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Chronic Kidney Disease in the Elderly: Understanding Outcomes and Trajectories of Kidney Function Decline, towards an Individualized Care

Josefina Santos

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Chronic Kidney Disease in the Elderly: Understanding Outcomes and Trajectories of Kidney Function Decline, towards an Individualized Care.

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ABSTRACT

Background

The management of the elderly patient with chronic kidney disease (CKD) is a clinical challenge. Although mortality outweighs the risk of progression to end stage renal disease (ESRD), elderly patients comprise the most rapidly growing population initiating dialysis therapy. To improve patient-centred care and outcomes in this elderly population, it is particularly relevant to better manage the knowledge needed to make critical and shared decisions throughout the entire CKD trajectory in the elderly. For the development of this thesis, we defined four hypotheses:1) mortality, mainly from cardiovascular disease (CVD), outweighs the risk of progression to ESRD in older patients with CKD; a competing-risk analysis could identify risk factors predictors for ESRD and differentiating them from those that increase mortality; 2) renal function in patients with CKD may follow different trajectory profiles; identifying different patterns of trajectories before dialysis initiation, would help to identify those patients who are more likely to experience an accelerated decline in kidney function, with impact on pre ESRD care and in the mortality risk after dialysis; 3) predictive mortality models focused in elderly ESRD patients, have been developed in other countries; developing and validating a prognostic model based on the specificities of our one CKD population, increases its predictive performance and clinical usefulness; 4) cystatin C-based estimated glomerular function rate (eGFR) seems to detect significantly larger declines in kidney function than creatinine-based formulas in the elderly; higher eGFR decline identified by cystatin C-based formulas will correlate with significant worse outcomes.

Materials and Methods

The research studies within this thesis involved four cohorts of CKD patients, aged 65 and older, from Nephrology Department from Centro Hospitalar Universitario do Porto (CHUP): one retrospective cohort including all consecutive patients referred for the first time to outpatient clinic, between January 1, 2012 and December 31, 2012 (hypothesis 1); one retrospective cohort including patients who initiated chronic dialysis, as their first renal replacement therapy (RRT), between January 1, 2009 and December 31, 2016 (hypothesis 2 and 3); one prospective cohort including all patients who started dialysis as their first RRT between January 1, 2017 and December 31, 2019 (hypothesis 3); and one prospective cohort study, including all consecutive patients referred for the first time to outpatient clinic between, January 1, 2016 and December 31, 2016 (hypothesis 4).The studies were conducted to address specific aims under the hypotheses defined:1) to characterize newly referred elderly CKD patients and to describe their baseline demographic and clinical characteristics, with particular emphasis for the cardiovascular disease burden; to identify

the independent predictors of ESRD or death through a competing-risk analysis; 2) to understand the different kidney function trajectories patterns in older CKD patients before dialysis initiation and to evaluate the association of different trajectories with patient characteristics, renal care practices and mortality after dialysis initiation; 3) to develop a risk score in elderly CKD patients to predict 6-month mortality after dialysis initiation and to validate this prognostic score in an independent cohort and compare its performance with other known scoring system; 4) to evaluate the association of severe CKD (stage 4) defined by either serum creatinine or cystatin C alone, or by both, with all-cause mortality and progression to ESRD; to determine the association of severe CKD (stage 4) defined by either creatinine or cystatin C alone, or by both, with cardiovascular events and hospital admissions. Variables regarding demographic, clinical characteristics and laboratory data were collected by nephrologists included in the research team. Mixed models using linear quadratic and cubic models were developed to define the eGFR trajectories together with probabilistic clustering procedures. Survival analysis methods, including a survival analysis that accounted for competing risks were used to identify the predictive factors of ESRD and death.

Results

Under hypothesis 1, we observed that new referral elderly CKD patients had a higher burden of CV risk profile and CVD, higher than other European CKD cohorts. We found an increase in the prevalence of CVD with worsening CKD stage, more pronounced in patients with diabetes. These CKD patients were near threefold more likely to die, mainly from CVD, than progress to ESRD. A competing risk framework in addition to identifying predictors for both ESRD and mortality (creatinine higher than 1.6 mg/dl, hemoglobin lower than 11 g/dl, and one or more hospitalizations during the follow-up) identified prognostic factors for a particular event (ESRD or death) in the presence of competing risks. We have demonstrated that peripheral vascular disease increases the cumulative incidence of ESRD but is not associated with increased pre-ESRD mortality; conversely, a modified Charlson comorbidity index (mCCI) ≥5 increased the hazard for pre-ESRD death, but not for RRT initiation. Regarding the hypothesis 2, we have identified four distinct groups of eGFR trajectories decline before dialysis. Patients with rapid eGFR decline were more likely to have diabetes, more cognitive impairment, to have been hospitalized before dialysis, and were less likely to have received pre-dialysis care compared to the patients with slower decline. Patients with rapid loss of kidney function had a higher risk of death within the first and fourth year after dialysis initiation, and after being more than four years in dialysis.
Under hypothesis 3 we have developed a prognostic score to predict 6-months mortality after dialysis initiation. Five independent predictors were identified, and a points system was

constructed: age 75 years or older (2 points), coronary artery disease (2), cerebrovascular disease with hemiplegia (2), time of nephrology care before dialysis [< 3.0 months (2); ≥ 3 to < 12 months (1)], serum albumin levels [3.0 - 3.49 g/dL (1); < 3.0 g/dL (2)]. As an example, a score of 6 identified patients with a 70% risk of 6-months mortality. Model performance was good and significantly higher than Couchoud score [79]. Our prognostic score achieved a good performance in a validation cohort, which confirms their predictive accuracy in a different source population, i.e., it was independently validated.

Concerning hypothesis 4, we demonstrated that CKD-EPI cystatin C was superior to CKD-EPI creatinine equation in predicting CV events, all-cause and acute kidney injury (AKI) admissions and all-cause mortality at the first year, when used in older patients with severe non-end stage CKD. Patients with stage 4 CKD defined by serum creatinine alone appeared to behave more alike those with less severe CKD, while outcomes in patients with stage 4 CKD defined by cystatin C alone were similar to the more severe group defined as CKD stage 4 by both serum cystatin and serum creatinine.

Conclusions

The burden of cardiovascular disease is very high in our patients, which contributes to the risk of mortality outweighing the risk of developing ESRD. Identifying elderly patients likely to die early regardless of whether RRT is started, may avoid the unnecessary anxiety induced by preparing for dialysis, and the burden of dialysis itself. Conversely, in patients correctly identified as those who will reach ESRD before dying, shared decisions on management, require counselling patients and families on different treatment options. Using a competing-risk approach based on available clinical and laboratory data, risk factors predictors of CKD progression were identified while distinguishing them from those that increase mortality, which may allow to use that approach as a decision-making tool to guide clinical decision process. Correctly estimating risk of death after starting dialysis may provide a more accurate perception of the desirability of starting dialysis. A simple and accurate prediction score to predict early mortality after dialysis initiation developed and independently validated is an easily implemented tool to apply in daily practice to guide patient care. Understanding kidney function trajectories before dialysis initiation, and its incorporation into clinical practice, improves the early detection of high-risk patients with impact on to pre-ESRD care and on prediction of mortality after dialysis initiation. In continuing concern about the prognosis of our patients we have demonstrated that elderly patients with discordant CKD staging, cystatin C-based eGFR is a better predictor of adverse outcomes than creatinine-based eGFR. So, its capacity to better predict the likelihood of adverse events and worse outcomes will be helpful in the clinical decision making.

RESUMO

Contexto

A gestão do doente idoso com doença renal crónica (DRC) é um desafio clínico. Embora a mortalidade ultrapasse o risco de progressão da DRC até ao estádio terminal da doença renal (DRCt), os idosos constituem o grupo da população em diálise com crescimento mais rápido. Para melhorar os cuidados centrados no doente e os resultados nesta população é particularmente relevante gerir melhor os conhecimentos necessários para a tomada de decisões críticas e partilhadas ao longo de toda a trajetória da DRC. Para o desenvolvimento desta tese, foram definidas quatro hipóteses: 1) nos idosos, a mortalidade, principalmente relacionada com a doença cardiovascular (DCV), ultrapassa o risco de progressão para a DRCt; uma abordagem estatística baseada em eventos competitivos poderá melhor identificar fatores de risco preditores de DRCt e diferenciá-los dos fatores preditores de mortalidade; 2) a função renal em doentes com DRC pode evoluir seguindo diferentes trajetórias; identificar diferentes padrões de trajetórias antes do início da diálise, ajudará a identificar os doentes com maior probabilidade de apresentarem um declínio acelerado da função renal, com impacto nos cuidados pré no risco de mortalidade após a diálise; 3) modelos preditivos de mortalidade centrados nos idosos com DRC tem sido desenvolvidos noutros países; o desenvolvimento e validação de um modelo de prognóstico baseado nas especificidades da nossa população com DRC, aumentará o seu desempenho e a sua aplicabilidade clínica; 4) nos idosos, a estimativa do filtrado glomerular (eFG) definida pela cistatina C parece detetar declínios significativamente maiores na função renal do que a eFG baseada na creatinina; um declínio maior da eFG identificado pela cistatina C irá correlacionar-se com pior prognóstico.

Materiais e métodos

Os estudos de investigação no âmbito desta tese envolveram quatro coortes de doentes com DRC e idade igual ou superior a 65 anos, do Serviço de Nefrologia do CHUP: uma coorte retrospetiva que incluiu todos os doentes referenciados pela primeira vez para a consulta entre 1 de janeiro de 2012 e 31 de dezembro de 2012 (hipótese 1); uma coorte retrospetiva que incluiu os doentes que iniciaram diálise crónica, como primeira terapêutica de substituição renal (TSR), entre 1 de janeiro de 2009 e 31 de dezembro de 2016 (hipótese 2 e 3); uma coorte prospetiva com todos os doentes que iniciaram a diálise como primeira TSF entre 1 de janeiro de 2017 e 31 de dezembro de 2019 (hipótese 3); e uma coorte prospetiva que incluiu todos os doentes consecutivos que foram referenciados pela primeira vez para a consulta entre 1 de janeiro de 2016 e 31 de dezembro de 2016 (hipótese 4)**.**

Os estudos foram conduzidos para abordar os objetivos específicos de cada uma das hipóteses definidas: 1) caracterizar os doentes idosos com DRC referenciados, descrever as suas características demográficas e clínicas, com particular ênfase para a carga da doença cardiovascular; identificar os preditores independentes de DRCt (definido como o início de diálise) ou morte através de uma análise de eventos competitivos; 2) compreender os diferentes padrões de trajetórias da função renal antes do início da diálise e avaliar a associação destas diferentes trajetórias com as características dos doentes, os cuidados nefrológicos e mortalidade após o início da diálise; 3) desenvolver um modelo preditivo da mortalidade aos 6 meses após o início da diálise, validar esse modelo numa coorte independente e comparar o seu desempenho com outro modelo existente; 4) avaliar a associação da DRC severa (estádio 4) definida quer pela creatinina sérica ou cistatina C isoladamente, quer por ambas, com a mortalidade e com progressão para a DRCt; determinar a associação de DRC estádio 4 definida quer pela creatinina ou cistatina C isoladamente, quer por ambas, com eventos cardiovasculares e admissões hospitalares. As variáveis demográficas, clínicas e dados laboratoriais foram recolhidas por nefrologistas incluídos na equipa de investigação. Modelos mistos, lineares quadráticos e cúbicos foram desenvolvidos para definir as trajetórias da função renal juntamente com procedimentos de agrupamento probabilístico. Métodos de análise de sobrevivência, incluindo a componente de eventos competitivos, foram usados para identificar fatores preditivos de DRCt e morte.

Resultados

Na hipótese 1, observamos que os idosos com DRC referenciados à nossa consulta, apresentavam um risco vascular e uma prevalência de DCV mais elevados do que outras coortes Europeias. Encontrámos uma relação entre a prevalência de DCV e o agravamento do estádio de DRC, mais pronunciado em doentes com diabetes. Estes doentes apresentavam um risco de quase três vezes superior de morrer, principalmente de DCV do que de progredir para a DRCt. Uma análise de risco competitivo para além de identificar fatores preditores tanto para a DRCt como para a morte (creatinina superior a 1,6 mg/dl, hemoglobina inferior a 11 g/dl, e uma ou mais hospitalizações durante o seguimento) identificou fatores de prognóstico para um determinado evento (DRCt ou morte) na presença de eventos competitivos; verificamos que a presença da doença vascular periférica aumentou a incidência acumulada de DRCt mas não se associou ao aumento da mortalidade pré diálise; um índice de comorbilidade de Charlson modificado (ICCm) ≥5 aumentou o risco de morte pré diálise, mas não se associou à progressão para DRCt.

Relativamente à hipótese 2, identificámos quatro grupos distintos de trajetórias de declínio do eFG antes da diálise. Os doentes com um declínio mais rápido do eFG tinham maior

probabilidade de terem diabetes, de terem défice cognitivo, de terem sido hospitalizados antes da diálise, e tinham menor probabilidade de terem recebido cuidados nefrológicos pré diálise em comparação com os doentes com um declínio mais lento. Os doentes com perda rápida da função renal tinham um risco de morte mais elevado no primeiro e quarto ano após o início da diálise, que se mantinha após mais de quatro anos em diálise.

Sob a hipótese 3 desenvolvemos um modelo preditivo de mortalidade aos 6 meses após o início da diálise. Foram identificados cinco preditores independentes, e foi construído um sistema de pontuação para cada preditor: idade igual ou superior a 75 anos (2 pontos), doença coronária (2), doença cerebrovascular com hemiplegia (2), tempo de cuidados nefrológicos antes da diálise [< 3,0 meses (2); ≥ 3 a < 12 meses (1)], níveis de albumina sérica [3,0 - 3,49 g/dL (1); < 3,0 g/dL (2)]. Como exemplo, uma pontuação de 6 identificou doentes com um risco de 70% de mortalidade aos 6 meses após a diálise. O nosso modelo obteve um bom desempenho, e significativamente melhor quando comparado com o modelo de Couchoud [79].

Relativamente à hipótese 4, demonstrámos que em doentes idosos com DRC severa (estádio 4) a equação CKD-EPI definida pela cistatina C era superior à equação CKD-EPI definida pela creatinina na previsão de eventos CV, nas admissões por todas as causas e por lesão renal aguda (LRA) e na mortalidade ao primeiro ano. Os doentes com DRC estádio 4 definida apenas pela creatinina sérica pareciam comportar-se de forma semelhante aos doentes com DRC menos grave, enquanto que os eventos e o prognóstico em doentes com DRC estádio 4 definida apenas pela cistatina C eram semelhantes aos do grupo com DRC mais severa definido tanto pela cistatina C sérica como pela creatinina sérica.

Conclusões

O peso da DCV é muito elevado nos nossos doentes, o que contribui para que o risco de mortalidade ultrapasse o risco de desenvolver DRCt. A identificação de doentes idosos com DRC com maior probabilidade de morrer precocemente, independentemente de a TSR ser iniciada, pode evitar a ansiedade desnecessária induzida pela preparação para a diálise, e a carga associada à própria diálise. Pelo contrário, em doentes corretamente identificados como aqueles que chegarão à DRCt antes de morrer, decisões partilhadas, requerem o aconselhamento dos doentes e famílias sobre diferentes opções de tratamento. A utilização de uma abordagem de risco competitivo baseada em dados clínicos e laboratoriais disponíveis identificou os fatores de risco que predizem a progressão da DRC e distingue-os daqueles que aumentam a mortalidade, permitindo utilizar esta abordagem como instrumento para orientar o processo de decisão clínica. Estimar corretamente o risco

de morte após o início da diálise pode proporcionar uma perceção mais clara sobre a pertinência de iniciar a diálise. Um score preditivo da mortalidade precoce após o início da diálise, simples e preciso, desenvolvido e validado independentemente é uma ferramenta de fácil implementação na prática diária para orientar o tratamento do doente. A compreensão das trajetórias da função renal antes do início da diálise e a sua incorporação na prática clínica melhoram a deteção precoce de doentes de alto risco com impacto nos cuidados pré diálise e na previsão da mortalidade após o início da diálise. Na contínua inquietação sobre o prognóstico dos nossos doentes, demonstramos que em idosos com estádio discordante de DRC, o FG estimado pela cistatina C é um melhor preditor de eventos adversos quando comparado com o FG estimado pela creatinina. Assim, a sua capacidade de melhor prever eventos adversos e pior prognóstico será útil na tomada de decisões clínicas.

SCIENTIFIC OUTPUTS

In accordance with “Artigo 34º do Decreto-Lei nº 115/2013”, this thesis contains materials and results from the following published and submitted papers (listed by date of publication or submission).

Original Articles

Santos J, Fonseca I, Malheiro J, Beirão I, Lobato L, Oliveira P, Cabrita A. End-stage renal disease versus death in a Portuguese cohort of elderly patients: an approach using competing event analysis. J Investig Med. 2017 Oct; 65(7): 1041-1048. doi: 10.1136/jim-2017-000480. Epub 2017 Jul 19. PMID: 28729248.

Lascasas JMSS, Fonseca I, Malheiro J, Santos S, Campos A, Castro A, Moreira C, Correia S, Beirão I, Lobato L, Cabrita A. Demographic, clinical characteristics and cardiovascular disease burden in a Portuguese cohort of older chronic kidney disease patients. J Bras Nefrol. 2019 Jan-Mar; 41(1): 29-37. doi: 10.1590/2175-8239-JBN-2018-0120. Epub 2019 Jan 10. PMID: 31063177; PMCID: PMC6534027.

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Review articles

Malheiro J. Santos J. (2014). Use of equations for glomerular filtration rate estimation in the elderly. Port J Nephrol Hypert. 2014; 28(1), 22-30.

Santos J. ESRD management in elderly patients: towards an individualized patient-centred approach. Port J Nephrol Hypert. 2015; 29(4): 365-367.

Santos J, Fonseca I. Incorporating Scoring Risk Models for Care Planning of the Elderly with Chronic Kidney Disease. Curr Gerontol Geriatr Res. 2017;2017: 8067094. doi: 10.1155/2017/8067094. Epub 2017 Nov 28. PMID: 29317867; PMCID: PMC5727624.

Book chapter

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TABLE OF CONTENTS

ACKNOWLEDGMENTS VII
ABSTRACT IX
RESUMO XII
SCIENTIFIC OUTPUTS XVI
TABLE OF CONTENTS XIX
KEYWORDS XXIII
ABBREVIATIONS XXIV
CHAPTER I - INTRODUCTION 1
1. Thesis motivation 3
2. Thesis hypotheses 5
3. Specific aims 6
4. Thesis outline 7
CHAPTER II - LITERATURE REVIEW 9
1. CKD diagnosis 12
   1.1. CKD diagnosis in Elderly 12
   1.2. Assessment of kidney function in the elderly 13
2. Renal function trajectory in elderly CKD patients 13
   2.1. Methods of measuring renal function trajectory 14
   2.2. Patterns of renal function trajectory 14
3. Risk factors for CKD progression in the elderly 15
   3.1. Proteinuria 15
   3.2. Gender 15
   3.3. Hypertension and Diabetes 16
   3.4. Acute Kidney Injury 16
4. Competing risk of death 17
5. Prognostic models 18
   5.1. Prognostic models for CKD progression 18
   5.2. Prognostic models for mortality 18
      5.2.1. Available models 19
CHAPTER III - MATERIALS & METHODS 23
1. Study designs 25
2. Subjects 25
3. Data collection 25
4. Laboratory assessments 26
5. Statistical analysis 27

6. Institutional and ethical approval 27
CHAPTER IV - RESULTS 29
1. Thesis studies outline 31
2. Hypothesis 1 32
2.1. Independent predictors of ESRD or death through a competing risk analysis 32
2.2. Cardiovascular disease burden and risk profile in a referred cohort of older CKD patients. 35
3. Hypothesis 2 38
3.1. Different kidney function trajectories patterns before dialysis in older CKD patients: Implications for clinical management 38
4. Hypothesis 3 43
4.1. Development of a model to predict 6-month mortality in incident elderly dialysis patients. 43
4.2. Validation of a predictive mortality score on a new cohort of incident elderly dialysis patients. 47
5. Hypothesis 4 50
5.1. Association between severe CKD defined by cystatin-c and creatinine and clinical outcomes in an elderly population 50
CHAPTER V - DISCUSSION 55
1. The heavy burden of CVD in newly referred CKD patients and competing-risk events analysis (hypothesis 1) 57
2. Patterns of trajectories before dialysis initiation, impact on pre ESRD care and in the mortality after dialysis (hypothesis 2) 62
3. Development and validation of a prognostic score to predict early mortality after dialysis (hypothesis 3) 65
4. Cystatin C-based eGFR is a better predictor of adverse outcomes than creatinine-based eGFR (hypothesis 4) 68
CHAPTER VI - CONCLUSIONS & FURTHER DIRECTIONS 71
REFERENCES 77
APPENDICES 87
1 End-stage renal disease versus death in a Portuguese cohort of elderly patients: an approach using competing event analysis 89
2 Demographic, clinical characteristics and cardiovascular disease burden in a Portuguese cohort of older chronic kidney disease patients. 99
3 Different kidney function trajectories patterns before dialysis in older CKD patients: Implications for clinical management. 109
4 Predicting 6-month mortality in incident elderly dialysis patients: a simple prognostic score 133
5 Validation of a model to predict six-month mortality in incident elderly dialysis patients 147

6 Association between severe chronic kidney disease defined by cystatin-C and creatinine and clinical outcomes in an elderly population – an observational study. 155
7 Use of equations for glomerular filtration rate estimation in the elderly. 165
8 ESRD management in elderly patients: towards an individualized patient-centred approach 175
9 Incorporating scoring risk models for care planning of the elderly with chronic kidney disease. 179

LIST OF FIGURES

Figure 1 - Cumulative incidence rates for the competing endpoints of ESRD or death. 32
Figure 2 - Prevalence (%) of individual causes of cardiovascular disease stratified by CKD stages. 36
Figure 3 - Trajectories decline for the identified groups. 38
Figure 4 - Kaplan-Meier survival curves after dialysis initiation by eGFR trajectory group 41
Figure 5 - Comparison of receiver operating characteristics (ROC) curves for predicting 6-month mortality after starting dialysis, among our (Santos) and Couchoud scores. 45
Figure 6 - Mean predicted mortality risks and observed proportions for ranges of total scores. 45
Figure 7 - Score chart to predict 6-months mortality risk after dialysis initiation. 46
Figure 8 - Performance of risk score in validation cohort. 47
Figure 9 - Comparison of survival curves of the CKD stage 4 groups. 51

LIST OF TABLES

Table 1 - Thesis publications according the studied hypotheses and objectives. 31
Table 2 - Risk factors associated with death and ESRD (Cox regression analysis). 33
Table 3 - Risk factors associated with death and ESRD (Fine & Gray model) 34
Table 4 - Cardiovascular disease burden stratified by gender and presence and absence of DM. 35
Table 5 - Cardiovascular disease burden, stratified by CKD stages and presence and absence of diabetes mellitus. 36
Table 6 - Characteristics of each and overall trajectory decline groups. 39
Table 7 - Multivariable adjusted multinomial logistic regression analysis for the associations of demographic and clinically relevant factors with trajectories eGFR decline. 40
Table 8 - Adjusted risk of death over different periods after dialysis initiation by trajectory group using cox proportional hazards regression model. 41

Table 9 - Multivariable logistic regression model for 6-month mortality. 44
Table 10 - Predictors of 6-month mortality and associated risk scoring system. 44
Table 11 - Baseline Characteristics of development and validation cohorts for predicting 6-months mortality in elderly ESDR. 48
Table 12 - Extended Cox regression exploring predictors of death, considering CKD stage 4 groups at two time-periods. 51
Table 13 - Incident rate ratio of CV events, all-cause admissions, admissions due to AKI and infectious events in the CKD stage 4 groups. 52
Table 14 -Main results regarding proposed aims for the hypothesis 1. 57
Table 15 - Main results regarding proposed aims for the hypothesis 2. 62
Table 16 - Main results regarding proposed aims for the hypothesis 3. 65
Table 17 - Main results regarding proposed aims for the hypothesis 4. 68

KEYWORDS

Cardiovascular disease

Chronic Kidney Disease

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Cystatin C

Dialysis

End Stage Renal Disease

eGFR

Elderly

Kidney function trajectories

Mortality

Patient-centred approach to care

Prognostic models

Shared-decision process

ABBREVIATIONS

AKI	Acute Kidney Injury
AUC	Area under the curve
aHR	adjusted hazard ratio
BP	Blood pressure
BMI	Body mass index
csHR	Cause-specific hazard ratio
CCI	Charlson Comorbidity Index
CHUP	Centro Hospitalar Universitário do Porto
CI	Confidence Interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CVD	Cardiovascular Disease
Cys	Cystatin C
DM	Diabetes mellitus
DCV	Doença Cardiovascular
eGFR	Estimated glomerular filtration rate
eFG	Estimativa do filtrado glomerular
GFR	Glomerular function rate
Hb	Hemoglobin
HDL	High-density lipoprotein
HR	Hazard Ratio
ICCm	Índice de Comorbilidade de Charlson modificado
IQR	Interquartile range
KDIGO	Kidney Disease Improving Global Outcomes group
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low-density lipoprotein
mCCI	Modified version of the Charlson comorbidity index
MDRD	Modification of Diet in Renal Disease
MMSE	Mini Mental State Examination
OD	Odds Ratio
REIN	Renal Epidemiology and Information Network
ROC	Receiver operating characteristic
RRT	Renal replacement therapy
sCr	Serum creatinine
sCys	Serum cystatin C
SD	Standard Deviation
sHD	Subdistribution hazard ratio
UK	United Kingdom
uPCr	Urine protein-to-creatinine ratio
US	United States
USRDS	United States Renal Data System

CHAPTER I

INTRODUCTION

1. Thesis motivation

As nephrologist my work for the last twenty years has been in the Nephrology and Kidney Transplantation Unit of Centro Hospitalar Universitario do Porto (CHUP) and in an Outpatient Haemodialysis Unit. In both, most of my patients are older adults with a chronic kidney disease (CKD) and end-stage renal disease (ESRD).

Older population of patients has unique care issues, from controversies in the diagnosis and treatment of specific disease entities to increased number of complicating comorbidities to competing issues of quality of life versus aggressive care options. In my daily practice I became aware that these competing, interacting and causative comorbid conditions require monitoring by the nephrologist in a holistic, collaborative, and individualized program of care in which decisions regarding treatment of CKD and ESRD have important socioeconomic, functional, psychologic, and ethical implications. This was the scenario that motivated me to start the studies included in this thesis.

The main motivations to perform this research was to answer some questions regarding the management of CKD in elderly patients and the specific and unique aspects of care for geriatric patients that as nephrologist I am confronted every day. These aspects will range from controversies over the diagnosis, treatment, and prognosis of CKD in elderly, and the increased number of complicating comorbidities to competing issues of quality of life versus aggressive care options, like renal replacement therapy (RRT).

When reflecting on elderly CKD patients and designing this research, three issues were particularly meaningful to me, hoping that the outcomes of these patients will be favourably affected by the results obtained in this work. The first is related with one crucial clinical issue that involves nephrologists, patients, and their families in informed, shared decisions as to whether to choose dialysis or a more conservative treatment approach as kidney function progressively deteriorates. These decisions were associated with prognostic information that depends on the ability to determine each patient's risk for progressive disease and likelihood for requiring RRT in relation to the competing risk of death.

Considering that elderly CKD people are far less likely to develop kidney failure than to die of other cause, especially cardiovascular disease (CVD), highlights the importance of strategic targeting vascular risk screening and reduction in this population. Also, on our daily clinical practice it is important to develop and apply predictive mortality models based on readily available clinical and laboratory data that can be useful tools to assess short-term prognosis in elderly ESRD patients, which may help to inform patients and their families about ESRD treatment options and provide a more patient-centred overall approach to care.

Secondly, the understanding of how CKD progresses in the aged population based on the study of renal function decline trajectory, considering its different patterns, factors

associated, and potential impact in outcomes, may enable a more targeted provision of care.

Finally, an accurate assessment of kidney function has several clinical implications, particularly in elderly. Available estimated glomerular function rate (eGFR) equations based on endogenous markers (creatinine and cystatin C) have several limitations, and none of these equations have been validated in a large population of elderly patients. However, potentially more important than the diagnoses and CKD staging, an individualized use of eGFR equations in the elderly, in whom they should be regarded less as accurate estimators, but more as predictors of clinical outcomes, would allow its use to be more judicious and clinically relevant.

To address these issues, the hypotheses, aims and design of this study thesis were defined.

2. Thesis hypotheses

Hypothesis 1.

Mortality, mainly from CVD, outweighs the risk of progression to ESRD in older patients with CKD. A heavy burden of CVD is present in newly referred CKD patients. A competing-risk analysis could identify risk factors predictors for ESRD and differentiating them from those that increase mortality.

Hypothesis 2.

Renal function in patients with CKD may follow different trajectory profiles. Identifying different patterns of trajectories before dialysis initiation, would help to identify those patients who are more likely to experience an accelerated decline in kidney function, with impact on pre ESRD care and in the mortality risk after dialysis.

Hypothesis 3.

Predictive mortality models focused in elderly ESRD patients, have been developed in other countries. Developing and validating a prognostic model based on the specificities of our one CKD population, increases its predictive performance and clinical usefulness.

Hypothesis 4.

Cystatin C-based eGFR seems to detect significantly larger declines in kidney function than creatinine-based formulas in the elderly. Higher eGFR decline identified by cystatin C-based formulas will correlate with significant worse outcomes.

3. Specific aims

Concerning hypothesis 1 the aims were:

- To characterize newly referred elderly CKD patients and to describe their baseline demographic and clinical characteristics, with particular emphasis for the cardiovascular disease burden.
- To confirm the higher likelihood of death before ESRD vs. initiating dialysis using a competing analysis approach.
- To identify the independent predictors of ESRD or death through a competing-risk analysis.

Concerning hypothesis 2 the aims were:

- To understand the different kidney function trajectories patterns in older CKD patients before dialysis initiation
- To evaluate the association of different trajectories with patient characteristics, renal care practices and mortality after dialysis initiation.

Concerning hypothesis 3 the aims were:

- To develop a risk score in elderly CKD patients to predict 6-month mortality after dialysis initiation.
- To validate this new prognostic score in an independent dataset and compare its performance with others known scoring system.

Concerning hypothesis 4 the aims were:

- To evaluate, in a cohort of elderly CKD patients, the association of severe CKD (stage 4) defined by either serum creatinine (sCr) or cystatin C (sCys) alone, or using both, with all-cause mortality and progression to ESRD.
- To determine the association of severe CKD (stage 4) defined by either sCr or sCys alone, or using both, with cardiovascular events and in-hospital admissions.

4. Thesis outline

The present thesis is divided into six chapters.

Chapter 1 establishes the main motivations, hypotheses and aims of the work.

Chapter 2 contain the scientific background and reviews the literature concerning the most important and significant works in the field of CKD in elderly patients.

Chapter 3 presents an overall description of the procedures and methodology used within this thesis. Detailed methodologies are described in the corresponding published articles.

Chapter 4 describes the results obtained in the different studies (presented as appendices), conducted under the defined thesis hypotheses. All published papers are reproduced with permission from the publisher.

Chapter 5 provides a general discussion of the main findings of the papers included in this thesis and considers aspects that were not included in the papers.

Chapter 6 resumes the major findings as a conclusion to the thesis and comprises reflections over future perspectives.

CHAPTER II

LITERATURE REVIEW

The world's population is aging, and this is one of the most significant trends of the 21st century. The global share of older people increased from 9.2 per cent in 1990 to 11.7 per cent in 2013 and will continue to grow, reaching 21.1 per cent by 2050, from 841 million people in 2013 to more than 2 billion in 2050 [1]. Similarly, to what occurs at world level, the Portuguese society has also suffered from demographical aging. The number of people aged 65 years has increased approximately 42% between 1992 and 2011, and at the end of this period, accounted for 19.1% of the total population, a value that is clearly above the European Union average (17.5%) [2].

Population ageing is the result of socioeconomic development, improved life expectancy and reduced fertility, having important implications for health systems, labour markets, public policy, social programs, and family dynamics [3]. On the other hand, CKD is rising worldwide, and has emerged as a serious public health problem, as shown by the increase in global and cardiovascular mortality and the growing incidence and prevalence of ESRD [4], requiring RRT (dialysis or transplantation), with very high health-care costs. Parallel to this, the prevalence of CKD is higher in older people, and patients over 65 years of age represent the most rapidly growing segment of the ESRD population in western countries [5,6], as well as showing a high prevalence of earlier stages of CKD, with relative prevalence equally striking for populations in the USA, Canada, and Europe [5,7-9]. Portugal has one of the highest incidences and prevalence of ESRD in the world [5,6] and 64% of the incident dialysis patients in 2018 were over 65 years with a mean age of 67 years for prevalent patients [10].

The high prevalence of CKD in the elderly reflects the presence of a variety of different traditional risk factors for CKD such as diabetes and hypertension in older individuals, but it may also occur because of an age-associated decline in kidney function that is not explained by other risk factors [11]. Chronic kidney disease is associated with increased prevalence of both traditional (e.g., hypertension), non-traditional cardiovascular risk factors (e.g., proteinuria, elevated uric acid levels, and hyperhomocysteinemia) and predisposing factors to microvascular disease (e.g., inflammation, increased oxidative stress, and abnormal calcium–phosphate homeostasis) [12], with several studies confirming that in the elderly, even in early stages of CKD, cardiovascular mortality outweighs the risk of progression to ESRD [13,14]. Chronic kidney disease is also related with impaired functional status [15] and frailty [16] particularly in older patients with higher risk for accelerated physical and cognitive decline, disability, hospital admissions and death.

The management of older adults with CKD has become a clinical challenge, but additional and potentially more important than CKD diagnosis and staging, is the change in renal function over time, that can be defined as the annual rate of eGFR progression, called "renal

function trajectory", which predicts decline in kidney function and ESRD [17-19] and is also associated with increased risk for mortality [20-22].

Although the elderly individuals represent the fastest growing group with ESRD, more than 90% of older adults with CKD die, mainly from CVD, rather than survive and require dialysis or kidney transplantation [13,23]. This reflects not only a greater competing risk of mortality in older patients, lower rates of CKD progression [24,25], besides also reflecting differences between patients of different ages in how often dialysis is offered or accepted when indications arise [26]. So, it is extremely important to identify the small percentage but large absolute number of older patients who will experience progression of their underlying CKD to ESRD [26], as well the risk factors for progression, because this is the group most likely to benefit from efforts to slow progression, decisions regarding renal replacement therapy such as referrals and procedures for dialysis access placement or transplant decision.

1. CKD diagnosis

The Kidney Disease Outcomes Quality Initiative (KDOQI) has described a definition and a staging system of CKD that relied on eGFR, considered at present the best indicator of kidney function. Chronic kidney disease is defined by a reduction of GFR <60 mL/min/1.73m^2 and/or evidence of kidney damage, if there is proteinuria, renal haematuria, or abnormal renal imaging and renal pathology for 3 months or longer [27]. These guidelines had been reviewed and updated by the Kidney Disease Improving Global Outcomes (KDIGO) group [28].

1.1. CKD diagnosis in Elderly

The main goal of increasing the scope of CKD diagnosis and management was to improve outcomes by identifying CKD earlier in the course of the disease, and potentially prevent the loss of kidney function, slow the progression of the disease, and treat CKD-related comorbid conditions. There are no specific recommendations regarding the early identification and management of CKD in the elderly and current CKD classification may overestimate the prevalence of CKD in the elderly [29]. Still, the fact that new classification requires the same criteria in all age groups was based on evidence that reduced eGFR and albuminuria predicted ESRD onset and mortality, irrespective of age [30].

1.2. Assessment of kidney function in the elderly

An accurate assessment of kidney function has several clinical implications, particularly in elderly, such as timely referral to nephrology, adequate drug dose adjustment, improve decision making in imaging testing and adequate RRT consideration. Furthermore, an early detection and treatment of CKD may prevent or delay progression to ESRD [31].

The GFR is the best indicator of kidney function, but methods to measure GFR using exogenous markers, such as inulin clearance, Cr-EDTA or Tc-DTPA, are laborious as well as expensive, being rarely used in clinical practice. Therefore, endogenous markers, such as serum creatinine (sCr) and more recently, cystatin C (Cys) are used to estimate kidney function. Equations using these markers adjusted to other variables (mainly demographical) are an attempt to improve accuracy in eGFR. However, none of these eGFR equations have been validated in a large population of elderly patients [31]. So, the assessment of kidney function has evolved from using simple sCr to more complex formulae such as the Cockcroft–Gault [32], Modification of Diet in Renal Disease (MDRD) [33] and Chronic kidney disease Epidemiology Collaboration (CKD–EPI) [34].

The KDIGO [28] currently use the CKD–EPI formula that seems to improve significantly GFR estimation in subjects with no or mild kidney dysfunction, in comparison with the MDRD equation, without jeopardizing eGFR performance in subjects with advanced CKD. Its use, particularly in the epidemiological setting, has proven to be useful in identifying subjects with a more relevant CKD, patients not only with a reduction in kidney function but also with high comorbidity and more prone to CKD progression, selecting those that would profit more from specific interventions, as referral to a nephrologist.

However, growing evidence has shown Cys, a marker less susceptible than sCr to metabolic and extrarenal factors [35], to be a stronger predictor of clinical outcomes, as death and ESRD than sCr in the elderly [36]. This observation illustrates the usefulness of Cys, in the elderly with CKD, in whom important decisions about CKD management and ESRD preparation must be considered, as it may allow us to better predict CKD progression and appreciate the competitive ESRD versus death risk [31].

2. Renal function trajectory in elderly CKD patients

Independently from the eGFR formula used, the prevalence of CKD in the elderly is high. Yet, as important as CKD detection, is the understanding of how CKD progresses in the aged population, because it would enable a more targeted provision of care, particularly for ESRD-related assessments [31].

Evaluating longitudinal eGFR trajectory is a novel approach to predicting decline in kidney function [17-19], with important outcome impact [20-22]. Until recently, most studies have

used either a doubling of sCr or time to initiation of RRT, as an outcome measure. However, time to initiation RRT is a very subjective parameter, while doubling of sCr, although an objective measure it does not consider the multiple factors related to renal function trajectory [17].

2.1. Methods of measuring renal function trajectory

The most usual method of measuring renal trajectory is a regression line (slope) fitted to all a patient's sCr data points. However, other simpler methods are used in some population studies like the difference between the patient's initial and latest available eGFR divided by years of observation to get change in eGFR in ml/min/1.73 m^2/ year, called "basic renal trajectory" [17]. Alternatively, the mean values of the patient's first year creatinine data points can be used together with most recent year's data points which may decrease the variance of the result [17].

2.2. Patterns of renal function trajectory

The patterns of renal function trajectory are also matter of debate. Many CKD patients have a non-linear GFR trajectory or a prolonged period of no progression, and these diverse patterns are due to a combination of chronic and acute factors, such as acute kidney injury (AKI) episodes [37], particularly frequent in older patients.

Our current knowledge of the progression of CKD is based on studies conducted in patients referred for specialist care, with rates of eGFR loss of approximately 7-8ml/min/ year [38]. Few studies have addressed this issue, specifically in the elderly.

