

Original Articles

Differences in initial treatment modality for end-stage renal disease among glomerulonephritis subtypes in the USA

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ABSTRACT

Background. Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD), while peritoneal dialysis affords certain benefits over hemodialysis. Distributions and determinants of first ESRD treatment modality have not been compared across glomerulonephritis (GN) subtypes.

Methods. We identified all adult (18–75 years) patients with ESRD attributed to any of six GN subtypes [focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranous nephropathy (MN), membranoproliferative GN (MPGN), lupus nephritis (LN) and vasculitis] who were first registered in the US Renal Data System (USRDS) between 1996 and 2011. We used multinomial logistic regression—adjusting for temporal, geographic, demographic, socioeconomic and comorbid factors—to determine odds ratios (ORs) with 95% confidence intervals (CIs) for transplantation versus hemodialysis, and for peritoneal dialysis versus hemodialysis, comparing other GN subtypes to IgAN.

Results. Among the 75 278 patients studied, patients with comparator GN subtypes were significantly less likely than those with IgAN to receive either transplantation or peritoneal dialysis. After adjusting for potentially confounding covariates, patients with comparator primary GN subtypes (FSGS, MN, MPGN) were at least as likely to receive transplantation [FSGS OR 0.98 (95% CI 0.93–1.15), MN OR 1.19 (95% CI 1.01–1.39), MPGN OR 1.08 (95% CI 0.93–1.26)] or peritoneal dialysis [FSGS OR 1.05 (95% CI 0.98–1.12), MN OR 1.30 (95% CI 1.18–1.43), MPGN OR 0.95 (95% CI 0.85–1.06)] as patients with IgAN. Conversely, patients with the secondary GN subtypes LN and vasculitis remained significantly less likely to receive either modality [transplantation OR 0.49 (95% CI 0.43–

0.56) for LN and 0.27 (95% CI 0.22–0.34) for vasculitis, peritoneal dialysis OR 0.76 (95% CI 0.70–0.82) for LN and 0.54 (95% CI 0.48–0.60) for vasculitis].

Conclusions. Significant differences in ESRD treatment practice patterns are apparent among GN subtypes. To ensure equitable care for all patients, regardless of GN subtype, reasons for observed disparities should be elucidated and—if appropriate—eliminated.

Keywords: clinical epidemiology, dialysis modality, end-stage renal disease, glomerulonephritis, kidney transplantation

INTRODUCTION

Collectively, glomerulonephritides (GN) constitute the third leading cause of end-stage renal disease (ESRD) in the USA [1]. Once ESRD develops, three active treatment options are available: hemodialysis, peritoneal dialysis and kidney transplantation. Among these, kidney transplantation is considered the optimal approach: compared with hemodialysis or peritoneal dialysis, it prolongs survival [2, 3], reduces morbidity [4] and improves quality of life [5], particularly as a first ESRD treatment (i.e. preemptive kidney transplantation) [6–8]. Patients with ESRD attributed to GN also derive a survival benefit from kidney transplantation, which is at least comparable to the magnitude of benefit observed in other causes of ESRD [2, 9–11]. Among dialysis modalities, survival with peritoneal dialysis and hemodialysis is similar overall [12], including in patients with ESRD due to GN [13–15]. However, peritoneal dialysis offers certain advantages over hemodialysis, including reduced early mortality [16], better patient satisfaction [17, 18] and a lower infection risk [19]. Peritoneal dialysis is also a better

value [20], costing Medicare an average of \$16 315 less per patient per year than hemodialysis [1].

Investigators examining access to ESRD treatments have identified important demographic and socioeconomic factors influencing ESRD treatment modality distributions. Patient age [21–25], sex [21], race [21–23, 25, 26], Hispanic ethnicity [27, 28], insurance payer [7, 29], employment status [23, 25] and neighborhood poverty [22, 30] have all been found to independently associate with access to kidney transplantation and/or peritoneal dialysis. Little is known, however, regarding determinants of initial ESRD treatment modality in patients with GN, nor have differences across GN subtypes been determined. We recently identified strong associations between GN subtype and patient survival after ESRD therapy initiation in the USA [31]. We further observed that ESRD treatment modality differences partially explained survival disparities. However, we did not systematically compare modality distributions across GN subtypes, nor examine determinants of ESRD treatment modality using rigorous statistical methods. Elucidating such information might identify nonuniform practice patterns warranting further consideration by physicians, researchers and policymakers aiming to achieve equitable care for all patients, regardless of their underlying cause of ESRD.

In this study, we sought to compare initial ESRD treatment modality distributions across GN subtypes in the treated US ESRD population. After accounting for temporal, geographic, demographic, socioeconomic and comorbidity imbalances between groups, we hypothesized that GN subtype would independently associate with initial ESRD therapy. Specifically, we anticipated that patients with the secondary GN subtypes lupus nephritis (LN) and vasculitis (who may experience a more rapid progression to ESRD or a higher systemic illness burden at ESRD onset) would be less likely to receive either a kidney transplant or peritoneal dialysis as a first ESRD treatment modality than patients with renal-limited primary GN subtypes.

