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ORIGINAL ARTICLE

Prevalence and determinants of anemia in the immediate postkidney transplant period

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Summary

At the time of renal transplantation, erythropoiesis-stimulating agents and iron supplementation are routinely discontinued in the prospect of recovery of renal function. This recovery, however, is often delayed and suboptimal. In addition, blood loss because of frequent diagnostic phlebotomies may be substantial. Renal transplant recipients may thus be considered at high risk of anemia in the immediate post-transplant period. We performed a single-center observational study, including 391 recipients of a single kidney. Hemoglobin levels and parameters of iron metabolism were monitored during the immediate post-transplant period, i.e., the first 3 months after transplantation. Hemoglobin levels decreased by 3.8 ± 1.5 g/dl to reach a nadir of 9.1 ± 1.2 g/dl at day 7. Transient severe anemia was observed in 91.3% of the patients. Donor age, gender, renal diagnosis of polycystic disease, pretransplant hemoglobin and ferritin level, estimated glomerular filtration rate at month 3, and duration of initial hospitalization were observed to be independently associated with the hemoglobin level at month 3. Transient severe anemia is an almost universal observation in incident renal transplant recipients. Poor graft function, high donor age, and low iron stores are independently associated with low hemoglobin levels at month 3.

Introduction

Anemia in the setting of chronic kidney disease (CKD) is a well-recognized phenomenon that is associated with decreasing renal function and deficiency of or resistance to erythropoietin. Renal transplantation is considered the treatment modality of choice in patients with CKD. A transplanted kidney is supposed to take over not only the blood purifying and homeostatic functions of the native kidneys, but also the endocrine functions of which the production of erythropoietin and active vitamin D are the most important ones. As only one kidney is transplanted, these functions are only partially corrected, resulting not only in an impaired glomerular filtration rate but also in an incomplete correction of anemia. Prevalences of post-transplant anemia (PTA) reported in literature range between 20% and 70%. This large variability is at least partly explained by differences in diagnostic criteria and interval since transplantation [1–12]. Current research is mainly focused on anemia, persisting 3 months after transplantion, with a distinction made between early (between 3 and 6 months) and late (more than 6 months) PTA. In contrast, less is known about the prevalence and pathophysiology of anemia within the first 3 months after renal transplantation (further referred to as immediate PTA).

At the time of engraftment, erythropoiesis-stimulating agents (ESA) and iron supplementation are routinely discontinued in the prospect of a restoring renal function. However, correction of kidney function may not only be partial but also delayed and blood loss related to diagnostic phlebotomies may be substantial. Consequently, renal transplant recipients should be considered at high risk of anemia in the immediate post-transplant period.

The purpose of the present study was to elucidate the natural history of hemoglobin (Hb) levels and iron stores in incident renal transplant recipients discontinuing ESAs and iron therapy at the time of engraftment and to evaluate the prevalence, severity, and determinants of anemia 3 months after successful renal transplantation.

Material and methods

Study population

We performed a single-center observational study, including 391 recipients of a single kidney, transplanted between March 2003 and January 2009 at the University Hospitals Leuven. Only patients who consented to participate in our protocol biopsy program and those with a graft survival exceeding 3 months were eligible for inclusion. The study adhered to the principles of the Declaration of Helsinki and was approved by the ethical committee of the Catholic University of Leuven. All patients provided informed consent.

Measurements

All relevant clinical and biochemical data of both donors and recipients were collected prospectively in an automated database. Patients were monitored for 3 months after transplantation. Recipient demographics included age at transplantation, gender, primary kidney disease, dialysis vintage, and number of previous transplants.

Immediately pretransplant, blood was sampled for hematology, biochemistry, and virologic and immunologic screening (estimated blood volume: 200 ml). During hospitalization, hematology and biochemistry were monitored almost daily (estimated blood volume: 13 ml). After discharge, routine outpatient follow-up consisted of thrice, twice, and once weekly visits during the first, second, and third postoperative month, respectively, with hematology and biochemistry checked at every visit. All blood samples were analyzed using standard laboratory techniques. The total amount of blood collected during follow-up was estimated by multiplying the number of phlebotomies by 13 ml, i.e., the estimated mean blood volume collected.

