

ANNUAL REPORT

2017 Annual Report Digest of the Renal Epidemiology Information Network (REIN) registry

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SUMMARY

The French Renal Epidemiology and Information Network (REIN) registry started in 2002 with the goal to provide a tool to evaluate renal replacement therapy (RRT) practices and outcomes, to provide data for research and to support public health decisions related to end-stage renal disease ESRD. This summary presents the incidence and prevalence of RRT including kidney transplantation and wait-listing activity in 2017, and patients' survival and trends over 5 years. In 2017, 11 543 patients started RRT for ESRD, that is, incidence of 172 pmp. Between 2012 and 2017, the incidence of RRT increased by 1% per year [CI 95% (0.0; +2.0)]. On 31 December 2017, 87 275 patients were receiving RRT, that is, prevalence of 1294 pmp, 55% on dialysis, 45% with a functioning transplant. In 2017, 3782 kidney transplantations have been performed including 16% from a living donor, 13% being retransplantations and 15% pre-emptive transplantations. The median time on the waiting list was 19.7 months when only taking into account active waiting periods on the list. In 2017, 5280 new patients were registered on the renal transplant waiting list (i.e. 78.7 pmp). The number of patients considered as 'inactive' represented 45% of the patients on the list.

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Key words

end-stage renal disease, incidence, prevalence, registry, survival, transplantation

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Introduction

The French Renal Epidemiology and Information Network (REIN) registry started in 2002 with the goal to provide a tool to evaluate renal replacement therapy (RRT) practices and outcomes, to provide data for research and to support public health decisions related to end-stage renal disease (ESRD) [1]. Every year, the REIN Registry's Annual Report describes the epidemiology of RRT for ESRD in France (mainland and overseas territories). This summary presents the incidence and prevalence of RRT including kidney transplantation and wait-listing activity in 2017, and patients' survival and trends over 5 years [2].

Methods

The REIN registry relies on a network of nephrologists, epidemiologists, patients and public health representatives, coordinated regionally and nationally. The REIN data warehouse is fed from two main sources of information: the information that comes directly from the dialysis centre via a specific application (DIADEM) and the information that comes directly from the transplant centre via a specific application (CRISTAL) that is coordinated by the French Organ Transplant registry. Both databases share a unique identifier that allows analysing the overall RRT trajectory of the patients.

Continuous registration covers all dialysis and transplanted patients in the 13 regions of Mainland France and four overseas territories. Thus far, it does not include patients with stage 5 Chronic Kidney Disease (CKD) on conservative treatment. The registry progressively spread throughout the country and reached the nationwide coverage in 2012.

New (incident) patients are reported from the first day of RRT (dialysis or renal transplantation). Patients with a diagnosis of acute renal failure are not included. The incidence rate per million population (pmp) represents the number of patients starting RRT for ESRD in 2017 divided by the general population on the 30 June 2017 and multiplied by one million. The prevalence rate pmp represents the number of patients alive receiving renal RRT for ESRD on 31 December 2017 divided by the general population on this same date multiplied by one million. The age and sex distribution of the general population was provided by The National Institute of Statistics and Economic Studies [3]. Adjusted rates (direct standardization) were derived by applying the weights of the French population to the observed variable-specific rates (e.g. incidence rate per age group). For each RRT modality, we provide the absolute number of patients and rates in per cents and pmp.

Patient survival on RRT was analysed from day 1 until death of the patient or censoring date (recovery of renal function or loss to follow-up of 31 December 2017). This analysis includes all incident patients who started RRT between 2002 and 2017. Unadjusted survival rates were calculated using the Kaplan-Meier method with the corresponding confidence intervals. Trends in mortality rates are presented for prevalent patients treated each year, according to the number of patients-years at risk in dialysis or with a renal graft or overall.

Access to renal transplantation waiting list and to renal transplantation was estimated by taking into account the competing risk of death. In the first case, the event of interest was the time between dialysis start and registration on the waiting list up to 31 December 2016. In case of pre-emptive registration (registration before dialysis start), time to registration on the waiting list was set to 0. Considering the access to renal transplantation, the outcome was the time between RRT start and renal transplantation up to 31 December 2016. Similarly, time to transplantation was set to 0 in case of pre-emptive transplantation. These analyses include all incident patients who started RRT between 2011 and 2016. Cumulative incidences were calculated by the method described by Fine and Gray. We consider the period of active status on the waitlist, or eligible for a transplant if a kidney is offered.

To detect potential significant changes in trends over the past 5 years, a Joinpoint regression model was used and expressed as Annual Percentage changes (APC) [4].

Analysis was performed using SAS Enterprise Guide 7.1 and the Joinpoint Trend Analysis Software from the National Cancer Institute [5].

The French health care system

The French health care system is based on a Statutory health insurance (SHI), made of several subsystems depending on professional status of insured persons [6]. Since 2000s, 100% of the French population are covered by the SHI, thanks to the 'Couverture Maladie Universelle' (CMU) Fund. Patients with ESRD, in particular those starting RRT, are eligible for 100% reimbursement rate of necessary health care, through the 'affection de longue durée' (ALD) program. The ALD program thus provides good financial accessibility to nephrologist and dialysis care for all patients, despite their individual level of income. If usually patients pay providers directly for ambulatory care, payment is paid directly by the SHI for the most expensive cares, such as dialysis sessions. Health care services include both public and private providers: general practitioners (GPs) providing primary care are usually private self-employed professionals. Outpatient nephrology and dialysis care are mainly provided by specialists working in public or private non-profit hospitals, while a little share of the care is delivered to private for-profit hospitals. Patients are free to choose their physicians and hospitals, but GPs have a role in the coordination of the care, through a system that provides incentives to patients to visit their GP prior to being referred to a specialist. In order to better regulate health care expenditures, the state plays an important role in planning and regulating health system. At the regional level, a regional health agency (Agence régionale de santé; ARS) is in charge of planning ambulatory and hospital care, through building a regional health project (Projet Régional de Santé; PRS), based on the population's needs. In particular, the ARS has the responsibility for improving cooperation between primary and secondary care and between outpatient and inpatient services within the region. Nevertheless, since both GPs and private specialists remain free to establish their practice where they wish, certain areas are underserved with an insufficient number of physicians. Thus, geographic disparities in the distribution of physicians and health services across the country induce geographic disparities in access to primary care, nephrologist and dialysis care.

