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Alemtuzumab induction is associated with decreased hospitalization rates in pediatric kidney transplant: A UNOS data review for safety and outcomes with common induction regimens

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Abstract

Background: We hypothesized that alemtuzumab use is safe in pediatric kidney transplant recipients (KTRs) with equivalent long-term outcomes compared to other induction agents.

Methods: Using pediatric kidney transplant recipient data in the UNOS database between January 1, 2000, and June 30, 2022, multivariate logistic regression, multivariable Cox regression, and survival analyses were utilized to estimate the likelihoods of 1st-year and all-time hospitalizations, acute rejection, CMV infection, delayed graft function (DGF), graft loss, and patient mortality among recipients of three common induction regimens (ATG, alemtuzumab, and basiliximab).

Results: There were no differences in acute rejection or graft failure among induction or maintenance regimens. Basiliximab was associated with lower odds of DGF in deceased donor recipients (OR 0.77 [0.60–0.99], $p = .04$). Mortality was increased in patients treated with steroid-containing maintenance (HR 1.3 [1.005–1.7] $p = .045$). Alemtuzumab induction correlated with less risk of CMV infection than ATG (OR 0.76 [0.59–0.99], $p = .039$). Steroid-containing maintenance conferred lower rate of PTLD compared to steroid-free maintenance (HR 0.59 [0.4–0.8] $p = .001$). Alemtuzumab was associated with less risk of hospitalization within 1 year (OR 0.79 [0.67–0.95] $p = .012$) and 5 years (HR 0.54 [0.46–0.65] $p < .001$) of transplantation. Steroid maintenance also decreased 5 years hospitalization risk (HR 0.78 [0.69–0.89] $p < .001$).

Conclusions: Pediatric KTRs may be safely treated with alemtuzumab induction without increased risk of acute rejection, DGF, graft loss, or patient mortality. The decreased risk of CMV infections and lower hospitalization rates compared to other agents make alemtuzumab an attractive choice for induction in pediatric KTRs, especially in those who cannot tolerate ATG.

Abbreviations: AR, Acute rejection; ATG, Antithymocyte globulin; CNI, Calcineurin inhibitor; CMV, Cytomegalovirus; CPRA, Calculated panel reactive antibody; DCD, Donor with cardiac death; DDKT, Deceased donor kidney transplant; DGF, Delayed graft function; ECD, Expanded criteria donor; IL-2, Interleukin-2; IL-2RA, Interleukin-2 receptor antagonist; IS, Immunosuppression; KDPI, Kidney donor profile index; KTR, Kidney transplant recipient; LDKT, Live donor kidney transplant; MPA/MMF, Mycophenolic acid/Mycophenolate mofetil; NK, Natural killer; OR, Odds ratio; QOL, Quality of life; SRTR, Scientific Registry of Transplant Recipients.

KEYWORDS
acute rejection, complications, induction, pediatric kidney transplant

1 | INTRODUCTION

Kidney transplantation is the most effective treatment for children with kidney failure. Advances in immunosuppression have improved graft survival in kidney transplant recipients (KTRs). Optimal immunosuppressive regimens promote allograft longevity while minimizing side effects. This is accomplished with a short-term induction phase followed by a long-term maintenance phase. In the induction phase, treatment is administered before or immediately after the transplant with the goal of preventing early rejections. The lymphocyte-depleting effects of certain induction agents can last for 12 months or longer and may be an important determinant of long-term success.[1] Induction therapy is now the standard of care for pediatric kidney transplantation. In fact, 94.3% of pediatric KTRs received induction therapy in 2020.[2] Common agents include lymphocyte-depleting antibodies (alemtuzumab and antithymocyte globulin [ATG]), which are more commonly used in high immunological risk recipients, and non-depleting agents such as antibodies to interleukin-2 (IL-2) receptors that target T cells (basiliximab) which are used in low immunological risk recipients. ATG is a preparation of antibodies (most commonly from rabbits) that target T cells. Alemtuzumab is a humanized IgG1 monoclonal antibody directed against CD52, a glycoprotein expressed on T and B lymphocytes, monocytes, and natural killer (NK) cells. There has historically been a paucity of robust evidence supporting its safety in pediatric KTRs. A 2005 case series of four patients reported unfavorable outcomes.[3] Subsequently, numerous publications have demonstrated the safety and effectiveness of alemtuzumab induction therapy in pediatric populations, though these are limited by small sample sizes and lack of control groups.[4–9] A multi-center retrospective analysis reported that alemtuzumab induction had similar outcomes compared to ATG in 36 low immunologic risk patients, though findings were limited by sample size and different maintenance regimens.[10] In another small single-center review, alemtuzumab induction had similar graft survival and functional outcomes compared to IL-2 receptor antagonists (IL-2RAs) in highly sensitized patients, though there were higher levels of acute cell-mediated rejection in the alemtuzumab group.[11] Two recent large retrospective cohort studies with a combined n = 7687 participants compared induction regimens from the Scientific Registry of Transplant Recipients (SRTR) data. Recipients of live-donor allografts experienced significantly higher rates of rejection at 6 and 12 months in the alemtuzumab group compared to ATG and IL-2RA, without long term differences in graft or recipient survival.[12] The researchers also examined SRTR data during the same period for recipients of deceased-donor allografts and observed that rejection rates, allograft survival, and recipient survival were not statistically different at 6- and 12-month follow-up.[13]

This research aims to add to the previously reported data on alemtuzumab induction for pediatric kidney transplant, addressing the effects of alemtuzumab compared to ATG and basiliximab on safety measures and surrogates of healthcare expenditure and utilization. The authors hypothesized that alemtuzumab may be utilized in pediatric kidney transplant induction safely and with equivalent or fewer long-term costs compared to other induction regimens. We also sought to identify differential adverse outcomes among induction and maintenance regimens as well as across various graft recipient characteristics.

2 | MATERIALS AND METHODS

2.1 | Data and data sources

A retrospective analysis was performed using pediatric kidney transplant recipient data in the UNOS database between January 1, 2000, and June 30, 2022. Transplant recipients aged 17 or older were excluded, as were recipients of multiple organ transplants. Separate UNOS data files that record follow-up recipient information and immunosuppressive maintenance therapies were merged with the main transplant recipient data that record information at the time of transplant and basic transplant outcome data (e.g., graft failure and patient mortality). For the immunosuppression induction therapies, we queried the following drugs: ATG, alemtuzumab, basiliximab, and daclizumab. Daclizumab-induced patients were removed from the analysis due to the discontinuation of the drug in 2009 and how this impacted comparison to other agents in later eras. For immunosuppression maintenance therapies, recipients of the following drugs were retained: calcineurin inhibitors (Cyclosporine or Tacrolimus), mycophenolic acid (MPA) and steroids. After merging the files and excluding those pediatric transplant recipients without any follow-up or immunosuppressive regimen information, there were 10 204 pediatric transplant recipients.