Immunosuppressive agents, blockers of the Renin–Angiotensin–Aldosterone System (RAAS) and antimicrobials were recorded at month 3. Anemia management therapies (i.e., ESA, iron supplementation, and transfusion of leukocyte-depleted packed red cells) during the study period were also recorded.

The estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease equation [13].

In each individual, the Hb nadir (i.e., lowest registered value within time of follow-up) was identified. For descriptive purposes, data were grouped and averaged per week, relative to the time of transplantation.

As in the TRESAM study [1], anemia was defined following the Clinical Practice Guidelines for Outpatient Surveillance of Renal Transplant Recipients, i.e., Hb levels of ≤13 g/dl for males and ≤12 g/dl for females [14]. Anemic patients were further subdivided into four subcategories based on the severity of the anemia:

1 Mild: males: Hb > 12 g/dl and Hb ≤ 13 g/dl, females: Hb > 11 g/dl and Hb ≤ 12 g/dl.
2 Moderate: males: Hb > 11 g/dl and Hb ≤ 12 g/dl, females: Hb > 10 g/dl and Hb ≤ 11 g/dl.
3 Severe: males: Hb > 8 g/dl and Hb ≤ 11 g/dl, females: Hb > 8 g/dl and Hb ≤ 10 g/dl.
4 Very severe: Hb ≤ 8 g/dl or need for transfusion.

Statistical methods

All continuous parameters are expressed as mean ± SD. Differences between periods were analyzed using the Chi-square and paired *t*-test, as appropriately. Simple and multiple linear regression analyses were used to examine associations. Regression analysis was performed to identify determinants of the Hb level at month 3 in a subgroup of patients free of blood transfusion and anemia related therapy ($n = 281$). The SAS version 9.1 (SAS Institute, Cary, NC, USA) software program was used for the statistical analysis. A probability value of alpha 0.05 or less was considered statistically significant.

Results

Study population

Relevant patient and donor characteristics of the study population are summarized in Table 1. Autosomal dominant polycystic kidney disease (ADPKD) was the primary renal disease in 72 patients (18.4%). Twenty-seven of these seventy-two patients (37.5%) underwent a nephrectomy prior to transplantation. The initial hospitalization duration was 17.2 ± 7.4 days. Readmission was required in 14.6% of the patients, resulting in a mean cumulative hospitalization duration of 20.1 ± 10.0 days. Diagnostic phlebotomies were performed on 40.0 ± 8.2 occasions (in hospital and outpatient clinic). The total amount of blood sampled within the first 3 months post-transplantation was estimated at 516 ± 105 ml.

Maintenance immunosuppression included steroids (98.5%), an antimetabolite (mycophenolate mofetil, 81.8%), a calcineurin inhibitor (tacrolimus, 85.2% or cyclosporin, 13.0%) and/or a mTOR-inhibitor (1.8%). Seventy-nine patients (20.3%) experienced at least one

Table 1. Baseline recipient characteristics at time of transplantation.

Recipient age (years)	52.2 ± 13.6
Recipient gender (male), *n* (%)	231 (59.1)
Transplant number: first/second/third, *n* (%)	346 (88.5)/41 (10.5)/4.0 (1)
Dialysis vintage (days)	1050.1 ± 688.3
Type of latest dialysis: HD/PD/pre-emptive, *n* (%)	302 (77.2)/84 (21.5)/5 (1.3)
Renal diagnosis, *n* (%)	
Glomerulonephritis/vasculitis	111 (28.4)
Hereditary kidney disease	98 (25.1)
Tubulointerstitial disease	41 (10.5)
Diabetic nephropathy	25 (6.4)
Hypertensive/vascular disease	13 (3.3)
Miscellaneous	19 (4.9)
Unknown	84 (21.5)
Blood pressure (mmHg)	
Systolic	139.8 ± 21.3
Diastolic	80.2 ± 12.4
Body weight (kg)	72.2 ± 14.4
Donor type: cadaver/living, *n* (%)	365 (93.4)/26 (6.6)
Donor age (years)	45.2 ± 14.7
Donor gender (male), *n* (%)	225 (57.5)

episode of acute rejection. One hundred and nine patients (27.9%) were treated with RAAS-blockade. Eighty-two percent of patients received *Pneumocystis jirovecii* pneumonia prophylaxis with trimethoprim–sulfamethoxazole. Delayed graft function, defined by the need for dialysis within the first postoperative week, occurred in 12% of the patients. Three months after engraftment, the mean serum creatinine was 1.5 ± 0.5 mg/dl, corresponding to an eGFR of 50.3 ± 16.6 ml/min/1.73 m^2 (Fig. 1).

