Fasting Plasma Total Homocysteine Levels and Mortality and Allograft Loss in Kidney Transplant Recipients: A Prospective Study

Wolfgang C. Winkelmayer,*† Reinhard Kramar,‡ Gary C. Curhan,‡ Anil Chandraker,‡
Georg Endler,§ Manuela Födinger,§ Walter H. Hörl,‖ and Gere Sunder-Plassmann‖

*Division of Pharmacoepidemiology and Pharmacoeconomics and the †Renal Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; ‡Austrian Dialysis and Transplant Registry, Krankenhaus der Kreuzzschwestern Wels, Wels, Austria; §Clinical Institute of Medical and Chemical Laboratory Diagnostics and ‖Division of Nephrology and Dialysis, Department of Medicine III, Vienna General Hospital, Medical University Vienna, Vienna, Austria

Homocysteine is implicated to be an atherogenic amino acid and has been associated with increased risk of adverse cardiovascular outcomes. The prognostic significance of plasma total homocysteine (tHcy) levels for mortality and allograft loss in kidney transplant recipients has not been established. A total of 733 kidney transplant recipients who were seen for a routine visit at this transplant clinic in 1996 to 1998 were studied prospectively. During that visit, clinical information was collected and blood was drawn for laboratory evaluation. Information on the previous transplant procedure and the organ donor was obtained from the Eurotransplant Foundation database. Patients were followed prospectively using the Austrian Dialysis and Transplant Registry. With the use of proportional-hazards regression, the independent relations of fasting plasma tHcy levels to the risk of death from any cause and kidney allograft loss were examined. During a median follow-up of 6.1 yr, 154 participants died and 260 kidney allografts were lost. After adjustment for several important risk factors, elevated tHcy levels (≥12 μmol/L) were associated with 2.44 times the mortality risk of patients with normal tHcy levels (hazards ratio 2.44; 95% confidence interval 1.45 to 4.12; P < 0.001). Similarly, elevated tHcy levels were associated with 1.63 times increased risk of kidney allograft loss (hazards ratio 1.63; 95% confidence interval 1.09 to 2.44; P = 0.02). In this single-center sample, baseline fasting plasma tHcy levels were independently associated with the risk of death and kidney allograft loss. The clinical utility of homocysteine-lowering therapy, such as multivitamin therapy, to reduce the rates of these end points needs to be studied.


Kidney transplantation is the preferred treatment option for patients with ESRD, because it offers greater longevity and quality of life at a lower cost compared with hemodialysis and peritoneal dialysis (1). However, donor organs are scarce, and waiting times for cadaveric kidneys have soared. Currently, more than 55,000 patients are on the waiting list for a kidney transplant in the United States alone (2). Luckily, the median patient and graft survival for kidney transplant recipients (KTR) has increased in the past decades. Nevertheless, with improved immunosuppression and early allograft survival, chronic allograft nephropathy is now the dominant cause of kidney transplant failure, which imposes a great burden on this patient population and on society as a whole (3). Hence, identification of risk factors and development of effective treatment strategies to prevent these outcomes are of paramount public health importance.

Several prospective studies have demonstrated that elevated plasma levels of total homocysteine (tHcy) are associated with an increased risk of congestive heart failure, ischemic heart disease, stroke, and cardiovascular and all-cause mortality in the general population, elderly patients, patients with diabetes, and patients who undergo maintenance dialysis (4–8). In KTR, tHcy has also been shown to be associated with arteriosclerotic events (composite end point of coronary heart disease, stroke/cerebrovascular disease, and abdominal aortic or lower extremity arterial disease) (9). Only limited information is available on the putative association between tHcy levels and patient or graft survival in KTR. One study examined the association between a single nucleotide polymorphism of the 5,10-methylenetetrahydrofolate reductase gene, MTHFR 677C>T, and kidney allograft survival in 336 KTR patients over 36 mo of follow-up (10). The homozygous variant of MTHFR 677C>T is well known to be an important determinant of higher plasma tHcy levels in individuals both with normal and with reduced renal function (11,12). However, that study did not reveal an effect of this genetic variant on kidney allograft survival (10). Another study failed to detect an association between tHcy and mortality but was limited by small sample size and short fol-
low-up (13). To our knowledge, no prospective and long-term studies have been published on the associations between plasma tHcy levels and patient or graft survival in KTR. To fill this void, we tested prospectively the hypothesis that baseline fasting plasma tHcy level was associated with patient or allograft survival in KTR.

