Blood transfusions in kidney transplant candidates are common and associated with adverse outcomes

Ibrahim HN, Skeans MA, Li Q, Ishani A, Snyder JJ. Blood transfusions in kidney transplant candidates are common and associated with adverse outcomes.

Abstract: Surprisingly, there are no data regarding transfusion frequency, factors associated with transfusion administration in patients on the kidney transplant waiting list, or transfusion impact on graft and recipient outcomes. We used United States Renal Data System data to identify 43 025 patients added to the waiting list in 1999–2004 and followed through 2006 to assess the relative risk of post-listing transfusions. In 69 991 patients who underwent transplants during the same time period, we assessed the association between pre-transplant transfusions and level of panel-reactive antibody (PRA) at the time of transplant, and associations between PRA and patient outcomes. The three-yr cumulative incidence of transfusions was 26% for patients added to the waiting list in 1999, rising to 30% in 2004. Post-listing transfusions were associated with a 28% decreased likelihood of undergoing transplant, and a more than fourfold increased risk of death. There was a graded association between percent PRA at the time of transplant and adjusted risk of death-censored graft failure, death with function, and the combined event of graft failure and death. These data demonstrate that transfusions remain common and confirm the adverse association between transfusions and PRA, and high PRA and inferior graft and patient outcomes.

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The kidney transplant waiting list continues to grow, and candidates with high levels of panel-reactive antibody (PRA) experience an increasingly prolonged waiting time and incur increased risk of graft failure when they undergo transplant (1–6). This is of major relevance as 39.6% of currently listed transplant candidates have PRA >10%, 15.8% have PRA >20%, and 5.1% have PRA >80% (7). We recently demonstrated surprisingly high frequency of blood transfusion administration, a major cause of sensitization, in dialysis patients and also in non-dialysis-dependent chronic kidney disease (CKD) patients (8, 9). Interestingly, despite the common and firmly held belief that the relationship between blood transfusions, sensitization, and adverse outcomes is well established, we found no detailed accounts of how often transfusions are administered to waitlisted patients. Furthermore, there is no information regarding the impact of transfusions on kidney transplant outcomes in recent years.

Therefore, we determined the frequency of and factors associated with post-listing blood transfusions, and the effect of these transfusions on the likelihood of death or undergoing transplant while on the list and elevated PRA level at the time of transplant. We also assessed the association of elevated PRA level at the time of transplant with the adjusted risk of adverse patient and graft outcomes. We hypothesized that transfusions occur much more frequently in this population than is currently appreciated by the transplant community and that these transfusions are not inconsequential.
Materials and methods

We conducted a retrospective cohort study using the United States Renal Data System (USRDS) standard analytic files, which contain all Organ Procurement and Transplantation Network (OPTN) data related to kidney transplants, including the kidney transplant waiting list and OPTN form data, which include transplant candidate registration data (candidate demographic and clinical characteristics recorded at the time of wait listing), transplant recipient registration data for patients who undergo transplants, and recipient histocompatibility data (PRA information). The USRDS standard analytical files contain all Centers for Medicare & Medicaid Services (CMS) end-stage renal disease (ESRD) data, including data from the Medical Evidence Report (form CMS-2728), the Medicare enrollment database (coverage periods and patient demographics), the ESRD Death Notification (form CMS-2746), Medicare Part A institutional claims (inpatient, outpatient, skilled nursing facility, home health, and hospice), and Medicare Part B physician (inpatient and outpatient) and supplier claims (used to identify blood transfusions).

Study population

The study population consisted of 43,025 Medicare patients added to the kidney transplant waiting list in 1999–2004. Patients listed for combined organ transplants (kidney–pancreas, kidney–liver, kidney–lung, kidney–heart, or any other combination), patients with prior kidney transplants, and patients who were ESRD certified after listing were excluded. Assessment of trends in transfusion use was limited to patients with Medicare primary coverage because claims for transfusions are available for them but not for patients without Medicare coverage. To assess the trends in most recent and peak PRA at the time of transplant and the impact of PRA on graft and patient outcomes, we studied 69,991 transplant recipients who underwent transplants during the same time period, 1999–2004 with follow-up through 2006.

Blood transfusion use was assessed after listing for patients with Medicare primary coverage. Blood transfusions were identified in inpatient, outpatient, skilled nursing, and physician/supplier Medicare claims using Current Procedural Terminology and International Classification of Diseases, Ninth Edition, Clinical Modification procedure codes. For patients undergoing transplant, OPTN collects current and peak PRA data and supplies them to the USRDS. More than 90% of PRA values are complete for transplant patients.