Hemoglobin level and iron stores in the immediate post-transplant period

Table 2 summarizes relevant hematology and biochemistry data. The mean pretransplant Hb level was 12.8 ± 1.5 g/dl. Remarkably, 269 patients (68.8%) had a Hb level >12 g/dl at the time of transplantation. In 173 of these patients, Hb levels exceeded 13 g/dl. A Hb level below 11 g/dl was observed in only 38 patients (9.7%). After transplantation, Hb levels (Fig. 1) showed a biphasic time course with an early fall followed by a steady increase. The Hb nadir (9.1 ± 1.2 g/dl) was reached at day 7 (3–15). Hb levels decreased on average by 3.8 ± 1.5 g/dl. Transient anemia was almost universal within the immediate post-transplant period, occurring in >98% of recipients (Table 3).

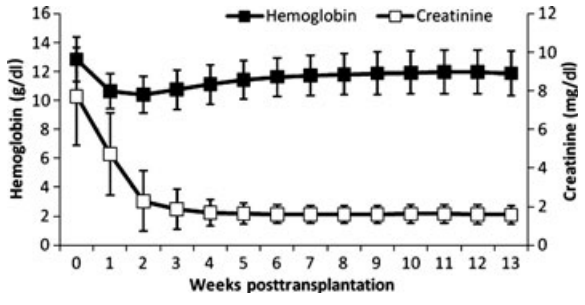

Figure 1 Natural history of hemoglobin and serum creatinine levels in the immediate post-transplant period.

According to K/DOQI guidelines, iron stores were appropriate in the majority of patients at the time of transplantation (57.3%). Follow-up data on iron status were available in an unselected cohort of 191 patients (48.9%). In patients free of anemia-related therapy, as opposed to the overall cohort, serum ferritin levels modestly but significantly decreased after transplantation ($P < 0.0001$).

Anemia management therapy in the immediate post-transplant period

One hundred and ten renal transplant recipients (28.1%) had at least one kind of anemia management therapy in the immediate post-transplant period. The prevalence of anemia at month 3 amounted to 79.9% when defining anemia by WHO thresholds and/or the need for anemia management therapy. Within the first 3 months after transplantation, 2.6 ± 1.8 (range 1–12) units of red blood cells were administered in 84 patients (21.5%). One hundred and ninety-one of these 215 units (89%) were administered during the initial hospitalization. The first unit was administered on day 8 (4–17). The level of Hb triggering transfusion was 8.0 ± 0.8 g/dl. The transfusion prevalence was significantly higher in patients experiencing an acute rejection (40.5% vs. 16.7%, $P < 0.0001$). At month 3 post-transplantation, 44 recipients (15.1%) were substituted with iron and 21 patients (5.4%) were on ESA therapy (darbepoetin alpha, 54 ± 39 mc/2 weeks). ESA therapy was started on day 60 (23–77). The level of Hb triggering ESA therapy was 9.0 ± 1.0 g/dl.

Determinants of anemia in the immediate post-transplant period

Regression analysis was performed to identify determinants of the Hb level at month 3 in patients free of anemia management therapy ($n = 281$; Table 4). In multivariate analysis, male gender, initial duration of hospitalization, donor age, a renal diagnosis of ADPKD, pretransplant Hb and ferritin level, and eGFR at month 3 were observed to be independently associated with the Hb level at month 3. These variables explain 27% of the variation of the Hb level at month 3 ($P < 0.0001$).

Table 2. Complete blood count, hematinics, and kidney function at time of transplantation and at month 3.