Materials and Methods

Study Population and Data Collection

Between 1996 and 1998, we prospectively enrolled into this study 733 stable KTR who received routine follow-up at the transplant clinic of the Vienna General Hospital. All patients gave informed consent in accordance with the Declaration of Helsinki and the Austrian Law on Gene Technology, and the study was approved by the Institutional Review Board. At baseline, we assessed each patient’s age, gender, underlying renal disease that likely caused the kidney failure, number of previous kidney transplants, time from first renal replacement therapy to transplantation, and time since the most recent kidney transplantation. Body mass index was calculated as the weight in kilograms divided by the squared height in meters. The immunosuppressive regimen at study baseline was also recorded.

During the baseline visit, blood was drawn from each patient for laboratory analysis. Plasma tHcy was measured using standard methods as described previously (12). Furthermore, we measured each patient’s total cholesterol, triglyceride, C-reactive protein, and creatinine level. We then used the Cockercroft-Gault formula to estimate the GFR (14), which was standardized to a body surface area of 1.73 m$^2$.

From the registry of the Eurotransplant Foundation, the joint organ procurement agency for Austria, Belgium, Germany, Luxembourg, The Netherlands, and Slovenia, we obtained information on the organ donor (donor age, gender, and living versus deceased donor) and on the specific circumstances of the transplantation procedure (cold ischemia time, number and type of human leukocyte antigen mismatch, and recipient panel reactive antibody titer). Longitudinal information on all dialysis patients and KTR residing in Austria is routinely collected by the Austrian Dialysis and Transplant Registry (OeDTR). Follow-up in this database has been 100% complete for many years, and reliable information on timing and occurrence of patient death and modality switches, such as reinitiation of maintenance dialysis after kidney graft failure, is available for study.

The outcomes of this study were all-cause mortality and kidney allograft failure; the latter was defined as the composite end point of patient death and modality switches, such as reintroduction of maintenance dialysis after kidney graft failure.

Statistical Analyses

All patients were followed up from the date of study inclusion until they reached an end point or the date when they were last seen at the transplant clinic. Baseline characteristics were compared using the $t$ test for continuous variables and Pearson $\chi^2$ test for categorical variables. We used Kaplan-Meier survival curves to describe the cumulative incidence of patient and allograft survival over time, and the log-rank test was used to test for differences among the four quartiles of baseline tHcy level. Univariate and multivariate Cox proportional hazards models then were fit to test for potential risk factors of the outcomes. The measure of association was the hazards ratio (HR) accompanied by the corresponding 95% confidence interval (CI). Associations between continuous variables and the outcomes were examined for linearity and used in categories otherwise. Body mass index was used in five categories because the associations between this variable and all outcomes of this study are known to be U-shaped (15).

variable of interest, plasma tHcy, was dichotomized at 12 μmol/L, a commonly used cutoff point for normal versus elevated levels of that atherogenic marker (16). For multivariate model building, we used an automated stepwise variable selection procedure that included into the model all variables at $P < 0.20$. Recipient age and gender as well as estimated GFR were forced into all models. From there, we introduced all other variables individually and then assessed whether they confounded the association between the main exposure variable (defined as a change in the regression coefficient >10%), in which case the variable would be included regardless of the significance level. We used the SAS for Windows (Release 8.2; SAS Corp, Cary, NC) software for all statistical analyses.