The Agence de la biomédecine, under the auspices of the French Ministry of Health, manages the national waiting list for organ transplantation and the national register of refusal for organ and tissue donation. It also maintains the register of cross-over donations of organs between living people. It devises rules for the allocation of organs. It is responsible for regulating the procurement and allocation of organs and monitoring the state of health of living organ donors.

Results

Figure 1 presents some key results on incidence, prevalence and status changes for patients on renal replacement therapy in France in 2017.

Incidence of RRT

In 2017, 11 543 patients started RRT for ESRD, resulting in an unadjusted incidence of 172 pmp. Of the patients starting RRT, 64% were men and 38% were

aged ≥ 75 years (64% ≥ 65 years). The median age at RRT initiation was 70.5 years old. The leading causes of ESRD were hypertension (24%) and diabetic (23%) nephropathies; only 19% of the patients have had a renal biopsy. Patients starting RRT present a high rate of comorbidities especially diabetes (47% of the new patients) and cardiovascular diseases (57% of the new patients; Table 1). Dialysis was initiated in an emergency manner in 28% of the patients. This finding contrasts with the fact that 56% of patients started haemodialysis on a catheter. The incidence rates varied greatly between age groups and sex (Fig. 2). The majority of patients started on haemodialysis (HD, 85.2%, 146 pmp), while 10.1% of patients started with peritoneal dialysis (PD, 17 pmp), and 4.7% received a preemptive kidney transplant (8 pmp). Age and gender standardized RRT incidence was almost twice as high in the overseas territories than in mainland France, 310 vs. 168 pmp. Between 2012 and 2017, the incidence of RRT increased by 1% per year [CI 95% (0.0; +2.0); Fig. 3].

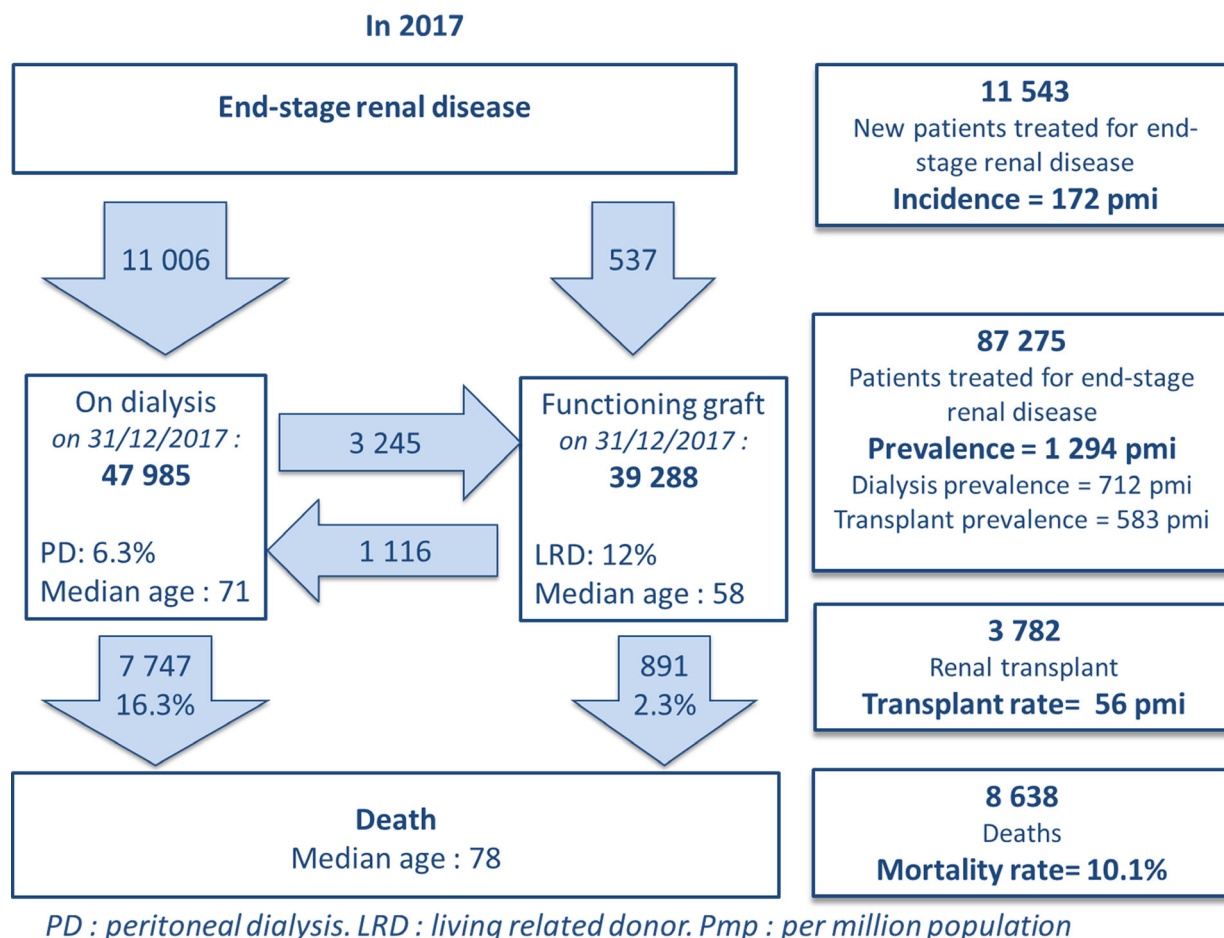
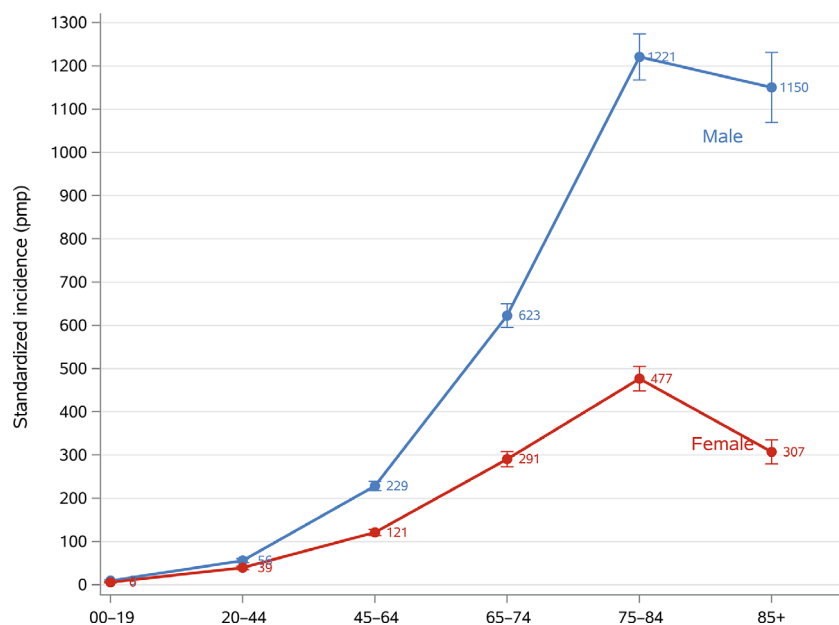


