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TITRE

Analyse de la mortalité globale et cardiovasculaire chez les patients hémodialysés chroniques en région Centre-Val de Loire

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En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
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Table des matières

Résumé :

Introduction : La mortalité subite (MS) représente près de 11 à 25% des causes de décès chez les patients hémodialysés chroniques. Cette étude rétrospective a pour but d'analyser la mortalité globale et cardiovasculaire afin de déterminer les facteurs de risque de MS en se basant sur le registre des patients hémodialysés en région Centre-Val de Loire.

Méthodes : Cette étude rétrospective multicentrique a inclus consécutivement tous les patients traités par hémodialyse en région Centre-Val de Loire. Les événements évalués étaient les décès toute cause, les MS, les décès cardiovasculaires non subits et les décès de causes non cardiovasculaires.

Résultats : 3978 patients ont été inclus entre Janvier 2003 à Décembre 2017. 2542 patients sont décédés (63.9%) dont 332 de cause cardiovasculaire non subite (13.1%), 334 de MS (13.1%) et 1876 de cause non cardiovasculaire (73.8%). La durée de suivi moyenne était de 3.030±2.723 années. L'incidence annuelle de la mortalité toute cause et de la MS étaient respectivement de 21.08% et de 2.77%. Celles-ci semblent stables dans le temps. Bien que moins fréquente, la survenue de la MS était plus précoce dans l'évolution comparativement aux autres causes de décès. Après analyse multivariée, les facteurs de risque de MS étaient l'insuffisance cardiaque (HR 1.38 (IC 95%: 1.08-1.77); p=0.01), les arythmies (HR 1.41 (IC 95%: 1.08-1.83); p=0.011) et la néphropathie hypertensive (HR 1.44 (IC 95%: 1.13-1.85); p=0.003). Le sexe féminin était un facteur protecteur (HR 0.71 (IC 95%: 0.55-0.93); p=0.012). A partir de ces données, nous avons réalisé un nouveau score prédicteur de MS.

Conclusion : La mortalité chez les patients hémodialysés chronique en région Centre-Val de Loire reste élevée avec 13.1% de mort subite. Nous avons créé un score prédictif de mort subite afin d'identifier précocement les patients à haut risque à l'entrée en dialyse.

Mots clés : dialyse, mort subite, facteur prédictif

Abstract

Background and Purpose: Sudden death (SD) accounts for 11% to 25% of death in hemodialysis (HD) patients. The aim of this study was to analyze global and cardiovascular mortality in order to determine SD risk factors by using the Region Centre-Val de Loire Registry of HD patients.

Methods: This observational retrospective multicenter study has included all consecutive patients treated with HD in the Region Centre-Val de Loire. Events evaluated were all-cause mortality, SD, nonsudden cardiovascular death (NSCD) and noncardiovascular death (NCD).

Results: 3978 patients were included between January 2003 to December 2017 in whom 2542 deaths were recorded (63.9%): 334 SD (13.1%), 332 NSCD (13.1%) and 1876 NCD (73.8%). The mean duration of follow-up was 3.030±2.723 years. The annual incidence of all-cause mortality and SD were respectively 21.08% and 2.77%. These ones seem to remain stable over the time. SCD was less frequent but occurred earlier compared to other causes of death. By multivariate analysis, risk factors of SD were heart failure (HR 1.38 (IC 95%: 1.08-1.77); p=0.010), arrhythmia (HR 1.41 (IC 95%: 1.08-1.83); p=0.011) and hypertensive nephropathy (HR 1.44 (IC 95%: 1.13-1.85); p=0.003). Female sex was a protective factor of SD (HR 0.71 (IC 95%: 0.55-0.93); p=0.012). Based on these results, we developed a new predictive risk score of SD

Conclusion: The mortality in HD patients of Region Centre-Val de Loire remains high with 13.1% of SD. We created a predictive score of SD in order to determine precociously patients at high risk at the start of dialysis.

Key words: dialysis, sudden death, risk factor

Abbreviations

AUC: Area under the curve

CI: Confidence interval

CKD: Chronic kidney disease

CV: Cardiovascular

HD: Hemodialysis

HR: Hazard ratio

ICD: Implantable cardioverter-defibrillators

LV: Left ventricular

LVEF: Left ventricular ejection fraction

NCD: Noncardiovascular death

NSCD: Nonsudden cardiovascular death

ROC: Receiver operating characteristic

SCD: Sudden cardiac death

SD: Sudden death

INTRODUCTION

Chronic hemodialysis (HD) patients experience a high annual mortality rate of 17% in a United-States (US) Registry. The primary cause of death in these patients is cardiovascular (CV), with sudden death (SD) constituting a significant proportion (from 11% to 25% of all-cause mortality according to registries) [1,2].

This high SD rate in this population may be explained by the combination of a vulnerable myocardium and an acute proarrhythmic trigger [3].

Ischemic and hypertrophic cardiomyopathy are particularly prevalent in this population (41% and 75% respectively) [1,4].

Techniques modalities such as the frequency, duration sessions, ultrafiltration rate, potassium and calcium dialysate levels play a significant role in SD genesis [5,6,7]. Indeed, cardiac arrhythmias are highly sensitive to volume and electrolyte shifts which occur during dialysis. Moreover, repetitive myocardial injury brought on by hypoperfusion during dialysis lead to ureamic heart disease [8].

According to the French national registry from 2016, annual mortality rate doesn't decrease in the few past [2]. Accurate clinical identification of high-risk patients is so crucial for correct management, given the highlighted effectiveness of implantable cardioverter-defibrillators (ICD) in preventing SD [9].

Our retrospective study aims to analyze global and CV mortality in order to determine SD risk factors by using the Region Centre-Val de Loire Registry of hemodialyzed patients.

METHODS

Patients characteristics and study design

This observational retrospective multicenter study has included all consecutive patients treated with HD in the Region Centre-Val de Loire, from January 2003 to December 2017.

54 dialysis units are spread out over the Region Centre-Val de Loire which covers 39 151 km2. With 2.58 million habitants on January 2016, either 4% of the metropolitan population, the region is one of the least populated of metropolitan. According to the French national registry, 432 new patients started chronic HD therapy in 2016, yielding an incidence of 167 patients per million population.

