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Long-Term Outcomes of Kidney Transplant Recipients with Glomerulonephritides by Induction Type and Steroid Avoidance

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Abstract: Kidney transplant programs have different approaches to induction immunosuppression, and conflicting data exist on the role of steroid maintenance in recipients with glomerulonephritis (GN). GN patients are unique because of a higher risk for immune system exhaustion due to prior exposure to immunosuppressants to treat their GN; this raises questions regarding the optimal immunosuppression needed for transplant success and reduction of complications. We sought to assess the effect of induction type and steroid maintenance on the recipient and kidney graft survival in those with IgA nephropathy (IgAN), systemic lupus erythematosus related GN (SLE), small-vessel vasculitis (SVV), and anti-glomerular basement membrane disease (anti-GBM). We analyzed the Scientific Registry of Transplant Recipients (SRTR) database for adult, primary kidney recipients with the above glomerulonephritides through September 2019. Kaplan–Meier curves were generated to examine kidney graft and recipient survival. We used multivariable Cox proportional hazard models to investigate the impact of induction type and steroid maintenance in each group separately. Our study included 9176 IgAN, 5355 SLE, 1189 SVV, and 660 anti-GBM recipients. Neither induction type nor steroid maintenance therapy influenced recipient or death-censored graft survival in this cohort of recipients. Our findings provide an opportunity for recipients with a history of one of the studied glomerulonephritides to receive a more tailored immunosuppression regimen, considering their previous exposure to immunosuppressants.

Keywords: glomerulonephritis; immunosuppression; corticosteroids; induction

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1. Introduction

In the United States, glomerulonephritis (GN) is the etiology of end-stage kidney disease (ESKD) in approximately 7% of patients initiating dialysis and the third leading indication for kidney transplantation [1].

The mainstay of managing glomerulonephritides is immunosuppression to induce and maintain disease remission. Steroid regimens, including pulse doses or maintenance, are frequently utilized in glomerulonephritides with the customary goal to wean or replace with other immunosuppressive agents as soon as possible. For those unable to achieve disease remission, ongoing disease activity may lead to end-stage kidney disease (ESKD), as well as immune system exhaustion (loss of essential functional activity of immune cells such as anti-viral activity and tumor surveillance), and immune senescence (reduced proliferative capacity of immune cells or replicative senescence) due to chronic antigen stimulation and repeated treatment attempts [2,3].

Given that GN patients typically undergo transplantation during disease remission and have risk factors for functional immune exhaustion and replicative senescence, it is unclear if depletional induction immunosuppression is needed. Additionally, although an increasing number of transplant recipients are managed with a steroid-free regimen, there is conflicting data on the role of steroid maintenance in recipients with glomerulonephritis [4–6]. Accordingly, we sought to evaluate the role of induction immunosuppression and steroid avoidance in the setting of kidney transplant recipients with a history of glomerulonephritis, including IgA nephropathy (IgAN), systemic lupus erythematosus-related GN (SLE), anti-glomerular basement membrane disease (anti-GBM), and small-vessel vasculitis (SVV).

2. Materials and Methods

2.1. Data Source

This study utilized data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration provides oversight and regulation of the activities of the OPTN and SRTR contractors.

This study was approved by the University of Minnesota Institutional Review Board and was compliant with SRTR and HRSA data user agreement. The study authors were included in the project design and were approved to participate by the SRTR. The data consist of solid organs and recipient characteristics, as well as outcomes after transplantation.

2.2. Study Population

We examined all adult, primary kidney-alone recipients with IgAN, SLE, SVV, and anti-GBM disease between 1996 and 2019. IgAN group included those with IgA nephropathy or Henoch-Schoenlein purpura. The anti-GBM group included those with Goodpasture syndrome or anti-GBM glomerulonephritis. The SVV group included those with anti-neutrophilic cytoplasmic antibodies. The SLE group included those with lupus nephritis being the primary cause of their ESKD. We included only recipients who received induction with either a depletional or non-depletional agent and were discharged on tacrolimus and mycophenolate with or without steroid maintenance. Depletional induction was defined as receiving anti-thymocyte globulin or alemtuzumab. Non-depletional induction included recipients of interleukin-2 receptor antagonists (IL-2RA).

Patients were excluded if they received an obsolete agent such as Minnesota anti-lymphocyte globulin or OKT3, no induction (corticosteroids alone), dual induction with depletional and non-depletional or had missing induction data. Recipients who were discharged on any alternative maintenance immunosuppression regimen other than tacrolimus and mycophenolate were excluded.

2.3. Outcomes of Interest

The primary outcomes were ten-year recipient survival and death-censored graft survival (DCGS) according to the type of GN. Additionally, we evaluated the one-year rejection rate by induction type for each GN group.

2.4. Statistical Analysis

Kaplan–Meier curves were generated to examine the primary outcomes of interest in each of the groups separately. Follow-up was censored at ten years. Multivariable Cox proportional hazard models were utilized to investigate the impact of induction regimens and steroid maintenance in each GN group separately. Models were adjusted for recipient and donor age, sex, race, recipient diabetes and peripheral vascular disease, human leukocyte antigen (HLA) matching, pre-transplant dialysis status and duration, donor type, and payor type. To account for between center variability, transplant centers

were included as a random effect. Subjects with missing data for any of the covariates were excluded from the multivariable analysis.

3. Results

3.1. Baseline Characteristics

Overall, the volumes of recipients with glomerulonephritides increased over the study period (Figure 1). Our study cohort consisted of 9176 recipients with IgAN, 5355 recipients with SLE, 1189 recipients with SVV, and 660 anti-GBM recipients. Baseline characteristics of the cohort are listed in Table 1. SLE recipients were younger on average and more likely to be female compared to the other groups. Regarding race, white recipients were predominant among all groups. The largest group of Black recipients was observed in the SLE group constituting 42% (n = 2283). Among the groups, the majority of patients were on dialysis before transplant. Panel reactive antibody (PRA) percentage was higher in the SLE group. In terms of HLA matching, most patients in all groups received a kidney with 4–6 antigen mismatches. Regarding immunosuppression, the majority of patients in all groups received depletional induction and steroid maintenance therapy. The majority of patients with SLE, SVV, and anti-GBM disease were publicly insured. On the contrary, 54.8% of IgAN recipients were privately insured.

