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# The Risk of Postkidney Transplant Outcomes by Induction Choice Differs by Recipient Age

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**Background.** Among adult kidney transplant (KT) recipients, the risk of post-KT adverse outcomes differs by type of induction immunosuppression. Immune response to induction differs as recipients age; yet, choice of induction is barely tailored by age likely due to a lack of evidence of the risks and benefits. **Methods.** Using Scientific Registry of Transplant Recipients data, we identified 39 336 first-time KT recipients (2010–2016). We estimated the length of stay (LOS), acute rejection (AR), graft failure, and death by induction type using logistic and Cox regression weighted by propensity score to adjust for confounders. We tested whether these estimates differed by age (65+ versus 18–64 y) using a Wald test. **Results.** Overall, rabbit antithymocyte globulin (rATG) was associated with a decreased risk of AR (odds ratio = 0.79, 95% confidence interval [CI], 0.72–0.85) compared with basiliximab. The effect of induction on LOS and death (interaction  $P = 0.03$  and 0.003) differed by recipient age. Discharge was on average 11% shorter in rATG among younger recipients (relative time = 0.89; 95% confidence interval [CI], 0.81–0.99) but not among older recipients (relative time = 1.01; 95% CI, 0.95–1.08). rATG was not associated with mortality among older (hazard ratio = 1.05; 95% CI, 0.96–1.15), but among younger recipients (hazard ratio = 0.87; 95% CI, 0.80–0.95), it was associated with reduced mortality risk. **Conclusions.** rATG should be considered to prevent AR, especially among recipients with high-immunologic risk regardless of age; however, choice of induction should be tailored to reduce LOS and risk of mortality, particularly among younger recipients.

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## INTRODUCTION

Since the 1990s, there has been a shift in the age distribution of kidney transplantation (KT) recipients in the United States.<sup>1</sup> KT is a growing treatment option for older patients with end-stage kidney disease (ESKD).<sup>2</sup> The number of older KT recipients (aged  $\geq 65$ ) increased gradually since 1999, representing 18.4% of all KT recipients in 2011,<sup>3</sup> and continued to increase to 20.8% in 2018.<sup>4</sup> As

the new kidney allocation system prioritizes lower Kidney Donor Risk Index (KDPI) kidneys for the candidates with better expected graft and patient survival, higher KDPI kidneys are likely to be allocated to older patients, raising risk of acute rejection (AR) and worse graft outcomes in older population.<sup>5,6</sup>

Despite the need for strategies to prevent AR and sustain allograft function across the age spectrum, few studies

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on the efficacy of induction immunosuppressive agents have been conducted, leading clinicians to guide therapy based on research averaged in general population of adult KT recipients.<sup>7</sup> There are age-related changes to the immune system, which impact the risk of rejection and immunosuppression intolerance.<sup>8-10</sup> Evidence is emerging that older recipients are more likely to be frail,<sup>11,12</sup> which also leads to immunosuppression intolerance and subsequent adverse outcomes like longer length of stay (LOS) and mortality.<sup>13-16</sup> Yet, given the age-dependent differences, it is unclear whether induction therapy should be tailored by recipient age to prevent adverse outcomes including a longer LOS after KT, mortality, and graft loss.

Therefore, we sought to test whether the effect of type of induction immunosuppressive on post-KT outcomes differed by recipient age. Specifically, using real-world data that reflected the broad age distribution of KT recipients, we compared post-KT outcomes between recipients who received rabbit antithymocyte globulin (rATG) and those who received basiliximab, the most commonly used (~80%) induction agents in the United States.<sup>4</sup> Then, we examined whether the effect of these induction agents on post-KT adverse outcomes differed broadly by recipient age as well as specifically between older ( $\geq 65$  y) and younger (18–64) recipients.

## MATERIALS AND METHODS

### Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. This study was reviewed by the Johns Hopkins School of Medicine Institutional Review Board and was determined to be exempt.

This study was reviewed by the institutional review board at Johns Hopkins School of Medicine and was determined to qualify for an exemption under 45 CFR 46.101(b), as study participants cannot be identified directly or through linked identifiers. All clinical and research activities being reported are consistent with the Declaration of Helsinki and the Declaration of Istanbul.

### Study Design and Population

We studied first-time KT recipients (aged  $\geq 18$ ) from deceased donors between January 1, 2010, and December 31, 2016, by using the SRTR data. Those with no available immunosuppression data ( $n = 1148$ ; 1.7%) were excluded.

