 1-year graft survival rates (fig.4).

To further support the validity of these findings, multivariate Cox regression analyses were performed. Recipient and donor age and gender, number of HLA mismatches, original disease, type of immunosuppression, PRA, number of rejections in the first month after transplantation and cold ischemia time were considered as co-variables. Serum CXCL10 level was confirmed to play a crucial role in determining both graft failure ($p = 0.004$) (tab. 2) and frequency of rejection within the first month after transplantation ($p = 0.013$) (tab. 3).

Discussion

Pre-transplant determination of a recipient risk of graft rejection is an important prerequisite for the application of recipient-tailored immunosuppression. Administration of potent immunosuppressive regimens has been shown to improve graft outcome in preimmunized recipients. In low risk recipients, one would like to avoid high dose immunosuppression to reduce drug side effects, such as toxicity, infection, and development of cancer. So it should be extremely important to have a pretransplant marker of the post-transplant immune response.

Growing evidence also suggests that different chemokines may be crucial for the recruitment of Th1 or Th2 cells in the inflamed tissue, in as much as some chemokine receptors have been found to be preferentially associated with one or the other Th cell subset (2). Th1 cells preferentially express the chemokine receptors CXCR3 and CCR5, while Th2 cells more frequently exhibit the expression of CCR4 and CCR8. The

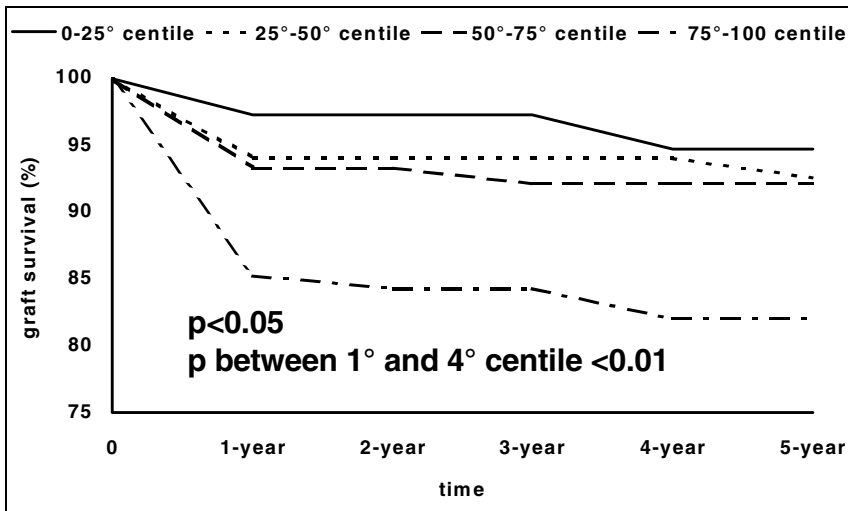


Fig. 4: 5-year graft survival rate according pre-transplant CXCL10 serum levels

Tab. 2: Cox regression analysis results for predicting graft loss

Covariates	β	SEM	Exp β (95% CI)	P-value
Cold Ischemia time	0,35	,030	1,036 (0,977-1,098)	0,040
IP-10	,003	,001	1,003 (1,001-1,005)	0,004
Rec. gender	-,315	,444	0,730 (0,306-1,742)	0,478
Rec. age	,014	,018	1,014 (0,979-1,050)	0,447
Original disease	,037	,047	1,038 (0,947-1,138)	0,427
Pre-transplant dialysis	-,063	,524	0,939 (0,336-2,623)	0,04
HLAMM	,100	,297	1,105 (0,618-1,978)	0,036

Tab. 3: Cox regression analysis results for predicting early acute rejection

Covariates	β	SEM	Exp β (95% CI)	P-value
Cold Ischemia time	0,022	0,018	1,022 (0,986-1,060)	0,074
IP-10	0,002	0,001	1,002 (1,000-1,003)	0,013
Gender	0,229	0,260	1,257 (0,755-2,092)	0,379
Age	0,001	0,011	1,001 (0,979-1,024)	0,933
Original Disease	0,18	0,31	1,018 (0,959-1,082)	0,555
Pre-transplant dialysis	0,411	0,333	1,508 (0,785-2,896)	0,017
HLA MM	-,039	0,191	0,962 (0,661-1,398)	0,037