2.2 | Population and variables

Recipients of the three induction regimens (ATG, alemtuzumab, basiliximab) were compared for the following seven outcomes: (1) acute rejection within the first year after transplant; (2) delayed graft function (DGF) defined by the administration of dialysis in the first week after transplant; (3) post-transplant CMV and EBV infection within the first year after transplant (defined as positive IgG or IgM at 0.5 years post-transplant follow-up); (4) hospitalization within the first year after transplant; (5) hospitalization at

any time during the follow-up period; (6) death-censored graft failure; and (7) patient mortality. Potential risk factors and commonly used covariates explored in our analyses included age, sex, race/ethnicity, days on the waitlist, prior history of transplant, body mass index (BMI), dialysis, glomerular filtration rate (GFR), calculated panel reactive antibody (cPRA) at the time of transplant, and use of steroid as part of the immunosuppressive maintenance regimen. For donor characteristics, we queried age, sex, race, and measures for organ quality such as Kidney Donor Profile Index (KDPI), BMI and creatinine levels at the time of transplant, kidneys from donors with cardiac death (DCD), expanded criteria donors (ECD), as well as living donor status and history of diabetes. Additional transplant-related variables such as cold ischemic time, HLA mismatch level, and organ sharing status (local, regional, or national) were also included. A variable representing transplant eras consisting of 4 periods (2000–2005, 2006–2010, 2011–2016 (or 2nd era), and 2017–2022 (or 3rd era)) was also included in the final data.

2.3 | Statistical analysis

The basic recipient, donor, and transplant characteristics were compared across induction regimens received by the study subjects. The comparisons were made using *t*-tests for continuous, and chi-square tests for nominal variables. Depending on the distribution of a continuous variable and the sample size of a nominal variable, Wilcoxon–Mann–Whitney and Fisher's exact tests were used to replace t- and chi-square tests, respectively. For the investigations of DGF, CMV and EBV infection, acute rejection (defined as biopsy-proven or clinically based acute rejection as reported in the database), post-transplant lymphoproliferative disorders (PTLD), and hospitalization in the first year and at any time during the follow-up period, multivariable logistic regressions were performed using the event as the dependent variable, which has the value 1 representing the presence of the event and the value 0 otherwise. Factors associated with post-transplant length of stay (LOS) at the hospital were assessed using negative binomial regressions using the same set of independent variables as logistic regressions. Negative binomial regression was chosen over Poisson regression based on both smaller Akaike and Bayesian Information Criteria "(AIC: 32900.59 vs. 35071.31; BIC: 33000.85 vs. 35164.88)."

Survival analyses were performed to investigate the time to graft failure and patient mortality by different induction and maintenance regimens using the Kaplan–Meier Product Limit method. In the survival analysis of transplant outcomes, patient death and graft failure were the endpoints. Recipients who did not experience any of the endpoints or whose life and graft status were unknown were censored on the last follow-up or the last day of the study (30 June 2022). The equality of the survival curves was tested using the chi-squared-based log-rank test. Multivariable Cox regression analyses were performed to measure the impact of each regimen on the outcome measures after adjusting for covariates. We also performed survival analyses using the Kaplan–Meier Product Limit method and multivariable Cox regression for other outcome measures where data on time to event were available. These measures included hospitalization all years, CMV, acute rejection, and PTLD. were also performed for these outcome measures. For these analyses, episodes of hospitalization, CMV, acute rejection, and PTLD were the endpoints. Recipients who did not experience any of the endpoints were censored on the last follow-up or the last day of the study (30 June 2022).

No bias correction was made to address "loss to follow up" as they comprised 2.2% (n = 225) of all recipients and 8.9% of the censored population. No one was lost before 1 year and the first loss to follow up occurred 584 days after transplant.

For all regressions, covariates and other clinically suspected risk factors explored included recipient and donor demographics, clinical factors including the use of steroids as part of the immunosuppressive regimen, donor characteristics linked to organ quality including KPDI and additional donor characteristics that are not part of the KPDI calculation, transplant eras, and transplant-related variables. Since some of the risk factors are available only for deceased donor transplant recipients (e.g., KDPI, organ sharing status) and our intention is to keep as many observations as possible for statistical significance and validity of the results, living and deceased donor transplant recipients were analyzed separately when variables available only for deceased donor transplants were statistically significant in the regressions. For all regressions, the initial model used all known risk factors as well as demographic variables for control listed in the descriptive table. The final models retained only statistically significant covariates. All regression results were assessed to ensure the coefficient robustness and the absence of collinearity within the models. All statistical analyses were performed using STATA (ver. 8), and statistical significance was defined by $p \leq .05$.

3 | RESULTS

Between January 1, 2000, and June 30, 2022, we identified 16 878 pediatric kidney transplant recipients aged 16 and younger induced with ATG, alemtuzumab or basiliximab. Multi-organ recipients and those missing significant donor-related data, immunosuppressive regimen data, and follow-up data, were excluded leading to a total of 10 204 patients for our analysis (Figure 1). Of those, 6355 (62.2%) were deceased donor kidney transplant (DDKT) recipients while 3849 (37.8%) were living donor kidney transplant (LDKT) recipients. Demographics and characteristics stratified by induction regimen are listed in Table 1A and those stratified by maintenance regimen are listed in Table 1B. Receiving ATG for induction and prednisone for maintenance correlated with a slightly higher age. The male population made up 59.1% of the total cohort. The white population

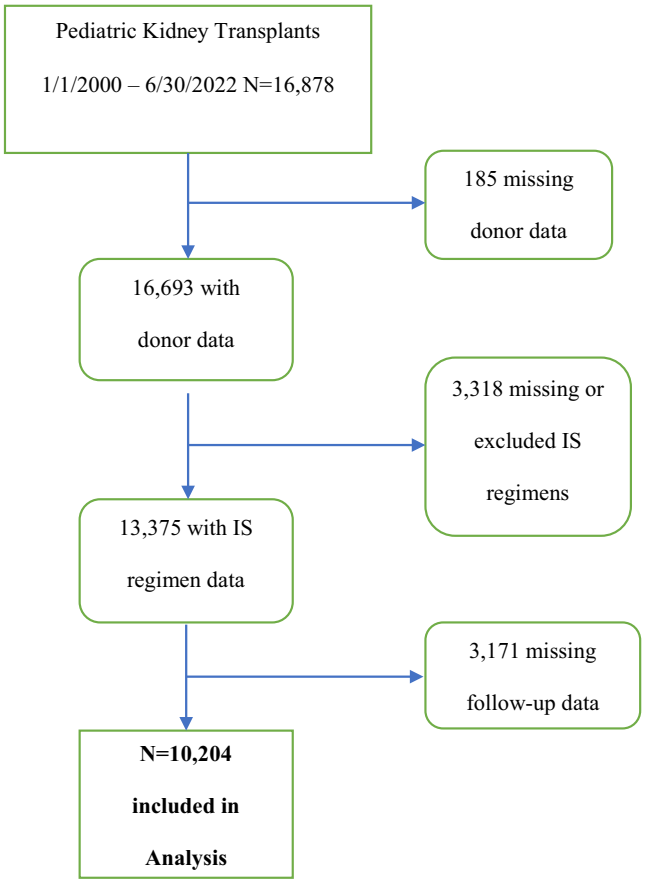

FIGURE 1 Exclusion Criteria.

was more likely to be treated with alemtuzumab induction, while the Hispanic population was more likely to receive basiliximab and the African American population was more likely to receive ATG. These trends were more pronounced in the deceased donor group, and characteristics of living and deceased donors stratified by induction and maintenance regimens are listed in Tables S1A,B and S2A,B. Patients in the ATG and alemtuzumab groups had higher mean calculated panel reactive antibody (cPRA) scores than those in the basiliximab group. Recipients of basiliximab were less likely to have a prior transplant or diabetes at the time of transplant, and more likely to have a lower BMI compared to recipients of other induction agents. Deceased donors were younger (average 22–23 years of age) than live donors (average 36–37 years of age) in all induction cohorts (Tables S1A,B). The mean length of follow-up was 2135 days (5.85 years).