Figure 1 Key figures for renal replacement therapy in France in 2017. PD, peritoneal dialysis; LRD, living related donor; pmp, per million population.

Table 1. Frequency of comorbidities at dialysis start and various initial conditions

Comorbidities	Aged less than 70 years <i>n</i> = 5132		Aged over 70 years <i>n</i> = 5874		Missing value (%)	<i>P</i> value
	<i>n</i>	%	<i>n</i>	%		
BMI ≥ 30 kg/m ²	1206	28.3	1136	22.7	15.8	<0.0001
Diabetes	2175	42.7	2989	51.3	0.8	<0.0001
Ischaemic heart disease	918	18.6	1865	32.8	3.5	<0.0001
Chronic heart failure	884	17.8	1938	34.0	3.1	<0.0001
Dysrhythmia	562	11.3	1965	34.3	2.8	<0.0001
Peripheral vascular disease	770	15.8	1410	25.2	4.9	<0.0001
Stroke	425	8.6	774	13.5	2.9	<0.0001
cancer	422	8.5	766	13.4	2.7	<0.0001
Autonomous for transfer	4265	90.6	4227	78.8	8.5	<0.0001
Peritoneal dialysis	576	11.2	592	10.1	0	0.0516
Start in emergency	1403	28.6	1480	26.4	4.6	0.0117
Start with a central vascular catheter	2569	54.4	3053	56.6	11.1	0.0063
Start with eGFR >20 ml/min/1.73 m ²	181	3.9	318	6.0	10.0	<0.0001

**Figure 2** 2017 Incidence rates of treated end-stage renal disease, by age and gender (per million population).

The increase in the absolute number of incident patients was especially noticeable for patients aged 65–74 and 85 years and over. In patients without diabetes, a decrease started in 2013 with a marked decrease in 2016. In patients with diabetes, the increase was important between 2012 and 2015, stabilized in 2016 and increased again in 2017 (Fig. 4).

Prevalence of RRT

On 31 December 2017, 87 275 patients were receiving RRT for ESRD resulting in an overall unadjusted

prevalence of 1294 pmp. Median age was 65 years old. The majority of prevalent patients (51.5%, 667 pmp) were receiving HD, 45% of patients were living with a functioning kidney transplant (583 pmp) and only 3.5% were receiving PD (45 pmp). The median age of the patients on dialysis was 71 years old and 57.8 years old in patients living with a functioning transplant. An increase in the absolute number of patients receiving RRT was especially obvious in elderly patients (Fig. 5). Between 2012 and 2017, annual percentage changes in the absolute number of patients on dialysis and living with a functioning graft

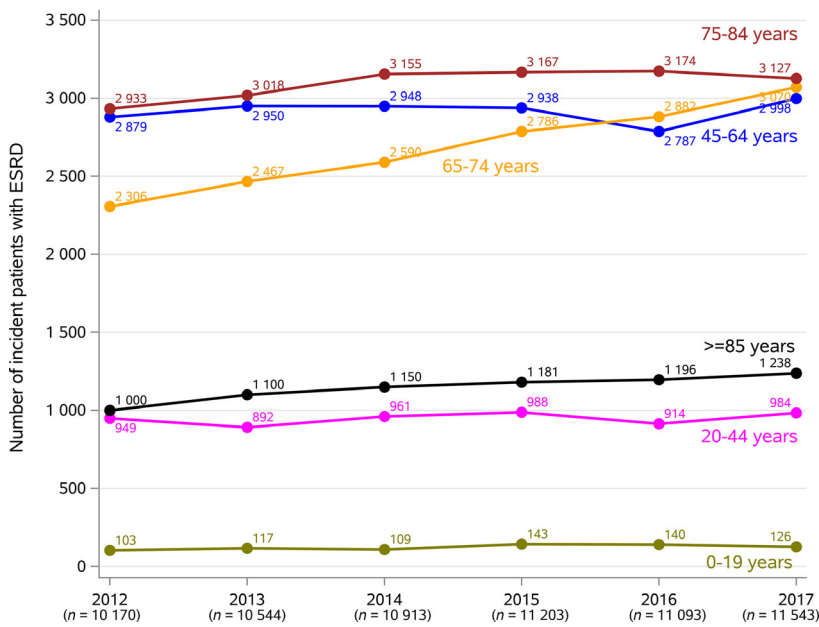


Figure 3 Trends in Incidence rates of treated end-stage renal disease, by age group, between 2012 and 2017.