Data were retrieved from the Region Centre-Val de Loire Registry of HD patients. No news datas were collected, and the data-abstraction forms were authorized by the regional coordinators.

All patients treated by chronic HD were included. Were excluded renal transplanted and peritoneal dialyzed patients.

Baseline characteristics were collected at the start of dialysis : Age (years), sex, body weight, tall, initial nephropathy, CV risk factors (diabetes, tobacco), CV diseases (heart failure, coronary insufficiency, myocardial infarction, arrhythmia (supraventricular and ventricular tachycardia), stroke, abdominal aortic aneurysm, peripheral artery occlusive disease), other comorbidities (chronic respiratory failure, cancer, cirrhosis, viral infection, amputation etc..), HD modalities (first seance in emergency, intravenous access etc..), laboratory parameters (glomerular filtration rate, hemoglobin, serum albumin) and treatment (erythropoietin, insulin).

Events evaluated were all-cause mortality, SD, nonsudden cardiovascular death (NSCD), and noncardiovascular death (NCD). SD was defined as unexpected natural death occurring within 1 h after the onset of symptoms, as commonly accepted. Some pre-existing heart diseases could already be known, but neither the time nor the cause of death was expectable. Patient died from hyperkalemia were not included in this definition.

This study was approved by the HD Regional Centre. Ethical review was, therefore, not required. Patient consent was not sought. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care.

Statistical analysis

Descriptive analyses were used to summarize baseline characteristics of the study patients. Continuous variables are presented as mean ± standard derivation or median [interquartile range], as appropriate, and categorical variables are given as proportions. Comparisons were made using non-parametric tests as appropriate: The Wilcoxon W and Kruskal – Wallis tests were used for comparing values between two independent groups and the Khi2 test for comparing categorical data.

The Kaplan-Meier event rate estimates were used to assess mortality. The hazard ratio (HR) and 95% confidence interval (CI) were calculated from the Cox proportional-hazards model.

Univariate and multivariate associations between baseline variables and mortality were assessed by means of the log-rank test and a Cox regression model. A p-value < 0.05 was considered statistically significant.

Multivariate analysis was realized for all variables with a P value of 0.05 or less in univariate analysis for SD. A parsimonious model for SD was developed by including only predictors that were found to be significant for SD in multivariate analysis.

Receiver operating characteristic (ROC) curves were constructed and areas under the curve (c-indexes) were calculated. A c-statistic of 0.5 was taken to represent a chance discrimination, and a value of 1 to correspond to perfect discrimination. The Harrell's c statistics with 95% confidence intervals were calculated as a measure of model performance. All analyses were performed using STATA version 12.0 (Stata Corp, College Station, TX).

Follow-up

Patients were followed until death, kidney transplantation, or the end of the study period on December 2017.

RESULTS

Baseline characteristics

3978 patients were included between January 2003 to December 2017 in whom 2542 deaths were recorded (63.9%) : 334 SD (13.1%), 332 NSCD (13.1%) and 1876 NCD (73.8%).

Table 1 and 2 present characteristics baseline of HD patients according to their final events status (i.e., alive, all cause of death, SD, NSCD and NCD). Dead patients were, at the time of the start of dialysis, significantly older than living patients, were more often men and had more frequently comorbidities such as CV diseases (hypertensive nephropathy, heart failure, coronary insufficiency, myocardial infarction, arrhythmia, abdominal aortic aneurysm, peripheral artery occlusive disease), viral infection (HBV, HIV) and cancer. These patients were thinner and had more often a low serum albumin rate which reflects of malnutrition. They received more often dialysis on catheter and were less treated with erythropoietin. The other comorbidities such as diabetes, stroke, chronic respiratory failure, cirrhosis and handicap were statistically similar between the two groups (Table 1).

Patients that died from SD had similar baseline characteristics compared to patients that died from NSCD, except for treatments (erythropoietin and insulin) and initial nephropathy (Table 2).

Follow-up

The mean duration of follow-up was 3.030±2.723 years (Median 2.222 years [0.89 ; 4.24]).

The annual incidence of all-cause mortality, SD, CD and NCD were respectively 21.08%, 2.77%, 2.75% and 15.56%.

Figure 1 shows the mortality trends according to the year of dialysis initiation. The incidence of mortality seems to remain constant over the study period.

Figure 2 shows survival curves of cumulative death incidence according to the type of death. The survival at 1 and 2 years was 70.3% and 51.8% respectively. The mean time to onset of death was 2.787±2.468 years for all patients (Median 2.098 years [0.79 ; 4.13]), 2.220±2.351 years for patients dead suddenly (Median 1.787 years [0.52 ; 3.43]), 2.857±2.494 years for patients dead of nonsudden CV cause (Median 2.156 years [0.86 ; 4.23]) and 2.832±2.520 years for patients dead of noncardiovascular cause (Median 2.144 years [0.76 ; 4.33]). SD was less frequent but occurred earlier compared to other causes of death (SD versus NSCD: p=0.0005; SD versus NCD: p=0.0092).

Comparing SD according to sex, men were more exposed than women (71.3% versus 28.7%; OR 0.66 (IC 95% : 0.52-0.84); p=0.001) (Figure 3).

Univariate Cox regression models demonstrated that the significant risk factors of SD were older age, male sex, tobacco, heart failure, coronary insufficiency, myocardial infarction, arrhythmia, peripheral artery occlusive disease and hypertensive nephropathy (Table 3).

Multivariate Cox model results are presented in Table 4. By the analysis, the independent significant predictors of SD in our population were heart failure (HR 1.38 (IC 95%: 1.08-1.77); p=0.010), arrhythmia (HR 1.41 (IC 95%: 1.08-1.83); p=0.011) and hypertensive nephropathy (HR

1.44 (IC 95%: 1.13-1.85); p=0.003). At the opposite, female sex was a protective factor of SD (HR 0.71 (IC 95%: 0.55-0.93); p=0.012).