Hemmelgarn et al. [25], in a cohort of 10184 subjects 66 years of age or older, with an eGFR by MDRD equation at baseline < 90 ml/min, founded that most subjects have no or minimal progression of kidney disease over 2 years, between 0.8 and 2.7 ml/min/year, with male gender, diabetes mellitus, and eGFR< 30ml/min at baseline being associated with the highest rates of decline. The indolent nature of CKD progression in the elderly, was also emphasized by data from the Cardiovascular Health Study [39] showing that deterioration in kidney function was seen in less than 3% of the subjects with mean age 73 years, after a follow-up of at least 3 years.

As discussed above, CKD progression in the elderly seems to be more significant when Cys-based formulas are considered, and Cys-based eGFR detected significantly larger declines in kidney function than creatinine-based formulas in the elderly [40]. However, it still needs to be confirmed if this higher eGFR decline identified by Cys-based formulas are associated with significant clinical outcomes, as ESRD or death.

An understanding of trajectories of kidney function decline may help to guide clinical decision-making, and to anticipate health-care needs, namely clarify the optimal timing of nephrology referral, vascular access, or transplant referral, evaluating the competitive risk of death versus the requirement RRT and to guide treatment choices.

3. Risk factors for CKD progression in the elderly

3.1. Proteinuria

Proteinuria is a major risk factor for progression of renal dysfunction, and proteinuria level may help determine who will require RRT. Even in the early stages of CKD the presence of higher proteinuria significantly increased the risk of ESRD in older patients, as shown by Nicola et al. [41], suggesting that aging kidney is more vulnerable to the 'toxic' effects of proteinuria due to the greater degree of ischemia and renal fibrosis [42]. One study evaluated the impact of overt proteinuria according to age on ESRD incidence in tertiary nephrology care in a Japanese cohort of CKD 3–5 patients followed for 3 years [43] and found that overt proteinuria was associated with ESRD in elderly patients, and for those patients over 65 without proteinuria, none required RRT. Another study [44], found that for patients over 75 with less than 1 g/24 h proteinuria, 90% avoided RRT during an average follow-up of 10 years. In addition, proteinuria, regardless of baseline eGFR is strongly and independently associated with worse clinical outcomes, as a risk factor for a systemic vascular disease including kidney disease rather than only a sign of CKD [45,46].

Several studies have shown an additive risk of death among those with albuminuria and a low eGFR [47-50]. Hallan et al. [47], confirmed the presence of this association in the elderly, in a large-scale Norwegian general health survey (Hunt II study), and demonstrated that among patients with a similar level of eGFR, mortality risk increased with increasing level of albuminuria. Furthermore, mortality risk increased with falling eGFR only in those with microalbuminuria and not among those with lower levels of urinary albumin excretion.

3.2. Gender

Male gender is a strong risk factor for progression of kidney disease in the general population, and the rate of decline of renal function was reported to be faster in males than females [51-54]. This may also be the case in the elderly. In the study of Hemmelgarn et al. [25], an elderly Canadian cohort, the rate of progression was greater in men than in women. But, in contrast to these results, other study showed that the rate of renal disease progression may not be slower and may even be faster in post-menopausal women compared with men [55]. This may suggest the lack of an independent female gender effect,

particularly in elderly women, on slowing renal disease progression, confounded by imbalances between men and women of other factors, such as the level of blood pressure or proteinuria, associated with renal disease progression [55].

3.3. Hypertension and Diabetes

Hypertension is a well-known risk for progression of renal disease in the overall population, although this association may be attenuated at older ages [56], emphasizing the little evidence support for current guidelines for the treatment of hypertension in elderly CKD patients, and the risk of a strict control. Similarly, diabetes is also a risk factor for progression of CKD in older as it is in younger patients, but it remains unclear whether the strength of this association is the same in patients of different ages [25].

3.4. Acute Kidney Injury

The incidence of AKI is increasing [57], particularly among older patients [58], and elderly individuals with AKI, particularly those with previously diagnosed CKD, are at significantly increased risk for ESRD [59], suggesting that episodes of AKI may accelerate progression of renal disease. This is especially true if the AKI episode required dialysis and if a patient had underlying CKD.

In a United States (US) cohort of 233,803 hospitalized elderly patients who survived to discharge, the adjusted hazard ratio for developing ESRD was 41.2 for patients with AKI and CKD relative to those without kidney disease, compared to 8.4 for patients with CKD and without AKI [59]. A meta-analysis (n=5529 patients) showed that patients 65 and older with AKI were 28% less likely to recover renal function than younger ones [56]. Because the development of AKI is associated with a higher risk for mortality, interpretation of these studies should be balanced with the understanding that mortality from AKI is an important competing risk during the analyses [57].

The elderly population is more prone to AKI than younger, because they have less renal reserve due to morphological and functional changes of the aging kidney [60-63]. Moreover, the elderly is more susceptible to the development of AKI due to their comorbidities, polypharmacy and aggressive diagnostic and therapeutic procedures, and various interventions that introduce injury to their kidneys [61,62].

4. Competing risk of death

Elderly people with CKD are far less likely to develop kidney failure than to die from other cause, especially cardiovascular disease. Related with a greater competing risk of mortality in older patients, several studies have attempted to identify which patients with CKD were more likely to die prior needing RRT.

Demoulin et al. [64], studied 386 with stage 4 CKD patients and found that after 80 years of age, the risk of death always exceeded the risk of ESRD. Similarly, O'Hare et al. [13], in a national cohort US Veterans Affairs patients, followed for 3 years, found that for patients over 85 the risk of death always exceeded the risk of need for dialysis and for patients 65–84 years old this was true for patients with initial eGFR greater than 15 ml/min/ 1.73 m^2. In another study, Conway et al. [44], examined a CKD 4 population, over 75 years old, and found that only in those patients with a decline over 4 ml/min/1.73m^2/ year was dialysis prior to death required. In Cardiovascular Health Study participants, a cohort study of community-dwelling adults aged 65 years and older with CKD, during 9.7 years of follow-up, older CKD patients were 13-fold more likely to die from any cause than progress to ESRD and were 6-fold more likely to die from cardiovascular causes than develop ESRD [65].

A French prospective study in elderly CKD patients (≥80 years) newly referred to nephrologists [66], assessed predictive factors of death and dialysis initiation, using competing-risk analyses. They founded that the 3-year probabilities of death and dialysis initiation reached 27% and 11%, respectively, and the leading cause of death was cardiovascular (32%), and acute congestive heart failure was a comorbid condition both predictor of death and dialysis initiation. Moreover, no other predictor of death was found to be also a predictor of dialysis initiation suggesting that death and dialysis were independent events.

One of the major challenges to clinicians caring for older patients with CKD is to determine each patient's risk for progressive disease and the likelihood of requiring RRT in relation to the competing risk of death. This can have important clinical implications, for example to decide, if or when an access for dialysis needs to be placed. Results from studies in older stage 4 CKD patients, or even stage 5, with slower trajectory and higher comorbidities who have higher probability of death before RRT, makes placement of an arteriovenous access potentially unnecessary [67,68].

Thus, care for patients with CKD should focus more on reducing cardiovascular risk and mortality than only on progression to ESRD, and to incorporate in clinical management other outcomes, such as physical and cognition functioning, that might be more important in older patients with CKD.

5. Prognostic models

5.1. Prognostic models for CKD progression

There is growing interest in prognostic models for CKD progression to ESRD, using some of the risk factors discussed above and others that were predictive of CKD progression in specific study populations.

In a recent study, Tangri et al. [69], developed and validated a tool to predict progression in patients with stage 3-5 CKD from two large Canadian cohorts, using eight variables: age, sex, eGFR, albuminuria, serum calcium, phosphate, bicarbonate, and serum albumin. This study confirmed, that a lower eGFR, higher albuminuria, younger age, and male sex predict faster progression to kidney failure. In addition, a lower serum albumin, calcium, and bicarbonate, and a higher serum phosphate also predict a higher risk of ESRD, adding to the predictive ability of estimated GFR and albuminuria. One of this model advantages is the use of routinely available laboratory data.

Similarly, Drawz et al. [70], developed and validated a 1-year predictive model in elderly patients with advanced CKD (<30mL/min/1.73m^2), from 2 Veterans Affairs cohorts, which was comparable to Tangri's model [69] in the validation cohort. The score also uses commonly available clinical variables, and risk factors for ESRD within 1 year in the final model were age, congestive heart failure, systolic blood pressure, eGFR, potassium, and albumin. One of this Veterans Affairs risk score strengths is the one-year period over which risk for ESRD was analysed, as it is approximately the time required for preparation for dialysis (e.g., placement of dialysis access).

Although these models may be useful in the shared decision-making process, caution is warranted however, when using them in populations with different characteristics than the original cohorts [71]. Also, these predictor models have several limitations, because they do not account for the reversible factors like decrease in proteinuria, or superimposed AKI episodes, nor do they attempt to separate patients who have stable renal function, and more importantly they do not help to determine whether the risk of death will override the need to prepare for RRT [17].

5.2. Prognostic models for mortality

Another challenge in caring for older patients expected to progress to ESRD lies in evaluating the overall benefit of offering RRT to them. Although survival may have improved over time for older patients initiating dialysis [72], dialysis may be associated with only a limited survival benefit, when comparing to conservative management, as demonstrated by Chandna el al. [73], in a United Kingdom (UK) cohort of 844 CKD older patients, and also an overall decline in functional status as showed by Tamura et al. [74], using data from

United States Renal Data System (USRDS) registry. Carson et al. [76], in another UK observational study of 202 elderly patients, showed a survival advantage of dialysis compared to conservative management (37.8 versus 13.9 months), but dialysis patients had significantly more hospitalization and when accounting for hospital days and time spent on dialysis, the difference in "hospital/ dialysis free" survival between the two groups was just a few months. So, among elderly patients with a high burden of comorbidity, conservative management may therefore be a therapeutic option, as dialysis is unlikely to prolong or improve quality of life. For evaluating RRT benefits and risks and informing patients and their families about ESRD treatment options, there is recently an interest in developing predictive mortality models for incident and prevalent dialysis patients. Prognostic mortality models may help to inform shared decision-making in the trajectory of the elderly with chronic kidney disease.

5.2.1. Available models

Cohen et al. [77], in US prevalent dialysis patients, developed and validated a prognostic tool to identify patients who have an increased risk for short-term (6-month) mortality, and it is available online. Patient charts were reviewed for actuarial predictors [e.g., Charlson Comorbidity Index (CCI)], and nephrologists answered the "surprise" question, "Would I be surprised if this patient died within the next 6 months?". Five variables were independently associated with early mortality: older age, dementia, peripheral vascular disease, hypoalbuminemia, and the "surprise" question. The authors' concluded that this integrated predictive model, is more specific and sensitive than any of its components (e.g., the "surprise" question).

Chua et al. [78], conducted a single-centre observational study of multi-ethnic Asian patients with ESRD who were newly initiated on haemodialysis or peritoneal dialysis. They developed a risk prediction model for first-year mortality, and mortality predictors included advanced age, left ventricular dysfunction, cerebrovascular and peripheral vascular disease, high serum alkaline phosphatase, hypoalbuminemia, and extremes of serum urate. These factors constituted a prognostic score, and an increasing score correlated with worsening of mortality rates.

In 2009, Couchoud et al. [79], using data from the French Renal Epidemiology and Information Network (REIN) registry, developed a prognostic score to predict 6-month prognosis for elderly patients (75 years or older) starting dialysis. They selected and pointed for the score, nine risk factors: body mass index <18.5 kg/m^2, diabetes, congestive heart failure stages III to IV, peripheral vascular disease, dysrhythmia, active malignancy, severe behaviour disorders, total dependency for transfers and unplanned dialysis. Mortality rates ranged from 8% in the lowest risk group (0-point score) to 70% in the highest risk group (≥9

points). Since mortality may be high in the first few months after initiating dialysis, in 2015, in an attempt to improve their previous prognostic score [79], using the REIN registry, Couchoud et al. [80] chose to focus on very early mortality during the first 3 months of dialysis, in patients aged 75 years and older. They founded that male gender, age over 85 years, congestive heart failure, severe peripheral vascular disease, dysrhythmia, severe behavioural disorders, active malignancy, serum albumin, and impaired mobility were independently associated with 3-month mortality.

Also, focused on early mortality after dialysis initiation (3 months), Thamer et al. [81], using the USRDS (patients aged ≥ 67 years), validated a score and proposed a simple risk assessment questionnaire, based on readily available information (age, low albumin, assistance with daily living, nursing home residence, cancer, heart failure, and hospitalization).

Liu et al. [82], modified the CCI and developed a new comorbidity index for dialysis patients, that covers comorbid conditions but not age, and founded that it was a better predictor than the CCI. This new comorbidity index was also applied in a population of Taiwan's elderly patients (65 years or older) on maintenance dialysis [83], and even without the age component, it was still a strong predictor of mortality in elderly dialysis patients.

Bansal et al. [84], developed a tool using traditional risk factors to predict mortality among elderly persons with CKD in the Cardiovascular Health Study and subsequently externally validated in a separate cohort of community-living elders with CKD. This simple prediction tool using nine available clinical variables (age, gender, race, eGFR, urine albumin-to-creatinine ratio, smoking, diabetes mellitus, and history of heart failure and stroke) was able to predict 5-year mortality in elderly patients with CKD.

Recently, Wick et al. [85] developed a risk score (Alberta score) that potentially could be used to estimate mortality risk during the next 6 months for older patient initiating dialysis. They identify several independent predictors of mortality, which include age of 80 years or older, early dialysis therapy, atrial fibrillation, congestive cardiac failure, lymphoma, metastatic cancer, and hospitalization in the prior 6 months.

In an excellent review, Tamura et al. [86] outlined a framework for individualizing ESRD management decisions in older patients, considering three factors: life expectancy, the risks and benefits of competing treatment strategies, and patient preferences. They applied it to choose of dialysis modality, choice of vascular access, and referral for kidney transplantation.

Although with several limitations (lack of external validation, inherent selection bias, amongst others), using these predictive outcome models described above would help when following such framework. Moreover, applying predictive mortality models can be useful to identify elderly patients at very low risk, who are in the best position to benefit from RRT,

and it may also help to identify patients at high risk of early death with whom conservative management may be a better option.

CHAPTER III

MATERIALS AND METHODS

1. Study designs

This research involved four cohorts of CKD patients comprising two retrospective and two prospective studies. Detailed methodology concerning study design, patient selection, data collection and statistical analysis can be found in the published and submitted manuscripts (appendices).

2. Subjects

Retrospective cohort study: All consecutive CKD patients aged 65 and older referred for the first time to outpatient clinic of Nephrology Department from CHUP, between January 1, 2012 and December 31, 2012, with a minimal follow-up period of one-year (hypothesis 1).

Retrospective cohort study: Patients aged 65 years and older followed in Nephology Department from CHUP who initiated chronic RRT (hemodialysis or peritoneal dialysis) between January 1, 2009 and December 31, 2016 (hypothesis 2 and 3).

Prospective cohort study: All patients aged 65 years and over referred to the Nephrology Department from CHUP, who started dialysis as their first RRT between January 1, 2017 and December 31, 2019 (hypothesis 3).

Prospective cohort study: All consecutive CKD patients aged 65 and older referred to the outpatient Nephology Department from CHUP between January 1, 2016 and December 31, 2016 (hypothesis 4).

3. Data collection

Data were collected by nephrologists included in the research team. The following variables at baseline were usually recorded: gender, age, weight, height, body mass index (BMI), CKD etiology and stage, medication use, comorbid conditions (diabetes, ischemic heart disease, congestive heart failure, stroke, peripheral arterial disease, pulmonary disease, and cancer), and functional and cognitive status.

Cardiovascular disease was defined as the history of at least one of the following: cardiac disease, cerebrovascular and peripheral vascular disease. Cardiac disease was defined as the history of coronary artery disease, congestive heart failure and severe valvular heart disease with or without valvular replacement. Criteria for the diagnosis of coronary artery disease included previous myocardial infarction, angina pectoris, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty with or without stent implantation.

Cerebrovascular disease included previous transient ischemic attack, stroke, or cerebral haemorrhage. Peripheral artery disease was defined as the presence of intermittent claudication or with the need of peripheral revascularization or amputation.

All diabetic patients met the classification criteria established by the American Diabetes Association. Hypertension was considered if the patient had systolic blood pressure (BP)> 140 mmHg or diastolic BP >90 mmHg or need for antihypertensive drugs. Dyslipidaemia included total serum cholesterol > 200 mg/dL, or triglycerides > 150 mg/dL, or high-density lipoprotein (HDL) cholesterol < 40 mg/dL in males or < 48 mg/dL in females or low-density lipoprotein (LDL) cholesterol > 100 mg/dL or need of lipid-lowering drugs.

The diagnosis of CKD was done by the KDIGO 2012 criteria [28]. Glomerular filtration rate was estimated (eGFR) using the CKD-EPI 2009 creatinine equation [34] or using CKD-EPI cystatin C equation [88]. Etiological diagnosis of CKD was based on the patient's history, kidney ultrasound, and kidney biopsy, when available.

Cognitive status was evaluated and screened using the Mini Mental State Examination (MMSE) [89], classified as cognitive impairment if the score was 23 or lower. Functional dependency was defined as the requiring of assistance in the activities of daily living, and classified as totally dependent, partially dependent, and autonomous.

A modified version of the Charlson comorbidity index (mCCI) [90] i.e., by excluding subject's age and presence or absence of kidney disease, was calculated to assess severity of comorbidities.

During the follow-up, number and reasons for hospitalizations were registered, namely all-cause hospitalization and cardiovascular-related hospitalization, and AKI episodes (inpatient diagnostic code for AKI (ICD-9 codes 584.5–584.9).

The date of RRT initiation and death and cause of death were also registered and categorized. After RRT initiation, patients treated in other Hemodialysis Centers outside the Dialysis Unit from CHUP were followed and their information was updated through contacts with each Dialysis Unit.

4. Laboratory assessments

Fasting blood and urine samples were collected as a part of routine measurements: haemoglobin, serum albumin, urea nitrogen, creatinine, calcium, phosphorus, intact parathyroid hormone (PTH), glucose, uric acid, lipid profile, iron, unsaturated iron binding capacity, ferritin, and urine protein-to-creatinine ratio (uPCr) in spot urine sample.

All measurements were performed and analysed in the Clinical Chemical laboratory from CHUP, using standard biochemical methods.

Serum creatinine was analysed using a calibrator for automated system (Roche Diagnostics) and serum cystatin C was measured by a particle-enhanced nephelometric assay (DADE-Behring, Siemens Company, European Format).

5. Statistical analysis

Continuous data were described using mean ± standard deviation (SD) or median (IQR) and categorical data were expressed as number (and percentages). Categorical data were compared using Pearson $\chi 2$ test or Fisher´s exact test, and continuous variables were compared, if their distribution was parametric, with Student t-test or analysis of variance (ANOVA) test. In the case of continuous variables with asymmetrical distribution, comparison was done by Mann–Whitney U test or Kruskal-Wallis test.

Survival curves were constructed using Kaplan–Meier method, with comparison between groups being done by log-rank test. Risk factors for time-independent binary outcomes were determined by univariate and multivariable logistic regression models. Potential predictors of time-to-event outcomes were explored by univariate and multivariable Cox proportional hazards models. Hazards proportionality was checked by plotting log minus log of distribution hazard and using Schoenfeld residuals of distribution hazards.

Mixed models using linear quadratic and cubic models were developed to define the eGFR trajectories together with probabilistic clustering procedures. Survival analysis methods, including a survival analysis that accounted for competing risks were used to identify the predictive factors of ESRD and death.

A two-sided P-value of <0.05 was considered as statistically significant. Statistical calculations were performed using SPSS, version 24.0 (SPSS Inc., Chicago, IL, USA), GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA), Stata/MP, version 14.1 (Stata Corp, College Station, TX) and using R (R Development Core Team 2006) package mclust available as a contributed package from the Comprehensive R Archive Network (CRAN)

Distinct statistical analyses used in some studies will be described in the Results chapter.

6. Institutional and ethical approval

The studies were reviewed and authorized by the Institutional Review Board of CHUP [214-15 (178-DEFI/ 160-CES)]. The principles of the Declaration of Helsinki and the internal rules of the CHUP were observed. In all studies the confidentiality of participants identity and data collected were guaranteed. All databases were constructed and analysed anonymously.

CHAPTER IV

RESULTS

1. Thesis studies outline

The results presented in this thesis are derived from the studies published as original articles (Table 1).

Table 1 - Thesis publications according the studied hypotheses and objectives.

Hypotheses	Aims	Publications
1 Mortality, mainly from CVD, outweighs the risk of progression to ESRD in older patients with CKD. A heavy burden of CVD is present in newly referred CKD patients.	Characterize newly referred elderly CKD patients, describe their baseline demographic and clinical characteristics, with particular emphasis for the CVD burden.	1. Santos J, Fonseca I et al. End-stage renal disease versus death in a Portuguese cohort of elderly patients: an approach using competing event analysis. J Investig Med. 2017 Oct; 65 (7):1041-1048.
A competing-risk analysis could identify risk factors predictors for ESRD and differentiating them from those that increase mortality.	To determine the independent predictors of ESRD or death through a competing-risk analysis.	2. Lascasas J, Fonseca I et al. Demographic, clinical characteristics and CVD burden in a Portuguese cohort of older chronic kidney disease patients. J Bras Nefrol. 2019 Jan-Mar;41(1):29-37.
2 Renal function in patients with CKD may follow different trajectory profiles. Identifying different patterns of trajectories before dialysis initiation, would help to identify those patients who are more likely to experience an accelerated decline in kidney function, with impact on pre ESRD care and in the mortality risk after dialysis.	To understand the different kidney function trajectories patterns in CKD patients before dialysis initiation. To evaluate the association of different trajectories with patient characteristics, renal care practices and mortality after dialysis initiation.	3. Santos J, Oliveira P et al. Different kidney function trajectories patterns before dialysis in older CKD patients (submitted).
3 Predictive mortality models focused in elderly ESRD patients, have been developed in other countries. Developing and validating a prognostic model based on the specificities of our one CKD population, increases its predictive performance and clinical usefulness.	To develop a risk score in elderly CKD patients to predict 6-month mortality after dialysis initiation. To validate the previously developed prognostic score in an independent dataset and compare its performance with other known scoring system .	4.Santos J, Oliveira P et al. Predicting 6-Month Mortality in Incident Elderly Dialysis Patients: A Simple Prognostic Score. Kidney Blood Press Res. 2020;45(1):38-50. 5.Santos J, Oliveira P et al Validation of a model to predict six-month mortality in incident elderly dialysis patients. Port J Nephrol Hypert. 2020; 34(3): 167-173.
4 Cystatin C-based eGFR seems to detect significantly larger declines in kidney function than creatinine-based formulas in the elderly. Higher eGFR decline identified by cystatin C-based formulas will correlate with significant worse outcomes.	Evaluate, the association of severe CKD defined by either sCr or sCys alone, or by both, with all-cause mortality and progression to ESRD. To determine the association of severe CKD (stage 4) defined by either sCr or sCys alone, or by both, with CV events and in-hospital admissions.	6.Tavares J. Santos S, et al. Association between severe chronic kidney disease defined by cystatin-c and creatinine and clinical outcomes in an elderly population – an observation study. J Bras Nefrol. 2020

2. Hypothesis 1

2.1. Independent predictors of ESRD or death through a competing risk analysis

Santos J, Fonseca I et al. J Investig Med. 2017 Oct; 65 (7):1041-1048
doi:10.1136/jim-2017-000480

Appendix 1

The main goal of this study was to determine the independent predictors of ESRD or death through a competing-risk analysis. Furthermore, we sought to identify potential variables that may indicate a higher likelihood of death before ESRD or of attaining first ESRD status. This was a longitudinal study of consecutive CKD patients aged 65 years over, newly referred to Nephrology outpatient department (CHUP), between January 1, 2012 and December 31, 2012, followed until the time of the first event (ESRD or death), or until the end of the study (April 30, 2016).

Regression models taking competing risks into account were carried out to analyse the independent effect of covariates on each of two competing endpoints: progression to ESRD and all-cause mortality before any RRT (pre-ESRD death). This analysis was performed considering two types of hazards: cause-specific hazard (Cox standard survival analysis) and subdistribution hazard (model proposed by Fine and Gray [87]).

During a median follow-up of 3.6 years (min-max: 0.02- 4.3 years), among 416 patients, 36 progressed to ESRD (8.7%) and 103 died (24.8%) prior to ESRD, giving an ESRD rate of 2.7/100 patient-years and a mortality rate of 7.8/100 patient-years, respectively (Figure 1).

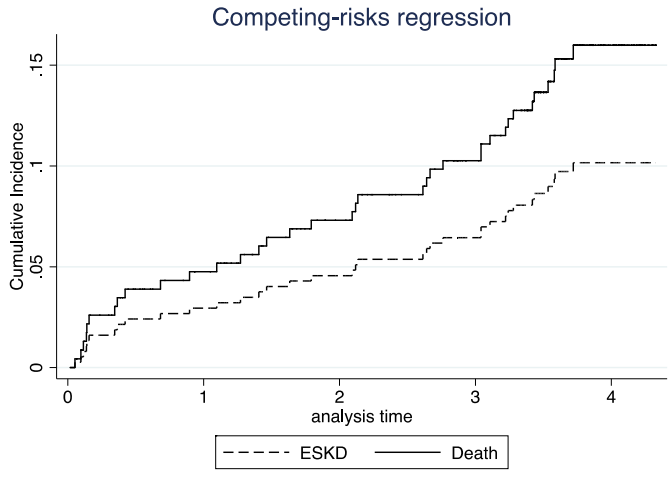


Figure 1 - Cumulative incidence rates for the competing endpoints of ESRD or death.

The multivariable Cox proportional hazards model indicated that baseline younger age, sCr > 1.6mg/dL, Hb < 11g/dL, peripheral vascular disease diagnosis, and the occurrence of one or more hospitalizations during the follow-up were associated with higher risk of ESRD (Table 2). Older age, sCr > 1.6mg/dL, Hb < 11g/dL, mCCI score ≥5, and the occurrence of hospitalizations during the follow-up were associated with death before ESRD. Cox analysis was performed censoring all patients without the event of interest. If a patient initiated dialysis, then the endpoint of mortality was censored. If a patient died, then the outcome of dialysis initiation was censored.

Table 2 - Risk factors associated with death and ESRD (Cox regression analysis).

	ESRD		**Death**	
Baseline	csHR (95% CI)	*P* value	csHR (95% CI)	*P* value
Age, years	0.95 (0.91 - 1.00)	0.049	1.04 (1.01 - 1.07)	0.004
sCr (>1.6 vs. <1.6 mg/dl)	3.64 (1.58 – 8.38)	0.002	2.27 (1.44 - 3.57)	<0.001
Hb (<11.0 vs. >11.0 g/dl)	2.72 (1.35 – 5.49)	0.005	2.20 (1.49 - 3.26)	<0.001
CCI score (3-4 *vs*. 1-2)	0.55 (0.22 - 1.39)	0.205	1.35 (0.80 - 2.29)	0.258
(≥5 *vs*. 1-2)	0.80 (0.33 - 1.96)	0.626	2.82 (1.70 - 4.67)	<0.001
Peripheral vascular disease (yes *vs*. no)	3.60 (1.70 - 7.60)	0.001	1.03 (0.64- 1.68)	0.890
DM vs other CKD etiologies	1.75 (0.85 - 3.58)	0.127	1.02 (0.67 - 1.55)	0.930
During the follow-up				
Hospitalizations (yes *vs*. no)	1.72 (1.17 - 2.52)	0.006	1.84 (1.44 - 2.36)	<0.001

Values given as cause-specific hazard (csHR) (95% confidence interval) for risk factors associated with ESRD and death prior to ESRD.
Hb, hemoglobin; CCI, Charlson comorbidity index; DM, Diabetes Mellitus; CKD, chronic kidney disease; ESRD, end-stage renal disease

Conversely, subhazard ratios estimated from competing-risk regression that necessarily discriminated between the two endpoints. Those who are older, with sCr >1.6mg/dL, Hb < 11g/dL, mCCI score ≥5 and one or more hospitalizations during the follow-up, were more likely to die (Table 3). Significant risk factors for ESRD included younger age, sCr >1.6mg/dL, HB < 11g/dL, peripheral vascular disease, and the occurrence of one or more hospitalizations during the follow-up (Table 3).

Table 3 - Risk factors associated with death and ESRD (Fine & Gray model)

	ESRD		**Death**	
Baseline	sHR (95% CI)	*P* value	sHR (95% CI)	*P* value
Age, years	0.94 (0.89 - 0.98)	0.009	1.06 (1.03 - 1.09)	<0.001
sCr (>1.6 *vs.* <1.6 mg/dl)	3.26 (1.40 - 7.60)	0.006	2.03 (1.25 - 3.29)	0.004
Peripheral vascular disease (yes *vs*. no)	3.45 (1.68 - 7.10)	0.001	0.82 (0.49- 1.34)	0.435
CCI score (3-4 *vs*. 1-2)	0.57 (0.24 - 1.35)	0.202	1.53 (0.87 - 2.69)	0.137
(≥5 *vs*. 1-2)	0.54 (0.23 - 1.28)	0.164	3.01 (1.75 - 5.19)	< 0.001
Hb (<11.0 *vs*. >11.0 g/dl)	2.15 (1.09 - 4.24)	0.027	1.91 (1.25 - 2.92)	0.003
DM *vs* other CKD etiologies	1.72 (0.84 - 3.53)	0.139	0.84 (0.54 - 1.32)	0.447
During the follow-up				
Hospitalizations (yes *vs*.no)	1.56 (1.04 - 2.35)	0.031	1.73 (1.33 - 2.25)	<0.001

Values given as subdistribution hazard ratio (sHR) (95% confidence interval) for risk factors associated with ESRD and death prior to ESRD. Abbreviations: Hb, hemoglobin; CCI, Charlson comorbidity index; DM, Diabetes Mellitus; CKD, chronic kidney disease; ESRD, end-stage kidney disease.

In summary, the main results were:

- Newly referred CKD patients aged over 65 years were near threefold more likely to die than progress to ESRD;
- By using a competing risk analysis, we shown that peripheral vascular disease increases the cumulative incidence of ESRD but is not associated with increased pre-ESRD mortality;
- Similarly, a mCCI score ≥5 increased the hazard for pre-ESRD death, but not for RRT initiation.

2.2. Cardiovascular disease burden and risk profile in a referred cohort of older CKD patients

Lascasas JMSS, Fonseca I et al. J Bras Nefrol. 2019 Jan-Mar;41(1):29-37
doi: 10.1590/2175-8239-JBN-2018-0120

Appendix 2

In this report we described the baseline demographic and clinical characteristics of the same cohort of elderly CKD patients, with emphasis for the CVD burden. As previously explained, these patients were newly referred to Nephrology outpatient department, between January 1, 2012 and December 31, 2012. This gave us information on the baseline characteristics of the patients before they received specific attention from nephrologist.

In a total of 416 patients aged ≥ 65 years, 50% were referred by primary care physicians, with a median eGFR of 32 ml/min/1.73m^2, 52% were male, with a mean age of 77 years, 36% of them aged 80 years or more, 26% were current/former smokers, and 24% had a body mass index > 30 kg/m^2. About 50% (n=206) of the patients were diabetic, and 96% (n=400) had hypertension. In only approximately 30% of the patients BP was <130/80 mmHg, and in just about 50% it was <140/90 mmHg. Men with diabetes were the group with worst BP control (BP goal <130/80mmHg). About 50% (n=207) of the patients were receiving two or more antihypertensive drugs (excluding diuretics), and 14 % (n=58) were under three or more antihypertensive drugs. Inhibitors of the renin angiotensin system were the drugs most frequently used (n=293; 70%). Dyslipidemia was present in 85 % of the patients (n=354), 60 % (n=248) were under lipid-lowering medication.

Cardiovascular disease was present in 62% (n=256) of the patients: coronary artery disease in 25% (n=103), cerebrovascular disease in 24% (n=100) and peripheral vascular disease in 19% (n=77) of the patients, respectively (Table 4).

Table 4 - Cardiovascular disease burden stratified by gender and presence and absence of DM.

	Total	**Male**		**Female**	
		n = 218		**n= 198**	
	n = 416	**Diabetics**	**Non-Diabetics**	**Diabetics**	**Non-Diabetics**
		n= 112	**n= 106**	**n = 94**	**n=104**
Cardiovascular disease*, n;(%)	256 (62)	74 (66)	65 (61)	60 (64)	57 (55)
Cardiac disease, n;(%)	282 (68)	78 (70)	62 (58)	85 (90)	57 (55)
Coronary artery disease	103 (25)	34 (30)	25 (24)	30 (32)	14 (13)
Congestive heart failure	164 (39)	42 (38)	34 (32)	50 (53)	38 (37)
Severe valvular heart disease	15 (4)	2 (2)	3 (3)	5 (5)	5 (5)
Cerebrovascular disease, n; (%)	100 (24)	35 (31)	25 (24)	18 (19)	22 (21)
Peripheral artery disease, n; (%)	77 (19)	33 (29)	18 (17)	16 (17)	10 (10)

Cardiovascular disease includes all patients with one or more of the following: cardiac disease, cerebrovascular and peripheral vascular disease. Categorical data are presented as numbers (n) of patients and percentages (%).

Stratifying the CKD stages in 3a, 3b and 4-5 the prevalence of coronary artery disease, congestive heart failure, and peripheral vascular disease were highest in stage 4-5 patients (Figure 2).

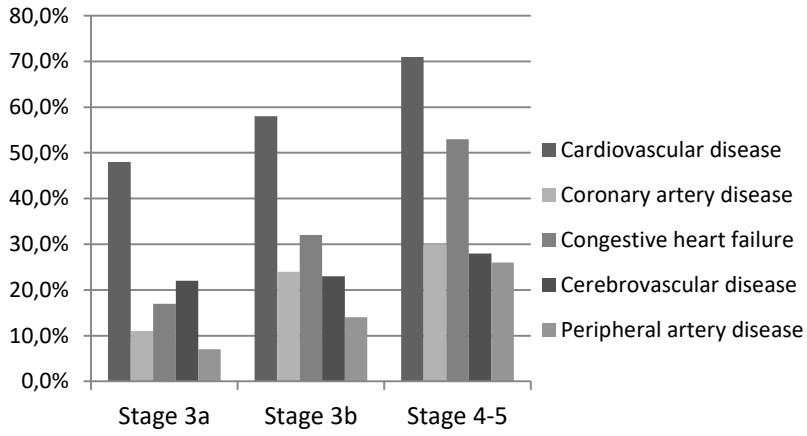


Figure 2 - Prevalence (%) of individual causes of cardiovascular disease stratified by CKD stages.

In patients with Diabetes Mellitus, the prevalence of CVD was gradually increasing with CKD progression (stage 3a<stage 3b<stage 4-5) (39% < 58% < 82%; p<0.001) (Table 5).

Table 5 - Cardiovascular disease burden, stratified by CKD stages and presence and absence of diabetes mellitus.

	Total n=377				Diabetics n=184				Non-Diabetics n= 193			
CKD Stage	**3a n=46**	**3b n=139**	**4-5 n=192**	**p**	**3a n=18**	**3b n=73**	**4-5 n=93**	**p**	**3a n=28**	**3b n=66**	**4-5 n=99**	**p**
Cardiovascular disease*, n (%)	22 (48)	80 (58)	137 (71)	0.002	7 (39)	42 (58)	76 (82)	<0.001	15 (54)	38 (58)	61 (62)	0.713
Cardiac disease, n(%)												
Coronary artery disease	5(11)	33 (24)	58 (30)	0.022	2 (11)	22 (30)	36 (39)	0.062	3 (11)	11 (17)	22 (22)	0.339
Congestive heart failure	8 (17)	45 (32)	102 (53)	<0.001	2 (11)	26 (36)	59 (63)	<0.001	6 (21)	19 (29)	43 (43)	0.040
Severe valvular heart disease	2 (4)	3 (2)	10 (5)	0.371	1 (6)	1 (1)	5 (5)	0.375	1 (4)	2 (3)	5 (5)	0.805
Cerebrovascular disease, n (%)	10 (22)	32 (23)	54 (28)	0.475	2 (11)	16 (22)	34 (37)	0.027	8 (29)	16 (24)	20 (20)	0.610
Peripheral artery disease, n(%)	3 (7)	20 (14)	49 (26)	0.003	3 (17)	13 (18)	30 (32)	0.071	0	7 (11)	19 (19)	0.022

*Cardiovascular disease includes all patients with one or more of the following: cardiac disease, cerebrovascular and peripheral vascular disease. Categorical data are presented as numbers (n) of patients and percentages (%). Cardiovascular disease burden was compared between CKD stages by Chi-squared test for trend for categorical variables. P-value <0.05 was considered statistically significant.

In summary the main results:

- This cohort of newly referred CKD patients was characterized by a higher prevalence of many established cardiovascular risk factors and a higher prevalence of CVD;
- Lower level of eGFR was associated with a greater burden of CVD;
- The prevalence of CVD was gradually increasing with CKD progression, pronounced in patients with diabetes, highlighting the importance of strategic targeting of cardiovascular risk reduction in these CKD patients.

3. Hypothesis 2

3.1. Different kidney function trajectories patterns before dialysis in older CKD patients: Implications for clinical management

Santos J, Oliveira P et al.
Manuscript submitted

Appendix 3

We aimed to identify and characterize trajectories of renal function decline before dialysis in CKD patients, and to investigate their association with mortality after dialysis.

This was a retrospective cohort study which include 378 CKD patients aged 65 years and over who had at least five consecutive serum creatinine measurements before dialysis initiation, between 2009 and 2016. Mixed models using linear quadratic and cubic models were developed to define the eGFR trajectories together with probabilistic clustering procedures.

Four distinct groups of eGFR trajectories decline before dialysis initiation were identified: slower eGFR decline (group 1, n=69; 18.3%), gradual eGFR decline (group 2, n=69; 18.3%), early rapid eGFR decline (group 3, n=156; 41.2%) and rapid eGFR decline (group 4, n=84; 22.2%) (Figure 3).

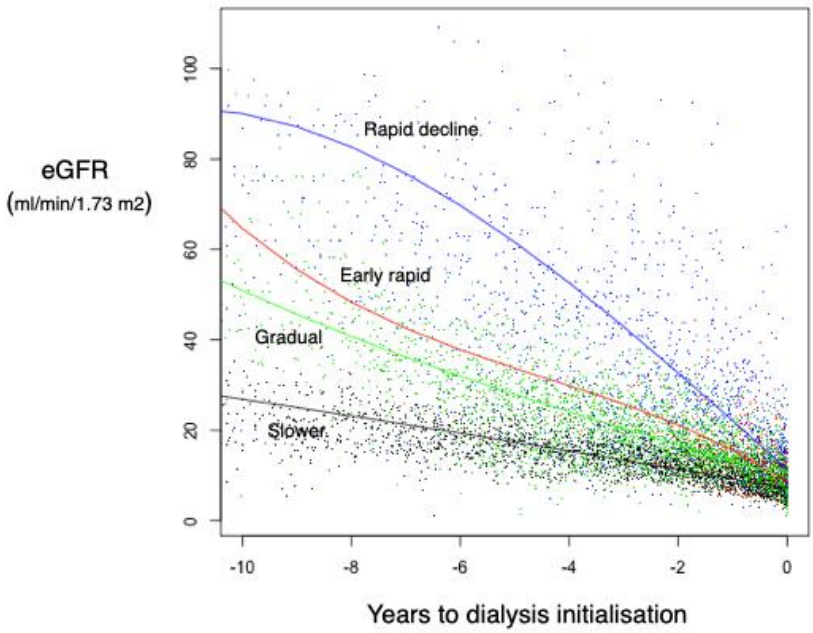


Figure 3 - Trajectories decline for the identified groups.