The population was restricted to recipients who were treated with either rATG or basiliximab. Basiliximab is the only available option that has been used as interleukin-2 receptor antagonist (IL-2-RA) since Roche discontinued Zenapax (daclizumab) in 2009 in the United States (Figure 1). We only included KT recipients who started triple maintenance immunosuppression therapy with tacrolimus, mycophenolate mofetil, and steroids at the time of transplant. This analytic study population included 39 336 first-time KT recipients.

### Effect of Type of Induction Agent on Post-KT Outcomes

To evaluate LOS by induction agent (rATG versus basiliximab), we treated time-to-discharge as a time-to-event analysis, as has been previously done among KT recipients.<sup>17</sup> We assumed that time-to-discharge followed an exponential distribution. We estimated the relative time-to-discharge using the accelerated failure time model as well as the relative hazard of discharge using the proportional hazard model to describe the effect of type of induction on LOS as 2 equivalent ways. For example, a relative time 0.5 indicates that LOS is 50% shorter for recipients with rATG compared with those with basiliximab and would be equivalent to a relative hazard  $> 1$ . For consistency, we are going to henceforth interpret them as hazard ratios in this article.

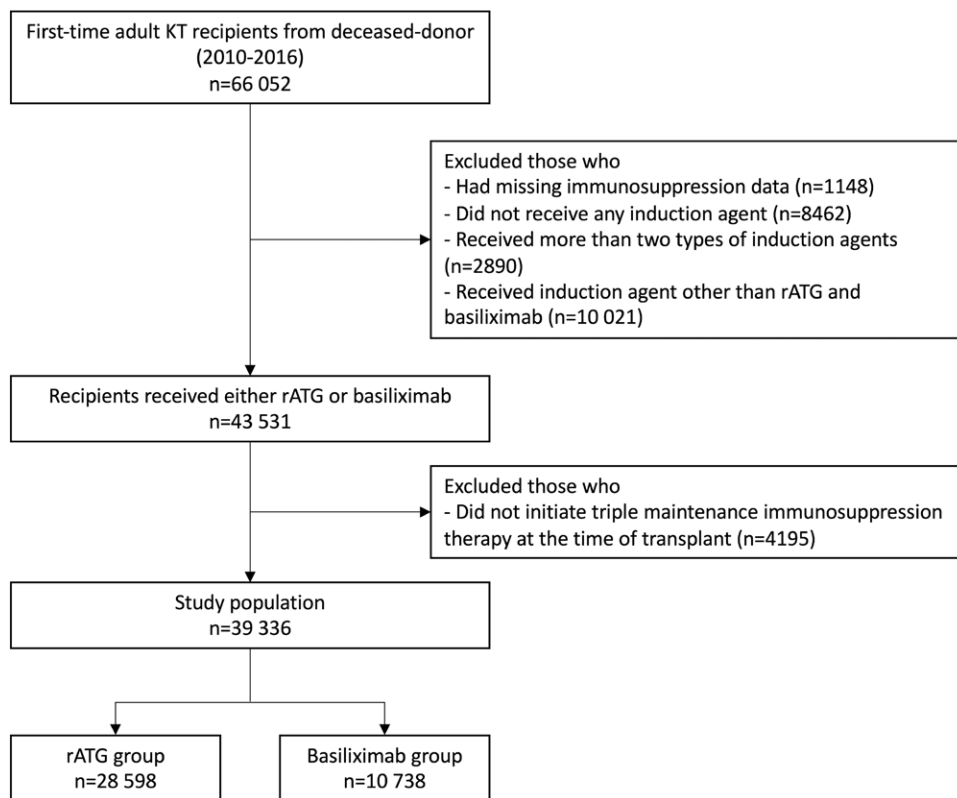
The SRTR data includes information on AR by specific periods (0–6, 7–12 mo, then annual periods), but exact dates of AR are not available.<sup>18-20</sup> Therefore, we defined AR as having any of AR episodes between transplant and discharge, biopsy-confirmed AR or treated rejection within 1-year post-KT. We used logistic model to compare the odds of 1-year AR by induction agent (rATG group versus basiliximab).

Death-censored graft failure (DCGF) was defined as returning to dialysis or retransplantation, censoring for death. Death was ascertained from multiple sources, including follow-up reports from transplant centers, Centers for Medicare & Medicaid Services ESKD Death Notification Form (CMS 2746), and the Social Security Death Master File. We administratively censored the cohort on December 31, 2017. We used the Cox proportional hazard model to compare the hazard of DCGF and post-KT mortality, separately, by induction agent (rATG versus basiliximab).