Based on these considerations and literature data, we developed a new predictive risk score of SD in this particular population. The weight of each item was determined according to the HR of the multivariate analysis. Here is the detail of this score: female sex = -1 point; heart failure, arrhythmia and hypertensive nephropathy = 1 point each (Table 5). Receiver operating characteristic (ROC) curve analysis showed an area under the curve (AUC) at 0.627, with a sensibility of 35.84%, a specificity of 84.87%, a positive predictive value of 24.4% and a negative predictive value of 76.4% for a cut off ≥ 2 (Figure 4).

DISCUSSION

1) Epidemiology

In our study, annual mortality rate was 21%, with SD constituting a significant proportion (13.1%). In a US registry and in French REIN Registry, the mortality rate was lower (17% and 16% respectively) [1,2]. Similarly, the survival at 1 and 2 years was 70.3% and 51.8% respectively in our HD population, which is substantially higher than survival rates found in French National Registry (84% and 74%).

However, our SD rate is similar to that observed in French REIN Registry (11%, with an annual incidence of 2.77% p/y), unlike to data from the US registry (25%) [1,2].

These differences may be explained by different reporting schemes, dialysis practices, baseline patient characteristics or definitions.

Classification of SD could be problematic in HD patients since deaths frequently occur at home and exact timing is often unknown. Due to this difficulty, SD definitions used in studies of HD population have been variables, leading to wide variations in reported SD rates [10]. In aim to reduce the misclassification risk, we exclude of SD the unknown causes of death and cardiac arrests in the setting of withdrawal from dialysis therapy or after missing dialysis treatment.

Despite the improvement of dialysis practices and a better understanding of SD mechanisms, the incidence of mortality seems to remain stable over the time. These results corroborate those found by the French REIN Registry. The probability of survival at 1 and 2 years was similar in patients who started treatment in 2011/2012 and in those who started in 2013/2014 [2].

2) Risk factors and pathophysiology of Chronic kidney disease (CKD) - related SD

Pathophysiology of SD in CKD is complex and results from overlap between transient events and underlying disease. In contrast to the general population, left ventricular (LV) dysfunction and traditional CV risk factors cannot fully account for the high rates of SD [11].

However, we found 4 independant SD risk factors in multivariate analysis: Heart failure, arrhythmia, hypertensive nephropathy and male sex. Those results corroborate with literature data. Indeed, Mangrum et al showed in a retrospective study that left ventricular ejection fraction (LVEF) <30% was strongly associated with SD, although the majority of SD (71%) occurred in patients with >30% LVEF [12]. Genovesi et al, in a historical cohort of HD patients, demonstrated that the presence of atrial fibrillation was a significant risk factor for SD [13]. Recently, Hiyamuta et al also showed that HD men were more at risk of SD [14]. To our knowledge, the role of initial nephropathy in SD genesis was poorly studied and it seems according to our study that hypertensive nephropathy was a major SD risk factor.

Surprisingly, in multivariate analysis, myocardial infarction, coronary insufficiency and the others CV risk factors such as tobacco, diabetes and weight were not significant. Although the involvement of those factors remains debated, diabetes and ischemic heart disease appear as authentic SD risk factor according to recent studies [14,15].

Coronary artery disease is the primary cause of significant ventricular arrhythmia in the general population, with an estimated prevalence in HD patients of 41% (versus 20% in our study) [1]. The prevalence of microangiopathy is also important and may partly explain why revascularization does not improve ventricular arrhythmia or mortality in this specific population [16].

Left ventricular hypertrophy (LVH) is also a well-recognized risk factor for SD [17]. Its incidence in HD patients may increase from 25% to 40% at the initiation of HD to 70% to 90% after several years [18]. LVH is multifactorial and has been associated with hypertension, anemia, chronic fluid overload, increased arterial stiffness, chronic inflammation, and increased sympathetic activity [18]. Unfortunately, this data is missing in our study. Systematic transthoracic ultrasound could be done to search LVH or another structural cardiopathy.

Involvement of dialysis modalities in SD have been largely studied. For practical reasons, HD is generally performed 3 times a week. The 24-hour period around the HD session following the long interdialytic period (3 days) was associated with ventricular arrhythmias and conduction abnormalities [19,20]. Prolongation of QT interval, an increase of QT dispersion and an alteration in the capacity to adapt QT interval to heart rate changes (QTc) have been reported during HD session [21,22,23].

Moreover, rapid electrolyte shifts, short HD session, high ultrafiltration rate, low potassium and calcium dialysate levels have also been associated with a higher mortality risk [5,6,7].

These data were not available in the registry. In French REIN registry, it seems that dialysis in emergency was associated with a premature mortality. This criterion has not been found as a SD risk factor, probably because the causes of death are different.

Recently, Sacher et al have implanted 71 dialysis patients with implantable loop recorders (ILRs) to determine risks factors depending on the mechanisms of SD. Thus, a higher risk for conduction disorder was associated with plasma potassium >5.0 mmol/l, bicarbonate <22 mmol/l, hemoglobin >11.5 g/dl, pre-HD systolic blood pressure >140 mm Hg, the longer interdialytic period, history of coronary artery disease, previous other arrhythmias, and diabetes mellitus. A higher risk for

ventricular arrhythmia was associated with potassium <4.0 mmol/l, no antiarrhythmic drugs, and previous other arrhythmias [24].

A secondary analysis of the HEMO Study created an SCD prediction model that included age, diabetes, peripheral vascular disease, ischemic heart disease, serum creatinine and serum alkaline phosphatase level. Although model discrimination (C statistic = 0.75) and calibration were good, this prediction model has not been validated in other populations [15].

Our study established a score with simple factors which are all collected at the start of dialysis to identify high SD risk patients.

3) Prevention of SCD and therapeutic perspectives by ICD implantation

In HD patients, ICD implantation in secondary prevention is associated with greater survival [25]. Nevertheless, the evidence supporting efficacy of these devices in primary prevention is inconsistent because of randomized trials of ICDs have excluded patients with end-stage renal disease [26]. In current guidelines, there are no special considerations for dialysis status but ICD implantation is not recommended when life expectancy is less than 1 year [27]. In our study, the delay between the beginning of dialysis and SD occurrence was superior to 1 year (median 1.787 years [0.52 ; 3.43]) making licit to implant an ICD in primary prevention in case of high SCD risk.