The characteristics of kidney function for each of the identified trajectories were described in Table 6.

Table 6 - Characteristics of each and overall trajectory decline groups.

	Overall n=378	**Slower eGFR decline (Group 1) n=69**	**Gradual eGFR decline (Group 2) n=69**	**Early rapid eGFR decline (Group 3) n=156**	**Rapid eGFR decline (Group 3) n=84**	**p-value**
SCr measures, nº	8253	2074	745	3745	1689	
Median and IQR	19.0 [11.0-28.0]	26.0 [19.5-38.5]	9.0 [17.0-13.0]	22.0 [14.0-22.8]	16.0 [9.3-29.0]	p<0.001 2-4 2-3
Mean, SD	21.1 ± 13.2	30.1 ± 15.3	10.8 ± 5.3	22.3 ±11.8	20.1 ± 12.6	2-1
Range	5-90	5-71	5-32	5-90	5-66	4-1 3-1
Follow-up (yrs)						
Median and IQR	6.0 [3.7-8.6]	9.4 [6.3-11.1]	2.0 [1.4-2.8]	6.3 [4.6-8.5]	6.5 [4.1-7.9]	p<0.001 2-4 2-3
Mean, SD	6.3 ± 3.5	9.1 ± 3.7	2.5 ± 1.9	6.8 ± 2.8	6.3 ± 2.7	2-1
Range	0.1-27.7	3.1-27.7	0.6-11.6	2.3-17.9	0.1-12.4	4-1 3-1
Time between SCr measures						
Median and IQR	0.29 [0.22-0.45)	0.30 [0.24-0.43]	0.22 [0.16-0.37]	0.29 [0.23-0.45]	0.31 [0.23-0.60]	p<0.001 2-1 2-3
Mean; SD	0.40 ± 0.34	0.40 ± 0.35	0.28 ± 0.16	0.43 ± 0.37	0.45± 0.36	2-4
Range	0.01-2.74	0.15-2.74	0.06-0.99	0.10-2.22	0.01-1.93	
eGFR initial						
Median and IQR	31.1 [20.5-47.7]	22.3 [17.7-29.7]	21.1 [16.8-26.8]	34.0 [23.4-44.0]	61.9 [46.2-76.1]	p<0.001 1-3 1-4
Mean, SD	36.8 ± 20.9	24.7 ± 10.0	22.8 ± 9.9	35.6 ± 16.1	60.7 ± 21.9	2-3
Range	1.5-109.0	9.9-58.5	5.4-58.0	1.5-100.1	12.7-109.0	2-4 3-4
eGFR final						
Median and IQR	6.6 [5.0-8.5]	5.8 [4.2-7.3]	6.7 [4.9-8.5]	6.7 [5.0-8.6]	7.4 [5.4-9.7]	p=0.04
Mean; SD	7.0 ± 3.0	6.0 ± 2.2	6.8 ± 2.5	7.0 ± 2.7	8.1 ± 4.1	1-4
Range	1.0-25.5	1.7-14.9	2.9-15.5	1.0-15.9	2.5-25.5	
% eGFR var⁺						
Median and IQR	77.9 [66.9-87.2]	74.1 [64.9-82.2]	69.3 [56.1-77.9]	78.8 [71.1-86.4]	88.3 [78.0-92.2]	p<0.001 2-3
Mean; SD	74.7 ± 16.6	72.5 ± 12.1	64.6 ± 19.6	76.1 ± 14.0	82.0 ± 17.3	2-4
Range	-4.6-97.2	35.0-97.2	-4.6-91.1	27.9-96.2	22.3-96.4	1-4 3-4

Data expressed as medians and interquartile ranges (IQR) or mean and standart deviation (SD) SCr, serum creatinine; yrs, years; eGFR, Estimated glomerular filtration rate eGFR, using the Chronic Kidney Disease Epidemiology ⁺Based on all patient serum creatinine measures during de the follow-up period before dialysis initiation

A multinomial logistic regression analysis was conducted to identify the predictors associated with falling into a particular trajectory group, with the distinct trajectory groups used as the dependent variable (Table 7). The trajectory group with the slower decline eGFR (group 1) was considered as the reference to which other groups were compared.

Table 7 - Multivariable adjusted multinomial logistic regression analysis for the associations of demographic and clinically relevant factors with trajectories eGFR decline.

Variables	Gradual eGFR decline (Group 2) n=69			Early rapid eGFR decline (Group 3) n=156			Rapid eGFR decline (Group 4) n=84		
	β	aOR (95%CI)	*p*-Value	β	aOR (95%CI)	*p*-Value	β	aOR (95%CI)	*p*-Value
Age (<75 vs. ≥75 yrs)	0.079	1.082 (0.543-2.157)	0.823	0.241	1.272 (0.705-2.294)	0.424	0.852	2.345 (1.182-4.652)	0.015*
Gender (female vs. male)	0.570	1.768 (0.881-3.548)	0.109	0.460	1.585 (0.868-2.893)	0.134	0.961	2.615 (1.313-5.206)	0.006*
Diabetes (yes vs. no)	0.597	1.816 (0.912-3.617)	0.090	0.650	1.916 (1.060-3.461)	0.031*	1.007	2.736 (1.379-5.431)	0.004*
Cognitive impairment (yes vs. no)	0.306	1.358 (0.470-3.927)	0.572	0.360	1.434 (0.571-3.601)	0.443	1.239	3.451 (1.320-9.026)	0.012*
Hosp.1-yr before dialysis (yes vs. no)	0.582	1.789 (0.850-3.765)	0.125	0.763	2.145 (1.142-4.028)	0.018*	0.976	2.653 (1.231-5.717)	0.013*

Values show the risk profile (aOR) for each trajectory group compared to trajectory Group 1 (slower decline). Predictors starred* are those that were statistically significant. aOR, adjusted odds ratio in relation to all the other variables in the table, CI, confidence interval

By the end of follow-up in October 2019, 233 patients (62%) had died, with a median survival of 4.4 years (1.8-8.7). Patients in the slower eGFR decline (group 1) had the best median survival (9.0 years) and patients with the more rapid eGFR decline (group 4) had the lowest median survival (2.4 years) (Figure 4).

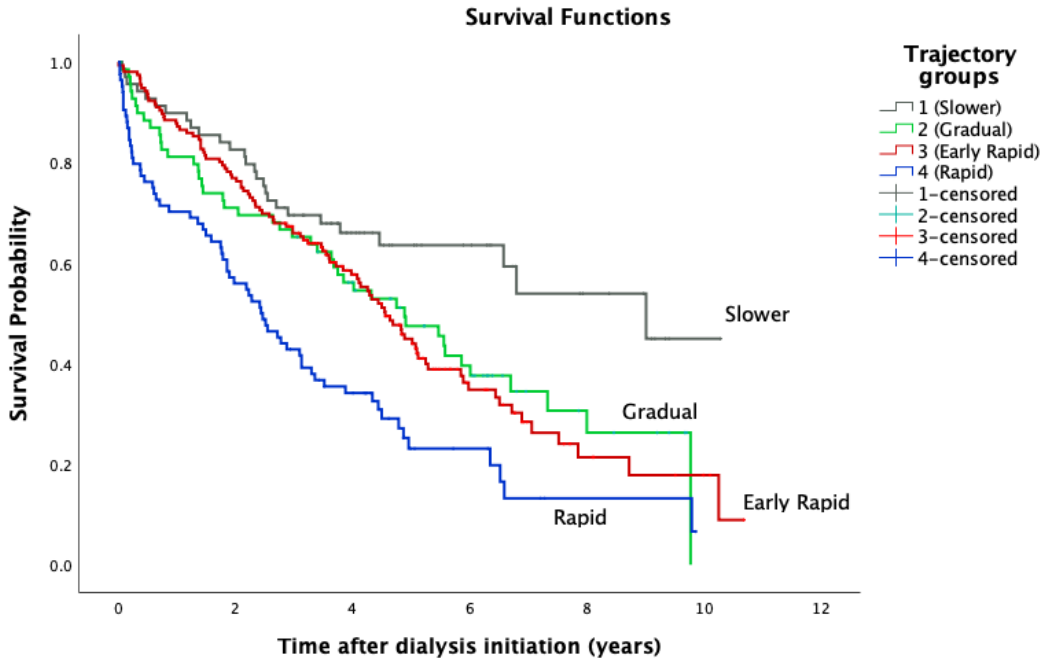


Figure 4 - Kaplan-Meier survival curves after dialysis initiation by eGFR trajectory group

After adjustment for patient characteristics significant for eGFR trajectories, compared to patients with slower eGFR decline, patients with rapid loss of eGFR (groups 3 and 4) were associated with higher mortality within the first and fourth year after dialysis initiation (HR: 1.805; 95%CI 1.005-3.243, and HR: 3.260; 95%CI 1.693-6.277, for early rapid and rapid eGFR decline, respectively) (Table 8).

Table 8 - Adjusted Risk of Death Over Different Periods After Dialysis Initiation by Trajectory Group using Cox proportional hazards regression model.

FUp time	Gradual eGFR decline (Group 2) n=69		Early rapid eGFR decline (Group 3) n=156		Rapid eGFR decline (Group 4) n=84)	
	aHR (95%CI)	*p*-Value	aHR (95%CI)	*p*-Value	aHR (95%CI)	*p*-Value
< 1 year	0.584 (0.213-1.601)	0.296	0.549 (0.211-1.426)	0.218	1.185 (0.473-2.973)	0.717
1 to 4 years	1.653 (0.830-3.292)	0.153	1.805 (1.005-3.243)	0.048*	3.260 (1.693-6.277)	<0.001*
> 4 years	3.628 (1.171-11.24)	0.026*	4.259 (1.468-12.35)	0.008*	6.347 (1.868-21.56)	0.003*

Values shown are adjusted hazard for death (95% confidence interval); referent group is slower eGFR decline (group 1). Adjusted for demographic characteristics (age and gender), diabetes, cognitive status, and hospitalization during the 1-year period before dialysis initiation. Abbreviation: eGFR, estimated glomerular filtration rate.; aHR, adjusted hazard ratio; CI, confidence interval.

In summary the main results were:

- Women, younger patients (age <75 vs. ≥75 years), and patients with cognitive impairment were more likely to be included in the rapid decline trajectory (group 4);
- Diabetic were more likely than non-diabetic patients to be placed into any of the rapid eGFR decline trajectories (group 3 and 4), as well as patients hospitalized within one-year before dialysis;
- By the end of follow-up, 233 patients (62%) had died, with a median survival of 4.4 years (1.8-8.7). Patients in the slower eGFR decline (group 1) had the best median survival (9.0 years) and patients with the more rapid eGFR decline (group 4) had the lowest median survival (2.4 years) (Figure 4);
- Patients with rapid loss of eGFR (groups 3 and 4) were associated with higher mortality within the first and fourth year after dialysis compared to patients with slower eGFR decline;
- After being more than four years in dialysis, patients in trajectories 2, 3 and 4 were at increased significant risk of dying compared with the reference group.

4. Hypothesis 3

4.1. Development of a model to predict 6-month mortality in incident elderly dialysis patients.

Santos J, Oliveira P et al. Kidney Blood Press Res. 2020;45(1):38-50.
Doi: 10.1159/000504136

Appendix 4

We aimed to develop a risk score in elderly CKD patients to predict 6-month mortality after dialysis initiation.

In a retrospective cohort study, data from 421 patients aged 65 years and over, referred to the Nephrology Department from CHUP, who started dialysis as their first RRT, between January 2009 and December 2016, were used.

Using 6-month mortality after dialysis initiation as the dichotomous outcome variable, several risk factors were first examined by univariable logistic regression. Multivariable models were then built using backward selection.

The discrimination of the risk score was evaluated using the area under the receiver operating characteristic curve (AUC). A bootstrapping procedure was used to internally validate the risk score and determine optimism.

A total of 60 patients (14%) died within 6 months of starting dialysis. Five independent predictors of 6 months mortality after starting dialysis were retained in the final model (multivariable logistic regression analyses) (Table 9) and a points system was constructed (Table 10): age 75 years or older (2 points), coronary artery disease (2), cerebrovascular disease with hemiplegia (2), time of nephrology care before dialysis [< 3.0 months (2); ≥ 3 to < 12 months (1)], serum albumin levels [3.0 - 3.49 g/dL (1); < 3.0 g/dL (2)].

Table 9 - Multivariable logistic regression model for 6-month mortality.

	Regression Coefficient	Adjusted OR	95% CI	*P*
Age category (≥75 years vs. <75 years)	0.97	2.63	(1.38 - 5.02)	0.003
Coronary artery disease (yes vs. no)	0.93	2.54	(1.35 – 4.79)	0.004
Cerebrovascular disease with hemiplegia (yes vs. no)	0.95	2.58	(1.07 – 6.21)	0.035
Albumin category (ref: ≥ 3.5 g/dL)				
3.0 - 3.49 g/dL	0.85	2.35	(1.09 – 5.05)	0.029
< 3.0 g/dL	1.46	4.31	(2.07 – 8.97)	< 0.001
Time of nephrology care before dialysis (ref: ≥ 12 months)				
< 3.0 months	1.41	4.09	(2.06 – 8.12)	<0.001
≥ 3 to < 12 months	0.63	1.88	(0.72 – 4.90)	0.199
Intercept	-3.91	0.18		
C-statistic: 0.793				
Hosmer-Lemeshow test: *P*=0.584				

Variables were retained in the model using backward elimination (Wald) procedure. OR odds ratio; CI, confidence interval.

Table 10 - Predictors of 6-month mortality and associated risk scoring system.

	Shrunken β-Regression Coefficient‡	*Risk score*§
Age category (≥75 years vs. <75 years)	0.86	2
Coronary artery disease (yes vs. no)	0.83	2
Cerebrovascular disease with hemiplegia (yes vs. no)	0.84	2
Albumin category (ref: ≥ 3.5 g/dL)		
3.0 - 3.49 g/dL	0.76	1
< 3.0 g/dL	1.30	2
Time of nephrology care before dialysis (ref: ≥ 12 months)		
< 3.0 months	1.26	2
≥ 3 to < 12 months	0.56	1

‡Original β-regression coefficient multiplied by heuristic shrinkage factor.
§Scores assigned by dividing the shrunken β-regression coefficients by 0.528 (two-fifths of the two small β-coefficients in the model) and rounded to nearest integer.

Model performance was good in both discrimination [AUC of 0.793; (95% confidence interval, 0.73 to 0.86)] and validation [concordance statistics of 0.791 (95% confidence interval, 0.73 to 0.85)].

The performance of our developed score was significantly higher than Couchoud score [79] (P=0.026), that was calculated for all patients in our cohort according to corresponding formula [79] (Figure 5). Therefore, for this set of individuals, for a given specificity, our severity score always presents a better sensitivity.

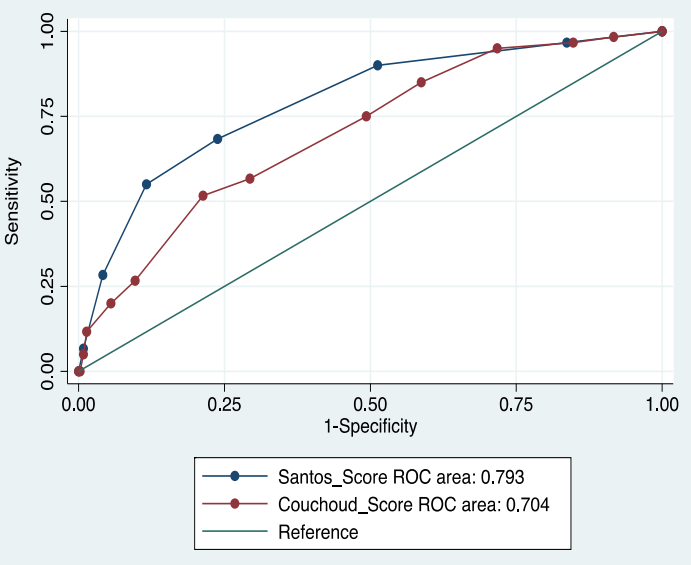


Figure 5 - Comparison of receiver operating characteristics (ROC) curves for predicting 6-month mortality after starting dialysis, among our (Santos) and Couchoud scores.

The risk score derived ranged from 0 to 10 points. Prognostic score calculated well predicts 6-month mortality after maintenance dialysis initiation. (Figure 6). As an example, a score of 6 identified patients with a 70% risk of 6-month mortality.

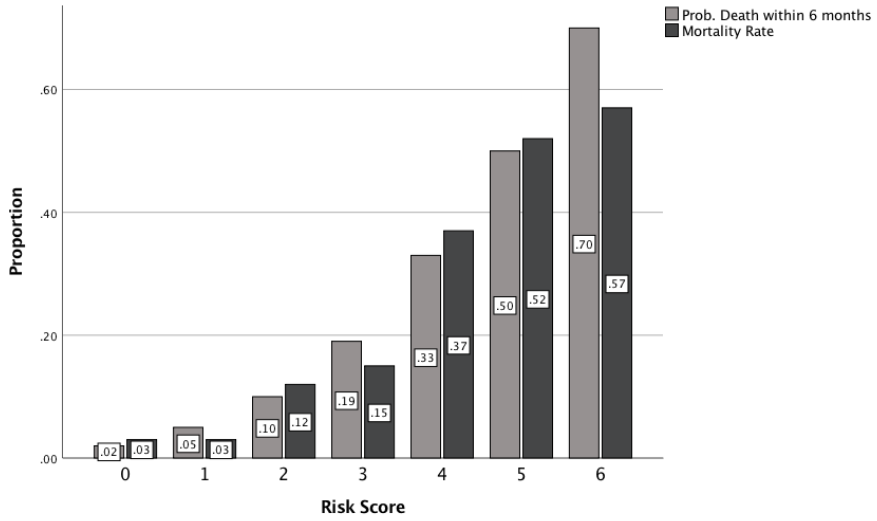
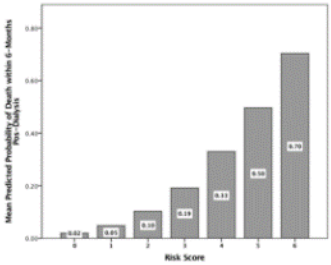


Figure 6 - Mean predicted mortality risks and observed proportions for ranges of total scores.

A risk assessment questionnaire for clinicians and patients' use was illustrate in Figure 7, exposing a simple method for establishing a patient's risk for the outcome depending on an individual's status for the five variables included in the tool.

6-months mortality predictors	Assigned Points
Age (years) Points < 75 ..... 0 ≥ 75 2	
Coronary artery disease …….. 2	
Cerebrovascular disease with hemiplegia ……..2	
Albumin (g/dL) ≥ 3.5 ……0 3.0 - 3.49 ……. 1 < 3.0 ……2	
Time of nephrology care (months) ≥ 12 ……0 ≥ 3 to < 12 ……. 1 < 3.0 ……2	

Total Score



Points correspond to each predictor value and are added to give a total score. Points along the x-axis of the plot corresponds to approximate probability of mortality within 6 months along the y-axis.

Figure 7 - Score chart to predict 6-months mortality risk after dialysis initiation.

In summary the main results were:

- We have developed a prognostic score, based in readily available variables, for predicting early death in a cohort of elderly Portuguese ESRD patients;
- Five independent mortality predictors were identified: age 75 years or older, coronary artery disease, cerebrovascular disease with hemiplegia, time of nephrology care before dialysis and serum albumin levels;
- In our population the performance of our risk score was good and significantly higher than Couchoud score [79].

4.2. Validation of a predictive mortality score on a new cohort of incident elderly dialysis patients.

Santos J, Oliveira P et al. Port J Nephrol Hypert. 2020; 34(3): 167-173
Doi.org/10.32932/ pjnh.2020.10.082

Appendix 5

Before adopting our previous developed mortality risk score (Santos J, Oliveira P et al. Kidney Blood Press Res. 2020) into practice, its performance was assessed on a new data set. A prospective cohort study was performed to external validation, applying the score to an independent cohort of ESRD patients, aged 65 years and over who started dialysis between 2017 and 2019, in our Nephrology department.

The baseline characteristics of development and validation cohorts are presented in Table 11. Comparing with patients from the development cohort, patients from the validation set (n=168) had lower eGFR at dialysis initiation and had fewer hospitalizations within 6-months before dialysis. Furthermore, patients included in the validation sample were more functionally autonomous and were referred earlier to nephrology care before dialysis.
Among patients in the validation cohort, there were 21 deaths (12.5%) within the first 6 months after dialysis initiation.

Model performance in the validation cohort had and acceptable discrimination [AUC of 0.79; (95% confidence interval, 0.70 to 0.88)]. The Hosmer and Lemeshow goodness-of-fit test was not statistically significant, indicating good calibration of the model (χ^2,5 degrees of freedom = 2.311; P = 0.805) (Figure 8).

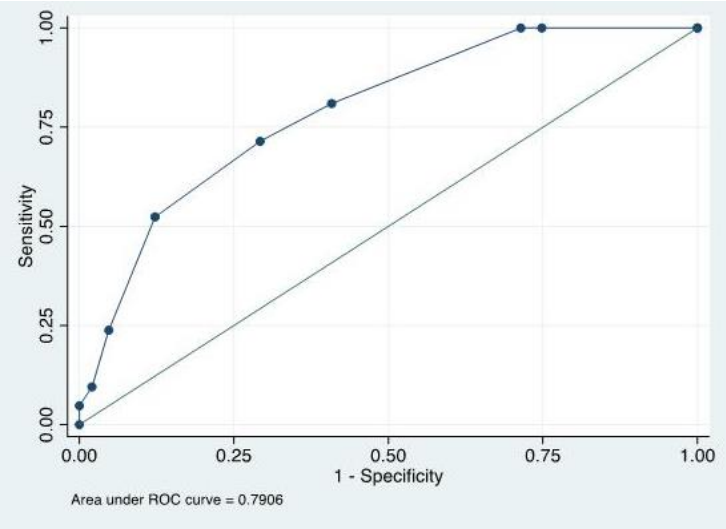


Figure 8 - Performance of risk score in validation cohort.

Table 11 - Baseline Characteristics of development and validation cohorts for predicting 6-months mortality in elderly ESDR.

	Development Cohort n=421	**Validation Cohort n =168**	***P* Value**
Age (years), median and IQR	75.5 [70-80]	74.7 [69-80]	0.428
Age ≥75 years, n (%)	217 (51.5)	83 (49.4)	0.549
Female, n (%)	195 (46.3)	63 (37.5)	0.051
Primary renal disease, n (%)			
Diabetic nephropathy	156 (37.1)	59 (35.1)	
Ischemic nephropathy	69 (16.4)	28 (16.7)	
Glomerulonephritis	50 (11.9)	24 (14.3)	0.135
ADPKD	21 (5.0)	15 (8.9)	
Other	73 (17.3)	17 (10.1)	
Unknown etiology	52 (12.4)	25(14.9)	
BMI (kg/m^2), median and IQR	25.7 [23.5-28.7]	26.1 [22.9-29.2]	0.840
< 25, n (%)	170 (40.4)	67 (40.6)	
25-30	148 (35.2)	63 (38.2)	0.791
> 30	75 (17.8)	35 (21.2)	
Cognitive impairment, n (%)	63 (15.0)	16 (9.5)	0.121
Totally dependent for transfer, n (%)	37 (8.8)	13 (7.7)	
Need assistance for transfer, n (%)	188 (44.7)	45 (26.8)	<0.001
Autonomous, n (%)	196 (46.6)	110 (65.5)	
Institutionalization, n (%)	22 (5.2)	8 (4.8)	0.817
mCCI, median and IQR	3.8 [2-5]	3.0 [2-5]	0.083
0-2, n (%)	127 (30.1)	59 (35.1)	
3-4	130 (30.9)	54 (32.1)	0.326
≥ 5	164 (39.0)	55 (32.7)	
Current/ Former smoking, n (%)	96 (22.8)	49 (29.1)	0.105
Diabetes, n (%)	212 (50.4)	88 (52.4)	0.657
Hypertension, n (%)	409 (97.1)	163 (97.0)	0.934
Dyslipidemia, n (%)	375 (89.1)	156 (92.9)	0.164
Congestive heart failure, n (%)	262 (62.2)	106 (63.0)	0.845
Coronary artery disease, n (%)	126 (29.9)	54 (32.1)	0.598
Cardiac arrhythmia, n (%)	101 (24.0)	41 (24.4)	0.915
Cerebrovascular disease, n (%)	137 (32.5)	40 (23.8)	0.116
with hemiplegia	43 (10.2)	14 (8.3)	0.486
Peripheral vascular disease, n (%)	165 (39.2)	55 (32.7)	0.144
Neoplasia, n (%)	64 (15.2)	31 (18.5)	0.333
COPD, n (%)	74 (17.6)	36 (21.4)	0.279
Chronic liver disease,, n (%)	30 (7.1)	8 (4.8)	0.292
Autoimmune disease, n (%)	16 (3.8)	11 (6.5)	0.150
Peptic ulcer, n (%)	62 (14.7)	27 (16.0)	0.681
Albumin <3.5 g/dL, median and IQR	3.6 [3.2-4.0]	3.7 [3.1-4.2]	0.198
≥ 3.5, n (%)	255 (60.6)	101 (60.1)	
3.0 - 3.49	87 (20.7)	36 (21.4)	0.978
< 3.0	79 (18.8)	31 (18.5)	
Creatinine (mg/dL), median and IQR	6.3 [4.7-7.5]	6.6 [5.1-8.2]	0.003*
eGFR EPI (ml/min/1.73 m^2), median	6.5 [4.8-8.4]	5.6 [4.3-7.7]	0.003*
and IQR ≥ 15, n (%)	12 (2.9)	2 (1.2)	
10 – 14.9	43 (10.2)	7 (4.1)	
< 10	366 (86.9)	159 (94.6)	0.025*
Time of nephrology care before dialysis (months), median and IQR	43.9 [18.0-89.0]	65.2 [27.4-126.5]	<0.001*
< 3; n (%)	83 (19.7)	17 (10.1)	
≥3 to < 12	43 (10.2)	9 (11.3)	0.02*
≥12	295 (70.1)	142 (84.5)	
Dialysis modality: hemodialysis; n (%)	411 (97.6)	154 (91.7)	0.001*
Unplanned dialysis, n (%)	249 (59.1)	85 (50.6)	0.059
Access at first dialysis: catheter, n(%)	181 (42.9)	68 (40.5)	0.577
Hosp.6-months before dialysis, n (%)	144 (34.2)	75 (44.6)	0.018*

Data expressed as medians and interquartile ranges (IQR) or n (%) when appropriate. Comparisons between continuous variables were done using a nonparametric test (Mann-Whitney test); associations between categorical variables were analysed using the χ^2 test; *P<0.05. BMI, body mass index; mCCI, modified Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; Nº. hospitalizations, number of hospitalizations based on 6 months prior to dialysis initiation. *P<0.05

In summary the main results were:

- Our prognostic score for predict 6-months mortality in elderly ESRD patients initiating dialysis had a good performance on the new data (validation group), indicated that the model was likely not overfit, and demonstrated their predictive accuracy.

5. Hypothesis 4

5.1. Association between severe CKD defined by cystatin-c and creatinine and clinical outcomes in an elderly population

Tavares J, Santos J et al. J Bras Nefrol. 2020
Doi: 10.1590/2175-8239-JBN-2020-0092

Appendix 6

We evaluated, the association of severe CKD (stage 4) defined by either sCr or sCys alone, or using both, with all-cause mortality and progression to ESRD, and secondly, with cardiovascular events and in-hospital admissions (all-cause, and for infection or AKI).
In a longitudinal prospective study 348 patients aged over 65 years old, who had non-ESRD (CKD except stage 5) referred to the outpatient Nephology Department during the year of 2016 were studied. They were followed until death or until December 31, 2018; eGFR was estimated by the equations derived from the CKD-EPI: CKD-EPI creatinine equation (eGFR-sCr) and CKD-EPI cystatin C equation (eGFR-sCys).

Patients were divided into four exclusive categories:

- 1. CKD stage 4 neither (eGFR-sCr ≥ 30 mL/min per 1.73m^2; eGFR-sCys ≥ 30 mL/min per 1.73m^2)
- 2. CKD stage 4 sCr only (eGFR-sCr < 30 mL/min per 1.73m^2; eGFR-sCys ≥ 30 mL/min per 1.73m^2)
- 3. CKD stage 4 sCys only (eGFR-sCr ≥ 30 mL/min per 1.73m^2; eGFR-sCys < 30 mL/min per 1.73m^2)
- 4. CKD stage 4 combined (eGFR-sCr < 30 mL/min per 1.73 m^2; eGFR-sCys < 30 mL/min per 1.73 m^2)

The cohort had a mean age of 77 years old. After excluding the CKD stage 4 neither group, there were no significant differences between the characteristics of the four groups.
By the end of the follow-up period 54 patients had died and only 4 initiated dialysis. No difference between the groups was observed considering patient death (overall or by cause) and ESRD at the end of the follow-up.
As proportionality was not met, survival analysis was stratified by follow-up time at 12 months (Figure 9). In the first year, survival curves of the CKD stage 4 combined and sCys only groups were significantly lower (P=0.028) when compared to the CKD stage 4 neither and sCr only groups. However, this difference was not found after 12 months (P=0.148).

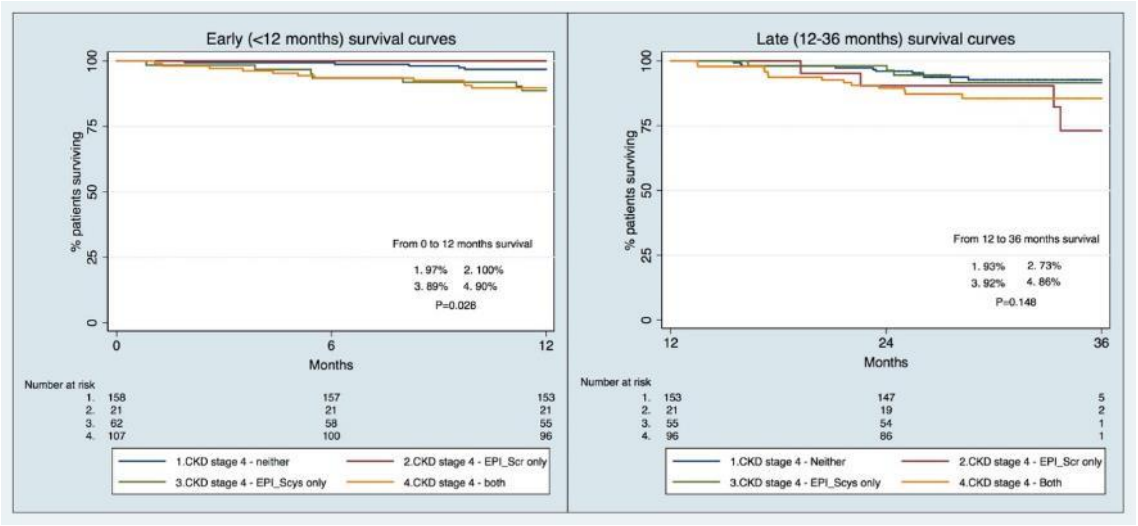


Figure 9 - Comparison of survival curves of the CKD stage 4 groups.

Similarly, CKD stage 4 combined and sCys only groups were better predictors of early death (<12 months) in both unadjusted and adjusted extended Cox models (Table 12). Importantly, only CKD stage 4 sCys only group was an independent predictor of early mortality in the adjusted model. No differences were detected for the risk of late mortality between the groups in any of the models analysed (Table 12).

Table 12 - Extended Cox regression exploring predictors of death, considering CKD stage 4 groups at two time-periods.

			Unadjusted		**Adjusted**	
	n per group	n events	HR (95% CI)	***P***	HR (95% CI)	***P***
CKD stage 4 **[0-12 months]**						
Neither	158	5	Ref.	Ref.	Ref.	Ref.
sCr only	21	0	- (no events)	-	- (no events)	-
sCys only	62	7	3.7 (1.2-11.7)	**0.025**	3.5 (1.1-11.0)	**0.033**
Combined	107	11	3.4 (1.2- 9.8)	**0.024**	2.2 (0.8-6.6)	0.138
CKD stage 4 **[12-36 months]**						
Neither	153	10	Ref.	Ref.	Ref.	Ref.
sCr only	21	4	2.7 (0.8-8.5)	0.099	2.2 (0.7-7.1)	0.188
sCys only	55	4	1.1 (0.4-3.6)	0.839	1.1 (0.3-3.4)	0.911
Combined	96	13	2.2 (1.0-5.0)	0.060	1.5 (0.7-3.6)	0.330
Adjusted to: Age, Sex, mCCI						

CKD – Chronic kidney disease; mCCI – Modified Charlson Comorbidity Index; Ref. – Reference; sCr – Serum Creatinine; sCys – Serum cystatin C

Concerning to secondary outcomes, cardiovascular events and in-hospital admissions, incident rate ratio (IRR) for each type of event (Table 13), with an unadjusted model, CV events occurred more often in the sCys-based only group and in the combined group. However, when using an adjusted model for potential confounders, as age, sex and mCCI,

this difference only remained true for the sCys-based only group. As for all-cause admissions and admissions due to AKI, there was a higher IRR in the sCys-based only group and in the combined group for both unadjusted and adjusted models. The IRR for infectious events in the combined group was two times higher than the IRR in sCys-based only group and almost four times higher than the IRR of the sCr-based only and stage 4 neither group.

Table 13 - Incident rate ratio of CV events, all-cause admissions, admissions due to AKI and infectious events in the CKD stage 4 groups.

	CV Events	**Unadjusted**		**Adjusted**	
	Event rate (100 patients-year)	IRR (95% CI)	**P**	IRR (95% CI)	**P**
CKD stage 4					
Neither	5.3	Ref.		Ref.	
sCr only	9.0	1.7 (0.6-4.6)	0.227	1.4 (0.5-3.8)	0.486
sCys only	12.3	2.4 (1.2-4.5)	**0.010**	2.2 (1.1-4.2)	**0.021**
Combined	10.3	2.0 (1.1-3.5)	**0.026**	1.5 (0.8-2.8)	0.214
	All Admissions events	**Unadjusted**		**Adjusted**	
	Event rate (100 patients-year)	IRR (95% CI)	**P**	IRR (95% CI)	**P**
CKD stage 4					
Neither	11.5	Ref.		Ref.	
sCr only	10.8	0.9 (0.4-2.2)	0.885	0.8 (0.3-1.8)	0.543
sCys only	29.0	2.5 (1.6-3.9)	**<0.001**	2.3 (1.5-3.5)	**<0.001**
Combined	35.5	3.1 (2.1-4.4)	**<0.001**	2.2 (1.5-3.3)	**<0.001**
	AKI Events	**Unadjusted**		**Adjusted**	
	Event rate (100 patients-year)	IRR (95% CI)	**P**	IRR (95% CI)	**P**
CKD stage 4					
Neither	6.0	Ref.		Ref.	
sCr only	5.4	0.9 (0.30-3)	0.861	0.7 (0.2-2.4)	0.597
sCys only	17.4	2.9 (1.6-5.1)	**<0.001**	2.5 (1.4-4.5)	**0.002**
Combined	24.0	3.9 (2.4-6.4)	**<0.001**	2.6 (1.6-4.4)	**<0.001**
	Infectious Events	**Unadjusted**		**Adjusted**	
	Event rate (100 patients-year)	IRR (95% CI)	**P**	IRR (95% CI)	**P**
CKD stage 4					
Neither	3.7	Ref.		Ref.	
sCr only	3.6	1.0 (0.2-4.3)	0.983	0.8 (0.2-3.4)	0.726
sCys only	8.0	2.2 (1.0-4.8)	0.054	1.8 (0.8-4.1)	0.134
Both	14.1	3.8 (2.0-7.2)	**<0.001**	2.5 (1.3-4.8)	**0.006**
Adjusted to: Age, Sex, mCCI					
AKI – Acute kidney injury; CKD – Chronic kidney disease; CV – Cardiovascular; mCCI – Modified Charlson Comorbidity Index; Ref. – Reference; sCr – Serum Creatinine; sCys – Serum cystatin C					

In summary the main results were:

- CKD-EPI cystatin C was superior to CKD-EPI creatinine equation in predicting all-cause mortality at the first year, CV events, all-cause and AKI admissions, when used in older patients with severe non-end stage CKD (stage 4);
- In our elderly patients with severe non-end stage CKD (stage 4), sCys-based eGFR was a better predictor of adverse outcomes than sCr-based eGFR in patients with discordant staging.

CHAPTER V

DISCUSSION

This discussion incorporates the thoughts reflected in each hypothesis by reformulating and integrating them into a broader perspective.

1. **The heavy burden of CVD in newly referred CKD patients and competing-risk events analysis** (hypothesis 1)

The discussion of hypothesis 1 is based on the objectives and results presented in Table 14.

Table 14 -Main results regarding proposed aims for the hypothesis 1.

AIMS	MAIN RESULTS
To describe demographic and clinical characteristics of newly referred elderly CKD patients, with particular emphasis for the CVD burden.	New referral CKD patients had a higher burden of CV risk profile and disease. Stratifying the CKD stages in 3a, 3b and 4-5, it was observed that the prevalence CVD was highest in stage 4-5 patients and more pronounced in patients with diabetes.
To examine independent predictors of ESRD or death through a competing-risk analysis.	Newly referred CKD patients aged over 65 years were near threefold more likely to die than progress to ESRD. By using a competing risk analysis, we shown that peripheral vascular disease increases the cumulative incidence of ESRD but is not associated with increased pre-ESRD mortality; similarly, a mCCI score ≥5 increased the hazard for pre-ESRD death, but not for RRT initiation.

CKD is associated with increased prevalence of both traditional and nontraditional cardiovascular risk factors [12], with several studies confirming that in the elderly, even in early stages of CKD, cardiovascular mortality outweighs the risk of progression to ESRD [13,14]. Even so patients over 65 years of age represent the most rapidly growing segment of the ESRD population requiring RRT in Western countries [5,6].

When we designed our longitudinal cohort study, the main objective was to identify the main predictors for CKD progression and death in CKD patients newly referred to our outpatient department. Bearing in mind this objective it seemed important to us to explore in detail the characteristics of these patients, especially regard to their vascular risk profile. This gives us information on the baseline characteristics of the patients before they receive specific attention from nephrologist.

Fifty percent of the patients were referred by primary care physicians. At baseline, with mean age of 76 years, they had a median eGFR of 32 ml/min per 1.73 m^2, and almost 80% of the patients above CKD stage 3b, which is in accordance with the proposed criteria to nephrology referral from KDIGO 2012 guidelines [28].

About 25% of the patients had a high comorbidity index (mCCI score ≥ 5), 43% have some degree of functional dependency and 11% had a cognitive impairment. Furthermore, our cohort fits the frailty phenotype associated with CKD and geriatric syndrome [91], in contrast with other elderly CKD European cohorts newly referred to nephrologists [92], that despite older than our patients, had a good health status, reflecting a selection bias in referring patients for nephrology care, not found in our group.

The leading causes of CKD were diabetic and ischemic nephropathy, which are the leading causes ok CKD, particularly in older patients. However, in the absence of specific diagnostic tests and given the very low biopsy rate (4%), the diagnostic certainty for both CKD etiologies may be not accurate. Nowadays, there is consensus that older age is not a contraindication to renal biopsy, which is safe and reveal unanticipated diagnoses in 15-33% of cases in the elderly population [93]. So, we consider that renal biopsy should be used more often in our elderly CKD population as a tool to provide diagnostic and prognostic information, which can have an impact in patient care.

