



ORIGINAL ARTICLE

Spatiotemporal trends and prognosis of end-stage renal disease patients with biopsy-proven immunoglobulin A nephropathy in France from 2010 to 2014

Thomas Robert^{1,*}, Rodolphe Jantzen^{2,*}, Alexandra Cambier³,
Matthieu Jamme⁴, Cecile Couchoud⁵, Philippe Brunet^{1,5},
Stéphanie Gentile^{1,5}, Eric Rondeau^{4,6}, Laurent Mesnard^{4,6} and
Nathanael Lapidus², on behalf of the REIN registry

¹Department of Nephrology and Renal Transplantation, Assistance Publique-Hôpitaux de Marseille, Hôpital de la Conception, Marseille, France, ²Department of Public Health, Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique IPLESP, AP-HP, Saint-Antoine Hospital, Paris, France, ³Pediatric Department of Nephrology and Transplantation, Assistance Publique-Hôpitaux de Paris, Hôpital Robert-Debré, Paris, France, ⁴Department of Intensive Care Nephrology, Transplantation Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Sorbonne Université Paris, Paris, France, ⁵REIN Registry, Agence de la Biomédecine, Saint-Denis la Plaine, France and ⁶Université Pierre et Marie Curie, INSERM, IMR 1155, Hôpital Tenon, Paris, France

*These authors contributed equally to this work.

Correspondence to: Thomas Robert; E-mail: thomas.robert@ap-hm.fr

ABSTRACT

Background. Although end-stage renal disease (ESRD) is frequently used as an outcome marker for primary immunoglobulin A nephropathy (IgAN), the clinical course after reaching ESRD is not well documented. This study examined patients' characteristics and survival in ESRD-related biopsy-proven IgAN in France.

Methods. French Renal Epidemiology and Information Network Registry data from 2010 to 2014 were used to analyse patients' survival and outcome in incident ESRD patients >16 years of age with biopsy-proven primary IgAN, in comparison with other primary and secondary glomerulonephritis (GN), adult polycystic kidney disease (ADPKD) or diabetes. Multivariable survival analysis was adjusted for age, sex, time on dialysis and comorbidities.

Results. Among 17 138 incident dialysis patients with ESRD, IgAN (242.8/10 000 dialysis initiation) represents the most common GN related to ESRD during 2010. IgAN patients were the youngest, and had the fewest comorbidities and the highest use of peritoneal dialysis (PD) (17%). In comparison with the haemodialysis group, hazard ratios for death were not different in the preemptive transplantation group [0.46, 95% confidence interval (CI) 0.17–1.28] and in the PD group (0.77, 95% CI 0.44–1.33). Mortality rates in IgAN patients with preemptive transplantation and in those receiving dialysis waiting

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for transplantation were 2.9% (95% CI 0.0–5.6) and 6.7% (95% CI 0.9–12.3). Mortality rates of ADPKD patients receiving dialysis waiting for transplantation were higher (18%, 95% CI 3.1–30.6).

Conclusion. IgAN has the best prognosis among primary and secondary GN. IgAN patients receiving dialysis waiting transplantation seem to have a more favourable prognosis than ADPKD patients, who usually comprise the reference population. The underlying reasons for the difference in access treatment modalities should be investigated to improve survival with respect to renal disease.

Keywords: clinical epidemiology, dialysis modality, glomerulonephritis, IgA nephropathy end-stage renal disease, mortality, outcomes

INTRODUCTION

Glomerulonephritis (GN) is one of the four major causes of end-stage renal disease (ESRD), along with diabetes, hypertension and cystic kidney disease. Primary immunoglobulin A nephropathy (IgAN or Berger's disease) is the most frequent primary GN leading to ESRD requiring dialysis or renal transplantation worldwide. Approximately 30–50% of patients with IgAN will progress to ESRD in the 30 years following diagnosis. About 1500 new cases are diagnosed each year in France [1]. IgAN occurs at any age, with a peak of incidence during the second and third decades of life. Prevalence of IgAN is particularly high in Asians and Caucasians people, while it is much rarer among African patients [2]. The northward gradient in Europe with a higher prevalence of ESRD related to IgAN is well known [3]. The ERA-EDTA data demonstrate that Nordic countries have >2-fold higher incidence and prevalence of ESRD-related IgAN compared with the Southern European countries (ERA-EDTA Registry, unpublished data presented at the 2013 ERA-EDTA Congress).

In transplanted patients, those with IgAN have substantially lower mortality than other ESRD patients. The prognosis of IgAN at start of ESRD dialysis therapy has been well described in the USA and Japan [4, 5]. Mortality is increased after initiation of renal replacement therapy (RRT) in patients with IgAN [6, 7]. O'Shaughnessy *et al.* [5] showed that patients with IgAN had the fewest comorbidities and the lowest mortality compared with other GN and non-GN subtypes. Little is known in Europe, and notably in France, about IgAN patients' characteristics and mortality risk after starting ESRD therapy according to kidney-related cause of ESRD.

We conducted this study to examine characteristics and quantify long-term disease-specific risks and outcomes in patients with biopsy-proven IgAN starting ESRD treatment (dialysis and/or transplantation) in France, with transitions between these treatment modalities over time, compared with other GN and non-GN ESRD subtypes.

MATERIALS AND METHODS

Study population and data source

About 50 908 patients aged >16 years who initiated ESRD therapy with haemodialysis (HD), peritoneal dialysis (PD) or preemptive kidney transplantation in France between 1 January 2010 and 31 December 2014 were retrospectively identified from the Renal Epidemiology and Information Network (REIN) registry, a national registry of all patients with treated ESRD. Its organizational principles and quality control measures have been described elsewhere [8]. All analyses relied on records of patients with 11 kidney-related causes of ESRD: IgAN, focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), Types 1 and 2 membranoproliferative GN (MPGN1 and MPGN2), lupus nephritis (LN), anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV),

Goodpasture disease (GD), Henoch-Schönlein purpura (HSP), autosomal-dominant polycystic kidney disease (ADPKD) and diabetes-related ESRD [diabetic nephropathy (DN)]. We included patients with kidney-related causes of ESRD confirmed by a biopsy except for patients with a DN or an ADPKD, who were classified on clinical and/or radiological criteria. Genetic analysis was not available to confirm ADPKD. Missing or uncertain causes of ESRD or a defined cause other than one of these were the only non-inclusion criteria. We estimated the incidence of each renal disease according to the number of inhabitants aged >16 years in France between 2010 and 2014 using the French Institute for Demographic Studies.

Outcomes and exposures

In this retrospective cohort setting, death was our primary study outcome. Cause of death defined by categories was a secondary outcome.

Biopsy-proven IgAN was the primary exposure. We examined four groups as external comparator groups: two groups of biopsy-proven GN subtype-related causes of ESRD (primary GN subgroup: FSGS, MN; secondary GN subgroup: MPGN, LN, AAV, GD and HSP) and two non-GN-related causes of ESRD (DN and ADPKD). Causes of ESRD were assessed by either clinical diagnosis or kidney biopsy confirmation.