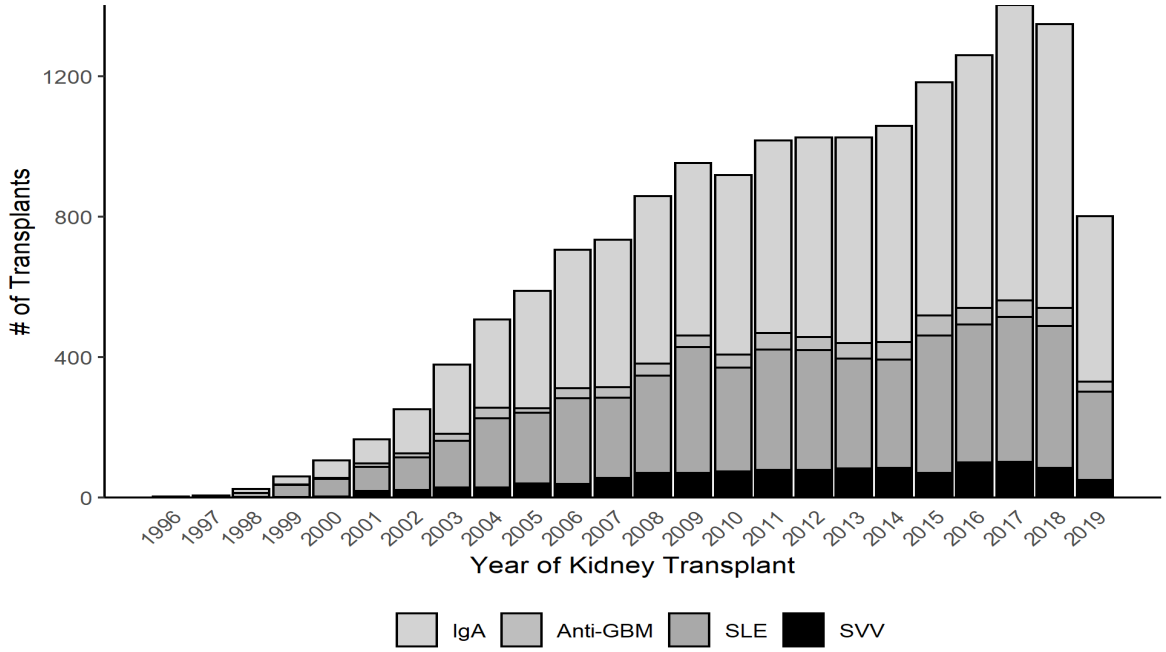

Figure 1. Transplant Number by Glomerulonephritis Type.

Table 1. Baseline Characteristics by Glomerulonephritis Type (N (%) or Mean (SD)).

	IgAN n **= 9176**	**SLE** n **= 5355**	**Anti-GBM** n **= 660**	**SVV** n **= 1189**
Recipient Age in Years	44.61 (12.83)	40.92 (12.23)	49.05 (16.18)	52.45 (15.23)
Recipient Sex (Male)	5910 (64.4)	994 (18.6)	303 (45.9)	680 (57.2)
Recipient Ethnicity				
Black	471 (5.1)	2283 (42.6)	62 (9.4)	91 (7.7)
Other	1994 (21.7)	521 (9.7)	24 (3.6)	44 (3.7)
White	6711 (73.2)	2551 (47.7)	574 (87.0)	1054 (88.6)

Table 1. *Cont.*

	IgAN ***n* = 9176**	**SLE** ***n* = 5355**	**Anti-GBM** ***n* = 660**	**SVV** ***n* = 1189**
Diabetes Mellitus	429 (4.7)	239 (4.5)	38 (5.8)	91 (7.7)
Peripheral Vascular Disease	160 (1.8)	162 (3.1)	12 (1.8)	48 (4.1)
Preemptive Transplant	2368 (25.6)	697 (12.8)	41 (6.2)	195 (16.2)
Dialysis Vintage (years)	2.08 (2.55)	3.64 (3.37)	2.87 (2.28)	2.68 (2.58)
Panel Reactive Antibody	11.87 (23.96)	27.44 (34.44)	17.83 (28.94)	15.07 (27.35)
HLA Antigen Mismatches				
0	716 (7.9)	436 (8.2)	73 (11.1)	94 (7.9)
1–3	2948 (32.4)	1523 (28.6)	221 (33.8)	416 (35.1)
4–6	5437 (59.7)	3369 (63.2)	361 (55.1)	676 (57.0)
Non-Depletional Induction	2613 (28.5)	1319 (24.6)	165 (25.0)	380 (32.0)
Steroid Maintenance Therapy	6093 (66.4)	4225 (78.9)	456 (69.1)	841 (70.7)
Primary Public Payer	4129 (45.2)	3601 (67.5)	429 (65.1)	723 (61.1)
Donor Age in Years	38.60 (14.41)	36.57 (14.61)	40.11 (15.18)	40.69 (14.09)
Donor Sex (Male)	4601 (50.1)	2908 (54.3)	329 (49.8)	564 (47.4)
Donor Race				
Black	610 (6.6)	999 (18.6)	59 (8.9)	87 (7.3)
Other	796 (8.7)	287 (5.4)	12 (1.8)	38 (3.2)
White	7770 (84.7)	4069 (76.0)	589 (89.3)	1064 (89.5)
Donation after Cardiocirculatory Death	792 (8.6)	489 (9.1)	64 (9.7)	111 (9.3)
Donation after Brain Death	3526 (38.4)	2843 (53.1)	276 (41.8)	515 (43.3)
Living Donor	4857 (52.9)	2022 (37.8)	320 (48.5)	563 (47.4)
Cold Ischemia Time [1]	17.14 (8.66)	17.24 (8.53)	18.28 (7.95)	17.74 (8.88)

[1] Cold ischemia time is calculated for deceased donor and set to missing for live donor kidneys. HLA: human leukocyte antigen, IgAN: IgA Nephropathy, SLE: systemic lupus erythematosus, Anti-GBM: anti-glomerular basement membrane, SVV: small vessel vasculitis.

The 10-year recipient (Figure 2) and kidney death-censored graft survival (Figure 3) varied between recipients by GN type. Recipients with SLE glomerulonephritis had the poorest graft survival compared to other GN types, whereas SVV recipients had the poorest recipient survival.

3.2. Outcomes of Recipients with IgA Nephropathy

In the univariable analysis (Figure 4), there was no difference in recipient survival or DCGS in patients who received depletional induction or steroid maintenance therapy compared to those who did not.

In the multivariable analysis (Table 2), recipient survival was not associated with induction type (HR 0.83, 95% CI (0.67, 1.03), $p = 0.09$) or steroid maintenance therapy (HR 1.21, 95% CI (0.97, 1.51), $p = 0.08$). DCGS was not associated with induction type (HR 0.98, 95% CI (0.83, 1.15), $p = 0.78$) or steroid maintenance therapy (HR 0.97, 95% CI (0.83, 1.13), $p = 0.66$). As compared to recipients of a zero-antigen mismatched kidney, lower DCGS was observed in those who received a kidney with 1–3 antigen mismatches (HR 1.47, 95% CI (1.08, 1.98), $p = 0.01$) or 4–6 antigen mismatches (HR 1.48, 95% CI (1.11, 1.99), $p = 0.01$). Other predictors of recipient survival and DCGS are reported in Table 2.