MATERIALS AND METHODS

Study population

We identified all adult (18–75 years) patients who initiated ESRD treatment and were registered in the US Renal Data System (USRDS) between 1 January 1996 and 31 December 2011 with ESRD attributed to one of four primary GN subtypes [focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranous nephropathy (MN) and membranoproliferative GN (MPGN)] or two secondary GN subtypes (LN and vasculitis). Missing or uncertain cause of ESRD or a defined cause other than one of these six GN subtypes were the only exclusion criteria.

Data sources

The USRDS is a national registry that collects demographic, clinical and treatment-related information regarding virtually all patients receiving ESRD treatment in the USA. Baseline data are largely derived from Medical Evidence Reports (MERs) submitted by nephrologists, by federal mandate, within 45 days of a patient starting a new ESRD treatment. For this study, data

regarding GN subtype, date and modality of first ESRD treatment, demographic characteristics, insurance payer, employment status, residential zip code, comorbidities and baseline laboratory values were extracted from USRDS Patients and MedEvid files. To better characterize socioeconomic status, residential zip codes (or dialysis facility zip code if residential zip code was missing) were matched to year 2000 US census data to obtain neighborhood-level socioeconomic variables.

Exposures, outcomes and covariates

Primary exposure. GN subtype was defined as the cause of ESRD cited in patients' first MERs. The sensitivity of this measure for detection of GN subtype is poor overall, but specificity is excellent, with a reported false-positive rate of <2% [32].

Outcomes. The first ESRD treatment modality (transplantation, peritoneal dialysis or hemodialysis) was the primary study outcome. Transplantation was defined as deceased or living donor kidney transplantation performed on the same day as a patient's first ESRD treatment.

Covariates. Variables that might potentially confound exposure–outcome associations were considered a priori and grouped into clinically meaningful categories: temporal (year of first ESRD treatment); geographic [region of residence in the USA (Northeast, Midwest, South or West)]; demographic [age, sex, race (white, black, Asian, other), Hispanic ethnicity (yes/no)]; patient-level socioeconomic [insurance payer (Medicare, Medicaid, Veterans Administration, employer group, other) and employment status (employed/unemployed)]; neighborhood-level socioeconomic status [percent below poverty line, percent with less than a high school education, percent unemployment, median household income, median rent]; and clinical, including comorbidities (diabetes, heart failure, coronary heart disease, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease, current smoking, cancer, peripheral vascular disease and inability to ambulate), body mass index (BMI, kg/m²) and laboratory values reported at ESRD treatment initiation [albumin, hemoglobin, serum creatinine and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula [33]].

Statistical analyses

We used cross tabulation and distribution plots to examine unadjusted differences in baseline characteristics across GN subtypes. Categorical variables were summarized as frequencies and proportions. Continuous variables were summarized as medians and interquartile ranges or as means and standard deviations, as appropriate.

Relative log odds of transplantation versus hemodialysis and peritoneal dialysis versus hemodialysis were compared between GN subtypes using multinomial logistic regression. IgAN was the exposure reference group; dummy variables were assigned to comparator GN subtypes. To account for confounding, we sequentially added groups of covariates to regression models: first temporal and geographic (Model 1), then demographic (Model 2), then patient-level and neighborhood-level socioeconomic (Model 3) and finally clinical, including

comorbidities, laboratory variables and BMI (Model 4). Due to high collinearity between the variables serum creatinine and eGFR, only the former was retained in statistical models. Squared terms were included for continuous variables (age, BMI, albumin, hemoglobin and creatinine) based on the statistical significance of the squared term in logistic models.

Missing data

The proportion of variables with missing data ranged from <0.1% (age, sex and race) to 23.0% (serum albumin). A total of 32.2% of patients had at least one variable missing. We assumed data to be missing at random and used a fully conditional specification approach [34, 35] to obtain 30 imputed data sets [36]. The imputation model included all the variables in Model 4. Log odds ratios (ORs) from models applied to each imputation data set were combined using the rules described by Little and Rubin [37] and exponentiated to obtain estimated ORs and corresponding 95% confidence intervals (CIs). As a sensitivity analysis, we also report complete case analysis results, which included only patients with complete outcome and covariate data (67.8% of the total sample).

Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and StataMP version 13 (StataCorp, College Station, TX, USA). An internal review board of the Stanford University School of Medicine approved the study.

RESULTS

Patient characteristics

The final study population comprised 75 278 patients with ESRD due to GN: 30 604 (40.7%) with FSGS, 15 805 (21.0%) with LN, 12 178 (16.2%) with IgAN, 6084 (8.1%) with vasculitis, 6001 (8.0%) with MN and 4606 (6.1%) with MPGN, Table 1. The mean age was 47.0 ± 15.5 years. The study population was 53% male, 61% white and 12% Hispanic. Demographic characteristics differed considerably across GN subtypes: mean age ranged from 40 to 57 years in LN and vasculitis, respectively; male sex ranged from 18 to 68% in LN and IgAN, respectively; and black race ranged from 7 to 50% in IgAN and LN, respectively. Most comorbidities were least common in IgAN and LN. Patients with LN lived in the most socioeconomically disadvantaged neighborhoods, relied most upon Medicaid insurance and had a relatively high prevalence of unemployment.