REIN is a registry used to provide support, evaluation and research on public health for patients starting RRT. Baseline demographics and clinical data at the dialysis onset were extracted from the REIN registry and included: health care centre location, age, gender, primary renal disease, body mass index (BMI), creatinine and estimated glomerular filtration rate (eGFR), haemoglobin (Hb) and serum albumin. We studied the following comorbidity conditions: diabetes, hypertension, congestive heart failure, cardiac arrhythmia, peripheral vascular disease, coronary heart disease, cerebrovascular disease, chronic respiratory disease, active malignancy, chronic C hepatitis (HCV), chronic B hepatitis (HBV), positive HIV serology, mobility status and smoking. Malnutrition was defined as a serum-albumin level of <3 g/dL and/or a BMI of <20 kg/m². HBV, HCV and HIV missing status were considered as negative. Frailty was defined as an inability to walk without help. Primary renal diseases were coded according to the thesaurus of the French Society of Nephrology. Dialysis started in an emergency context was defined as a life-threatening circumstance that required dialysis within 24 h. All deaths were registered from the first day of dialysis up to the study's endpoint on 31 August 2016. Geographic data [region of residence in France (department)] were recorded from the REIN registry.

Statistical methods

For the population with dialysis as first RRT, we described continuous variables with medians and interquartile ranges (IQRs),

and categorical variables with frequencies and proportions. We performed a Kruskal–Wallis test for continuous variables. For categorical variables, we performed a Chi-square test, or the Fisher's exact test for small sample sizes.

For each renal pathology group, proportions of treatment modalities as first RRT (HD, PD and preemptive kidney transplantation) were calculated. The yearly incidence of ESRD per 10 000 dialyses as first RRT in France was calculated for each renal pathology group.

For IgAN patients, overall dialysis onset incidence for every French department was estimated with standardization on age and gender globally and stratified on age (under or above 45 years). This cut-off was chosen because of the reported higher incidence of ESRD in IgAN patients <45 years of age [9]. Further standardization on nephrologists' density was carried out in a sensitivity analysis. Incidences were represented on maps of France using an exponential spatial interaction from a Stewart model with a beta coefficient of 2 and a span of 50 km. [10] Hot spots were defined as incidences >9 million people.

To compare the probabilities of treatment modalities as first RRT (preemptive kidney transplantation versus dialysis and PD versus HD) among renal pathology groups, three different models of logistic regression were carried out with IgAN as reference: Model 1: adjustment on age at first RRT, gender, starting year of first RRT and first RRT started in emergency; Model 2: Model 1 with additional adjustment on comorbidities (history of diabetes, heart failure, arrhythmia, cerebrovascular accident, coronary artery disease, peripheral artery disease, respiratory insufficiency, cancer and BMI); Model 3: Model 2 with additional adjustment on frailty status.

We used a Gray estimator of cumulative mortality over a 6-year follow-up, accounting for change of treatment modality between dialysis and kidney transplantation during the follow-up as a competing risk. The follow-up began at the first RRT date and was censored on 31 August 2016. Unless a death occurred, a patient could not be lost to follow-up since the vital status is updated every year by the dialysis centre. Unadjusted Fine–Gray 6-year mortality estimates and mortality curves were stratified on (i) first RRT modalities in IgAN patients and (ii) subgroups of kidney disease. Instead of a Fine–Gray model, we used a Kaplan–Meier estimation for the 6-year mortality and the mortality curves for the stratification on patient care pathways (dialysis only, on and off the transplant list, dialysis then transplantation and preemptive transplantation) as all the patients in the 'dialysis then transplantation' group would be censored. Fine–Gray competing risk regression models adjusted on age, comorbidities and frailty status were carried out, accounting for change of treatment modality as a competing risk. Results are presented as sub-distribution hazard ratios (SHRs) with their 95% confidence intervals (CIs). These models were used to compare mortality risk (i) between the five subgroups of kidney disease and (ii) in IgAN patients between HD, PD and preemptive kidney transplantation. Missing data were imputed by chained equations and results obtained after combining estimates over imputed datasets using Rubin's rule [11]. All analyses were performed with the R software, version 3.4 [12].

RESULTS

Patient characteristics

The final study population comprised 17 976 patients with ESRD. About 17 138 patients were treated by dialysis (HD or PD) as their first RRT and attributed to five subgroups of kidney

disease (Table 1): (i) IgAN ($n=1199$, 7.0%); (ii) other primary GN subtypes: FSGS ($n=856$, 5.0%) and MN ($n=346$, 2.0%); (iii) secondary GN subtypes: MPGN ($n=227$, 1.3%), LN ($n=138$, 0.8%), AAV ($n=543$, 3.2%), GD ($n=27$, 0.2%) and HSP ($n=48$, 0.3%); (iv) ADPKD ($n=2783$, 16.3%); (v) DN ($n=10 971$, 64.2%). Among diabetic patients, with ESRD, 1642 (13.9%) received a renal biopsy among whom histological diagnoses fell into IgAN ($n=146$, 9.8%), primary GN subgroup ($n=245$, 16.7%), secondary GN subgroup ($n=175$, 12.3%) and DN ($n=1076$, 61.2%). Diabetic patients with no renal biopsy were classified as DN based on clinical and biological arguments but a superimposed non-diabetic condition on underlying DN may also exist.

In dialysis-treated patients, demographic and comorbidity characteristics at baseline differed considerably according to kidney-related ESRD subtypes (Table 1). IgAN patients were the youngest patients at dialysis onset (HD or PD) with median (IQR) age 53.6 (39.9–65.6) years. Male sex was the most represented in IgAN (75.8%). The proportion of frail patients was the lowest in IgAN (4.1%) and the highest in DN patients (23.0%). Cardiovascular comorbidities were the least common in IgAN (22.9%). Conversely, cirrhosis was the most common in IgAN (5.4%). Chronic C and B hepatitis were the least common in IgAN (0.5% and 0.6%, respectively). Proportion of patients starting dialysis with eGFR <10 mL/min/1.73 m² was the highest in secondary GN subgroup and IgAN (79.3 and 78.4%, respectively). Proportion of patients registered on the transplant waitlist before dialysis onset was the highest in ADPKD and IgAN (35.8% and 30.6%, respectively). Patients with IgAN were the most frequently evaluated for kidney transplantation (57.4%).

Most patients (95.3%) received dialysis as their first RRT modality: 85.3% for HD and 10% for PD. The use of PD as the first RRT modality was the highest in patients with IgAN (17%), as well as the proportion of patients receiving preemptive kidney transplants (12.2%) (Table 2).

Incidence of ESRD due to IgAN

Incidences of IgAN, and primary and secondary GN patients starting dialysis as first RRT among inhabitants of France aged >16 years were, respectively, 4.5, 3.8 and 3.5 per million in 2010 and 4.8, 4.7 and 3.2 per million in 2014. Incidences of DN and ADPKD patients starting dialysis were the highest between 2010 and 2014, respectively (41.9 and 9.3 per million of inhabitants in 2010 and 45.3 and 9.9 per million of inhabitants in 2014, respectively).

In comparison with primary and secondary GN, IgAN was the most frequent disease in patients starting dialysis as first RRT, with a yearly incidence between 242.8 and 263.4 per 10 000 dialyses as first RRT (Table 3). There was no evidence for a northward gradient related to ESRD-IgAN. In the subgroup of patients >45 years old, we found six hotspots with a high incidence of ESRD related to IgAN, ranging from 9 to 18 per million. In comparison, the incidence in the subgroup of patients aged <45 years was lower (3.5–7 per million) with no identified hotspot (Figure 1). Standardization on nephrologists' density did not change these results (data not shown).