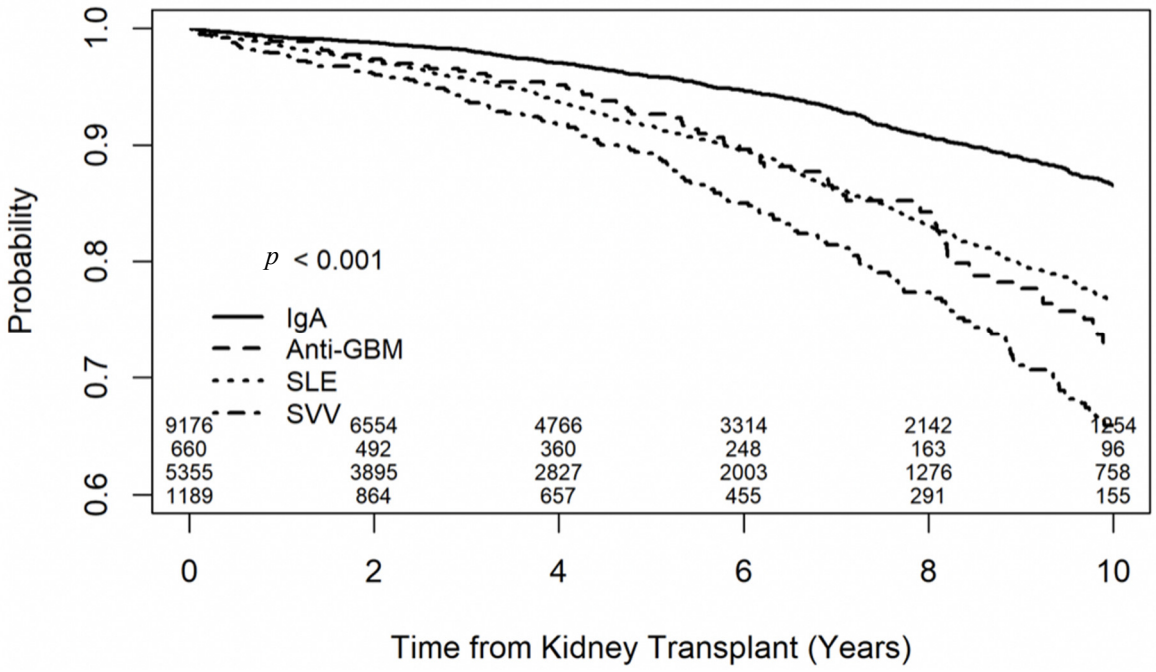

Figure 2. Recipient Survival by Glomerulonephritis Type.

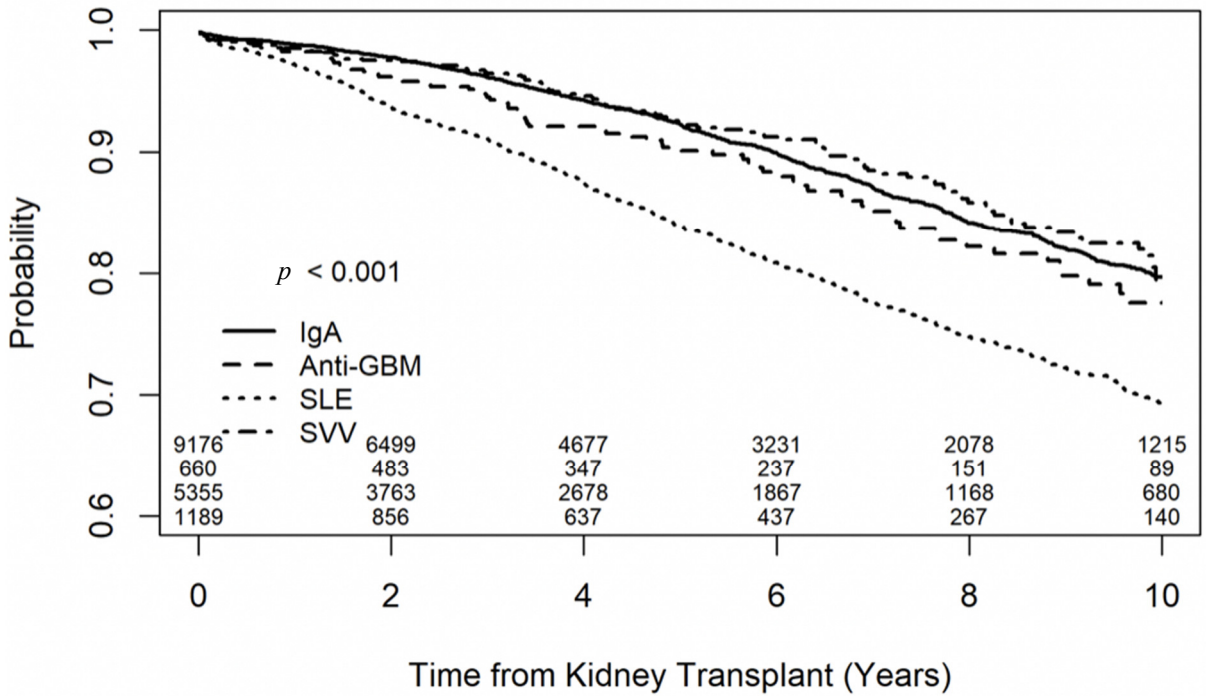

Figure 3. Death-Censored Graft Survival by Glomerulonephritis Type.

3.3. Outcomes of Recipients with SLE-Related Glomerulonephritis

In the univariable analysis (Figure 5), there was no difference in recipient survival in patients who received depletional induction compared to those who did not. Patients managed with steroid maintenance therapy had decreased recipient survival compared to those who did not (overall log-rank $p = 0.033$). In terms of graft survival, DCGS was not associated with induction type or steroid maintenance.

