Self-rated health and mortality after kidney transplantation

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Part III

Patient and graft mortality as a health outcome

Chapter 6

Anemia is an independent predictor of mortality in kidney transplant recipients: results from a 10-year follow-up study

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Abstract

Background

Findings on the association between post-transplant anemia (PTA) and mortality in patients after kidney transplantation (KT) are scarce. This study explored whether PTA shortly after KT predicts mortality at up to 10 years follow-up.

Methods

PTA was divided into 3 categories according to the hemoglobin (Hb) value: severe (Hb<10g/dl), mild (10.0g/dl≤Hb<11.9g/dl), or no PTA (Hb≥12g/dl). Chronic kidney disease (CKD) stages were estimated using the CKD-EPI formula and divided into 2 groups: CKD stages 1-2, CKD stages 3-5. Cox regression, stratified according to CKD, was performed to identify whether different categories of PTA predicted mortality in KT recipients.

Results

Age, being female, and both mild and severe PTA contributed significantly to the Cox regression model on mortality in CKD1-2. In the Cox regression model for mortality in CKD3-5, age and severe PTA contributed significantly to this model.

Conclusion

PTA shortly after KT increased the risk of mortality at up to 10 years follow-up. Even mild PTA is associated with a 6-fold higher risk of mortality, and severe PTA with a 10-fold higher risk of mortality in CKD1-2. Clinical evaluation and treatment of anemia might reduce the higher risk of mortality in patients with PTA in early stages of CKD after KT.

Key words

anemia, kidney transplantation, mortality

Introduction

The definition and grades of anemia were established decades ago by the World Health Organization (WHO) as being among the important factors influencing health outcomes: decreased hemoglobin concentration predicts morbidity and mortality in the general population;[1] this definition was consequently adopted by nephrologists. According to "The National Kidney Foundation Disease Outcomes Quality Initiative" (NKF/KDOQI), "Kidney Disease Improving Global Outcomes" (KDIGO) and "European Best Practice Guidelines" (EBPG), anemia is defined as a target hemoglobin (Hb) <13.5 g/dl in adult males/post-menopausal females, <12.0 g/dl in pre-menopausal females, and <5th percentile for children;[2-4] alternatively, the target Hb should generally be < 11.0 g/dl.[5,6]

However, in most individuals there is a considerable amount of variation in the Hb-value over time, and the consequences of this variability in Hb-levels have been thoroughly studied in dialysis patients, though not in transplant recipients.[7] Renal anemia after transplantation, or post-transplant anemia (PTA), has a multifactorial etiology including the progress of transplant kidney failure, comorbidity, infections, inflammation, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) and immunosuppressive treatment.[2-6,8-10] Thus far, some evidence has been found suggesting that kidney transplant recipients may have an Hb-level lower than can be expected based on the level of their kidney function.[2]

Guidelines from NKF/KDOQI, KDIGO and EBPG recommend treating anemia of renal origin in order to reduce both morbidity and mortality.[2-5] KDIGO guidelines for kidney transplant recipients state that treatment should be directed at the underlying cause. In contrast, regular testing for anemia is not recommended by the above-mentioned guidelines, and treatment of post-transplant anemia should be managed according to the guidelines for chronic kidney disease (CKD) in the pre-dialysis period, with no specific recommendation for treatment of this specific population.[2]

Additionally, the impact of the variability of hemoglobin over time in transplant recipients as compared with dialyzed patients has been considered in only a few studies. Some relationships between rejection episodes, immunosuppressant use and increased anemia prevalence,[9,10] as well as between anemia of renal origin and mortality,[11-13] have been shown.

Renal anemia after transplantation and its association with transplant outcomes have not been sufficiently explored; moreover, longitudinal studies on the association between anemia and mortality are rather rare, and PTA is still an underestimated problem.[7,13-15] Therefore, the aim of this study was to explore whether anemia shortly after kidney transplantation predicts mortality at up to 10 years follow-up.