Treatment modality outcomes

A majority of patients (79.7%) received hemodialysis as their first ESRD treatment modality. By comparison, only 13.8% received peritoneal dialysis and 6.4% received a pre-emptive kidney transplant (Table 2).

In Model 1, which adjusted for region of residence and year of ESRD only, patients with all other primary and secondary GN subtypes were less likely to receive either a transplant or peritoneal dialysis than patients with IgAN (Table 3). Sequentially accounting for demographic, socioeconomic and clinical differences among subtypes (Models 2, 3 and 4, respectively) substantially attenuated ORs for both transplantation and peritoneal dialysis

when comparing all other primary GN subtypes (FSGS, MN and MPGN) to IgAN (Table 3 and Supplementary data, Figure S1). In the fully adjusted model (Model 4), transplantation [OR 1.19 (95% CI 1.01–1.39)] and peritoneal dialysis [OR 1.30 (95% CI 1.18–1.43)] were more likely in MN than in IgAN and were equally as likely in the other primary GN subtypes (FSGS and MPGN) as in IgAN (Table 3 and Figure 1).

For secondary GN subtypes (LN and vasculitis), the odds for transplantation and peritoneal dialysis remained significantly lower than in IgAN, even after adjusting for confounding. In the fully adjusted model (Model 4), ORs for preemptive kidney transplantation were 0.49 (95% CI 0.43–0.56) for LN and 0.27 (95% CI 0.22–0.34) for vasculitis, comparing with IgAN, (Table 3 and Figure 1). Odds ratios for peritoneal dialysis were 0.76 (95% CI 0.70–0.82) and 0.54 (95% CI 0.48–0.60), respectively.

Sensitivity analysis

Analyses of 51 071 patients with complete data for all covariates did not identify any meaningful differences in effect estimates or statistical inferences compared with analyses using multiply imputed data (Supplementary data, Table S1 and Figures S2 and S3).

DISCUSSION

We have demonstrated in a national cohort of 75 278 patients with ESRD attributed to GN that GN subtype independently associates with first ESRD treatment modality. After accounting for temporal, geographic, demographic, socioeconomic and comorbidity differences among GN subtypes, patients with two common secondary GN subtypes—LN and vasculitis—had approximately one-half and one-quarter the odds, respectively, of receiving a preemptive kidney transplant as patients with IgAN. Patients with LN or vasculitis were also significantly less likely to receive peritoneal dialysis. In contrast, patients with comparator primary GN subtypes (FSGS, MN and MPGN) were less likely to receive a kidney transplant or peritoneal dialysis than patients with IgAN in unadjusted analyses only. After adjustment for demographic, socioeconomic and clinical factors previously reported to influence ESRD modality distributions, these differences disappeared and did not appear to independently relate to GN subtype.

These imbalances in initial ESRD treatment modality suggest that approaches to ESRD treatment in patients with GN—rightly or wrongly—differ considerably depending upon GN subtype. We suspect that this finding previously escaped detection in research and public health reporting as patients with GN are conventionally grouped in to a single disease category when examining ESRD practice patterns and outcomes, ignoring potential heterogeneity among subtypes [38]. In a recent study challenging this paradigm, we identified strong and independent associations between GN subtype and mortality in a national ESRD patient cohort [39]. The present study advances upon these findings by focusing on a potentially important, and modifiable, explanation for survival imbalances.

There are several potentially plausible reasons for the reduced access to pre-emptive kidney transplantation we

Table 1. Patient characteristics at initiation of ESRD therapy (transplantation, PD or HD), according to GN subtype, 1996–2011 (n = 75 278)