ESRD therapy modality access

According to Model 1 (adjusted on the year of ESRD, age, sex and emergency context of dialysis onset), patients with GN and non-GN subgroups were less likely to receive PD than IgAN patients. After adjustment on comorbidities and frailty status (Model 3), all subgroups of kidney disease were less likely to

Table 1. Baseline characteristics at the initiation of dialysis in France between 2010 and 2014

Variable	IgAN n = 1199	Other primary GN subgroup n = 1202	Secondary GN subgroup n = 983	ADPKD n = 2783	DN n = 10 971	P-value
Age, median (IQR), years	53.6 (39.9–65.6)	60 (46.8–71.7)	63 (48.8–74.6)	58.5 (50.1–68.4)	70.1 (61.6–77.8)	<0.001
Males, n (%)	909 (75.8)	806 (67.1)	579 (58.9)	1 545 (55.5)	6 675 (60.8)	<0.001
Kidney biopsy, n (%)	1199 (100)	1202 (100)	983 (100)	0 (0)	873 (8)	–
BMI, median (IQR), kg/m ²	24.5 (21.8–27.9)	25.4 (22.2–29.2)	23.5 (20.7–27.3)	24.8 (22.1–28.1)	28.4 (24.6–32.7)	<0.001
BMI < 20 kg/m ² , n (%)	111 (11)	105 (10.5)	152 (18.9)	222 (9.8)	329 (3.9)	–
BMI > 30 kg/m ² , n (%)	150 (14.9)	217 (21.6)	103 (12.8)	349 (15.4)	3316 (39.6)	–
Missing, n	192	198	180	519	2596	–
Smoker, n (%)	–	–	–	–	–	<0.001
Never	560 (54.9)	534 (52.1)	451 (54.8)	1 533 (65.7)	5470 (60.5)	–
Current	197 (19.3)	199 (19.4)	148 (18)	291 (12.5)	922 (10.2)	–
Former	263 (25.8)	292 (28.5)	224 (27.2)	511 (21.9)	2650 (29.3)	–
Missing, n	179	177	160	448	1929	–
Frailty, n (%)	45 (4.1)	83 (7.4)	87 (9.5)	120 (4.7)	2263 (23)	<0.001
Missing, n	89	84	71	235	1150	–
Diabetes, n (%)	140 (11.8)	239 (20)	175 (17.9)	245 (8.8)	10 971 (100)	–
Missing, n	8	5	5	13	0	–
Number of cardiovascular co-morbidities, n (%)	–	–	–	–	–	<0.001
0	861 (77.1)	757 (66.9)	581 (62.7)	1 856 (71.4)	3188 (31.7)	–
1	148 (13.2)	229 (20.2)	215 (23.2)	460 (17.7)	2849 (28.3)	–
2	76 (6.8)	98 (8.7)	87 (9.4)	204 (7.9)	2148 (21.4)	–
3	22 (2)	35 (3.1)	29 (3.1)	69 (2.7)	1291 (12.8)	–
4 or more	10 (0.9)	13 (1.1)	14 (1.5)	9 (0.3)	583 (5.8)	–
Missing, n	82	70	57	185	912	–
Heart failure, n (%)	109 (9.3)	134 (11.3)	141 (14.6)	262 (9.6)	3301 (31)	<0.001
Missing, n	26	16	19	64	322	–
Coronary artery disease, n (%)	114 (9.8)	167 (14.2)	118 (12.3)	319 (11.8)	3761 (35.4)	<0.001
Missing, n	30	22	22	81	357	–
Cardiac arrhythmia, n (%)	108 (9.2)	139 (11.7)	158 (16.4)	281 (10.4)	2404 (22.6)	<0.001
Missing, n	26	15	18	76	325	–
Peripheral artery disease, n (%)	78 (6.7)	118 (10)	79 (8.3)	160 (5.9)	3530 (33.4)	<0.001
Missing, n	34	26	26	78	409	–
Cerebrovascular disease, %	39 (3.4)	77 (6.6)	64 (6.7)	181 (6.8)	1447 (13.8)	<0.001
Missing, n	56	43	34	128	464	–
Chronic lung disease, n (%)	92 (7.9)	116 (9.8)	122 (12.7)	130 (4.8)	1504 (14.2)	<0.001
Missing, n	29	22	22	73	351	–
Malignancy, n (%)	51 (4.3)	81 (6.8)	68 (7)	110 (4)	633 (5.9)	<0.001
Missing, n	26	16	15	58	314	–
Cirrhosis, n (%)	63 (5.4)	13 (1.1)	31 (3.2)	15 (0.6)	233 (2.2)	<0.001
Missing, n	28	22	22	62	321	–
Chronic C hepatitis, n (%)	6 (0.5)	21 (1.7)	24 (2.4)	19 (0.7)	186 (1.7)	<0.001
Missing, n	0	0	0	0	0	–
Chronic B hepatitis, n (%)	7 (0.6)	22 (1.8)	11 (1.1)	20 (0.7)	86 (0.8)	0.002
Missing, n	0	0	0	0	0	–
Positive HIV serology, n (%)	11 (0.9)	35 (2.9)	8 (0.8)	6 (0.2)	42 (0.4)	<0.001
Missing, n	0	0	0	0	0	–
Albumin, median (IQR), g/dL	34.6 (30–38.4)	31 (25–36)	29.4 (24.9–34)	37.5 (33.6–41)	33 (28.8–37)	<0.001
Albumin < 3.0 g/dL, n (%)	188 (23.4)	370 (43)	372 (51.7)	179 (10.7)	2084 (30.4)	–
Missing, n	397	341	263	1105	4126	–
Hb, median (IQR), g/dL	10.3 (9.2–11.4)	10.3 (9.3–11.4)	9.5 (8.4–10.8)	10.7 (9.7–11.7)	10.1 (9.1–11.1)	<0.001
Hb < 9.0 g/dL, n (%)	223 (21.4)	207 (19.6)	300 (35.3)	309 (13.3)	2 013 (22.1)	–
Missing, n	158	144	133	461	1878	–
eGFR, median (IQR), mL/min/1.73 m ²	7.5 (5.7–9.6)	7.9 (6–10.1)	7.2 (5.4–9.4)	7.8 (6.2–9.7)	8.7 (6.7–11)	<0.001
eGFR between 10 and 15 mL/min/1.73 m ² , n (%)	193 (21.6)	259 (26)	170 (20.7)	456 (22.5)	2451 (34.7)	–
eGFR < 10 mL/min/1.73 m ² , n (%)	702 (78.4)	736 (74)	652 (79.3)	1567 (77.5)	4615 (65.3)	–
Missing, n	304	207	161	760	3905	–
Dialysis start in emergency, n (%)	256 (22.8)	283 (24.9)	410 (43.9)	352 (13.7)	3 310 (32.7)	<0.001

Table 1. (continued)

Variable	IgAN n = 1199	Other primary GN subgroup n = 1202	Secondary GN subgroup n = 983	ADPKD n = 2783	DN n = 10 971	P-value
Missing, n	77	67	49	217	847	–
Waiting list registration before start dialysis, n (%)	349 (30.6)	218 (19)	120 (12.6)	955 (35.8)	494 (4.8)	<0.001
Missing, n	57	52	32	117	703	–
Out of list registration for kidney transplantation before start dialysis, n (%)						<0.001
Kidney transplantation evaluation in progress	434 (57.4)	388 (44.9)	236 (30.2)	793 (49.8)	1656 (18.4)	–
Medical contraindication	239 (31.6)	379 (43.9)	432 (55.3)	565 (35.5)	6262 (69.6)	–
Patient refusal	13 (1.7)	7 (0.8)	12 (1.5)	63 (4)	96 (1.1)	–
Others	70 (9.3)	90 (10.4)	101 (12.9)	171 (10.7)	986 (11)	–
Missing, n	37	68	50	119	774	–

Quantitative variables are described as median (IQR) and categorical variables as n (percentage of non-missing values). Primary GN subgroup comprises MN and primary FSGS; secondary GN subgroup comprises LN, MPGN, AAV, GP and HSP. List of cardiovascular comorbidities: hypertension, heart failure, cardiac arrhythmia, peripheral artery disease, coronary heart disease, cerebrovascular disease.