Recently, a retrospective study including 203 patients showed that there is no benefit to implant an ICD in primary prevention [28]. This difference can be partially explained by a higher prevalence of major complications related to ICD such as hematoma, thrombosis, infection and elevated defibrillation threshold [29]. Lead-associated endocarditis requires not only removal of the ICD, but also often removal of the vascular access.

Perspectives

Subcutaneous implantable defibrillators appear as an advantageous alternative for HD patients to avoid vascular access complications and minimize infectious risk. Although they are not able to deliver cardiac pacing, 2 single-center studies reported favorable safety data with no device infection and no excess of inappropriate shocks in HD patients compared to non dialysed patients studied (7-13% in the S-ICD literature, due to SVT and T-Wave Oversensing) [30,31]. Moreover, there was a 100% success in cardioverting ventricular tachyarrhythmias, showing efficacy of the S-ICD in these patients.

4) Study limitations

A main limitation of this study was inherent to its retrospective observational nature.

Some deaths may be prone to misclassification because of a lack of systematic adjudication process. Moreover, many deaths are unwitnessed and limited information is available about the circumstances of death, making the exclusion of a noncardiac cause challenging.

Only variables at start of dialysis were available. It will be interesting to have some data (for example serum potassium levels) during the last dialysis seance immediately preceding the death.

Moreover, we don't have data about ICD implantation that can be a major bias when judging the occurrence of SD.

Some data known to be authentic SD risk factors in HD patients were unavailable, such as

echocardiographic parameters (LVEF, LVH) and some dialysis modalities (duration of session, ultrafiltration rate, potassium and calcium dialysate levels used). This may partially explain why our predictive score of SD isn't perfect.

CONCLUSION

The mortality in HD patients of Region Centre-Val de Loire remains high with 13.1% of SD. We identified simple independent predictive factors of SD presents at the beginning of dialysis that allowed us to create a predictive score of SD in order to determine precociously patients at high risk.

From these results, further analysis would be interesting if applied to the national French cohort of HD patients.

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Table 1: Baseline characteristics of hemodialysis patients according to the occurrence of death during follow-up (Part 1).

Variables	Dead patients (n= 2,542; 63.9%)	Survivors (n= 1,436; 36.1%)	p value
Age (years)	75.43±10.64	69.3±14.29	<0.0001
Weight	71.68±17.03	75.52±18.46	<0.0001
Tall	165.4±8.77	166.4±10.01	0.002
BMI	26.21±5.92	27.25±6.02	<0.0001
Female sex	856 (33.7%)	559 (38.9%)	0.001
Type of nephropathy			
- Diabetic	609 (24.0%)	342 (23.8%)	0.920
- Hypertensive	648 (25.5%)	288 (20.1%)	<0.0001
Renal biopsy	205 (8.4%)	231 (17.2%)	<0.0001
Comorbidities, n			
- Diabetes	1,132 (46.7%)	675 (48.2%)	0.37
- Tobacco	700 (30.4%)	356 (26.6%)	0.01
- Chronic respiratory failure	628 (32.2%)	620 (31.7%)	0.78
-> Home oxygen	72 (3.2%)	29 (2.2%)	0.07
- Heart failure	891 (38.5%)	355 (26.2%)	<0.0001
- Coronary insufficiency	554 (24.1%)	228 (16.9%)	<0.0001
- Myocardial infarction	256 (11.1%)	97 (7.2%)	0.0001
- Arrhythmia	599 (25.9%)	234 (17.2%)	<0.0001
- Abdominal aortic aneurysm	39 (5.3%)	21 (2%)	0.0002
- Peripheral artery occlusive disease	602 (26.2%)	203 (5.1%)	<0.0001
- Stroke	213 (9.1%)	130 (9.6%)	0.75
- Cancer	405 (17.5%)	179 (13.2%)	0.0005
- HBV	7 (0.3%)	13 (1%)	0.01
- HCV	21 (0.9%)	15 (1.1%)	0.57
- HIV	2 (0.1%)	6 (0.4%)	0.03
- Cirrhosis	48 (2.1%)	24 (1.8%)	0.52
- Handicap	317 (12.8%)	203 (14.9%)	0.07
- Amputation of the lower limbs	66 (2.7%)	34 (2.5%)	0.77
- Paraplegia	38 (1.6%)	28 (2.1%)	0.23
- Blindness	44 (1.8%)	35 (2.6%)	0.09
- Behavioral disorder	58 (2.4%)	31 (2.3%)	0.9
Hemodialysis modalities			
- First seance in emergency	1,199 (48.6%)	619 (46.4%)	0.2
- First seance on KT	1,571 (62.2%)	829 (58.5%)	0.03
- First seance in intensive care unit	87 (3.5%)	66 (4.7%)	0.05
- Days between AVF creation and first séance	158.55±365.88	174.05±316.43	0.32
- FAV made before first seance	1,990 (75.3%)	1,165 (81.1%)	0.033
- Type of dialysis			
-> Hemodialysis	112 (4.4%)	169 (11.8%)	<0.0001
-> Hemodiafiltration / hemofiltration	2,430 (95.6%)	1,267 (88.2%)	
- Heavy center	2,405 (94.6%)	1,292 (90.0%)	<0.0001
- Intravenous access			
-> FAV	714 (42.1%)	690 (52.2%)	<0.0001
-> KT	922 (54.4%)	603 (45.6%)	
-> Bridge or else	59 (3.5%)	30 (2.27%)	

Table 1: Baseline characteristics of hemodialysis patients according to the occurrence of death during follow-up (Part 2).

Variables	Dead patients (n= 2,542; 63.9%)	Survivors (n= 1,436; 36.1%)	p value
Laboratory parameters			
- MDRD	10.94±5.78	10.19±5.38	0.0002
- CKD-EPI	9.55±5.51	9.02±4.98	0.005
- Haemoglobin (g/dl)	10.1±1.67	10.05±1.62	0.36
- Serum albumin (g/dl)	33.84±5.67	34/78±5.93	<0.0001
Treatment			
- Erythropoietin	1,772 (72.7%)	1,092 (82.9%)	<0.0001
- Insulin	677 (26.6%)	426 (29.7%)	0.13

Table 2: Baseline characteristics of hemodialysis patients according to the cause of death: Nonsudden cardiovascular death (NSCD), sudden death (SD) and noncardiovascular death (NCD) (Part 1).