	Primary GN subtypes				Secondary GN subtypes	
	FSGS	IgAN	MN	MPGN	LN	Vasculitis
	[n = 30 604 (40.7%)]	[n = 12 178 (16.2%)]	[n = 6001 (8.0%)]	[n = 4606 (6.1%)]	[n = 15 805 (21.0%)]	[n = 6084 (8.1%)]
Age (years), mean (SD)	48.1 (15.3)	44.1 (14.2)	54.1 (13.9)	49.6 (15.1)	39.8 (13.9)	57.3 (14.1)
Male sex	18 801 (61.4)	8235 (67.6)	4002 (66.7)	2798 (60.7)	2851 (18.0)	3291 (54.1)
Race						
White	17 173 (56.1)	9144 (75.1)	3999 (66.7)	3391 (73.7)	6735 (42.6)	5299 (87.1)
Black	11 984 (39.2)	823 (6.8)	1735 (28.9)	888 (19.3)	7909 (50.1)	533 (8.8)
Asian	1011 (3.3)	1851 (15.2)	174 (2.9)	216 (4.7)	848 (5.4)	130 (2.1)
Other	432 (1.4)	360 (3.0)	91 (1.5)	107 (2.3)	309 (2.0)	120 (2.0)
Hispanic ethnicity	2658 (9.1)	1527 (13.0)	594 (10.3)	484 (11.0)	2482 (16.3)	600 (10.1)
Insurance payer						
Medicaid	5940 (19.6)	1644 (13.6)	1078 (18.1)	994 (21.8)	5123 (32.6)	809 (13.3)
Medicare	8216 (27.1)	1968 (16.3)	2193 (36.9)	1347 (29.5)	3913 (24.9)	2602 (42.9)
Veterans	528 (1.7)	178 (1.5)	132 (2.2)	118 (2.6)	104 (0.7)	77 (1.3)
Employer group	12 874 (42.4)	6547 (54.2)	2243 (37.7)	1740 (38.1)	5516 (35.1)	2230 (36.8)
Other	5954 (19.6)	2232 (18.5)	1463 (24.6)	954 (20.9)	2491 (15.8)	1745 (28.8)
Employed	8912 (29.4)	5176 (42.8)	1432 (24.1)	1103 (24.2)	3115 (19.8)	1071 (17.7)
Neighborhood characteristics						
Percent below poverty line, mean (SD)	14.0 (9.6)	11.7 (8.6)	13.5 (9.3)	13.1 (9.2)	15.5 (10.1)	12.0 (8.4)
Percent less than high school, mean (SD)	21.5 (11.6)	19.5 (11.8)	21.4 (11.6)	20.6 (11.4)	23.5 (12.7)	19.9 (11.1)
Percent unemployment, mean (SD)	6.7 (4.4)	5.8 (3.9)	6.4 (4.1)	6.3 (4.2)	7.3 (4.6)	5.8 (3.7)
Median household income, mean (SD)	41 840 (15 774)	45 741 (16 801)	42 067 (15 777)	42 542 (15 465)	41 085 (15 724)	43 348 (15 631)
Median rent, mean (SD)	520 (253)	562 (291)	514 (256)	524 (260)	537 (249)	515 (273)
Comorbidities						
Diabetes	3979 (13.1)	1067 (8.8)	881 (14.8)	674 (14.8)	1390 (8.8)	963 (15.9)
Heart failure	3783 (12.5)	847 (7.0)	1011 (17.0)	744 (16.3)	2283 (14.5)	919 (15.2)
Coronary heart disease	3075 (10.1)	674 (5.6)	778 (13.1)	406 (8.9)	929 (5.9)	713 (11.8)
CVA/TIA	1063 (3.5)	256 (2.1)	303 (5.1)	175 (3.8)	803 (5.1)	298 (4.9)
Hypertension	23 958(78.9)	9638 (79.8)	4667 (78.4)	3557 (78.0)	11 872 (75.5)	4023 (66.3)
COPD	1562 (5.1)	289 (2.4)	395 (6.6)	296 (6.5)	355 (2.3)	570 (9.4)
Current smoker	2429 (8.0)	597 (4.9)	496 (8.3)	432 (9.5)	675 (4.3)	320 (5.3)
Cancer	1220 (4.0)	281 (2.3)	330 (5.5)	231 (5.1)	237 (1.5)	297 (4.9)
PVD	1284 (4.2)	298 (2.5)	344 (5.8)	197 (4.3)	516 (3.3)	415 (6.8)
Nonambulant	373 (1.2)	88 (0.7)	116 (1.9)	84 (1.8)	351 (2.2)	163 (2.7)
BMI (kg/m ²), mean (SD)	29.2 (8.0)	27.8 (6.9)	28.0 (7.0)	26.6 (6.6)	26.4 (7.2)	26.9 (6.6)
BMI, missing	1451 (4.7)	555 (4.6)	298 (5.0)	233 (5.1)	643 (4.1)	257 (4.2)
Laboratory variables						
Albumin (g/dL), mean (SD)	3.3 (0.8)	3.5 (0.7)	2.9 (0.9)	3.0 (0.8)	2.9 (0.8)	3.0 (0.7)
Albumin missing	7074 (23.1)	2743 (22.5)	1321 (22.0)	1031 (22.4)	3745 (23.7)	1422 (23.4)
Hemoglobin (g/dL), mean (SD)	10.1 (1.9)	10.1 (1.9)	9.9 (1.8)	9.8 (1.8)	9.4 (1.8)	9.6 (1.7)
Hemoglobin missing	3563 (11.6)	1406 (11.5)	696 (11.6)	547 (11.9)	1601 (10.1)	649 (10.7)
eGFR (mL/min/1.73 m ²) mean (SD)	8.5 (4.1)	8.3 (4.0)	9.0 (4.5)	9.4 (4.6)	9.3 (4.6)	8.4 (4.2)
eGFR missing	825 (2.7)	259 (2.1)	163 (2.7)	138 (3.0)	390 (2.5)	108 (1.8)
Creatinine (mg/dL), mean (SD)	8.6 (4.3)	8.5 (4.0)	8.0 (3.9)	7.6 (3.7)	7.4 (3.5)	7.8 (3.7)
Creatinine, missing	649 (2.1)	182 (1.5)	106 (1.8)	83 (1.8)	218 (1.4)	75 (1.2)

All values represent n (%) except where otherwise stated.