type of chemokine receptors expressed by different populations of T cells may thus dictate the tissue infiltration by Th1 and Th2 cells, as well as the direction of the ongoing immune response. As above mentioned the chemokine CXCL10 has been documented to be involved in several Th1 disease. High CXCL10 serum levels have been documented in patients affected by peritonitis, type 1 diabetes mellitus, Grave's disease, multiple sclerosis (21-24). In 1999 we documented the role of CXCL10 and its receptor CXCR3 in proliferative glomerulonephritis (7) where CXCL10 could not only act as chemoattractant for infiltrating mono-

nuclear cells in the inflamed tissue, but also may directly induce the proliferation of mesangial cells. In the field of transplantation high serum expression of CXCL10 and CXCR3 is predictive for chronic allograft nephropathy (25). In 2001 Segerer et al. (27) found that during renal allograft rejection there is an upregulation of the CXCR3 and its ligand CXCL10 as well as CCR5 and its ligand. The latter findings were confirmed by the epidemiological study of Fischereder (18). This is clearly indicating that renal allograft rejection is primarily the result of a Th1-type immune response. In renal acute rejection high levels of

CXCL10 has been found in glomerular capillaries, in tubular cells, but mainly in infiltrating cells. CXCL10 and its receptor CXCR3 were highly expressed on vessels and infiltrating inflammatory cells, mainly those surrounding vascular structures. Double immunostaining allowed to identify endothelial cells, lymphocytes and also tubular cells as main source of CXCL10 (28). These data, coupled with the recent finding that the attenuation of graft rejection in IFN- γ -/- mice is reversed by injection of Mig into the graft tissue and that the same phenotype has been observed in the CXCR3 -/- mouse, allow us to suggest that CXCL10/Mig and CXCR3 interaction may play an important role in pathogenesis of acute rejection, similar to the previously described role in proliferative glomerulonephritis. The activity of such chemokines seems not limited to chemotaxis, but could also induce proliferation of both glomerular and vascular cells.

Based on this experimental evidence and histological findings in human transplants, we investigated whether pre-transplant determination of CXCL10 serum levels may predict the recipient's risk of graft rejection and transplant failure.

First of all we documented higher serum CXCL10 levels in dialysis patients on waiting list for renal transplantation with respect to healthy volunteers. This could be ascribed to the fact that end-stage renal disease is associated with severe alterations of immune system, including defective antigen presentation, insufficient generation of Th-2-type responses, and consistently associated Th1-type-mediated chronic inflammation.

We also found higher pre-transplant CXCL10 serum levels in patients whose graft failed after transplantation with respect to patients with functioning graft: this fact was particularly relevant in the case of early failure.

Due to the not bell-shaped distribution of pre-transplant CXCL10 levels, we divided our patients according to centiles. Both 1-year graft loss and frequency of rejection episodes after transplantation were significantly higher in patients whose CXCL10 levels were above the 50° centile.

We observed a striking difference, both in acute rejection incidence and 1-year graft survival, in pre-transplant CXCL10 serum levels, comparing pa-

tients belonging to 0-25 centiles with patients belonging to 75-100 centiles: in the latter patients we observed an acute rejection incidence of 57.4% versus 31.2% and 1-year graft survival of 82.05% versus 94.7%.

To further support the validity of these findings, a multivariate Cox regression analysis was performed, including as co-variables recipient and donor age, gender, number of HLA-mismatches, original disease, type of immunosuppression, PRA, and cold ischemia time: serum CXCL10 levels were confirmed to play a crucial role in determining both graft failure and frequency of rejection.

The overall mentioned results documented that pre-transplant CXCL10 levels are, in some way, predictive of the graft outcome. The reason why CXCL10 pre-transplant serum levels appear to be so important in predicting the risk of renal allograft rejection, is partially understandable.

CXCL10 is, indeed, an interferon-inducible chemokine whose expression is associated with Th1-type immune response. Furthermore, high serum CXCL10 levels can be related to higher risk of vascular injury, due to the established role of CXCL10 in generating intimal hyperplasia and chronic endothelial cell damage (29-31).

In conclusion, our clinical data, coupled with the previously documented harmful role of CXCL10 in the pathogenesis of acute rejection, allow us to speculate that patients with higher CXCL10 pre-transplant levels are more prone to develop severe acute rejection predisposing to chronic rejection and resulting in graft failure.

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