### Adjusting for Confounders Using Propensity Scores

There are known differences between KT recipients who receive rATG and those who receive basiliximab. For example, Kidney Disease: Improving Global Outcomes (KDIGO) recommended IL-2 receptor antagonist as the first choice with lymphocyte-depleting agent reserved for recipients at high-immunologic risk.<sup>21</sup> As such, we were concerned about confounding by indication or channeling bias, a common challenge in pharmacoepidemiology,<sup>22</sup> which might occur when an indication (or a contraindication) for the use of rATG is also associated with outcomes of interest. Therefore, we used the overlap weighting method for propensity scores to adjust for confounders and to address extreme propensity scores (Figure S1, SDC, <http://links.lww.com/TXD/A335>).<sup>23</sup> The method downweights patients with propensity scores close to 0 or 1 and leads to the small contribution, by which improves balance and precision compared with the inverse probability weighting method.<sup>24</sup>

First, we fit multivariable logistic model to estimate propensity of being treated with rATG versus basiliximab. This logistic model included recipient, donor, and transplant variables that might be related to choice of induction agent and post-KT outcomes such as recipient's age, sex, race, BMI, education level, peak panel reactive antigens, cause of ESKD, hepatitis C virus (HCV) infection, years on dialysis, Medicare-covered transplant, and delayed graft function; donor's age, sex, race, terminal serum creatinine, and HCV; calendar year of transplant, HLA mismatches, cold ischemia time, and ABO incompatibility. The propensity scores denoted the estimated



**FIGURE 1.** Population selection for study of association between induction type with a length of stay and kidney transplant outcomes by recipient age (n=39 336). KT, kidney transplant; rATG, rabbit antithymocyte globulin.

probability ( $\hat{e}_i$ ) of receiving rATG conditional upon these variables in our study population.

Then, we calculated the overlap weights,  $w_i = 1 - \hat{e}_i$  for the rATG group and  $w_i = \hat{e}_i$  for the basiliximab group, and fit all models using the weights. Missing covariates were imputed using chained equations<sup>25-28</sup> throughout the analysis (SDC, Materials and Methods). Balance of confounders after weighting was checked using standardized mean differences (Table S1, SDC, <http://links.lww.com/TXD/A335>).<sup>29</sup>

### Differences in the Impact of Type of Induction on Post-KT Outcomes Between Older and Younger Recipients

We then tested whether the impact of type of induction on post-KT outcomes differed between older and younger recipients via an interaction term analysis. To test the effect measure modification by recipient age, we included an interaction term of age (older versus younger) and type of induction agent (rATG versus basiliximab) in our weighted models. We used a Wald test to evaluate the statistical significance of the interaction terms. Interaction  $P$  value  $<0.05$  suggested that the effect of induction agent on post-KT outcomes differed between older and younger recipients.

### The Impact of Type of Induction on Post-KT Outcomes by Recipient Age

We aimed to identify the most appropriate threshold to define younger versus older recipients with regards to induction tailoring. To achieve this, we characterized the interaction between age and induction agent using a flexible technique with fewer modeling assumptions. We estimated adjusted hazard ratios of discharge, DCGF, death, and odds ratios of AR

using recipient age at the time of transplant as a continuous variable using restricted cubic splines with 3 knots. Knots were placed at percentiles based on Harrell's recommendation.<sup>30</sup>

### Statistical Analysis

For sensitivity analysis, we used E-values to assess a minimum strength of association of an unmeasured confounding with both the induction agent (rATG versus basiliximab) and KT outcomes on the risk ratio scale for explaining away the observed associations, conditional on the measured covariates.<sup>31,32</sup> We calculated E-values using the formula as follows:  $RR + \sqrt{RR \times (RR - 1)}$ . For an estimate  $<1$ , we took the inverse of the observed estimate and applied the formula. We obtained E-values using the formula for odds ratio (OR) of AR and applying the approximation for hazard ratio (HRs) of LOS and death as follows:  $RR \approx (1 - 0.5^{\sqrt{RR}}) / (1 - 0.5^{\sqrt{OR}})$ .

A  $P$  value  $<0.05$  was considered statistically significant. All analyses were performed using Stata 16.0/MP for Linux (College Station, TX) and R version 3.6.2.