The prevalence of CVD in our referral patients was very high, present in 62% of the patients, higher than that reported from other European CKD cohorts (German GCKD [94], Spanish MERENA [95], Italian CARHES [96]), even when age adjusted.

Data available from several epidemiological studies revealed that cardiovascular events and cardiovascular mortality increased inversely with eGFR [97,98]. Conversely, CVD is associated with increased risk of CKD progression [99]. In our cohort we also found an increase in the prevalence of CVD with worsening CKD stage, more pronounced in patients with diabetes.

Some characteristics of our patients may provide indirect evidence for several risk factors for CKD and for CVD prevalence. Among the traditional risk factors for CKD and for CVD, diabetes prevalence of 50% in our cohort is higher than that reported from other Europeans CKD cohorts [94-96], even when age adjusted. Obviously, diabetes is an important contributor to the disease burden in CKD patients far beyond those with presumed diabetic nephropathy. The presence of hypertension was almost universal (96%), and importantly blood pressure was not optimally controlled (in only one-half of the patients receiving antihypertensive drugs the blood pressure was <140/90 mmHg). This gap between targets and clinical practice demonstrate the difficulties of blood pressure control in CKD, and a potential for improvement. Dyslipidemia was also very prevalent in our patients (85%), more prevalent in patients with diabetes, which reinforces de cardiovascular risk in those patients. Among other risk factors, most of patients were nonsmokers (74%) and 24% were obese (BMI > 30 kg/m^2), a prevalence lower than that reported in the other CKD cohorts [95,96].

Therefore, these cardiovascular risk factors were not the major contributors to CVD prevalence in our study group. Even so, obesity and overweight were more prevalent in diabetic.

Incorporation of albuminuria into the kidney disease staging is likely to improve the prediction of the renal and cardiovascular risks in CKD patients [28,100,101]. Obviously, the amount of proteinuria was higher in our patients with diabetes when compared to patients without diabetes, confirming that the proteinuria is a hallmark of diabetic nephropathy, but also an important contributor to the cardiovascular risk in diabetic patients. The degree of proteinuria in our cohort was similar to that reported in other European CKD cohorts [95,96], but is higher than other cohorts (CRIC) [100], with a proportion of diabetic patients like ours, which should be related to the better BP control in those [100].

Concerning to anemia and CKD-mineral bone disorder control our data suggest that there is a need for further optimization of these CKD complications.

The heavy burden of cardiovascular risk profile present in our patients, may also reflect an important role of several risk factors for kidney disease development and CKD prevalence, in our population. In a recent review, elaborated on the factors that potentially underly observed international differences in CKD prevalence in the elderly within Europe [102], the authors concluded that Portugal had the highest estimate of CKD prevalence, and also the highest average score on CKD risk factors (i.e., diabetes mellitus, raised blood pressure, physical inactivity, and salt intake). More recently, the RENA study [103] carried out with the aim of providing an estimate of the prevalence of CKD at the national level, corroborated these data. After data adjustment by gender, age group, and geographical region, the global prevalence of CKD in Portugal was 20.9% above the worldwide and Europe average [103].

One of the major challenges to clinicians caring for older CKD patients is to identify each patient's risk for progressive CKD and likelihood for requiring RRT in relation to the competing risk of death. This may involve important clinical decisions, such as referrals and procedures for dialysis access placement or transplant decision, or on the contrary the possibility to identify patients with higher comorbid conditions, at high risk of early death for which conservative management may be the best option.

Hence, along with the characterization of elderly CKD patients newly referred to our department, it seemed important to us to determine the independent predictors of ESRD (defined as the need for RRT initiation) or death through a competing-risk analysis. To our knowledge, and until now, no study has specifically addressed this issue in a Portuguese cohort of elderly CKD patients.

In standard survival data, subjects are supposed to experience only one event at a time, such as ESRD or death before dialysis initiation. The remaining possible events are treated as censored observations. When only one of these different types of event can occur, they

are called “competing events”, in a sense that they compete with each other to deliver the event of interest, and the occurrence of one type of event will prevent the occurrence of the others. Thus, we applied two different methodologies to deal with competing events, a standard survival analysis (Cox regression) considering one event at a time and a competing regression model proposed by Fine & Gray [87], to better identify prognostic factors each event, adjusting for other potential risk factors.

During a median follow-up of 3.6 years our patients were near 3-fold more likely to die than progress to ESRD. The leading causes of death prior to ESRD were cardiovascular (35%), followed by infection (29%). These results were consistent with those found in previous studies confirming that elderly CKD are far less likely to develop kidney failure than to die, especially from cardiovascular disease [13,23,64,92].

The prognostic factors identified by both methodologies used in the competing risk framework were overlapping. Patients who are younger, with creatinine higher than 1.6 mg/dl, hemoglobin lower than 11 g/dl, had previous peripheral vascular disease and one or more hospitalizations during the follow-up, are more likely to reach ESRD. Those who are older, with creatinine higher than 1.6 mg/dl, hemoglobin lower than 11 g/dl, mCCI score ≥ 5, and one or more hospitalizations during the follow-up, are more likely to die. Several factors were able to predict ERSD as well as death before dialysis (creatinine higher than 1.6 mg/dl, hemoglobin lower than 11 g/dl, and one or more hospitalizations during the follow-up). However, the presence of peripheral vascular disease at baseline was consistently an independent predictor for ESRD, but it was not associated with increased pre-ESRD mortality. And mCCI score ≥ 5 was a prognostic factor for death before dialysis, but no to ESRD.

Peripheral vascular disease is the result of an atherosclerotic process similar to that one seen in cardiovascular disease, and atherosclerosis is a potentially important mechanism of kidney disease in older persons [39, 104], and increases the susceptibility for AKI and CKD progression [105]. Peripheral arterial disease must be reflected by a reduced ankle-brachial Index and some studies demonstrated that this marker predicted accelerated renal function decline, in general population [106], and in peritoneal dialysis patients [107]. Our study suggests that the presence of peripheral arterial disease, although reflecting an atherosclerotic systemic process also involving the kidneys, may be a potential marker for renal function decline in CKD patients, through other mechanisms, in addition to the traditional association of CKD with vascular damage and it deserves more research. However, it reinforces the importance of strategic targeting vascular risk screening and reduction in our population. In addition, the higher burden of CV risk factors, and prevalent vascular disease, present in our cohort, and the association between peripheral vascular

disease and ESRD that we found, may partially explain the highest incidence of ESRD of Portuguese population among European countries [6].

As previously stated, a high comorbidity index (mCCI score ≥ 5) was an independent predictor for pre-ESRD death, but not for RRT initiation. In CKD patients, the CCI seemed to be significantly more predictive for mortality than other comorbidity scoring systems [108]. Although, old age alone should not be used as an absolute barrier to treatment when considering the benefits of dialysis in elderly CKD patients [72], in the elderly patients with a high burden of comorbidity, conservative management may be a therapeutic option [73,74,76], considering the likelihood of death prior to ESRD makes preparation for RRT, as the placement of an arteriovenous access unnecessary and potentially harmful [67].

By using a competing-risk approach using two methodologies on available clinical and laboratory data, we could identify risk factors predictors of CKD progression and distinguishing them from those that increase mortality, which may allow us to use them as a decision-making tool to guide clinical decision process.

2. Patterns of trajectories before dialysis initiation, impact on pre ESRD care and in the mortality after dialysis (hypothesis 2)

The discussion of hypothesis 2 is based on the objectives and results presented in Table 15.

Table 15 - Main results regarding proposed aims for the hypothesis 2.

AIMS	MAIN RESULTS
To understand the different kidney function trajectories patterns in older CKD patients before dialysis initiation.	We identified four distinct groups of eGFR trajectories decline before dialysis.
To evaluate the association of different trajectories with patient characteristics, renal care practices and mortality after dialysis initiation.	Patients with rapid eGFR decline were more likely to have diabetes, more cognitive impairment, to have been hospitalized before dialysis, and were less likely to have received pre-dialysis care compared to the patients with slower decline. Patients with rapid loss of kidney function had a higher risk of death within the first and fourth year after dialysis initiation, and after being more than four years in dialysis.

To predict complex clinical pathways of kidney disease progression that do not follow a steady linear decline, is a challenge to nephrologists. Many CKD patients have a non-linear GFR trajectory, influenced by several factors, such as AKI episodes, and the competing risk of mortality, particularly frequent in older CKD patients [109,110].

On the other hand, some studies have demonstrated strong associations between decline in eGFR and risk of cardiovascular disease and mortality among CKD patients [21,22].

Considering dialysis initiation, a seminal event, we believe that an understanding of trajectories of kidney function before initiation of maintenance dialysis may help to clarify the optimal timing of care (e.g., nephrology referral, vascular access placement, transplant referral) and to guide clinical decision-making [17,111]. Only a few studies have addressed this issue in patients who initiate dialysis [19,112-115] and only one study have provided a detailed description of different chronic trajectories of kidney function before dialysis initiation [19].

Concerning to the model to define the trajectories, we used mixed models using linear quadratic and cubic slopes. Ciampi et al. [116] refer the use of clustering to study disease trajectories specifically in the study of longitudinal data where the number of observations or the time between observations may differ across patients. Probabilistic clustering procedures [117-119] were used to assign the individual trajectories to the different clusters.

In our cohort four distinct patterns of eGFR decline preceding dialysis initiation were identified: slower eGFR decline (n=69; 18.3%), gradual eGFR decline (n=69; 18.3%), early

rapid eGFR decline (n=156; 41.2%) and rapid eGFR decline (n=84; 22.2%). Patients in the slower and gradual eGFR decline groups, were those with a baseline eGFR under 25 mL/min/ 1.73 m^2 (37%) and had relatively slower slopes than the other trajectory groups. In opposition, 22% of patients had a catastrophic rate of decline (rapid decline group) with a baseline eGFRs >60 mL/min/1.73 m^2.

Patient characteristics and care practices that could be determinants of those trajectories were then identified, and patients with diabetes or diabetes being the cause of ESRD were more likely to be in eGFR rapid decline trajectories. Thus, diabetes was very prevalent in our cohorts, as we showed previously, but beyond that diabetic patients presented faster eGFR decline. These results suggest that chronic hyperglycaemia *per si* plays a crucial role in accelerating GFR decline in diabetic patients [120,121], which reinforces the need for tighter monitoring in diabetic patients, whether they have proteinuria or not.

Like others [19,112], we also found that patients who experienced more rapid eGFR decline were younger compared with patients who progressed slower, which can be explained by the fact that older patients who survive long enough to reach more advanced stages of CKD are less likely than their younger counterparts to experience fast eGFR decline.

One particularity of our findings is that rapid eGFR decline group had a higher proportion of women compared with the group progressed slower. Although several studies indicate that renal disease progression is faster in men than women [122], a meta-analysis published in 2003 [55] suggested that the progression of renal disease may not be slower in women as compared to men, though most of the women were on post-menopausal age. In the Chronic Renal Insufficiency Cohort (CRIC) study, despite women having a significantly decreased risk of developing ESRD, after adjusting for demographic and clinical factors there were no significant differences in eGFR slopes between women and men [123]. Thus, it is not clear whether sex is independently associated with faster renal disease progression, or whether the association reflects confounding by imbalances between men and women of non-controlled factors associated with renal disease progression.

We also found that the patients who experienced rapid eGFR decline had more cognitive impairment than patients with slower decline. Cognitive impairment is remarkably prevalent in older CKD patients [124], and the celerity of eGFR decline had an increased risk of cognitive deterioration [125]. Recently, in data from SPRINT trial [126], the authors found an association between a large decline in eGFR and increased incidence of probable dementia and mild cognitive impairment. We believe eGFR decline would be an indicator that shows renal function change is caused by vascular effects, particularly in the elderly, which supports the hypothesis of a cognition-kidney axis.

As previous discussed, trajectories of kidney function decline may hold important implications for the optimal timing of RRT preparation. Although, there is no universally

accepted definition for optimal timely evaluation, a period of 12 months seems to be reasonable [127]. In our study, the level of eGFR approximately 12 months before dialysis initiation varies from 10 mL/min/1.73m^2 for patients with slower eGFR decline, to 25 mL/ min/1.73 m^2 for patients with rapid eGFR decline. In fact, in our cohort, patients without vascular access and who had inpatient dialysis initiation, were more likely to be in the rapid decline trajectory group, maybe to non-recognition of their potential to rapid progress. These results suggest the need for more flexible approaches to preparation for RRT with awareness of the heterogeneity of eGFR trajectories [19].

About 75 % of our patients, have been hospitalized within one-year before starting dialysis, and it was 2.5-fold more frequent in patients with rapid eGFR decline trajectory. It is likely that higher rates of hospitalization were attributable in part to deteriorating kidney function and its complications, or that the rate of kidney function decline may be a surrogate marker of poor overall health.

Although, episodes of AKI in CKD patients are associated with more rapid transition between stages of CKD and increased risk for progression ESRD, particularly in the elderly [59], in our work, inpatient diagnosis of AKI and the presence of AKI at dialysis initiation were not associated with being placed into any faster decline trajectory compared with the slower eGFR decline. This may be related to the fact that AKI episodes were very prevalent among all our trajectories groups, although lower in the slower eGFR decline group.

Mortality on dialysis therapy have historically been attributed to factors measurable at the time of dialysis itself [128]. However, our results showed that rapid loss of eGFR add information about prognostic over and above known comorbid conditions and confounders. In fact, contrary to other studies [19,113], trajectory group had no significant impact at the risk for death during the first year after dialysis initiation, but the impact of rapid decline of kidney function in mortality after one year of dialysis is notorious.

One of the strengths of our study is that we identified and provided a description of different chronic trajectories of kidney function leading up to dialysis initiation through the entire spectrum of CKD progression, not only at transitioning period to dialysis. Hence, kidney function trajectory before to dialysis must be regarded as clinically relevant, and their incorporation into everyday clinical practice could improve the early detection of high-risk patients with more time to pre-ESRD care, and to take preventive measures targeted at subsequent clinical adverse events, which may have an impact on the medium and long-term prognosis after dialysis.

3. Development and validation of a prognostic score to predict early mortality after dialysis (hypothesis 3)

The discussion of hypothesis 3 is based on the objectives and results presented in Table 16.

Table 16 - Main results regarding proposed aims for the hypothesis 3.

AIMS	MAIN RESULTS
To develop a risk score in elderly CKD patients to predict 6-month mortality after dialysis initiation and compare its performance with other known scoring system.	Five predictors of 6-month mortality (and their associated scores) were identified: age 75 years or older, coronary artery disease, cerebrovascular disease with hemiplegia, time of nephrology care before dialysis and low serum albumin. This prognostic score has good a performance and is based on simple and readily available information. The performance of our score was significantly higher than Couchoud score [79].
To validate the previously developed prognostic score in an independent dataset.	Our model achieved a good performance in the validation cohort, which confirms their predictive accuracy in an independent sample.

Incorporating mortality predictive models into CKD management for older patients may help to inform patients and their families about ESRD treatment options and provide a more patient-centred overall approach to care. In the past years, several mortality scores have been developed based on various combinations of comorbidities and laboratory data, but only a few of them focused on short-term survival including only elderly CKD patients [77,79-81,85]. Only few of these models were externally validated [84, 129,130].

Differences in patients' profile, namely distinct sociodemographic and clinical characteristics between the cohorts used to derive those scores, reinforce the need to develop predictive scores adapted to the specificities of each population. Keeping this in mind, we have developed and external validated a prognostic score for predicting early death in a cohort of Portuguese ESRD patients.

Five predictors of 6-month mortality were identified, which allowed to build a prognostic score: age 75 years or older (2 points), coronary artery disease (2 points), cerebrovascular disease with hemiplegia (2 points), time of nephrology care before dialysis [< 3.0 months (2 points); ≥ 3 to < 12 months (1point)], low serum albumin [3.0- 3.49 g/dL (1 point); < 3.0 g/dL (2 points)].

The presence of clinically manifest CVD such as coronary artery disease and cerebrovascular disease with hemiplegia had a significant impact on 6-months mortality after starting dialysis. The prevalence of CVD in our cohort was very high related to high

prevalence of many established risk factors of CVD (diabetes, hypertension, dyslipidemia), also present in our patients. Those two variables were not considered or were not predictive in previous models in elderly ESRD patients [79-80,85]. So, the incorporation of variables as mortality predictors, may add clinical utility in contexts in which these conditions appear with reasonable frequency. The presence of cerebrovascular disease with hemiplegia as mortality predictor, may also reflect the impact of frailty in mortality of CKD patients [23] related to the functional dependency of these patients. These factors provide further evidence of the importance, beyond the usual clinical criteria, of incorporating in the RRT decisions in elderly the assessment of physical and cognitive function, and other components of geriatric syndrome.

Hypoalbuminemia has been associated with poor clinical outcomes in CKD patients [132]. In our patients the association of lower albumin levels with mortality was significant. This association might reflect the role of hypoalbuminemia as a marker of acute illness or inflammatory state [133], rather than nutrition by itself, and may offer an opportunity to improve patient outcomes by identifying and treating the underlying disorders [134] and improve albumin levels.

Time of nephrology care before dialysis initiation, was strongly predictive of early mortality in our cohort, particularly within 3 months prior to dialysis initiation, but also between 3 and 12 months, compared to more than 12 months. Although there is no universally accepted definition of timely referral of patients with CKD, considering a period of 12 months as adequate to provide an acceptable nephrology care [127] was consistent with our results.

The lack of timely evaluation defined as adequate evaluation to allow for patient and family education, management, and preparation for RRT (e.g., creation of a permanent access) is particularly common in elderly patients. Besides being a major reason for higher morbidity and mortality on dialysis, late referral, also leads to increased costs because of longer initial hospitalization times, the lack of option for de optimal RRT, and the lower transplantation rates [135].

The validation of prognostic models is a determinant step before implementation in the clinical practice. Prognostic models should be internally and especially externally validated to obtain reliable estimates of model performance [136]. Internal validation implies assessment of model performance directly in the derivation cohort. However, this approach yields an optimistic estimate of model performance [137,138]. To minimize this limitation the model can be developed on the whole dataset and techniques of data reuse, such as cross-validation and bootstrapping, applied to assess performance [136-138]. In the derivation of our score, we performed a bootstrapping procedure (5000 bootstrap samples) to internally validate the risk score. A concordance statistic of 0.791 (95% confidence interval, 0.73 to 0.85) and an optimism of 0.002, meaning that our prognostic model

achieved a good performance. We choose to compare the performance of our model with the Couchoud score [79] because in addition of being a predictive mortality model of reference in the elderly ESRD population, it was a prognostic score for predicting early death (6 months) in elderly ESRD patients, initiating dialysis, as our predictive score. As in our model, Couchoud score [79] includes readily available clinical variables, based in a European (REIN registry) cohort of referred patients. The performance of our risk score was significantly higher than Couchoud score [79], which reflects the different characteristics of the populations involved in derivation of the models.

Even with a good performance achieved in the same sample used to develop the model (internal validation), before adopting any risk score into clinical practice, it is expected to examine if the score accurately predicts outcomes in a different sample; therefore, validation in an independent sample should be done. We could confirm the good performance (its calibration and discrimination) of our model on the new data (validation group), indicating that the model was not overfitted, and demonstrating its predictive accuracy. Likewise, in the validation cohort, although not statistically significant, the performance of our score was higher than Couchoud score [79].

It is important to highlight some differences that might affect model translation between the validation sample and the original study sample. Patients from the validation set had lower eGFR at dialysis initiation, had fewer hospitalizations within 6-months before dialysis, were more functionally autonomous and were referred earlier to nephrology care, compared with patients from the development cohort. These differences may be due to the difference in timing of dialysis initiation, the validation cohort was more recent than the development cohort (patients aged 65 years and who started dialysis between 2017 and 2019 *vs*. patients aged 65 years and who started dialysis between 2009 and 2016, respectively). Even so, our model achieved a good performance in the validation cohort, which confirms their predictive accuracy in an independent sample.

Simplicity of models and reliability of measurements are important criteria in developing clinically useful prognostic models [11]. Our prognostic score included variables that are well defined, measurable, and readily available, in other words our model is clinical useful. Moreover, we made a risk assessment questionnaire for clinicians and patients' use, displayed in a simple figure, exposing an easy and understandable method for all involved in shared decision-making process.

Shared decision making is a process of communication. This is particularly relevant before the initiation of dialysis, where patients should understand the benefits, burdens, and alternatives to dialysis. A simple and accurate prognostic score based on readily available data, can be an easily implemented tool to apply in daily practice to guide patient care, as shared decision-making process.

4. Cystatin C-based eGFR is a better predictor of adverse outcomes than creatinine-based eGFR (hypothesis 4)

The discussion of hypothesis 4 is based on the objectives and results presented in Table 17.

Table 17 - Main results regarding proposed aims for the hypothesis 4.

AIMS	MAIN RESULTS
To evaluate, in a cohort of elderly CKD patients, the association of severe CKD (stage 4) defined by either sCr or sCys alone, or by both, with all-cause mortality and progression to ESRD.	CKD-EPI cystatin C was superior to CKD-EPI creatinine equation in predicting all-cause mortality at the first year, CV events, all-cause and AKI admissions, when used in older patients with severe non-end stage CKD.
To determine the association of severe CKD (stage 4) defined by either sCr or sCys alone, or by both, with cardiovascular events and in-hospital admissions.	Cystatin C-based eGFR was a better predictor of adverse outcomes than sCr-based eGFR in patients with discordant staging. .

Chronic kidney disease progression in the elderly seems to be more significant when cystatin C-based formulas are considered [40]. The close relationship between muscle mass and sCr accounts largely for the inaccuracy of this marker in the elderly, with sCys presenting a better performance as GFR estimator. Several studies have suggested that the use of sCys, a marker less susceptible than sCr to metabolic and extrarenal factors, for eGFR calculation significantly improves the risk classification for death, cardiovascular disease and ESRD [36,139].

Our elderly new referral patients with severe CKD defined by sCys had a higher mortality when compared to severe CKD defined only by sCr and patients with CKD from stage 1 to 3. After extended cox regression analysis and adjusting by age, sex and mCCI, just the sCys only group (eGFR-sCr ≥ 30 mL/min per 1.73m^2; eGFR-sCys < 30 mL/min per 1.73m^2) remained as a predictor of early death. This tendency was also verified when analysing CV events rate, which was the main cause of death.

Some studies, however, alerted that the association between sCys and all-cause plus CV mortality could be due to other confounding factors, since the populations studied had variable ages and different characteristics as BMI and other comorbidities [140, 141]. In order to exclude confounding factors that could biased our results, we made an extensive characterization of our baseline population and among the patients with severe CKD (stage 4) no detectable differences were found concerning cardiovascular risk factors as BMI, blood pressure, diabetes, smoking, dyslipidaemia and CVD as heart disease, cerebrovascular disease, and peripheral arterial disease.

It would have strengthened our study a larger follow-up time, especially for the primary outcome of dialysis start, in order to increase the number of incident cases; only 4 patients initiated dialysis during de follow-up period [29 (IQR: 26 - 33) months]. Even so, elderly patients are more likely to die from any cause than to progress to ESRD [65], as we previously observed, and confirmed in this study. On contrary, for the primary outcome of death, we realize that increasing the follow-up would not change our results, since the differences between the survival rates of the groups vanished after twelve months of follow-up.

Considering secondary outcomes, all-cause admissions, and AKI admissions, when compared with CKD stage 1 to 3, stage 4 sCys only and stage 4 both groups had significant higher Incident rate of these events. Our results, as others [142] suggest that sCys is a useful detection marker in AKI and hospitalizations and my improve its negative impact on outcome.

Hence, in our elderly patients with severe non-end stage CKD (stage 4), sCys-based eGFR seemed to be a better predictor of adverse outcomes than sCr-based eGFR in patients with discordant staging. Patients with stage 4 CKD defined by sCr alone appeared to behave more alike those with less severe CKD (Stage 4 neither), while outcomes in patients with stage 4 CKD defined by sCys alone were similar to the more severe group defined as CKD stage 4 by both sCys and sCr.

Other equations, as BIS equations [143] have been designed for older adults, but little evidence exists showing that these equations improve patient outcomes prediction [144].

In the last years, an attempt has been made to create equations that incorporate sCys and sCr in a unified estimate of GFR [88,145]. However important clinical information may be lost by this practice, particularly in the in elderly, because muscle mass influences sCr concentration more than sCys. Very recently, in a cohort analysis of SPRINT trial [146], the authors examined the intraindividual difference in eGFRs using sCys versus sCr ($eGFR_{Diff}$) and found that $eGFR_{Diff}$ may hold prognostic information: a negative $eGFR_{Diff}$ at any level of kidney function was associated with higher risk for frailty, cardiovascular disease, and death. These results reinforce our findings.

We believe that our results suggest a possible targeted approach whereby sCys can be used in manner to identify CKD patients at higher risk for poor outcomes, which could help in the clinical decision making: to intervene in the group of patients that will benefit the most and to avoid overtreatment in the ones that will not.

CHAPTER VI

CONCLUSIONS & FUTURE DIRECTIONS

The results achieved and presented in this dissertation were able to address all the formulated study hypotheses. The results contributed to the understanding of multiple aspects related with CKD progression, treatment, and outcomes in elderly and raise new fields of investigation.

The consideration that elderly CKD people are far less likely to develop kidney failure than to die mainly from CVD highlights the importance of better characterization of the cardiovascular risk profile and CVD prevalence of our patients. Patients aged over 65 years with CKD were near threefold more likely to die, mainly from CVD, than progress to ESRD. In fact, the prevalence of many established risk factors and CVD was higher than other CKD elderly cohorts. Lower level of eGFR was associated with a greater burden of CVD, more pronounced in patients with diabetes, confirming the importance of CKD as an additional risk factor for CVD.

Additionally, our studies identify risk factors for CKD and for CVD prevalence, as many characteristics of the patients enrolled provided indirect evidence for several predisposing factors, which may partly explain the high prevalence of CKD in Portugal.

Our results gave us important information on the baseline characteristics of the patients before they receive specific attention from nephrologist, meaning that the role of primary care is fundamental for the prevention of risk factors and early detection of CKD. At this point, we think that there is an urgent need to capacitate primary healthcare providers and other referring physicians in this area. It is necessary to develop awareness and educational programs to prevent CKD and its associated diseases, like diabetes and hypertension, to reduce the CKD burden on patients, caregivers, and society. Nephrologists should try to support a local network linking primary and renal care, with a joint strategy. Surely, open communication channels, such as teleconsulting, will optimize the prevention and treatment of CKD.

The competing-risk approach that we used, based on available clinical and laboratory data, identify risk factors predictors of CKD progression and distinguishing them from those that increase mortality. Our findings contribute to respond to a crucial clinical question involving nephrologists, elderly patient, and their families whether to choose dialysis or a more conservative treatment approach as kidney function progressively deteriorates.
We found that a high comorbidity index (mCCI score ≥ 5) was an independent predictor for pre-ESRD death, but not for RRT initiation. In the elderly patients with a high burden of comorbidity, conservative management may be a therapeutic option considering the

likelihood of death prior to ESRD, which makes preparation for RRT, as the placement of an arteriovenous access unnecessary and potentially harmful.

Unequivocally, frailty is also a common syndrome in elderly CKD patients that may influence treatment choices and outcomes. More than half of our patients have some degree of functional dependency and cognitive impairment. Hence it will be important in a future study, to apply a simple and validate frailty scale, as the Clinical Frailty Scale [147], to access the prevalence of frailty in our patients and to address its impact on patient outcomes.

Peripheral vascular disease was an independent predictor for ESRD but was not associated with increased pre-ESRD mortality. Although reflecting an atherosclerotic systemic process also involving the kidneys, the presence of peripheral vascular disease may be a potential marker for renal function decline in CKD patients, through other mechanisms, in addition to the traditional association of CKD with vascular damage and it deserves more research. Ankle-Brachial Index is a simple, inexpensive, and non-invasive marker of peripheral artery disease and systemic atherosclerosis, so it will be interesting in a future work to investigate the role of this tool in our CKD patients to risk-stratify those patients at risk of ESRD.

We have developed a simple and accurate prognostic score for predicting early death in a cohort of Portuguese ESRD patients. The performance of our risk score was significantly higher than Couchoud score [79], which reflects the different characteristics of the populations involved in derivation of the models and reinforce the need to develop predictive scores adapted to the specificities of each population. This score developed was validated in an independent sample and is a tool easily and readily available. Moreover, a risk assessment questionnaire for clinicians and patients use was made, displayed in a figure, exposing a simple understandable method for all involved in shared decision-making process. Correctly estimating risk of death after starting dialysis may provide a more accurate perception of the desirability of starting dialysis.

However, a limitation of our score, which is common to other predictive scores in CKD patients, is that it was derived from patients who have commenced dialysis and do not include those who decline, are not selected for, or do not survive to dialysis therapy initiation. Hence, a score that evaluates older patients at the point of decision making, rather than at the point of starting dialysis therapy, would be very valuable, and it deserves further investigation. Moreover, it should be considered to conduct studies to address the impact of potential mortality predictors in older patients CKD, both those initiating dialysis therapy and those choosing a conservative pathway.

We identify four distinct groups of eGFR trajectories decline before dialysis initiation: slower decline, gradual decline, early rapid decline, and rapid decline. These trajectories of kidney function decline hold important implications in the optimal timing of RRT preparation. In fact, patients without vascular access and who had inpatient dialysis initiation, were more likely to be in the rapid decline trajectory group, maybe to non-recognition of their potential to rapid progress. The heterogeneity of eGFR trajectories awareness for a more flexible approaches for preparation to RRT.

Another important conclusion was the impact of kidney function trajectory before dialysis on the mortality after dialysis. Patients with rapid loss of kidney function had a higher risk of death within the first and fourth year after dialysis initiation. The impact on mortality was maintained after the fourth year on dialysis. So, the incorporation of eGFR trajectory into clinical practice will guide shared decision making on pre ESRD care, and prediction of late mortality after dialysis initiation.

In continuing concern about the prognosis of our patients we stress the need for an individualized use of eGFR equations in the elderly, in whom they should be regarded less as accurate estimators, but more as predictors of clinical outcomes. We have demonstrated, in our cohort that the CKD-EPI cystatin C was superior to CKD-EPI creatinine equation in predicting all-cause mortality in the first year, CV events, and all-cause and AKI admissions when used in old patients with severe non-end stage CKD. Further investigations with cost-effectiveness data are necessary to validate our hypothesis that cystatin C could be a reliable tool to identify patients at a higher risk of adverse outcome.

Finally, further than hard outcomes like CV events, and death, another point that should be discussed with patients is quality of life, which in elderly patients seems to be highly affected after starting dialysis. Concerned about this issue, we recently started a study focusing on quality of life, psychosocial impact, and symptom burden, comparing elderly incident dialysis patients with patients whose choice was conservative management. This research would enable more information to choose a trajectory of care most likely to achieve patient goals and expectations.

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APPENDICES

APPENDIX 1

End-stage renal disease versus death in a Portuguese cohort of elderly patients: an approach using competing event analysis.

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Original research

End-stage renal disease versus death in a Portuguese cohort of elderly patients: an approach using competing event analysis

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ABSTRACT

Chronic kidney disease (CKD) is higher in elderly, but mortality outweighs the risk of end-stage renal disease (ESRD). Our aim was to identify prognostic markers for ESRD or death in elderly CKD, within a competing-risk analysis. This is a longitudinal study of consecutive newly referred patients with CKD ages 65 years, followed until the time of the first event (ESRD or death), using a competing-risk analysis. A modified Charlson Comorbidity Index (mCCI) was subdivided into subgroups (0-2, 3-4, ≥5). Patients were followed for hospitalizations that occurred prior to the outcomes. Among 416 patients, age 76±8 years, 52% male, median estimated glomerular filtration rate of 32 mL/min per 1.73 m^2, 50% had diabetes, and 67% cardiovascular disease. Over a median follow-up of 3.6 years, 36 patients progressed to ESRD (8.7%) and 103 died (24.8%). Older age (subdistribution HR (sHR)=1. 06; p<0.001), creatinine≥1.6 mg/dL (sHR=2.03, p=0.004), hemoglobin <11 g/dL (sHR=1.91, p=0.003), mCCI score≥5 (sHR=3.01, p<0.001) and having one or more hospitalizations (sHR=1.73, p<0.001) were associated with death before ESRD. The independent predictors for ESRD with competing risk of death were: lower age (sHR=0.94; p=0.009), creatinine≥1.6 mg/dL (sHR=3.26, p=0.006), hemoglobin <11 g/dL (sHR=2.15, p=0.027), peripheral vascular disease (sHR=3.45, p=0.001) and having one or more hospitalizations (sHR=1.56, p=0.031). Elderly referred patients with CKD are near threefold more likely to die than progress to ESRD. A competing-risk framework based on available clinical and laboratory data may discriminate between those outcomes and could be used as a decision-making tool.

Significance of this study

What is already known about this subject?
- Prevalence of chronic kidney disease (CKD) is rising worldwide, and the elderly represent the most rapidly growing segment of the end-stage renal disease (ESRD) population requiring renal replacement therapy.
- Mortality, mainly from cardiovascular disease, outweighs the risk of progression to ESRD in older patients with CKD.

What are the new findings?
- Our study includes the rigorous exploration of the first Portuguese CKD cohort that included patients aged 65 years over, newly referred to nephrology.
- We demonstrated that peripheral vascular disease was an independent predictor for ESRD, but was not associated with increased pre-ESRD mortality.
- We implemented a competing risk framework for the statistical analysis to examine risk factors based on available clinical and laboratory data, for ESRD and differentiating them from those that increase mortality.

How might these results change the focus of research or clinical practice?
- Identifying predictors of death and ESRD within a competing-risk approach may allow us to use them as a decision-making tool, enabling more targeted therapeutic intervention, in elderly patients with CKD.

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INTRODUCTION

The world's population is aging, and by demographic projections, in 2050, about 32% of the Portuguese population is projected to be aged 65 and over, meaningfully above the European Union average of 25.7%.[1]

Parallel to this, the prevalence of chronic kidney disease (CKD) is rising worldwide, and the elderly represent the most rapidly growing segment of the end-stage renal disease (ESRD) population requiring renal replacement therapy (RRT) in wealthier countries.[2 3] Portugal has the highest unadjusted incidence and prevalence of ESRD among European countries[4] and 67.7% of the incident dialysis patients, in 2015, were over 65 years with a mean age of prevalent patients of 66.7 years.[5]

Despite the growing number of older patients initiating dialysis, another problem stands out in this group: mortality, mainly from cardiovascular disease, outweighs the risk

of progression to ESRD.[6 7] One of the major challenges to clinicians caring for older patients with CKD is to identify each patient's risk for progressive CKD and likelihood for requiring RRT in relation to the competing risk of death. This may involve important clinical decisions, such as referrals and procedures for dialysis access placement or transplant decision or on the contrary the possibility to identify patients with higher comorbid conditions at high risk of early death for which conservative management may be the best option.

Our aim was to characterize elderly patients with CKD who were newly referred to our outpatient department to determine the independent predictors of ESRD or death through a competing-risk analysis. Furthermore, we sought to identify potential variables that may indicate a higher likelihood of death before ESRD or of attaining first ESRD status.

METHODS

Study design and population

This longitudinal retrospective study included consecutive patients aged ≥65 years with CKD (non-dialyzed and non-transplanted), newly referred to our outpatient Nephrology department in Hospital de Santo António, CHUP, between January 1, 2012 and December 31, 2012, followed until the occurrence of the first event (ESRD or death) or until the end of the study (April 30, 2016). Hospital de Santo António is a tertiary-care hospital affiliated with the Abel Salazar Institute of Biomedical Sciences, University of Porto, which serves a diverse population of 500,000 inhabitants in the North region of country.

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of CHP.

The diagnosis of CKD was done by the KDIGO 2012 criteria.[8] ESRD was defined as the need for RRT initiation or transplantation.

Baseline data included gender, age, weight, height, body mass index (BMI), CKD stage, proteinuria level, medication use, and associated comorbid conditions, such as diabetes, dyslipidemia, hypertension, smoking status, and cardiovascular disease (coronary artery disease, peripheral artery disease, and cerebrovascular accident). Coronary artery disease was defined as a previous myocardial infarction, angina pectoris, coronary artery bypass grafting, or coronary stent implantation. Peripheral artery disease was defined as the presence of intermittent claudication or with the need of peripheral revascularization or amputation.

Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology (CKD-EPI) 2009 creatinine equation.[9] Etiological diagnosis of CKD was based on the patient's history, proteinuria, kidney ultrasound, and kidney biopsy, when available. Data blood and urine routine measurements were collected: hemoglobin, platelet, serum albumin, urea nitrogen, creatinine, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, intact parathyroid hormone (PTH), glucose, hemoglobin A1c, uric acid, lipid profile, iron, unsaturated iron binding capacity, ferritin, urinary sediment, and urine protein-to-creatinine ratio in spot urine sample.

Cognitive status was evaluated and screened using the Mini Mental State Examination,[10] and classified as cognitive impairment if the score was 23 or lower.

Functional dependency was defined as the requiring of assistance in the activities of daily living and classified as totally dependent, partially dependent, and autonomous.

A modified version of the Charlson Comorbidity Index (mCCI),[11 12] that is, by excluding subject's age and presence or absence of kidney disease, was calculated to assess severity of comorbidities and subdivided into three subgroups (0–2, 3–4, and ≥5).

During the follow-up, number and reasons for hospitalizations were registered, all-cause hospitalization and cardiovascular-related hospitalization, defined as hospitalization secondary to cardiovascular events (coronary artery disease, congestive heart failure, stroke or transient ischemic attack, peripheral artery disease). The cause of death was categorized as cardiovascular (defined as death due to cardiac, cerebrovascular, atherosclerotic or other vascular causes), malignancy, infection, other, and unknown causes.

Statistical analysis

Baseline characteristics for the all sample and by primary outcomes of interest are presented as medians with IQRs for continuous non-normally distributed variables and as proportions for categorical variables. Subgroups were compared using the χ^2 for categorical and Mann-Whitney test for continuous variables.

Unadjusted incidence rates for progression of ESRD (defined as renal failure requiring RRT or transplant) and all-cause mortality before any RRT (pre-ESRD death) were calculated per 100 person-years.

Hospitalization rate was calculated as the number of hospital admissions, divided by years at risk, expressed as hospitalizations per patient-year, using Poisson regression.

Survival analysis was performed and the two outcomes of interest were progression of ESRD and all-cause mortality before any RRT (pre-ESRD death). These two events were considered as competing risks. Patients without any of these outcomes were censored at the date of their last recorded visit or at the end of the study period.

Regression models taking competing risks into account were carried out to analyze the independent effect of covariates on each of two competing endpoints. This analysis was performed considering two types of hazards: cause-specific hazard and subdistribution hazard. Proportional cause-specific hazard regression models were performed using the standard Cox (cause-specific hazard regression model), censoring all patients without the event of interest. If a patient initiated dialysis, then the endpoint of mortality was censored. If a patient died, then the outcome of dialysis initiation was censored. An alternative model proposed by Fine and Gray[13] was the approach used in the current study to model the subdistribution hazard.

An exploratory analysis was performed to examine the unadjusted effect of the potential predictors of ESRD progression and patient death by fitting univariable models. The cause-specific HR and the subdistribution HR for ESRD or for patient death before any RRT were then estimated in multivariable analyses. The covariates were selected on the basis of univariate analysis and because of their potential

biological plausibility to predict progression of ESRD and/or death.

