Predicting early renal allograft function using clinical variables

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Abstract
Background. Suboptimal early graft function following renal transplantation remains a significant challenge. It is suggested that clinical variables (or scoring systems based thereon) may predict the occurrence of delayed graft function (DGF), defined as post-operative dialysis requirement. However, data is conflicting, and suboptimal renal function not requiring dialysis has been little investigated. This study tested the ability of clinical variables to predict suboptimal early function variably assessed by: (i) DGF (dialysis requirement during the first week); (ii) DGF duration; (iii) slow graft function (creatinine >3 mg/dl on day 5); (iv) creatinine reduction ratio on day 2.

Methods. Details on 217 consecutive renal transplant recipients were collected. All received ciclosporin-based immunosuppression. Multiple regression analysis was used to assess the association between individual clinical variables and suboptimal early graft function. Also tested were three scoring systems incorporating clinical variables [US Renal Database System (USRDS score), deceased donor score (DDS) and expanded criteria donor kidneys]. Receiver operated-characteristic curve analysis was used to assess the predictive power of clinical variables and scoring systems.

Results: Early graft function was associated with donor age, donor body mass index, donor hypertension, donation following cardiac death, black recipient ethnicity, recipient weight and cold ischaemic time (P ≤ 0.05 for all). All scoring systems showed associations with early graft function, although only USRDS score remained in the multiple regression model. The overall utility of the USRDS score in predicting DGF was moderate at best, although improved at extreme scores (specificity: 95%; positive predictive value: 73%; for USRDS score ≥150).

Conclusions. Clinical variables and scores have moderate predictive ability for early graft function and although of potential use in clinical practice, caution should be exercised before altering patient management based solely on them.

Keywords: allograft; function; kidney; post-operative; predictors

Introduction
A number of recent analyses demonstrate the importance of events early post-renal transplantation in determining long-term allograft outcomes [1–4]. In particular, worse long-term outcomes are associated with delayed graft function (DGF), irrespective of the occurrence of acute rejection [2–4]. Attempts have therefore been made to improve early graft function by a variety of mechanical, pharmacological and organ allocation strategies [5–8]. If suboptimal early graft function could be accurately predicted, the success of these strategies may be improved.

A recent analysis of US Renal Database System (USRDS) data by Irish highlighted variables associated with delayed graft function, defined as dialysis requirement in the first week post-transplantation [9]. These variables were subsequently incorporated into a score which showed good predictive ability when validated in over 20 000 patients reported to the Scientific Renal Transplant Registry (SRTR). However, two subsequent analyses of North American [10] and Australian [11] populations have yielded conflicting results. The predictive performance of this scoring system has not been tested in a European population.

Other scoring systems include the deceased donor score (DDS), derived by Nyberg from data reported to the SRTR [12], and the concept of expanded criteria donor (ECD) kidneys as defined by the United Network for Organ Sharing (UNOS) [13]. High DDS
scores and ECD kidney donation are associated with poorer long-term function and reduced survival and are also associated with DGF [14,15]. Although the results of such scoring systems are associated with early graft function, the utility of them to predict DGF has not been studied.

The purpose of this study was to test the predictive utility of each of these scoring systems in a multi-ethnic European urban population. We also sought to identify other risk factors for DGF which are not incorporated into these existing scoring systems. Since there are limitations to using dialysis requirement during the first-week post-transplantation as the sole marker of early graft function, this study also assessed two other definitions of early graft function: 'creatinine reduction ratio at day 2' (CRR2 [16]) and 'slow graft function' (SGF [17,18]). These markers of early graft function are associated with long-term outcomes and are therefore potentially useful surrogates which can be identified early post-transplantation [2–4,16,18].

**Subjects and methods**

Two hundred and seventeen consecutive deceased donor renal transplant procedures between 2003 and 2006 were studied. Donor and recipient variables were collected from the prospectively maintained institutional database. Donated kidneys were perfused with Marshall’s solution and stored on ice until transplantation. No machine perfusion was used. Frusemide 200 mg intravenously was administered upon release of the vascular clamps. No mannitol was administered.