ESRD, end-stage renal disease; PD, peritoneal dialysis; HD, hemodialysis; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate.

observed in LN and vasculitis. On the one hand, delaying kidney transplantation might be clinically appropriate or unavoidable in these patient groups. Patients with secondary GN subtypes might be more likely than patients with primary GN subtypes to be systemically unwell at the onset of ESRD, contraindicating early kidney transplantation. Rapidity of onset of ESRD may be another important discriminating factor. Progression to ESRD can be particularly rapid in vasculitis,

necessitating emergent commencement of dialysis and precluding timely counseling, planning and preparation for kidney transplantation. For example, one study of 136 patients with ESRD due to ANCA vasculitis reported that ESRD was already established at the time of vasculitis diagnosis in 51% of patients [40]. In LN, however, rapid progression to ESRD occurs much less frequently [41], with a median time from LN diagnosis to ESRD of 36 months in one study [42]. This pace of progression

Table 2. Proportion of patients receiving transplantation, PD and HD as a first ESRD treatment, 1996–2011, according to GN subtype (*n* = 75 278)

	Primary GN subtypes				Secondary GN subtypes	
	FSGS	IgAN	MN	MPGN	LN	Vasculitis
	[<i>n</i> = 30 604 (40.7%)]	[<i>n</i> = 12 178 (16.2%)]	[<i>n</i> = 6001 (8.0%)]	[<i>n</i> = 4606 (6.1%)]	[<i>n</i> = 15 805 (21.0%)]	[<i>n</i> = 6084 (8.1%)]
Kidney transplantation	2061 (6.7)	1523 (12.5)	300 (5.0)	322 (7.0)	496 (3.1)	121 (2.0)
Living donor	1583 (76.8)	1268 (83.3)	228 (76.0)	234 (72.7)	385 (77.6)	97 (80.2)
Deceased donor	464 (22.5)	247 (16.2)	72 (24.0)	82 (25.5)	107 (21.6)	24 (19.8)
Unknown donor	14 (0.68)	8 (0.53)	0 (0.0)	6 (1.9)	4 (0.8)	0 (0.0)
Peritoneal dialysis	4638 (15.3)	2107 (17.5)	828 (13.9)	553 (12.2)	1720 (11.0)	456 (7.5)
CCPD/IPD	3064 (65.9)	1400 (66.3)	564 (68.0)	360 (65.0)	1190 (69.0)	315 (69.1)
CAPD	1585 (34.1)	712 (33.7)	266 (32.0)	194 (35.0)	534 (31.0)	141 (30.9)
Hemodialysis	23 566 (77.9)	8390 (69.8)	4808 (81.0)	3669 (80.7)	13 478 (85.9)	5477 (90.5)
Missing modality	339 (1.1)	158 (1.3)	65 (1.1)	62 (1.3)	111 (0.7)	30 (0.5)

All values represent *n* (%).

PD, peritoneal dialysis; HD, hemodialysis; ESRD, end-stage renal disease; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; CCPD, continuous cycling PD; IPD, intermittent PD; CAPD, continuous ambulatory PD.

Table 3. ORs with 95% CIs for transplantation versus hemodialysis and for PD versus hemodialysis, according to GN subtype

	Primary GN subtypes				Secondary GN subtypes	
	FSGS	IgAN	MN	MPGN	LN	Vasculitis
	[<i>n</i> = 30 604 (40.7%)]	[<i>n</i> = 12 178 (16.2%)]	[<i>n</i> = 6001 (8.0%)]	[<i>n</i> = 4606 (6.1%)]	[<i>n</i> = 15 805 (21.0%)]	[<i>n</i> = 6084 (8.1%)]
TX versus HD						
Model 1	0.50 (0.46–0.54)	Ref	0.36 (0.31–0.41)	0.50 (0.44–0.57)	0.22 (0.19–0.24)	0.12 (0.10–0.15)
Model 2	0.85 (0.79–0.92)	Ref	0.61 (0.54–0.70)	0.68 (0.59–0.77)	0.35 (0.31–0.39)	0.18 (0.15–0.22)
Model 3	0.95 (0.88–1.03)	Ref	0.73 (0.63–0.83)	0.84 (0.73–0.96)	0.41 (0.37–0.46)	0.21 (0.17–0.25)
Model 4	0.98 (0.93–1.15)	Ref	1.19 (1.01–1.39)	1.08 (0.93–1.26)	0.49 (0.43–0.56)	0.27 (0.22–0.34)
PD versus HD						
Model 1	0.79 (0.74–0.83)	Ref	0.68 (0.63–0.75)	0.60 (0.54–0.66)	0.50 (0.47–0.54)	0.33 (0.30–0.37)
Model 2	0.95 (0.90–1.01)	Ref	0.85 (0.78–0.93)	0.66 (0.59–0.73)	0.53 (0.49–0.57)	0.37 (0.33–0.42)
Model 3	1.02 (0.96–1.08)	Ref	0.93 (0.85–1.02)	0.74 (0.67–0.82)	0.60 (0.55–0.64)	0.40 (0.36–0.45)
Model 4	1.05 (0.98–1.12)	Ref	1.30 (1.18–1.43)	0.95 (0.85–1.06)	0.76 (0.70–0.82)	0.54 (0.48–0.60)