Table 2. Proportion of patients receiving transplantation, PD and HD as a first ESRD treatment between 2010 and 2014

	IgAN (n = 1366)	Primary GN subgroup (n = 1277)	Secondary GN subgroup (n = 1015)	ADPKD (n = 3144)	DN (n = 11174)
Pre-emptive kidney transplantation	167 (12.2)	75 (5.9)	32 (3.2)	361 (11.5)	203 (1.8)
HD	967 (70.8)	1 032 (80.8)	915 (90.1)	2 412 (76.7)	10 011 (89.6)
PD	232 (17.0)	170 (13.3)	68 (6.7)	371 (11.8)	960 (8.6)

All values are reported as n (%). Primary GN subgroup comprises MN and primary FSGS; secondary GN subgroup comprises LN, MPGN, AAV, GP and HSP.

Table 3. ESRD yearly incidence according to renal diseases, 2010–14 (10 000 first RRT) only for dialysis RRT

	2010	2011	2012	2013	2014
IgAN	224 (242.8)	246 (263.4)	235 (241)	251 (248.1)	243 (233.7)
FSGS	149 (161.5)	151 (161.7)	171 (175.3)	179 (176.9)	206 (198.1)
MN	67 (72.6)	75 (80.3)	70 (71.8)	68 (67.2)	66 (63.5)
MPGN Type 1	31 (33.6)	33 (35.3)	30 (30.8)	47 (46.5)	27 (26)
MPGN Type 2	18 (19.5)	11 (11.8)	8 (8.2)	9 (8.9)	13 (12.5)
LN	27 (29.3)	27 (28.9)	30 (30.8)	30 (29.7)	24 (23.1)
HSP	13 (14.1)	11 (11.8)	13 (13.3)	6 (5.9)	5 (4.8)
GD	7 (7.6)	6 (6.4)	2 (2.1)	7 (6.9)	5 (4.8)
AAV	102 (110.5)	109 (116.7)	106 (108.7)	113 (111.7)	113 (108.7)
ADPKD	531 (575.5)	543 (581.3)	531 (544.5)	601 (594)	577 (555)
DN	2083 (2257.5)	2101 (2249.2)	2194 (2249.8)	2296 (2269.2)	2297 (2209.3)

All values are reported as n (n/10 000 first dialysis RRT in France); primary GN subgroup comprises MN and primary FSGS; secondary GN subgroup comprises LN, MPGN, AAV, GP and HSP.

receive PD than IgAN patients: odds ratio (OR) = 0.74 (95% CI 0.59–0.92) for GN subgroup; OR = 0.40 (95% CI 0.30–0.53) for secondary GN subgroup; OR = 0.54 (95% CI 0.45–0.65) for ADPKD; OR = 0.68 (95% CI 0.51–0.92) for DN (Tables 4 and 5).

According to Model 1, access to preemptive transplantation in comparison with IgAN patients was lower in all subgroups of kidney disease except ADPKD (OR = 1.19, 95% CI 0.96–1.74). After adjustment on comorbidities and frailty status (Model 3), access to preemptive transplantation remained lower in primary (OR = 0.60, 95% CI 0.44–0.81) and secondary (OR = 0.41, 95% CI 0.27–0.61) GN subgroups and were not different for ADPKD (OR = 1.09, 95% CI 0.88–1.36) and DN (OR = 0.82, 95% CI 0.49–1.36) patients (Tables 4 and 5).

ESRD therapy modality and survival in IgAN patients

We observed 6-year survival differences across IgAN patients with respect to ESRD therapy modalities. Mortality rates were 2.9% (95% CI 0.1–5.6) for preemptive kidney transplantation, 8.5% (95% CI 4.2–12.7) for PD and 16.5% (95% CI 13.6–19.3) for HD (Figure 2). SHRs were 0.5 (95% CI 0.2–1.3) for preemptive transplantation and 0.8 (95% CI 0.4–1.3) for PD compared with HD.

Mortality rates for IgAN patients with respect to medical care pathways ranged from 2.9% (95% CI 0.0–5.6) for preemptive transplantation, 2.9% (95% CI 0.7–5.0) for dialysis followed by transplantation, 6.7% (95% CI 0.9–12.3) for dialysis in patients on the transplant waitlist and 38.5% (95% CI 31.3–44.9) for dialysis in patients off the waitlist (Figure 3 and Table 6).