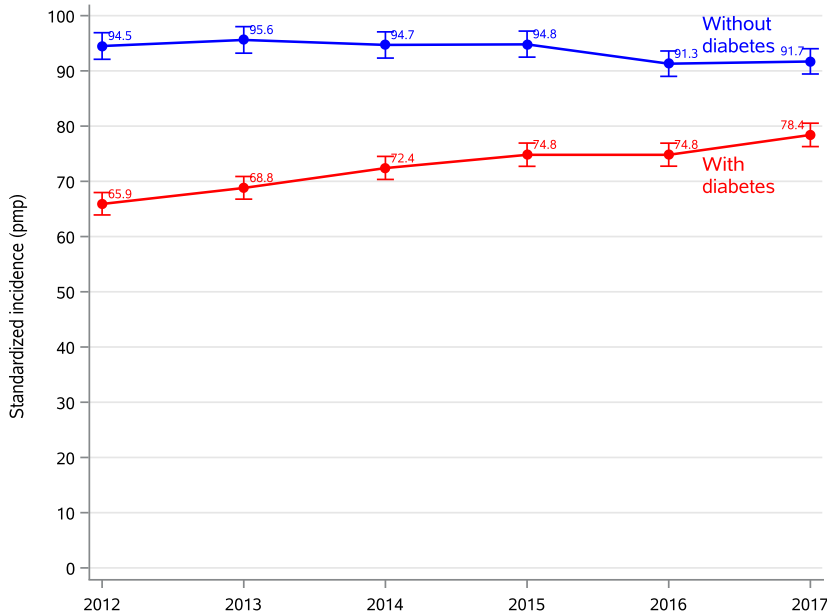


Figure 4 Trends in standardized incidence rates of treated end-stage renal disease associated or not with diabetes (per million population).

were similar [dialysis: +3.9% IC 95% (+3.5; +4.2), transplantation +3.8% IC 95% (+3.5; +4.2)]. Over the same period, the annual percentage changes in the adjusted prevalence were higher for patients living with a functioning graft [+3%, IC 95% (+2.7; +3.3)] than for dialysis patients [+1.9%, IC 95% (+1.3; +2.5)] (Fig. 6).

Survival

Patient's age was strongly associated with survival. Indeed, 1-year survival of patients under age 65 was

93% vs. 78% among patients over 65 years. Five-year survival rates were only 77% and 35% in these two age groups respectively (Fig. 7). Mortality rates are stable in dialysis and in transplanted patients around 16% and 10% respectively (Fig. 8).

Access to kidney transplantation

In 2017, 3782 kidney transplantations have been performed including 16% from a living donor, 13% being retransplantations and 15% pre-emptive transplantations. The median time on the waiting list (50% of the

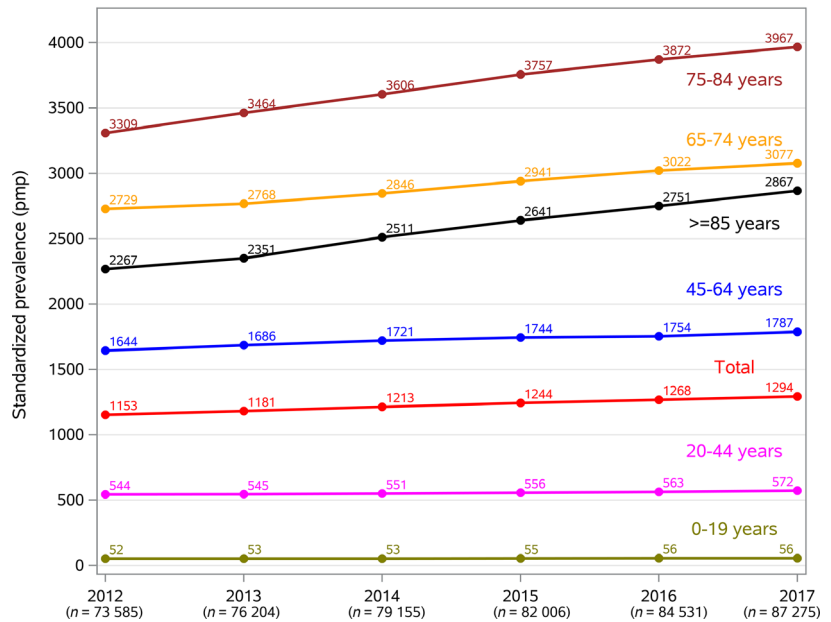


Figure 5 Trends in standardized prevalence rates of treated end-stage renal disease, by age group, between 2012 and 2017.