Multiple imputation analysis (*n* = 75 278).

HD, hemodialysis; PD, peritoneal dialysis; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; TX, transplantation.

Model 1: adjusted for year of first ESRD therapy and region of residence.

Model 2: adjusted for Model 1 variables plus demographic variables (age, sex, race, ethnicity).

Model 3: adjusted for Model 2 variables plus patient-level (employment status, insurance payer) and neighborhood-level (percent below poverty line, percent less than high school education, percent unemployment, median income, median rent) socioeconomic variables.

Model 4: adjusted for Model 3 variables plus comorbidities (diabetes, heart failure, coronary heart disease, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease, current smoking, cancer, peripheral vascular disease, nonambulant status), body mass index (BMI) and laboratory variables (serum albumin, hemoglobin, serum creatinine).

should allow sufficient time to plan for pre-emptive kidney transplantation (and/or peritoneal dialysis).

On the other hand, reduced access to kidney transplantation in LN and vasculitis could be viewed as an example of inequitable care, i.e. these patient groups are being denied the best available ESRD treatment. Supporting this possibility, lower odds of transplantation in LN or vasculitis persisted even after adjusting for differences in laboratory surrogates of inflammation or malnutrition (hemoglobin, albumin and serum creatinine), in severity of renal dysfunction (as measured by serum creatinine) at initiation of ESRD treatment and in medical comorbidity burden. While residual confounding by illness acuity and severity undoubtedly persists, we suggest that it is unlikely to explain the magnitude of the differences in access to transplantation we observed. We wonder whether it is instead possible that the management of patients with these secondary GN subtypes focuses more on controlling systemic disease manifestations and less on current and future aspects of renal care.

We speculate that physician biases and preferences might also influence transplant-related decisions in LN and vasculitis. Uncertainty among physicians regarding the safety and optimal timing of kidney transplantation in vasculitis has previously been reported. In a survey of 32 nephrologists in Europe, 40% agreed that transplantation should be delayed for at least 12 months after vasculitis remission induction and 16% felt that transplantation should be postponed until ANCA antibodies become undetectable [43]. This tendency to delay kidney transplantation in vasculitis is poorly supported by data. Although a higher mortality in patients transplanted within a year of receiving vasculitis induction therapy has been reported [43], this finding has not been replicated. The presence of detectable ANCA antibody at the time of kidney transplantation has not been shown to negatively impact posttransplant outcomes [43, 44]. Patient and allograft survival rates after transplantation are comparable, if not superior, to those in other causes of ESRD [11, 45, 46]. Finally, delaying kidney transplantation by