All patients received ciclosporin (Neoral®; Novartis) 5 mg/kg daily adjusted to whole blood levels 2 h following administration (C2) of 800–1400 ng/ml, measured by fluorescence-polarization assay (TDx analyser; Abbott laboratories). Adjunctive immunosuppression consisted of azathioprine (Imuran®; GSK) in most patients [19/217 (89.4%)], mycophenolate mofetil (MMF; Cellcept®; Roche) was used in nine recipients of kidneys donated after cardiac death (DCD) and in another 14 sporadic patients by virtue of pre-operative methylprednisolone 500 mg intravenously, followed by prednisolone 20 mg daily. Basiliximab (Simulect®; Novartis) 20 mg was administered pre-operatively and repeated on day 4 in 121 patients due to a change in immunosuppressive protocol midway through the study period.

Early graft function was assessed as follows:

(i) Delayed graft function (DGF), defined as dialysis requirement during the first week post-operatively.

(ii) The duration of DGF, calculated as the time between the transplant operation and the last dialysis session.

(iii) Slow graft function (SGF) was defined in patients without DGF, whose creatinine remained above 3 mg/dl (266 μmol/l) by post-operative day 5.

(iv) Immediate graft function (IGF) was defined as present in patients without DGF or SGF (i.e. serum creatinine <3 mg/dl by day 5).

(v) CRR2 was calculated (in patients not displaying DGF) by the equation: CRR2 (%) = ([Cr1 – Cr2] × 100)/Cr1, where Cr1 and Cr2 represent serum creatinine on days one and two post-transplantation respectively.

Patients displaying DGF underwent regular allograft imaging during the period of DGF to confirm vascular perfusion and exclude renal tract obstruction. All patients remaining dialysis dependent 5 days post-transplantation underwent renal allograft biopsy. The Banff system was used to grade the biopsies [19]. No protocol biopsies of grafts without DGF were undertaken.

Three scoring systems for expected graft function were studied:

(i) The USRDS score [9] is continuously distributed and incorporates the following variables: Donor: age, history of hypertension, terminal creatinine, donation following cardiac death (DCD), death due to anoxia or cerebrovascular accident (CVA); cold ischaemic time; HLA mismatch; combined organ transplantation; Recipient: gender, race, diabetes, history of previous transplantation, history of dialysis prior to transplantation, peak panel reactive anti-HLA antibodies (PRA).

(ii) The DDS [12] is also a continuously distributed score incorporating the following variables: donor age, donor history (and duration) of hypertension, donor creatinine clearance (CrCl; derived from the Cockcroft and Gault formula), donor death due to CVA, HLA mismatch.

(iii) ECD kidneys [13] are characterized by either (a) donor age over 59 years or (b) donor age between 50 and 59 years with, additionally, two of the following: death due to CVA; terminal creatinine >1.5 mg/dl; history of hypertension.

Values for each of these scoring systems were derived and applied as an explanatory variable for each parameter of early graft function as defined above. Three analyses were then conducted for each of these parameters:

**Analysis 1:** Only the three scoring systems were analysed.

**Analysis 2:** The three scoring systems were analysed together with the following clinical variables not included in any of the other scoring systems: recipient age; recipient dialysis modality; recipient comorbidity (assessed by the Charlson Comorbidity index as in previous renal transplantation studies [20]); C2 levels during the first week post-transplantation (measured at days 3, 5 and 7); donor body mass index (BMI); use of inotropes (epinephrine; norepinephrine; dopamine) in the donor; donor mean blood pressure at the time of organ retrieval; donor sepsis (identification of a bacterial infection on body fluid culture); estimated glomerular filtration rate (eGFR; calculated from the abbreviated Modification of Diet in Renal Disease [MDRD] formula [21]); kidney transplanted (left vs right); presence of multiple renal vessels; anastomosis time; recipient BMI and ratio of BMI between donor and recipient; recipient mean blood pressure for the first 6 h post-operatively; recipient parathyroid hormone, serum calcium and phosphate levels pre-transplantation. The three scoring systems were retained in the multiple regression model (see ‘statistical analysis’) even if they lost significance during the construction of this model. This was done because the aim was to identify clinical factors not contained within the existing scoring systems, thereby requiring inclusion of
these scoring systems in the final model (non-significance of a covariate does not necessarily imply a lack of information contained within).

**Analysis 3:** Each separate clinical variable (either incorporated into a scoring system or out of any scoring system) was applied to each parameter of early graft function. For this analysis, the scoring system’s results were not included in the analysis.