Materials and Methods

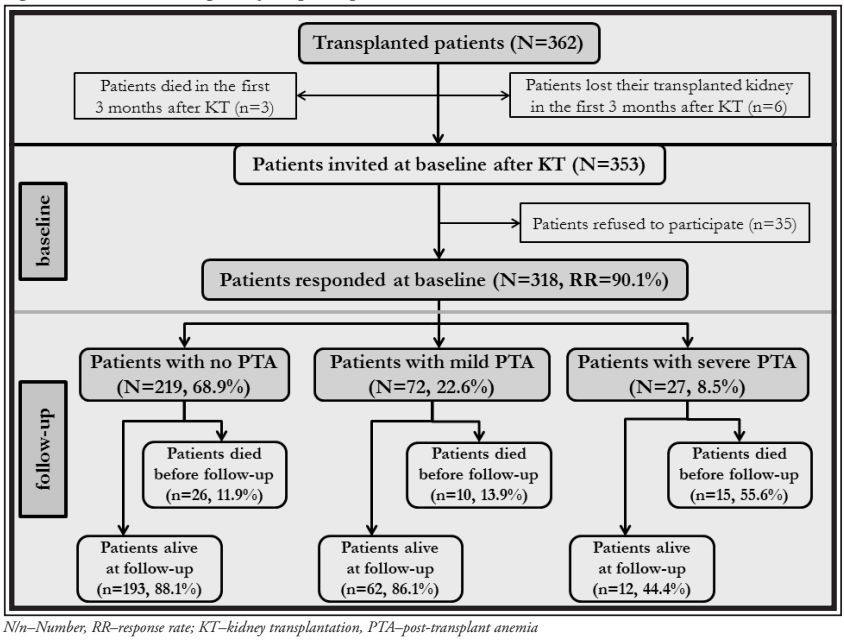
Sample and procedure

A total of 362 consecutive patients who underwent KT between January 2001 and January 2011 at the Transplant Centre of Kosice in the eastern region of Slovakia were enrolled in the study. The presented findings are a part of a bigger study focused on quality of life measured using several questionnaires; the collection of medical data for this study took place during the collection of the questionnaires. The baseline examination of the participants took place between the 3rd and 12th month after successful KT during regular outpatient clinical visits in our centre. The first 3 months after KT are usually considered to be the most problematic period, connected to dramatic changes

and increased morbidity and mortality.[16] Additionally, the degree of renal anemia during a period shorter than 3 months after successful transplantation depends on the pre- and peri-transplantation period.[2] In the case of any severe medical problem (infection, rejection, surgery, etc.) data collection was postponed by one month after overall clinical stabilization.

Nine patients dropped out prior to reaching 3 months after transplantation: 3 (0.8%) died and 6 (1.7%) lost their transplanted kidney. In total 353 kidney-transplant recipients after successful transplant surgery were invited to participate. Out of these, 35 (9.9%) refused to participate, resulting in a total of 318 patients (an effective response rate of 90.1%) at the start of the study. Figure 6.1 presents more detailed information about the sample. Only patients who signed an informed consent form prior to the study were included. The local Ethics Committee in Kosice approved the study.

Figure 6.1 Flow-chart diagram of the participants



N/n–Number, RR–response rate; KT–kidney transplantation, PTA–post-transplant anemia

Measures

Sociodemographic data included age and gender. Age was treated as a continuous variable. Male gender was the reference category.