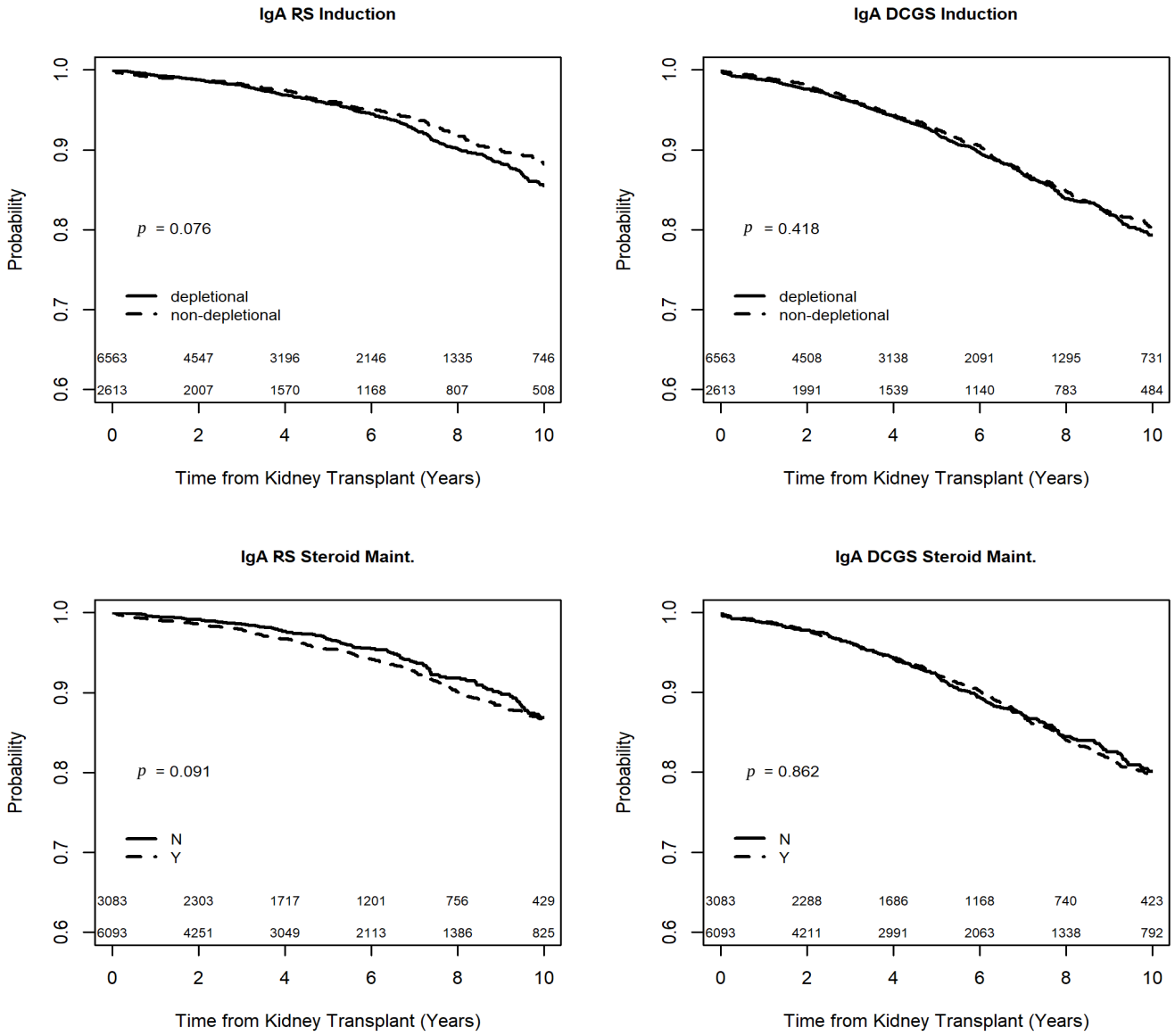

Figure 4. Univariable Kaplan–Meier Estimates of Recipient Survival (RS) and Death-Censored Graft Survival (DCGS) by Induction Type and Steroid Maintenance in IgAN.

Table 2. Multivariable Cox Proportional Hazards Models for Recipient and Death-Censored Graft Survival in IgA Nephropathy.

Variable	Recipient Survival			Graft Survival		
	HR	**95% Confidence Interval**	***p*-Value**	**HR**	**95% Confidence Interval**	***p*-Value**
Non-Depletional Induction	0.83	(0.67, 1.03)	0.09	0.98	(0.83, 1.15)	0.78
Steroid Maintenance	1.21	(0.98, 1.51)	0.08	0.97	(0.83, 1.13)	0.66
HLA Antigen Mismatches						
0	Ref			Ref		
1–3	1.41	(0.94, 2.11)	0.10	1.47	(1.08, 1.98)	0.01
4–6	1.26	(0.85, 1.87)	0.24	1.48	(1.11, 1.99)	0.01
Recipient Age (Year)	1.06	(1.05, 1.07)	<0.001	0.97	(0.96, 0.97)	<0.001
Recipient Sex (Male)	1.33	(1.07, 1.64)	0.01	0.85	(0.74, 0.99)	0.03

Table 2. *Cont.*

Variable	Recipient Survival			Graft Survival		
	HR	**95% Confidence Interval**	***p*-Value**	**HR**	**95% Confidence Interval**	***p*-Value**
Recipient Race						
Black	Ref			Ref		
Other	0.61	(0.38, 0.98)	0.04	0.37	(0.28, 0.50)	<0.001
White	1.04	(0.69, 1.57)	0.85	0.58	(0.45, 0.75)	<0.001
Diabetes Mellitus	1.65	(1.22, 2.22)	0.001	1.60	(1.15, 2.23)	0.005
Pre-Transplant Dialysis	1.71	(1.30, 2.27)	<0.001	1.44	(1.17, 1.78)	0.001
Dialysis Vintage (per year)	1.06	(1.02, 1.10)	0.004	1.02	(0.98, 1.06)	0.28
Deceased Donor Kidney	1.27	(1.01, 1.61)	0.04	1.69	(1.42, 2.02)	<0.001
Peripheral Vascular Disease	2.05	(1.24, 3.39)	0.005	1.75	(1.03, 2.98)	0.04
Donor Age (Year)	1.00	(0.99, 1.01)	0.43	1.01	(1.01, 1.02)	<0.001
Donor Sex (Male)	0.83	(0.69, 1.00)	0.053	0.69	(0.60, 0.80)	<0.001
Donor Race						
Black	Ref			Ref		
Other	0.67	(0.37, 1.21)	0.18	0.98	(0.65, 1.47)	0.92
White	0.84	(0.60, 1.18)	0.32	1.02	(0.78, 1.34)	0.89
Public Primary Payor	1.39	(1.13, 1.72)	0.002	1.17	(0.99, 1.38)	0.06

HLA: human leukocyte antigen.

In the multivariable analysis (Table 3), recipient survival was not associated with induction type (HR 1.04, 95% CI (0.86, 1.26), $p = 0.69$) or steroid maintenance therapy (HR 1.24, 95% CI (0.99, 1.57), $p = 0.07$). DCGS was not associated with induction type (HR 0.90, 95% CI (0.76, 1.06), $p = 0.21$) or steroid maintenance therapy (HR 1.01, 95% CI (0.85, 1.21), $p = 0.91$). Recipients of a kidney with 1–3 antigen mismatches had improved survival when compared to those who received a zero-antigen mismatched kidney (HR 0.71, 95% CI (0.52, 0.98), $p = 0.04$). There was no difference in recipient survival in patients who received a zero-antigen mismatched kidney compared to those who received a kidney with 4–6 antigen mismatches (HR 0.80, 95% CI (0.60, 1.06), $p = 0.12$). Additional predictors of recipient survival and DCGS are included in Table 3.

3.4. Outcomes of Recipients with Anti-GBM Glomerulonephritis

In the univariable analysis (Figure 6), there was no difference in recipient survival or DCGS in patients who received depletional induction or steroid maintenance therapy compared to those who did not.

In the multivariable analysis (Table 4), recipient survival was not associated with induction type (HR 1.11, 95% CI (0.62, 1.98), $p = 0.73$) or steroid maintenance therapy (HR 1.19, 95% CI (0.66, 2.16), $p = 0.56$). DCGS was not associated with induction type (HR 0.73, 95% CI (0.40, 1.31), $p = 0.29$) or steroid maintenance therapy (HR 1.03, 95% CI (0.60, 1.77), $p = 0.91$). Recipients of a zero-antigen mismatched kidney had improved survival compared to those who received a kidney with 4–6 antigen mismatches (HR 2.77, 95% CI (1.10, 6.91), $p = 0.03$). Other predictors of recipient survival and DCGS are included in Table 4.