## RESULTS

### Characteristics of KT Recipients

In our study, a population of 39 336 adult KT recipients, 30 083 (76.5%) were aged 18–64 years old at KT. Among these younger recipients, 22 535 received rATG and 7548 received basiliximab. Among the 9253 recipients aged 65 years or older, 6063 received rATG and 3190 received basiliximab. Compared with those with basiliximab, recipients with rATG induction were more likely to be female (42.5% versus 34.0% among younger; 42.1% versus 32.3% among older), African American (38.1% versus 29.0% among younger; 26.0% versus 18.4%

among older), have longer time on dialysis (median: 4.0 versus 3.5 y among younger; 3.1 versus 2.7 y among older), and experience delayed graft function (27.2% versus 23.7% among younger; 27.8% versus 27.5% among older) (Table 1).

### Induction and LOS Among Older and Younger Recipients

Among adult KT recipients, those with rATG had a median LOS of 5 days (interquartile range, 4–7) and those with basiliximab had a median of 5 days (interquartile range, 4–8).

After adjusting for confounders, the relative hazard of discharge was higher in adult recipients with rATG compared with those with basiliximab (aHR=1.08; 95% confidence interval [CI], 1.00-1.17), which means recipients with rATG had 8% higher chance of discharge on a given day. However, the estimate of induction agent and LOS differed by recipient age (interaction  $P=0.03$ ). Among younger recipients, the relative hazard of discharge was 1.12 (95% CI, 1.01-1.24) for those with rATG compared with those with basiliximab; this indicates that those with rATG had a 12% higher chance of

**TABLE 1.**

**Characteristics of adult deceased donor kidney transplant recipients in 2010–2016 (n=39336) by induction agent and recipient age (younger, 18–64; older, ≥65)**

	rATG; younger (n = 22 535)	Basiliximab; younger (n = 7548)	rATG; older (n = 6063)	Basiliximab; older (n = 3190)
<b>Recipient factors</b>				
Female sex	42.5%	34.0%	42.1%	32.3%
Race and ethnicity				
White	33.4%	39.9%	50.6%	58.2%
African American	38.1%	29.0%	26.0%	18.4%
Hispanic/Latino	18.9%	20.0%	13.9%	12.4%
Other/multiracial	9.5%	11.1%	9.5%	10.9%
Attended college	44.5%	46.4%	48.5%	55.3%
BMI (kg/m <sup>2</sup> )	28.2 (24.4, 32.3)	27.6 (24.0, 31.8)	28.0 (24.8, 31.6)	27.6 (24.6, 31.3)
Cause of ESKD				
Glomerulonephritis	22.0%	21.3%	11.8%	12.3%
Diabetes	27.5%	27.9%	39.6%	37.1%
Hypertension	24.9%	19.7%	24.8%	22.8%
Others	25.6%	31.1%	23.8%	27.8%
Years on dialysis	4.0 (1.9, 6.3)	3.5 (1.1, 6.2)	3.1 (1.2, 5.2)	2.7 (0.7, 4.8)
Preemptive transplant	8.7%	11.6%	13.1%	16.3%
Peak PRA (%)	3.0 (0.0, 39.0)	0.0 (0.0, 12.0)	1.0 (0.0, 30.0)	0.0 (0.0, 9.0)
HCV+	6.0%	9.8%	4.2%	5.5%
Medicare as primary insurance	52.1%	49.5%	58.1%	62.8%
<b>Transplantation factors</b>				
Transplant year				
2010	12.1%	13.4%	11.9%	11.8%
2011	13.2%	14.3%	13.4%	13.1%
2012	13.1%	13.9%	12.8%	13.9%
2013	13.7%	14.3%	14.0%	15.3%
2014	14.0%	14.0%	15.6%	15.1%
2015	15.5%	14.4%	14.1%	13.9%
2016	18.6%	15.7%	18.2%	16.9%
Zero HLA mismatch	5.7%	6.2%	5.4%	6.4%
ABO incompatibility	0.7%	0.7%	0.8%	0.8%
Cold Ischemic time (h)	16.0 (11.0, 22.1)	14.3 (9.6, 20.0)	17.0 (11.5, 23.3)	16.1 (10.7, 22.0)
Delayed graft function	27.2%	23.7%	27.8%	27.5%
<b>Donor factors</b>				
Age (y)	37 (24, 49)	38 (24, 50)	48 (33, 57)	48 (33, 57)
Female sex	38.7%	39.4%	42.5%	42.2%
Race and ethnicity				
White	67.6%	66.3%	70.3%	69.4%
African American	14.7%	13.4%	13.9%	12.9%
Hispanic/Latino	14.2%	15.8%	11.8%	12.4%
Other/multiracial	3.6%	4.6%	3.9%	5.2%
Terminal serum creatinine (mg/dL)	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)
Expended donor criteria kidney	11.1%	11.8%	30.8%	31.3%
Donation after circulatory death	19.8%	12.9%	19.7%	14.6%

Continuous variables are shown in median (IQR).