Clinical data were retrieved from medical files. These included serum hemoglobin, creatinine (laboratory methods by Scheffe), primary kidney diagnosis, previous duration of dialysis (in years), source of transplanted kidney, comorbidity, current and anti-rejection immunosuppressive treatment, acute rejection episodes, chronic renal allograft dysfunction, uroinfection – which included pyelonephritis and diagnosis of graft loss – and mortality. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula in mililiters per minute.[17] CKD stages were determined as recommended by guidelines.[2,6] In the second step, patients were stratified into two groups: the first group consisted of stages 1 and 2 CKD patients, and the second group of stages 3-5 CKD patients, according to

the known impact of deceased kidney function on anemia of renal origin.[6] Acute rejection episodes and chronic renal allograft dysfunction were diagnosed from a biopsy according to the Banff 2009 update of diagnostic categories for renal allograft biopsies.[18] According the hemoglobin value, PTA was divided into 3 categories: 1) severe PTA (Hb<10 g/l), 2) mild PTA (10≤Hb<12 g/l) and 3) no PTA (Hb≥12 g/dl).[3,4]

Mortality data were obtained from our database of medical reports and completed with data from the "Health care surveillance authority of the Slovak Republic" up to 10 years after KT.

Statistical analyses

Frequencies, means and standard deviations were calculated for the sample description. The Mann-Whitney U-test and χ^2 test were used to identify the association between the dependent variable (mortality) and the other variables: age, gender, duration on dialysis before KT (in years), eGFR and CKD stages at baseline, PTA (severe, mild and no anemia, which was the reference category) at baseline, uroinfection (pyelonephritis included), number of acute rejection episodes, chronic renal allograft dysfunction, source of transplanted kidney, cardiovascular disease (coronary artery disease, severe cardiac failure, myocardial infarction) and categories of diabetes mellitus (no diabetes mellitus, already existing diabetes mellitus and new-onset diabetes mellitus after transplantation). Stratification by CKD was performed with regard to the known impact of decreased kidney function on anemia of renal origin,[6] and Cox regression was performed in order to identify the predictors of mortality (censored for graft loss). The independent variables in both stratified Cox regression models were all variables with $p < 0.1$ in the Mann-Whitney U-test and the χ^2 test, as appropriate. The Statistical Package for the Social Science (IBM SPSS Inc. Chicago, IL, USA) version 20 was used for statistical analyses.

Results

No significant differences were found at baseline between participants and non-participants regarding age, gender, graft loss and mortality. The observation period of follow-up was from 1 to 10 years (mean 5.6±2.7); the mean period for severe PTA was 4.3±2.6 years, for mild PTA 5.3±2.6 years and for the category without PTA 5.9±2.7 years. The prevalence of renal anemia therapy was 14% with Erythropoiesis-Stimulating Agents (ESA), 48% iron supplementation, 33% folic acid, 14% ascorbic acid, 10% pyridoxine and 6% cobalamin. Table 6.1 displays detailed information about the characteristics of the sample (N=318).

The Mann-Whitney U-test showed that age ($p<0.001$) and eGFR ($p<0.001$) were associated with mortality. The χ^2 test performed in order to identify factors associated with mortality found that female gender ($\chi^2=1.5$; $p<0.1$), categories of PTA ($\chi^2=33.1$; $p<0.001$), CKD stages ($\chi^2=32.7$; $p<0.001$) and cardiac failure ($\chi^2=2.4$; $p<0.1$) were associated with mortality. These associations are marked in Table 6.1. These variables were used as independent factors in the Cox regression models for mortality, stratified according to the two groups of CKD.

Table 6.1 Characteristics of the sample (N=318)