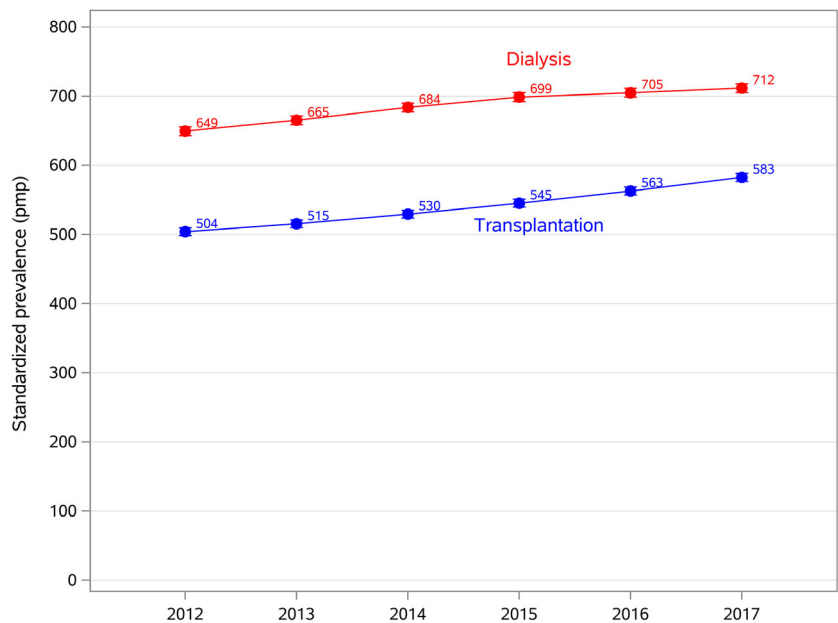
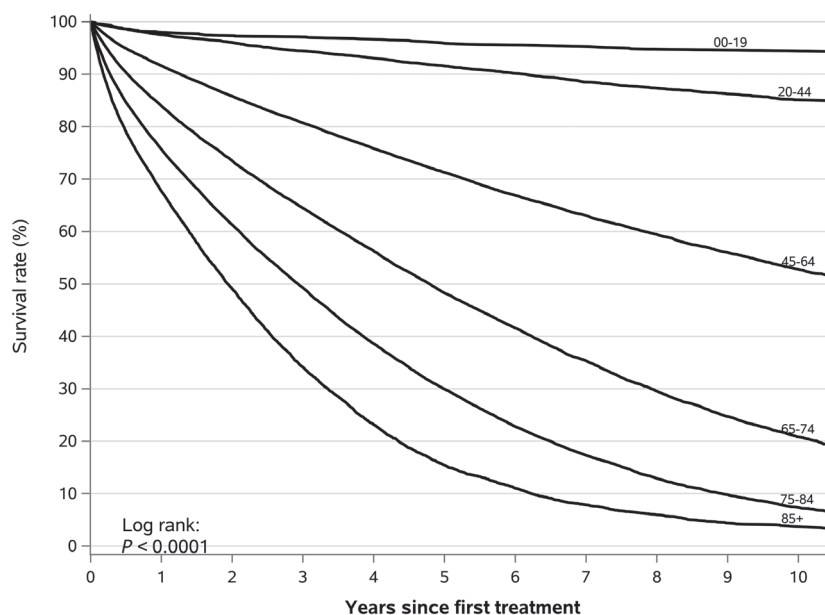


Figure 6 Trends in standardized prevalence rates of treated end-stage renal disease according to renal replacement therapy (per million population).

patients being transplanted before this date) was 32.4 months for the patients listed between 2012 and 2016 after excluding patients with a living donor or a combined transplantation. However, the median waiting time was reduced to 19.7 months when only taking into account active waiting periods on the list. In France, registration of renal transplant candidates on the national waiting list is mandatory, including those with living donors. Despite the increasing activity of transplantation 18 793 patients were still waiting for a kidney transplant in 2017 (+6% vs. 2016). In 2017, 5280 new patients were registered on the renal transplant waiting

list (i.e. 78.7 pmp; Fig. 9). It is important to note that the number of patients considered as ‘inactive’ represented 45% of the patients on the list. This finding attenuates the apparent inadequacy between the number of candidates and the number of transplantation performed. Access to the waiting list was analysed in a cohort of 61 234 new patients who started dialysis between 2011 and 2016 in France. The probability of being listed at dialysis initiation was 5% (pre-emptive registrations) and increased from 16% at 12 months to 26% at 36 months and 29% to 60 months. Fifty-six per cent of waitlisted patients were initially on inactive



Age	Survival rate (CI 95%)	Survival rate (CI 95%)			
		at 1 year	at 3 years	at 5 years	at 10 years
00-19	(n = 1 588)	98,0 [97,3-98,7]	97,2 [96,3-98,0]	96,0 [94,9-97,1]	94,6 [93,2-96,0]
20-44	(n = 11 850)	97,5 [97,2-97,8]	94,4 [94,0-94,9]	91,6 [91,0-92,1]	85,1 [84,2-86,0]
45-64	(n = 34 673)	91,6 [91,3-91,9]	80,7 [80,3-81,2]	71,3 [70,7-71,8]	52,8 [52,0-53,6]
65-74	(n = 30 832)	84,0 [83,5-84,4]	64,5 [63,9-65,1]	48,3 [47,6-48,9]	20,8 [20,1-21,6]
75-84	(n = 36 692)	75,7 [75,2-76,1]	49,3 [48,7-49,8]	30,0 [29,4-30,5]	7,4 [6,9-7,9]
Over 85 years	(n = 11 836)	67,7 [66,8-68,6]	34,1 [33,2-35,1]	15,4 [14,6-16,3]	3,7 [3,1-4,4]

Figure 7 Crude survival rate in 2002–2017 incident patients, by age.

status for a median time of 4 months before being on the ‘active’ list. The probability of being registered was strongly associated with age (Fig. 10). Among 15 630 patients less than 60 years old, the probability of being registered was 14% at the start of dialysis, 41% at 12 months, 64% at 36 months and 70% at 60 months (median dialysis duration: 17 months).