BMI, body mass index; ESKD, end-stage kidney disease; HCV, hepatitis C virus; PRA, panel reactive antigen.

**TABLE 2.**

**Association of rabbit antithymocyte globulin vs basiliximab with length of stay and post-KT outcomes among older and younger recipients between 2010 and 2016 (n=39336)**

	Overall (n = 39336)	Recipient age		Interaction P
		18–64 (n = 30083)	65+ (n = 9253)	
Length of stay	1.08 (1.00–1.17)	1.12 (1.01–1.24)	0.99 (0.93–1.05)	0.03
Acute rejection	0.79 (0.72–0.85)	0.82 (0.75–0.91)	0.68 (0.57–0.80)	0.05
Death-censored graft failure	1.00 (0.92–1.08)	0.96 (0.88–1.05)	1.11 (0.95–1.31)	0.11
Death	0.95 (0.89–1.01)	0.87 (0.80–0.95)	1.05 (0.96–1.15)	0.003

Adjusted odds ratio of acute rejection and adjusted hazard ratios of death-censored graft failure and death were presented. The relative hazard of discharge was presented for length of stay. For example, if the hazard ratio is >1, then KT recipients with rATG are more likely to be discharged on a given day than those who received basiliximab. 95% confidence intervals are indicated between parentheses.

being discharged on a given day after KT. However, among older recipients, the relative hazard of discharge did not differ between those with rATG and basiliximab (aHR=0.99; 95% CI, 0.93-1.05) (Table 2).

### Induction and Acute Rejection Among Older and Younger Recipients

Among adult KT recipients, 7.6% of those with rATG and 9.1% of those with basiliximab developed AR within 1-year post-KT. After adjusting for confounders, adult recipients with rATG were at a lower risk of AR at 1-year post-KT (adjusted odds ratio [aOR]=0.79; 95% CI, 0.72-0.85) compared with those with basiliximab. This interaction between recipient age and induction agents did not reach statistical significance (aOR, 0.82 among younger recipients and 0.68 among older recipients; interaction  $P=0.05$ ).

### Induction and Graft Survival Among Older and Younger Recipients

Among adult KT recipients, the cumulative incidence of DCGF among recipients with rATG was similar at 1 year (2.8% versus 2.8%) and higher at 3 years (6.6% versus 6.2%), and 5 years (10.9% versus 10.2%) compared with those with basiliximab. The cumulative incidence of DCGF was similar between those with rATG and basiliximab regardless of age (Figure 2A).

After adjusting for confounders, there was no difference in the risk of DCGF between rATG and basiliximab (aHR = 1.00; 95% CI, 0.92-1.08) in the entire population of adult KT recipients. Furthermore, the risk of DCGF comparing rATG with basiliximab did not differ by recipient age (interaction  $P=0.11$ ).

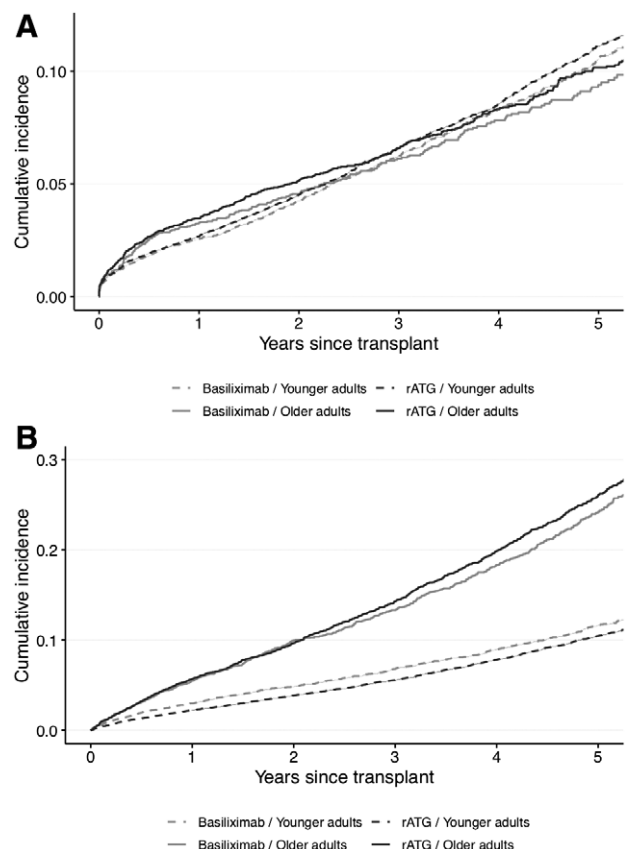
### Induction and Patient Survival Among Older and Younger Recipients