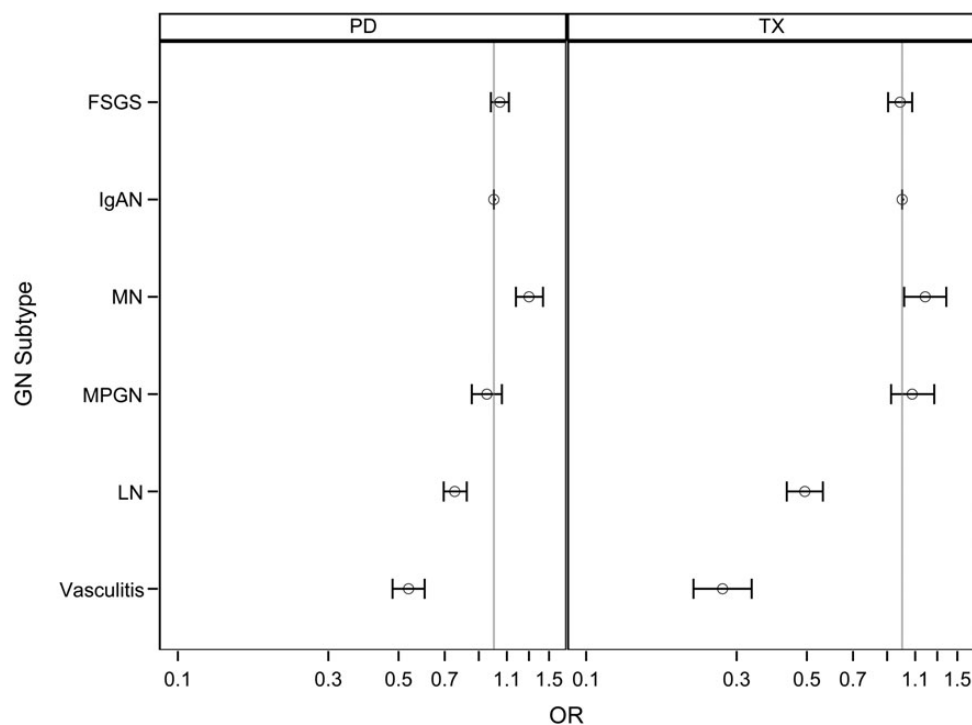


FIGURE 1: ORs with 95% CIs for peritoneal dialysis (PD) versus hemodialysis and kidney transplantation (TX) versus hemodialysis, comparing focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), lupus nephritis (LN) and vasculitis to the reference group IgA nephropathy (IgAN). ORs were computed using multinomial regression, adjusting for year of ESRD, geographic region, sociodemographic factors, comorbidities and laboratory variables (Model 4). Missing data were imputed using multiple imputation techniques ($n = 75\,278$).

preceding it with a longer duration of dialysis is not protective against posttransplantation vasculitis relapse [44]. On balance, there is little reason to believe that patients with vasculitis should not enjoy the same benefits afforded by preemptive kidney transplantation as the general ESRD population, and clinical practice guidelines advising caution appear unsupported by data [47, 48]. Clearly, studies aiming to establish best practices with respect to the timing of kidney transplantation in vasculitis are urgently needed. We are hopeful that recent reports demonstrating superior patient and allograft outcomes following pre-emptive and early kidney transplantation in patients with ESRD due to LN [49–51] will not only promote increased uptake of these transplant strategies in LN, but will also encourage the conduct of similar studies in other GN subtypes, including vasculitis.

While the reduced likelihood of transplantation we identified in patients with LN and vasculitis is the most striking and concerning finding arising from this study, the reduced likelihood of peritoneal dialysis (versus hemodialysis) in these GN subtypes also merits discussion. Although peritoneal dialysis does not prolong overall patient survival over hemodialysis, it offers some important health benefits, including greater treatment-related satisfaction [17, 18], reduced healthcare costs [20] and possibly less early mortality [16]. Peritoneal dialysis compared with hemodialysis before transplantation is also associated with superior allograft outcomes [52, 53]. Peritoneal dialysis is also viable—and associated with less infectious complications than hemodialysis—in patients who require urgent, unplanned dialysis initiation, factors relevant to patients with

rapidly progressive GN or to those receiving immunosuppressive therapy [19]. Accordingly, we posit that concerns over potentially (and unproven) increased risks for peritonitis among patients with LN or vasculitis should not preclude peritoneal dialysis as a treatment option in these patient groups, and that any potential risks are likely counterbalanced by high risks for vascular access infection with hemodialysis. Ultimately, the relative merits of peritoneal dialysis and hemodialysis should be weighed carefully for each individual patient commencing dialysis therapy. Our study did not attempt to address the relative efficacy of these dialysis approaches in patients with GN. However, our findings suggest that peritoneal dialysis might be a grossly underutilized modality in LN and vasculitis.

One final and somewhat unexpected finding arising from this study was the greater use of transplantation and peritoneal dialysis we observed in MN than in IgAN, after adjusting for differences in case mix. A priori, we hypothesized that patients with IgAN—which typically exhibits a relatively slow rate of progression to ESRD and a low requirement for immunosuppressive therapy—would be the group most likely to receive transplantation or peritoneal dialysis as an initial ESRD treatment modality. Membranous nephropathy, on the other hand, typically presents with nephrotic syndrome, is often treated with immunosuppressive therapy and is associated with earlier recurrence in the transplanted kidney, factors that might discourage physicians from recommending peritoneal dialysis or kidney transplantation in this patient group. Although we cannot confirm this hypothesis, we wonder whether the more florid presentation of MN with nephrotic syndrome, compared

with nephritic syndrome in IgAN, might result in earlier presentation of otherwise similar patients to a nephrologist, which might expedite ESRD planning. Clearly, this specific finding has less face validity than the consistently lower odds for transplantation and peritoneal dialysis we observed in all unadjusted and adjusted analyses in either LN or vasculitis, and should be interpreted cautiously.