Variables	NSCD (n= 332; 13.1%)	SD (n= 334; 13.1%)	NCD (n= 1,876; 73.8%)	p value (CC vs SCD)
Age (years)	75.25±10.24	73.66±11.76	75.78±10.48	0.06
Weight	73.93±17.67	72.56±17.12	71.13±16.87	0.34
Tall	165.84±9.43	166.24±8.3	165.18±8.73	0.6
BMI	27.06±6.51	26.33±5.75	26.04±5.83	0.171
Female sex	103 (31.0%)	96 (28.7%)	657 (35.0%)	0.52
Type of nephropathy				
- Diabetic	91 (27.4%)	93 (27.8%)	425 (22.7%)	0.035
- Hypertensive	78 (23.5%)	109 (32.6%)	461 (24.6%)	0.005
Renal biopsy	19 (6.1%)	24 (7.5%)	162 (9.0%)	0.5
Comorbidities, n				
- Diabetes	170 (53.5%)	158 (49.1%)	804 (45.0%)	0.27
- Tobacco	89 (30.0%)	108 (34.6%)	503 (29.7%)	0.22
- Chronic respiratory failure	64 (21.3%)	54 (17.5%)	262 (15.5%)	0.24
-> Home oxygen	8 (2.7%)	11 (3.6%)	53 (3.2%)	0.54
- Heart failure	137 (45.8%)	136 (43.7%)	618 (36.2%)	0.6
- Coronary insufficiency	91 (30.6%)	85 (27.2%)	378 (22.3%)	0.36
- Myocardial infarction	46 (15.3%)	49 (15.8%)	161 (9.5%)	0.89
- Arrhythmia	84 (27.9%)	96 (30.4%)	419 (24.7%)	0.5
- Abdominal aortic aneurysm	4 (3.9%)	5 (7.1%)	30 (5.3%)	0.35
- Peripheral artery occlusive disease	87 (29.2%)	85 (27.3%)	430 (25.5%)	0.61
- Stroke	27 (9.1%)	24 (7.7%)	162 (9.6%)	0.54
- Cancer	35 (11.7%)	36 (11.5%)	334 (19.7%)	0.91
- VHB	0 (0%)	1 (0.3%)	6 (0.4%)	0.33
- VHC	1 (0.3%)	3 (1.0%)	17 (1.0%)	0.34
- VIH	1 (0.3%)	0 (0%)	1 (0.1%)	0.31
- Cirrhosis	6 (2.0%)	5 (1.6%)	37 (2.2%)	0.7
- Handicap	38 (11.6%)	41 (12.4%)	238 (13.0%)	0.76
- Amputation of the lower limbs	11 (3.4%)	8 (2.4%)	47 (2.6%)	0.47
- Paraplegia	6 (1.9%)	3 (0.9%)	29 (1.6%)	0.3
- Blindness	4 (1.2%)	6 (1.8%)	34 (1.9%)	0.55
- Behavioral disorder	1 (0.3%)	6 (1.8%)	51 (2.8%)	0.06
Hemodialysis modalities				
- First seance in emergency	151 (46.6%)	145 (44.5%)	903 (49.7%)	0.59
- First seance on KT	200 (60.8%)	199 (59.9%)	1,172 (62.8%)	0.82
- First seance in intensive care unit	12 (3.7%)	12 (3.6%)	63 (3.4%)	0.99
- Days between AVF creation and first séance	172.61±402.56	135.64±252.41	160.45±377.36	0.299
- FAV made before first seance	270 (83.3%)	278 (83.2%)	1,558 (83.0%)	0.89
- Type of dialysis				
-> Hemodialysis	15 (4.5%)	13 (3.9%)	84 (4.5%)	0.162
-> Hemodiafiltration / hemofiltration	317 (95.5%)	321 (96.1%)	1,792 (95.5%)	
- Heavy center	313 (96.6%)	685 (94.9%)	1,365 (94.1%)	0.224
- Intravenous access				
-> FAV	99 (43.4%)	89 (46.1%)	526 (41.1%)	0.679
-> KT	116 (52.0%)	98 (50.8%)	708 (55.4%)	
-> Brigde or else	8 (3.6%)	6 (3.1%)	45 (3.5%)	

Table 2: Baseline characteristics of hemodialysis patients according to the cause of death: Nonsudden cardiovascular death (NSCD), sudden death (SD) and noncardiovascular death (NCD) (Part 2).

Variables	NSCD (n= 332; 13.1%)	SD (n= 334; 13.1%)	NCD (n= 1876; 73.8%)	p value (CC vs SCD)
Laboratory parameters				
- MDRD	11.27±5.59	12.06±6.57	10.70±5.65	0.132
- CKD-EPI	9.81±5.07	10.76±6.82	9.29±5.29	0.0001
- Haemoglobin (g/dl)	10.06±1.65	10.28±1.82	33.67±5.76	0.12
- Serum albumin (g/dl)	34.02±5.07	33.65±5.64	10.08±1.65	0.18
Treatment				
- Erythropoietin	207 (65.7%)	252 (78.0%)	1,313 (73%)	0.001
- Insulin	111 (33.4%)	85 (25.5%)	481 (25.6%)	0.01