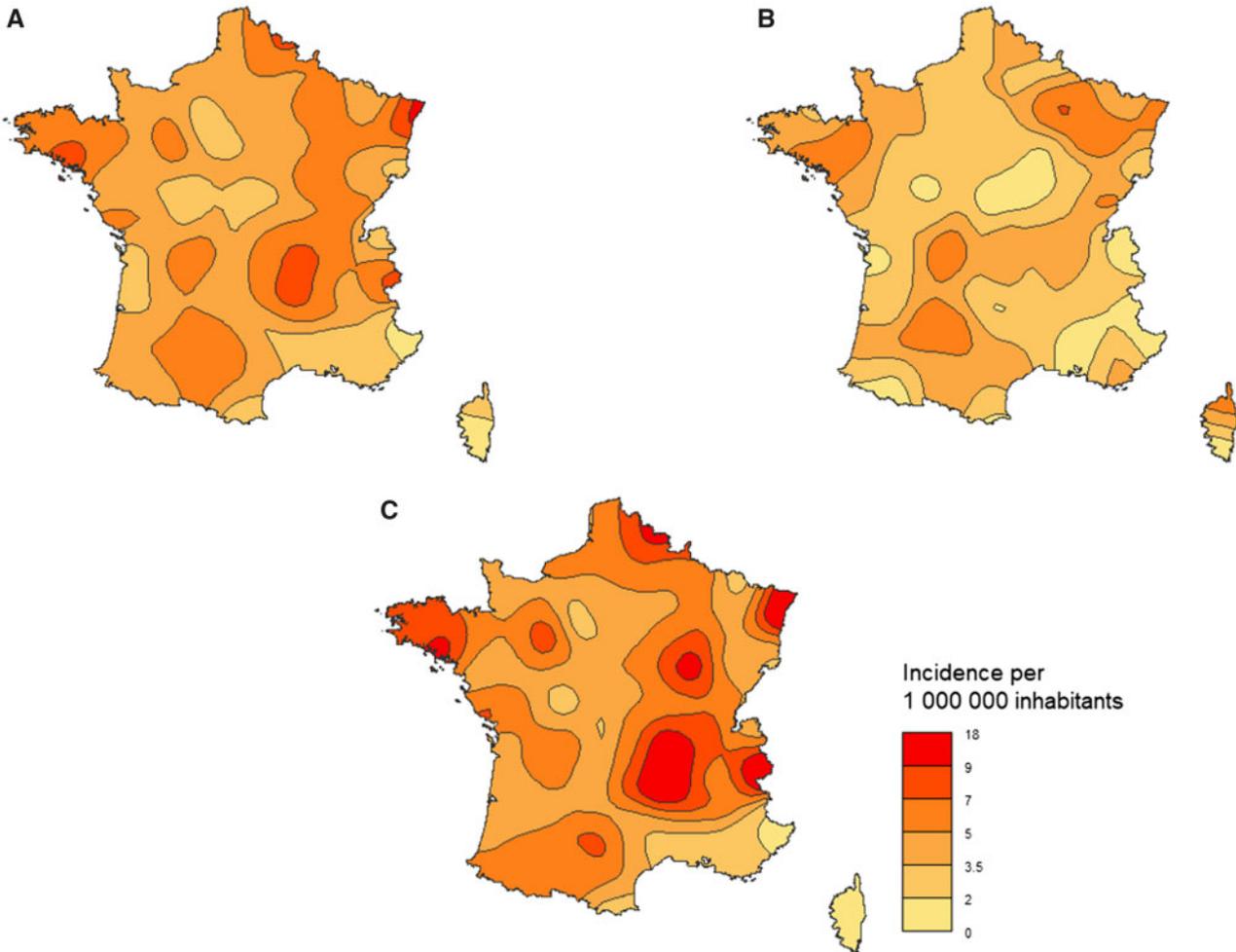


FIGURE 1: ESRD spatial density incidence of IgAN-related causes of ESRD starting dialysis across France, 2010–15. (A) Global cohort (≥16 years old); (B) patients 16- to 45-years old; (C) patient ≥45 years old.

Table 4. Comparison of pre-emptive kidney transplantation versus HD as the first RRT according to ESRD kidney disease

	Model 1	Model 2	Model 3
IgAN	1 (reference)	1 (reference)	1 (reference)
Primary GN	0.55 (0.41–0.74)	0.60 (0.44–0.81)	0.60 (0.44–0.81)
Secondary GN	0.38 (0.25–0.56)	0.41 (0.27–0.61)	0.41 (0.27–0.61)
ADPKD	1.19 (0.96–1.74)	1.11 (0.89–1.38)	1.09 (0.88–1.36)
DN	0.31 (0.24–0.39)	0.76 (0.46–1.27)	0.82 (0.49–1.36)

Results are reported as ORs with their CIs. Patients with medical contraindication for kidney transplantation are excluded from the comparison of pre-emptive kidney transplantation versus dialysis.

Model 1: adjusted for year of first ESRD therapy, age, sex and dialysis start in emergency.

Model 2: adjusted for Model 1 variables plus comorbid diseases (diabetes, heart failure, cardiac arrhythmia, coronary artery disease, cerebral artery disease, chronic lung disease, malignancy, BMI >30 kg/m²).

Model 3: adjusted for Model 2 variables plus frailty status. Primary GN subgroup comprises MN and primary FSGS; secondary GN subgroup comprises LN, MPGN, AAV, GP and HSP.

Table 5. Comparison of HD versus PD as the first RRT according to ESRD kidney disease

	Model 1	Model 2	Model 3
IgAN	1 (reference)	1 (reference)	1 (reference)
Primary GN	0.70 (0.56–0.87)	0.74 (0.59–0.92)	0.74 (0.59–0.92)
Secondary GN	0.39 (0.29–0.53)	0.40 (0.30–0.54)	0.40 (0.30–0.53)
ADPKD	0.56 (0.46–0.67)	0.54 (0.45–0.65)	0.54 (0.45–0.65)
DN	0.45 (0.38–0.54)	0.67 (0.50–0.90)	0.68 (0.51–0.92)

Results are reported as ORs with their CIs. Patients with medical contraindication for kidney transplantation are excluded from the comparison of pre-emptive kidney transplantation versus dialysis.

Model 1: adjusted for year of first ESRD therapy, age, sex and dialysis start in emergency.

Model 2: adjusted for Model 1 variables plus comorbid diseases (diabetes, heart failure, cardiac arrhythmia, coronary artery disease, cerebral artery disease, chronic lung disease, malignancy, BMI >30 kg/m²).

Model 3: adjusted for Model 2 variables plus frailty status. Primary GN subgroup comprises MN and primary FSGS; secondary GN subgroup comprises LN, MPGN, AAV, GP and HSP.

Kidney-related causes of ESRD and survival

In patients receiving dialysis (PD or HD) as first RRT, standardized 6-year mortality rates were 15.0% (95% CI 12.5–17.4) for

IgAN, 24.2% (95% CI 20.5–27.7) for the primary GN subgroup, 33.1% (95% CI 29.1–36.5) for the secondary GN subgroup, 16.8% (95% CI 14.8–18.7) for the ADPKD subgroup and 54.2% (95% CI 52.8–55.6) for the DN subgroup (Figure 4).

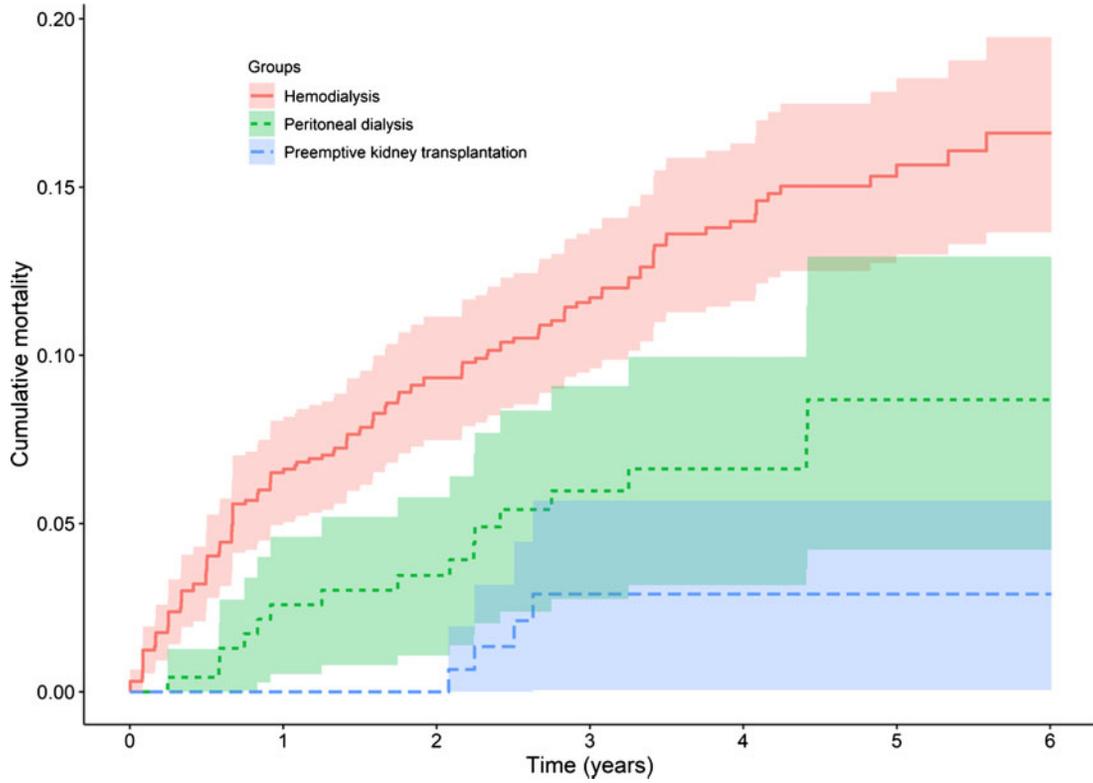


FIGURE 2: Cumulative mortality with respect to ESRD therapy modalities (preemptive kidney transplantation, PD and HD) in IgAN patients (Gray estimator).