The use of induction regimens changed over time in our population. ATG utilization increased from 52.92% of all transplants before 2010 to 60.58% between 2017 and 2022. 6.32% of KTRs in our population were induced with alemtuzumab before 2010. This number subsequently increased to 9.91%–9.98% in the following eras. Basiliximab use steadily decreased from 40.76% of transplants before 2010 to 29.50% of transplants in the 2017–2022 era. Alemtuzumab was the least utilized induction agent overall, and only 8.76% of analyzed KTRs were induced with alemtuzumab over the entire study period (Table 1A).

3.1 | Graft and patient outcomes

Patients who were induced with Basiliximab and/or treated with steroid-containing maintenance immunosuppression were less likely to have an acute rejection over 5 years ($p < .001$ and $p = .05$, respectively, Figure 2A,B). These associations attenuated, however, after controlling for other variables, and neither choice of induction nor maintenance regimen seems to confer superior outcomes with regard to acute rejection. Higher recipient age, African American recipients, increased HLA mismatch, and higher cPRA were associated with an increased risk of acute rejection (HR 1.03 [1.02–1.04] $p < .001$; HR 1.4 [1.26–1.56] $p < .001$; HR 1.13 [1.09–1.17] $p < .001$; HR 1.003 [1.001–1.005] $p = .004$, respectively). Male and Asian recipients and 3rd era transplant correlated with less risk of acute rejection (HR [0.85 [0.78–0.94 $p = .001$; HR 0.74 [0.56–0.98] $p = .035$; HR 0.64 [0.56–0.74] $p < .001$, respectively] (Table S3).

Basiliximab was associated with lower odds of DGF in deceased-donor recipients (OR 0.77 [0.60–0.99], $p = .040$), but not live-donor recipients, compared to ATG. Alemtuzumab did not confer significantly different odds of DGF compared to ATG (Table 2).

Neither the induction agent nor maintenance regimen had a significant impact on graft failure after controlling for other variables. In both living and deceased donor recipients, transplantation in the 2nd and 3rd era correlated with less graft failure compared to the pre-2010 era (deceased-donor: HR 0.74 [0.66–0.82] $p < .001$; HR, 0.56 [0.45–0.68] $p < .001$, respectively. Living-donor: HR 0.72 [0.57–0.91] $p = .005$; HR 0.67 [0.45–0.98] $p = .040$, respectively). Higher recipient age, African American recipients, dialysis at time of transplant, and DGF were all associated with an increased risk of graft failure in both deceased-donor (HR 1.06 [1.05–1.08] $p < .001$; HR 1.56 [1.40–1.74] $p < .001$; HR 1.30 [1.16–1.46] $p < .001$; HR 1.76 [1.50–2.06] $p < .001$) and living-donor recipients (HR 1.07 [1.05–1.09] $p < .001$; HR 1.50 [1.15–1.95] $p = .003$; HR 1.23 [1.01–1.49] $p = .035$; HR 2.17 [1.42–3.30] $p < .001$, respectively). Each point higher KDPI correlated with an increased risk of graft failure in the deceased donor cohort (HR 1.42 [1.02–1.98] $p = .040$) (Tables S4A and S4B).

Higher recipient age, African American recipients, recipients on dialysis at the time of transplant, and DGF also increased the risk of patient mortality (HR 1.06 [1.04–1.09] $p < .001$; HR 1.56 [1.27–1.93] $p < .001$; HR 1.77 [1.40–2.25] $p < .001$; HR 2.51 [1.92–3.28] $p < .001$, respectively) (Table S5). The risk of recipient mortality was not affected by the choice of induction agent but was increased in patients treated with a steroid-containing maintenance regimen (HR 1.31 [1.01–1.70] $p = .045$) (Figure S1A,B and Table S5).

3.2 | Infectious outcomes and PTLD

Use of Alemtuzumab induction correlated with less risk of CMV infection over time than ATG and Basiliximab (HR 0.78 [0.61–0.99], $p = .044$) (Figure 3 and Table S6). When compared with triple maintenance immunosuppression, steroid-free maintenance was associated

TABLE 1A Characteristics of pediatric transplants based on induction immunosuppression.