Parameter	At time of transplantation (mean ± SD)	At month 3 (mean ± SD)	*P*-value
Hemoglobin (g/dl)	12.8 ± 1.5	11.8 ± 1.5	<0.0001
Hematocrit (%)	39.4 ± 4.7	36.4 ± 4.7	<0.0001
Mean corpuscular volume (fl)	96.8 ± 6.3	94.7 ± 5.2	<0.0001
Mean corpuscular hemoglobin (pg)	31.6 ± 2.1	30.6 ± 1.9	<0.0001
Reticulocytes (%)	1.3 ± 0.6 (*n* = 141)	1.5 ± 0.6 (*n* = 339)	0.006
White blood cells (10^9/l)	7.0 ± 2.3	6.3 ± 2.5	<0.0001
Platelets (10^9/l)	216.7 ± 63	225.4 ± 70.6	0.03
Iron (μg/dl)	69.1 ± 33.8	74.8 ± 30.4 (*n* = 194)	0.0005
Ferritin (ng/ml)	348.5 ± 251.5	354.1 ± 409.0 (*n* = 191)	0.0005
Transferrin saturation (%)	24.4 ± 11.8	25.0 ± 10.9 (*n* = 194)	0.1
Vitamin B12 (ng/l)	806.8 ± 480.0	–	–
Folate (μg/l)	11.4 ± 6.1	–	–
C-reactive protein (mg/l)	6.7 ± 11.0	4.2 ± 8.7	<0.0001
Creatinine (mg/dl)	7.7 ± 2.5	1.54 ± 0.48	<0.0001
eGFR (ml/min/1.73 m^2)	8.3 ± 4.7	50.3 ± 16.6	<0.0001

Table 3. Prevalence of transient PTA and PTA at month 3.

	Male (*n* = 231)		Female (*n* = 160)	
Anemia*	At 3 months	Transient	At 3 months	Transient
Mild	68 (29.4)	5 (2.2)	46 (28.8)	2 (1.3)
Moderate	58 (25.1)	18 (7.8)	44 (27.5)	7 (4.4)
Severe	55 (23.8)	156 (67.5)	24 (15.0)	94 (58.8)
Very severe	1 (0.4)	52 (22.5)	1 (0.6)	55 (34.4)
Total	182 (78.8)	231 (100)	115 (71.9)	158 (98.8)

Values in parentheses are in percentages. *For definition see text.

Patients with a diagnosis of ADPKD were characterized by a higher Hb level at month 3, despite a higher mean donor age ($P < 0.01$), a less favorable iron status ($P \leq 0.05$), and a comparable pretransplant Hb level. In addition, patients with ADPKD who underwent a nephrectomy prior to transplantation were characterized by significantly lower Hb values at month 3 (11.8 ± 1.4 g/dl vs. 12.8 ± 1.3 g/dl, $P < 0.01$). Pretransplant serum ferritin levels were significantly lower in anemic versus nonanemic recipients at month 3 (319.5 ± 251.7 ng/ml vs. 401.6 ± 222.0 ng/ml, $P = 0.01$).

Discussion

The key findings of the present study are as follows: (i) PTA is a common finding in the immediate post-transplant period, being very severe – defined by Hb ≤ 8 g/dl or need for transfusion – in almost 30% of patients; (ii) diagnostic phlebotomies may represent an important but yet neglected cause of immediate PTA; and (iii) poor graft function, high donor age, and low iron stores are independently associated with low Hb levels at month 3.

The Hb levels showed a biphasic time course after transplantation with an initial sharp decrease followed by a gradual increase toward subnormal levels. Transient severe and very severe anemia were observed in 63.9% and 27.4% of the patients in the immediate postoperative period. It should be emphasized that in the absence of data linking Hb levels to hard outcomes, any threshold level used to define and to categorize anemia in renal transplant recipients should be considered arbitrary.

Duration of hospitalization, gender, and pretransplant Hb level were independently associated with the nadir Hb level, whereas renal transplant function and C-reactive protein at discharge, donor age, and renal diagnosis of ADPKD were not (data not shown). These observations suggest that besides hemodilution, blood loss related to the surgery and frequent phlebotomies are more important in the pathogenesis of the initial Hb drop than low erythropoietin production and/or erythropoietin resistance. Perioperative blood loss related to the surgery is difficult to quantitate, but generally estimated at a volume of 100–200 ml. In addition, blood collected during routine diagnostic phlebotomies may cumulate to approximately 180 ml during an uncomplicated routine 14 day-hospitalization for renal transplantation. Over a 3-month period, phlebotomy blood loss averaged 520 ml. This figure very well corresponds to what has been previously documented in a smaller cohort of renal transplant recipients [15].