The variables included in the univariate competing-risk model were baseline age, gender, baseline serum creatinine (<1.6 or ≥1.6 mg/dL, the median value for this sample), serum hemoglobin (<11 or ≥11 g/dL),[14] BMI (<18.5, 18.5–24.9, 25–29.9, or ≥30), estimated GFR (eGFR) (continuous or categorized as <60 or ≥60 mL/min), tobacco use (never, former, or current), dyslipidemia, hypertension, diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, number of antihypertensive drugs, referral from primary care versus another hospital appointment, CKD etiology (diabetes vs others), cognitive status, functional dependency, mCCI score at baseline, and the occurrence of hospitalizations during the follow-up period. For both outcomes, the occurrence of hospitalizations during the follow-up period was used as a time-varying covariate.

Statistical analyses were performed using SPSS V.22.0 and STATA V.13.0 software packages. A significance level of 0.05 was considered.

RESULTS

Baseline characteristics

Among 416 patients newly referred, 52% were male, with a mean age of 76 years, and 36% of them aged 80 years or more. Their baseline characteristics are summarized in table 1.

Fifty per cent of the patients were referred by primary care physicians. At baseline, they had a median eGFR of 32 mL/min per 1.73 m^2. The most frequent etiologies of renal disease were ischemic nephropathy (38%), diabetic nephropathy (25.5%) and unknown causes (13.5%).

Most of the patients were non-smokers (74%) and 22% were obese (BMI >30 kg/m^2). About 50% were diabetic, and 96% presented hypertension, of which 50% were receiving more than two antihypertensive drugs, renin–angiotensin blockade in 33% of them; 63% of the patients had a systolic blood pressure >130 mm Hg. Dyslipidemia was present in 85% of the patients, 60% were under lipid-lowering medication. An active or previous malignancy was present in 15% of the patients. Cardiovascular disease was present in 67% of the patients, including coronary artery disease in 25%, peripheral vascular disease in 19% and cerebrovascular disease in 23% of the patients.

Regarding functional dependency, 5% of the patients were totally dependent and 38% were partially dependent. Cognitive impairment was present in 11% of the patients.

Most patients had a hemoglobin level ≥11 g/dL (71%), with no iron deficiency (ferritin level ≥100 ng/mL: 75%; transferrin saturation ≥20%: 62%).

Intact PTH was elevated in 81% of the patients, despite good control of calcium–phosphorus levels.

Follow-up and outcomes

During a median follow-up of 3.6 years (min–max: 0.02–4.3 years), 36 patients progressed to ESRD (8.7%) and 103 patients died (24.8%) prior to ESRD, giving an ESRD rate of 2.7/100 patient-years and a mortality rate of 7.8/100 patient-years, respectively. Figure 1 shows the cumulative incidences of events, considering competing risks.

The leading causes of death prior to ESRD were cardiovascular (35%), infection (29%), malignancy (21%), other causes (8%), and unknown (7%).

Concerning the 36 patients who initiated RRT, all of them hemodialysis, 18 patients started treatment with an arteriovenous fistula and 18 patients with a venous catheter. It should be mentioned that eight patients of overall cohort (1.9%) that underwent fistula died without receiving dialysis.

Hospitalizations

During the follow-up period, 222 patients (53%) were hospitalized for any reason, with a global hospitalization rate of 0.38 per patient-year. Stratifying for the competing events, the hospitalization rate was 1.27 per patient-year in the patients with ESRD, and 1.06 hospitalizations per patient-year in the patients who died before ESRD.

Cardiovascular-related hospitalization accounted for almost 40% of the hospitalization events during the same period. The global cardiovascular hospitalization rate was 0.15 hospitalizations per patient-year, being 0.56 cardiovascular hospitalizations per patient-year in the patients with ESRD and 0.39 hospitalizations per patient-year in the patients who died before ESRD.

Competing-risk analysis of death and ESRD

The Cox proportional hazards model indicated that baseline younger age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, peripheral vascular disease diagnosis, and the occurrence of one or more hospitalizations (all-cause hospitalizations) during the follow-up were associated with higher risk of ESRD (table 2). Diabetes mellitus (vs other CKD etiologies) and mCCI score at baseline were not associated with higher risk of ESRD.

Older age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, mCCI score ≥5, and the occurrence of hospitalizations during the follow-up were associated with death before ESRD.

Conversely, subhazard ratios estimated from competing-risk regression necessarily discriminated between endpoints. Significant risk factors for ESRD included younger age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, peripheral vascular disease, and the occurrence of one or more hospitalizations during the follow-up (table 3).

Risk factors for pre-ESRD death included older age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, mCCI score ≥5, and the occurrence of one or more hospitalizations during the follow-up. By adjusting for these competing risks, we show that peripheral vascular disease increases the cumulative incidence of ESRD, but is not associated with increased pre-ESRD mortality. Similarly, a mCCI score ≥5 increased the hazard for pre-ESRD death, but not for RRT initiation.

DISCUSSION

In our cohort, newly referred patients aged over 65 years with CKD were near threefold more likely to die than progress to ESRD. These results were consistent with those found in previous studies confirming that elderly CKD are

Table 1 Baseline clinical characteristics of patients divided by outcomes

	Total, n=416	Alive without ESRD, n=277	ESRD, n=36	Dead without ESRD, n=103	p Value
Age (years)	71 (71–83)	76 (70–82)	74 (71–80)	81 (75–86)	0.017*
Age ≥80 years, n (%)	149 (36)	87 (31)	7 (19)	55 (53)	<0.001*
Male, n (%)	218 (52)	139 (50)	21 (58)	58 (56)	0.430
eGFR EPI (mL/min/1.73 m^2)	32 (23–42)	33 (25–44)	24 (16–38)	28 (22–34)	<0.001*
CKD stage, n(%)					
Stage 1	6 (2.0)	4 (1.0)	0 (0.0)	2 (2.0)	
Stage 2	34 (8.0)	30 (11)	1 (3.0)	2 (2.0)	0.004*
Stage 3a	46 (11)	45 (16)	1 (3.0)	0 (0.0)	
Stage 3b	139 (33)	101 (37)	7 (19)	31 (30)	
Stage 4	158 (38)	88 (32)	11 (31)	59 (57)	
Stage 5	34 (8.0)	9 (3.0)	16 (44)	9 (9.0)	
Referral, n(%)					
Primary care	206 (50)	123 (44)	21 (58)	50 (49)	0.013*
Hospital appointment	194 (47)	148 (53)	14 (39)	44 (43)	
Other	16 (3.8)	6 (2.2)	1 (2.8)	9 (8.7)	
Primary renal disease, n (%)					
Ischemic nephropathy	158 (38)	105 (38)	13 (36)	40 (39)	
Diabetic nephropathy	106 (26)	63 (23)	15 (42)	28 (27)	0.222
Glomerulonephritis	16 (3.8)	10 (3.6)	1 (2.8)	5 (4.9)	
Other/unknown	136 (33)	99 (36)	7 (19)	30 (29)	
BMI (kg/m^2)	27 (24–30)	27 (24–31)	26 (24–30)	26 (23–29)	0.112
Cognitive impairment, n (%)	47 (11.3)	30 (10.8)	3 (8.3)	14 (13.6)	0.632
Totally dependent	24 (5.8)	15 (5.4)	2 (5.6)	7 (6.8)	
Partially dependent	156 (38)	96 (35)	17 (47)	43 (42)	0.430
Autonomous	236 (57)	166 (60)	17 (47)	53 (52)	
mCCI, n (%)					
0–2	184 (44.2)	148 (53.4)	12 (33.3)	24 (23.3)	<0.001*
3–4	127 (30.5)	84 (30.3)	12 (33.3)	31 (30.1)	
>5	105 (25.2)	45 (16.2)	12 (33.3)	48 (46.6)	
Diabetes, n (%)	207 (50)	133 (48)	52 (61)	49 (51)	0.330
Former/current smoking, n (%)	110 (27)	66 (24)	11 (31)	33 (32)	0.246
SBP (mm Hg)	140 (125–155)	141 (127–158)	138 (120–159)	132 (121–150)	0.037*
DBP (mm Hg)	70 (63–80)	71 (64–80)	77 (60–81)	68 (60–76)	0.017*
Antihypertensive ≥2, n (%)	207 (50)	140 (51)	18 (50)	49 (48)	0.876
Renin–angiotensin blockade	137 (33)	88 (32)	16 (44)	33 (32)	0.306
Diuretics	295 (71)	196 (71)	30 (83)	69 (67)	0.177
Dyslipidemia, n (%)	354 (85)	238 (86)	30 (83)	86 (84)	0.801
Lipid-lowering medication, n (%)	248 (60)	168 (61)	22 (61)	58 (56)	0.712
Antiplatelet medication, n (%)	203 (49)	135 (39)	14 (52)	54 (49)	0.376
Cardiovascular diseases, n (%)	277 (67)	172 (62)	22 (61)	65 (63)	0.739
Peripheral vascular disease, n (%)	78 (19)	43 (16)	15 (42)	20 (19)	0.001
Albumin <3.5 g/dL, n (%)	40 (11)	24 (10)	5 (15)	11 (12)	0.667
Uric acid (mg/dL)	7.3 (5.6–9.8)	7.2 (5.4–9.6)	7.4 (5.9–9.3)	7.7 (6.2–11.3)	0.367
Total cholesterol (mg/dL)	176 (147–205)	179 (150–205)	175 (142–207)	168 (142–204)	0.355
HDL (mg/dL)	47 (38–57)	48 (39–57)	48 (36–59)	45 (37–58)	0.720
LDL (mg/dL)	98 (75–123)	99 (79–121)	95 (71–118)	95 (74–132)	0.673
Hemoglobin (g/dL)	11.9 (10.6–13.6)	12.0 (10.9–13.4)	11.3 (10.6–13.1)	11.6 (10.1–13.1)	0.086
TSAT (%)	21(14–28)	21(15–28)	21(15–33)	21(14–28)	0.642
Ferritin (ng/mL)	160 (80–337)	150 (77–344)	151 (70–256)	181 (90–363)	0.407

Continued

Table 1 Continued

	Total, n=416	Alive without ESRD, n=277	ESRD, n=36	Dead without ESRD, n=103	p Value
iPTH (pg/mL)	100 (61–155)	98 (61–161)	115 (69–140)	99 (61–156)	0.446
Calcium (mg/dL)	2.4 (2.3–2.5)	2.4 (2.3–2.5)	2.4 (2.3–2.5)	2.3 (2.2–2.5)	0.158
Phosphate (mg/dL)	1.1 (0.99–1.25)	1.1 (0.99–1.24)	1.1 (0.90–1.17)	1.2 (1.00–1.33)	0.292
uPCr (g/g)	0.25 (0.1–1.0)	0.28 (0.11–1.11)	0.19 (0.07–0.47)	0.19 (0.10–0.85)	0.147

Note: Data expressed as medians and IQRs or n (%) when appropriate. Comparisons between continuous variables were done using a non-parametric test (Kruskal-Wallis); associations between categorical variables were analyzed using the χ^2 test; *p<0.05.
BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high density lipoprotein; iPTH, intact parathyroid hormone; LDL, low density lipoprotein; mCCI, modified Charlson Comorbidity Index; SBP, systolic blood pressure; TSAT, transferrin saturation; uPCr, urinary protein-to-creatinine ratio.

far less likely to develop kidney failure than to die, especially from cardiovascular disease, even with higher CKD stage.[6 7 15 16]

However, our results differ from others, also from patients with CKD referred for nephrologist care,[17 18] who have been showed to have either similar or even higher risk of ESRD compared with death. We can speculate about the reasons for these differences, namely our patients were older, with a higher burden of comorbidity and frailty. In fact, 25% of our patients have a severe mCCI score (CCI ≥5), 43% have some degree of functional dependency and 11% had a cognitive impairment.

Our cohort fits the frailty phenotype associated with CKD and geriatric syndrome,[19 20] in contrast with other elderly CKD European cohorts newly referred to nephrologists,[16] that despite older than our patients, had a good health status, reflecting a selection bias in referring patients for nephrology care, not found in our group.

To better understand the chances associated with the competing risks between mortality and ESRD, in elderly patients with CKD, where the supply of conservative management is weighed against the benefits and costs of RRT, we have applied a competing-risks model[13] that looks at the cumulative incidence of ESRD or death before ESRD while also taking into consideration competing risk of the alternate outcome. We believe that such approach better identifies prognostic factors for a particular event in the presence of competing risks and provide an important tool for better decision-making.[21]

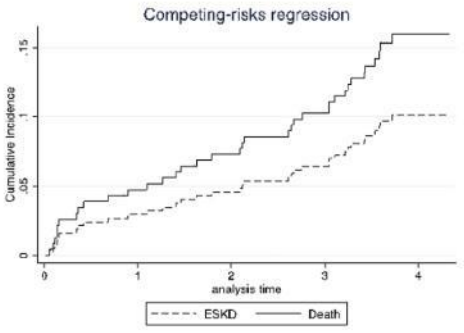

Figure 1 Cumulative incidence rates for the competing endpoints of end-stage renal disease or death.

In the competing-risk framework, patients who are younger, with creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, had previous peripheral vascular disease and one or more hospitalizations during the follow-up, are more likely to reach ESRD. Those who are older, with creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, mCCI score ≥5 and one or more hospitalizations during the follow-up, are more likely to die.

Our findings confirm that renal function at baseline was an important predictor for both ESRD and mortality[6 22–25] although this association was stronger for ESRD than for death, still reinforce the importance of early nephrology referral. In fact, in our cohort a shorter time between referral and ESRD was also associated with RRT initiation by catheter as primary access.

We found, as others,[26] that anemia (hemoglobin <11 g/dL) was a predictor of mortality and ESRD, undoubtedly related with adverse cardiovascular effects and the potential role of hypoxia on CKD progression, particularly important in this elderly population. This highlights the importance of anemia treatment although the target hemoglobin is still a matter of debate.[14 27]

The occurrence of one or more hospitalizations was common in our cohort and it was associated with both outcomes (ESRD and death). The increased risk for mortality among patients with hospitalization is consistent with other studies, assuming that the majority of those hospitalizations were cardiovascular-related,[28 29] or associated with an infection event, also known a risk factor for increased cardiovascular events and mortality in patients with CKD.[30]

The occurrence of hospitalizations events during the follow-up was also associated with ESRD. In our group the global and cardiovascular hospitalization rate was higher in patients with ESRD, than in the patients who died before RRT initiation. These findings are consistent with other studies,[29 31 32] as cardiovascular admissions may have served as a marker for patients who had more progressive ischemic nephropathy, or more important, related to a superimposed acute kidney injury (AKI) episode on the underlying CKD.[29 33] AKI episodes, frequent in elderly population, may accelerate progression of renal disease.[34 35]

We demonstrated that peripheral vascular disease was an independent predictor for ESRD, but was not associated with increased pre-ESRD mortality. These findings extend

Table 2 Risk factors associated with death and ESRD (Cox regression analysis)

	ESRD		Death	
	csHR (95% CI)	p Value	csHR (95% CI)	p Value
Baseline				
Age, years	0.95 (0.91 to 1.00)	0.049	1.04 (1.01 to 1.07)	0.004
Creatinine (>1.6 vs <1.6 mg/dL)	3.64 (1.58 to 8.38)	0.002	2.27 (1.44 to 3.57)	<0.001
Hb (<11.0 vs >11.0 g/dL)	2.72 (1.35 to 5.49)	0.005	2.20 (1.49 to 3.26)	<0.001
CCI score				
(3–4 vs 1–2)	0.55 (0.22 to 1.39)	0.205	1.35 (0.80 to 2.29)	0.258
(≥5 vs 1–2)	0.80 (0.33 to 1.96)	0.626	2.82 (1.70 to 4.67)	<0.001
Peripheral vascular disease (yes vs no)	3.60 (1.70 to 7.60)	0.001	1.03 (0.64 to 1.68)	0.890
DM vs other CKD etiologies	1.75 (0.85 to 3.58)	0.127	1.02 (0.67 to 1.55)	0.930
During the follow-up				
Hospitalizations (yes vs no)	1.72 (1.17 to 2.52)	0.006	1.84 (1.44 to 2.36)	<0.001

Note: Values given as csHR (95% CI) for risk factors associated with ESRD and death prior to ESRD.
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; csHR, cause-specific HR; DM, diabetes mellitus; ESRD, end-stage renal disease; Hb, hemoglobin.

the association between vascular disease and CKD progression founded in other studies,[31 36 37] given that peripheral vascular disease is the result of an atherosclerotic process similar to that one seen in cardiovascular disease. As we know, atherosclerosis is a potentially important mechanism of kidney disease in older persons[38 39] and increases the susceptibility for AKI and CKD progression.[40] A study in European cohort,[41] also using a competing risks modeling approach, showed that the endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine, considered one of the strongest markers of atherosclerosis, was an independent predictor of progression to dialysis and death in patients with CKD.

A reduced ankle–brachial index reflects peripheral arterial disease, and some studies demonstrated that this atherosclerotic disease marker predicted accelerated renal function decline, in general population,[42] and also in peritoneal dialysis patients.[43]

Given that finding, our study suggests that the presence of peripheral arterial disease, although reflecting an atherosclerotic systemic process also involving the kidneys, may be a potential marker for renal function decline in patients with CKD, through other mechanisms, in addition to the traditional association of CKD with vascular damage.

The higher burden of CV risk factors, and prevalent vascular disease, present in our cohort, and the association between peripheral vascular disease and ESRD that we found, may partially explain the highest incidence of ESRD of Portuguese population among European countries,[4] because data from the PREVADIAB Study[44] have shown that the prevalence of CKD stages 3–5 was 6.1%, which is similar to that in other Western countries. The reasons for this disparity are still a matter of debate. Although socioeconomic and political factors still play a part in RRT rates around the world, other important factors are genetics, birth weight, dietary habits, and diabetes prevalence. Another important issue is the age pattern at beginning of RRT. In countries with lower RRT incidence, the median age at start of RRT appears to be lower, suggesting that countries with higher RRT incidence, like Portugal, start older patients in RRT and this may contribute to differences in RRT epidemiology between countries.[45] In this respect, there is an urgent need for concrete evidence on the relative benefit of conservative treatment versus RRT

Table 3 Risk factors associated with death and ESRD (Fine and Gray model[13])

	ESRD		Death	
	sHR (95% CI)	p Value	sHR (95% CI)	p Value
Baseline				
Age, years	0.94 (0.89 to 0.98)	0.009	1.06 (1.03 to 1.09)	<0.001
Creatinine (>1.6 vs <1.6 mg/dL)	3.26 (1.40 to 7.60)	0.006	2.03 (1.25 to 3.29)	0.004
Peripheral vascular disease (yes vs no)	3.45 (1.68 to 7.10)	0.001	0.82 (0.49 to 1.34)	0.435
CCI score				
(3–4 vs 1–2)	0.57 (0.24 to 1.35)	0.202	1.53 (0.87 to 2.69)	0.137
(≥5 vs 1–2)	0.54 (0.23 to 1.28)	0.164	3.01 (1.75 to 5.19)	<0.001
Hb (<11.0 vs >11.0 g/dL)	2.15 (1.09 to 4.24)	0.027	1.91 (1.25 to 2.92)	0.003
DM vs other CKD etiologies	1.72 (0.84 to 3.53)	0.139	0.84 (0.54 to 1.32)	0.447
During the follow-up				
Hospitalizations (yes vs no)	1.56 (1.04 to 2.35)	0.031	1.73 (1.33 to 2.25)	<0.001

Note: Values given as sHR (95% CI) for risk factors associated with ESRD and death prior to ESRD.
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease.; Hb, hemoglobin; sHR, subdistribution HR.

in the elderly as well as on the optimal timing of RRT initiation.

Finally, we found that mCCI score ≥5 was an independent predictor for pre-ESRD death, but not for RRT initiation. The CCI has been widely used and validated in patients with ESRD and seemed to be significantly more predictive for mortality than other comorbidity scoring systems[46 47] This is evidenced by studies demonstrating that elderly patients with CKD are likely to have a higher burden of comorbidity and frailty, which are markers of worst survival.[46]

Old age alone should not be used as an absolute barrier to treatment when considering the benefits of dialysis in elderly patients with CKD.[48] However, in the elderly patients with CKD with a high burden of comorbidity, conservative management may be a therapeutic option, as dialysis is unlikely to prolong or improve quality of life.[49–51]

Also, considering the likelihood of death prior to ESRD makes preparation for RRT, as the placement of an arteriovenous access unnecessary and potentially harmful.[52]

The strengths of our study include the rigorous exploration of the first Portuguese CKD cohort that included patients aged 65 years over, newly referred to nephrology, reflecting current clinical practice. We implemented a competing-risk framework for the statistical analysis to examine risk factors based on available clinical and laboratory data, for ESRD and differentiating them from those that increase mortality, which is an important tool to guide clinical decision process.

The effect of peripheral vascular disease as an independent predictor for ESRD in our cohort, although it deserves more research, reinforces the importance of strategic targeting vascular risk screening and reduction in this population.

There are certain limitations to our research. First, this is a single-center retrospective study. Second, due to the overall small number of patients who initiated RRT (n=36), it is not possible to identify the risk factors for progression within each CKD stage. In the stages 3 and 4, only 8 and 11 patients progressed to dialysis, respectively. Thus, we do not have sufficient number of events for performing a reliable survival analysis using mortality as a competing event.

Third, defining ESRD as the RRT initiation has the disadvantage of being dependent on local clinical practice. Fourth, proteinuria could not be included in the multivariable models due to the percentage of missings and, therefore, we could not analyze the effect of proteinuria on the risk of ESRD or death. Finally, because this cohort only comprised patients attending nephrology outpatient clinic, which can introduce a bias of referral, the results may not be generalizable to a non-referred population.

CONCLUSION

In summary, we found that newly referred older patients with CKD are substantially more likely to die than to reach ESRD. By using a competing-risk approach based on available clinical and laboratory data, we could identify risk factors predictors of CKD progression and distinguishing them from those that increase mortality, which may allow us to use them as a decision-making tool to guide clinical decision process.

Contributors JS, IF and JM were involved in research design, writing and in data collection. IB, LL, PO and AC were involved in editing.

Competing interests None declared.

Ethics approval The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Centro Hospitalar Universitário do Porto.

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APPENDIX 2

Demographic, clinical characteristics and cardiovascular disease burden in a Portuguese cohort of older chronic kidney disease patients.

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Dados demográficos, características clínicas e peso da doença cardiovascular em uma coorte portuguesa de pacientes idosos com doença renal crônica

Demographic, clinical characteristics and cardiovascular disease burden in a Portuguese cohort of older chronic kidney disease patients

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RESUMO

Introdução: Doença renal crônica (DRC) é fator de risco independente para vários desfechos desfavoráveis, incluindo doença cardiovascular (DCV), particularmente em idosos, o segmento de crescimento mais rápido da população com doença renal terminal (DRT). Portugal tem a maior incidência europeia não-ajustada e a maior prevalência de DRT. Neste artigo caracterizamos uma coorte de idosos com DRC, referenciados para a nefrologia, com particular ênfase para o risco e carga de doença cardiovascular. **Métodos:** Foram incluídos todos os pacientes com DRC com 65 anos ou mais encaminhados ao nosso departamento em 2012. Os dados basais incluíram: demografia, estágio da DRC, medicação e comorbidades. A taxa de filtração glomerular (TFGe) foi calculada pela fórmula CKD-EPI. **Resultados:** Metade dos 416 pacientes incluídos foram encaminhados por médicos da atenção primária; sua idade era 77 ± 7 anos; 52% eram homens; a TFGe mediana era de 32 mL /min/1,73 m². Metade tinha diabetes (DM), 85% dislipidemia, 96% hipertensão; 26% eram fumantes atuais/ antigos; 24% tinham índice de massa corporal > 30 kg/m². A prevalência de DCV foi de 62%, sendo maior entre pacientes nos estágios 4-5; em diabéticos, aumentou gradualmente com a progressão da DRC (estágio 3a < estágio 3b < estágio 4-5) (39%, 58%, 82%; $p < 0,001$). **Conclusões:** A coorte de idosos com DRC apresentava inicialmente maior carga de DCV. A prevalência de DCV foi maior que em outras coortes europeias com DRC. Níveis menores de TFGe foram associados a carga maior de DCV e foram mais pronunciados entre diabéticos, destacando a importância de objetivar estrategicamente a redução do risco cardiovascular nesses pacientes.

Palavras-chave: Insuficiência Renal Crônica; Doenças Cardiovasculares; Idoso.

ABSTRACT

Introduction: Chronic kidney disease (CKD) is an independent risk factor for several unfavorable outcomes including cardiovascular disease (CVD), particularly in the elderly, who represent the most rapidly growing segment of the end-stage kidney disease (ESKD) population. Portugal has the highest European unadjusted incidence and prevalence rates of ESKD. In 2012, we started to follow a cohort of elderly CKD patients, we describe their baseline characteristics, risk profile, and cardiovascular disease burden. **Methods:** All CKD patients aged 65 years and older referred to our department during 2012 were enrolled. Baseline data included: demographic, CKD stage, medication, comorbid conditions. Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula. **Results:** A total of 416 patients, 50% referred by primary care physicians, aged 77 ± 7 years, 52% male, with a median eGFR of 32 mL/min/1.73m² participated in the study. Fifty percent had diabetes (DM), 85% dyslipidemia, 96% hypertension; 26% were current/former smokers, and 24% had a body mass index > 30 kg/m². The prevalence of CVD was 62% and higher in stage 4-5 patients; in diabetics, it gradually increased with CKD progression (stage 3a < stage 3b < stage 4-5) (39, 58, 82%; $p < 0.001$). **Conclusions:** At baseline, our CKD elderly cohort had a higher burden of CVD. The prevalence of CVD was greater than in other European CKD cohorts. Lower level of eGFR was associated with a greater burden of CVD and was more pronounced in diabetics, highlighting the importance of strategically targeting cardiovascular risk reduction in these patients.

Keywords: Renal Insufficiency, Chronic; Cardiovascular Diseases; Aged.

Introdução

A doença renal crônica (DRC) surgiu como um sério problema de saúde pública, como demonstrado pelo aumento da mortalidade geral e cardiovascular e a crescente incidência e prevalência de doença renal terminal (DRT), com pacientes que necessitam de terapia de substituição renal e custos muito elevados de atenção à saúde[1]. Paralelamente, a prevalência de DRC é maior em pessoas idosas, e pacientes com mais de 65 anos representam o segmento de crescimento mais rápido da população com DRT em países mais ricos.[2,3]

Portugal tem a maior prevalência e incidência não-ajustada de DRT entre os países europeus,[4] e 62,3% dos doentes incidentes em diálise de 65 anos, com uma idade média de 67 anos.[5]

A DRC está associada ao aumento da prevalência de fatores de risco tradicionais (por exemplo, hipertensão) e não tradicionais (por exemplo, proteinúria, níveis elevados de ácido úrico, hiper-homocisteinemia) e fatores predisponentes à doença microvascular (por exemplo, inflamação e homeostase anormal do metabolismo fosfo-cálcio,[6,7]) com estudos confirmando que, nos idosos, mesmo nos estágios precoces da DRC, a mortalidade cardiovascular supera o risco de progressão para DRT.[8]

Em 2012, começamos a acompanhar uma coorte de pacientes idosos até a ocorrência do primeiro evento (DRT ou óbito).[9] Neste artigo, descrevemos suas características clínicas e demográficas iniciais, com particular ênfase para a carga de doença cardiovascular, para definir melhores estratégias de tratamento.

Pacientes e métodos

Formato do estudo e população

Este estudo incluiu doentes com DRC (não dialisados e não transplantados) consecutivos com idade ≥ 65 anos, referenciados de novo para o nosso ambulatório no Centro Hospitalar do Porto (CHP), entre 1º de janeiro de 2012 e 31 de dezembro de 2012. O CHP é uma instituição terciária, hospital que atende uma população diversa de 500.000 habitantes na região Norte do país.

A coleta de dados foi realizada por nefrologistas usando formulários eletrônicos de notificação de casos. O relato de doença cardiovascular foi baseado no auto-relato dos pacientes e na revisão de seus prontuários por equipe treinada na mesma data da anamnese inicial. O estudo foi realizado de acordo com a Declaração de Helsinque e aprovado pelo Comitê de Ética em Pesquisa do CHP.

Os dados basais incluem gênero, idade, índice de massa corporal (IMC), estágio da DRC, proteinúria, medicação e comorbidades, como diabetes, dislipidemia, hipertensão, tabagismo e doença cardiovascular. A doença cardiovascular foi definida como a história de pelo menos um dos seguintes: doença cardíaca, doença cerebrovascular e doença vascular periférica. A doença cardíaca foi definida como a história de doença arterial coronariana, insuficiência cardíaca congestiva e doença cardíaca valvular grave com ou sem substituição valvular. Os critérios para o diagnóstico de doença arterial coronariana incluíram infarto prévio do miocárdio, angina pectoris, cirurgia de revascularização do miocárdio ou angioplastia coronariana transluminal percutânea com ou sem implante de stent. A doença cerebrovascular incluiu ataque isquêmico transitório prévio, acidente vascular cerebral ou hemorragia cerebral. A doença arterial periférica foi definida como a presença de claudicação intermitente, necessidade de revascularização periférica ou amputação.

Todos os pacientes diabéticos preencheram os critérios de classificação estabelecidos pela American Diabetes Association. A hipertensão foi considerada se o paciente tivesse pressão arterial sistólica (PA) > 140 mmHg ou PA diastólica > 90 mmHg ou necessidade de drogas anti-hipertensivas. A dislipidemia incluiu colesterol sérico total > mg/dL ou triglicerídeos > 150 mg/dL, ou lipoproteína de alta densidade (HDL) < 40 mg/dL em homens e < 48 mg/dL em mulheres, ou lipoproteína de baixa densidade (LDL) colesterol > 100 mg/dL, ou necessidade de drogas hipolipemiantes.

A taxa de filtração glomerular foi estimada (TFGe) usando a equação usando a equação da creatinina CKD-EPI 2009[10]. O diagnóstico etiológico da DRC foi baseado na história do paciente, na ultrassonografia renal e na biópsia renal, quando disponíveis. Foram coletadas análises de rotina de sangue e urina: hemoglobina, albumina sérica, nitrogênio ureico, creatinina, cálcio, fósforo, paratormônio intacto (PTH), glicose, hemoglobina A1c, ácido úrico, perfil lipídico, ferro, capacidade de ligação insaturada de ferro, ferritina e relação proteína/creatinina na urina (uPCr) na amostra de urina ocasional.

O estado cognitivo foi avaliado e rastreado pelo Mini-exame do Estado Mental (MEEM)[11], classificado como comprometimento cognitivo se o escore foi 23 ou menor. A dependência funcional foi definida como a exigência de assistência nas atividades da vida diária e classificada como totalmente dependente, parcialmente dependente e autônoma.

Uma versão modificada do índice de comorbidade de Charlson (mCCI)[12], ou seja indivíduo e a presença ou ausência de doença renal, foi calculada para avaliar a gravidade das comorbidades.

Análise estatística

As características basais são descritas usando média ± desvio padrão ou mediana com intervalos interquartis para variáveis contínuas, enquanto dados categóricos são apresentados como números e porcentagens. O peso das doenças cardiovasculares foi comparado entre os estágios da DRC pelo teste do qui-quadrado para tendência das variáveis categóricas. As análises estatísticas foram realizadas no programa SPSS versão 22.0. Valor de $p < 0,05$ foi considerado estatisticamente significativo.

Resultados

Características demográficas e clínicas iniciais

De um total de 848 pacientes recém-encaminhados ao nosso departamento de Nefrologia durante 2012, 416 deles tinham 65 anos ou mais. Destes, todos eram caucasianos, 52% eram do sexo masculino, com uma idade média de 77 anos, e 36% deles tinham 80 anos ou mais. Cerca de 50% (n = 206) dos pacientes eram diabéticos. A maioria (85%) da população do estudo veio de áreas urbanas.

Suas características basais, divididas por gênero e pela presença ou ausência de diabetes, estão resumidas na Tabela 1. Cinquenta por cento dos pacientes foram encaminhados por médicos da atenção primária. No início, eles tinham uma mediana de creatinina sérica de 1,6 mg/dL e uma TFGe mediana de 32 mL/min por 1,73 m². As etiologias mais frequentes da doença renal foram nefropatia isquêmica (n = 159; 38%) e nefropatia diabética (n = 106; 26%); causas desconhecidas de doença renal foram 55 (13%). Apenas 4% (n = 17) dos pacientes tiveram biópsia renal.

A maioria dos pacientes era não-tabagista (n = 307; 74%). A proporção de fumantes atuais ou por antigos fumantes foi maior entre homens (n = 52; 46%) e sem diabetes (n = 50; 47%). No geral, 24% (n = 101) dos pacientes eram obesos (IMC > 30 kg/m²). O IMC variou de um valor médio de 25,7 ± 4,1 kg/m² em homens sem diabetes a 29,5 ± 5,5 kg/m² em mulheres com diabetes.

Cerca de 96% (n = 400) dos pacientes apresentavam hipertensão, com uma pressão média de 141/72 mmHg. Em aproximadamente 30% dos pacientes a pressão arterial era < 130/80mmHg e em aproximadamente 50% era < 140/80mmHg; homens com diabetes foram o grupo com pior controle da PA (objetivo da PA < 130/80 mmHg). Cerca de 50% (n = 207) dos pacientes estavam recebendo dois ou mais anti-hipertensivos (excluindo diuréticos), e 14% (n = 58) usavam três ou mais drogas anti-hipertensivas. Inibidores do sistema renina-angiotensina foram os medicamentos mais utilizados (n = 293; 70% dos pacientes): inibidores da enzima conversora da angiotensina (iECA) em 33% (n = 137), bloqueadores dos receptores da angiotensina II (BRA) em 41 pacientes (n = 172), e combinação de iECA e BRA em 4% (n = 16) dos pacientes. O uso desses agentes foi mais frequente em homens com diabetes (77%). Cerca de 71% (n = 296) dos pacientes estavam em uso de diuréticos.

A dislipidemia esteve presente em 85% dos pacientes (n = 354) e 60% (n = 248) estavam sob medicação hipolipemiante. A dislipidemia foi mais prevalente em pacientes com diabetes (n = 189; 92%).

Uma malignidade ativa ou prévia estava presente em 15% (n = 62) dos pacientes. Cerca de 25% (n = 105) dos pacientes apresentavam um alto índice de comorbidade (mCCI ≥ 5), particularmente homens com diabetes (n = 55; 49%).

Cerca de 50% (n = 206) dos pacientes eram diabéticos, mas em apenas 51% (n = 106) deles, a nefropatia diabética foi considerada a etiologia da doença renal; 48% dos pacientes com etiologia da DRC, que não a nefropatia diabética, tinham diabetes. Quando analisamos as características basais em pacientes com diabetes separadamente para pacientes com e sem nefropatia diabética em comparação com pacientes sem diabetes (Tabela Suplementar S1), os dados clínicos e demográficos foram muito semelhantes nos três grupos, com exceção de maior pressão sistólica, o uso

TABELA 1 CARACTERÍSTICAS BASAIS ESTRATIFICADAS POR GÊNERO E A PRESENÇA OU AUSÊNCIA DE DIABETES *MELLITUS*

		Homens n = 218		Mulheres n= 198	
	Total n = 416	Diabéticos n = 112	Não-diabéticos n = 106	Diabéticas n = 94	Não-diabéticas n = 104
Idade (anos), média; DP	76,9 ± 7,4	75,2 ± 7,1	77,6 ± 7,6	75,9 ± 7,2	78,8 ± 7,2
Idade ≥ 80 anos, n (%)	149 (36)	28 (25%)	43 (41%)	30 (32%)	49 (47%)
TFGe EPI (ml/min/1,73 m²), mediana; IIQ	32 [23-42]	30 [22-39]	27 [21-37]	33 [25-43]	34 [27-47]
Creatinina sérica (mg/dL), mediana; IIQ	1,6 [1,3-2,0]	1,7 [1,3-2,1]	1,7 [1,4-2,2]	1,4 [1,2-1,9]	1,4 [1,1-1,8]
Estágio da DRC, n (%)					
Estágio 1	6 (1,4)	0 (0,0)	0 (0,0)	3 (3,2)	3 (2,9)
Estágio 2	33 (7,9)	11 (9,8)	8 (7,5)	8 (8,5)	6 (5,8)
Estágio 3a	46 (11,0)	9 (8,0)	10 (9,4)	9 (9,6)	18 (17,3)
Estágio 3b	139 (33,4)	36 (32,1)	24 (22,6)	37 (39,4)	42 (40,4)
Estágio 4	158 (38,0)	43 (38,4)	50 (47,2)	33 (35,1)	32 (30,8)
Estágio 5	34 (8,2)	13 (11,6)	14 (13,2)	4 (4,3)	3 (2,9)
Encaminhamento, n (%)					
Atenção primária	207 (49,8)	54 (48,2)	50 (47,2)	49 (52,1)	54(51,9)
Atendimento hospitalar	191 (45,9)	54 (48.2)	52 (49.1)	41 (43,6)	44 (42,3)
Outros	18 (4,3)	4 (3.6)	4 (3,8)	4 (4,3)	6 (5,8)
Etiologia da doença renal, n (%)					
Nefropatia isquêmica	159 (38,2)	36 (32,1)	52 (49,1)	22 (23,4)	49 (47,1)
Nefropatia diabética	106 (25,5)	62 (55,4)	0 (0,0)	44 (46,8)	0 (0,0)
Glomerulonefrite	16 (3,8)	1 (0,9)	8 (7,5)	3 (3,2)	4 (3,8)
Doença renal policística	7 (1,7)	1 (0,9)	4 (3,8)	1 (1,1)	1 (1,0)
Miscelânea	73 (17,5)	9 (8,0)	25 (23,6)	13 (13,8)	26 (25,0)
Desconhecido	55 (13,2)	3 (2,7)	17 (16,0)	11 (11,7)	24 (23,1)
Escore mCCI ≥ 5, n (%)	105 (25,2)	55 (49,1)	14(13,2)	31(32,9)	5(4,8)
IMC (kg/m²), média; DP	27,3±4,8	27,1 ± 4,9	25,7 ± 4,1	29,5±5,5	27,0 ± 4,6
IMC > 30 (kg/m²), n (%)	101 (24,4)	19 (16,9)	13 (12,3)	43 (45,7)	23 (22,1)
IMC > 25 a ≤ 30 (kg/m²), n (%)	174 (42,0)	60 (53,6)	43 (40,5)	31 (33,0)	44 (42,3)
IMC ≤ 25 (kg/m²), n (%)	139 (33,6)	33 (29,5)	50 (47,2)	20 (21,3)	37 (35,6)
Tabagistas atuais, n (%)	22 (5,3)	8 (7,1)	10 (9,4)	2 (2,1)	2 (1,9)
Ex-tabagistas, n (%)	87(20,9)	44 (39,3)	40 (37,8)	2 (2,1)	1 (1,0)
Nunca fumaram, n (%)	307(73,8)	60 (53,6)	56 (52,8)	90 (95,8)	101 (97,1)
PAS (mm Hg), média; DP	140,9 ± 24,1	142,7 ± 22,6	139,4 ± 22,1	140,9 ± 26,7	140,5 ± 25,2
PAD (mm Hg), média; DP	71,7 ± 12,5	71,8 ± 11,4	72,5 ± 12,4	71,3 ± 12,5	71,3 ± 13,9
PAM (mmHg), média; DP	94,8 ± 14,7	95,9 ± 13,5	93,7 ± 13,5	94,7 ± 16,2	94,7 ± 15,9
PA < 130/80 mmHg, n (%)	130 (31,3)	30 (26,8)	31 (29,2)	32 (34,0)	37 (35,6)
PA < 140/90 mmHg, n (%)	198 (47,6)	48 (42,9)	49 (46,2)	49 (52,1)	52 (50,0)
Anti-hipertensivos ≥3, n (%)	58 (13,9)	20 (17,9)	16 (15,1)	10 (10,6)	12 (11,5)
Bloqueio renina-angiotensina, n (%)	293 (70,4)	86 (76,8)	72 (67,9)	65 (69,1)	70 (67,3)
Dislipidemia, n (%)	354 (85)	104 (92,9)	81 (76,4)	85 (90,4)	84 (80,8)
Medicação redutora de Lípidos, n (%)	248 (59,6)	73 (65,2)	60 (56,6)	54 (57,4)	61 (58,7)

Continuação Tabela 1.