Characteristics	Antithymocyte globulin ($n=5660$)	Alemtuzumab ($n=894$)	Basiliximab ($n=3650$)	p-value
Recipient Characteristics				
Demographics				
Age, mean (sd)	11.33 (4.92)	10.80 (5.23)	10.67 (5.21)	<.001
Male, *n* (%)	3321 (58.67%)	550 (61.52%)	2164 (59.29%)	.267
Ethnicity/race, *n* (%)				
White	2754 (48.66%)	556 (62.19%)	1862 (51.01%)	<.001
African American	1141 (20.16%)	112 (12.53%)	585 (16.03%)	
Hispanic	1365 (24.12%)	186 (20.81%)	1010 (27.67%)	
Asian	224 (3.96%)	25 (2.80%)	116 (3.18%)	
Other	176 (3.11%)	15 (1.68%)	77 (2.11%)	
Days on waitlist, median (sd)	172 (388.63)	120 (337.63)	161.50 (351.70)	<.001
Clinical factors				
Prior transplant, *n* (%)	615 (10.87%)	99 (11.07%)	141 (3.86%)	<.001
BMI at the time of transplant, mean (sd)	19.97 (5.03)	20.11 (5.51)	19.43 (4.63)	<.001
Dialysis at the time of transplant, *n* (%)	3475 (67.57%)	477 (60.15%)	2094 (67.20%)	<.001
Diabetes at the time of transplant, *n* (%)	69 (1.23%)	13 (1.46%)	18 (0.50%)	<.001
GFR at the time of transplant, mean (sd)	12.96 (4.87)	13.40 (4.59)	12.36 (5.17)	.001
cPRA at the time of transplant, mean (sd)	12.17 (26.07)	11.19 (25.49)	4.84 (14.92)	<.001
Immunosuppressive maintenance regimen, *n* (%)				
CNI + MMF	2471 (43.66%)	648 (72.48%)	401 (10.99%)	<.001
CNI + MMF + steroids	3189 (56.34%)	246 (27.52%)	3249 (89.01%)	<.001
Donor/Organ/Transplant Characteristics				
Demographics				
Age, mean (sd)	27.96 (10.97)	29.37 (11.36)	28.81 (10.98)	<.001
Male, *n* (%)	3333 (58.89%)	523 (58.50%)	2045 (56.03%)	.022
Ethnicity/race, *n* (%)				
White	3727 (65.85%)	647 (72.37%)	2321 (63.59%)	<.001
African American	626 (11.06%)	90 (10.07%)	429 (11.75%)	
Hispanic	1065 (18.82%)	134 (14.99%)	773 (21.18%)	
Asian	152 (2.69%)	12 (1.34%)	84 (2.30%)	
Other	90 (1.59%)	11 (1.23%)	43 (1.18%)	
BMI at the time of transplant, mean (sd)	25.63 (5.24)	26.09 (5.09)	25.82 (5.14)	.011
Diabetes *n* (%)	23 (0.41%)	5 (0.56%)	20 (0.55%)	.520
Hypertension, *n* (%)	132 (2.42%)	12 (1.36%)	57 (1.69%)	.020
DCD, *n* (%)	179 (3.16%)	20 (2.24%)	77 (2.11%)	.006
Organ/transplant factors				
Living donor, *n* (%)	1905 (33.6%)	404 (45%)	1540 (42.1%)	
Deceased donor, *n* (%)	3755 (66.4%)	490 (55%)	2110 (57.9%)	
HLA mismatch level (0–6), mean (sd)	4 (1.47)	3.78 (1.62)	3.75 (1.51)	<.001
KDPI, mean (sd)	0.14 (0.13)	0.12 (0.13)	0.14 (0.12)	<.001
Cold ischemic time in hrs, mean (sd)	9.85 (7.88)	8.81 (8.34)	8.76 (7.68)	<.001
Locally shared, *n* (%)	5078 (89.72%)	813 (90.94%)	3414 (93.53%)	<.001
Regionally shared, *n* (%)	316 (5.58%)	44 (4.92%)	109 (2.99%)	<.001
Nationally shared, *n* (%)	266 (4.70%)	37 (4.14%)	127 (3.48%)	.017

(Continues)

TABLE 1A (Continued)

Characteristics	Antithymocyte globulin (*n* = 5660)	Alemtuzumab (*n* = 894)	Basiliximab (*n* = 3650)	*p*-value
Transplant Outcome				
Graft failure rate, *n* (%)	1404 (24.81%)	186 (20.81%)	943 (25.84%)	.008
Patient mortality rate, *n* (%)	278 (4.91%)	33 (3.69%)	209 (5.73%)	.030
Hosptailization within 1 year, *n* (%)	3826 (76.43%)	560 (69.83%)	2540 (74.77%)	<.001
Delayed graft function (DGF), *n* (%)	334 (5.90%)	30 (3.36%)	148 (4.05%)	<.001
Acute rejection, *n* (%)	1492 (29.80%)	249 (31.05%)	868 (25.55%)	<.001
CMV, *n* (%)	621 (12.41%)	73 (9.10%)	388 (11.42%)	.020
EBV, *n* (%)	2936 (51.87%)	417 (46.64%)	1763 (48.30%)	<.001
Length of stay, mean (sd)	9.12 (5.04)	8.52 (4.58)	8.91 (4.62)	.028
Transplant Year, *n* (%)				
Pre-2010	1766 (52.92%)	211 (6.32%)	1360 (40.76%)	<.001
2011–2016	1822 (52.86%)	344 (9.98%)	1281 (37.16%)	<.001
2017–2022	2072 (60.58%)	339 (9.91%)	1009 (29.50%)	<.001

TABLE 1B Characteristics of pediatric transplants based on maintenance immunosuppression.

Characteristics	CNI + MPA (*n* = 3520)	CNI + MPA + Steroids (*n* = 6684)	*p*-value
Recipient Characteristics			
Demographics			
Age, mean (sd)	10.73 (5.12)	11.22 (5.03)	<.001
Male, *n* (%)	2107 (59.86%)	3928 (58.77%)	.287
Ethnicity/Race, *n* (%)			
White	1932 (54.89%)	3240 (48.47%)	<.001
African American	479 (13.61%)	1359 (20.33%)	
Hispanic	843 (23.95%)	1718 (25.70%)	
Asian	156 (4.43%)	209 (3.13%)	
Other	110 (3.13%)	158 (2.36%)	
Days on waitlist, median (sd)	151 (366.36)	168 (376.10)	<.001
Clinical factors			
Prior transplant, *n* (%)	147 (4.18%)	708 (10.59%)	<.001
BMI at the time of transplant, mean (sd)	19.62 (4.93)	19.89 (4.96)	<.001
Dialysis at the time of transplant, *n* (%)	1908 (60.69%)	4138 (70.04%)	<.001
Diabetes at the time of transplant, *n* (%)	43 (1.23%)	57 (0.86%)	.072
GFR at the time of transplant, mean (sd)	13.27 (4.54)	12.55 (5.16)	<.001
cPRA at the time of transplant, mean (sd)	7.65 (19.89)	10.90 (24.92)	<.001
Immunosuppressive maintenance regimen, *n* (%)			
Antithymocyte globulin	2471 (70.20%)	3189 (47.71%)	<.001
Alemtuzumab	648 (18.41%)	246 (3.68%)	<.001
Basiliximab	401 (11.39%)	3249 (48.61%)	<.001
Donor/Organ/Transplant Characteristics			
Demographics			
Age, mean (sd)	29.13 (11.03)	28 (10.99)	<.001
Male, *n* (%)	1992 (56.59%)	3909 (58.48%)	.066
Ethnicity/Race, *n* (%)			

TABLE 1B (Continued)