Access to kidney transplant was evaluated on a cohort of 63 582 new patients who started a renal replacement therapy (dialysis or pre-emptive renal transplant) between 2011 and 2016 in France (Fig. 11). The probability of receiving a first kidney transplant was 8% at 12 months, 18% at 36 months and 24% at 60 months. Among the 17 275 new patients aged less than 60 years old, the probability of being transplanted was of 20% at 12 months, 44% at 36 months and 57% at 60 months (median waiting time: 45 months). When pre-emptive transplants were excluded, these probabilities decreased to 12% at 12 months, 38% at 36 months and 53% at 60 months.

Discussion

Compared to other European ESRD registries, the French REIN registry collects specific information such as initial care (i.e. emergency start, temporary vascular access) and several patient’s comorbidities at dialysis initiation that are updated annually during patient’s follow-up. In France, median age at RRT start is among the oldest in Europe with a median age of 70 years old and 65% with age >65 years [7]. As in other countries, the leading causes of RRT are hypertension and diabetes. Although the prevalence of diabetes in the general population is lower than in other part of the world, incident patients present high rates of diabetes (i.e. 47%) and cardiovascular comorbidities (i.e. 57%). We found a consistent high rate of patients starting dialysis in an emergency manner (28%) and a high rate of haemodialysis initiation on a temporary vascular catheter (i.e. 56%) [8,9]. The distribution of RRT modalities is within the average distribution observed in European registries with a relatively low

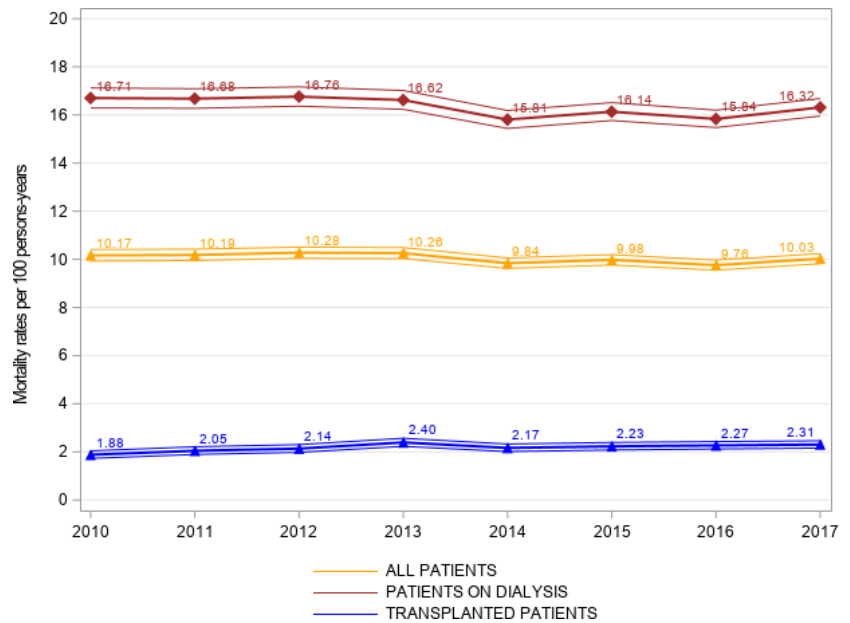


Figure 8 Evolution of the mortality rates (number of death per 100 patients-years at risk).

access to pre-emptive transplantation and living donor transplantation and a relatively low use of peritoneal dialysis [10].

Unlike other European countries, the number of new patients starting RRT has steadily increased mainly because of ageing and growth of the French general population but the increase of the adjusted incidence rate is exclusively found in patients with diabetes [11].

Identification of these growing subgroups suggests a need for improvement in the screening for CKD in ageing and diabetes patients and the need to facilitate research to develop new specific treatment and models of care to slow down CKD progression.

Compared to other countries, pre-emptive kidney transplantation remains low, even if it is increasing steadily. However, the benefit of such strategy is still in debate

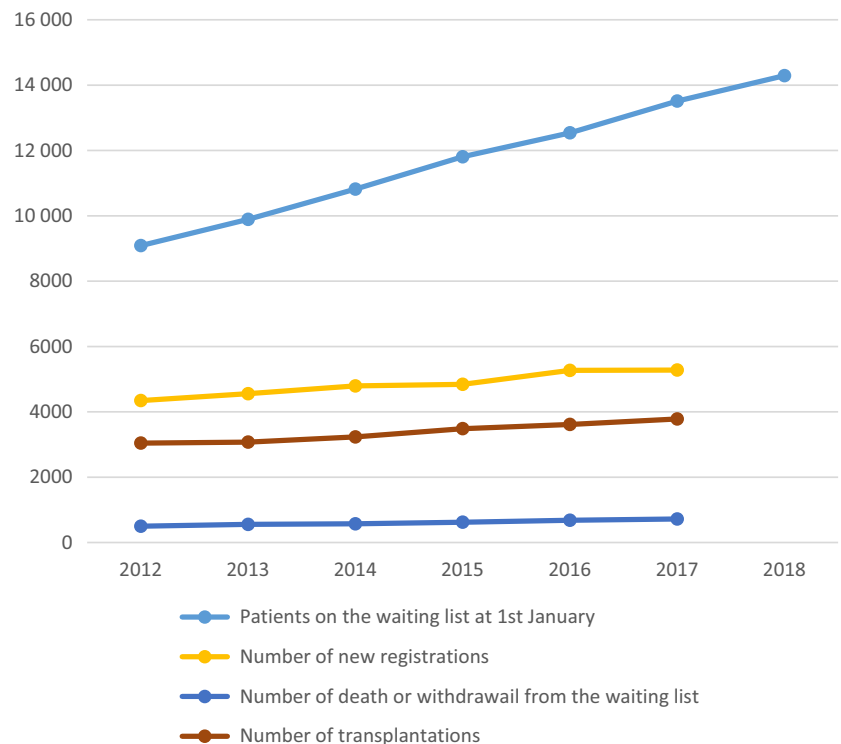
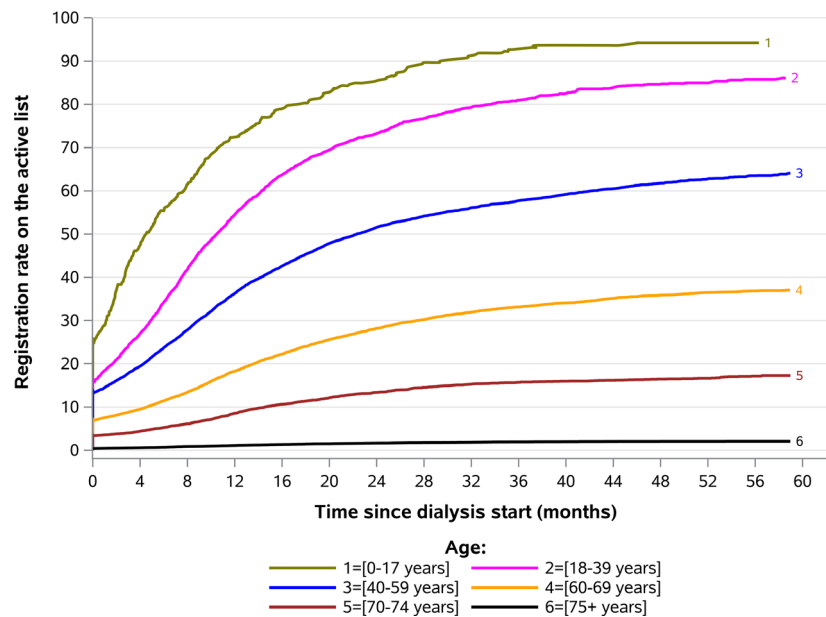