Table 3: Univariate analysis of predictive factors of sudden death

Variables	Hazard Ratio (95% CI)	P Value
Age	**1.05 (1.01-1.09)**	**0.016**
Female	**0.66 (0.52-0.84)**	**0.001**
Tobacco	**1.42 (1.12-1.79)**	**0.004**
Heart failure	**1.69 (1.35-2.11)**	**<0.001**
Coronary insufficiency	**1.44 (1.12-1.85)**	**0.004**
Myocardial infarction	**1.67 (1.23-2.27)**	**0.001**
Arrythmia	**1.77 (1.39-2.25)**	**<0.001**
Peripheral artery occlusive disease	**1.46 (1.14-1.87)**	**0.003**
Hypertensive nephropathy	**1.63 (1.30-2.05)**	**<0.001**
Diabetic nephropathy	1.17 (0.92-1.49)	0.195
Diabetes	1.08 (0.87-1.35)	0.482
Chronic respiratory failure	1.29 (0.96-1.73)	0.091
Home oxygen	1.54 (0.84-2.82)	0.16
Abdominal aortic aneurysm	2.39 (0.96-5.93)	0.061
Stroke	0.87 (0.57-1.31)	0.495
BMI	0.97 (0.93-1.01)	0.113
VHB	0.42 (0.06-2.97)	0.382
Cancer	0.83 (0.58-1.17)	0.285
Amputation of the lower limbs	1.08 (0.53-2.17)	0.835
Paraplegia	0.51 (0.16-1.59)	0.247
Blindness	0.87 (0.39-1.96)	0.74
Behavioral disorder	0.73 (0.33-1.96)	0.443
First seance in emergency	1.03 (0.83-1.29)	0.771
First seance on KT	1.20 (0.96-1.49)	0.107
FAV made before first seance	1.21 (0.91-1.62)	0.187
Hb	1.02 (0.98-1.06)	0.341
Erythropoietin	1.19 (0.91-1.55)	0.198
Insuline	0.76 (0.55-1.04)	0.084

Table 4: Multivariate analysis of predictive factors of sudden death

Variables	Hazard ratio (95% CI)	P Value
Age	1.03 (0.98-1.07)	0.233
Female sex	**0.71 (0.55-0.93)**	**0.012**
Tobacco	1.12 (0.86-1.45)	0.408
Heart failure	**1.38 (1.08-1.77)**	**0.010**
Coronary insufficiency	1.05 (0.79-1.39)	0.755
Myocardial infarction	1.26 (0.90-1.77)	0.177
Arrhythmia	**1.41 (1.08-1.83)**	**0.011**
Peripheral artery occlusive disease	1.15 (0.88-1.52)	0.306
Hypertensive nephropathy	**1.44 (1.13-1.85)**	**0.003**

Table 5: Details of items constituting our sudden death predictive score

Score risk factors	Points
- Female sex	- 1
- Heart failure	+ 1
- Arrythmia	+ 1
- Peripheral artery occlusive disease	+ 1
- Hypertensive nephropathy	+ 1

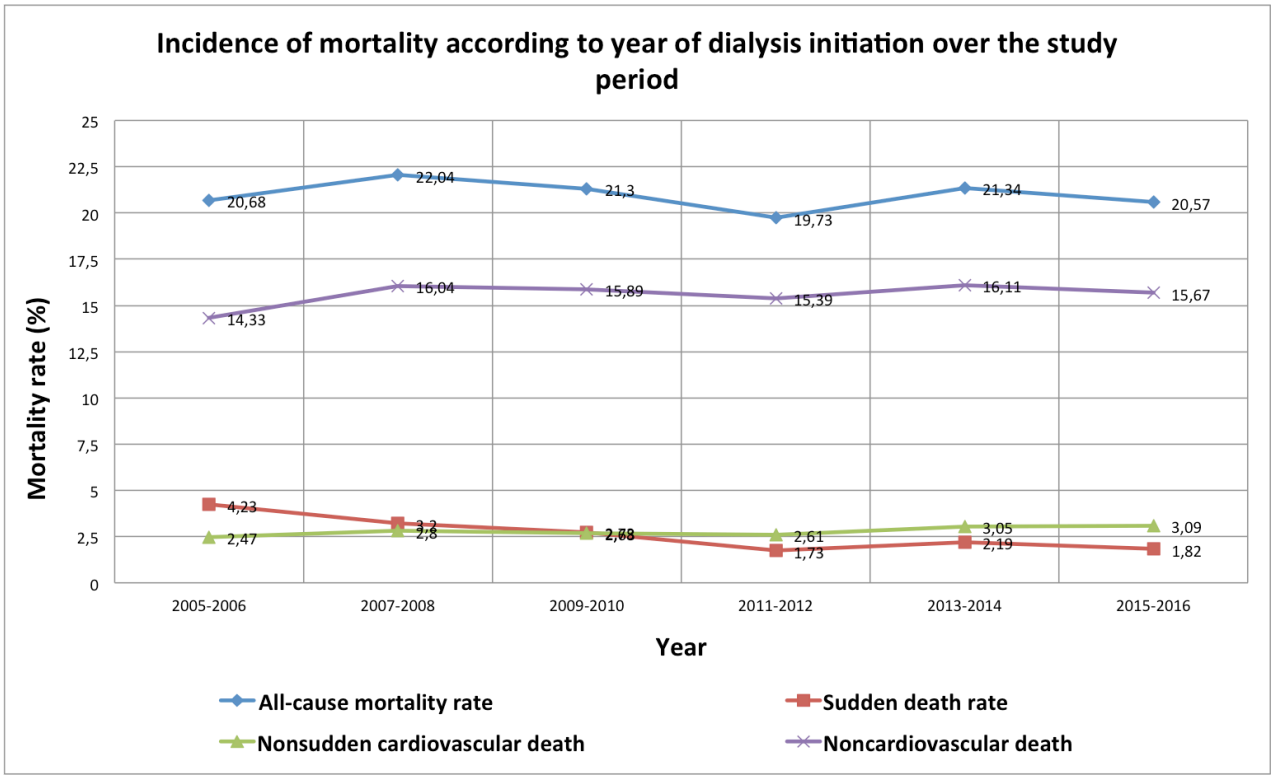

Figure 1: Incidence of mortality according to the year of dialysis initiation over the study period.