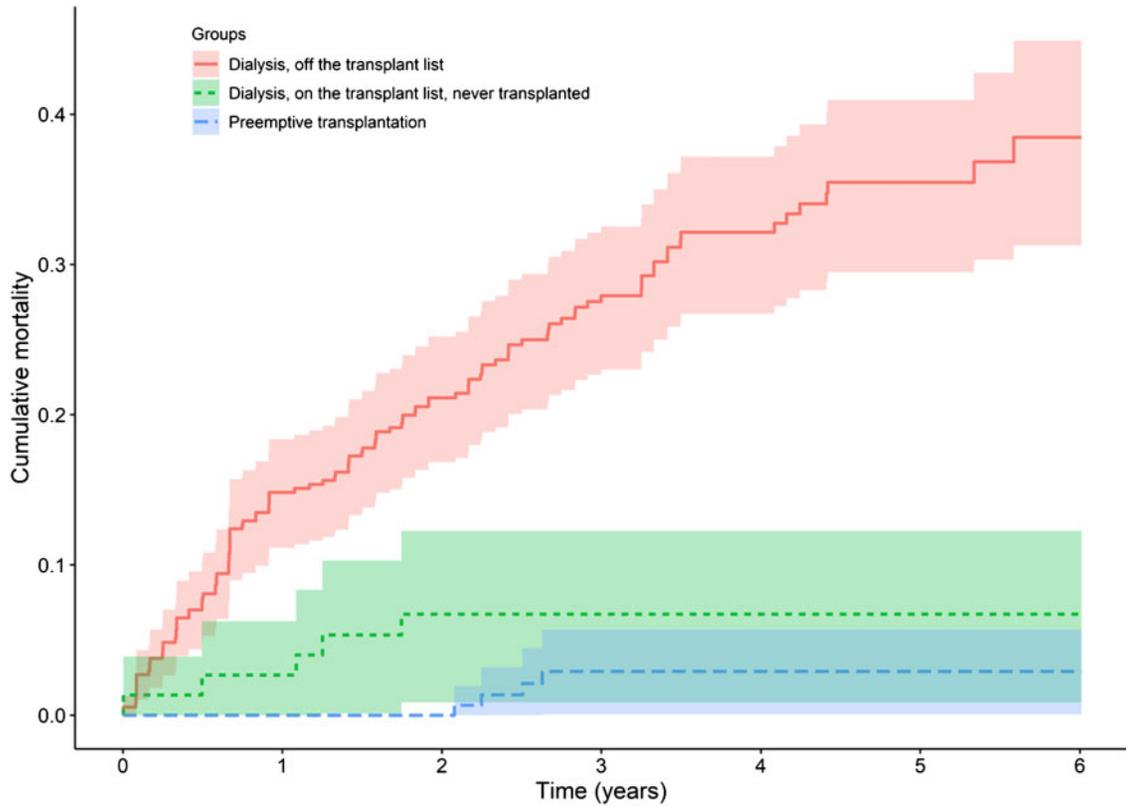


FIGURE 3: Cumulative mortality in IgAN ESRD patients with respect to medical care pathway (Gray estimator).

Table 6. Mortality rates with respect to kidney disease subgroups and medical care pathways in ESRD patients after 6 years of follow-up (Gray estimator)

	All patients		Preemptive transplantation		Dialysis on the transplant waitlist, never transplanted		Dialysis off the transplant waitlist	
	No. of patients	% death (95% CI)	No. of patients	% death (95% CI)	No. of patients	% death (95% CI)	No. of patients	% death (95% CI)
IgAN	1366	12.0 (10.2–13.8)	167	2.9 (0–5.6)	75	6.7 (0.9–12.3)	371	38.5 (31.3–44.9)
Primary GN subgroup	1277	19.7 (17.2–22.0)	75	9.0 (0.7–16.6)	59	11.4 (0–25.8)	545	41.0 (33.8–47.4)
Secondary GN subgroup	1015	29.8 (26.6–32.9)	32	19.3 (0–41.7)	40	20.9 (1.1–36.8)	530	50.6 (44.3–56.3)
ADPKD	3144	12.3 (11.0–13.6)	361	2.0 (0.2–3.7)	247	18 (3.1–30.6)	874	41.3 (36–46.2)
DN	11 174	49.8 (48.6–50.9)	203	7.0 (2.1–11.6)	250	46.2 (34.1–56.1)	7430	62.3 (60.6–64)

Primary GN subgroup comprises MN and primary FSGS; secondary GN subgroup comprises LN, MPGN, AAV, GP and HSP.

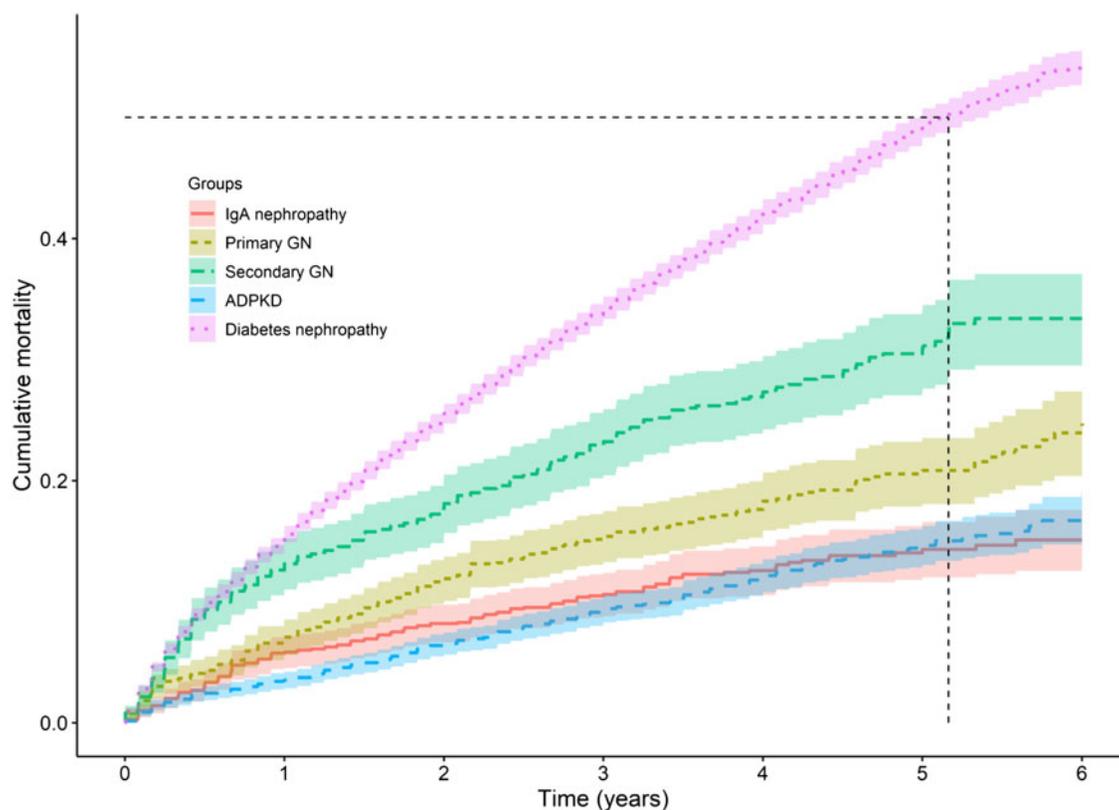


FIGURE 4: Cumulative mortality in ESRD patients with respect to kidney disease subgroups in patients receiving dialysis as a first treatment (Gray estimator). Kidney disease subgroups: (i) IgAN; (ii) primary GN subgroup (FSGS and MN); (iii) secondary GN subgroup (MPGN, LN, AAV, GP and HSP); (iv) ADPKD; (v) DN.