Analysis

The cumulative incidence of post-listing transfusions through three yr after listing was assessed using the Kaplan–Meier method as 1 minus the Kaplan–Meier estimate and presented as a percentage. Adjusted hazard ratios for post-listing transfusions were estimated using a Cox proportional hazards model. The association between the first post-listing transfusion and the subsequent likelihood of transplant and risk of death was estimated using an adjusted time-dependent Cox proportional hazards model with the time to first transfusion entered as a time-dependent covariate. The adjusted odds ratios of having PRA ≥10%, 20%, and 80% at the time of transplant by prior transfusion status were estimated using logistic regression for patients who underwent transplants during 1999–2004. A Cox proportional hazards model was then used to compute the adjusted hazard ratios for death-censored graft failure, death with function, or the combined outcome by PRA at the time of transplant. Adjustments were made for sex, prior pregnancy, age, race, ethnicity, pre-transplant dialysis duration, dialysis modality, primary cause of ESRD, transplant year, body mass index (BMI), recipient and donor hepatitis C and cytomegalovirus status, number of HLA matches, primary insurance, and presence of congestive heart failure, ischemic heart disease, cerebrovascular accidents, peripheral vascular disease, cancer, and tobacco use. Adjustments were also made for the following donor factors: donor type, cold ischemia time, age, sex, BMI, race, and history of diabetes. Adjusted hazard ratios were calculated for a PRA of 1–19%, 20–79%, and ≥80%, all in comparison with a PRA of 0% at the time of transplant.

All analyses were conducted using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

In total, 43,025 US Medicare patients were added to the waiting list in 1999–2004 (Table 1). Men, whites, and patients with diabetic nephropathy accounted for most listings. Regarding comorbid conditions, 11% had atherosclerotic heart disease, 15% had congestive heart failure, and 3.6% had a history of cerebrovascular accidents. In 1999, 26% received one or more transfusions in the first three yr after listing; that proportion was 30% in 2004. Patients with a higher likelihood of
transfusions while on the list were older, women, and white, with diabetes as cause of ESRD, lower BMI, and longer dialysis duration before wait listing (Table 1). Interestingly, peritoneal dialysis patients were more likely to receive transfusions (31% vs. 28% for hemodialysis patients, p < 0.0001). As one may expect, candidates with comorbid conditions were more likely to receive transfusions.

The one-yr cumulative incidence of transfusions while on the waiting list for all patients added to the list between 1999 and 2004 was 10.8%; three-yr cumulative incidence was 27.7%. Cumulative incidence of transfusions was highest for patients aged >65 (Fig. 1). Erythropoiesis-stimulating agent (ESA) use was not entered into the primary model assessing predictors of transfusions, as 80% of waitlisted patients were receiving ESAs. When ESA use was entered into the model, however, it was associated with a twofold increase in the risk of receiving a transfusion (hazard ratio [HR] 2.06, 95% confidence interval [CI] 1.86–2.29). Including ESA use in the regression model predicting transfusions did not change the magnitude of the associations of other variables with transfusion risk (data not shown).

In a model adjusting for year of listing, age, sex, race, ethnicity, primary cause of ESRD, blood type, education, BMI, pre-listing dialysis duration, dialysis modality, and comorbid conditions, receiving a blood transfusion while on the list was associated with a more than fourfold increase in the risk of death (HR 4.04, 95% CI 3.78–4.31), and a 28% lower likelihood of undergoing transplant (Fig. 2).

Receiving any pre-transplant transfusion was associated with higher odds of PRA ≥10%, 20%, 30% at baseline.
and 80% at the time of transplant (Fig. 3). This risk was highest for multiparous women.

PRA at the time of transplant was associated with a step-wise graded association with death-censored graft failure, death with function, and the combined outcome (Fig. 4). Patients with PRA of 20–79% were 21% more likely (95% CI 1.12–1.32) to experience death-censored graft failure, 15% more likely (95% CI 1.05–1.26) to experience death with function, and 18% more likely (95% CI 1.11–1.26) to experience the combined outcome. For highly sensitized patients (PRA ≥80%), the adjusted hazard ratios for these events were 1.41 (95% CI 1.22–1.62), 1.19 (95% CI 1.00–1.41), and 1.30 (95% CI 1.17–1.45), respectively. We also provide the parallel hazard ratios for the subsets of patients with and without transfusion history.
(Table 2). We did not include transfusion history as a main effect in the models, as it is on the causal pathway for PRA elevation. In prior modeling, we found no significant interaction between transfusion history and PRA category for any of the outcomes.

Discussion

These results demonstrate that a significant proportion of waitlisted kidney transplant candidates receive blood transfusions after being listed. The transfusions were not inconsequential, as they were associated with sensitization, excess death, and a significantly lower likelihood of undergoing kidney transplant. These data also strengthen the link between higher PRA and poor graft outcomes, in a regression model that adjusted for many important donor and recipient factors.

A third of patients received transfusions in the first three yr after being listed; these data are very surprising in an era with effective strategies to treat anemia of CKD, heightened awareness against transfusions, and declining ability to administer transfusions in dialysis units. Prior studies have shown that introduction of epoetin has resulted in a significant decrease in blood transfusion incidence among listed candidates and that ESA use is associated with markedly reduced sensitization and waiting time (10).