**Statistical Analysis**

Analysis was performed using Stata (version 7.0, Stata Corporation, USA). Categorical and continuous variables were analysed by chi-squared test, Fisher’s exact test and Student’s $t$-test as appropriate. Multiple regression models were constructed as follows: linear regression for continuously distributed dependent variables (DGF duration and CRR2); logistic regression for categorical dependent variables (DGF and SGF); ordered logistic regression for dependent variables which fell into three or more categories of increasing ‘severity’ (IGF vs SGF vs DGF). Skewed data underwent logarithmic transformation to obtain a better fitting regression model.

Initially the individual effect of each clinical variable upon each parameter of early graft function was examined by univariate analysis, followed by a backward selection procedure to construct the multiple regression model. Finally, a forward selection process was used to verify the robustness of the model. Linearity for the continuous variables was not assumed; models with polynomials were examined for all continuous measures. This was done by graphical means and by examining the relationship which gave the best fit to the data. Colinearity was assessed by the use of correlation coefficients between variables. Even for categorical variables, correlation may still give an estimate of the agreement between variables. There was particular concern regarding potential colinearity between the three scoring systems. Therefore, as well as the use of correlation, the colinearity between these variables (USRDS score, DDS and ECD kidney donation) was examined in analysis 1 with all three variables as predictor variables. The variance inflation factors (VIFs) were then examined. A VIF of over five suggests colinearity may be a significant problem.

The effect sizes are reported in the form of odds ratios (OR) for categorical dependent variables (DGF; SGF) and as $\beta$ values for continuously distributed dependent variables (DGF duration; CRR2). A two-tailed $P < 0.05$ was considered significant. Coefficients of determination for the linear regression models ($R^2$ values) were calculated to identify the proportion of the model variability explained by the studied clinical variables. This measure is well established in the analysis of continuous data, but can also be applied to categorical data (logistic regression analysis) as a pseudo-$R^2$ value.

Receiver operated characteristic (ROC) curves were generated to identify the performance of explanatory variables in predicting outcomes. The c-statistic (area under ROC curve) was used as a measure of the predictive performance of the studied variables.

**Results**

Seven patients experienced early graft failure, all due to renal vein thrombosis within the first week post-transplantation, and were excluded from the analysis, leaving 210 studied patients. There were no deaths in the early post-transplantation period. The clinical characteristics of the 210 transplantations are shown in Table 1.

Seventy-five patients (35.7%) developed DGF. The median duration of dialysis requirement in these patients was 7 days (range 1–30 days; interquartile range 4–12 days). Of the 135 patients without DGF, a further 39 patients displayed SGF (28.9% of patients without DGF; 18.6% of the entire study group). The mean CRR2 was $26.9 \pm 23.6\%$ ($-21.4\%$ to $65.0\%$).

Mean USRDS score was $133.9 \pm 16.9$ (median 133.7; range 61–183). Mean DDS was $16.6 \pm 8.0$ (median 16.8; range 0–34). Fifty-seven patients received ECD kidneys. Actual results between groups for the scores are shown in Table 1. Weak correlations were seen between the three scoring systems (USRDS vs DDS: $r = 0.37$, USRDS vs ECD kidney: $r = 0.24$, DDS vs ECD kidney: $r = 0.27$).

**Delayed graft function**

Analysis 1 revealed DGF was associated with a higher USRDS score, higher DDS and ECD kidney donation on univariate analysis, but only USRDS score retained significance in the multiple regression model (Table 2). The relationship between USRDS score and DGF was non-linear (Figure 1A) and is expressed as its linear and quadratic terms in (Table 2).

Despite the strong association between USRDS score and DGF, only 15% of the variability in DGF was explained by the score (pseudo-$R^2$:0.15). ROC curve analysis suggested the predictive utility of the USRDS scoring system was moderate, with a c-statistic of 0.71 (95% CI: 0.63–0.78; Figure 2). Although there was no easily discernable discriminatory value, a USRDS score of 135 best discriminated patients with and without DGF [sensitivity 71% (95% CI: 59–81%); specificity 66% (95% CI: 58–74%)]. Other discriminatory values are shown in Figure 2. Of note, high specificity (95%) and reasonable positive and negative predictive values (73% and 69%, respectively) were seen at a USRDS score of 150, although the sensitivity was poor (25%) and only 26/210 (12.4%) of patients displayed such a score of ≥150. The 10 patients (4.8%) with scores >165 all displayed DGF.
According to the previously published nomogram [9], the expected incidence of DGF in those patients displaying DGF was only 45% (mean score: 141), and the expected incidence in patients not displaying DGF was 34% (mean score 129).