		Characteristics of the sample at baseline	Status of the sample at follow-up	
		N(%) or mean±SD	Died (N=51;16%)	Survived (N=267;84%)
Age (mean±SD)		47.94±12.24	#	$
Gender	Male	183(57.5%)	#	
	Female	135(42.5%)	#	
Duration on dialysis before KT (in years)		3.55±2.72		
Primary diagnosis of kidney failure	Glomerulonephritis	115(36.2%)		
	Tubulointerstitial nephritis	78(24.5%)		
	Vascular disease	31(9.7%)		
	Polycystic kidneys adult type	21(6.6%)		
	Diabetic nephropathy	21(6.6%)		
	Other or unknown	52(16.4%)		
Source of transplanted kidney	Deceased donor	303(95.3%)		
	Living donor	15(4.7%)		
Function immediately after KT	Immediate function	177(55.7%)		
	Delayed function	141(44.3%)		
Estimated glomerular filtration rate (ml/min)		62.4±19.8	#	$
CKD stage	1	23(7.2%)	#	$
	2	135(42.5%)	#	$
	3a+3b	122(38.4%)	#	
	4	14(4.4%)	#	
	5	24(7.5%)	#	
Hemoglobin value (g/dl)		12.5±1.8	#	$
Post-transplant anemia	Severe (Hb<10.0g/dl)	27(8.5%)	#	$
	Mild (10.0≤Hb<12.0g/dl)	72(22.6%)	#	$
	No anemia (Hb≥12.0g/dl)	219(68.9%)	#	$
Therapy for anemia	ESA	14(14.1%)		
	Iron	47 (47.5%)		
	Folic acid	33(33.3%)		
	Cobalamin	6(6.1%)		
	Pyridoxine	10(10.1%)		
	Ascorbic acid	14(14.1%)		
Acute rejection episodes		95(29.9%)		
Type of rejection treatment	Steroids	72(22.6%)		
	Antithymocyte globulin	10(3.1%)		
	Plasmapheresis	6(1.9%)		
	Plasmapheresis+i.v.immunoglobuline	7(2.2%)		
Chronic renal allograft dysfunction		42(13.2%)		
Uroinfection (including pyelonephritis of graft)		85(26.7%)		
Immunosuppression treatment	CsA+P	36(11.4%)		
	CsA+AZA/CsA+AZA+P	24(7.5%)		
	CsA+MMF/CsA+MMF+P	154(48.4%)		
	Tac+MMF/Tac+MMF+P	97(30.5%)		
	SIR+MMF+P/EVER+CsA+MMF	7(2.2%)		
Comorbidities	Coronary artery disease	78(24.5%)		
	Severe cardiac failure	72(22.6%)	#	
	Myocardial infarction	17(5.3%)		
	Hypertension	226(71.1%)		
	Diabetes mellitus identified before KT	30(9.4%)		
	New onset diabetes mellitus after transplantation	17(5.3%)		
	CKD-MBD	163(51.3%)		
	Other comorbidities:≥2	9(2.8%)		
Graft loss		55(17.3%)		
Diagnosis of graft loss	Acute rejection episodes	5(9.1%)		
	Chronic renal allograft dysfunction	16(29.1%)		
	Uroinfections	15(27.3%)		
	Others/unknown	19(34.5%)		
Diagnosis of mortality	Acute myocardial infarction	23(46.9%)		
	Pulmonary disease/pulmonary embolism	7(14.3%)		
	Stroke	3(6.1%)		
	Carcinoma with metastasis/liver disease	6(12.2%)		
	Others/unknown	10(20.4%)		

N–Number, SD–Standard deviation; AZA–azathioprine, CKD–Chronic kidney disease, MBD–Mineral bone disorder, CsA–cyclosporine A, ESA–erythropoiesis-stimulating agents, EVER–everolimus, Hb–hemoglobin, KT–kidney transplantation, MMF–mycophenolate mofetil/ mycophenolate sodium, P–prednisone, SIR–sirolimus, Tac–tacrolimus; #–association with mortality (p<0.1); $–association with survival (p<0.1)

Model 1: Cox regression model for mortality in CKD stages 1-2

The $\chi 2$ of the Cox regression model 1 for mortality in CKD stages 1-2 was 39.6. Age (HR 1.1, p≤0.001), female gender (HR 0.1, p≤0.05), mild PTA (HR 6.2, p≤0.05) and severe PTA (HR 9.8, p≤0.001) contributed significantly to this model. The risk of death increased by 10% for each year of age, while on the other hand, the risk of death decreased by 90% among females. In addition, the presence of mild PTA increased the risk 6-fold and severe PTA 10-fold (Table 6.2).