Many of these transfusions are likely given owing to acute events such as gastrointestinal bleeding or surgery and could not be prevented by anemia treatment. Some transfusions may also reflect a general feeling in the medical community that patients with cardiovascular disease need higher hemoglobin levels, despite lack of evidence to support such practice (11). While the reason for transfusions was not included in the Medicare claims data, the recent observation by Lawler et al. (12), using data from the Veterans Administration Health Care System, supports the suggestion that CKD patients with anemia receive transfusions more often than other patients. In this analysis and even after excluding transfusions that occurred as a result of an acute bleeding event, diagnosis of pernicious or hemolytic anemia, or surgery within the month preceding the index hemoglobin value that triggered the transfusion, CKD patients, particularly those not receiving ESAs or iron, received transfusions at an alarming frequency of 22–58% depending on the hemoglobin level (12). As there is little doubt that patients with multiple comorbid conditions, who would have been excluded from undergoing transplants in the past, now undergo transplants, these high rates of transfusions may not be entirely surprising. The adjustments made in our model attempt to address this issue but likely cannot address it completely.

Some blood transfusions given to waitlisted patients may have been given intentionally to improve graft survival, as has been previously described (13–16). However, the practice of giving transfusions to potential kidney transplant patients, from their directed donors or from random donors, has fallen out of favor more recently, as the introduction of modern immunosuppressants, particularly calcineurin inhibitors, has dramatically reduced the incidence of acute rejection, and showing benefit of such a practice became difficult. In fact, a recent analysis of the relationship between pre-transplant blood transfusions and transplant outcomes did not demonstrate any benefit (16). Therefore, this possibility is unlikely to have contributed to the surprisingly high prevalence of transfusions that we observed.

It is worth mentioning that pre-listing transfusions are also common. In fact, over 40% of kidney transplant candidates received transfusions before being waitlisted before 2001. While they were not the main focus of the current analysis, we studied pre-listing transfusions in the cohort of patients added to the waiting list in 1995–2001, the timeframe in which the question regarding “any previous transfusions” was included on the OPTN Transplant Candidate Registration form, and answers were collected and routinely reported for new transplant candidates. We found that 41% of patients reported pre-listing transfusions in 2001. Within one yr of wait listing, 30.5% of patients who received pre-listing transfusions received kidney transplants, compared with 32.2% of patients who did not receive pre-listing transfusions (p < 0.001). Pre-listing transfusions were associated with a higher likelihood of receiving transfusions while on the list and a higher risk of death and lower likelihood of undergoing transplant (data not shown).

This analysis has limitations. The demonstrated effect of high PRA on graft outcomes may be related to development of donor-specific antibodies, which are clearly linked to antibody-mediated rejection (6, 17–19). Our data source does not allow us to distinguish between high-PRA recipients with and without donor-specific antibodies. Moreover, we did not address results of crossmatch at the time of transplant. Most recently, flow cytometry-based PRA assays have almost become the standard; whether the association observed with cytotoxic PRA and outcomes is similar is yet to be seen, but trends are likely to be the same. Identifying blood transfusions using
Medicare claims required that we limit the population studied to the Medicare-primary-payer population, which makes up only 50% of incident wait listings in any given year.

Medicare-based data also lack important laboratory values, such as hemoglobin levels at which transfusions took place. This is an analysis of primary kidney transplant patients only, who currently account for 83% of all transplant patients. Patients listed for combined kidney–pancreas transplants were excluded, possibly reducing the number of diabetic patients studied; diabetic patients have a high comorbidity burden and not uncommonly receive transfusions.

The adverse impact of post-listing transfusions on patient and graft outcomes may be at odds with the recent analysis by Scornik et al. (20). These investigators found that 45% of their 746 kidney transplant patients received transfusions mainly in the first month after transplant. Interestingly, the incidence of post-transplant antibodies was similar for patients who received transfusions and for those who did not, and only one-twelfth of patients who received ≥10 units became sensitized. The incidence of rejection and allograft loss were numerically but not statistically higher for patients who received transfusions. Conceivably, receiving transfusions while heavily immunosuppressed may not be as deleterious. One must seriously consider that these surprisingly high rates of transfusions may become more common, as ESA use is not without risks and may harm some patients.

While the transplant community proactively avoids transfusions in potential transplant candidates, transfusions are clearly common, and this issue needs further study. An additional challenge involves choosing whether to treat anemic CKD patients, particularly those with type 2 diabetes mellitus, with transfusion or ESA, as ESA use may increase risk of stroke in this population. This issue is very relevant because type 2 diabetes is a major reason patients are referred for transplants (21).

In summary, these data reveal a surprisingly high frequency of blood transfusions among ESRD patients on the kidney transplant waiting list. These transfusions appear to be associated with higher risk of death, lower likelihood of undergoing transplant, and sensitization with its attendant inferior long-term graft survival. More studies are needed to understand the reasons for these transfusions, and efforts directed at minimizing their frequency should be carefully balanced against the potential adverse consequences of ESA use, particularly in CKD patients with type 2 diabetes.

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Author contributions

Hassan N. Ibrahim, research design, data analysis, preparation of manuscript; Melissa A. Skeans, data analysis, preparation of manuscript; Qi Li, data analysis, preparation of manuscript; Areef Ishani; research design, data analysis, preparation of manuscript; Jon J. Snyder, research design, data analysis, preparation of manuscript.

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