In the multivariable analysis, mortality hazards were lower in ADPKD (SHR = 0.78, 95% CI 0.64–0.94), higher in the secondary GN subgroup (SHR = 1.73, 95% CI 1.42–2.12) and in DN (SHR = 1.39, 95% CI 1.14–1.70), and not significantly different in the primary GN subgroup (SHR = 1.17, 95% CI 0.95–1.44) (Figure 5).

Six-year mortality rates varied across care pathways (Table 6). Patients off the transplant waitlist for transplantation had the highest mortality rate in both GN and non-GN subgroups. In ADPKD, IgAN and DN groups, the lowest mortality rates were reached for patients with preemptive transplantation (2.0%, 95% CI 0.0–5.6; 2.9%, 95% CI 0.0–5.6; and 7.0%, 95% CI 2.1–11.6, respectively). Conversely, in the primary and secondary GN subgroups, the lowest mortality rates were reached for patients treated first by dialysis before transplantation (6.0%, 95% CI 2.2–9.6; and 6.7%, 95% CI 2.9–10.3, respectively). Mortality

rates for patients with preemptive transplantation versus those treated by dialysis waiting transplantation but never transplanted varied according the nephropathy were 2.9% (95% CI 0–5.6) versus 6.7% (95% CI 0.9–12.3) for IgAN, 9% (95% CI 0.7–16.6) versus 11.4% (95% CI 0–25.8) in the primary GN subgroup, 19.3% (95% CI 0–41.7) versus 20.9% (95% CI 1.1–36.8) in the secondary GN subgroup, 2% (95% CI 0.2–3.7) versus 18% (95% CI 3.1–30.6) for ADPKD and 7.0% (95% CI 2.1–11.6) versus 46.2% (95% CI 34.1–56.1) for DN (Table 6).

Mortality and risk factors

After adjustment on kidney-related causes of ESRD, frailty accounted for the main risk factor for mortality (SHR = 1.73, 95% CI 1.61–1.85), followed by malignancy (SHR = 1.44, 95%

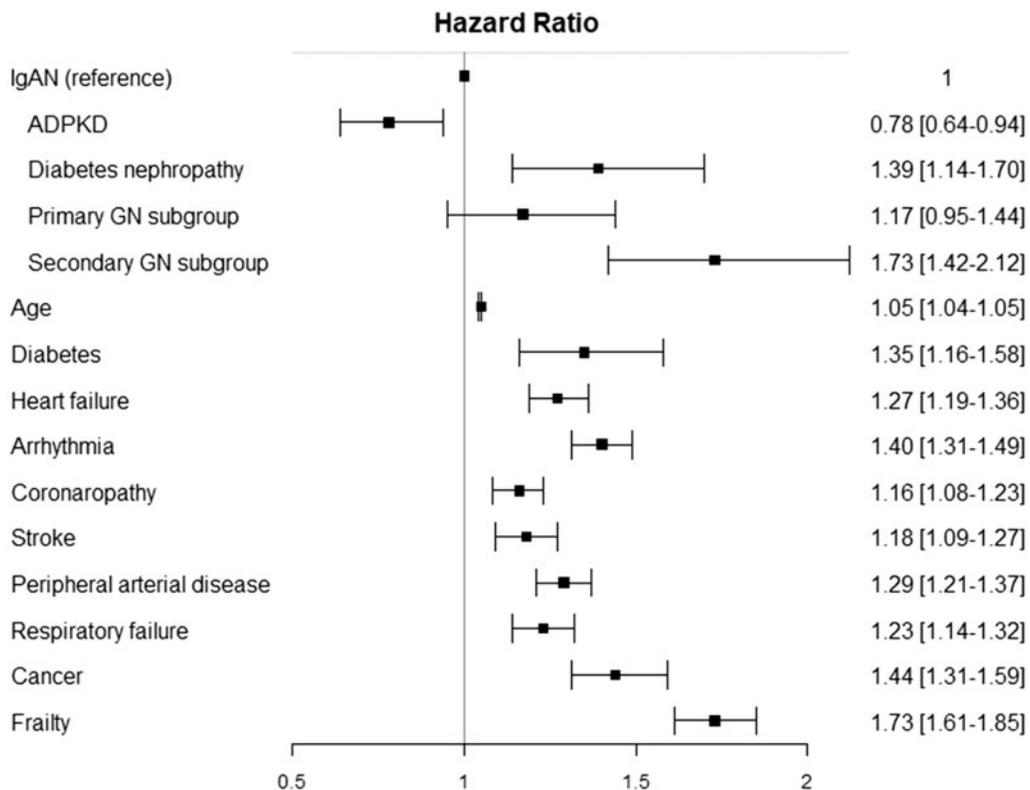


FIGURE 5: Multivariable HRs of mortality regarding patients' characteristics and renal disease in ESRD patients receiving dialysis.

CI 1.31–1.59), arrhythmia (SHR = 1.40, 95% CI 1.31–1.49), diabetes (SHR = 1.35, 95% CI 1.16–1.58), heart failure (SHR = 1.27, 95% CI 1.19–1.36), coronaropathy (SHR = 1.16, 95% CI 1.08–1.23), cerebrovascular disease (SHR = 1.18, 95% CI 1.09–1.27) and peripheral artery disease (SHR = 1.29, 95% CI 1.21–1.37) (Figure 5).

We observed some differences in primary causes of death across kidney-related causes of ESRD. Cardiovascular disease accounted for the highest proportion of deaths within all subgroups, ranging from 19.7% in ADPKD to 27.1% in DN. The highest proportion of infection-related deaths was observed in secondary GN subgroup (18.5%), contrasting with a 7.7% rate in ADPKD patients. Malignancy-related deaths were the highest in IgAN (11.9%) and the lowest in DN (4.6%) (Figure 6).

DISCUSSION

Few studies have reported the survival outcomes of ESRD related to biopsy-proven IgAN receiving dialysis and/or renal transplantation [13–16]. Most studies examining mortality outcomes after ESRD in GN and non-GN were restricted to single renal disease or combined renal diseases into a composite category [4]. Recently, O'Shaughnessy et al. [5] reported from the description of US Renal Data System that post-ESRD survival highly depended on kidney disease and could not be estimated globally. To our knowledge, our study is the first to report comorbidities, survival and outcomes in biopsy-proven IgAN compared with other biopsy-proven GN subtypes, ADPKD and diabetes in Europe.