Results

From the 733 patients originally included in the study, 7 were found to receive their routine transplant care outside Austria and were excluded. For 16 patients, information on their donors was unavailable from the Eurotransplant Foundation registry. The remaining 710 patients constituted the final study cohort. On average, patients had received their current transplant 5 yr before enrollment. The mean age was 52.2 yr, and 60.1% were men. The mean estimated GFR was 55.8 ml/min per 1.73 m$^2$, and the mean plasma tHcy level was 17.2 μmol/L. One quarter (24.8%) of the patients had a tHcy level within the normal range (<12 μmol/L), and the remaining patients (75.2%) had an elevated plasma tHcy.

Patients with an elevated tHcy level were more likely to be male ($P = 0.003$); were more likely to have a lower kidney function ($P < 0.001$); differed with regard to their native kidney disease ($P = 0.03$); and were more likely to have an immunosuppressive regimen that contained cyclosporine A, corticosteroids, and azathioprine ($P = 0.002$; Table 1). These KTR also had received their organ from an older donor ($P = 0.04$) and were more likely to have had a panel reactive antibody titer $>50\%$ before transplantation ($P = 0.02$; Table 2). Other baseline characteristics (Table 1) and specific characteristics regarding the transplantation procedures (Table 2) did not differ by baseline tHcy level.

Endpoint: All-Cause Mortality

During a median follow-up of 6.1 yr (3798 person-years), 154 patient deaths were recorded (crude incidence rate 40.6/1000 person-years). From a Kaplan-Meier plot of cumulative survival stratified by quartile of tHcy ($\leq12$, $>12$ to $15$, $>15$ to 19.8, and $>19.8$ μmol/L), it was evident that all-cause mortality increased monotonously with higher tHcy levels ($P < 0.001$, log-rank test; Figure 1). From Cox proportional hazards models, we found that KTR with elevated baseline tHcy levels ($\geq12$ μmol/L) experienced nearly three times the mortality rate of patients with normal tHcy levels in univariate analyses ($HR = 0.001$, log-rank test; Figure 1). From Cox proportional hazards models, we found that KTR with elevated baseline tHcy levels ($\geq12$ μmol/L) experienced nearly three times the mortality rate of patients with normal tHcy levels in univariate analyses (HR 2.72; 95% CI 1.66 to 4.45). After multivariate adjustment for other risk factors and confounders, this association was slightly attenuated (Table 3). Patients with elevated tHcy experienced a 2.44-fold mortality risk compared with patients whose tHcy was within the normal range (HR 2.44; 95% CI 1.45 to 4.12). Next, when testing the robustness of this finding by excluding the 70 patients whose graft function seemed already to be substantially impaired at baseline (GFR <30 ml/min per 1.73 m$^2$), we obtained a very similar result (Table 3).
Table 1. Baseline characteristics of 710 kidney transplant recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 710)</th>
<th>tHcy &lt; 12 μmol/L (n = 176; 24.8%)</th>
<th>tHcy ≥ 12 μmol/L (n = 534; 75.2%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from first RRT to transplantation (yr)</td>
<td>3.2 (±3.6)</td>
<td>3.0 (±3.5)</td>
<td>3.2 (±3.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Time since transplantation (yr)</td>
<td>5.0 (±4.0)</td>
<td>4.9 (±4.0)</td>
<td>5.0 (±4.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Recipient age (yr)</td>
<td>52.2 (±13.3)</td>
<td>52.2 (±13.7)</td>
<td>52.2 (±13.1)</td>
<td>0.97</td>
</tr>
<tr>
<td>Recipient gender (male)</td>
<td>427 (60.1%)</td>
<td>89 (50.6%)</td>
<td>338 (63.3%)</td>
<td>0.003</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m^2)</td>
<td>55.8 (±20.0)</td>
<td>64.6 (±18.0)</td>
<td>50.4 (±19.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>25.4 (±4.3)</td>
<td>25.0 (±4.4)</td>
<td>25.5 (±4.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Plasma tHcy (μmol/L)</td>
<td>17.2 (±8.8)</td>
<td>10.0 (±1.5)</td>
<td>19.5 (±9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>234 (±56)</td>
<td>232 (±49)</td>
<td>235 (±58)</td>
<td>0.59</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>193 (±153)</td>
<td>180 (±135)</td>
<td>198 (±159)</td>
<td>0.14</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)^b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.5</td>
<td>531 (75.5%)</td>
<td>130 (74.7%)</td>
<td>401 (75.8%)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5–1.0</td>
<td>86 (12.2%)</td>
<td>22 (12.6%)</td>
<td>64 (12.1%)</td>
<td>0.96</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>86 (12.2%)</td>
<td>22 (12.6%)</td>
<td>64 (12.1%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Underlying renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetic nephropathy</td>
<td>47 (6.6%)</td>
<td>19 (10.8%)</td>
<td>28 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>243 (34.2%)</td>
<td>56 (31.8%)</td>
<td>187 (35.0%)</td>
<td></td>
</tr>
<tr>
<td>interstitial nephritis</td>
<td>114 (16.1%)</td>
<td>23 (13.1%)</td>
<td>91 (17.0%)</td>
<td></td>
</tr>
<tr>
<td>polycystic kidney disease</td>
<td>97 (13.7%)</td>
<td>28 (15.9%)</td>
<td>69 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>various other, specified</td>
<td>59 (8.3%)</td>
<td>9 (5.1%)</td>
<td>50 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>unspecified/unknown</td>
<td>150 (21.1%)</td>
<td>41 (23.3%)</td>
<td>109 (20.4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Immunosuppressive regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine A + corticosteroid + azathioprine</td>
<td>317 (44.7%)</td>
<td>59 (33.5%)</td>
<td>258 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>cyclosporine A + corticosteroid</td>
<td>185 (26.1%)</td>
<td>57 (32.4%)</td>
<td>128 (24.0%)</td>
<td></td>
</tr>
<tr>
<td>cyclosporine A + corticosteroid + MMF</td>
<td>126 (17.8%)</td>
<td>31 (17.6%)</td>
<td>95 (17.8%)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>82 (11.6%)</td>
<td>29 (16.5%)</td>
<td>53 (9.9%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