Characteristics	CNI + MPA ($n = 3520$)	CNI + MPA + Steroids ($n = 6684$)	p-value
White	2422 (68.81%)	4273 (63.93%)	<.001
African American	338 (9.60%)	807 (12.07%)	
Hispanic	607 (17.24%)	1365 (20.42%)	
Asian	101 (2.87%)	147 (2.20%)	
Other	52 (1.48%)	92 (1.38%)	
BMI at the time of transplant, mean (sd)	25.86 (4.97)	25.67 (5.31)	.017
Diabetes *n* (%)	12 (0.34%)	36 (0.54%)	.166
Hypertension, *n* (%)	64 (1.84%)	137 (2.20%)	.239
DCD, *n* (%)	82 (2.33%)	194 (2.90%)	.090
Organ/Transplant factors			
Living donor, *n* (%)	1518 (43.1%)	2331 (34.8%)	
Deceased donor, *n* (%)	2002 (56.9%)	4353 (65.2%)	
HLA mismatch level (0–6), mean (sd)	3.88 (1.53)	3.90 (1.49)	.497
KDPI, mean (sd)	0.12 (0.12)	0.14 (0.13)	<.001
Cold ischemic time in hrs, mean (sd)	8.67 (8.14)	9.77 (7.70)	<.001
Locally shared, *n* (%)	3246 (92.22%)	6059 (90.65%)	.008
Regionally shared, *n* (%)	144 (4.09%)	325 (4.86%)	.077
Nationally shared, *n* (%)	130 (3.69%)	300 (4.49%)	.057
Transplant Outcome, *n* (%)			
Graft failure rate, *n* (%)	649 (18.44%)	1884 (28.19%)	<.001
Patient mortality rate, *n* (%)	106 (3.01%)	414 (6.19%)	<.001
Hospitalization within 1 year, *n* (%)	2370 (76.72%)	4556 (74.49%)	.019
Delayed graft function (DGF), *n* (%)	124 (3.52%)	388 (5.80%)	<.001
Acute rejection, *n* (%)	903 (29.23%)	1706 (27.89%)	.178
CMV, *n* (%)	333 (10.78%)	749 (12.25%)	.039
EBV, *n* (%)	1701 (48.32%)	3415 (51.09%)	.008
Length of stay, mean (sd)	9.06 (4.98)	8.95 (4.79)	.636
Transplant Year, *n* (%)			
Pre-2010	814 (24.39%)	2523 (75.61%)	<.001
2011–2016	1318 (38.24%)	2129 (61.76%)	<.001
2017–2022	1388 (40.58%)	2032 (59.42%)	<.001

with less risk of CMV occurrence, but this effect attenuated after controlling for other variables, leaving no significant difference in CMV risk between maintenance therapies. African American and Asian recipients had a higher rate of CMV infection as did patients transplanted in the 2nd era (HR 1.44 [1.25–1.67] $p < .001$; HR 1.74 [1.33–2.72] $p < .001$; HR 1.32 [1.49–1.51] $p < .001$, respectively), while the 3rd era had significantly less risk of CMV (HR 0.81 [0.69–0.96] $p = .014$) (Table S6).

In logistic regression, higher recipient age, African American, Asian, and Hispanic recipients, and patients with re-transplantations were associated with a higher rate of EBV infections (HR 1.13 [1.12–1.14] $p < .001$; 2.00 [1.79–2.25] $p < .001$; HR 2.10 [1.68–2.64] $p < .001$; HR2.39 [2.16–2.64] $p < .001$; HR 2.09 [1.78–2.46] $p < .001$, respectively), whereas male recipients had the inverse correlation with EBV positivity (HR 0.81 [0.75–0.89] $p < .001$) (Table S7).

Only 204 cases of PTLD were identified based on the WHO classification. PTLD free survival was not different among different induction regimens or any other variables except for steroid-containing maintenance immunosuppression. This group showed a lower rate of PTLD occurrence compared to steroid-free maintenance (HR 0.59 [0.44–0.82] $p = .001$) (Figure 4 and Table S8).

3.3 | Length of stay and hospitalization

There was less risk for hospitalization within 1 year of transplant in patients induced with Alemtuzumab (OR 0.80 [0.67–0.95] $p = .012$) as well as in older age and Hispanic recipients (OR 0.98 [0.97–0.00] $p < .001$; HR0.83 [0.75–0.93] $p = .001$, respectively). (Table S9 and Table 3). The association between alemtuzumab and decreased hospitalization risk remained when examining 5 years

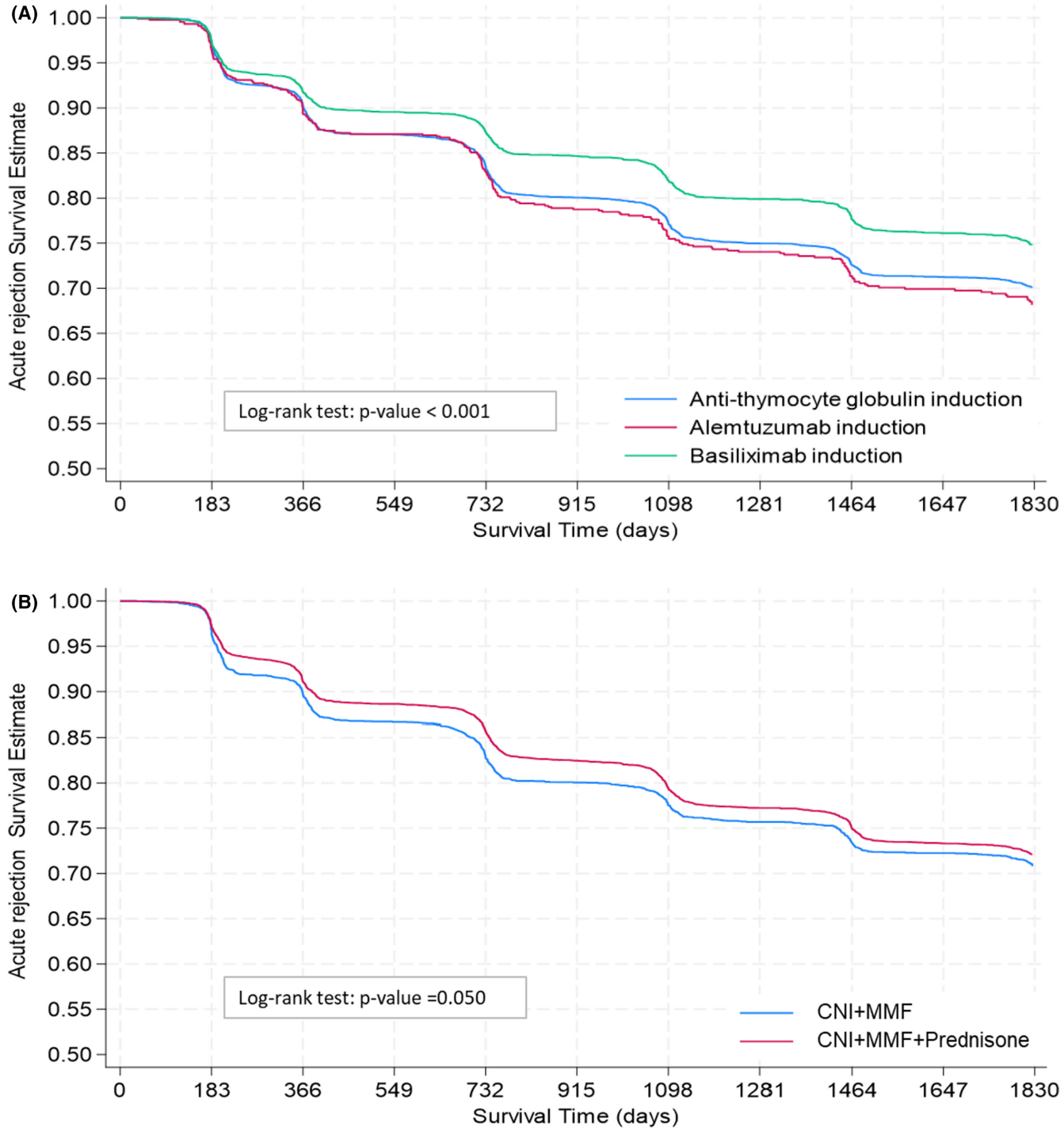

FIGURE 2 (A). Acute rejection survival comparison among different induction regimens. (B) Acute rejection survival comparison among different maintenance regimens.

hospitalization-free survival (HR 0.63 [0.52–0.77] $p < .001$) (Figure 5 and Table 3). There was also a decrease in 5 years hospitalization risk with steroid-containing maintenance regimen (HR 0.78 [0.69–0.89] $p < .001$ (Table 3).