Model 2: Cox regression model for mortality in CKD stages 3-5

The $\chi 2$ of the Cox regression model 2 for mortality in CKD stages 3-5 was 32.1. Age (HR 1.1, p≤0.01) and severe PTA (HR 10.8, p≤0.001) contributed significantly to this model. The risk of death increased by 10% for each year of age, and the presence of severe PTA increased the risk 10-fold (Table 6.2).

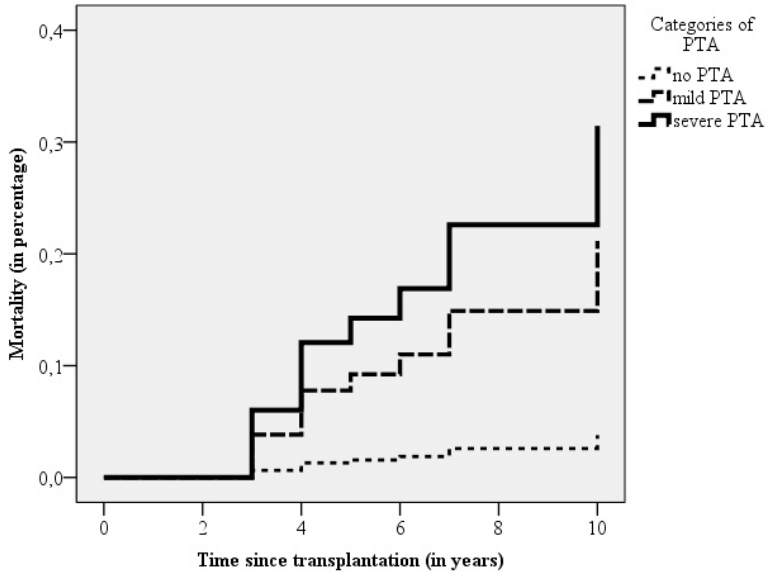
The risk of death in patients with mild and severe PTA in CKD stages 1-2 compared with no PTA starts to rise at 3 years after KT; the hazard ratio for mild and severe PTA compared with no PTA increased after this period independently of kidney function. However, the risk of death in patients with severe PTA in CKD stages 3-5 starts to rise already at 2 years after KT. Figures 6.2 and 6.3 display the differences in mortality between those with severe PTA, mild PTA and no PTA.

Table 6.2: Final models of Cox regression [stratified due to 2 CKD groups (CKD stages 1-2 and 3-5)] containing predictors of mortality

Models for mortality (N=318)		Score		B(SE)	HR	95%CI for HR	p
		2Log Likelihood	χ^2				
Model 1 in CKD stages 1-2 (n=158); log-rank test: χ^2=39.62* **							
age		131.44	10.31	0.12(0.04)	1.12	1.05;1.20	0.001
gender	male	124.85	6.59		Reference		
	female			-2.44(1.14)	0.09	0.09;0.82	0.033
severe cardiac failure	no	123.08	15.23		Reference		
	yes			0.60(0.57)	1.82	0.60;4.23	0.316
PTA	no	112.07	21.36		Reference		
	mild			1.82(0.88)	6.16	1.12;34.33	0.038
	severe			2.28(0.68)	9.79	2.57;37.26	0.001
Model 2 in CKD stages 3-5 (n=160); log-rank test: χ^2=32.09* **							
age		320.97	4.2	0.05(0.02)	1.06	1.02;1.09	0.003
gender	male	320.51	0.47		Reference		
	female			-0.52(0.36)	0.59	0.29;1.20	0.593
severe cardiac failure	no	319.71	0.80		Reference		
	yes			0.72(0.63)	1.92	0.82;5.56	0.835
PTA	no	298.35	21.36		Reference		
	mild			0.25(0.42)	1.29	0.56;2.98	0.554
	severe			2.38(0.49)	10.78	4.15;28.08	<0.001