Albumina (g/dL)	4,09 ± 0,50	4,08 ± 0,49	4,20 ± 0,46	3,98 ± 0,55	4,08 ± 0,49
Ácido úrico (mg/dL), média; DP	7,3 ± 2,2	7,3 ± 2,1	7,3 ± 2,2	7,1 ± 2,3	7,2 ± 2,4
Colesterol total (mg/dL), média; DP	180± 49	176 ± 46	173 ± 45	178 ± 50	192 ± 53
HDL (mg/dL), média; DP	48 ±14	45 ± 13	50 ± 16	44 ± 12	52 ± 15
LDL (mg/dL), média; DP	105 ± 40	102 ± 38	101 ± 37	104 ± 42	113 ± 42
Hemoglobina (g/dL), média; DP	12,1 ± 1,8	12,4 ± 1,7	12,7 ± 2,1	11,3 ± 1,5	11,9 ± 1,5
Hemoglobina < 11g /dL, n (%)	110 (26,4)	23 (20,5)	26 (24,5)	36 (38,3)	25 (24,0)
TSAT (%), média; DP	22 ± 10	22 ± 10	25 ± 11	18 ± 9	23 ± 11
Ferritina (ng/mL), média; DP	245 ± 251	246 ± 269	286 ± 263	188 ± 187	271 ± 261
iPTH (pg/mL), média; DP	125,0 ± 90,3	120,5 ± 101,0	134,6 ± 81,7	114,5 ± 74,5	132,2 ± 98,6
Cálcio (mg/dL), média; DP	2,37 ± 0,18	2,36 ± 0,16	2,37 ± 0,16	2,38 ± 0,22	2,39 ± 0,20
Fosfato (mg/dL), média; DP	1,14 ± 0,22	1,13 ± 0,25	1,06 ± 0,23	1,18 ± 0,21	1,17 ± 0,22
uPCr (g/g), média; DP	1,10 ± 2,20	1,33 ± 2,27	0,72 ± 1,48	1,29 ± 2,38	0,99 ± 2,46

As variáveis contínuas são apresentadas como média ± desvio padrão ou medianas e intervalos interquartis, onde apropriado. Os dados categóricos estão apresentados como número (n) de pacientes e porcentagens (%). O número de valores faltosos foi < 1% para todos os parâmetros, exceto ara UPCr (20%). TFGe, taxa estimada de filtração glomerular; índice mCCI modificado de comorbidade de Charlson; IMC, índice de massa corporal; PAS, pressão arterial sistólica; PAD, pressão arterial diastólica; PAM, pressão arterial média; HDL, lipoproteína de alta densidade; LDL, lipoproteína de baixa densidade; TSAT, saturação de transferrina; iPTH, hormônio intacto da paratireóide; uPCr, coeficiente urinário de proteína-para-creatinina

de mais anti-hipertensivos, maior prevalência de dislipidemia e maior nível de proteinúria naqueles com nefropatia diabética presumida.

Quanto à dependência funcional, 6% (n = 25) dos pacientes eram totalmente dependentes, e 38% (n = 158) eram parcialmente dependentes, sem diferença entre os grupos. O comprometimento cognitivo esteve presente em 12% (n = 50) dos pacientes, sem diferença entre os grupos.

Globalmente, a TFGe foi ligeiramente menor nos homens, particularmente naqueles sem diabetes. A taxa média de uPCr foi 1,1, maior em pacientes com diabetes quando comparados com pacientes sem diabetes.

A maioria dos pacientes apresentou níveis de hemoglobina ≥ 11 g/dL (n = 306; 74%), e a porcentagem de pacientes com saturação de transferrina < 20% foi de 38% (n = 158) e o nível de ferritina < 100 foi de 25% (n=104), respectivamente. Apenas 5% (n = 21) da coorte total estava recebendo agentes estimuladores da eritropoiese (AEE). A porcentagem de pacientes recebendo suplementação de ferro oral e EV foi de 10% (n = 42) e 0,7% (n = 3), respectivamente.

O hormônio paratireoideo intacto estava elevado em 81% (n = 337) dos pacientes, apesar do bom controle dos níveis de cálcio-fósforo. A porcentagem de pacientes tratados com suplementação de vitamina D e ligantes de fosfato foi de 7% (n = 28) e 4% (n = 17), respectivamente.

Prevalência de doença cardiovascular basal

Doença cardiovascular esteve presente em 62% (n = 256) dos pacientes: doença arterial coronariana em 25% (n = 103), doença cerebrovascular em 24% (n = 100) e doença vascular periférica em 19% (n = 77), respectivamente (Tabela 2).

A doença arterial coronariana estava presente em 31% (n = 64) dos pacientes com diabetes, em comparação com 19% (n = 39) em pacientes sem diabetes.

Eventos cerebrovasculares anteriores foram mais frequentes em homens em comparação com mulheres: 28% (n = 60) e 20% (n = 40), respectivamente; a prevalência foi apenas ligeiramente maior em pacientes com diabetes em comparação com pacientes sem diabetes: 26% (n = 53) e 22% (n = 47), respectivamente.

A doença vascular periférica foi mais prevalente em pacientes com diabetes em comparação com pacientes sem diabetes, 24% (n = 49) e 13% (n = 28), respectivamente; e em homens comparados a mulheres, 23% (n = 51) e 13 % (n = 26), respectivamente.

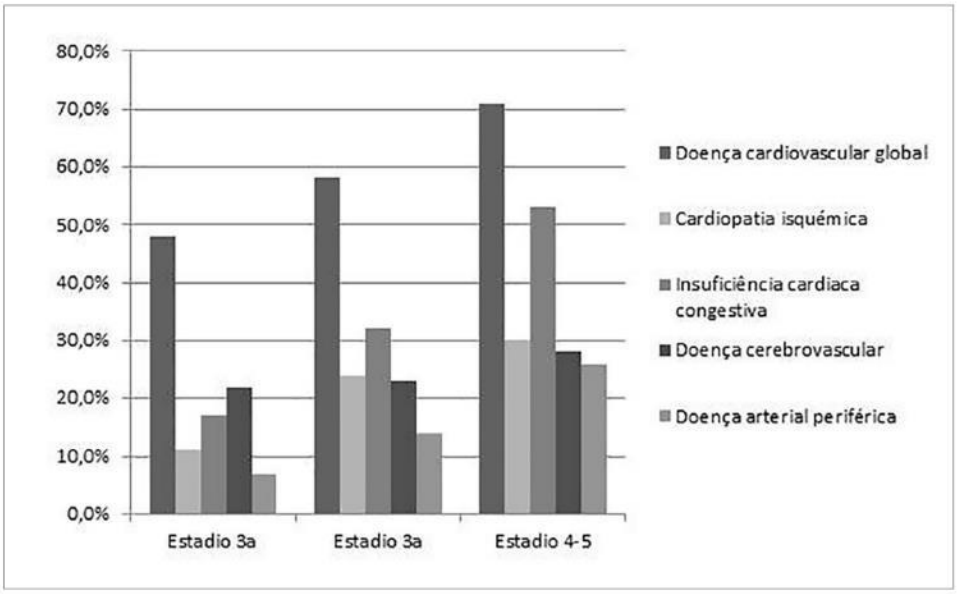
Estratificando os estágios da DRC em 3a, 3b e 4-5, a prevalência de doença arterial coronariana, insuficiência cardíaca congestiva e doença vascular periférica foi mais alta no estágio 4-5, aumentando gradualmente com a progressão da DRC (Figura 1). O peso da doença cardiovascular associada ao declínio de TFGe foi mais pronunciado em pacientes com diabetes, em comparação com pacientes sem diabetes (Tabela 3).

Tabela 2 Cardiovascular disease burden stratified by gender and presence and absence of diabetes *mellitus*

	Total	Homens		Mulheres	
	n = 416	n = 218		n= 198	
		Diabéticos	Não-diabéticos	Diabéticos	Não-diabéticos
		n = 112	n = 106	n = 94	n = 104
Doença cardiovascular*, n; (%)	256 (62)	74 (66)	65 (61)	60 (64)	57 (55)
Doença cardíaca, n;(%)	282 (68)	78 (70)	62 (58)	85 (90)	57 (55)
Doença coronariana	103 (25)	34 (30)	25 (24)	30 (32)	14 (13)
Insuf. cardíaca congestiva	164 (39)	42 (38)	34 (32)	50 (53)	38 (37)
Doença cardíaca valvular grave	15 (4)	2 (2)	3 (3)	5 (5)	5 (5)
Doença cerebrovascular, n; (%)	100 (24)	35 (31)	25 (24)	18 (19)	22 (21)
Doença arterial periférica, n; (%)	77 (19)	33 (29)	18 (17)	16 (17)	10 (10)

*Doença cardiovascular inclui todos os pacientes com um ou mais dos seguintes: doença cardíaca, doença vascular periférica e cerebrovascular. Os dados categóricos estão apresentados como número de pacientes (n) e porcentagens.

Figura 1. Prevalência (%) de causas individuais de doença cardiovascular estratificada por estágios de DRC.



Discussão

Quando projetamos nosso estudo de coorte longitudinal, o objetivo principal foi identificar os principais preditores para progressão da doença renal crônica e óbito em idosos portadores de DRC encaminhados ao nosso ambulatório.[9] Neste artigo, analisamos suas características basais, perfil de risco cardiovascular e prevalência de doença cardiovascular.

Uma característica particular deste estudo é que todos os pacientes foram encaminhados ao nosso departamento de nefrologia. Isso nos dá informações sobre as características básicas dos pacientes antes que eles recebam atenção específica do nefrologista.

Em nossa coorte, as duas causas mais frequentes de DRC foram a nefropatia isquêmica e diabética,

Tabela 3 Peso da doença cardiovascular, estratificado por estágios da DRC e presença ou ausência de diabetes *mellitus*

	Total n = 377				Diabéticos n = 184				Não-Diabéticos n = 193			
Estágio DRC	3a n = 46	3b n = 139	3b n = 139	*p*	3a n = 18	3b n = 73	4-5 n = 93	*p*	3a n = 28	3b n = 66	4-5 n = 99	*p*
Doença cardiovascular *, n (%)	22 (48)	80 (58)	137 (71)	0,022	7 (39)	42 (58)	76 (82)	< 0,001	15 (54)	38 (58)	61 (62)	0,713
Doença cardíaca, n(%) Doença coronariana	5(11)	33 (24)	58 (30)	0,001	2 (11)	22 (30)	36 (39)	0,062	3 (11)	11 (17)	22 (22)	0,339
Insuf. Cardíaca congestiva	8 (17)	45 (32)	102 (53)	< 0,001	2 (11)	26 (36)	59 (63)	< 0,001	6 (21)	19 (29)	43 (43)	0,040
Doença cardíaca valvular grave	2 (4)	3 (2)	10 (5)	0,371	1 (6)	1 (1)	5 (5)	0,375	1 (4)	2 (3)	5 (5)	0,805
Doença cerebrovascular, n (%)	10 (22)	32 (23)	54 (28)	0,475	2 (11)	16 (22)	34 (37)	0,027	8 (29)	16 (24)	20 (20)	0,610
Doença arterial periférica, n(%)	3 (7)	20 (14)	49 (26)	0,003	3 (17)	13 (18)	30 (32)	0,071	0	7 (11)	19 (19)	0,022

*Doença cardiovascular inclui todos os pacientes com um ou mais dos seguintes: doença cardíaca, doença vascular periférica e cerebrovascular. Os dados categóricos estão apresentados como número de pacientes (n) e porcentagens (%). O peso da doença cardiovascular foi comparado entre estágios da DRC pelo teste do qui-quadrado para tendências para as variáveis categóricas. Valor de $p < 0.05$ foi considerado estatisticamente significativo.

que são consideradas as principais causas de DRC em todo o mundo,[13,14] particularmente em pacientes idosos. Em 13% dos pacientes, a etiologia da DRC foi considerada desconhecida. No entanto, na ausência de testes diagnósticos específicos e dada a baixa taxa de biópsia renal de 4%, a certeza diagnóstica foi baixa.

A prevalência de doença cardiovascular em nossa coorte de idosos com DRC foi muito alta, presente em 62% dos pacientes. Pacientes com DRC são mais propensos a desenvolver doença cardiovascular.[15] Dados disponíveis de diversos estudos epidemiológicos revelaram que eventos cardiovasculares e mortalidade cardiovascular aumentaram inversamente com a TFGe.[16,17] Por outro lado, a doença cardiovascular está associada ao aumento do risco de progressão da DRC.[18] Além disso, quanto mais velho o indivíduo com DRC, maior o risco de doença cardiovascular e mortalidade, e ainda mais se condições comórbidas adicionais, incluindo diabetes, hipertensão, obesidade e outros fatores de risco vasculares estiverem presentes.[19]

Em nossa coorte, muitos fatores de risco estabelecidos para doença cardiovascular apresentaram alta prevalência; maior prevalência de doença cardiovascular foi observada com pior estágio da DRC (Tabela 3 e Figura 1). O peso da doença cardiovascular associada ao declínio de TFGe foi pronunciada em pacientes com diabetes (Tabela 3). A prevalência de doenças cardiovasculares foi maior do que a relatada em coortes europeias da DRC (GCKD[20] alemã, MERENA[21] espanhola, CARHES[22] italiana), mesmo quando ajustada para idade.

Embora nosso estudo não tenha sido projetado para identificar fatores de risco para DRC e para doença cardiovascular, diversas características dos pacientes forneceram evidências indiretas de vários fatores predisponentes.

Em primeiro lugar, a prevalência de diabetes de 50% é quase o dobro daquela do PREVADIAB[23], um estudo de base populacional para avaliar a prevalência de diabetes em Portugal. Além disso, a prevalência de diabetes em nossa coorte foi maior do que a relatada em outras coortes europeias de DRC (GCKD[20] alemã: 35%; MERENA[21] espanhola: 41%; CARHES[22] italiana: 28%), mesmo quando se ajusta para a idade.

Entre os fatores de risco tradicionais para DRC e para doença cardiovascular, a presença de hipertensão

em nossa coorte foi quase universal (96%), sem diferenças significativas entre pacientes diabéticos e não-diabéticos. Em termos de controle da hipertensão, a pressão arterial era < 130/80 mmHg em apenas aproximadamente um terço dos pacientes. Essa lacuna entre as metas e a realidade clínica é consistente com outros estudos de coorte de DRC[20-22], que ilustram as dificuldades do controle da pressão arterial na DRC e um potencial de melhora. Uma grande porcentagem de pacientes estava tomando inibidores do sistema renina angiotensina (70%), particularmente homens com diabetes (77%). No entanto, homens com diabetes foram o grupo com pior controle da PA, o que pode contribuir para o papel do gênero masculino e do diabetes no peso das doenças cardiovasculares.

Tabagismo atual foi relatado em 5% da coorte, e ex-tabagismo em 21% (Tabela 1), com preponderância masculina. Essa é uma prevalência menor do que aquela relatada nas outras coortes da DRC.[20-22,24]

No geral, 24% dos pacientes incluídos eram obesos (IMC > 30 kg/m^2), o que é menor do que a prevalência em outras coortes europeias de DRC.[20-22] Portanto, a obesidade não foi um dos principais contribuintes para a prevalência de doenças cardiovasculares em nosso grupo de estudo. Mesmo assim, obesidade e excesso de peso foram mais prevalentes em pacientes diabéticos.

É provável que a previsão de riscos renais e cardiovasculares em pessoas com DRC seja melhorada pela incorporação da albuminúria no estadiamento da doença renal.[25] Os dados do nosso estudo sobre proteinúria foram semelhantes aos relatados em outras coortes europeias da DRC.[21,22] Por outro lado, o grau de proteinúria em nossa coorte é maior do que em outras coortes (CRIC),[24] o que pode estar relacionado ao melhor controle da PA nesses estudos. O nível de proteinúria foi maior em pacientes com diabetes em comparação com pacientes sem diabetes, confirmando que a proteinúria é uma característica da nefropatia diabética, mas também um importante contribuinte para o risco cardiovascular em pacientes diabéticos.

A dislipidemia também é um fator de risco cardiovascular tradicional que é frequentemente observado em pacientes com DRC, com uma incidência crescente com a progressão da DRC.[26] A dislipidemia foi muito prevalente em nossa coorte (85%), e mais prevalente em pacientes com diabetes, o que reforça o risco cardiovascular nesses pacientes.

A anemia também é um fator associado à prevalência e mortalidade por doença cardiovascular e progressão da DRC.[27] A hemoglobina média da coorte foi de 12,1 g/dL e a maioria dos pacientes apresentou hemoglobina maior que 11 g/dL (74%). Como apenas 5% dos pacientes na coorte total recebendo terapia com AEE, a hemoglobina relativamente alta do grupo como um todo não pode ser atribuída ao tratamento excessivo com esses agentes. Apenas 10% dos pacientes estavam recebendo terapia com ferro, mas a saturação de transferrina < 20% foi documentada em 38% dos pacientes, refletindo o tratamento insuficiente com ferro antes do encaminhamento para nefrologia.

O distúrbio ósteo-mineral da DRC é um dos principais contribuintes para a calcificação vascular e doença cardiovascular[28] em pacientes com DRC. Com relação aos níveis de cálcio-fósforo e PTH, um achado evidente foi que apenas 19% dos pacientes em nossa coorte tinham níveis de PTH dentro dos alvos recomendados com base nas diretrizes K-DOQI[29], apesar do bom controle dos níveis de cálcio-fósforo. Houve uma porcentagem muito baixa de pacientes que receberam vitamina D e seus análogos, sugerindo a necessidade de uma otimização adicional no tratamento do distúrbio mineral-ósseo na DRC.

A prevalência de diabetes, bem como outros fatores de risco para DRC, pode explicar em parte a variação internacional na prevalência de DRC. Numa recente revisão narrativa sobre os fatores que potencialmente estão na base das diferenças internacionais observadas na prevalência de DRC em idosos na Europa[30], os autores concluíram que Portugal apresentava a maior estimativa de prevalência de DRC e a maior pontuação média nos fatores de risco da DRC (por exemplo, diabetes mellitus, hipertensão arterial, inatividade física e ingestão de sal).

Os pontos fortes do nosso estudo incluem a exploração rigorosa da primeira coorte de DRC em Portugal com pacientes com 65 anos e referenciados para uma clínica de nefrologia, e conhecer suas características basais e morbidade cardiovascular permitirá uma melhor compreensão da epidemiologia da DRC, política de encaminhamento para a nefrologia em nossa área geográfica e a abordagem global para o risco cardiovascular.

Existem certas limitações à nossa pesquisa. Primeiro, este é um estudo de centro único. Em segundo lugar, alguns vieses de classificação errônea talvez tenham sido introduzidos com base na auto-relato dos pacientes com comorbidade. Por fim, como essa coorte consistia apenas de pacientes atendidos no ambulatório de nefrologia, nossos resultados podem não

se traduzir necessariamente em pacientes com DRC que não são encaminhados para nefrologistas.

Conclusões

Em resumo, as características da nossa coorte de idosos com DRC demonstraram o pesado fardo do perfil de risco e doença cardiovascular, e refletiram um papel importante de vários fatores de risco para o desenvolvimento da doença renal. A prevalência de diabetes e doença cardiovascular é maior do que em outras coortes europeias de DRC.

O nível mais baixo de TFGe foi associado a um peso maior de doenças cardiovasculares, destacando a importância de direcionar estrategicamente a redução do risco cardiovascular nesses pacientes idosos. Este é um grupo importante de pacientes que devem ser caracterizados e compreendidos; espera-se que os resultados possam melhorar o manejo destes pacientes ao longo do tempo.

Material suplementar

O seguinte material on-line está disponível para este artigo:

Tabela S1 - Comparação de pacientes com diabetes mellitus (DM) com e sem nefropatia diabética (DN) presumida e pacientes sem diabetes *mellitus*

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APPENDIX 3

Different kidney function trajectories patterns before dialysis in older CKD patients: Implications for clinical management.

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Different kidney function trajectories patterns before dialysis in older chronic kidney disease patients

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ABSTRACT

Background. Identify trajectories of kidney disease progression in chronic kidney disease (CKD) patients, may help to deliver better care. We aimed to identify and characterize trajectories of renal function decline in CKD patients, and to investigate their association with mortality after dialysis.

Methods. This retrospective cohort study included 378 CKD patients who initiated dialysis (aged 65 years and over) between 2009 and 2016. Were considered mixed models using linear quadratic and cubic models to define the trajectories, and we used probabilistic clustering procedures. Patient characteristics and care practices at and before dialysis were examined by multivariable multinomial logistic regression. Association of these trajectories with mortality after dialysis was examined using Cox models.

Results. Four distinct groups of eGFR trajectories decline before dialysis were identified: slower decline (18.3%), gradual decline (18.3%), early rapid decline (41.2%) and rapid decline (22.2%). Patients with rapid eGFR decline were more likely to have diabetes, more cognitive impairment, to have been hospitalized before dialysis, and were less likely to have received pre-dialysis care compared to the patients with slower decline. They had a higher risk of death within the first and fourth year after dialysis initiation, and after being more than four years in dialysis.

Conclusions. There are different patterns of eGFR trajectories before dialysis initiation that may help to identify those who are more likely to experience an accelerated decline in kidney function, with impact on pre ESRD care and in the mortality risk after dialysis.

Keywords: CKD, ESRD, Outcomes, Renal trajectory

INTRODUCTION

Chronic kidney disease (CKD) is rising worldwide, and has emerged as a serious public health problem, as shown by the increase in mortality and the growing incidence and prevalence of end-stage renal disease (ESRD)[1], requiring renal replacement therapy (RRT).

Renal function trajectory defined by the change in a patient's estimated glomerular filtration rate (eGFR) over time is an approach supported by the dynamic changes in kidney function overtime, that predicts CKD progression [2,3], and is associated with mortality [4-7].

Although renal function progressively decreases over time, many CKD patients have a prolonged period of non-progression or a non-linear GFR trajectory due to several factors, such as acute kidney injury (AKI) episodes [2], particularly frequent in older patients [7]. Moreover, mortality outweighs the risk of progression to ESRD in elderly [8], which further complicates the study of patterns of kidney disease progression in this group of patients.

Stratifying CKD patients into different groups according to patterns of renal function trajectory may help to anticipate the optimal timing of nephrology referral, to guide the care of CKD patients.

Since the pioneering work of Mitch et al [9], kidney function trajectories have been subject of different research approaches [4,10-13]. Only few studies have addressed this issue in the elderly [15-17] and in patients who initiate dialysis [4,12,14,18,19].

Therefore, the aims of this study were to identify and characterize distinct trajectories of renal function decline in CKD patients older than 65 years at dialysis initiation, and to investigate the association of these trajectories with mortality after starting dialysis.

PATIENTS AND METHODS

A retrospective cohort study was conducted in patients, referred to Nephrology Department in Centro Hospitalar Universitário do Porto (CHUP) who started dialysis as their first RRT between January 2009 and December 2016. This hospital is a tertiary-care hospital which

serves a population of 500 000 inhabitants in the North region of Portugal. The study was performed in accordance with the Declaration of Helsinki and it was approved by the Institutional Review Board of CHUP.

The inclusion criteria for this study were age over 65 years at dialysis initiation and having at least five consecutive serum creatinine measurements. Patients, who initiated maintenance dialysis due to AKI without CKD, were excluded.

Clinical data from baseline included sex, age, weight, height, body mass index (BMI), and associated comorbid conditions, such as diabetes, dyslipidemia, hypertension, smoking status, *malignancy,* coronary artery disease, congestive heart failure, arrhythmia, peripheral artery disease and stroke. Laboratory data were collected over time and included: serum creatinine, and urinary protein-to-creatinine ratio (uPCr). All measurements were performed in the same central laboratory of CHUP using standard biochemical methods.

In the 12 months prior to dialysis initiation, number of all-cause hospitalizations were collected, including hospitalizations with an inpatient diagnostic code for AKI (ICD-9 codes 584.5–584.9).

Glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology (CKD-EPI) 2009 creatinine equation [20]. Etiological diagnosis of CKD was based on the patient's history, kidney ultrasound, and kidney biopsy, when available.

Cognitive status was evaluated using the Mini Mental State Examination (MMSE) [21], classified as cognitive impairment if the score was 23 or lower.

Functional dependency was defined as the requiring of assistance for transfer and classified as totally dependent, need assistance for transfer or autonomous.

A modified version of the Charlson comorbidity index (mCCI) [22], i.e., by excluding subject's age and presence of kidney disease, was calculated.

Variables related to renal care included timing of nephrologist care, vascular access placement (graft/fistula/peritoneal catheter vs. hemodialysis catheter), and whether dialysis was initiated in the hospital.

We also analyze whether there was a diagnostic of AKI associated with inpatient dialysis initiation; AKI was identified by using the criteria of the KDIGO-AKI Work Group guidelines [23].

Vital status was checked for all patients until 2019, October 31st.

Statistical Analysis

To define the trajectories, mixed models using linear quadratic and cubic models were considered. Ciampi et al. [24] refer the use of clustering to study disease trajectories specifically in the study of longitudinal data where the number of observations or the time between observations may differ across patients. Probabilistic clustering procedures [25-27] were used to assign the individual trajectories to the different clusters, through the package mclust available as a contributed package from the Comprehensive R Archive Network (CRAN). The number of cluster trajectories was defined based on the Bayesian Information Criterion (BIC).

Demographic and clinical characteristics were summarized as mean and standard deviation (or as median and interquartile range) for continuous variables and as counts and percentages for categorical variables in trajectory groups. For quantitative variables, one-way ANOVA or the Kruskal Wallis test were used to compare the different trajectory groups; multiple comparisons were adjusted by the Bonferroni correction.

Univariate logistic regression analysis was used to study the association of each trajectory group with binary patient characteristics and care practices at and before dialysis association. Determinants of the identified trajectories were examined by multivariable multinomial logistic regression. The independent effects of age, gender, diabetes, cognitive impairment, and hospitalizations on the eGFR trajectories were examined in the logistic regression model. These variables were selected as covariates since they were associated with trajectory groups.

Because proteinuria was a strong determinant for all eGFR trajectories and because the percentage of missing of this variable (8.7%) we decided not to include this variable in the multivariable model of multinomial logistic regression.

Median survival was estimated for each trajectory group using Kaplan-Meier analysis. Multivariable Cox proportional hazard was used to evaluate the association of eGFR trajectory with survival after dialysis initiation, adjusting for patient demographic and clinically relevant factors with trajectories eGFR decline. The assumption of proportional hazards was checked graphically using the log cumulative hazard plots for death according to subgroups of trajectory eGFR decline. Hazard ratios are presented for three time periods (< 1 year, 1 to 4 years, and > 4 years) to fulfill the proportional hazards assumption for the principal predictor variable (trajectory subgroups).

All statistical analyses were performed using R (R Development Core Team 2006) package mclust [25-27] available as a contributed package from the Comprehensive R Archive Network (CRAN) at http://CRAN.R-project.org/ and SPSS 25.0. at an a priori significance level of 0.05.

RESULTS

Identification of eGFR trajectories decline before dialysis initiation

Four distinct groups of eGFR trajectories decline before dialysis initiation were identified: slower eGFR decline (group 1, n=69; 18.3%), gradual eGFR decline (group 2, n=69; 18.3%), early rapid eGFR decline (group 3, n=156; 41.2%) and rapid eGFR decline (group 4, n=84; 22.2%) (Figure 1).

Table 1 describes the characteristics of kidney function for each of the identified trajectories. During the period before dialysis initiation, among the overall cohort there was a median (IQR) of 19 (11,28) serum creatinine measurements per patient, and a median eGFR variation (IQR) of 77.9 (66.9, 87.2) percent over a median (IQR) period of 6.0 (3.7, 8.6)

years. The median (IQR) eGFR variation in the slower, gradual, early rapid, and rapid decline trajectories groups were 74.1 (64.9, 82.2), 69.3 (56.1, 77.9), 78.8 (71.1, 86.4) and 88.3 (78.0, 92.2) percent over time, respectively.

Patient characteristics and nephrology care practices determinants of eGFR trajectories

Table 2 shows baseline characteristics of the overall cohort and according to trajectory group. Table 3 summarizes the nephrology care practices of the overall cohort and stratified by each trajectory's groups. The patient characteristics and care practices significantly associated with each trajectory are shown in Table 4. The trajectory group with the slower decline eGFR (group 1) was considered as the reference to which other groups were compared.

Congestive heart failure, coronary artery disease, arrhythmia, stroke, peripheral vascular disease, pulmonary disease, cancer, outpatient visit to a nephrologist, inpatient diagnosis of AKI and AKI at dialysis initiation were not associated with being placed into any trajectory compared with the slower eGFR decline.

Patients with diabetes or diabetes being the cause of ESRD and with hospitalizations within one year before dialysis were more likely to be in early rapid (group 3) and rapid decline (group 4) trajectories. Moreover, patients with cognitive impairment and without vascular access were more likely to be in the rapid decline trajectory (group 4). Patients in rapid decline trajectory (group 4) were also younger and included more female patients.

A multinomial logistic regression was then conducted to identify the predictors associated with falling into a particular trajectory group, with the distinct trajectory groups used as the dependent variable (Table 5). As in the previous analysis, group 1 trajectory was specified as the reference category.

Women, younger patients (age <75 vs. ≥75 years), and patients with cognitive impairment

were more likely to be included in the rapid decline trajectory (group 4). Diabetic were more likely than non-diabetic patients to be placed into any of the rapid eGFR decline trajectories (group 3-early rapid decline, OR=1.916; 95% CI, 1.06-3.46 or group 4-rapid eGFR =2.736, OR=1.379-5.431), as well as patients hospitalized within one-year before dialysis (group 3-early rapid decline, OR=1.916; 95% CI, 1.06-3.46 or group 4-rapid eGFR decline =2.736, OR=1.379-5.431).

Mortality after dialysis initiation according to eGFR decline trajectories

By the end of follow-up in October 2019, 233 patients (62%) had died, with a median survival of 4.4 years (1.8-8.7). Patients in the slower eGFR decline (group 1) had the best median survival (9.0 years) and patients with the more rapid eGFR decline (group 4) had the lowest median survival (2.4 years) (Figure 2).

After adjustment for patient characteristics significant for eGFR trajectories, trajectory group had no significant impact at the risk for death during the first year after dialysis, compared with the slower decline trajectory (Table 6). However, compared to patients with slower eGFR decline, patients with rapid loss of eGFR (groups 3 and 4) were associated with higher mortality within the first and fourth year after dialysis initiation (HR: 1.805; 95%CI 1.005-3.243, and HR: 3.260; 95%CI 1.693-6.277, for early rapid and rapid eGFR decline, respectively).

After being more than four years in dialysis, patients in trajectories 2, 3 and 4 were at increased significant risk of dying compared with the reference group (group 1)(HR: 3.628; 95%CI 1.171-11.24, HR: 4.259; 95%CI 1.468-12.35, and HR: 6.347; 95%CI 1.868-21.56, respectively) (Table 6). Beyond trajectories, age higher than 75 years was associated with higher mortality. The remaining variables (gender, cognitive status and hospitalizations within 1-year before dialysis) were not associated with increased mortality risk.

DISCUSSION

In this current study, four distinct patterns of eGFR decline preceding initiation of chronic dialysis were identified. A significant proportion of patient who initiated dialysis therapy within the follow-up period were those with a baseline eGFR <25 mL/min/ 1.73 m^2 (37%) (group 1 and 2) and had relatively slower slopes, other were patients with higher eGFRs who had early faster rates of decline (41%) (group 3), whereas 22% of patients with eGFRs >60 mL/min/1.73 m^2 at baseline, had a catastrophic rate of decline (group 4).

This study was able to identify patient characteristics and care practices that could be determinants of those trajectories. Patients with diabetes or diabetes being the cause of ESRD were more likely to be in eGFR rapid decline trajectories. In a cohort of 18,874 US veterans, Sumida et al [12], examined the association of eGFR trajectories in late-stage CKD with mortality after dialysis found that patients with fast eGFR decline had a higher prevalence of diabetes mellitus. These results suggest that despite of the role of proteinuria in the progression of CKD, chronic hyperglycemia *per si* play a crucial role in accelerating GFR decline in diabetic patients [28, 29], which reinforces the need for tighter monitoring in diabetic patients. whether they have proteinuria or not.

O'Hare et al [4], using data from 5,606 Veteran Affairs patients, identified 4 distinct trajectories of eGFR during the 2-year period before dialysis initiation. Like these two previous studies [4,12], we found that patients who experienced more rapid eGFR decline were younger compared with patients who progressed slower. This can be explained by the fact that older patients who survive long enough to reach more advanced stages of CKD are less likely than their younger counterparts to experience fast eGFR decline [4,12].

One particularity of our study is that rapid eGFR decline group had a higher proportion of women compared with the group progressed more slowly. Several studies suggest that renal disease progression is faster in men than women [30]. However, a meta-analysis published in 2003 [31] suggested the progression of renal disease may not be slower in women as compared to men, though most of the women were on post-menopausal age. In the Chronic

Renal Insufficiency Cohort (CRIC) study, despite women having a significantly decreased risk of developing ESRD, after adjusting for demographic and clinical factors there were no significant differences in eGFR slopes between women and men [32]. Thus, it is not clear whether sex is independently associated with faster renal disease progression, or whether the association reflects confounding by imbalances between men and women of non-controlled factors associated with renal disease progression.

We found that patients who experienced rapid eGFR decline had more cognitive impairment than patients with slower decline. Cognitive impairment is remarkably prevalent in older CKD patients [33] and the celerity of eGFR decline had an increased risk of cognitive deterioration. Chen, et al [34], shows that participants with severe decline in eGFR (>20% per year) had an increased risk of cognitive deterioration, when compared with those who had stable eGFR, during a median follow-up of 5.4 years. Severe eGFR decline would be an indicator that shows renal function change is caused by vascular effects, which supports the hypothesis of a cognition-kidney axis.

Trajectories of kidney function decline have been identified as independent predictors of ESRD [35,36], so they may hold important implications for the optimal timing of RRT preparation. In our cohort, patients without vascular access and who had inpatient dialysis initiation, were more likely to be in the rapid decline trajectory group. These findings are not unpredictable since those with the highest levels of kidney function at beginning of follow-up were least likely to receive pre-dialysis care, maybe to non-recognition of their potential to rapid progress.

Although there is no universally accepted definition for optimal timely evaluation, considered as adequate to allow for patient and family information, preparation for RRT (e.g., vascular access placement), a period of 12 months seems reasonable to provide an acceptable nephrology care [37]. In our study, the level of eGFR approximately 12 months before dialysis initiation was 10 mL/min/1.73m^2 for patients with slower eGFR decline, 15 mL/ min/1.73 m^2 for patients with gradual eGFR decline, around 20 mL/ min/1.73 m^2 for patients with early

rapid eGFR decline, and around 25 mL/ min/1.73 m^2 for patients with rapid eGFR decline, respectively (Figure 1). As in other groups [4], these results serve to remind that patients who reach ESRD do so in various ways and suggest the need for more flexible approaches to preparation for RRT with awareness of the heterogeneity of eGFR trajectories.

Our results showed that patients with rapid eGFR decline trajectories were more likely to have been hospitalized within one-year before starting dialysis. In a cohort of US veterans, with CKD stage 3A, Xie et al [38], founded that a steeper decline in kidney function was associated with a higher risk of hospitalizations, readmissions, and prolonged length of hospital stay. It is likely that higher rates of hospitalization were attributable in part to deteriorating kidney function and its complications, or that the rate of kidney function decline may be a surrogate marker of poor overall health.

Episodes of AKI in CKD patients are associated with more rapid transition between stages of CKD and increased risk for progression ESRD [39], particularly in the elderly [40]. In our work, inpatient diagnosis of AKI and the presence of AKI at dialysis initiation were not associated with being placed into any trajectory compared with the slower eGFR decline. This may be related to the fact that AKI episodes were very frequent among all our patients. Several studies have demonstrated strong associations between decline in eGFR and risk of cardiovascular disease and mortality among CKD patients [6,7,35]. However, only a few studies have examined the association of different changes in eGFR with mortality following dialysis initiation [4,12,14].

In our cohort, patients with rapid loss of kidney function had a 3.6-fold increase in adjusted risk for death within the first and fourth year after dialysis initiation. The impact on mortality was maintained after being more than four years in dialysis, in whom patients in gradual, early rapid and rapid trajectory decline were at increased significant risk of dying compared with the slower trajectory group (3.6-,4.2- and 6.2-fold higher risk, respectively).

Hsu et al [14] in the CRIC study, revealed that an abrupt decline in kidney function, defined as having an eGFR > 30 mL/min/ 1.73 m^2 at 3 months prior to the start of dialysis, was

associated with a 3-fold higher risk for death within the first year after dialysis initiation. O'Hare et al [8], were able to demonstrate that those patients with accelerated or abrupt loss of eGFR before dialysis initiation were at nearly twice the risk for dying during the first year after initiation, compared with those patients with persistently low levels of eGFR. Similarly, Sumida et al [16], examined the association of eGFR trajectories in late-stage CKD with all-cause and cause-specific mortality during the post-ESRD period over a median follow-up of 2.0 years, and reported that rapid eGFR decline (<-5 mL/min/1.73 m2 /y) was associated with higher all-cause and cardiovascular mortality.

In our cohort, trajectory group had no significant impact at the risk for death during the first year after dialysis initiation, but the impact of rapid decline of kidney function in late mortality after dialysis is notorious, and it was even higher after being more than four years in dialysis. Although, mortality on dialysis therapy has historically been attributed to factors measurable at the time of dialysis itself [41], or results shows that rapid loss of eGFR add information about prognostic over and above known comorbid conditions and confounders. Our study has several strengths, including detailed population phenotype characterization, using all available measurements of renal function.

There are certain limitations to our research. First, this is a single-center study. We also examine only those patients who ultimately ended up on dialysis therapy, so our results are limited by survivor bias.

In conclusion, it was observed different patterns of eGFR trajectories before dialysis initiation and identified associated demographic and clinical factors that may help to identify those who are more likely to experience an accelerated decline in kidney function, with impact on the risk for post-dialysis mortality.