Figure 9 Evolution of the waiting list and outcomes of the patients on the list.



Age (years)	n	Registration rate on the active waiting list											
		M0		M12		M24		M36		M48		M60	
	%	CI95%	%	CI95%	%	CI95%	%	CI95%	%	CI95%	%	CI95%	
0-17	447	23.3	[19.5-27.3]	70.6	[65.9-74.8]	84.6	[80.4-88.0]	91.8	[87.9-94.5]	93.8	[89.7-96.2]	95.5	[91.4-97.7]
18-39	3 487	15.3	[14.1-16.5]	54.9	[53.2-56.7]	72.4	[70.7-74.0]	79.5	[77.8-81.0]	83.0	[81.3-84.5]	85.2	[83.5-86.8]
40-59	11 696	12.8	[12.2-13.4]	36.3	[35.4-37.2]	51.8	[50.8-52.8]	58.0	[57.0-59.1]	61.8	[60.7-62.9]	64.1	[63.0-65.3]
<60	15 630	13.6	[13.1-14.2]	41.4	[40.6-42.3]	57.3	[56.5-58.2]	63.7	[62.9-64.6]	67.4	[66.5-68.3]	69.7	[68.7-70.7]
60-69	13 570	6.3	[5.9-6.8]	17.7	[17.1-18.4]	27.2	[26.4-28.1]	32.1	[31.2-33.0]	34.8	[33.8-35.7]	35.9	[34.9-37.0]
70-74	7 372	2.7	[2.4-3.1]	7.4	[6.8-8.1]	12.0	[11.2-12.9]	14.2	[13.3-15.2]	15.1	[14.1-16.1]	15.6	[14.6-16.7]
75+	24 662	0.3	[0.3-0.4]	0.9	[0.8-1.0]	1.4	[1.2-1.6]	1.6	[1.4-1.8]	1.7	[1.5-1.9]	1.7	[1.5-1.9]
Total	61 234	5.4	[5.2-5.5]	15.8	[15.5-16.1]	22.8	[22.4-23.2]	25.9	[25.5-26.3]	27.6	[27.2-28.0]	28.6	[28.1-29.0]

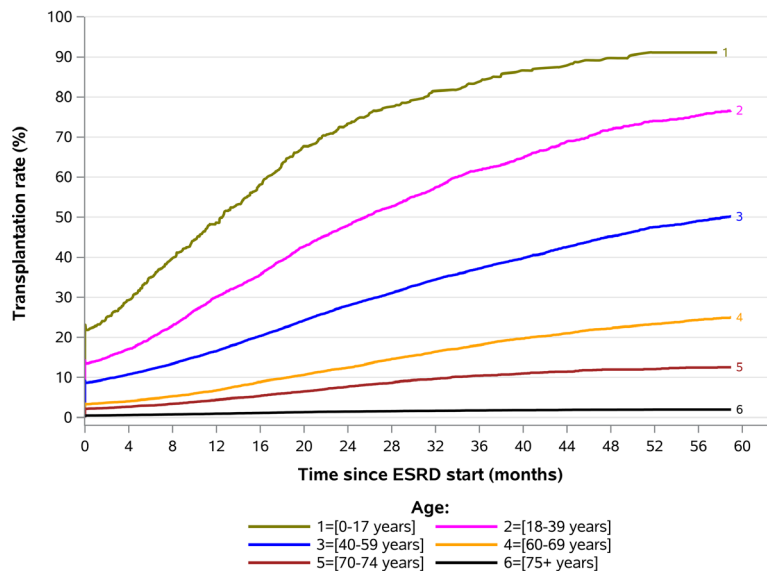
Figure 10 Cumulative incidence of registration on the national waiting list for a kidney transplantation, by age.

from a national point of view especially with regard to the consequential increase in the waiting list [12–14].

The majority of prevalent patients are treated with HD (52%) or are living with a kidney transplant (45%), when only 3.5% are treated with PD. The use of PD in France remains low even if assisted PD is fully covered by health care insurance and this technique is fully supported by the French Scientific Society [10,15,16]. No clear explanation can be given for this. Patients' education and their implication in a shared-decision process may be improved.