At month 3, 76.0% of the patients were still anemic, with a substantial proportion experiencing severe anemia.

Table 4. Univariate regression analysis using hemoglobin level at month 3 as the dependent variable.

Independent variables	β-coefficient	*P*	R^2
Univariate analysis			
Gender	−0.73	<0.0001	0.06
Donor age	−0.022	0.0002	0.05
ADPKD	0.59	0.007	0.03
Initial duration of hospitalization	−0.02	0.01	0.02
Number of rejection episodes	−0.34	0.16	0.007
Pretransplant Hb	0.26	<0.0001	0.06
Pretransplant ferritin	0.0007	0.06	0.01
eGFR at month 3	0.02	0.0006	0.04
Multivariate analysis		<0.0001	0.27
Gender	−0.65	<0.0001	
Donor age	−0.02	0.0003	
ADPKD	0.76	0.0001	
Initial duration of hospitalization	−0.02	0.01	
Pretransplant Hb	0.27	<0.0001	
Pretransplant ferritin	0.001	0.002	
eGFR at month 3	0.02	0.0002	

Parameters included in the model: gender (male 0; female 1), recipient age, body mass index, donor age, dialysis vintage, ADPKD (no 0; yes 1), pretransplant diagnosis of diabetes mellitus, initial duration of hospitalization, episodes of rejection, pretransplant Hb/iron/ferritin/transferrin saturation/folate/vitamine B12/C-reactive protein/PTH, eGFR/ iron/ferritin/transferrin saturation/C-reactive protein at month 3, use of RAAS blockade, mycophenolate mofetil, PCP profylaxis, and delayed graft function. Only parameters univariately associated at $P \leq 0.20$ are mentioned in the table.

Although direct comparison is difficult because of the use of different definition, the prevalence of PTA observed in the present cohort seemed to be higher than that reported previously in similar cohorts [7,9]. Case-mix and differences in anemia treatment policy may account for these differences.

In a subgroup of patients free of blood transfusion and anemia-related therapy, pretransplant Hb and ferritin level, eGFR at month 3, donor age, renal diagnosis of polycystic disease, gender, and duration of initial hospitalization were observed to be independently associated with Hb level at month 3. These results confirm and extend data from reported surveys [1,2,5,7,9,11]

The observation of an independent association between pretransplant ferritin level and Hb level at month 3 underscores the role of iron deficiency in the pathogenesis of PTA [1,9,11]. Serum ferritin levels modestly but significantly declined after renal transplantation. Blood loss related to the surgery itself, use of iron in the manufacture of Hb, (occult) gastrointestinal bleeding, and the frequent phlebotomies may all contribute to iron deficiency in the immediate post-transplant period.

In agreement with previous studies [1–6,8–10], a good renal transplant function and young donor age were associated with high Hb levels. It is well-known that restoration of erythropoietin production and response largely depends on recovery of graft function [16]. The observation of a direct association between donor age and Hb levels, independent of graft function, clearly suggests an age-related influence on the erythropoietin production capacity of the kidney. Although frequently hypothesized in the past, it has been shown only recently that anemia of unknown origin in the elderly might be caused by lower than normal erythropoietin levels [17].

We also observed higher Hb levels in patients with ADPKD. Not surprisingly, this benefit was lost in ADPKD patients who underwent a nephrectomy prior to transplantation. These data are consistent with the observation of high erythropoietin production by polycystic kidneys, probably as a result of enhanced regional hypoxia [18,19].

Unlike others [8,10,20–22], we failed to find an association between immunosuppressives and antimicrobial drugs and Hb levels at month 3. This was not unexpected as our population was treated with a homogeneous immunosuppressive and antimicrobial regimen. We also failed to demonstrate an association between recipient age and PTA. Literature data on this issue are not unequivocal, with some surveys demonstrating an association [2,4,6] and others not [1,7,8]. Finally, we did not find an association between anemia and RAAS blockade. Although there is consensus of its use in the treatment of post-transplant polycythemia [23], there is more debate about its role in the development of PTA [1,8,24].