These findings suggest that incorporation of eGFR trajectory into clinical practice will guide shared decision making on pre ESRD care and prediction of mortality after dialysis initiation.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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Table 1. Characteristics of each and overall trajectory decline

	Overall n=378	Slower eGFR decline (Group 1) n=69	Gradual eGFR decline (Group 2) n=69	Early rapid eGFR decline (Group 3) n=156	Rapid eGFR decline (Group 3) n=84	p-value
SCr measures, nº	8253	2074	745	3745	1689	p<0.001
Median and IQR	19.0 [11.0-28.0]	26.0 [19.5-38.5]	9.0 [17.0-13.0]	22.0 [14.0-22.8]	16.0 [9.3-29.0]	2-4
Mean; SD	21.1 ± 13.2	30.1 ± 15.3	10.8 ± 5.3	22.3 ±11.8	20.1 ± 12.6	2-3
Range	5-90	5-71	5-32	5-90	5-66	2-1
						4-1
						3-1
Follow-up (yrs)						
Median and IQR	6.0 [3.7-8.6]	9.4 [6.3-11.1]	2.0 [1.4-2.8]	6.3 [4.6-8.5]	6.5 [4.1-7.9]	p<0.001
Mean;SD	6.3 ± 3.5	9.1 ± 3.7	2.5 ± 1.9	6.8 ± 2.8	6.3 ± 2.7	2-4
Range	0.1-27.7	3.1-27.7	0.6-11.6	2.3-17.9	0.1-12.4	2-3
						2-1
						4-1
						3-1
Time between SCr measures						
Median and IQR	0.29 [0.22-0.45)	0.30 [0.24-0.43]	0.22 [0.16-0.37]	0.29 [0.23-0.45]	0.31 [0.23-0.60]	p<0.001
						2-1
Mean; SD	0.40 ± 0.34	0.40 ± 0.35	0.28 ± 0.16	0.43 ± 0.37	0.45± 0.36	2-3
Range	0.01-2.74	0.15-2.74	0.06-0.99	0.10-2.22	0.01-1.93	2-4
eGFR initial						
Median and IQR	31.1 [20.5-47.7]	22.3 [17.7-29.7]	21.1 [16.8-26.8]	34.0 [23.4-44.0]	61.9 [46.2-76.1]	p<0.001
Mean; SD	36.8 ± 20.9	24.7 ± 10.0	22.8 ± 9.9	35.6 ± 16.1	60.7 ± 21.9	1-3
Range	1.5-109.0	9.9-58.5	5.4-58.0	1.5-100.1	12.7-109.0	1-4
						2-3
						2-4
						3-4
eGFR final						
Median and IQR	6.6 [5.0-8.5]	5.8 [4.2-7.3]	6.7 [4.9-8.5]	6.7 [5.0-8.6]	7.4 [5.4-9.7]	p=0.04
Mean; SD	7.0 ± 3.0	6.0 ± 2.2	6.8 ± 2.5	7.0 ± 2.7	8.1 ± 4.1	1-4
Range	1.0-25.5	1.7-14.9	2.9-15.5	1.0-15.9	2.5-25.5	
% eGFR var*						
Median and IQR	77.9 [66.9-87.2]	74.1 [64.9-82.2]	69.3 [56.1-77.9]	78.8 [71.1-86.4]	88.3 [78.0-92.2]	p<0.001
						2-3
Mean; SD	74.7 ± 16.6	72.5 ± 12.1	64.6 ± 19.6	76.1 ± 14.0	82.0 ± 17.3	2-4
Range	-4.6-97.2	35.0-97.2	-4.6-91.1	27.9-96.2	22.3-96.4	1-4
						3-4

Data expressed as medians and interquartile ranges (IQR) or mean and standart deviation (SD)
SCr, serum creatinine; yrs, years; eGFR, estimated glomerular filtration rate eGFR, using the Chronic Kidney Disease Epidemiology
*Based on all patient serum creatinine measures during de the follow-up period before dialysis initiation

Table 2. Patient Characteristics by eGFR trajectory group

	Overall n=378	Slower eGFR decline (Group 1) n=69	Gradual eGFR decline (Group 2) n=69	Early rapid eGFR decline (Group 3) n=156	Rapid eGFR decline (Group 4) n=84
Age (years), mean; SD	75.4 ± 6.2	76.0±6.2	76.1±6.1	75.3±6.4	74.4±5.9
Age ≥75 years, n (%)	193 (51.1)	39 (56.5)	39 (56.5)	82 (52.6)	33 (39.3)
Female, n (%)	173 (45.8)	24 (34.8)	33 (47.8)	70 (44.9)	46 (54.8)
Primary renal disease, n (%)					
Diabetic nephropathy	142 (37.6)	17 (24.6)	25 (36.2)	63 (40.4)	37 (44.0)
Ischemic nephropathy	61 (16.1)	11 (16.0)	16 (23.2)	25 (16.0)	9 (10.7)
Glomerulonephritis	41 (10.8)	9 (13.0)	5 (7.2)	15 (9.6)	12 (14.3)
ADPKD	21 (5.6)	6 (8.7)	4 (5.8)	9 (5.8)	2 (2.4)
Other	67 (17.7)	11 (16.0)	11 (16.0)	26 (16.7)	19 (22.6)
Unknown etiology	46 (12.2)	15 (21.7)	8 (11.6)	18 (11.5)	5 (6.0)
BMI (kg/m^2), median and IQR	25.8 [23.5 - 28.7]	25.3 [24.0 - 28.3]	26.2 [24.0 - 28.3]	25.7 [23.5 - 29.4]	25.8 [22.4 - 28.2]
< 25, n (%)	154 (40.7)	30 (43.5)	24 (34.8)	62 (39.7)	34 (40.5)
25-29.9	135 (35.7))	26 (37.7)	30 (43.5)	51(32.7)	31 (36.9)
≥ 30	68 (18.0)	11 (15.9)	11 (15.9)	33 (21.2)	13 (15.5)
Cognitive impairment, n (%)	58 (15.3)	7 (10.1)	9 (13.0)	21 (13.5)	21 (25.0)
Totally dependent for transfer, n,(%)	34 (9.0)	4 (5.8)	5 (7.2)	9 (5.8)	16 (19.0)
Need assistance for transfer, n (%)	167 (44.2)	29 (42.0)	32 (46.4)	63 (40.4)	43 (51.2)
Autonomous, n (%)	177 (46.8)	36 (52.2)	32 (46.4)	84 (53.8)	25 (29.8)
Institutionalization, n (%)	19 (5.0)	3 (4.3)	4 (5.8)	7(4.5)	5 (6.0)
mCCI, median and IQR	4 [2 - 5]	5 [3 - 6]	3 [2 - 5]	4 [2 - 5]	4 [3 - 6]
0-2, n (%)	112 (29.6)	16 (23.2)	27(39.1)	56 (35.9)	13 (15.5)
3-4	112 (29.6)	16 (23.2)	20 (29.0)	42 (26.9)	34 (40.5)
≥ 5	154 (40.7)	37 (53.6)	22 (31.9)	58 (37.2)	37 (44.0)
Current/ Former smoking, n (%)	86 (22.8)	12 (17.4)	19 (27.5)	40 (25.7)	15 (17.9)
Diabetes, n (%)	194 (51.3)	26 (37.7)	35 (50.7)	82 (52.6)	51 (60.7)
Hypertension, n (%)	367 (88.6)	69 (100.0)	67 (97.1)	152 (97.4)	66 (78.6)
Dyslipidemia, n (%)	335 (89.1)	65 (94.2)	58 (84.0)	146 (93.6)	66 (78.6)
Congestive heart failure, n (%)	239 (63.2)	40 (58.0)	44 (63.8)	94 (60.3)	61 (72.6)
Coronary artery disease, n (%)	114 (30.2)	15 (21.7)	17(24.6)	51 (32.7)	31 (36.9)
Cardiac arrhythmia, n (%)	90 (23.8)	16 (23.2)	8 (11.6)	45 (28.8)	21 (25.0)
Stoke, n (%)	117 (31.0)	21 (30.4)	20 (29.0)	50 (32.1)	26 (31.0)
Peripheral vascular disease, n (%)	149 (39.4)	27 (39.1)	22 (31.9)	69 (44.2)	30 (35.7)
Cancer, n (%)	59 (15.6)	13 (18.8)	13 (18.8)	22 (14.1)	11 (13.1)
COPD, n (%)	70 (18.5)	11 (15.9)	17 (24.6)	28 (17.9)	14 (16.7)
Chronic liver disease, n (%)	30 (7.9)	4 (5.8)	4 (5.8)	9 (5.8)	13 (15.5)
Autoimmune disease, n (%)	15 (4.0)	3 (4.3)	4 (5.8)	5 (3.2)	3 (3.6)
Peptic ulcer, n (%)	57 (15.1)	11 (15.9)	9 (13.0)	21 (13.5)	16 (19.0)
Albumin (g/dL), median and IQR	3.7 [3.2 - 4.1]	3.8 [3.5 - 4.1]	3.8 [3.5 - 4.1]	3.7 [3.3 - 4.0]	3.4 [3.0 -3.8]
≥ 3.5, n (%)	234 (61.9)	39 (56.5)	54 (78.3)	104 (66.7)	37 (44.0)
3.0 - 3.49	82 (21.7)	14 (20.3)	9 (13.0)	32 (20.5)	27 (32.2)
< 3.0	62 (16.4)	16 (23.2)	6 (8.7)	20 (12.8)	20 (23.8)
uPCr (g/g) at baseline, median and IQR	1.0 [0.3 - 1.4]	0.8 [0.3 - 1.6]	1.4 [0.4 - 3.0]	0.9 [0.2 - 2.0]	1.7 [0.3 -3.4]
uPCr ≥ 3.5 (g/g), n (%)	48 (13.9)	2 (2.9)	8 (11.6)	21 (13.5)	17 (20.2)
uPCr (g/g), median and IQR^{+}	1.8 [0.5 - 3.7]	1.5 [0.5 - 2.8]	1.6 [0.3 - 3.1]	1.7 [0.5 - 3.7]	2.5 [0.4 - 6.0]
uPCr ≥ 3.5 (g/g), n (%)	102 (27.0)	11 (15.9)	15 (21.7)	43 (27.6)	33 (39.3)
Nº Hospitalizations^{++}	285 (75.4)	43 (62.3)	52 (75.4)	122 (78.2)	68 (81.0)
Inpatient diagnosis of AKI $^{+++}$	258 (68.3)	41 (59.4)	44 (63.8)	112 (71.8)	61 (72.6)

Data expressed as medians and interquartile ranges (IQR) or n (%) when appropriate.
ADPKD, Autosomal dominant polycystic kidney disease; BMI, body mass index; mCCI, modified Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; uPCr urinary protein-to-creatinine ratio (g/g); AKI, Acute Kidney Injury
uPCr urinary protein-to-creatinine ratio (g/g) at baseline
$^{+}$ uPCr most recent value before dialysis initiation
$^{++}$Nº hospitalizations, number of hospitalizations prior to dialysis initiation
$^{+++}$Among patients hospitalized at least once before dialysis initiation

Table 3. Nephrology care practices by eGFR trajectory group

	Overall n=378	Slower eGFR decline (Group 1) n=69	Gradual eGFR decline (Group 2) n=69	Early rapid eGFR decline (Group 3) n=156	Rapid eGFR decline (Group 3) n=84
Outpatient visit to a nephrologist, n (%)	346 (91.5)	69 (100.0)	59 (85.5)	151 (96.8)	67 (79.8)
Time from first nephrology visit do dialysis initiation (months) [+]	47.4 [21.0 - 92.6]	114.5 [55.2-144.1]	17.8 [9.6-28.7]	54.1 [29.5- 89.0]	34.8 [10.3 - 73.6]
eGFR[++] ≥ 15 ml/min/1.73 m^2, n (%)	11 (2.9)	0 (0)	1 (1.4)	2 (1.3)	8 (9.5)
Dialysis modality: hemodialysis, n (%)	268 (96.4)	62 (89.9)	69 (100.0)	153 (98.0)	84 (100.0)
Access at first dialysis:fistula/graft or PD catheter, n (%)	234 (61.9)	52 (75.4)	40 (58.0)	107 (68.6)	35 (41.7)
Impatient dialysis initiation, n (%)	213 (56.6)	24 (34.8)	43 (62.3)	85 (54.5)	62 (73.8)
AKI at dialysis initiation[+++]	134 (62.9)	17 (73.9)	27 (62.8)	54 (63.5)	36 (58.1)

Data expressed as medians and interquartile ranges (IQR) or n (%) when appropriate. eGFR, estimated Glomerular Filtration Rate using the Chronic Kidney Disease Epidemiology; PD, peritoneal catheter; AKI, Acute Kidney injury;
[+]Among patients referred to nephrologist;
[++] at dialysis initiation;
[+++]Among patients admitted to the hospital at dialysis initiation (n=213)

Table 4. Association of Patient Characteristics and Care Practices with the eGFR Trajectory Group

	Gradual eGFR decline (n=69)	Early rapid eGFR decline (n=156)	Rapid eGFR decline (n=84)	P for trend
Patient Characteristics				
Age ≥ 75 years	1.00 (0.51-1.96)	0.85 (0.48-1.51)	0.50 (0.26-0.95)*	0.096
Male	0.58 (0.29 -1.15)	0.66 (0.36-1.18)	0.44 (0.23-0.85)*	0.104
Diabetes	1.70 (0.86-3.35)	1.83 (1.03-3.27)*	2.56 (1.33-4.92)*	0.045*
Coronary artery disease	1.18 (0.53-2.60)	1.75 (0.90-3.39)	2.11 (1.02-4.34)*	0.137
Congestive heart failure	1.28 (0.64-2.53)	1.10 (0.62-1.96)	1.92 (0.98-3.79)	0.208
Cardiac arrhythmia	0.43 (0.17-1.10)	1.34 (0.70-2.59)	1.10 (0.52-2.33)	0.058
Stroke	0.93 (0.45-1.94)	1.08 (0.58-1.99)	1.03 (0.51-2.04)	0.974
Peripheral vascular disease	0.73 (0.36-1.47)	1.23 (0.69-2.20)	0.86 (0.45-1.67)	0.306
Pulmonary disease	1.72 (0.74-4.02)	1.15 (0.54-2.48)	0.90 (0.45 2.50)	0.529
Cancer	1.00 (0.43-2.35)	0.71 (0.33-1.50)	0.65 (0.27-1.56)	0.625
Cognitive impairment	1.33 (0.47-3.80)	1.38 (0.56-3.41)	2.95 (1.17-7.44)*	0.049*
Diabetes as a cause of ESRD *vs.* others	1.74 (0.83-3.63)	2.07 (1.10-3.91)*	2.41 (1.20-4.83)*	0.078
uPCr ≥ 3.5 (g/g)	4.9 (1.00-24.2)*	5.2 (1.19-22.9)*	10.5 (2.31-47.4)*	0.013*
Hospitalized within 1-year before dialysis	1.85 (0.89-3.85)	2.17 (1.17-4.02)*	2.57 (1.24-5.33)*	0.043*
Inpatient diagnosis of AKI[+]	0.41 (0.10-1.66)	0.84 (0.22-3.21)	0.65 (0.16-2.68)	0.473
Care practices at or before initiation				
Outpatient visit to a nephrologist[++]	0.65 (0.17-2.40)	0.50 (0.16-1.54)	0.51 (0.1-1.74)	0.653
Vascular access placement [+++]	0.52 (0.25-1.09)	0.80 (0.42-1.54)	0.27 (0.13-0.55)*	<0.001*
Inpatient dialysis initiation	3.31 (1.65-6.65)*	2.39 (1.33-4.33)*	5.64 (2.81-11.3)*	<0.001*
AKI at dialysis initiation[++++]	0.59 (0.19-1.82)	0.62 (0.22-1.72)	0.49 (0.17-1.41)	0.615

All dependent variables were categorized in yes vs. no. Values shown are odds ratio (95% confidence interval); trajectory reference group is persistently low eGFR (Group 1, n=378).
AKI, acute kidney injury; ESRD, end-stage renal disease; uPCr urinary protein-to-creatinine ratio (g/g);
[+] Inpatient diagnosis of AKI among patients hospitalized at least once before starting dialysis initiation;
[++] Outpatient visit to a nephrologist before dialysis initiation;
[+++] Vascular access placement among patients who initiated hemodialysis;
[++++] Among patients who initiated dialysis during an inpatient admission

Table 5. Multivariable adjusted multinomial logistic regression analysis for the associations of demographic and clinical factors with trajectories eGFR decline

Variables	Gradual eGFR decline (Group 2) n=69			Early rapid eGFR decline (Group 3) n=156			Rapid eGFR decline (Group 4) n=84		
	β	aOR (95%CI)	*p*-Value	β	aOR (95%CI)	*p*-Value	β	aOR (95%CI)	*p*-Value
Age (<75 vs. ≥75 yrs)	0.079	1.082 (0.543–2.157)	0.823	0.241	1.272 (0.705–2.294)	0.424	0.852	2.345 (1.182–4.652)	0.015*
Gender (female vs. male)	0.570	1.768 (0.881–3.548)	0.109	0.460	1.585 (0.868–2.893)	0.134	0.961	2.615 (1.313–5.206)	0.006*
Diabetes (yes vs. no)	0.597	1.816 (0.912–3.617)	0.090	0.650	1.916 (1.060–3.461)	0.031*	1.007	2.736 (1.379–5.431)	0.004*
Cognitive impairment (yes vs. no)	0.306	1.358 (0.470-3.927)	0.572	0.360	1.434 (0.571–3.601)	0.443	1.239	3.451 (1.320–9.026)	0.012*
Hospitalized within 1-year before dialysis (yes vs. no)	0.582	1.789 (0.850–3.765)	0.125	0.763	2.145 (1.142–4.028)	0.018*	0.976	2.653 (1.231–5.717)	0.013*

Values show the risk profile (aOR) for each trajectory group compared to trajectory Group 1 (slower decline). Predictors starred* are those that were statistically significant. aOR, adjusted odds ratio in relation to all the other variables in the table; CI, confidence interval.

Table 6. Adjusted Risk of Death Over Different Periods After Dialysis Initiation by Trajectory Group using Cox proportional hazards regression model

Follow-up Time	Gradual eGFR decline (Group 2) n=69		Early rapid eGFR decline (Group 3) n=156		Rapid eGFR decline (Group 4) n=84)	
	aHR (95%CI)	*p*-Value	aHR (95%CI)	*p*-Value	aHR (95%CI)	*p*-Value
< 1 year	0.584 (0.213-1.601)	0.296	0.549 (0.211-1.426)	0.218	1.185 (0.473-2.973)	0.717
1 to 4 years	1.653 (0.830-3.292)	0.153	1.805 (1.005-3.243)	0.048*	3.260 (1.693-6.277)	<0.001*
> 4 years	3.628 (1.171-11.24)	0.026*	4.259 (1.468-12.35)	0.008*	6.347 (1.868-21.56)	0.003*

Values shown are adjusted hazard for death (95% confidence interval); referent group is slower eGFR decline (group 1). Adjusted for demographic characteristics (age and gender), diabetes, cognitive status and hospitalization during the 1-year period before dialysis initiation. Abbreviation: eGFR, estimated glomerular filtration rate.; aHR, adjusted hazard ratio; CI, confidence interval.

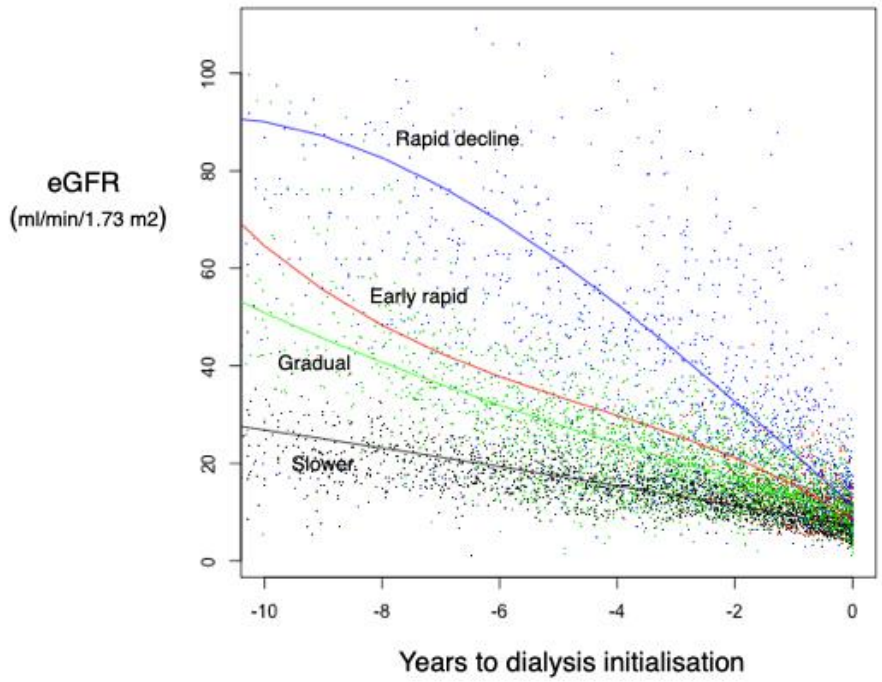

Figure 1. Trajectories decline for the identified groups

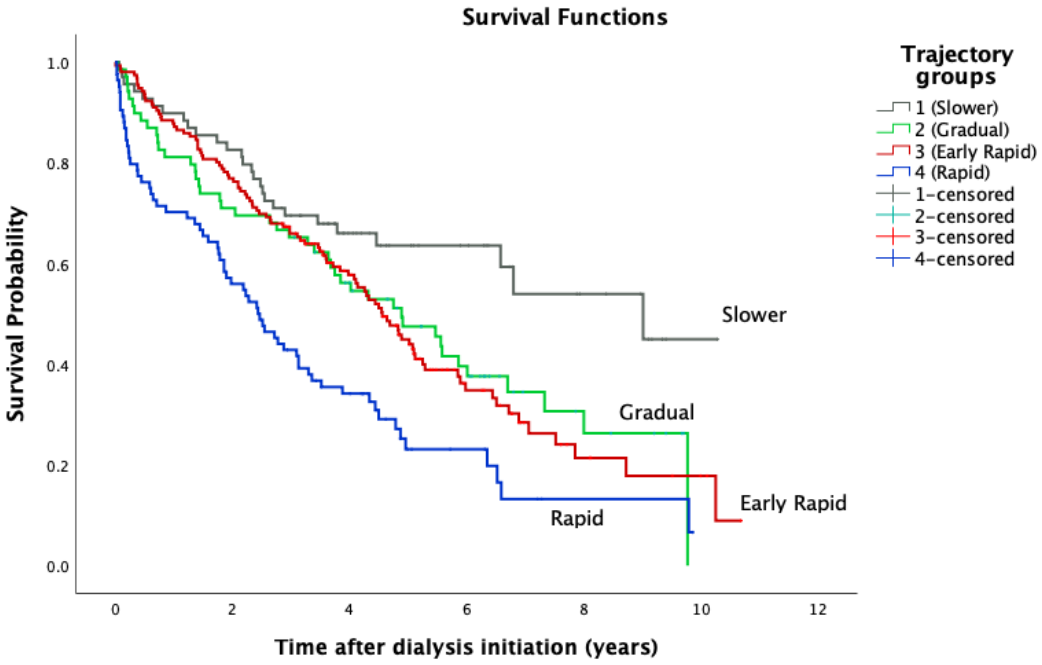

Figure 2: Kaplan-Meier survival curves after dialysis initiation by eGFR trajectory group.

APPENDIX 4

Predicting 6-Month Mortality in Incident Elderly Dialysis Patients: A Simple Prognostic Score.

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Research Article

Predicting 6-Month Mortality in Incident Elderly Dialysis Patients: A Simple Prognostic Score

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Keywords
Elderly · End-stage renal disease · Dialysis · Prognosis score · Shared decision making

Abstract
Aim: Mortality in end-stage renal disease (ESRD) remains high, particularly among elderly, who represents the most rapidly growing segment of the ESRD population in wealthier countries. We developed and validated a risk score in elderly patients to predict 6-month mortality after dialysis initiation. ***Methods:*** We used data from a cohort of 421 patients, aged 65 years and over who started dialysis between 2009 and 2016, in our Nephrology department. The predictive score was developed using a multivariable logistic regression analysis. A bootstrapping technique was used for internal validation. ***Results:*** The overall mortality within 6 months was 14.0%. Five independent predictors were identified, and a points system was constructed: age 75 years or older (2 points), coronary artery disease (2), cerebrovascular disease with hemiplegia (2), time of nephrology care before dialysis (<3.0 months [2]; ≥3 to <12 months [1]), and serum albumin levels (3.0–3.49 g/dL [1]; <3.0 g/dL [2]). A score of 6 identified patients with a 70% risk of 6-month mortality. Model performance was good in both discrimination (area under the curve of 0.793; [95% CI 0.73–0.86]) and validation (concordance statistics of 0.791 [95% CI 0.73–0.85]). ***Conclusions:*** We developed a simple prediction score based on readily available clinical and laboratory data that can be a practical and useful tool to assess short-term prognosis in elderly patients starting dialysis. It may help to inform patients and their families about ESRD treatment options and provide a more patient-centered overall approach to care.

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Introduction

One of the challenges to clinicians caring for older chronic kidney disease (CKD) patients expected to progress to end-stage renal disease (ESRD) lies in the evaluation of the overall benefit of offering renal replacement therapy (RRT) to them. Although survival may have improved over time for older patients initiating dialysis [1], in those patients with high comorbidity, dialysis did not offer better survival compared to conservative management [2], with an overall decline in functional and cognitive status [3], and more hospitalizations [4].

For evaluating RRT benefits and risks and informing patients and their families about ESRD treatment options, there is a growing interest in developing predictive mortality models [5–10].

Portugal has the highest unadjusted incidence and prevalence of ESRD among European countries [11]. Although several scoring systems focused on older adults have been developed in other countries [7–10], they may be unsuitable for widespread application due to unproven generalizability.

We aimed to develop and validate a simple predictive risk score of early death after initiating dialysis using readily available variables to help the decision of initiating dialysis among elderly patients.

Methods

We conducted a retrospective cohort study of patients aged 65 years and over, referred to the Nephrology Department in Centro Hospitalar do Porto (CHP), who started dialysis as their first RRT, between January 2009 and December 2016. CHP is a tertiary-care hospital, which serves a diverse population of 500,000 inhabitants in the Northern region of the country.

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of CHP.

Data were collected from medical records purposely for this study and included (at dialysis initiation): sex, age, weight, height, body mass index (BMI), medication, associated comorbid conditions, such as diabetes, dyslipidemia, hypertension, smoking status, history of malignancy, and cardiovascular disease (CVD). CVD included coronary artery disease, congestive heart failure (New York Heart Association stages I–IV), arrhythmia, peripheral artery disease, and cerebrovascular disease. Coronary artery disease was defined as a previous myocardial infarction, coronary artery bypass grafting, or coronary stent implantation. Peripheral artery disease was defined as the presence of intermittent claudication or with the need of peripheral revascularization or amputation. Cerebrovascular disease included both previous transient ischemic attacks and stroke, with or without hemiplegia.

Glomerular filtration rate (GFR) was estimated using the CKD Epidemiology 2009 creatinine equation [12]; all serum creatinine measurements were performed in the same laboratory calibrated using a calibrator for automated systems (*Roche Diagnostics*). Etiological diagnosis of CKD was based on the patient's history, kidney ultrasound, and kidney biopsy, when available.

Cognitive status was evaluated using the Mini Mental State Examination [13] with cognitive impairment defined for scores ≤23. Functional dependency was defined as the requiring of assistance for transfer, classified as totally dependent or need assistance for transfer and autonomous.

A modified version of the Charlson comorbidity index (mCCI) [14], that is, by excluding subject's age and presence of kidney disease, was calculated and subdivided into 3 subgroups (0–2, 3–4, ≥5).

Kidney & Blood Pressure Research

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Variables related to renal care included timing of nephrologist care prior to dialysis, dialysis modality, and vascular access (graft/fistula versus catheter) were collected. Timing of nephrologist care before dialysis was divided: under 3 months, between 3 and 12, and higher than 12 months. Late referral was defined as the first encounter with a nephrologist occurring within 3 months of the dialysis initiation. Unplanned dialysis was defined as any first treatment started for an emergency condition or not appropriate to delay for >24 h, even if a permanent dialysis access in place.

Since nephrology referral until RRT initiation, the number and reasons for hospitalizations were registered.

The study outcome was all-cause mortality within first 6 months following dialysis therapy initiation. Vital status was checked annually until August 30, 2017.

Statistical Analysis

Descriptive statistics on candidate predictors and the outcome variable are presented as median and interquartile range or percentage as appropriate.

Except for BMI (28 missing values), there was no missing among candidate predictors. Thus, no missing imputation approach was done in this study.

All p values are two-tailed. A p value <0.05 is considered to indicate statistical significance. Analyses were conducted with the use of the statistical package SPSS 24.0 (SPSS, Inc., Chicago, IL, USA) and STATA 13.0.

Model Development

Using 6-month mortality after dialysis initiation as the dichotomous outcome variable, several risk factors were first examined by univariable logistic regression: age (continuous or categorized as ≥75 vs. <75 year), sex, BMI (continuous or categorized as <25, 25–30, >30 kg/m^2), primary renal disease (diabetic nephropathy, autosomal dominant polycystic kidney disease, ischemic nephropathy, others and unknown vs. glomerulonephritis; diabetic nephropathy vs. other renal disease), smoking (current vs. former/never smoker), laboratory data (serum urea, serum creatinine, eGFR, and serum albumin), hypertension, diabetes mellitus, dyslipidemia, CVD history, chronic hepatic disease, chronic pulmonary disease, autoimmune disease, peptic ulcer, malignancy, mCCI, cognitive status (cognitive impairment/dementia vs. normal), dependency for transfer (totally dependent, need assistance vs. autonomous), institutionalized (yes vs. no), hospitalizations on 6 months prior to dialysis initiation (number and categorized as yes and no), and referral time (under 3 months, between 3 and 12, and higher than 12 months). Infection by hepatitis B, hepatitis C, and HIV was not tested due to small number of cases.

Variables that had an association with the outcome measure with a p value <0.2 were selected for multivariable analysis. Continuous predictor variables were categorized as appropriate for simplicity in clinical use and to allow assignment of integer points, namely, age, eGFR, BMI, serum albumin, and referral time. Multivariable models were then built using backward selection [15, 16]. Multicollinearity was checked using the variance influence factor.

Risk Scoring System

Considering the number of outcomes (n = 60) and the number of candidate predictors, the β-coefficients derived from final multivariable model were multiplied by a heuristic shrinkage factor to adjusting for overfitting [17–19]. The shrunken β-coefficients of the predictors in the final model were then divided by two-fifths of the 2 small β-coefficients in the model and rounded up to the nearest integer to give a simple point score [17].

Kidney & Blood Pressure Research

Kidney Blood Press Res 2020;45:38–50
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Model Validation

The discrimination of the risk score was evaluated using the area under the receiver-operating characteristic curve (AUC). Due to the relatively small size of our cohort, we did not divide the cohort into derivation and validation samples. A bootstrapping procedure was used to internally validate the risk score and determine optimism [8, 18, 19].

Risk Scores Comparison

The developed risk score in our work and Couchoud score [7] were calculated for each patient in order to determine the performance of each scoring system in predicting mortality. The discrimination of each scoring system was assessed and compared using AUC.

Results

Patient Characteristics at Baseline

Our study cohort included 421 individuals aged 65 years or older who started dialysis, during the study period. Table 1 shows their baseline characteristics, stratified by mortality status at 6 months after initiating dialysis. Their mean age was 75.5 ± 6.3 years, 195 patients (46%) were female, about 50% were diabetic, and 97% of patients had eGFR of <15 mL/min/1.73 m^2 at time of dialysis initiation. Most participants (98%) were on hemodialysis. About 34% of participants had been hospitalized in the 6 months prior to dialysis initiation. More than half of our patients that started dialysis in life-threatening circumstances (n = 140; 56%) were timely referred to a nephrologist (≥12 months).

Predictors of 6-Month Mortality

A total of 60 patients (14%) died within 6 months of starting dialysis. Table 2 shows the results of univariable logistic regression analyses associated with mortality within 6 months after starting dialysis. Briefly, patients who died were more likely to be older and female and to have experienced any of the following conditions: an unplanned dialysis, being late referral, higher eGFR, lower albumin, need of assistance for transfer, cognitive impairment, to have been institutionalized, to have coronary artery disease, congestive heart failure, arrhythmia, cerebrovascular disease with hemiplegia, and higher mCCI. They were also more likely to have a hospital stay in the 6 months preceding dialysis initiation.

Multivariable logistic regression analyses with backward elimination procedure showed that the following variables were retained in the final model: age, coronary artery disease, cerebrovascular disease with hemiplegia, serum albumin level, and referral time (Table 3). Among the 16 candidate predictors (Table 2), unplanned dialysis was not included in the multivariable analysis, because we considered that the final model intended to be a tool also for those patients for whom the dialysis was not scheduled. The remaining 15 variables were divided in 3 sets of 5 candidate predictors, and backward elimination was applied separately to each set. Predictors that were selected in all of the 3 data sets were chosen as the final set of selected predictors. In each set of 5 variables, multicollinearity was checked, as well as the 10 variables included in the final model. The variance inflating factors were all near 1 (the maximum variance influence factor was 1.519).

Based on the number of 6-month deaths (n = 60), the combination of 5 predictors was considered reasonably fitted to the final multivariable regression model. A Hosmer and Lemeshow goodness-of-fit test was not statistically significant, indicating good calibration of the model (χ^2, 7 degrees of freedom = 5.624; p = 0.584; Table 3).

Kidney & Blood Pressure Research

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Table 1. Demographic and clinical characteristics of study cohort

	Overall (n = 421)	Died within 6 months (n = 60)	Did not die within 6 months (n = 361)
Age, years	75.5 (70–80)	77.9 (73–84)	75.1 (70–80)
Age ≥75 years	217 (51.5)	42 (70.0)	175 (48.5)
Gender, female	195 (46.3)	33 (55.0)	162 (44.9)
Primary renal disease			
Diabetic nephropathy	156 (37.1)	24 (40.0)	132 (36.6)
Ischemic nephropathy	69 (16.4)	10 (16.7)	59 (16.3)
Glomerulonephritis	50 (11.9)	4 (6.7)	46 (12.7)
ADPKD	21 (5.0)	1 (1.7)	30 (5.5)
Other	73 (17.3)	16 (26.7)	57 (15.8)
Unknown etiology	52 (12.4)	5 (8.3)	47 (13.0)
BMI, kg/m^2	26 (23–29)	28 (22–28)	26 (24–29)
<25	170 (40.4)	27 (45)	143 (39.6)
25–30	148 (35.2)	22 (36.7)	126 (34.9)
>30	75 (17.8)	8 (13.3)	67 (18.6)
Cognitive impairment	63 (15.0)	16 (26.7)	47(13.0)
Totally dependent for transfer	37 (8.8)	12 (20.0)	25 (6.9)
Need assistance for transfer	188 (44.7)	32 (53.3)	156 (43.2)
Autonomous	196 (46.6)	16 (26.7)	180 (49.9)
Institutionalization	22 (5.2)	7 (11.7)	15 (4.2)
mCCI	3.8 (2–5)	4.7 (3–7)	3.7 (2–5)
0–2	127 (30.1)	11 (18.3)	116 (32.1)
3–4	130 (30.9)	17 (28.3)	113 (31.3)
≥5	164 (39.0)	32 (53.3)	132 (36.6)
Current/former smoking	96 (22.8)	13 (21.7)	83 (23.3)
Diabetes	212 (50.4)	32 (53.3)	180 (49.9)
Hypertension	409 (97.1)	58 (96.7)	351 (97.2)
Dyslipidemia	375 (89.1)	52 (86.7)	323 (89.5)
Congestive heart failure	262 (62.2)	45 (75.0)	217 (60.1)
Coronary artery disease	126 (29.9)	25 (41.7)	101 (28.0)
Cardiac arrhythmia	101 (24.0)	20 (33.3)	81 (22.4)
Cerebrovascular disease	137 (32.5)	20 (33.3)	117 (32.4)
With hemiplegia	43 (10.2)	10 (16.7)	33 (9.1)
Peripheral vascular disease	165 (39.2)	25 (41.7)	140 (38.8)
Neoplasia	64 (15.2)	10 (16.7)	54 (15.0)
COPD	74 (17.6)	14 (23.3)	60 (16.6)
Chronic liver disease	30 (7.1)	5 (8.3)	25 (6.9)
Autoimmune disease	16 (3.8)	1 (1.7)	15 (4.2)
Peptic ulcer	62 (14.7)	8 (13.3)	54 (14.9)
Albumin <3.5 g/dL	3.6 (3.2–4.0)	3.1 (2.8–3.5)	3.6 (3.3–4.0)
≥3.5	255 (60.6)	19 (31.7)	236 (65.4)
3.0–3.49	87 (20.7)	15 (25.0)	72 (19.9)
<3.0	79 (18.8)	26 (43.3)	53 (14.7)
Creatinine, mg/dL	6.3 (4.7–7.5)	6.1 (4.3–7.4)	6.3 (4.9–7.5)
eGFR EPI, mL/min/1.73 m^2	7 (5–8)	8 (5–9)	7 (5–8)
≥15	12 (2.9)	5 (8.3)	7 (1.9)
10–14.9	43 (10.2)	4 (6.7)	39 (10.8)
<10	366 (86.9)	51 (85.0)	315 (87.3)
Time of nephrology care before dialysis, months			
<3	83 (19.7)	28 (46.7)	55 (15.2)
≥3 to <12	43 (10.2)	7 (11.7)	36 (10.0)
≥12	295 (70.1)	25 (41.7)	270 (74.8)
Dialysis modality: hemodialysis	411 (97.6)	60 (100.0)	351 (97.2)
Unplanned dialysis	249 (59.1)	53 (88.3)	196 (54.3)
Access at first dialysis: catheter	181 (42.9)	47 (78.3)	134 (37.1)
Hospitalizations 6-months before dialysis	144 (34.2)	24 (40.0)	120 (33.2)
Hospitalizations per patient	0.46 (0.00–1.00)	0.72 (0.00–1.00)	0.41 (0.00–1.00)

Data expressed as medians and interquartile ranges (IQR) or n (%) when appropriate.

BMI, body mass index; mCCI, modified Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate using the chronic kidney disease epidemiology; n hospitalizations, number of hospitalizations based on 6 months prior to dialysis initiation.

Kidney & Blood Pressure Research

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Table 2. Results of the univariable logistic regression for 6-month mortality

	OR	95% CI	*p* value
Age (per 1-year older)	1.07	1.03–1.12	0.002
Age category (≥75 vs. <75 years)	2.48	1.37–4.47	0.030
Gender, female vs. male	1.50	0.87–2.60	0.147
Primary renal disease (ref. glomerulonephritis)			
Diabetic nephropathy	2.09	0.69–6.35	0.193
Ischemic nephropaty	0.56	0.06–5.47	0.630
ADPKD	1.95	0.57–6.62	0.284
Others	3.23	0.02–1.43	0.048
Unknown etiology	1.22	0.31–4.84	0.774
Cognitive status (impairment/dementia vs. normal)	2.43	1.27–4.65	0.007
Functional dependency (ref. autonomous)			
Totally dependent for transfer	5.40	2.3–12.7	<0.001
Need assistance for transfer	2.31	1.22–4.37	0.010
Institutionalization (yes vs. no)	3.05	1.19–7.82	0.021
mCCI score (per 1 unit greater)	1.23	1.08–1.39	0.002
m CCI score category (ref. 0–2)			
3–4	1.59	0.71–3.54	0.259
≥5	2.56	1.23–5.30	0.012
Congestive heart failure (yes vs. no)	1.99	1.07–3.71	0.030
Coronary artery disease (yes vs. no)	1.84	1.05–3.23	0.034
Cardiac arrhythmia (yes vs. no)	1.73	0.96–3.12	0.070
Cerebrovascular disease with hemiplegia	1.99	0.92–4.28	0.079
Albumin (per 1 g/dL greater)	0.30	0.19–0.47	<0.001
Albumin category (ref. ≥3.5 g/dL)			
3.0–3.49 g/dL	2.59	1.25–5.35	0.010
<3.0 g/dL	6.09	3.14–11.8	<0.001
eGFR-EPI (per 1 mL/min/1.73 m^2 greater)	1.09	1.00–1.18	0.047
eGFR-EPI category (ref. ≥15 mL/min/1.73 m^2)			
10–14.9 mL/min/1.73 m^2	0.14	0.03–0.67	0.014
<10 mL/min/1.73 m^2	0.23	0.07–0.74	0.014
Time of nephrology care before dialysis (ref. ≥12 months)			
<3	5.49	2.98–10.14	<0.001
≥3 to <12	2.10	0.85–5.20	0.109
Unplanned dialysis[‡]	6.4	2.8–14.4	<0.001
Hospitalizations in 6 months before dialysis			
(per 1 hospitalization greater)	1.80	1.35–2.39	<0.001
Hospitalizations in 6 months before dialysis (yes vs. no)	4.01	1.77–9.08	0.002

[‡] Unplanned dialysis was not included in the multivariable model, as explained in Discussion section.