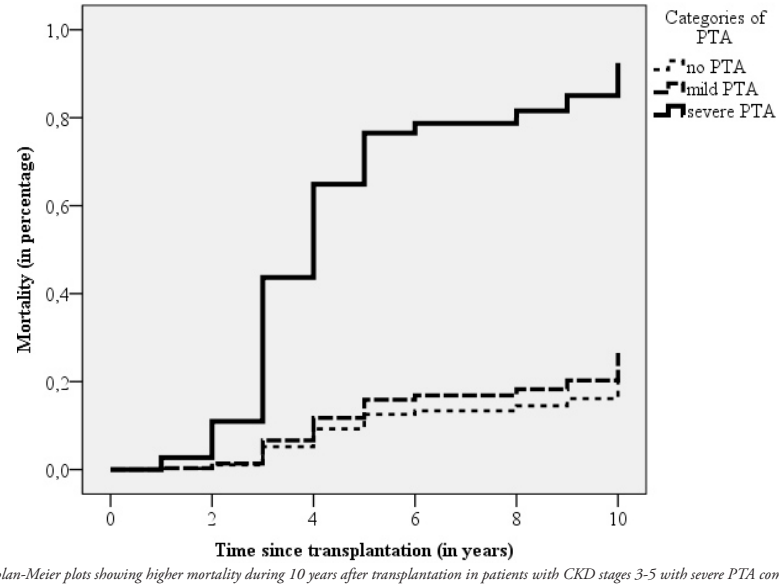
p–significant values; PTA–post-transplant anemia, CI–Confidence Interval, B(SE)–Unstandardized Coefficient B (Standard Error), HR–hazard ratio

Figure 6.2: Differences in mortality between severe PTA, mild PTA and no PTA over 10 years in CKD stages 1-2



Kaplan-Meier plots showing higher mortality during 10 years after transplantation in patients with CKD stages 1-2 with mild or severe anemia compared with patients without PTA

Figure 6.3: Differences in mortality between severe PTA, mild PTA and no PTA over 10 years in CKD stages 3-5



Kaplan-Meier plots showing higher mortality during 10 years after transplantation in patients with CKD stages 3-5 with severe PTA compared with patients without PTA

Discussion

We explored the independent effect of anemia on mortality in the early period after kidney transplantation. Mild and severe PTA in the first year after transplantation increased the higher risk of mortality independently of kidney function at up to 10 years follow-up. Mild PTA predicted a 6-fold higher risk of mortality and severe PTA a 10-fold higher risk of mortality compared with no PTA in CKD stages 1-2. However, patients with more advanced stages of CKD showed no association of mild PTA with mortality, probably as this only reflects their worse kidney function; however, severe PTA predicted a 10-fold higher risk of mortality. The other factor associated with increased risk of mortality was advanced age, and with decreased mortality female gender, which is in line with the others studies.[19,20]

NKF/KDOQI and KDIGO guidelines for diagnosis and treatment of renal anemia recommend a global assessment of the patient, which should consist of an inventory of complications of the dialyzed, perioperative and post-transplantation period, including inflammatory diseases, rejections, comorbidities, ACEi/ARB and immunosuppressant treatment.[2,3,6] In our study uroinfection (including pyelonephritis), rejection episodes, chronic renal allograft dysfunction, cardiovascular disease, already existing diabetes mellitus, new-onset diabetes mellitus after transplantation and the total number of other comorbidities were not associated with mortality in patients after KT.