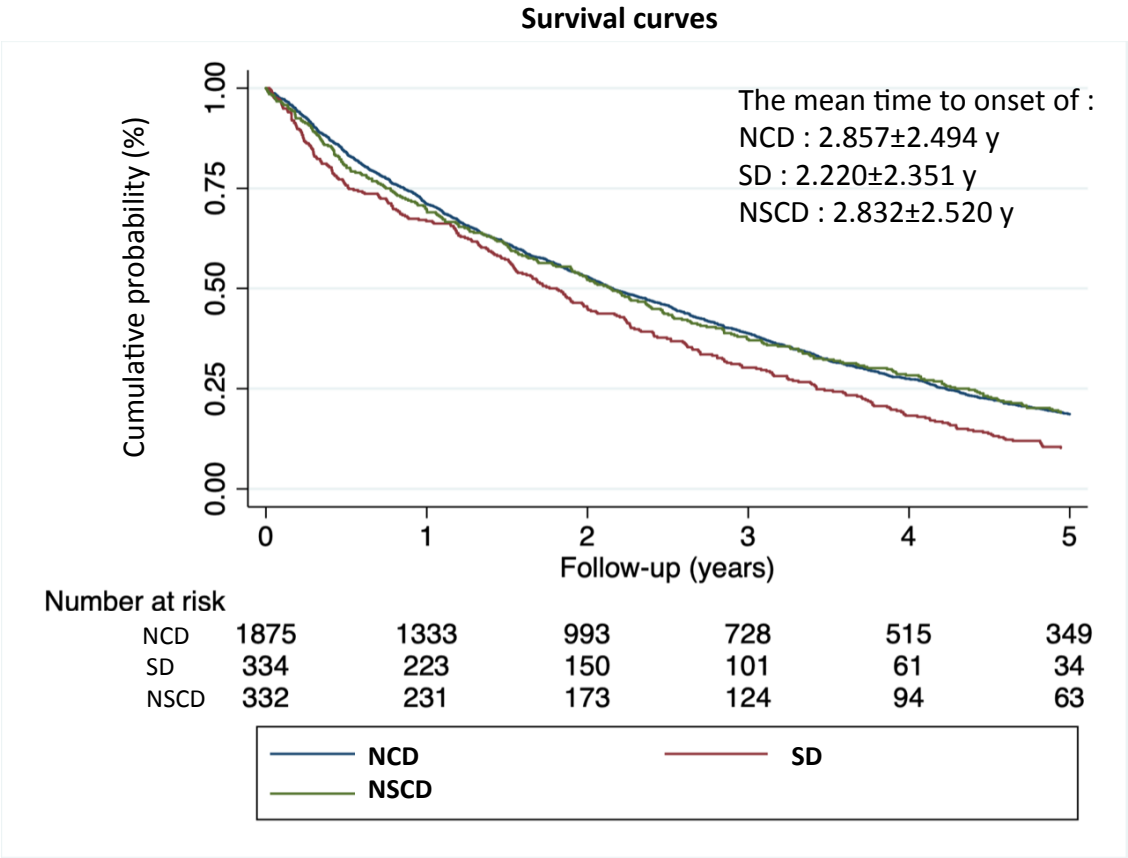

Figure 2: Kaplan-Meier curves comparing cumulative incidence of sudden death (SD), nonsudden cardiovascular death (NSCD) and noncardiovascular death (NCD).

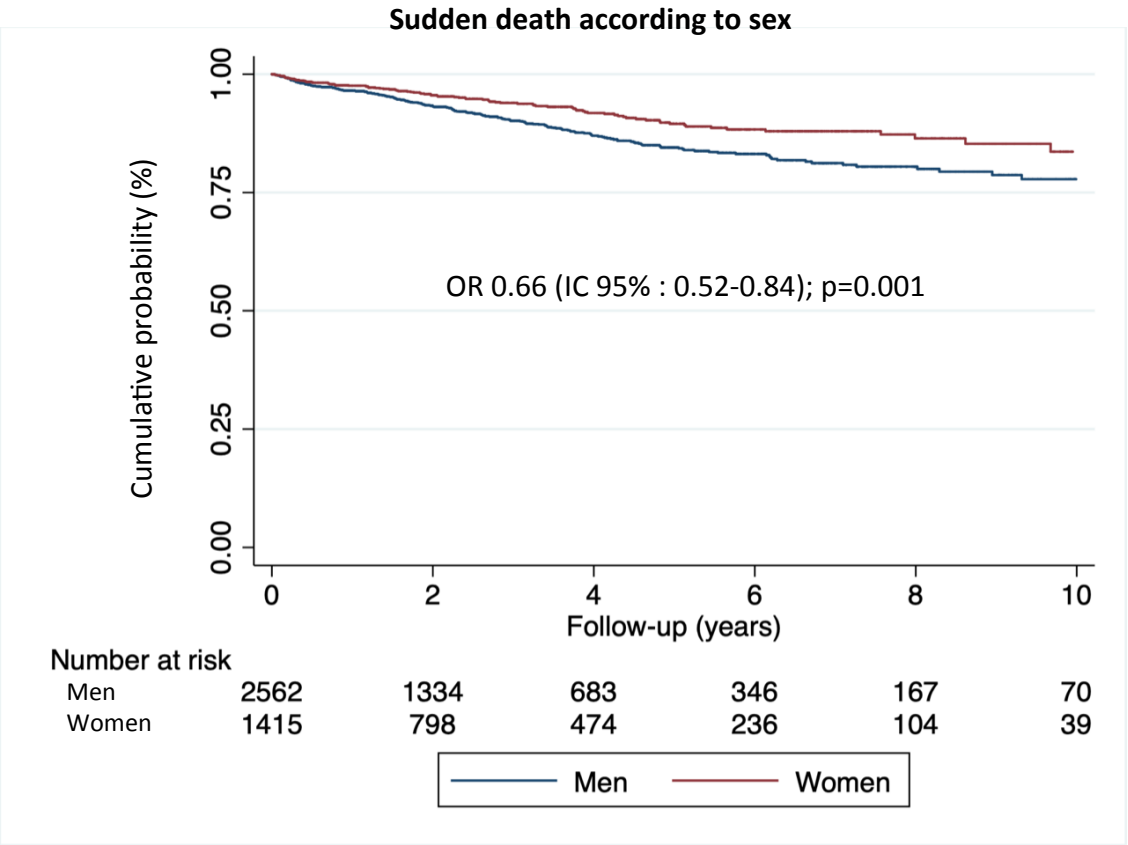

Figure 3: Sudden death occurrence according to sex.