We also examined the length of stay in the first 31 days (LOS31) post-transplant and found a negative correlation between length of stay and basiliximab induction in the deceased-donor recipients (coeff −1.02) whereas days waiting on dialysis, prior transplantation, and higher KDPI were associated with an increase in LOS31 in this cohort (coeff. 0.001, coeff. 0.471, coeff. 1.186, respectively). Triple maintenance immunosuppression was associated with an increase of the LOS31 in living donor recipients (coeff 0.445). Higher-age recipients were less likely to extend their LOS31 in both deceased donors (coeff. −0.288) and living donors (coeff. −0.323) while 3rd era recipients were more likely to have longer LOS31 in all cohorts (deceased-donors: coeff. 0.478; living-donors: coeff. 0.687) (Tables S10A and S10B).

TABLE 2 Logistic regression for delayed graft function occurrence in deceased-donor recipients.

Variable[a]	OR	*p*-value	[95%	C.I.]
Alemtuzumab[b]	0.837	.428	0.538	1.301
Basiliximab[b]	0.770	.040	0.599	0.989
CI + MMF + prednisone[c]	1.318	.038	1.016	1.711

[a]Covariates adjusted for included race, dialysis status at the time of transplant, KDPI, CIT, retransplant status, and era (2011–2016 and 2017–2022).

[b]The reference group is the recipients who received antithymocyte globulin for induction.

[c]The reference group is the recipients who received CI and MMF without prednisone for the maintenance regimen.

4 | DISCUSSION

We hypothesized that alemtuzumab may be utilized in pediatric kidney transplant induction safely and with equivalent or fewer long-term costs compared to other induction regimens. To our knowledge, the current analysis represents the largest evaluation of induction and maintenance therapies among pediatric KTRs with the longest follow-up. Our investigation has illuminated several interesting associations between various induction and maintenance regimens and our examined outcomes. Patients induced with alemtuzumab had less odds of hospitalization in the first year as well as less risk of hospitalization over the subsequent 5 years after transplant compared to ATG. Use of a steroid-containing maintenance regimen is also associated with decreased 5 year hospitalization risk compared to steroid-free maintenance. From an ethnic point of view, African Americans were more likely to receive steroids than other ethnicities. African Americans were also less likely to receive Alemtuzumab which probably accounts for the difference between Anti-thymocyte and Alemtuzumab vis-à-vis the use of steroids (Table 1A). We acknowledge that this could create bias in our results. Alemtuzumab induction reduced the odds of CMV infection in all recipients, while basiliximab induction reduced the odds of DGF in DDKT recipients only when compared to ATG. Steroid-containing maintenance reduced the risk of PTLD, though increased the risk of recipient mortality over the study period compared to a steroid-free approach.

A series by Riad et al. analyzing a total $n = 7687$ pediatric KTRs from 2000 to 2018 reported lower 1st-year hospitalizations with alemtuzumab vs ATG (58.2% vs 60.8%) in live-donor recipients, a trend that we also observed over our combined LDKT and DDKT recipient cohort [12,13]. The prior series also noted that male LDKT and DDKT recipients had better survival than females, and our finding that males have fewer odds of acute rejection, CMV and EBV infections, and 5 years hospitalization is in keeping with this pattern (Tables 3, S3, S6, S7). In the previous investigation, increased HLA mismatching translated to decreased patient and allograft survival in LDKT recipients. In our cohort, HLA mismatch is directly proportional to AR (Table S3). DDKT and LDKT recipients had an increased risk of graft loss with each year of age older in the prior reviews, and we report that older age is associated with increased odds of AR, graft failure, and recipient mortality (Tables S3, S4A,B, S5).

We also report the novel finding that alemtuzumab induction is associated with decreased odds of 5 years hospitalization (including and beyond the first year after transplant) in our population. This association was seen whether we analyzed our DDKT and LDKT recipients separately or as a single cohort (separate analysis not shown). The reason for this association is unclear. Acute rejection, graft failure, and patient mortality were unaffected by the choice of induction agent. Steroid use was independently associated with increased 5 years hospitalization rates, and while 56% of recipients treated with ATG and 89% of patients treated with basiliximab received steroid maintenance, only 28% of those induced with alemtuzumab received steroid maintenance (data not shown but available upon request). Additionally, the decreased CMV risk we demonstrate in patients treated with alemtuzumab induction may play a role in decreasing hospitalization. We do not have data on reasons for hospitalization in our population, and this is a major limitation in interpreting the possible meanings of this finding.

Our results differ from the earlier series in several ways. Riad et al showed significantly increased AR rates at 6 and 12 months post-transplant in live-donor, but not in deceased-donor recipients. We do not show a significant difference in rejection risk among induction agents in our population of combined LDKT and DDKT recipients. This discrepancy likely relates to our different analytic approaches. We did see a signal for decreased AR with alemtuzumab by log-rank analysis, but the association disappeared when we controlled for other variables. Additionally, where the prior report analyzed LDKT and DDKT recipients separately, we included LDKT and DDKT recipients as a single cohort (LDKT and DDKT recipients were only analyzed separately when KDPI was significantly different in multivariable analysis). This highlights the importance of analyzing well-matched populations as a whole to increase analytic power. Using this method, we were still able to demonstrate increased rates of AR with traditional risk factors (cPRA, HLA mismatch) (Table S3).