^a tHcy, total homocysteine; RRT, renal replacement therapy; MMF, mycophenolate mofetil.

^b Missing in 7 patients.

Endpoint: Kidney Allograft Loss

We had 3480 person-years of follow-up available for the study of allograft loss (alive or associated with death), and this event was observed in 260 patients (crude incidence rate 74.7/1000 person-years). As before, the Kaplan-Meier plot of cumulative allograft loss indicated that increasing tHcy levels were associated with increased risk of this end point as well (P < 0.001, log-rank test; Figure 2). The univariate Cox proportional hazards model revealed that patients with an elevated fasting tHcy plasma level at study baseline had nearly three times the rate of allograft loss compared with those whose tHcy was within the normal range (HR 3.28; 95% CI 1.98 to 5.43). However, when controlling for several other variables, the finding was substantially attenuated and was no longer significant (HR 1.35; 95% CI 0.79 to 2.32; Table 3).

For all three outcomes, we conducted additional analyses using information on anemia, serum calcium and phosphorus, or calcium/phosphorus ion product. Inclusion of these variables did not change the results in a meaningful way. Furthermore, we explored the possibility of effect modification among the available variables. Although we did not find any interaction terms to be significant, the power to do so was likely limited in this study. Finally, we did not find any indication that collinearity had led to artificially inflated CI in this study.

Discussion

From this prospective study, we found that patients with an elevated fasting tHcy plasma level at study baseline (≥12 μmol/L) experienced a 2.44 times greater mortality risk than those whose tHcy was below that threshold. Similarly, an elevated tHcy was associated with 1.63 times the risk of allograft loss. These results arose from multivariate regression models that simultaneously controlled for several important factors.
confounders and predictors of the outcomes under study. To our knowledge, this is the first prospective study of the association between tHcy and these important outcomes in KTR.