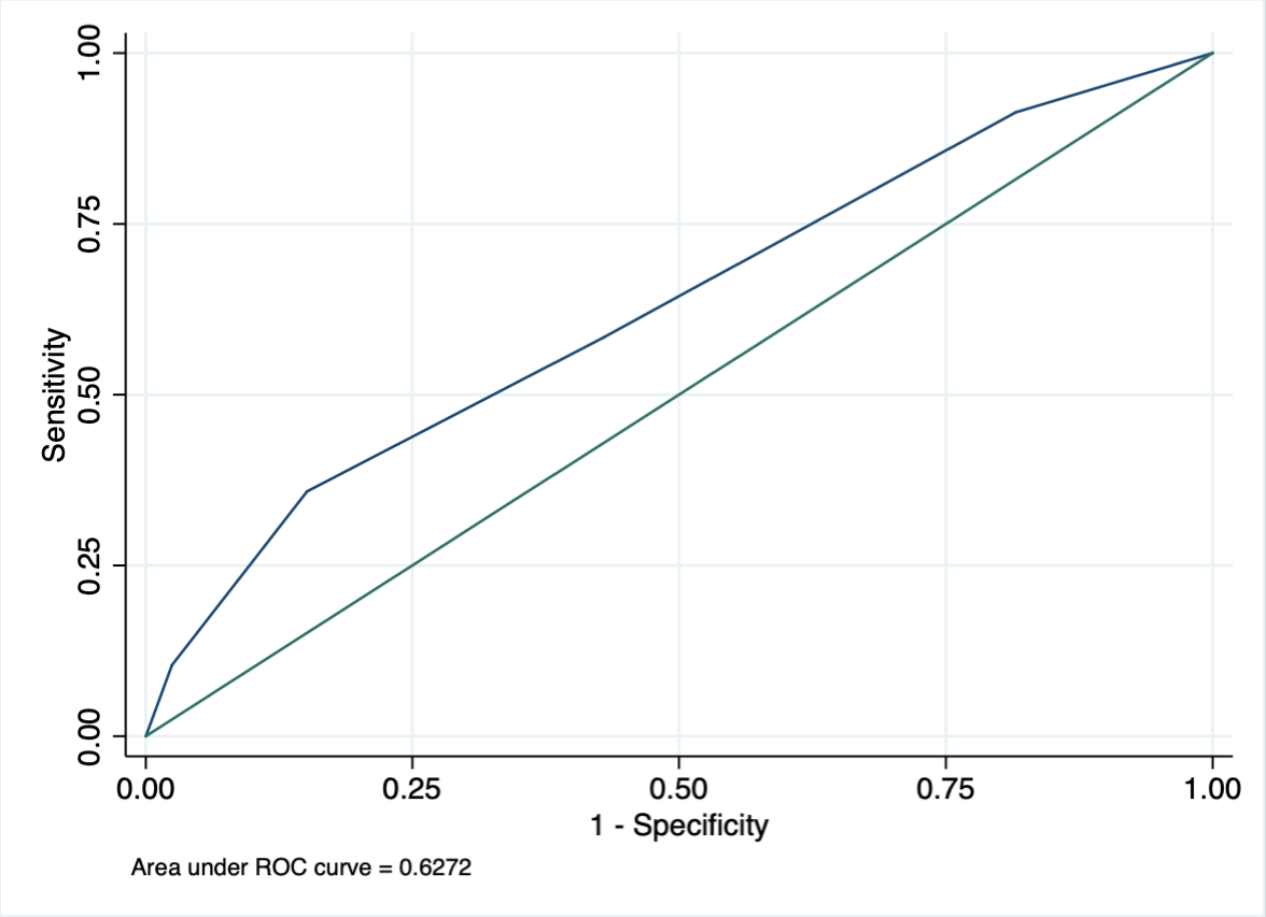

Figure 4: ROC curve of our predictive sudden death risk score.

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AH-FAT Vincent
45 pages – 5 tableaux – 4 figures

Résumé :

Introduction : La mortalité subite (MS) représente près de 11 à 25% des causes de décès chez les patients hémodialysés chroniques. Cette étude rétrospective a pour but d'analyser la mortalité globale et cardiovasculaire afin de déterminer les facteurs de risque de MS en se basant sur le registre des patients hémodialysés en région Centre-Val de Loire.

Méthodes : Cette étude rétrospective multicentrique a inclus consécutivement tous les patients traités par hémodialyse en région Centre-Val de Loire. Les événements évalués étaient les décès toute cause, les MS, les décès cardiovasculaires non subits et les décès de causes non cardiovasculaires.

Résultats : 3978 patients ont été inclus entre Janvier 2003 à Décembre 2017. 2542 patients sont décédés (63.9%) dont 332 de cause cardiovasculaire non subite (13.1%), 334 de MS (13.1%) et 1876 de cause non cardiovasculaire (73.8%). La durée de suivi moyenne était de 3.030±2.723 années. L'incidence annuelle de la mortalité toute cause et de la MS étaient respectivement de 21.08% et de 2.77%. Celles-ci semblent stables dans le temps. Bien que moins fréquente, la survenue de la MS était plus précoce dans l'évolution comparativement aux autres causes de décès. Après analyse multivariée, les facteurs de risque de MS étaient l'insuffisance cardiaque (HR 1.38 (IC 95%: 1.08-1.77); p=0.01), les arythmies (HR 1.41 (IC 95%: 1.08-1.83); p=0.011) et la néphropathie hypertensive (HR 1.44 (IC 95%: 1.13-1.85); p=0.003). Le sexe féminin était un facteur protecteur (HR 0.71 (IC 95%: 0.55-0.93); p=0.012). A partir de ces données, nous avons réalisé un nouveau score prédicteur de MS.

Conclusion : La mortalité chez les patients hémodialysés chronique en région Centre-Val de Loire reste élevée avec 13.1% de mort subite. Nous avons créé un score prédictif de mort subite afin d'identifier précocement les patients à haut risque à l'entrée en dialyse.

Mots clés : dialyse, mort subite, facteur prédictif

Jury :

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Membres du Jury : Professeur Dominique BABUTY, Cardiologie, Faculté de Médecine -Tours
Professeur Denis ANGOULVANT, Cardiologie, Faculté de Médecine -Tours
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Date de Soutenance : le jeudi 24 octobre 2019