Analysis 2 showed DGF was associated with higher USRDS scores and higher donor BMI in the multiple regression model (Table 2) into which DDS and ECD kidney donation (which were both significant in the univariate but not multiple regression model) were ‘forced’ (see ‘statistical analysis’). No relationship was seen between recipient BMI and DGF, or the donor: recipient BMI ratio and DGF. The total 18% of the variability in DGF was explained by the USRDS score and donor BMI (pseudo-R²:0.18).

The multiple regression model of analysis 3 revealed associations between DGF and increasing donor age, increasing donor BMI, the presence of hypertension in the donor, black recipient ethnicity, DCD kidney...
donation and increasing cold ischaemic time (Table 2). Only 20% of the variability in DGF was explained by these explanatory variables (sum pseudo-$R^2$: 0.20).

In addition, ROC curve analysis suggested the predictive ability of donor age and cold ischaemic time was poor with respective c-statistics of 0.65 (95% CI: 0.57–0.73) and 0.65 (95% CI: 0.56, 0.73), respectively. Donor age of 50 years and cold ischaemic time of 19 h best discriminated patients with and without DGF (sensitivity 63% and 59%, respectively; specificity 62% and 71%, respectively).

Duration of DGF was analysed for the 75 patients displaying DGF. As the data were logarithmically transformed, effect sizes reported are in the exponential form of the regression.

Table 2. Associations between clinical variables, scoring systems and early graft function

<table>
<thead>
<tr>
<th>Delayed Graft Function</th>
<th>OR (95% CI)</th>
<th>$P$-value</th>
<th>Pseudo-$R^2$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis 1</strong></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>USRDS score$^a$</td>
<td>0.29 (0.07, 1.24)$^j$</td>
<td>0.001</td>
<td></td>
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<tr>
<td></td>
<td>1.07 (1.02, 1.14)$^g$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Analysis 2</strong></td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>USRDS score$^a$</td>
<td>0.25 (0.06, 1.28)$^j$</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.06 (1.01, 1.16)$^g$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor BMI$^b$</td>
<td>2.19 (1.10, 3.87)</td>
<td>0.01</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Analysis 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor age$^c$</td>
<td>1.36 (1.06, 1.74)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Donor hypertension</td>
<td>2.79 (1.18, 6.63)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>DCD kidney</td>
<td>3.10 (1.99, 5.79)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Cold ischemic time$^d$</td>
<td>1.40 (1.04, 1.87)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Donor BMI$^b$</td>
<td>1.87 (1.09, 3.98)</td>
<td>0.02</td>
<td></td>
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<tr>
<td>Black recipient</td>
<td>2.55 (1.59, 3.12)</td>
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</table>

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<thead>
<tr>
<th>Duration of DGF</th>
<th>(exp) Beta (95% CI)$^h$</th>
<th>$P$-value</th>
<th>$R^2$ value</th>
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<tr>
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<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>USRDS score$^a$</td>
<td>1.25 (1.11, 1.81)</td>
<td>0.005</td>
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<td><strong>Analysis 2</strong></td>
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<tr>
<td>USRDS score$^a$</td>
<td>1.11 (1.03, 1.26)</td>
<td>0.01</td>
<td></td>
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<tr>
<td><strong>Analysis 3</strong></td>
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<td></td>
<td>0.16</td>
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<tr>
<td>Cold Ischemic Time$^a$</td>
<td>1.15 (1.01, 1.31)</td>
<td>0.01</td>
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<tr>
<td>DCD Kidney</td>
<td>1.79 (1.14, 2.81)</td>
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<table>
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<tr>
<th>Slow Graft Function</th>
<th>OR (95% CI)</th>
<th>$P$-value</th>
<th>Pseudo-$R^2$ value</th>
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<td>0.05</td>
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<tr>
<td>USRDS score$^a$</td>
<td>1.54 (1.19, 1.98)</td>
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<tr>
<td><strong>Analysis 2</strong></td>
<td></td>
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<td>0.11</td>
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<tr>
<td>USRDS score$^a$</td>
<td>1.43 (1.06, 2.16)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Recipient weight</td>
<td>1.39 (1.03, 2.22)</td>
<td>0.04</td>
<td></td>
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<tr>
<td><strong>Analysis 3</strong></td>
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<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Donor age$^c$</td>
<td>1.36 (1.19, 1.86)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Cold ischaemic time$^d$</td>
<td>1.92 (1.22, 3.03)</td>
<td>0.005</td>
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<tr>
<td>Recipient weight$^e$</td>
<td>1.54 (1.10, 2.14)</td>
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<table>
<thead>
<tr>
<th>CRR2</th>
<th>Beta (95% CI)</th>
<th>$P$-value</th>
<th>$R^2$ value</th>
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<td>0.18</td>
</tr>
<tr>
<td>USRDS score$^a$</td>
<td>18.3 (3.30, 3.320)$^j$</td>
<td>0.001</td>
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<tr>
<td></td>
<td>$-0.90 (-1.47, -0.30)$</td>
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<tr>
<td><strong>Analysis 2</strong></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>USRDS score$^a$</td>
<td>16.12 (5.42, 31.19)$^j$</td>
<td>0.001</td>
<td></td>
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<tr>
<td></td>
<td>$-0.81 (-1.64, -0.26)$</td>
<td></td>
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<tr>
<td><strong>Analysis 3</strong></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Donor age$^c$</td>
<td>$-3.91 (-6.40, -1.40)$</td>
<td>0.002</td>
<td></td>
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</tbody>
</table>