The findings from this study expand on a previous study of the association between tHcy levels and cardiovascular disease occurrence in KTR (9). Ducloux et al. (9) found that the risk of experiencing an aggregate end point of atherosclerotic events (coronary heart disease, stroke/cerebrovascular disease, abdominal aortic, or lower extremity arterial disease) and all-cause mortality increased with higher tHcy levels. However, the evidence from this study is limited by a small sample size \((n = 207)\), short follow-up (21.2 mo), and a small number of outcomes (30 cardiovascular events, 9 deaths), which precluded meaningful multivariate analysis. Two other studies examined the possible association between \(MTHFR\ 677C>T\) genotype and patient or kidney allograft survival (10,13). The homozygous variant of \(MTHFR\ 677C>T\) is well known to be an important determinant of higher tHcy plasma levels in individuals both with normal and with reduced renal function (11,12). Neither study found an association, but both were limited by small numbers of enrollees and limited power.

Although our findings of an association between tHcy levels and all-cause mortality are straightforward, our analyses of the association between tHcy levels and kidney allograft loss deserve more differentiated comment. The association between tHcy levels and allograft loss defined as the aggregate end point of return to dialysis and patient death are more pronounced than those using return to dialysis as the sole end point and censoring patients at death. Even after excluding patients whose kidney function was already severely impaired

Table 2. Transplantation-specific characteristics of study population\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total ((n = 710))</th>
<th>tHcy &lt; 12 (\mu\text{mol/L}) ((n = 176; 24.8%))</th>
<th>tHcy (\geq 12\ \mu\text{mol/L}) ((n = 534; 75.2%))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous kidney transplants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>576 (81.1%)</td>
<td>150 (85.2%)</td>
<td>426 (79.8%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>113 (15.9%)</td>
<td>20 (11.4%)</td>
<td>93 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>2/3</td>
<td>21 (3.0%)</td>
<td>6 (3.4%)</td>
<td>15 (2.8%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Donor organ type (living versus deceased)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33 (4.7%)</td>
<td>10 (5.7%)</td>
<td>23 (4.3%)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Donor age (yr)</td>
<td>38.4 (±15.6)</td>
<td>36.3 (±15.3)</td>
<td>39.1 (±15.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Donor gender (male)</td>
<td>449 (63.2%)</td>
<td>111 (63.1%)</td>
<td>338 (63.3%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Number of HLA mismatches</td>
<td>2.2 (±1.2)</td>
<td>2.1 (±1.2)</td>
<td>2.2 (±1.1)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cold ischemia time (h)</td>
<td>20.8 (±7.7)</td>
<td>20.5 (±7.8)</td>
<td>20.9 (±7.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Panel reactive antibody titer ((&gt;50% versus \leq50%))</td>
<td>47 (6.9%)</td>
<td>5 (2.8%)</td>
<td>42 (7.9%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\(^a\)HLA, human leucocyte antigen.

Figure 1. Cumulative patient survival plot by quartile of plasma total homocysteine level.
at study enrollment (GFR <30 ml/min per 1.73 m²), there was no association. The leading cause of long-term renal allograft loss is chronic allograft nephropathy (3). Immunologic and nonimmunologic factors have been shown to contribute to chronic allograft nephropathy. Many of the nonimmunologic factors such as hypertension and hyperlipidemia also contribute to cardiovascular disease. It therefore is plausible that elevated tHcy levels contribute to the progression of renal allograft dysfunction through similar mechanisms.