Among adult KT recipients, the cumulative incidence of death was lower among recipients with rATG compared those with basiliximab at 1 year (3.0% versus 3.7%), 3 years (7.4% versus 8.8%), and 5 years (13.8% versus 15.4%). Among younger recipients, the cumulative incidence of death was lower in recipients with rATG compared with those with basiliximab at 1 year (2.2% versus 3.0%), 3 years (5.6% versus 6.8%), and 5 years (10.5% versus 11.7%). Among older recipients, however, the cumulative incidence of death was higher in recipients with rATG compared with those with basiliximab at 1 year (5.8% versus 5.5%), 3 years (14.3% versus 13.4%), and 5 years (26.1% versus 24.3%) (Figure 2B).

After adjusting for confounders, mortality was not different between recipients with rATG and those with basiliximab (aHR=0.95; 95% CI, 0.89-1.01) among adult KT recipients. However, the risk of mortality comparing recipients with rATG to those with basiliximab differed by recipient age (interaction  $P=0.003$ ). Among younger recipients, the risk of death was 0.87 (95% CI, 0.80-0.95) for those with rATG compared with those with basiliximab. However, among older recipients, the risk of death did not differ between those with rATG and basiliximab (aHR = 1.05; 95% CI, 0.96-1.15).

### Induction and Post-KT Outcomes by Age

The odds ratios of 1-year AR, comparing recipients with rATG to those with basiliximab, started to be significantly lower



**FIGURE 2.** Cumulative incidence of death-censored graft failure and death, stratified by induction agent and recipient age (n=39336). (A) Death-censored graft failure. (B) Death. rATG, rabbit antithymocyte globulin.



(ie, aOR < 1) at age 34 and the associations between induction and AR continued to decrease for recipients aged 34 years and older (Figure 3B). For LOS and mortality, the benefit of rATG was likely to be the strongest in their middle age. Relative hazard of discharge, comparing recipients with rATG to those with basiliximab, was significantly > 1 among recipients aged 44–64 (Figure 3A). For example, at age 54, recipients with rATG had a 17% higher chance of being discharged on a given day after KT (aHR = 1.17, 95% CI: 1.04–1.31) compared with those with basiliximab. Relative risk of mortality was significantly lower than 1 among recipients aged 42–60 (Figure 3D). For example, at age 46, the risk of death was 0.86 (95% CI, 0.77–0.96) for those with rATG compared with those with basiliximab and the beneficial effect of rATG decreased after 46. To sum up, rATG was associated with reduced risk of AR for recipients aged 34 years and older, risk of mortality among those aged 42–60, and LOS among those aged 44–64 compared with basiliximab.

### Sensitivity Analysis

Based on the E-values (Table S2, SDC, <http://links.lww.com/TXD/A335>), there was modest evidence for potential unmeasured confounders impacting the effect of induction, on LOS, AR, and death. Among older recipients, moderate evidence for the effect of rATG on AR was observed. With the observed