Our study has certain limitations. First, we cannot verify the accuracy of GN subtype designations submitted to the USRDS. A previous study demonstrated poor agreement between cause of ESRD diagnoses submitted to the USRDS in MERs and those identified by kidney biopsy (the gold standard) in 217 patients with ESRD due to GN, a finding largely explained by a high proportion of patients with missing and nonspecific diagnoses in MERs [32]. However, once a specific GN subtype was selected in a MER, specificity for GN subtype was excellent, with a <2% false-positive rate. Agreement also improved after 1995, following a revision to cause of ESRD diagnosis categories in the MER in that year. Accordingly, we restricted our study population to patients with a specific GN subtype diagnosis who were enrolled in the USRDS after 1995. Thus, the internal validity of our study is strengthened, although study findings may not be directly applicable to patients with GN who are misclassified in the USRDS or who lack a definitive histologic or serologic diagnosis. Second, although we adjusted for multiple variables known to associate with access to transplantation or peritoneal dialysis [7, 21–24, 26, 29, 30, 54], residual confounding by misclassified or unmeasured covariates might persist. We anticipate that misclassification of measured covariates is likely to be nondifferential across GN subtypes and to bias toward the null. With respect to unmeasured covariates, we lacked data on some relevant socioeconomic variables that might impact modality choice, such as personal educational attainment [7, 23, 55] and marital status [23, 54]; however, we expect to have captured some of the effect from these variables by adjusting for employment status, insurance payer and neighborhood-level socioeconomic characteristics. Third, we could not distinguish the relative contributions from appropriate and inappropriate treatment-related decisions to study findings. For example, we lacked information regarding the duration of GN prior to ESRD, a factor that might strongly influence modality choice. Neither could we directly measure systemic disease activity or immunosuppressive medication burden at or before ESRD, relying instead upon laboratory markers and comorbidities as surrogate measures of acute illness. Finally, our study focused on first ESRD treatment modality and did not examine modality transitions over time. We nevertheless posit that first ESRD modality is a particularly important clinical outcome, in light of evidence supporting preemptive kidney transplantation as the optimal transplant approach [7, 50, 56] and reports advocating for peritoneal dialysis as the preferred first-line dialysis strategy [57].

Despite these limitations, our study has numerous strengths. To our knowledge, practice patterns regarding dialysis and transplantation have not previously been compared across GN subtypes, and imbalances identified in this study have not previously been reported. As a population-based study, our findings largely apply to all US patients with known ESRD due to GN and can guide the design of comparative

effectiveness research aiming to elucidate underlying reasons for, and consequences of, observed disparities. Misclassification of our primary exposure and outcome is likely to be infrequent and nondifferential, minimizing selection bias. We applied sophisticated statistical techniques to overcome shortfalls inherent to observational trial design, including multivariate regression to account for confounding and multiple imputation to handle missing data.

To conclude, we have demonstrated in a nationally representative ESRD population that initial ESRD treatment modality differs substantially across GN subtypes in ways that are fully explained by observed patient characteristics among primary GN subtypes but only partially so among the secondary GN subtypes LN and vasculitis. The underlying reasons for these disparities should be further investigated, and future studies comparing outcomes between ESRD treatment modalities in GN should consider the effect of GN subtype when designing study protocols and reporting study findings.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

W.C.W. reports having served as an advisor or consultant, unrelated to the topic of this article, to ACUMEN, Amgen, Astra-Zeneca, Bayer, Keryx, Medtronic, Mitsubishi-Tanabe and Rockwell Pharma. R.A.L. reports having served as an advisor or consultant, unrelated to the topic of this article, to Genentech, Fibrogen and Questcor. M.M.O. and M.E.M.-R. have no financial disclosures to report.

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Different impact of hemodialysis vintage on cause-specific mortality in long-term hemodialysis patients

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ABSTRACT

Background. Although dialysis vintage is associated with increased mortality risk in patients receiving hemodialysis (HD), the association of dialysis vintage with cause-specific mortality is unclear.

Methods. We conducted a nationwide registry-based retrospective cohort study of 216 246 patients receiving maintenance HD for >1 year at the end of 2009. The associations of dialysis vintage categories (1–<2, 2–<5, 5–<10, 10–<15, 15–<20, 20–<25, 25–<30 and ≥30 years) with 1-year all-cause and cause-specific mortality, including cardiovascular diseases (CVDs) and infection-related mortality, were examined using logistic regression models.

Results. During the 1-year study period, 18 614 deaths occurred from all causes, including 7263 and 3504 deaths from CVD and infection-related causes. From multivariate analysis, the dialysis vintage was incrementally associated with a higher risk for all-cause mortality, with worse outcome observed in the ≥30 years category {odds ratio [OR] = 2.43 (95% confidence interval (CI)

2.13–2.77)}. A similar association was apparent between the dialysis vintage and infection-related mortality, with a higher risk than that of all-cause mortality in each vintage category [≥30 years, OR = 3.55 (95% CI 2.72–4.66)], while the dialysis vintage was associated with only a modest increase in risk of CVD mortality [≥30 years, OR = 1.64 (95% CI 1.30–2.08)].

Conclusions. Dialysis vintage has a different impact on cause-specific mortality, with a higher risk for infection-related mortality than CVD mortality. This impact is most pronounced in long-term HD survivors, to whom much attention should be devoted to prevent infectious complications.

Keywords: cardiovascular disease (CVD), dialysis vintage, hemodialysis (HD), infection, mortality

INTRODUCTION

Along with therapeutic advances and increasing evidence for patients undergoing hemodialysis (HD), dialysis patients are likely to be managed with and remain on HD therapy for