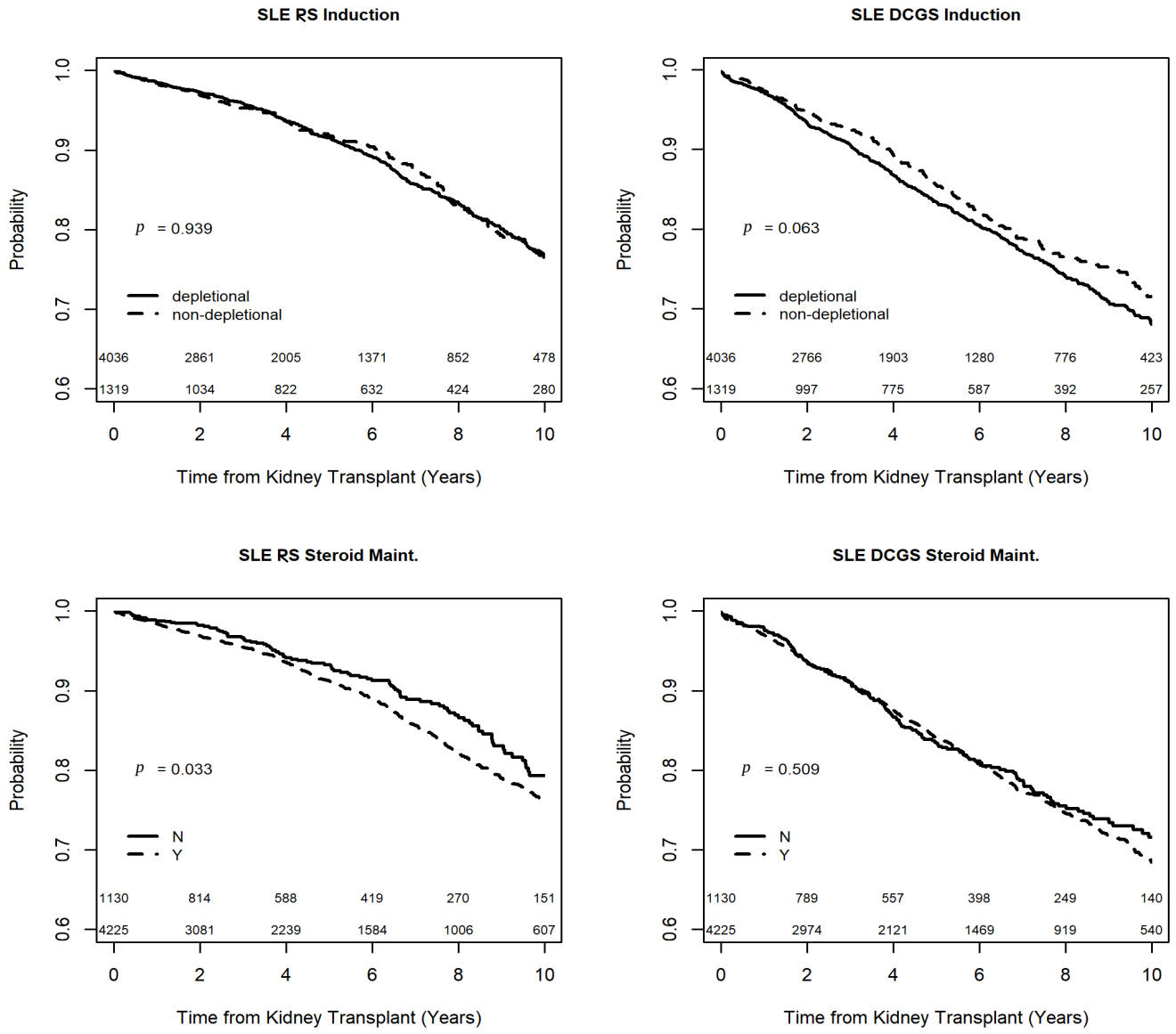

Figure 5. Univariable Kaplan–Meier Estimates of Recipient Survival (RS) and Death-Censored Graft Survival (DCGS) by Induction Type and Steroid Maintenance in SLE Related Glomerulonephritis.

Table 3. Multivariable Cox Proportional Hazards Models for Recipient Survival and Death-Censored Graft Survival in SLE Related Glomerulonephritis.

Variable	Recipient Survival			Graft Survival		
	HR	**95% Confidence Interval**	***p*-Value**	**HR**	**95% Confidence Interval**	***p*-Value**
Non-Depletional Induction	1.04	(0.86, 1.26)	0.69	0.90	(0.76, 1.06)	0.21
Steroid Maintenance	1.24	(0.99, 1.57)	0.07	1.01	(0.85, 1.21)	0.91
HLA Antigen Mismatches						
0	Ref			Ref		
1–3	0.71	(0.52, 0.98)	0.04	1.13	(0.85, 1.51)	0.39
4–6	0.80	(0.60, 1.06)	0.12	1.11	(0.84, 1.46)	0.46
Recipient Age (Year)	1.03	(1.02, 1.04)	<0.001	0.95	(0.95, 0.96)	<0.001
Recipient Sex (Male)	1.39	(1.13, 1.70)	0.002	1.30	(1.11, 1.54)	0.002

Table 3. *Cont.*

Variable	Recipient Survival			Graft Survival		
	HR	**95% Confidence Interval**	***p*-Value**	**HR**	**95% Confidence Interval**	***p*-Value**
Recipient Race						
Black	Ref			Ref		
Other	0.61	(0.41, 0.92)	0.02	0.54	(0.40, 0.73)	<0.001
White	0.98	(0.81, 1.19)	0.82	0.63	(0.53, 0.74)	<0.001
Diabetes Mellitus	1.51	(1.1, 2.09)	0.01	1.08	(0.74, 1.59)	0.68
Pre-transplant Dialysis	1.54	(1.1, 2.14)	0.01	1.41	(1.07, 1.86)	0.02
Dialysis Vintage (per year)	1.01	(0.99, 1.04)	0.34	0.99	(0.97, 1.02)	0.55
Deceased Donor Kidney	1.42	(1.13, 1.78)	0.003	1.62	(1.34, 1.95)	<0.001
Peripheral Vascular Disease	1.54	(1.03, 2.30)	0.04	1.11	(0.72, 1.72)	0.64
Donor Age (Year)	1.01	(1.01, 1.02)	<0.001	1.02	(1.01, 1.02)	<0.001
Donor Sex (Male)	0.93	(0.78, 1.10)	0.37	0.95	(0.83, 1.10)	0.50
Donor Race						
Black	Ref			Ref		
Other	0.65	(0.37, 1.14)	0.14	0.89	(0.60, 1.32)	0.55
White	0.87	(0.69, 1.10)	0.25	0.90	(0.74, 1.08)	0.24
Public Primary Payor	1.31	(1.06, 1.61)	0.01	1.07	(0.91, 1.26)	0.43

HLA: human leukocyte antigen.