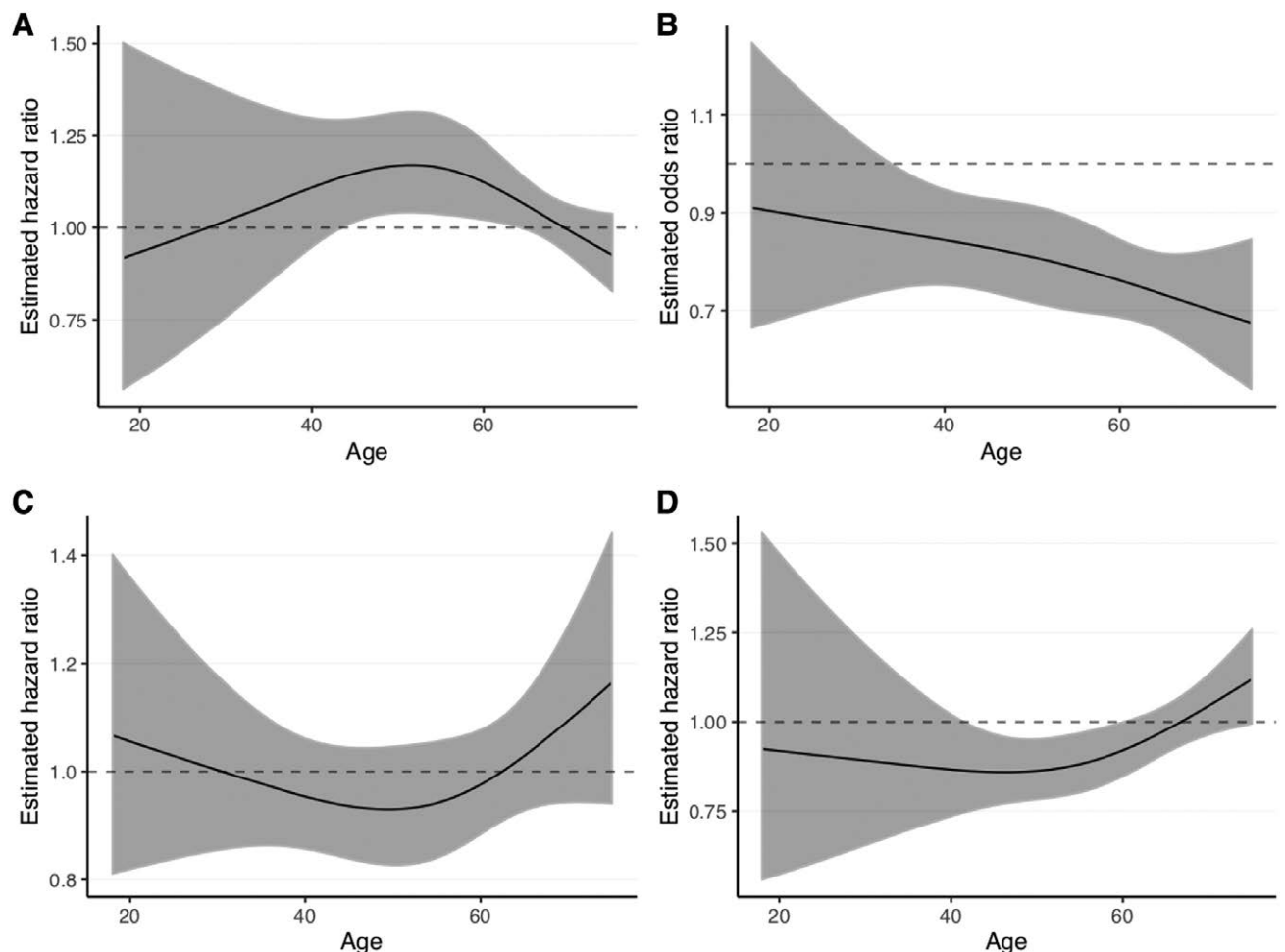
effect among older recipients (aOR = 0.68; 95% CI, 0.57–0.80), an RR of 2.3 between an unmeasured confounder and each of induction agent (rATG versus basiliximab) and AR conditional on the measured covariates is required to explain away the association. A weaker unmeasured confounder (ie, if 1 of each association were weaker than 2.3 on the risk ratio scale) could not explain away the association. An association between an unmeasured confounder and each of induction agent and AR would need to have a risk ratio of 1.81 each to make the confidence interval include 1.

For all outcomes, the effect estimates and statistical significance of interaction between type of induction agent and recipient age were not substantially changed after excluding delayed graft function in the multivariable logistic model to calculate propensity scores.

Although this analysis focused on rATG, as it is the most commonly used T-cell depleting agent in the United States, we also performed additional analyses comparing effect of rATG with alemtuzumab on post-KT outcomes (SDC, Results).