$^a$Effect shown for 10 unit increase in USRDS score.
$^b$Effect shown for 10 unit increase in BMI.
$^c$Effect shown for 10 year increase in donor age.
$^d$Effect shown for 5 h increase in cold ischemic time.
$^e$Effect shown for 10 kg increase in recipient weight.
$^f$Linear term; $^g$Quadratic term.
$^h$Exponential of the beta value shown due to log transformation of the data.

Duration of delayed graft function

Duration of DGF was analysed for the 75 patients displaying DGF. As the data were logarithmically transformed, effect sizes reported are in the exponential form of the regression.
coefficient (exp $\beta$) (Table 2). Analyses 1 and 2 revealed that only USRDS score was associated with DGF duration on either univariate or multiple regression analysis (Table 2). No other scoring systems or clinical variables were associated with DGF duration. The multiple regression model of analysis 3 revealed associations of DGF duration with increasing cold ischemic time and DCD kidney donation (Table 2). These two factors accounted for 16% of the variability in DGF duration ($R^2$: 0.16). No association was seen between DGF duration and C2 levels during the first week.

**Slow graft function**

Analysis 1 revealed SGF was associated with increasing USRDS score and DDS on univariate analysis, although only USRDS score held significance in the multiple regression model (Table 2; Figure 1B).

Despite the association between USRDS score and SGF, only 5% of the variability in SGF was explained by the score ($R^2$: 0.05). ROC curve analysis suggested the predictive ability of the USRDS scoring system was moderate, with a c-statistic of 0.70 (95% CI: 0.60–0.81; Figure 1B). A USRDS score of 131 best discriminated patients with and without SGF (sensitivity 69% (95% CI: 52–83%); specificity 58% (95% CI: 47–68%).

Analysis 2 revealed SGF was associated with increasing USRDS score and increasing recipient weight in the multiple regression model (Table 2). DDS reached significance in the univariate model. Eleven percent of the variability in SGF was explained by the USRDS score and recipient weight (sum pseudo-$R^2$: 0.11).

The multiple regression model of analysis 3 revealed associations between SGF and increasing donor age, increasing cold ischemic time and increasing recipient weight (Table 2). Only 16% of the variability in SGF was explained by these explanatory variables (sum pseudo-$R^2$: 0.16). In addition, ROC curve analysis suggested the predictive ability of donor age and cold ischemic time was poor with respective c-statistics of 0.65 (95% CI: 0.54–0.76) and 0.64 (95% CI: 0.53–0.75). Donor age of 46 years and cold ischemic time of 20h best discriminated patients with and without SGF (sensitivity 69% and 46%, respectively; specificity 67% and 82%, respectively).