Patient's characteristics are very different between dialysis-treated patients and patients living with a functioning graft highlighting the selection process to receive a transplant. We also observed an overall increase in the prevalence of transplanted patients, especially in older groups. This trend can be explained by the improvement of life expectancy with transplantation and also by the improvement in the access to kidney transplantation

for elderly patients. Despite these positive trends, the number of patients between the age 70 and 80 registered on the waiting list remains low. This evolution of patients' profile induces new specific expertise in the field of geriatric and diabetes besides infectious disease, immunology and cancer. However, the observed ageing of the population and access of more patients with comorbidities to RRT could limit further increase in the number of prevalent patients living with a functioning transplant. Transplant teams are already developing a geriatric-kidney transplantation activity and are using new tools for this population to develop access to kidney transplantation [17]. The benefit of kidney transplantation in elderly patients remains debated and further studies are needed to better identify good candidates for transplantation and to improve models of care and patient satisfaction [14]. Additionally, availability of kidney transplants is also [18] a limiting factor to develop kidney transplantation in elderly patients. The



		Access rate to transplantation											
		M0		M12		M24		M36		M48		M60	
Age (years)	n	%	CI95%	%	CI95%	%	CI95%	%	CI95%	%	CI95%	%	CI95%
0-17	584	23.5	[20.1-27.0]	49.4	[45.1-53.6]	72.0	[67.6-76.0]	84.1	[79.8-87.5]	90.0	[85.6-93.1]	90.8	[86.3-93.9]
18-39	3 980	12.4	[11.4-13.4]	28.6	[27.1-30.0]	45.6	[43.9-47.3]	59.8	[57.9-61.6]	69.9	[68.0-71.7]	75.1	[73.1-76.9]
40-59	12 711	8.0	[7.5-8.5]	15.8	[15.2-16.5]	26.8	[26.0-27.6]	36.6	[35.6-37.6]	44.2	[43.1-45.3]	50.0	[48.7-51.2]
<60	17 275	9.5	[9.1-10.0]	19.9	[19.3-20.5]	32.6	[31.8-33.4]	43.5	[42.6-44.4]	51.7	[50.7-52.7]	57.2	[56.1-58.3]
60-69	14 031	3.3	[3.0-3.6]	6.9	[6.5-7.4]	13.0	[12.4-13.6]	18.5	[17.7-19.2]	22.0	[21.1-22.9]	25.0	[23.9-26.1]
70-74	7 524	2.0	[1.7-2.4]	4.1	[3.7-4.6]	7.5	[6.8-8.2]	10.1	[9.3-11.0]	11.6	[10.7-12.5]	12.2	[11.2-13.2]
75+	24 752	0.4	[0.3-0.4]	0.8	[0.7-0.9]	1.2	[1.1-1.4]	1.5	[1.3-1.7]	1.6	[1.4-1.8]	1.6	[1.4-1.8]
Total	63 582	3.7	[3.5-3.8]	7.8	[7.5-8.0]	13.2	[12.9-13.5]	17.9	[17.5-18.2]	21.2	[20.8-21.7]	23.6	[23.2-24.1]

Figure 11 Cumulative incidence of kidney transplantation (including pre-emptive transplantation), by age.

use of transplants from expanded criteria donors may be a solution to improve the access of elderly patients to transplantation without decreasing the access to more optimal transplant for younger patients [19]. On the other end of the spectrum, access to renal transplantation is good for French children, even if the access to pre-emptive could be improved [20]. To respond to changes in patients' characteristics and expectations, the development of different model of care integrating conservative care and different modality of RRT according to their prognosis and comorbidities are needed [17].

Ageing and increasing diabetes frequency with several vascular comorbidities strongly influence access to waiting list and patient survival. Although it is difficult to compare survival rates without adjusting for comorbidities, age-specific survival rates in France are at least similar to survival rates reported in Europe as a whole, based on the results of the 12 countries contributing data to the ERA-EDTA registry [10].

The major strengths of the REIN registry are the nationwide inclusion of all patients with RRT for ESRD in a country of 65 million inhabitants and the number

and relevance of collected items. Completeness and accuracy are systematically ascertained for items deemed essential by a team of research assistants [1]. The participation rate of centres is 100%. One limitation of the REIN registry is its restriction to RRT patients only. It is planned to expand the registry to all CKD stage 5 patients in a near future to analyse the place of conservative care and factors associated with access to RRT.

In conclusion, these data underline the need to take into account the growing share of elderly and highly comorbid patients reaching ESRD. This rises new challenges such as the improvement of the screening of elderly patients, the evaluation of the individual benefit of renal replacement therapy in these patients and the development of conservative care. Considering kidney transplantation, current challenges encompass improving the selection of suitable patients, adapting surgical procedures to older and frailer patients as well as developing new strategy to expand the kidney donor pool such as the use of extended criteria donors, the development of kidney exchange programs and of incentives to increase deceased and living donation.

For more information (in French):

Annual Report of the French Transplant Agency:
<https://www.agence-biomedecine.fr/annexes/bilan2017/donnees/organes/06-rein/synthese.htm>

Annual Report of the French ESRD REIN Registry:
https://www.agence-biomedecine.fr/IMG/pdf/rapport_rein_2017_v2.pdf

Authorship

ML: contributed to the conception and design of the study, conducted the statistical analyses and interpreted

the results. EM, CA, OM and JH: contributed to the conception and the design, to the acquisition of the data and the interpretation of the results and revised the manuscript. CC: contributed to the conception and the design of the study, conducted the analyses, interpreted the results and drafted the manuscript. All authors reviewed and approved the final version.

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Conflict of interest

The authors have declared no conflicts of interest.

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