Twenty-eight percent of the recipients had at least one kind of anemia management therapy in the first 3 months after engraftment. The proportion of renal transplant recipients receiving red blood cell transfusions was 21.5%, which is lower than that reported by Scornik *et al.* [25]. This discrepancy may be explained by the rather low Hb level triggering transfusion in our center. Most transfusions were administered during the initial hospitalization. As severe PTA may trigger cardiovascular events and may hamper recovery of the graft function, a more liberal transfusion policy may be hypothesized to translate in better outcomes. However, the benefits of such a policy need to be balanced against the potential hazards [26] and the increased pressure on blood supply. With regard to the topic of transfusion-related immunomodulation, recent evidence indicates that, in contrast to transfusions given before the transplant, post-transplant transfusions are unlikely to induce HLA antibodies [25]. In lung transplant recipients, in addition, red blood cell transfusions appear to have an immunosuppressive effect, particularly early after engraftment [27]. Thus, at least from an immunological perspective, there is no objection against a more liberal transfusion policy.

Only 14.8% of the patients with severe anemia received ESA at month 3 post-transplantation. The observation of paucity of ESA use, disparate to the prevalence of anemia is not new and has clearly been demonstrated before [1,2]. Recent data, however, indicate that the prevalence of ESA use shows an increasing trend over the last 15 years [28]. Data on the impact of correction of PTA are limited or unavailable at all. The appropriate targets are equally uncertain. Three recent large randomized trials warrant against normalization of Hb levels in CKD patients not yet on dialysis [29–31]. Whether this also applies to renal transplant recipients, remains to be investigated. According to data from a recent large retrospective cohort study, increasing Hb levels to above 12.5 g/dl with ESA is associated with increased mortality in renal transplant recipients [28]. In line with this, we previously showed increased cardiovascular death with both low and high hematocrit values, with a hematocrit value of 38% (roughly corresponding to a Hb of 12.5 g/dl) as being the most ideal one [32]. Low hematocrit also results in decreased oxygen supply to the kidney. In a rat model, the microvascular partial pressure of oxygen declined by almost 50% when the hematocrit decreased from 45% to 25% (roughly corresponding to a Hb of 8 g/dl) through normovolemic dilution [33]. The kidney responds to declining ambient oxygenation by the activation of genes providing adaptation and endurance, as well as by the induction of pathways with a potential destructive nature. Through the latter responses, a vicious circle develops with an enhanced fibrosis and microvasculature depletion, and subsequent hypoxia and progressive kidney disease [34]. Despite encouraging animal data [35,36], recent randomized studies failed to demonstrate a clinically relevant advantage to immediate post-transplant administration of ESA [37(1953 /id),38(2196 /id)]. There is an urgent need of additional adequately designed and powered studies to investigate the impact of treatment of PTA with ESA (or other agents) on hard outcomes, such as patient and graft survival.

There are a few limitations to our study. First, the homogeneity of our study population with regard to race, immunosuppressive, and antimicrobial therapy (all been shown to be important determinants of PTA) can be regarded both as a strength and limitation of this study. Caution is clearly warranted when extrapolating our data to other cohorts. Second, because of the lack of widely accepted guidelines for administering ESA and blood transfusions in renal transplant recipients, these therapeutic measures are taken on an individual-based approach creating inevitable treatment bias. Third, it should be of note that pretransplant Hb levels were remarkably high in the present cohort. These high levels may be explained, at least partly, by case-mix and study era. Caution is warranted when extrapolating prevalence data to other cohorts. However, as pretransplant Hb level is independently and directly associated with post-transplant Hb level, one may predict that the prevalence of PTA will even be higher in cohorts characterized by a lower pretransplant Hb level. Finally, we did not have information on the pretransplant anemia treatment policy of patients enrolled in the present study as most were referred from other centers. Characteristics of the pretransplant ESA and iron therapy (type, interval, route of administration) may be hypothesized to affect the natural history of Hb levels post-transplantation.

In conclusion, transient severe anemia in the immediate postoperative period is observed in the large majority of renal transplant recipients. Pretransplant Hb and serum ferritin levels are directly associated with Hb levels at month 3, independent of graft function. Diagnostic phlebotomies may represent an important but yet neglected cause of immediate PTA. More observational and interventional studies are needed to better clarify the importance of immediate PTA and its correction on long-term outcomes.

Authorship

PE and RP: performed the main role, designing the study, collecting and analyzing the data, and writing the paper. BB, CK, DK, DM, and YVR: contributed to collecting the data.

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