The results from this study have important scientific impact. Elevated tHcy is more prevalent than all other traditional risk factors in KTR or other populations with already-limited kidney function. Treatment with folic acid and other B vitamins (B₁₂, B₆) has been shown to be effective in lowering or even normalizing

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**Table 3. Association between total plasma homocysteine and outcomes under study**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma tHcy ≥12 versus &lt;12 μmol/L</td>
<td>2.72</td>
<td>1.66–4.45</td>
<td>&lt;0.001</td>
<td>2.44</td>
<td>1.45–4.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>only patients with GFR ≥ 30 ml/min per 1.73 m²</td>
<td>2.57</td>
<td>1.56–4.22</td>
<td>&lt;0.001</td>
<td>2.37</td>
<td>1.40–4.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Allograft loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma tHcy ≥12 versus &lt;12 μmol/L</td>
<td>2.90</td>
<td>2.00–4.23</td>
<td>&lt;0.001</td>
<td>1.63</td>
<td>1.09–2.44</td>
<td>0.02</td>
</tr>
<tr>
<td>only patients with GFR ≥ 30 ml/min per 1.73 m²</td>
<td>2.42</td>
<td>1.65–3.55</td>
<td>&lt;0.001</td>
<td>1.76</td>
<td>1.17–2.66</td>
<td>0.007</td>
</tr>
<tr>
<td>Allograft loss, death censored</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma tHcy ≥12 versus &lt;12 μmol/L</td>
<td>3.28</td>
<td>1.98–5.43</td>
<td>&lt;0.001</td>
<td>1.35</td>
<td>0.79–2.32</td>
<td>0.27</td>
</tr>
<tr>
<td>only patients with GFR ≥ 30 ml/min per 1.73 m²</td>
<td>2.39</td>
<td>1.43–4.02</td>
<td>&lt;0.001</td>
<td>1.42</td>
<td>0.82–2.46</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*aHR, hazards ratio; CI, confidence interval.
*bMultivariate model adjusted for recipient age, gender, GFR, C-reactive protein, body mass index, diabetic nephropathy, donor gender, and time from first RRT to transplantation.
*cMultivariate model adjusted for recipient age, gender, GFR, C-reactive protein, body mass index, diabetic nephropathy, time from first RRT to transplantation.
*dMultivariate model adjusted for age, gender, GFR, body mass index, donor gender, immunosuppression with cyclosporine A + corticosteroids (versus all other regimens), and time from first RRT to transplantation.

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**Figure 2.** Cumulative allograft survival plot by quartile of plasma total homocysteine level.
tHcy plasma levels, providing a potentially easy and inexpensive way to reduce the rates of these undesirable outcomes in this vulnerable population. However, the utility of vitamin supplementation is unknown. This underscores the importance of the ongoing Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) study, a nationwide, multicenter, clinical trial in which KTR are randomly allocated to receive either high-dose folic acid, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> or no folic acid and customary low doses of the other vitamins (17).

There are limitations to this study. Although prospective, our analyses are still of observational nature; thus, confounding by unmeasured factors is possible. The only known potential confounder of the associations of interest that is missing from our database is smoking status. Smoking has been demonstrated to be a risk factor for both mortality and allograft loss and is also associated with tHcy levels (18). However, the prevalence of smoking is likely low in this population, and the independent association between smoking status and tHcy has been shown to be weak (18). Therefore, we suspect that the confounding from omitting smoking status is actually moderate at best. In an earlier study of tHcy and cardiovascular disease occurrence in KTR, smoking did not confound the association between tHcy and an aggregate end point of cardiovascular events and death (9). Furthermore, questions have recently been raised as to whether tHcy has any cause–effect relationship with the outcomes studied, and elevated tHcy concentration may possibly be a surrogate of certain disease conditions. We did not conduct any serial assessments of tHcy during follow-up. It is important to note that the present study does not prove causality of the associations found. Finally, repeat measures of renal function were unavailable for study, which precluded us from modeling the association between tHcy and the outcome of difference in renal function in this sample.

In summary, from this prospective study, we provide evidence that tHcy is associated not only with all-cause mortality but also with kidney allograft survival. Further research is urgently needed to establish successful treatment measures to lower tHcy in these patients and to establish the efficacy of such measures on reducing the rates of these important outcomes in KTR.

References