**Delayed vs slow vs immediate graft function**

Next, all 210 patients were considered as falling into three categories of increasingly severe graft dysfunction (DGF, SGF and IGF), creating an ordered response variable analysed by ordered logistic regression. Analysis 1 showed that USRDS score, DDS and ECD kidney donation showed univariate associations

![Fig. 1. Regression analysis showing association between USRDS score and early graft function. (A) DGF; (B) SGF; (C) CRR2. Outer, hashed lines represent 95% confidence interval.](image1)

![Fig. 2. ROC curve analysis showing ability of USRDS score to predict DGF. Discriminatory values are shown in accompanying table.](image2)
with worse graft function, however only USRDS score retained significance in the multiple regression model (OR per 10 units: 1.39; 95% CI: 1.19–1.61; \( P = 0.003 \)).

The multiple regression model of analysis 2 showed that only USRDS score (OR per 10 units:1.31; 95% CI: 1.07–1.67; \( P = 0.009 \)) was associated with progressively worsening graft function. DDS and ECD kidney donation were associated with worse function on univariate analysis (\( P < 0.01 \) for both), but failed to reach significance in the multiple regression analysis. Donor BMI was significant on univariate analysis (OR per 10 units:1.66; 95% CI:1.10–2.69; \( P = 0.02 \)), but failed to hold significance in the multiple regression model (OR per 10 units: 1.66; 95% CI: 0.97–3.15; \( P = 0.08 \)).

Analysis 3 revealed donor age (OR per 10 years: 1.42; 95% CI: 1.14–1.76; \( P = 0.001 \)), donor hypertension (OR: 2.53; 95% CI: 1.12–5.68; \( P = 0.01 \)), DCD kidney donation (OR: 3.14; 95% CI: 2.12–5.01; \( P = 0.001 \)), black recipient ethnicity (OR: 2.60; 95% CI: 1.67–3.23; \( P = 0.001 \)) and cold ischaemic time (OR per 5 min: 1.55; 95% CI: 1.19–2.01; \( P = 0.001 \)) were associated with poorer graft function. The sum pseudo-\( R^2 \) values for the models from analyses 1, 2 and 3 were 0.12, 0.16 and 0.20 respectively.

**Creatinine reduction ratio on day 2 (CRR2)**

CRR2 was studied in the 135 patients without DGF. As the data were not logarithmically transformed, effect sizes reported are in the form of the regression coefficient, \( \beta \) (Table 2). For continuous explanatory variables, the coefficients represent absolute changes in CRR2 for the stated increase in explanatory variable; for categorical explanatory variables the coefficients represent the absolute change in CRR2 relative to the baseline category.

In analyses 1 and 2, only USRDS score was associated with CRR2 in the multiple regression model (Table 2). The relationship between USRDS score and CRR2 was non-linear (Figure 1C) and is expressed as its linear and quadratic terms in Table 2. DDS was associated with CRR2 on univariate analysis, but not in the multiple regression model. Neither ECD kidney donation (analyses 1 and 2) nor other clinical variables (analysis 2) were associated with CRR2. USRDS score accounted for 18% and 17% of the variability in CRR2 in analyses 1 and 2, respectively.

The multiple regression model of analysis 3 revealed only donor age was associated with CRR2 (Table 2).

To verify the robustness of the conclusions derived from the multiple regression models, the model building was repeated using a forward instead of a backward selection procedure. No changes in the final models were observed. VIF values were tested for all analysis 1 models (see “statistical analysis”). In no cases were the values \( > 2.3 \), suggesting (along with the poor correlation found between the scoring systems; see results above) colinearity between scoring systems was not a significant problem in the analysis and interpretation.

**Discussion**

Suboptimal early renal allograft function is associated with increased early and late graft loss, increased hospitalization and costs [3,22,23]. This study investigated clinical characteristics associated with poor early function, in the (majority) subgroup not experiencing early technical failure. Novel aspects of this study include the simultaneous comparison of three validated scoring systems, investigation of clinical variables not included in the scoring systems and the use of a range of definitions of suboptimal graft function (all of which are associated with inferior long-term outcomes) rather than merely post-operative requirement for dialysis.

The USRDS score was clearly associated with DGF as recognized previously. In addition this study also showed an association between USRDS score and other aspects of early graft function such as DGF duration, SGF and CRR2. These associations have not been reported previously. However, the association with DGF was weaker at lower scores (as shown by the wide confidence interval in Figure 1A) and the score explained only a small proportion of the variability of measures of early graft function, as reflected in the low \( R^2 \) and pseudo-\( R^2 \) values. The USRDS score did, however, out-perform the DDS (associated with DGF, SGF and CRR2 on univariate but not multiple regression analysis), which in turn out performed ECD kidney criteria (associated with DGF on univariate analysis only). It should be pointed out that although these latter two scoring systems show associations with early graft function, they were initially developed with regard to medium and long-term graft outcomes [12–15], as opposed to the USRDS score which was specifically developed to identify patients at risk for DGF immediately following transplantation.