In line with our results, Amaral et al. showed that patients with mild and severe anemia of renal origin independently of CKD had an increased risk for mortality.[21] A few other studies have also shown that a low level of Hb is strongly associated with mortality.[7,12,13] In our sample, 31.1% of respondents had various grades of anemia, fitting in the range from 20 to 57%, as was found earlier for Central Europe.[22]

The study of Lawler et al., with CKD in the pre-dialyzed period, showed that anemia in this group was underestimated, with an absence of relevant blood tests and a lack of treatment.[23] Iseki and Kohagura showed that renal anemia is a marker of kidney failure and is associated with a higher incidence of stroke, heart failure and a relevant lower quality of life and survival.[24] Regarding the above mentioned outcomes, Amaral et al. suggested that the hazard ratio of mortality is increased proportionally according to the severity of the anemia. They discovered that a serum hemoglobin concentration of 11.0 g/dl and higher showed a 60-70% reduction in the risk of mortality.[21]

The prevalence of renal anemia treatment after KT is, according to the NKF/KDOQI guidelines, relevant to CKD in the pre-dialyzed period.[5] Surprisingly, Molnar et al. found in ten renal transplant units across Europe that the prevalence and management practices related to renal anemia after transplantation were quite variable and overall have remained largely unchanged over the last 5 years.[11] In our sample, more than two-thirds of the patients were treated by a combination of two drugs. Similar to our results, Spiegel and Chertow (2009) showed the benefit of renal anemia treatment by ESA and iron therapy.[8]

The most recent studies regarding renal anemia therapy have shown that there is a narrow boundary between safe treatment and therapy causing increased morbidity and mortality risk.[25] Reports on the relative adequate serum concentration of hemoglobin and iron and other essential components have shown a higher risk of stroke, thrombosis and progression of cancer.[25,26] These conclusions bring up new questions about dosing algorithms aimed at achieving and maintaining optimal target hemoglobin levels without endangering the patient.

Strengths and limitations

The main strength of this study is the prospective follow-up for 10 years, which enabled us to explore anemia and others factors as predictors of mortality in kidney transplant recipients. Moreover, all consecutive patients originating from one major transplant center in Slovakia over a number of years were asked to participate in the study to prevent selection bias.

A limitation of the study might be the lack of certain other biomarkers (serum concentration of ESA, iron, ferritin, transferrin, vitamins, etc.) and additional information (inflammatory markers, catabolism) which decrease hemoglobin concentration. The variable observation period between minimum and maximum (1 and 10 years) is also a limitation. Testing for anemia in this study was not conducted immediately after transplantation to prevent false findings due to perioperative complications. Therefore, patients who died or lost their transplanted kidney within the first 3 months after KT were not included in the study.

Recommendations

Our findings imply that mild and severe anemia in CKD stages 1-2 may be an independent element of the pathway to survival in kidney transplant recipients. In line with our results, we suggest treating mild and severe anemia in patients after the third month following successful transplantation to increase their probability for survival. Further studies should also be carried out to shed more light on this important pathway. According to these results, a randomized controlled trial in ESA treatment of post-transplant anemia with a target Hb-value above 10.0 g/dl would be appropriate. We could then verify whether treatment of anemia after KT decreases mortality in kidney transplant recipients and thus fill a gap in the guidelines for ESA in post-transplant anemia regarding the Hb-value. Furthermore, the pathways between other medical determinants associated with anemia and mortality should be studied as well.

Conclusion

Post-transplant anemia in an early period after transplantation increased the risk of mortality independently of kidney function at up to 10 years follow-up in CKD stages 1-2. Mild PTA is associated with a 6-fold higher risk of mortality and severe PTA with a 10-fold higher risk of mortality compared with no PTA in CKD stages 1-2. Thus, patients with a well-functioning transplanted kidney but with post-transplant anemia might benefit from clinical evaluation as well as treatment (e.g. Erythropoiesis-Stimulating Agents, iron therapy, etc.) to reduce their higher risk of mortality. However, patients with more advanced stages of CKD showed no association of mild PTA with mortality, probably as this may only reflect their worse kidney function; however, severe PTA predicted a 10-fold higher risk of mortality.

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