We demonstrate decreased rates of CMV infection in patients treated with alemtuzumab induction. This was an unexpected finding, given the more widespread (i.e. B cell depleting) immunosuppressive effect of alemtuzumab compared to ATG (which does not deplete B cells). B cells are known to confer protection against CMV infection,[14] and it would seem rational that B cell depletion would increase the risk of developing CMV. Alemtuzumab does not significantly deplete NK levels, and in CMV seropositive patients Ge et al have demonstrated that anti-CMV IgG levels are not reduced, leading to the recovery of CMV-specific T cell immunity in 75% of patients at 2 months and 95% of patients at 3 months after alemtuzumab.[15] We have shown a difference in the rate of CMV infection that becomes pronounced at 1 year after transplant (Figure 3), at a time when post-induction immune reconstitution is felt to be complete. This suggests there may be other factors causing decreased

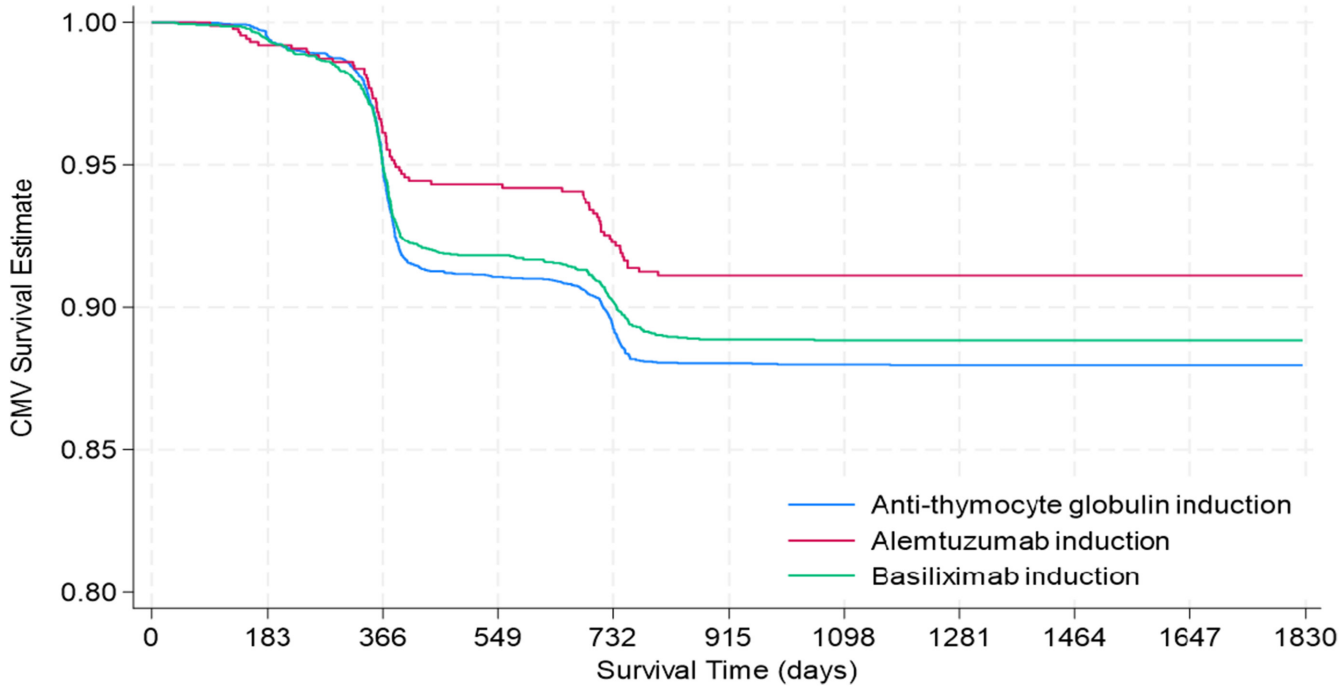

FIGURE 3 CMV survival comparison among different induction regimens.

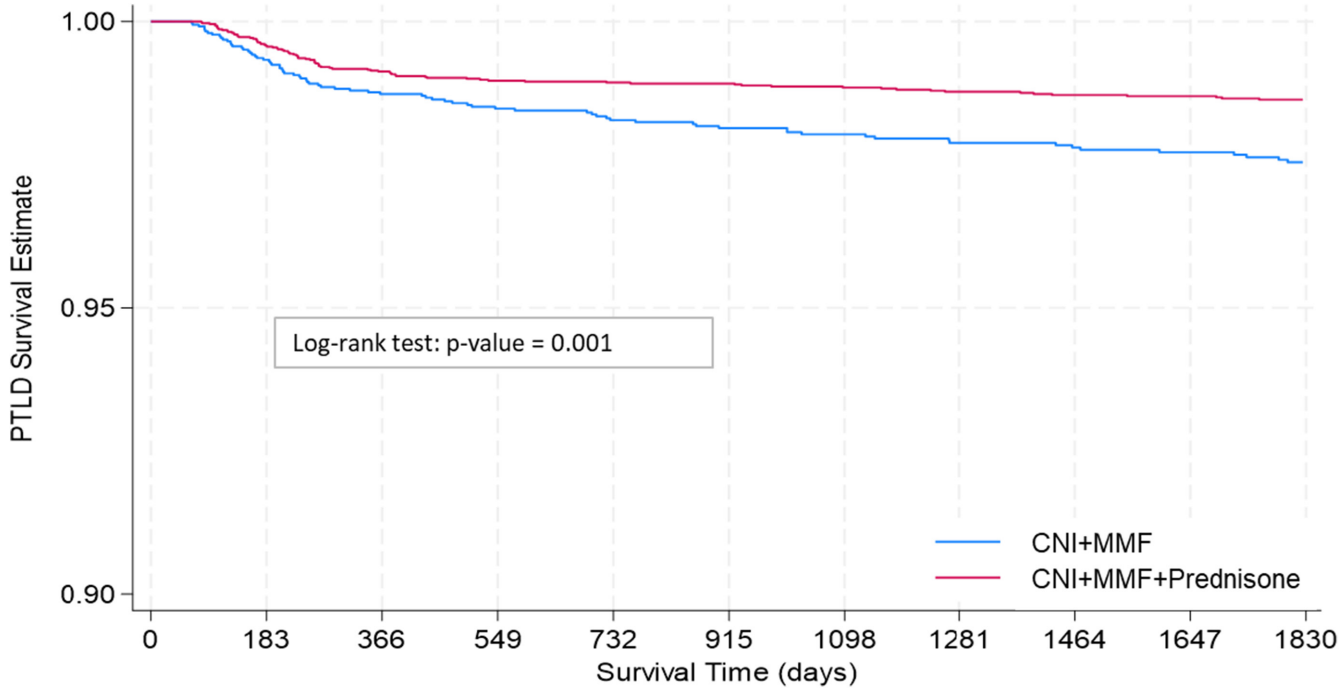

FIGURE 4 PTLD survival comparison among different maintenance regimens.

CMV risk in those treated with alemtuzumab. As has been already mentioned, alemtuzumab recipients were less likely to be treated with steroid maintenance, which did correlate with more CMV risk before controlling for additional variables.

PTLD risk was decreased in patients treated with steroid-containing maintenance therapy. This association occurred despite a lack of significant difference in EBV infections with steroid-free or steroid-containing maintenance. This finding suggests that there are additional factors aside from EBV driving PTLD. We hypothesize that the known cytotoxic effect of steroids on lymphocytes may have played a suppressive role on PTLD in steroid-treated patients. The choice of induction agent had no effect on PTLD risk.

Despite an increase in patient mortality with steroid-containing maintenance, we observed a decreased risk of 5 year

hospitalization with this regimen. This is difficult to interpret without data on reasons for hospitalization. We do show that steroid maintenance increased the duration of index hospitalization after transplant in living-donor KTRs, and this may be due to the known acute adverse effects (AEs) of steroids, including psychosis, hyperglycemia, and GI bleeding. The increased mortality with steroid regimens may be explained by these acute AEs, as well as established long-term AEs such as infections, weight gain, and cardiovascular disease.