3.5. Outcomes of Recipients with SVV

In the univariable analysis (Figure 7), there was no difference in recipient survival in patients who received depletional induction or steroid maintenance therapy compared to those who did not. Patients who received non-depletional induction had improved DCGS compared with those who received depletional induction (overall log-rank $p = 0.042$). There was no difference in DCGS in patients who received steroid maintenance therapy compared to those who did not.

In the multivariable analysis (Table 5), recipient survival was not associated with induction type (HR 0.96, 95% CI (0.70, 1.32), $p = 0.80$) or steroid maintenance therapy (HR 0.91, 95% CI (0.66, 1.25), $p = 0.56$). DCGS was not associated with induction type (HR 0.64, 95% CI (0.40, 1.04), p 0.07) or steroid maintenance therapy (HR 0.88, 95% CI (0.56, 1.38), $p = 0.57$). There was improved DCGS in patients who received a zero-antigen mismatched kidney compared to those who received a kidney with 1–3 antigen mismatches (HR 5.29, 95% CI (1.24, 22.47), $p = 0.02$) or 4–6 antigen mismatches (HR 6.13, 95% CI (1.48, 25.45), $p = 0.01$). Older recipient age was associated with lower recipient survival but superior DCGS. However, older donor age was a negative predictor of DCGS.

3.6. Secondary Outcomes

There was a statistically higher incidence of rejection in the first year among patients with SLE who received depletional induction ($n = 366$ (11.1%) vs. $n = 79$ (8.4%), $p = 0.020$). Among patients with IgAN, anti-GBM, and SVV, there were no significant differences between groups regarding rejection. Further details are in Supplementary Table S1.

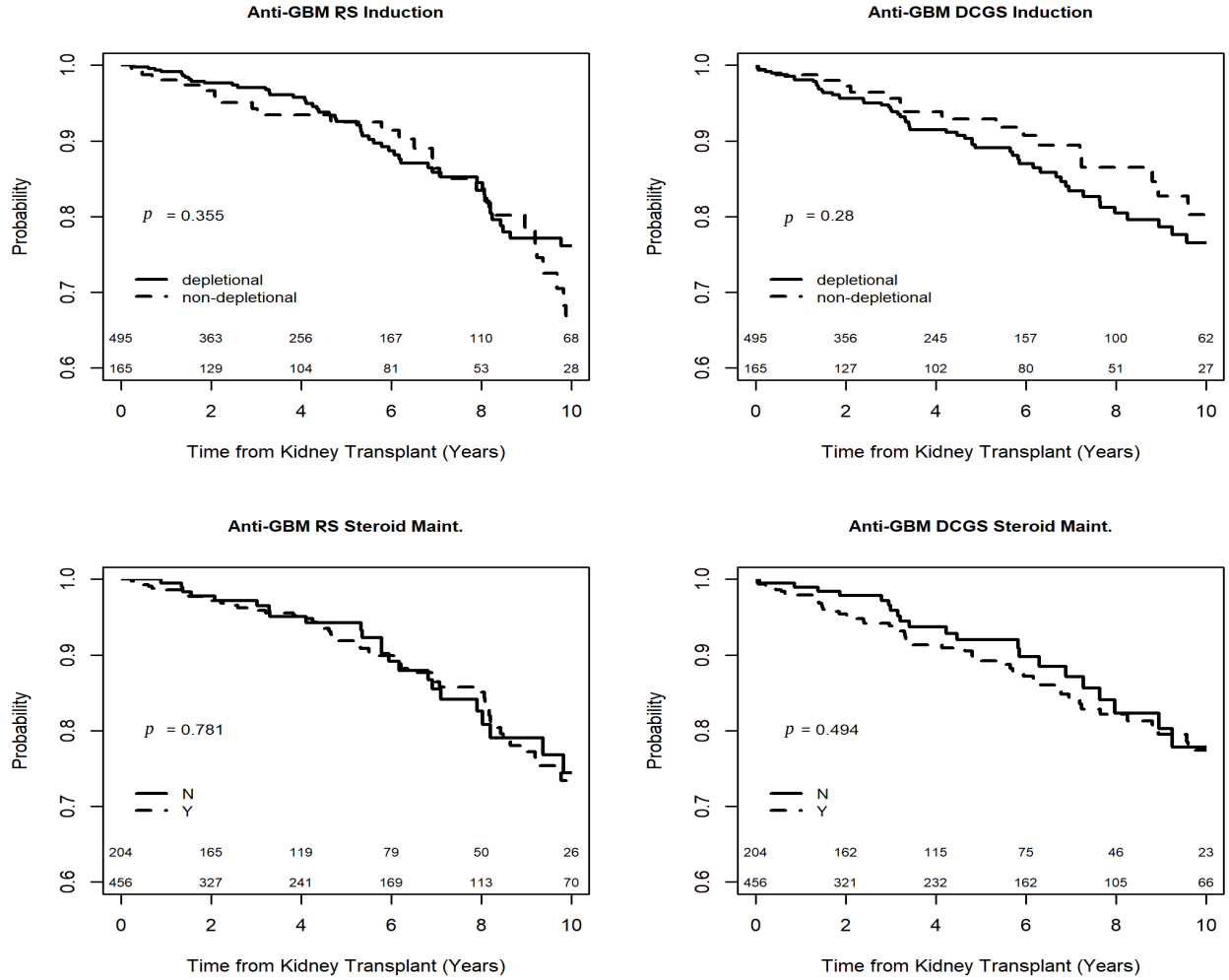

Figure 6. Univariable Kaplan–Meier Estimates of Recipient Survival (RS) and Death-Censored Graft Survival (DCGS) by Induction Type and Steroid Maintenance in anti-GBM Glomerulonephritis.

Table 4. Multivariable Cox Proportional Hazards Models for Recipient Survival and Death-Censored Graft Survival in anti-GBM Glomerulonephritis.

Variable	Recipient Survival			Graft Survival		
	HR	**95% Confidence Interval**	***p*-Value**	**HR**	**95% Confidence Interval**	***p*-Value**
Non-Depletional Induction	1.11	(0.62, 1.98)	0.73	0.73	(0.40, 1.31)	0.29
Steroid Maintenance	1.19	(0.66, 2.16)	0.56	1.03	(0.60, 1.77)	0.91
HLA Antigen Mismatches						
0	Ref			Ref		
1–3	1.70	(0.63, 4.61)	0.30	1.41	(0.58, 3.42)	0.45
4–6	2.77	(1.11, 6.91)	0.03	1.37	(0.60, 3.15)	0.46
Recipient Age (Year)	1.04	(1.02, 1.06)	<0.001	0.96	(0.95, 0.98)	<0.001
Recipient Sex (Male)	1.29	(0.77, 2.18)	0.33	0.98	(0.61, 1.59)	0.95
Recipient Race						
Black	Ref			Ref		
Other	0.37	(0.04, 3.95)	0.41	0.23	(0.03, 1.90)	0.17
White	2.70	(0.78, 9.34)	0.12	0.68	(0.31, 1.50)	0.34
Diabetes Mellitus	1.32	(0.57, 3.07)	0.51	0.38	(0.05, 2.77)	0.34
Pre-Transplant Dialysis	0.88	(0.29, 2.66)	0.82	0.78	(0.31, 1.97)	0.60