### DISCUSSION

In this national study of 39 336 adult KT recipients, we found that, as compared to basiliximab, rATG was effective in



**FIGURE 3.** Hazard ratios (rabbit antithymocyte globulin vs basiliximab) of discharge, death-censored graft failure, death and odds ratio of acute rejection by recipient age at the time of transplant (n = 39 336). Recipient age was treated as a continuous variable, and restricted cubic splines were used. 95% confidence intervals are indicated as gray-colored area. (A) Length of stay, (B) acute rejection, (C) death-censored graft failure, and (d) death.

preventing AR regardless of recipient age. Furthermore, that effect of induction on LOS and death (interaction  $P=0.03$  and  $0.003$ ) differed by recipient age. Among younger recipients, rATG was associated with a shorter time-to-discharge (aHR=1.12; 95% CI, 1.01-1.24) and reduced risk of mortality (aHR=0.87; 95% CI, 0.80-0.95) compared with basiliximab. However, the choice of induction did not impact these outcomes among older recipients. Our study suggests that rATG is an effective way to prevent AR in both older and younger recipients; however, tailoring induction among younger may reduce LOS and the risk of mortality.

Previous randomized controlled trials (RCTs) and observational studies have shown the efficacy of ATG in comparison with basiliximab in adult KT recipients.<sup>33-37</sup> For example, 1 of the largest RCTs in 2006 observed the effect of rATG on reducing 1-year biopsy-proven AR as compared with basiliximab (15.6% versus 25.5%, respectively;  $P=0.02$ ) when combined with tacrolimus, mycophenolate mofetil, and prednisone.<sup>33</sup> Additionally, an observational study using national registry data in the United States estimated lower odds of AR (OR=0.81; 95% CI, 0.75-0.87) at 6 months after KT among those with rATG compared with those with basiliximab in combination with steroid.<sup>36</sup> Our findings are consistent with the previous Cochrane review of effectiveness of rATG on preventing AR among recipients with rATG compared with those with basiliximab.<sup>38</sup> We further observed that the effect did not differ among older ( $\geq 65$  y) and younger (18–64) recipients.

We expanded upon the previous studies of induction among older and younger recipients. A secondary analysis<sup>2</sup> of an RCT reported that KT recipients aged 50 years or older who received rATG had a trend toward lower AR rates at 1-year post-KT. One observational study<sup>35</sup> among KT recipients aged 60 years or older found that the adjusted odds of AR at 1 year were significantly higher among recipients of IL2-RA (OR=1.65; 95% CI, 1.08-1.69) compared with rATG. For mortality, however, they<sup>35</sup> reported an increased risk of death for recipients of IL2-RA (HR = 1.12; 95% CI, 1.02-1.21) compared with rATG. The discrepancy between the study and our study might be partially attributable to using different age threshold as we found that the effect of rATG (versus basiliximab) on reducing mortality could not be found in those aged over 65.

Our findings suggest that rATG has a beneficial effect of preventing AR among younger and older recipients. In older KT recipients, the incidence of AR are lower, but these rejections may lead to graft loss more frequently.<sup>39</sup> However, immunosuppressive therapy strategy is required to consider long-term events such as frailty, infection, malignancy and other de novo chronic diseases followed by KT among older KT recipients with experiencing immunosenescence.<sup>2,7,40</sup> Therefore, future research is required to investigate the long-term events and induction agents.

We examined the effectiveness of rATG by recipient age that would not be attainable otherwise (ie, RCTs) using large national registry data. Through our real-world evidence study, we were able to include broader population (ie, older KT recipients) and expand our knowledge by asking clinically useful questions.<sup>41</sup> However, our study has some limitations. In all observational studies, unmeasured confounding may bias the results; this means that there may be some factors not collected by SRTR, which are associated with the choice of induction and the post-KT outcomes and explain our

observed associations. For example, some clinical characteristics, such as having allergy or anaphylactic reactions to rabbit proteins or infections which contraindicate rATG, were not available in the data. However, the causal inference methods used in this study are the strongest analytic tools that can be used to adjust for many of clinical factors available in the SRTR data to minimize the impact of unmeasured confounding. Furthermore, we reported the strength of the evidence for the effect of induction agents on LOS, AR, and death using E-values for estimates and CIs. As with efficacy studies using registry data, detailed dosage information was not available so that we expected the inconsistency of dose, timing and frequency of the induction agents in our study population. Here, we can interpret our results based on the history of description of rATG or basiliximab at the time of transplant.

In conclusion, we found that when compared with basiliximab, rATG has potent effect on preventing AR regardless of recipient age. However, rATG only reduced the LOS and the risk of mortality among younger KT recipients. Our findings suggest the effectiveness of rATG on AR among older recipients but no beneficial effect on LOS, DCGF, and mortality. Transplant centers should consider rATG to prevent AR especially among those with high-immunologic risk regardless of age; however, choice of induction should be tailored to reduce LOS and risk of mortality, particularly among younger recipients.

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