We analysed all ESRD-incident patients in France who started dialysis or received a preemptive kidney transplant between 2010 and 2014. Though a northward gradient related to IgAN is well described across European countries, we did not find this trend in biopsy-proven IgAN patients who needed RRT on this nationwide scale. O'Shaughnessy et al. [5] reported the

incidence of IgAN to be higher in Southern than in Northern USA. We found several hotspots with incidences up to 18 per million inhabitants in patients >45 years old. IgAN (35.4%) was the most frequent GN subtype leading to ESRD-related dialysis. O'Shaughnessy et al. reported IgAN (15.4%) as the third cause of ESRD, behind FSGS (40.7%) and LN (19.5%). This finding does not preclude a more severe phenotype of IgAN between US and European countries, but suggests different genetic predisposition across the broad spectrum of IgAN. Possible causes of the different prevalence of GN worldwide are divergent indications for renal biopsy, high discrepancies of annual renal biopsy rate across the world and various socioeconomic conditions. Our study reported lower baseline comorbidity for patients with IgAN, compared with other primary and secondary GN groups and the non-GN subgroup. Cirrhosis was more frequently observed in the IgAN group, indicating that liver disease may influence the development of IgAN.

Distribution of ESRD therapy modalities (PD, HD and preemptive transplantation) was consistent with findings from O'Shaughnessy et al. [17] Access to preemptive transplantation was similar between IgAN and ADPKD patients. Even after adjustment, patients with primary or secondary GN had significantly lower access to preemptive transplantation than DN. IgAN was the renal disease with the most important access to PD after adjustment on age, sex, cardiovascular comorbidities and frailty status. Our results differed from those reported by O'Shaughnessy et al., who found that primary GN subtypes (FSGS, MN and MPGN) were as likely as IgAN to receive transplantation or PD. This imbalance in initial ESRD treatment modalities suggests that they depend on practice patterns of renal disease management and may impact mortality.

In IgAN patients, patients receiving dialysis and on the transplant waitlist but never transplanted had a lower survival,

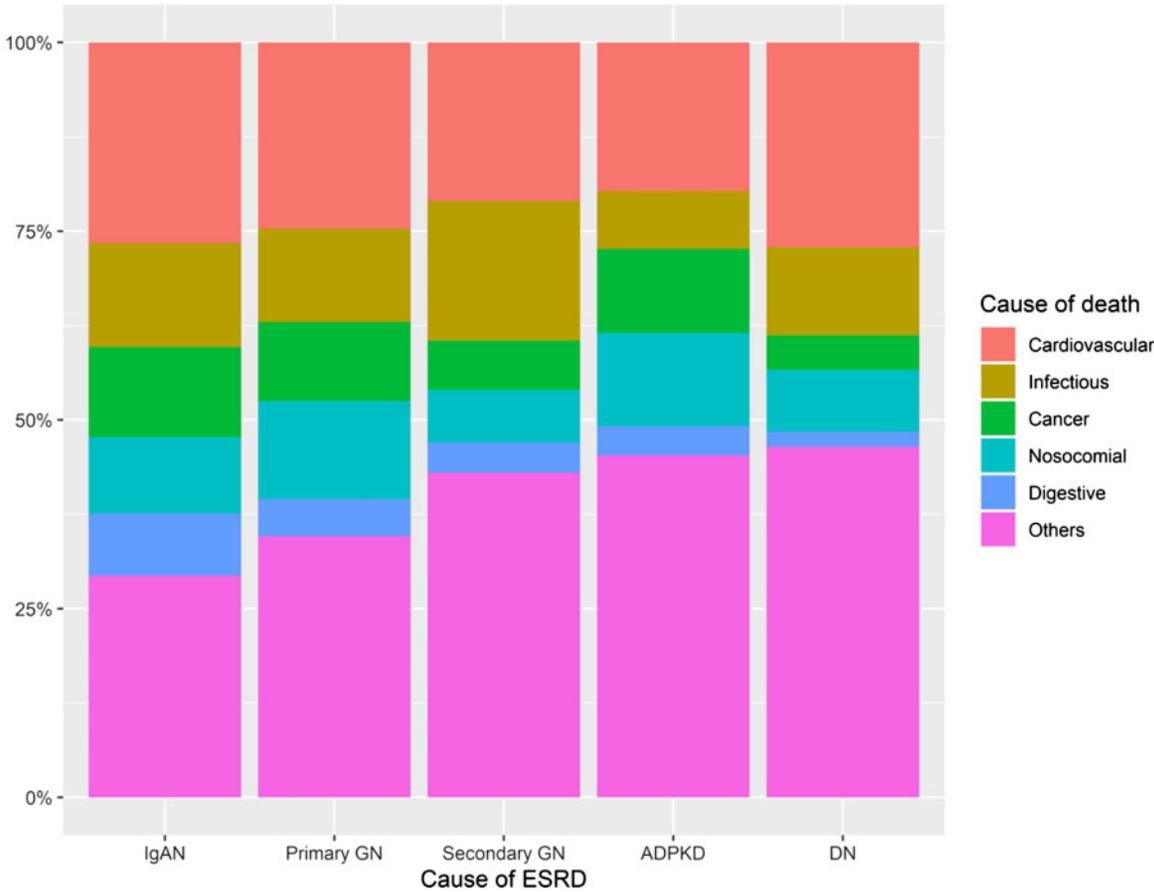


FIGURE 6: Causes of death with respect to kidney disease subgroups in patients receiving dialysis as first RRT. Kidney disease subgroups: (i) IgAN; (ii) primary GN subgroup (FSGS and MN); (iii) secondary GN subgroup (MPGN, LN, AAV, GP and HSP); (iv) ADPKD; (v) DN.

with 6-year mortality rates of 6.7% (95% CI 0.9–12.3). Patients off the waitlist had a dramatic survival decrease with a mortality rate of 38.5% (95% CI 31.3–44.9) (Figure 3 and Table 6). To our knowledge, survival differences between medical care pathways in post-ESRD patients with biopsy-proven IgAN had never been reported before.

After adjustment on age, comorbidities and frailty status, ESRD-related IgAN or ADPKD treated by dialysis had a survival advantage over other GN subgroups or DN patients. These results agree with those reported by O’Shaughnessy *et al.* [5], who highlighted the importance of distinguishing between renal diseases in ESRD outcomes research and especially between GN subtypes. Nonetheless, dialysis patients with ADPKD had a more favourable prognosis than those with IgAN (SHR = 0.78, 95% CI 0.64–0.94), which differs from data reported by O’Shaughnessy *et al.* Of note, mortality rates in patients on the transplant waitlist were the lowest among IgAN patients, which conferred a particularly favourable prognosis compared with ADPKD patients (Table 6). However, mortality rate at 6 years came from a Fine–Gray method, and is therefore not adjusted, requiring careful interpretation.

Our study has several limitations. Some patients classified in the DN without renal biopsy may have superimposed nephroangiosclerosis or primary GN like MN, FSGS or IgAN, and may represent a limitation in this study. As an observational study, mortality differences across renal diseases cannot be assumed as causation. Detailed socioeconomic data were not available (free social security programme, personal educational

attainment, employment status and neighbourhood-level socioeconomic characteristics). We could not distinguish the relative contributions from appropriate and inappropriate practice patterns of renal disease management decisions to study findings. Our findings apply to patients who survived to ESRD long enough to require RRT.

In conclusion, we have shown in a national biopsy-proven ESRD population study that IgAN represents the renal disease with the better prognosis among primary and secondary GN. These differences are mostly explained by patients’ characteristics and access to ESRD treatment modalities. Patients with IgAN receiving dialysis and on the transplant waitlist seem to have a more favourable prognosis than ADPKD patients. The underlying reasons for the difference in access treatment modalities should be investigated to improve survival according to renal disease.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

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