Table 4. *Cont.*

Variable	Recipient Survival			Graft Survival		
	HR	**95% Confidence Interval**	***p*-Value**	**HR**	**95% Confidence Interval**	***p*-Value**
Dialysis Vintage (per year)	1.05	(0.93, 1.18)	0.42	1.02	(0.91, 1.15)	0.70
Deceased Donor Kidney	1.67	(0.90, 3.08)	0.10	1.86	(1.04, 3.31)	0.04
Peripheral Vascular Disease	0.77	(0.10, 6.07)	0.80	Data Missing		
Donor Age (Year)	1.00	(0.99, 1.02)	0.78	1.02	(1.01, 1.04)	0.01
Donor Sex (Male)	0.96	(0.57, 1.63)	0.89	0.66	(0.40, 1.09)	0.10
Donor Race						
Black	Ref			Ref		
Other	0.76	(0.08, 7.07)	0.81	Data Missing		
White	1.29	(0.51, 3.27)	0.60	Data Missing		
Public Primary Payor	1.31	(1.06, 1.61)	0.01	1.88	(1.04, 3.41)	0.04

HLA: human leukocyte antigen.

Table 5. Multivariable Cox Proportional Hazards Models for Recipient Survival and Death-Censored Graft Survival in SVV.

Variable	Recipient Survival			Graft Survival		
	HR	**95% Confidence Interval**	***p*-Value**	**HR**	**95% Confidence Interval**	***p*-Value**
Non-Depletional Induction	0.96	(0.70, 1.32)	0.80	0.64	(0.40, 1.04)	0.07
Steroid Maintenance	0.91	(0.66, 1.25)	0.56	0.88	(0.56, 1.38)	0.57
HLA Antigen Mismatches						
0	Ref			Ref		
1–3	1.01	(0.54, 1.90)	0.97	5.29	(1.24, 22.47)	0.02
4–6	1.24	(0.69, 2.25)	0.47	6.13	(1.48, 25.45)	0.01
Recipient Age (Year)	1.04	(1.03, 1.05)	<0.001	0.98	(0.96, 0.99)	0.001
Recipient Sex (Male)	1.04	(0.77, 1.41)	0.81	0.80	(0.53, 1.21)	0.29
Recipient Race						
Black	Ref			Ref		
Other	0.40	(0.11, 1.48)	0.17	1.03	(0.30, 3.58)	0.97
White	0.81	(0.44, 1.49)	0.49	0.96	(0.43, 2.17)	0.92
Diabetes Mellitus	1.52	(0.98, 2.34)	0.06	1.73	(0.90, 3.32)	0.10
Pre-Transplant Dialysis	1.60	(0.89, 2.87)	0.12	1.65	(0.80, 3.38)	0.17
Dialysis Vintage (per year)	1.06	(0.99, 1.13)	0.10	0.98	(0.88, 1.09)	0.65
Deceased Donor Kidney	1.02	(0.71, 1.47)	0.93	1.37	(0.81, 2.32)	0.24
Peripheral Vascular Disease	1.08	(0.49, 2.40)	0.84	0.73	(0.17, 3.05)	0.66
Donor Age (Year)	1.005	(0.995, 1.02)	0.30	1.02	(1.00, 1.03)	0.04
Donor Sex (Male)	0.85	(0.63, 1.16)	0.31	1.26	(0.83, 1.92)	0.28
Donor Race						
Black	Ref			Ref		
Other	1.03	(0.36, 2.92)	0.96	1.69	(0.43, 6.60)	0.45
White	0.76	(0.46, 1.26)	0.29	1.20	(0.51, 2.82)	0.67
Public Primary Payor	1.26	(0.88, 1.82)	0.21	0.97	(0.61, 1.53)	0.88

HLA: human leukocyte antigen.

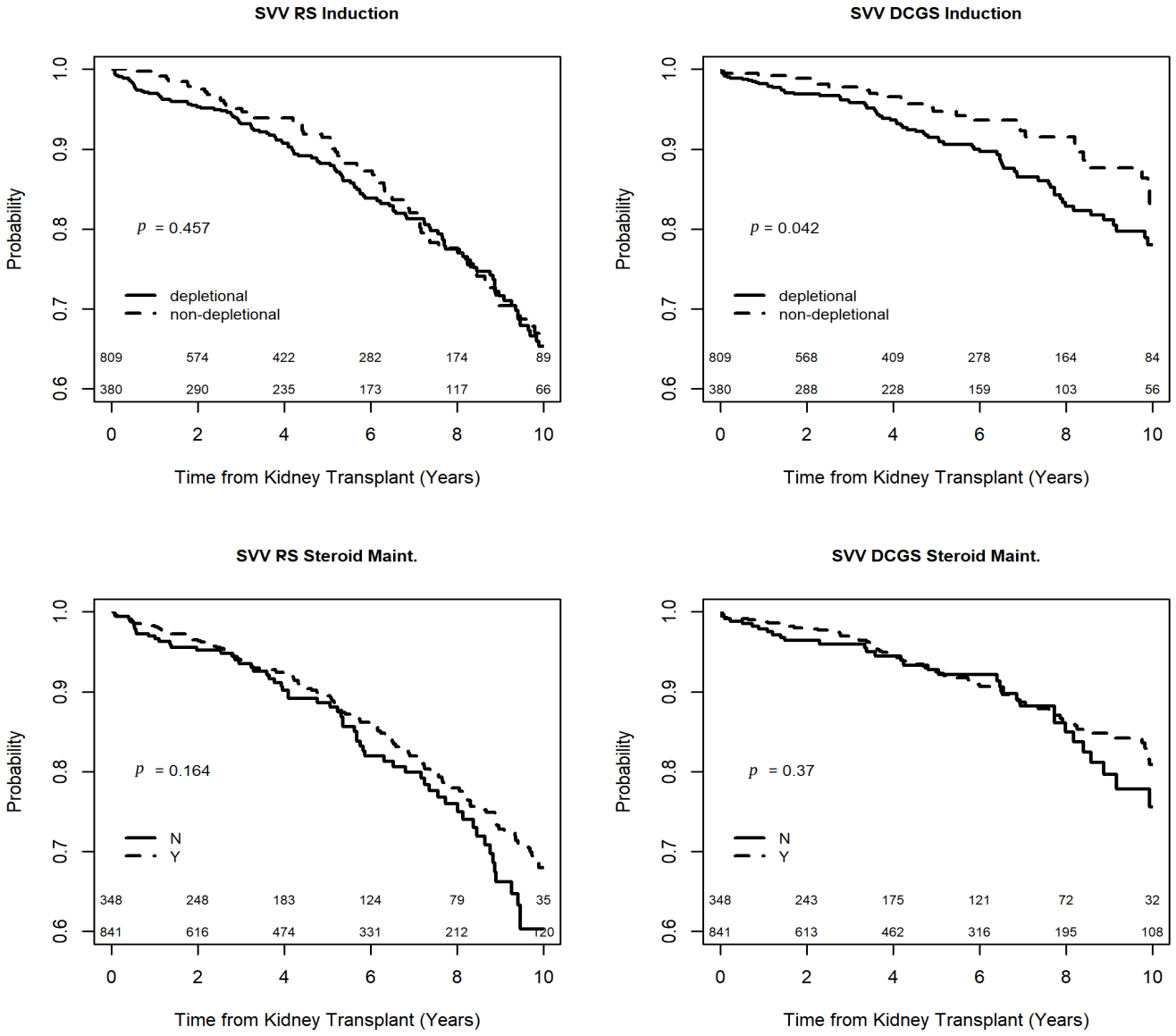

Figure 7. Univariable Kaplan–Meier Estimates of Recipient Survival (RS) and Death-Censored Graft Survival (DCGS) by Induction Type and Steroid Maintenance in SVV.