The concordance c-statistic for assessing the predictive ability of USRDS score for DGF was remarkably similar to that found in the original validation study (0.71 vs 0.70). It was claimed in the original validation study that the USRDS score was a good predictor for DGF [9], and one Australian study supports this conclusion [11]. A c-statistic of 0.70 suggests that at the optimal “cut-off” value (which was not described in the original study, but which was a value of 135 in the current study) episodes of DGF can be predicted in 70% of cases. However, because 50% of DGF episodes can be predicted by chance alone, we suggest that the overall utility of these scoring systems is somewhat limited. This conclusion is in keeping with the results of Grossberg’s study [10] which showed a poor association between the USRDS score and DGF in a North American population undergoing transplantation with delayed ciclosporin administration, although no ROC curve analysis was performed.
in that study and therefore firm conclusions cannot be drawn from it. The current study does however support and extend the conclusion of Grossberg that a scoring system based on clinical variables which accurately predicts suboptimal early graft function (however defined) is currently lacking and that the outcome of individual patients may not be improved by altering management on the basis of such scores.

A caveat to this conclusion may be relevant for patients displaying particularly high scores. In the current study, during which DGF occurred in 36% of patients, a USRDS score of >150 was associated with 95% specificity and a 73% positive predictive value for DGF. This suggests that it may be possible to predict DGF more reliably in the minority of patients (12% in this study) with extreme scores. Targeting therapeutic strategies to reduce DGF in this group may therefore be of particular benefit. Other strategies based on more complex measures of biochemical, physiological and genetic parameters may also refine the prediction of suboptimal early graft function [24–29] and allow therapeutic manoeuvres [5–8,14,30] to be directed to ‘high risk’ groups more appropriately, thereby potentially improving results. Indeed, one study has suggested that plasma levels of soluble interleukin-6 receptor show strong associations with acute tubular damage post-transplantation, with similar overall predictive utility to the USRDS score examined in the current study [24].

Of the studied variables not included in existing scoring systems, only donor BMI was associated with DGF (discussed subsequently), and recipient weight was associated with SGF (analysis 2). The latter association may be the result of larger patients (with greater muscle mass) displaying higher serum creatinine levels for a given level of renal function. The third analysis (analysis 3) investigated the relationship between individual clinical covariates and early graft function, splitting the scoring systems into their constituent parts. In agreement with previous studies, donor age, donor hypertension, DCD kidney donation, cold ischaemic time and black recipient ethnicity were strongly associated with suboptimal early graft function [5,9,17,18]. This analysis entered a large number of explanatory variables, increasing the chance of a type I statistical error. Nevertheless, the results were the same when a different selection process was used, adding a degree of robustness to the results. In addition, the degree of significance of the results, concordance with other studies and biological plausibility suggest that these findings are real and reproducible. However, despite these associations the ability of these factors in isolation to predict patients who will develop suboptimal early graft function was poor, as shown by the low c-statistics of the ROC curve analyses.

Donor BMI was associated with DGF, although there was no association seen with donor weight or the donor:recipient BMI ratio, suggesting that technical difficulties surrounding the organ retrieval operation in an overweight donor may explain this finding. Although protocols are in place for optimising organ donors in the intensive care setting [5], little attention has been paid to the organ retrieval procedure itself and certainly there is no standardisation within the UK. This is one area in which more accurate and complete information may aid in predicting DGF, as it is clear from this analysis that currently available clinical characteristics do not suffice.

In summary, this study suggests that clinical characteristics, particularly when collated into scoring systems, are associated with suboptimal graft function following renal transplantation. This was most evident for the USRDS score. However, other than at the extreme of this score, the predictive utility of this scoring system was at best moderate. This limitation should be recognized and caution should be exercised before altering the management of individual renal transplant recipients based solely upon clinical characteristics. Better predictive tools are required to guide strategies for optimising early renal allograft function, particularly in high risk individuals.

Conflict of interest statement. None declared.

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