Patients induced with basiliximab had less risk of DGF in DDKT recipients. This is not unexpected, as basiliximab is not depleting like the other induction agents and is more likely to be used in lower immunologic risk recipients and with lower risk allografts. The lack of a signal for improved DGF in living-donor allografts may be due to confounding by the shorter cold ischemia time and superior quality allografts inherent to living donation. Higher KDPI is indeed associated with an increased risk of DGF and exerts an independent effect on this risk (Table 2). The fact that we do not see differential rates of acute rejection, graft loss, or patient mortality among induction agents suggests we are appropriately matching the strength of induction therapy to the immunologic risk of patients and allografts.

Interestingly, we observed superior outcomes in several endpoints in transplants performed during our 3rd era, including fewer odds of acute rejection, 5 years hospitalization, PTLD, and less risk of CMV infection, acute rejection, and graft failure. We hypothesize this may be due to improvements in kidney transplant care over time, with better allocation of grafts, a more individualized approach to choosing immunosuppressive regimens, and improvements in prophylactic strategies. However, this hypothesis may be confounded by the lack of sufficient follow-up time in the most recent era to allow for observation of many of these outcomes.

The strengths of this analysis include its robust dataset of more than 10000 pediatric transplants performed in the US over a more than 22 years period. There are several limitations. Differential reporting protocols from hospitals across the country may lead to missing data on outcomes of interest. Secondary diagnoses and other covariates that may affect outcomes could be missing. Differential loss to follow-up was not assessed, though there is minimal loss on patient mortality and graft failure in the UNOS databank. It is possible that maintenance therapies have changed over time since the initial prescriptions. Limited data were available on these changes, potentially biasing the results. The study was not adequately powered to assess PTLD and infection risks. As already mentioned, when analyzing hospitalization data, we did not have access to admission diagnoses or reasons for hospitalization.

TABLE 3 Logistic regression for all hospitalizations post-transplant.

Variable[a]	OR	*p*-value	[95%	C.I.]
Alemtuzumab[b]	0.634	<.001	0.524	0.767
Basiliximab[b]	1.046	.513	0.914	1.197
CI + MMF + prednisone[c]	0.782	<.001	0.686	0.891

[a]Covariates adjusted for included race, sex, cPRA at the time of transplant, BMI, and era (2011–2016 and 2017–2022).

[b]The reference group is the recipients who received antithymocyte globulin for induction.

[c]The reference group is the recipients who received CI and MMF without prednisone for the maintenance regimen.

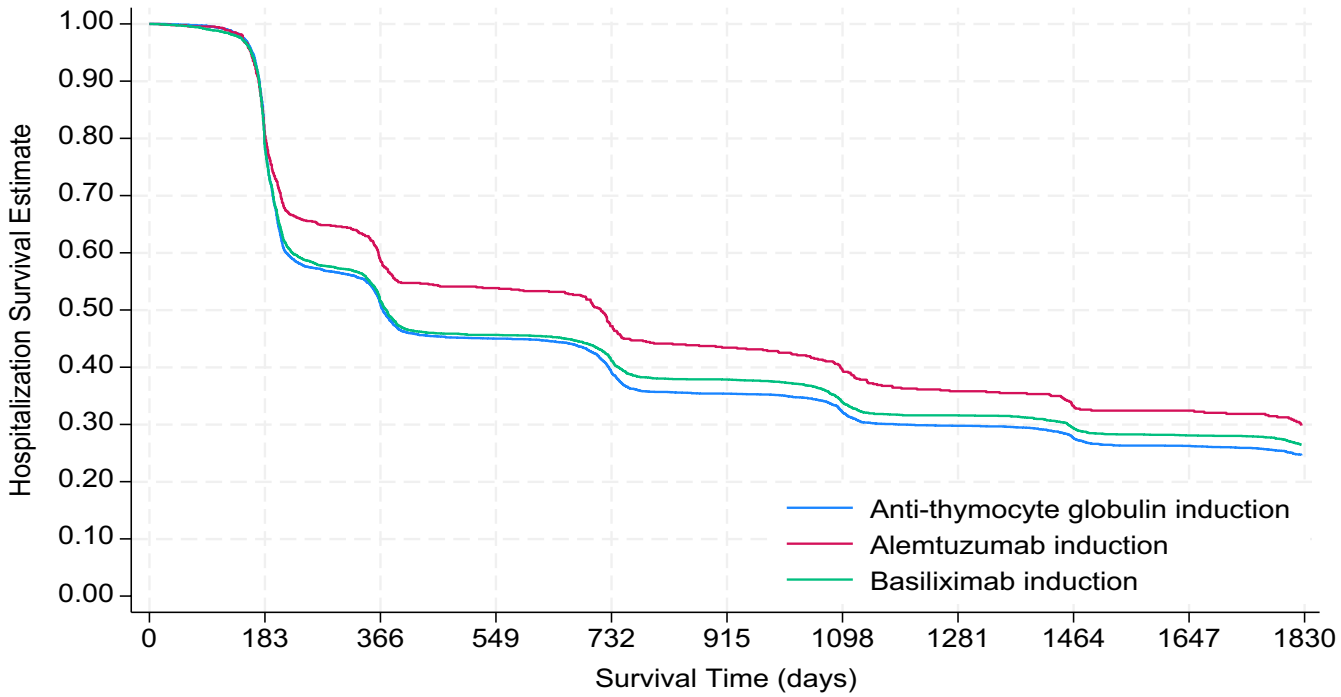

FIGURE 5 Hospitalization free survival comparison among different induction regimens.

We rely solely on UNOS data that are based on events reported by transplant centers. Thus, our analyses succumbed to all limitations typically seen in secondary data analysis, including potential biases attributable to confounding factors such as center-specific attributes and missing values not at random. Unreported factors such as CMV prophylaxis, PCP prophylaxis, and waning effect of induction could have impacted our outcome variables critically.

Despite a difference in the mechanism of action, alemtuzumab performed equally to other induction agents with regards to AR, graft failure, and patient mortality. We noted less hospitalization with alemtuzumab in the short and long term, and it is tempting to infer a decreased cost burden from this, although a firm conclusion cannot be drawn as we do not have data on length of hospital stays, reasons for hospitalization, or hospitalization and post-hospitalization healthcare costs. Regardless, alemtuzumab should be considered as having a safety profile that is at least equivalent to other induction agents and may be a superior choice in those who cannot tolerate ATG. Alemtuzumab remains a viable option for induction therapy in pediatric KTRs.

AUTHOR CONTRIBUTIONS

NK and ML performed data analysis and wrote the 'Materials and Methods' section. EAG and GF contextualized the results and analyzed the medical aspects of the data. EAG and GF wrote the manuscript with the exception of 'Materials and Methods'. JO and GF designed the study and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The UNOS data are available upon request at https://optn.transplant.hrsa.gov/data/view-data-reports/request-data/

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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