4. Discussion

In this comprehensive study of 16,380 transplant recipients whose etiology of ESKD was either IgAN, SLE, SVV, or anti-GBM disease, we examined the association between induction type and steroid maintenance on recipient survival and DCGS with contemporary immunosuppression maintenance. Our findings suggest depletional induction and steroid maintenance therapy do not improve recipient survival or DCGS compared to non-depletional induction and steroid-free maintenance immunosuppressive therapy.

Transplant programs worldwide have differing approaches to induction immunosuppression and steroid maintenance therapy based on patient characteristics. Previous studies looking at the use of depletional agents have shown them to reduce the risk of early acute rejection, particularly in highly-sensitized recipients [7,8]. However, the long-term recipient and graft outcomes are comparable between IL-2RA and depletional induction agents [9]. Overall, more patients received depletional induction than non-depletional induction in our cohort. It is unclear if this is due to transplant program practice variability or if clinicians view GN patients as having a higher immunologic risk. Viewing GN patients as having a higher immunologic risk may not take functional immune exhaustion or the

cumulative effect of previous immunosuppression into account. Immune exhaustion and senescence are complex processes that lead to a state of dysfunctional T cells where patients are more susceptible to viral infections, have reduced tumor surveillance, and have an impaired antibody response to stimulatory factors [3]. Thus, it may be prudent to factor in the risk of immune exhaustion and replicative senescence in GN patients when choosing an induction agent.

Our results suggest no added benefit to using depletional agents in the studied GN populations, which echoes previous results on the role of induction use in transplant recipients at risk for immune system exhaustion, such as those receiving kidneys after non-renal solid organ transplants [10–12]. Additionally, among SLE recipients who received depletional induction, there was an increased incidence of rejection in the first year. Moreover, a trend towards more frequent graft loss due to GN recurrence was observed in recipients of depletional induction (Supplementary Table S1). Although the etiology of these findings is uncertain, it may be related to possible over immunosuppression and leukopenia typically associated with depletional agents, which may require a reduction in immunosuppression or the use of granulocyte colony stimulating factor (G-CSF), increasing the risk of rejection and graft loss [13, 14]. Another theoretical mechanism is the loss of regulatory T cells (Tregs) with depletional induction. Previous data have shown that depletional induction can result in the depletion of Tregs [15,16]. In addition to their role in graft tolerance, Tregs may play an essential role in GN disease remission by counteracting the immune response and ameliorating nephritis [17]. Nonetheless, the finding of increased rejection associated with depletional induction was not seen in the other three GNs. Further research into potential reasons for the higher rejection rate in SLE nephritis associated with depletional induction would be beneficial.

Concerning corticosteroids, conflicting data exist on the role of steroid-free maintenance therapy in GN recipients. A previous study has shown increased GN recurrence with rapid steroid discontinuation [5]. However, additional studies have shown no increase in graft loss with steroid-free regimens [18]. Overall, in the United States, about one-third of kidney recipients are discharged on a steroid-free regimen. Between 2000 and 2006, the number of patients on a steroid-free regimen at discharge after transplant increased from 3% to 32% [19,20]. The adverse effects of long-term corticosteroids are well documented. However, given that a steroid-free regimen is associated with a slightly increased risk of acute rejection and conflicting long-term outcomes, many clinicians continue to use steroid maintenance in the United States. In our cohort of GN patients, the use of corticosteroids as part of immune suppression maintenance did not result in a significant difference in patient survival or DCGS. Our findings complement those of Leeaphorn et al.: similar to recipients with IgA nephropathy, recipients with other GNs had no improvement in recipient or overall graft survival associated with steroid maintenance [21]. Of note, in their adjusted analysis, steroid maintenance was associated with less graft loss due to IgA recurrence. However, they did not adjust for induction type, which has been shown to influence disease recurrence [22,23]. Since GN patients may have had considerable steroid exposure before transplantation to manage their native disease, utilizing a steroid-free regimen is appealing and should be considered.

Additional findings of interest include that among all four groups, older recipient age was associated with improved DCGS. As humans age, they develop a relative state of immune deficiency due to multiple mechanisms, including reduced signaling and proliferation of lymphocytes in response to an antigen [24], which may have contributed to the improved DCGS.

Similar to the outcome of publicly insured kidney recipients in general, recipients with IgAN, SLE, and anti-GBM had decreased recipient survival compared to their privately insured counterparts [25]. It will be of interest to reassess this association in the future, particularly after implementation of the recently approved lifetime immunosuppression drug coverage bill [26].

Strengths and Limitations

Our study is one of the most extensive studies of the effect of induction regimens and steroid maintenance in primary kidney recipients with different glomerulonephritides.

Compared to a single-center database, the SRTR database offered a large sample size. Additionally, we chose definitive endpoints, which allowed for robust multivariable analyses.

However, our study must be interpreted with several limitations in mind. As with all registry studies, inconsistency in center reporting patterns may have led to missing or incomplete data. Moreover, despite adjusting for the transplant year and the variabilities within and between centers, we may not have fully accounted for residual confounders, including the era effect. Although we reported the proportions of graft loss due to recurrent disease, we could not analyze overall disease recurrence as it is only captured if recurrence resulted in graft loss.

The lack of measured drug levels meant that we could not analyze or account for exposure levels of maintenance immunosuppression. Additionally, due to a lack of complete follow-up data, we could not evaluate the effect of induction immunosuppression on long-term infection, post-transplant lymphoproliferative disorders, or malignancies. Unfortunately, laboratory assessment of immune system function is not possible in the retrospective SRTR database due to the lack of a biorepository.

5. Conclusions

In this large cohort of transplant recipients with IgAN, SLE, anti-GBM, and SVV, depletional induction did not result in superior graft or recipient outcomes. Moreover, there was a significantly greater rejection rate in SLE associated with depletional induction. Additionally, steroid maintenance therapy did not result in superior outcomes compared to steroid avoidance. Therefore, a history of glomerulonephritis should not exclude patients from steroid-free immunosuppression maintenance. Ultimately, our findings provide an opportunity for recipients with a history of GN to receive a more tailored immunosuppression regimen, considering their risk of functional immune system exhaustion.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/transplantology3010007/s1, Table S1: Incident graft rejection, PTLD, graft loss due to recurrence, and death due to infection or malignancy by induction type (N %).

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