This table includes only the variables that showed a univariable association ($p < 0.20$) with 6-month mortality and then selected for multivariable logistic model.

mCCI, modified Charlson Comorbidiy Index; eGFR EPI, estimated glomerular filtration rate using the chronic kidney disease epidemiology equation; ADPKD, autosomal dominant polycystic kidney disease.

Derivation and Internal Validation of Risk Score

The risk score derived is displayed in Table 4, ranging 0–10 points. The score was calculated for each patient of our study sample (median risk score = 2). The distribution of patients and mortality according to score is presented in Table 5. As an example, a score of 5 identified patients with a 50% risk of 6-month mortality (Fig. 1).

A risk assessment questionnaire for clinicians and patients' use is shown in Figure 2, exposing a simple method for establishing a patient's risk for the outcome depending on an individual's status for the 5 variables included in the tool.

Kidney & Blood Pressure Research

Kidney Blood Press Res 2020;45:38–50
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Table 3. Multivariable logistic regression model for 6-month mortality

	Regression Coefficient	Adjusted OR	95% CI	*p* value
Age category (≥75 vs. <75 years)	0.97	2.63	1.38–5.02	0.003
Coronary artery disease (yes vs. no)	0.93	2.54	1.35–4.79	0.004
Cerebrovascular disease with hemiplegia (yes vs. no)	0.95	2.58	1.07–6.21	0.035
Albumin category (ref. ≥3.5 g/dL)				
3.0–3.49 g/dL	0.85	2.35	1.09–5.05	0.029
<3.0 g/dL	1.46	4.31	2.07–8.97	<0.001
Time of nephrology care before dialysis (ref. ≥12 months)				
<3.0 months	1.41	4.09	2.06–8.12	<0.001
≥3 to <12 months	0.63	1.88	0.72–4.90	0.199
Intercept	−3.91	0.18		
C-statistic: 0.793				
Hosmer-Lemeshow test: $p = 0.584$				

Variables were retained in the model using backward elimination (Wald) procedure.

Table 4. Predictors of 6-month mortality and associated risk scoring system

	Shrunken β-regression coefficient[‡]	*Risk score*[§]
Age category (≥75 vs. <75 years)	0.86	2
Coronary artery disease (yes vs. no)	0.83	2
Cerebrovascular disease with hemiplegia (yes vs. no)	0.84	2
Albumin category (ref. ≥3.5 g/dL)		
3.0–3.49 g/dL	0.76	1
<3.0 g/dL	1.30	2
Time of nephrology care before dialysis (ref. ≥12 months)		
<3.0 months	1.26	2
≥3 to <12 months	0.56	1

[‡] Original β-regression coefficient multiplied by heuristic shrinkage factor.
[§] Scores assigned by dividing the shrunken β-regression coefficients by 0.528 (two-fifths of the 2 small β-coefficients in the model) and rounded to nearest integer.

Table 5. Distribution of patients and mortality according to score

Score	0	1	2	3	4	5	6
Patients, *n* (%)	61 (14.5)	121 (28.7)	112 (26.6)	52 (12.4)	43 (10.2)	25 (5.9)	7 (1.7)
Deaths, *n* (%)	2 (3.3)	4 (6.7)	13 (21.7)	8 (13.3)	16 (26.7)	13 (21.7)	4 (6.7)

The predictive discrimination of 6-month mortality was good, with an AUC of 0.793 (95% CI 0.73–0.86). A bootstrapping procedure was performed (5,000 bootstrap samples) to internally validate the risk score, which generated a concordance statistics of 0.791 (95% CI 0.73–0.85) and an optimism of 0.002.

Kidney & Blood Pressure Research

Kidney Blood Press Res 2020;45:38–50
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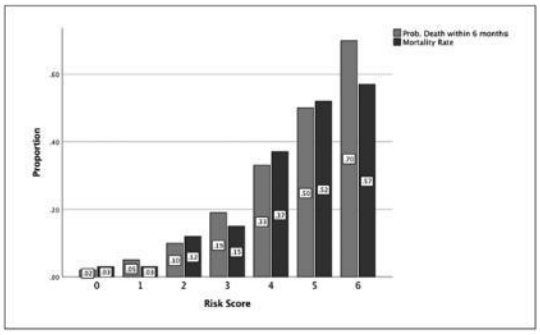

Fig. 1. Mean predicted mortality risks and observed proportions for ranges of total scores. Prognostic score calculated form the following 5 items well predicts 6-month mortality after maintenance dialysis initiation: age 75 years or older, coronary artery disease, cerebrovascular disease with hemiplegia, time of nephrology care before dialysis, low serum albumin levels.

6-months mortality predictors	Assigned Points
Age (years) Points < 75 ..... 0 ≥ 75 2	
Coronary artery disease 2	
Cerebrovascular disease with hemiplegia 2	
Albumin (g/dL) ≥ 3.5 .....0 3.0 - 3.49 ..... 1 < 3.0 2	
Time of nephrology care (months) ≥ 12 .....0 ≥ 3 to < 12 ..... 1 < 3.0 2	

Total Score

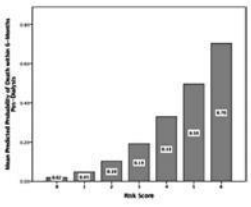

Fig. 2. Score chart to predict 6-month mortality risk after dialysis initiation. Points correspond to each predictor value and are added to give a total score. Points along the X-axis of the plot correspond to approximate probability of mortality within 6 months along the Y-axis.

Comparison with Alternative Risk Scores

Couchoud score [7] was calculated for all patients in our cohort according to corresponding formula, and the AUC was 0.704 (95% CI 0.64–0.77). In this cohort, the performance of our score was significantly higher than Couchoud score ($p = 0.026$; Fig. 3). It can be seen that the curve from our score is always above the curve of the Couchoud scale. Therefore, for this particular set of individuals, our score discriminates better between survived and deceased patients. Stated in other way, for a given specificity, our severity score always presents a better sensitivity.

Kidney & Blood Pressure Research

Kidney Blood Press Res 2020;45:38–50
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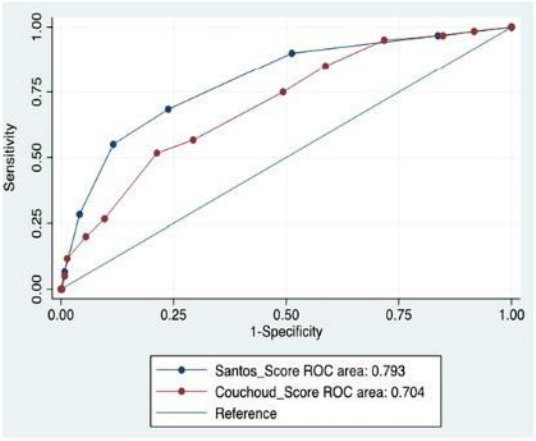

Fig. 3. Comparison of receiver operating characteristics curves for predicting 6-month mortality after starting dialysis, among our (Santos) and Couchoud scores. ROC, receiver operating characteristics.

Discussion

The prognostic score for early mortality developed in this study, defined as death in the 6 months after starting dialysis, is based on simple and ready available information.

Five predictors of 6-month mortality (and their associated scores) were identified: age 75 years or older (2 points), coronary artery disease (2 points), cerebrovascular disease with hemiplegia (2 points), time of nephrology care before dialysis (<3.0 months [2 points]; ≥3 to <12 months [1point]), and low serum albumin (3.0–3.49 g/dL [1 point]; <3.0 g/dL [2 points]).

In the past years, numerous scores of mortality on dialysis have been developed on the basis of various combinations of comorbidities and laboratory data, but only a few of them focused on short-term survival including only elderly patients [7–10].

Couchoud et al. [7] using just clinical features, based on the French registry data, predicted 6-month mortality in elderly (≥75 years) after initiating dialysis. Of the risk factors selected in that model [7], diabetes, peripheral vascular disease, and malignancy were not associated with 6-month mortality in our cohort.

Although diabetes is an important predictor of mortality in CKD patients, in our cohort, diabetes was not associated with early mortality. This agrees with other authors [8–10], and it can be explained by the fact that in our cohort, the burden of other comorbidities in elderly, such as coronary artery disease and cerebrovascular disease, also late complications of diabetes, diminish the significance of diabetes as a predictor of early mortality in ESRD patients.

Congestive heart failure, arrhythmia, and severe behavioral disorder (similar to dementia in our study) were associated with 6-month mortality but were not retained in our final model. This reveals the dissimilarities of the populations used to construct scores.

About 59% of our patients started with unplanned dialysis, which was not surprisingly associated with high mortality risk, with significantly elevated odds of 6-month mortality, like in Couchoud model [7]. More than half (n = 140; 56%) of those patients who started with unplanned dialysis were timely referred to nephrologist (≥12 months). This can be explained by the fact that this elderly population with high comorbidity has several acute intercurrent illness, which precipitates the need to initiate dialysis.

Kidney & Blood Pressure Research

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Keeping this in mind, we decided not to include unplanned dialysis in the multivariable analysis, because our final model intended to be a supporting tool even in those patients for whom the dialysis was not scheduled.

More recently, using also the French registry, Couchoud et al. [8] chose to focus on very early mortality (first 3 months of dialysis), in elderly patients. Thamer et al. [10] also focused in early mortality in the first 3 and 6 months using the US Renal Data System proposed a risk score for patients aged ≥67 years. Like these 2 scores [8, 10] in our study, age older than 75 and low albumin level were strongly associated with 6-month mortality.

The independent association between hypoalbuminemia and mortality in ESRD was first described in 1990 by Lowrie et al. [20], when a serum albumin <4 g/dL was found to be associated with increased risk for death in dialysis patients. Hypoalbuminemia might indicate malnutrition, but is an important biomarker of acute illness or inflammatory state [21]. Therefore, a multidisciplinary approach, including pre- and post-dialysis management for nutrition, but also dealing with the cause of hypoalbuminemia, might improve survival after initiation of dialysis.

CVD remains the most common cause of mortality in ESRD patients and coronary artery disease is the most frequent cause of cardiovascular death in those patients [22]. The prevalence of CVD in our cohort was very high related to high prevalence of many established risk factors of CVD (diabetes, hypertension, dyslipidemia), also present in our patients.

We have shown that the presence of clinically manifest CVD such as coronary artery disease and cerebrovascular disease with hemiplegia had a significant impact on 6-month mortality within starting dialysis. These 2 variables were not considered or were not predictive in previous models in elderly ESRD patients [7–10]. The presence of cerebrovascular disease with hemiplegia may also reflect the impact of frailty in mortality of CKD patients [23] related to the functional dependency of these patients. These factors provide further evidence of the importance, beyond the usual clinical criteria, of incorporating in the RRT decisions in elderly the assessment of physical and cognitive function, and other components of geriatric syndrome.

Recently, Wick et al. [9] developed a score to estimate mortality risk during the next 6 months for older patient initiating dialysis. They used a large population-based data source in outpatient settings to derive a score in patients 65 years and older, and not only in patients 75 years and older. This is important because as it happens in our cohort, there is an equal number of adults aged 65–74 years who initiate maintenance dialysis therapy as those 75 years and older.

Their final model for 6-month mortality [9] included 7 predictors: age (≥80 years), increased eGFR, hospitalization in the prior 6 months, atrial fibrillation, congestive heart failure, metastatic cancer, and lymphoma. None of those variables except older age were strongly predictive in our score, which could be related to differences in the populations from which they were derived. Namely, the incorporation of variables such as lymphoma or metastatic cancer, as mortality predictors, may add clinical utility in contexts in which these conditions appear with reasonable frequency.

In our study, time of nephrology care before dialysis initiation was strongly predictive of early mortality, particularly within 3 months prior to dialysis initiation, but also between 3 and 12 months, compared to >12 months. Several studies have demonstrated that late referral to nephrologist care was a major reason for higher morbidity and mortality on dialysis. This lack of timely evaluation, defined as adequate evaluation to allow for patient and family education, management, and preparation for RRT (e.g., creation of a permanent access) is particularly common in elderly patients [24, 25]. Although there is no universally accepted definition of timely referral of patients with CKD, considering a period of 12 months as adequate to provide an acceptable nephrology care [25] was consistent with

Kidney & Blood Pressure Research

Kidney Blood Press Res 2020;45:38–50
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our results. The appropriate timing of referral is often difficult for nonnephrology physicians. Especially in elderly patients, primary care physicians and nonnephrology specialists were less likely to refer patients to nephrologists than nephrologists were to accept patients for dialysis [26].

Nephrologists should make an effort to support the local network that links primary health-care providers and nephrologists, with improved referral guidelines, and open communication between nephrologists and referring physicians.

With respect to model performance, the proximity of the AUC generated by bootstrapping procedure to the observed AUC and a very acceptable optimism indicate a good discrimination ability of our score. In our population, the performance of our risk score was significantly higher than Couchoud score [7], which reinforces the need to develop predictive scores adapted to the specificities of each population.

To our knowledge, this is the first prognostic score for predicting early death in elderly ESRD patients initiating dialysis that have been developed and internally validated in a Portuguese population. Furthermore, we consider that they are a representative group of the elderly ESRD patients that start dialysis in our country. Differences in our patients' profile, namely, distinct sociodemographic and clinical characteristics compared to other countries, highlight the clinical specificity of our score and the dissimilarities from the other populations used to develop and derive prognostic scores.

Portugal has the highest unadjusted incidence and prevalence of ESRD among European countries [11]. In a recent review [27], elaborated on the factors that potentially underlying observed international differences in CKD prevalence in the elderly, the authors concluded that Portugal had the highest estimate of CKD prevalence, and also the highest average score on CKD risk factors (i.e., diabetes mellitus, raised blood pressure, physical inactivity, and salt intake).

Another important issue is the age pattern at the beginning of RRT. In Portugal, about 62% of the incident dialysis patients in 2016 were over 65 years with a mean age of 67 years for prevalent patients [28] being one of the oldest in the European registry [11]. In countries with lower RRT incidence, the median age at the start of RRT appears to be lower, suggesting that countries with higher RRT incidence, such as Portugal, start older patients in RRT and this may contribute to differences in RRT epidemiology between countries [29]. In this respect, there is an urgent need for concrete evidence on the relative advantages of conservative treatment versus RRT in the elderly.

There are some limitations of our study. First, this is a single-center retrospective study. Second, our population consisted of incident dialysis patients that were referred to nephrologists. Those who were not referred, not selected for, or not accept to dialysis initiation, were not included. Our model may, therefore, not be generalizable to the entire population of elderly ESRD patients and should not be used to withhold dialysis. Third, despite the internal validation, our model has not been externally validated, which should be a requisite before this tool should be promoted for use in clinical practice. At this moment, our score is being tested in our unit, and it will be applied during the next year with the incident patients and will be subsequently assessed the results.

In conclusion, we have developed and internally validated a predictive risk score for early mortality for elderly CKD patients who initiate dialysis. This simple and accurate prediction score based on readily available data can be an easily implemented tool. Incorporating this prediction model into CKD management for older patients may help to inform patients and their families about ESRD treatment options and provide a more patient-centered overall approach to care.

Kidney & Blood Pressure Research

Kidney Blood Press Res 2020;45:38–50
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Statement of Ethics

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of CHP. The subjects have given their informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

The authors contributed to this article in the following way: J.S. and I.F.: study design; J.S., A.C., and S.O.: data collect; J.S., P.O, and I.F.: data analysis; J.S., P.O., A.C., L.L., and I.F.: methodology; J.S. and I.F: manuscript preparation.

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APPENDIX 5

Validation of a model to predict six-month mortality in incident elderly dialysis patients.

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Validation of a model to predict six-month mortality in incident elderly dialysis patients

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ABSTRACT

Background and objectives: To evaluate RRT benefits and risks and to inform patients and their families about ESRD treatment options, we have developed a prognostic score to predict 6-month mortality in elderly ESRD patients initiating dialysis. Five independent predictors were identified and a point system was constructed: age 75 years or older (2 points), coronary artery disease (2 points), cerebrovascular disease with hemiplegia (2 points), time of nephrology care before dialysis [< 3.0 months (2 points); ≥ 3 to < 12 months (1 point)], serum albumin levels [3.0 - 3.49 g/dL (1 point); < 3.0 g/dL (2 points)]. Model performance was good in both discrimination and internal validation. Before adopting our risk score into practice, our aim is to externally validate this initial predictive model by assessing its performance on a new data set. **Methods:** We apply the predictive score developed in a cohort of CKD patients, aged 65 years and over who started dialysis between 2009 and 2016, to an independent cohort of ESRD patients, aged 65 years and over who started dialysis between 2017 and 2019, in our Nephrology department. The performance of the prediction equation created in development cohort, was assessed using discrimination and calibration metrics in the validation cohort. **Results**: Our validation study cohort included 168 individuals, with a mortality rate of 12.5% (n=21) within 6-months of dialysis initiation. Model performance in the validation cohort had an acceptable discrimination [AUC of 0.79; (95% confidence interval, 0.70 to 0.88)]. The Hosmer and Lemeshow goodness-of-fit test was not statistically significant, indicating good calibration of the model (χ^2, 5 degrees of freedom = 2.311; P = 0.805). **Conclusions**: Our predictive simple score based on readily available clinical and laboratory data demonstrates a good performance when externally validated, namely with respect to discrimination and calibration. Model validation is crucial for adequately informing patients and their families about ESRD treatment options and providing a more patient-centered overall approach to care. Before we start general implementation in clinical practice, our score needs further validation in larger patient cohorts.

Key Words: Prognosis Score; End-Stage Renal Disease; Elderly; Decision Making

INTRODUCTION

Mortality in chronic kidney disease (CKD) remains high, particularly among the elderly, who represent the most rapidly growing segment of the end-stage renal disease (ESRD) population in Western countries[1,2].

One of the challenges to clinicians caring for older CKD patients expected to progress to ESRD lies in the evaluation of the overall benefit of offering them renal replacement therapy (RRT). Thus, for evaluating RRT benefits and risks and informing patients and their families about ESRD treatment options based on a shared decision-making process, several scoring systems have been developed[3-7]. One of the concerns related to the available predictive scores is that those may be unsuitable for widespread application due to unproven generalizability.

Portugal has the one of the highest incidences and prevalence of ESRD in the world[8,9]. Considering the need to develop prognostic models adapted to the specificities of each population, we have recently developed a prognostic score for predicting early death in elderly ESRD patients initiating dialysis in a cohort of Portuguese patients[10].

This score had a good performance and it was internally validated using bootstrapping methods[11]. If possible, before adopting a risk score into practice, the prognostic score should be externally validated and tested in a group of patients different to the sample used to develop the score[11].

Therefore, the objective of this study is to validate the previously developed prognostic score in an independent dataset and compare its performance with other known scoring systems[4].

METHODS

A prospective cohort study was performed for external validation of our prognostic score[10]. The sample included all patients aged 65 years and over referred to the Nephrology Department of Centro Hospitalar Universitário do Porto (CHUP), who started dialysis as their first RRT between January 2017 and December 2019.

The study was performed in accordance with the Declaration of Helsinki and approved by CHUP's Institutional Review Board.

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Data was collected primarily from electronic clinical records and through information from dialysis centers. Demographic, clinical and functional variables were recorded. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology (CKD-EPI) 2009 creatinine equation[12]; all serum creatinine measurements were performed in the same laboratory using a calibrator for automated systems (*Roche Diagnostics*). Etiological diagnosis of CKD was based on the patient's history, kidney ultrasound, and kidney biopsy, when available.

Cognitive status was evaluated using the Mini Mental State Examination (MMSE)[13] with cognitive impairment defined for scores lesser or equal to 23. Functional dependency was defined as requiring assistance for transfer, classified as totally dependent or need assistance for transfer; otherwise, patients were classified as autonomous.

A modified version of the Charlson comorbidity index (mCCI)[14], i.e., by excluding subject's age and presence of kidney disease, was calculate and subdivided into three subgroups (0-2, 3-4, ≥5).

The outcome of interest was all-cause mortality within first 6 months of dialysis therapy initiation. In the validation cohort, vital status was checked until 30 December 2019.

The prognostic score that we intend to validate was developed in patients from the same center who started dialysis between January 2009 and December 2016. The design and detailed methodology used in the development of the prognostic model has been described previously[10].

■ Statistical Analysis

Data are reported as medians and interquartile range (IQR) or frequencies and proportions whenever appropriate.

Comparisons between groups for categorical data were made using the chi-square test. Continuous data were compared using the Mann-Whitney test for non-normally distributed variables.

The discriminative power of the prognostic score (i.e., the ability to identify patients at highest risk of dying within the first 6 months of starting dialysis) was assessed by calculating the area under the receiver operating characteristic (ROC) curves (AUC). Calibration of the risk score reflecting the link between predicted and observed risk was evaluated by the Hosmer-Lemeshow goodness-of-fit test (a P-value above 0.05 indicates acceptable calibration). The developed risk score in our work[10] and Couchoud score[4] was calculated for each patient to determine the performance of each scoring system in predicting mortality. The discrimination of each scoring system was assessed and compared using AUC.

A P value < 0.05 was considered statistically significant for all analyses. Data were analyzed using the STATA 13.0 and SPSS 26.0 (SPSS, Inc., Chicago, IL) statistical software.

■ Model Development

Briefly, our score[10] was developed using data from a cohort (development cohort) of 421 patients, aged 65 years and over who started dialysis between 2009 and 2016, in our Nephrology Service. Demographics and clinical variables were included as potential predictors. The predictive score was developed using a multivariable logistic regression analysis. A bootstrapping method[15,16] was used for internal validation.

Five independent predictors were identified and a point system was constructed: age 75 years or older (2 points), coronary artery disease (2 points), cerebrovascular disease with hemiplegia (2 points), time of nephrology care before dialysis [< 3.0 months (2 points); ≥ 3 to < 12 months (1 point)], serum albumin levels [3.0 - 3.49 g/dL (1 point); < 3.0 g/dL (2 points)] (Table I).

Table I

Predictors of 6-month mortality and associated risk scoring system

	Shrunken β-Regression Coefficient[a]	Risk score[b]
Age category (≥75 years vs. <75 years)	0.86	2
Coronary artery disease (yes vs. no)	0.83	2
Cerebrovascular disease with hemiplegia (yes vs. no)	0.84	2
Albumin category (ref: ≥ 3.5 g/dL)		
3.0 - 3.49 g/dL	0.76	1
< 3.0 g/dL	1.30	2
Time of nephrology care prior to dialysis (ref: ≥ 12 months)		
< 3.0 months	1.26	2
≥ 3 to < 12 months	0.56	1

[a] Original β-regression coefficient multiplied by heuristic shrinkage factor.
[b] Scores assigned by dividing the shrunken β-regression coefficients by 0.528 (two-fifths of the two small β-coefficients in the model) and rounded to nearest integer.

Model performance was good in both discrimination [AUC of 0.793; (95% confidence interval, 0.73 to 0.86)] and internal validation [concordance statistics of 0.791 (95% confidence interval, 0.73 to 0.85)].

With our model[10], we made a risk assessment questionnaire for clinicians' and patients' use, illustrated in Figure 1, exposing a simple understandable method for establishing a patient's risk for the outcome depending on an individual's status for the five variables included in the tool.

■ RESULTS

■ Baseline Characteristics of Study Participants

The validation cohort included 168 individuals aged 65 years or older. Baseline patient characteristics from the development and validation cohorts are summarized in Table II.

Compared to patients from the development cohort, patients from the validation set had lower eGFR at dialysis initiation and had fewer hospitalizations within 6-months prior to dialysis. Furthermore, patients included in the validation sample were more functionally autonomous and were referred earlier to nephrology care prior to dialysis.

Figure 1

Score chart to predict 6-months mortality

6-months mortality predictors	Assigned Points
Age (years) Points < 75 ..... 0 ≥ 75 2	
Coronary artery disease 2	
Cerebrovascular disease with hemiplegia 2	
Albumin (g/dL) ≥ 3.5 .....0 3.0 - 3.49 ..... 1 < 3.0 2	
Time of nephrology care (months) ≥ 12 .....0 ≥ 3 to < 12 ..... 1 < 3.0 2	

Total Score

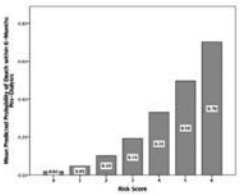


Figure 2

Performance of risk score in validation

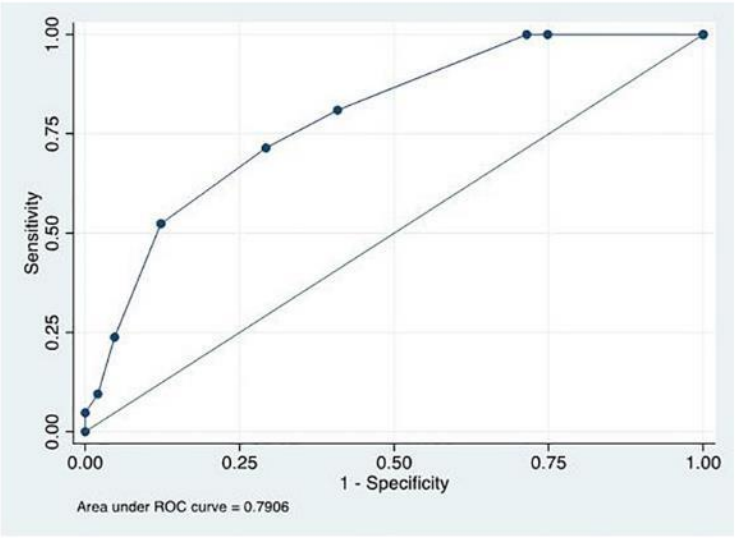


Table II

Baseline characteristics of development and validation cohorts for predicting 6-months mortality in elderly ESDR patients

	Development Cohort n=421	Validation Cohort n =168	*P* Value
Age (years), median and IQR	75.5 [70 – 80]	74.7 [69 – 80]	0.428
Age ≥75 years, n (%)	217 (51.5)	83 (49.4)	0.549
Female, n (%)	195 (46.3)	63 (37.5)	0.051
Primary renal disease, n (%)			
Diabetic nephropathy	156 (37.1)	59 (35.1)	
Ischemic nephropathy	69 (16.4)	28 (16.7)	
Glomerulonephritis	50 (11.9)	24 (14.3)	0.135
ADPKD	21 (5.0)	15 (8.9)	
Other	73 (17.3)	17 (10.1)	
Unknown etiology	52 (12.4)	25 (14.9)	
BMI (kg/m^2), median and IQR	25.7 [23.5 – 28.7]	26.1 [22.9 – 29.2]	0.840
< 25, n (%)	170 (40.4)	67 (40.6)	
25-30	148 (35.2)	63 (38.2)	0.791
> 30	75 (17.8)	35 (21.2)	
Cognitive impairment, n (%)	63 (15.0)	16 (9.5)	0.121
Totally dependent for transfer, n (%)	37 (8.8)	13 (7.7)	
Need assistance for transfer, n (%)	188 (44.7)	45 (26.8)	<0.001
Autonomous, n (%)	196 (46.6)	110 (65.5)	
Institutionalization, n (%)	22 (5.2)	8 (4.8)	0.817
mCCI, median and IQR	3.8 [2 – 5]	3.0 [2 – 5]	0.083
0-2, n (%)	127 (30.1)	59 (35.1)	
3-4	130 (30.9)	54 (32.1)	0.326
≥5	164 (39.0)	55 (32.7)	
Current/ Former smoking, n (%)	96 (22.8)	49 (29.1)	0.105
Diabetes, n (%)	212 (50.4)	88 (52.4)	0.657
Hypertension, n (%)	409 (97.1)	163 (97.0)	0.934
Dyslipidemia, n (%)	375 (89.1)	156 (92.9)	0.164
Congestive heart failure, n (%)	262 (62.2)	106 (63.0)	0.845
Coronary artery disease, n (%)	126 (29.9)	54 (32.1)	0.598
Cardiac arrhythmia, n (%)	101 (24.0)	41 (24.4)	0.915
Cerebrovascular disease, n (%)	137 (32.5)	40 (23.8)	0.116
with hemiplegia	43 (10.2)	14 (8.3)	0.486
Peripheral vascular disease, n (%)	165 (39.2)	55 (32.7)	0.144
Neoplasia, n (%)	64 (15.2)	31 (18.5)	0.333
COPD, n (%)	74 (17.6)	36 (21.4)	0.279
Chronic liver disease,, n (%)	30 (7.1)	8 (4.8)	0.292
Autoimmune disease, n (%)	16 (3.8)	11 (6.5)	0.150
Peptic ulcer, n (%)	62 (14.7)	27 (16.0)	0.681
Albumin <3.5 g/dL, median and IQR	3.6 [3.2 - 4.0]	3.7 [3.1 - 4.2]	0.198
≥ 3.5, n (%)	255 (60.6)	101 (60.1)	
3.0 - 3.49	87 (20.7)	36 (21.4)	0.978
< 3.0	79 (18.8)	31 (18.5)	
Creatinine (mg/dL), median and IQR	6.3 [4.7 - 7.5]	6.6 [5.1 – 8.2]	0.003*
eGFR EPI (ml/min/1.73 m^2), median and IQR	6.5 [4.8 – 8.4]	5.6 [4.3 – 7.7]	0.003*
≥ 15, n (%)	12 (2.9)	2 (1.2)	
10 – 14.9	43 (10.2)	7 (4.1)	
< 10	366 (86.9)	159 (94.6)	0.025*
Time of nephrology care before dialysis (months), median and IQR	43.9 [18.0 -89.0]	65.2 [27.4 -126.5]	<0.001*
< 3; n (%)	83 (19.7)	17 (10.1)	
≥3 to < 12	43 (10.2)	9 (11.3)	0.02*
≥12	295 (70.1)	142 (84.5)	
Dialysis modality: hemodialysis; n (%)	411 (97.6)	154 (91.7)	0.001*
Unplanned dialysis, n (%)	249 (59.1)	85 (50.6)	0.059
Access at first dialysis: catheter, n (%)	181 (42.9)	68 (40.5)	0.577
Hospitalizations 6-months before dialysis, n (%)	144 (34.2)	75 (44.6)	0.018*

Data expressed as medians and interquartile ranges (IQR) or n (%) when appropriate. Comparisons between continuous variables were done using a nonparametric test (Mann-Whitney test); associations between categorical variables were analyzed using the χ^2 test; *P<0.05. BMI, body mass index; mCCI, modified Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; eGFR, estimated Glomerular Filtration Rate using the Chronic Kidney Disease Epidemiology; Nº hospitalizations, number of hospitalizations based on 6 months prior to dialysis initiation. *P<0.05

Independent Validation

Among patients in the validation cohort, there were 21 deaths (12.5%) within the first 6 months of dialysis initiation.

In the validation set (n=168), the performance of the prognostic score is shown in Figure 2, with an AUC of 0.79 (95% CI 0.70-0.88) indicating acceptable (nearly good) discrimination. The Hosmer and Lemeshow goodness-of-fit test was not statistically significant, indicating good calibration of the model (χ^2, 5 degrees of freedom = 2.311; P = 0.805).

Comparison with Alternative Risk Score

Couchoud score[4] was calculated for all patients in the validation cohort according to corresponding formula, with an AUC of 0.766 (95% CI 0.65–0.88). In this cohort, the performance of our score was higher than Couchoud score, but not statistically significant (P = 0.63) (Figure 3).

DISCUSSION

Incorporating predictive models into CKD management for older patients may help to inform patients and their families about ESRD treatment options and provide a more patient-centered overall approach to care.

Risk prediction models are based on equations designed on the basis of prognostic factors and clinical outcomes, available at the time the prediction is made, and collected in specific and representative cohorts of individuals followed up for a given period of time[17,18].

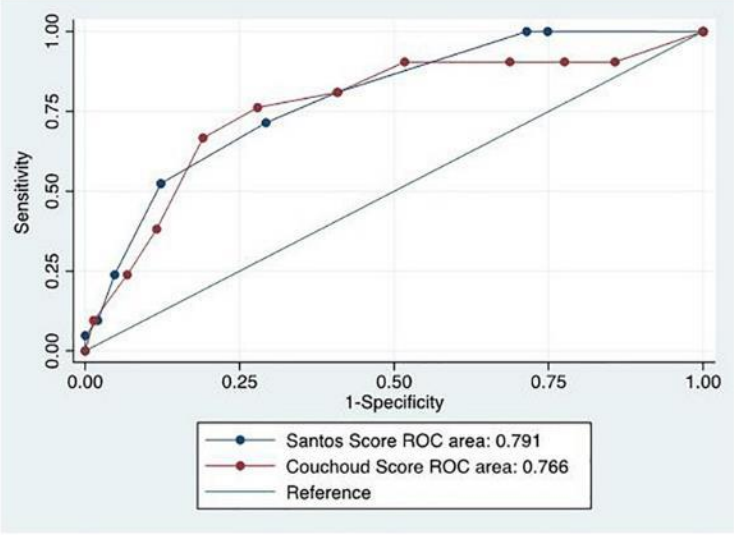
The performance of a risk prediction model is commonly assessed by testing its calibration and discrimination. Calibration describes the agreement of observed and predicted event rates[19]. Discrimination expresses the ability of the prediction model to distinguish individuals who will develop the outcome of interest from those who will not[20].

Another important question for physicians to consider is whether the score accurately predicts outcomes in people like their patients. So, validation of prognostic models is a determinant step before we start implementation in clinical practice. Models should be internally and especially externally validated to obtain reliable estimates of model performance[11].

Internal validation implies assessment of model performance directly in the derivation cohort. This approach yields an optimistic estimate of model performance[17,18]. To minimize this limitation, the model can be developed on the whole dataset and data reuse methods, such as cross-validation and bootstrapping, applied to assess performance[11,17,18].

In the derivation of our score[10] we performed a bootstrapping procedure (5000 bootstrap samples) to internally validate the risk

Figure 3
Comparison with Couchoud Score



score, which generated a concordance statistics of 0.791 (95% confidence interval, 0.73 to 0.85) and an optimism of 0.002.

Even with a good performance achieved in the same cohort as the one that was used to develop the model, before adopting a risk score into practice, clinicians need to decide whether the score accurately predicts outcomes in a sample similar to their patients but belonging to a different source population; therefore, validation in an independent sample is required[11].

In the past years, several mortality scores have been developed on the basis of various combinations of comorbidities and laboratory data, but only a few of them have focused on short-term survival including only elderly CKD patients[3-7]. Also, only a few of the models were externally validated [21-23].

Portugal has one of the highest unadjusted incidences of ESRD among European countries[8]. About 64% of the incident dialysis patients in 2018 were over 65 years with a mean age of 67.2 years for prevalent patients[24], above the mean age of the European registry[8].

Differences in patients' profiles, namely distinct sociodemographic and clinical characteristics between the cohorts used to derive those scores, reinforce the need to develop predictive scores adapted to the specificities of each population. With this in mind, we have recently developed a prognostic score for predicting early death in elderly ESRD patients initiating dialysis that has been derived and internally validated in a cohort of Portuguese patients[10].

This score is based on simple and readily available information. With respect to model performance, the proximity of the AUC generated by bootstrapping procedure to the observed AUC and a very acceptable optimism indicate a good discrimination ability of our score. The good performance (its calibration and discrimination) of our model on the new data (validation group), indicated that the model was likely not overfit, and demonstrated its predictive accuracy.

In the development cohort, the performance of our risk score was significantly higher than Couchoud score[4], which reflects the different characteristics of the populations involved in derivation of the models. Also, in the validation cohort, although not statistically significant, the performance of our score was higher than Couchoud score[4].

Bansal et al.[21] developed a prediction equation for 5-year risk of mortality for older people with CKD stages 3-5 not treated with dialysis. The equation included nine readily available clinical variables (age, sex, race, eGFR, urine albumin-to-creatinine ratio, smoking, diabetes mellitus, and history of heart failure and stroke), and it was externally validated in a large cohort of elderly CKD patients. This model has an acceptable calibration and discrimination in both the development (C-statistic = 0.72; 95% confidence interval, 0.68 to 0.74) and validation cohort (C-statistic = 0.69; 95% confidence interval, 0.64 to 0.74). However, one of its limitations is that the validation cohort did not fit the frailty phenotype associated with CKD[26] because the authors enrolled well-functioning men and women, and it has been well established that frailty is an additional risk factor for mortality in CKD patients [21].

It is important to highlight any differences that might affect model translation between the validation sample and the original study sample. The differences in the baseline characteristics between our validation and development population are shown in Table II. Patients from the validation set had lower eGFR at dialysis initiation, had fewer hospitalizations within 6-months prior to dialysis, were more functionally autonomous and were referred earlier to nephrology care than patients from the development cohort. These differences may be due to the difference in timing of dialysis initiation, as the validation cohort was more recent than the development cohort.

Even so, our model achieved a good performance in the validation cohort, which confirms its predictive accuracy in a different source population, i.e.; it is independently validated.

Floege et al.[23] have published another risk prediction model developed in a European hemodialysis cohort with a mean age of 64 years old, using objective measurements. This model was then validated in an external cohort of the Dialysis Outcomes and Practices Patterns Study (DOPPS) and exhibited a moderate discrimination (C-statistic of 0.68 to 0.79). Nevertheless, contrary to our model[10], the Floege et al. score[23] has not been developed nor validated in a cohort of elderly dialysis patients. In addition, because the development cohort includes only patients who survived the first 3 months, whereas the validation cohort of DOPPS includes mainly prevalent patients, it is still not a perfect risk predictor for frail elderly, in which the risk of short-term mortality is what needs to be predicted.

The Couchoud et al. model[4] was externally validated in a US population[22]; although investigators modified the score; poor performance was observed with respect to prediction of 6-month mortality in older patients with ESRD commencing dialysis. Although the sample size of our validation cohort has a limited pool of subjects compared to the development cohort, inherent to a single-center validation study, the validation sample included data on all the variables in the derivation model[10].

Simplicity of models and reliability of measurements are important criteria in developing clinically useful prognostic models[11]. Our predictive score[10] includes variables that are well defined, measurable, and readily available; in other words; our model is clinically useful.

There are some limitations in our study. First, this is a single-center study, with a relatively small sample size. Secondly, our population consisted of incident dialysis patients that were referred to nephrologists. Those who were not referred, not selected for, or not accepted for dialysis initiation, were not included. Our model may, therefore, not be generalizable to the entire population of elderly ESRD patients.

In conclusion, after development, our score was independently validated in a new dataset of patients indicating acceptable discrimination to predict early mortality for elderly CKD patients who initiate dialysis. This simple and accurate prediction score based on readily available data can be an easily implemented tool to apply in daily practice to guide patient care.

■ Ethical Statement

The study was performed in accordance with the Declaration of Helsinki and approved by the CHUP Institutional Review Board. The subjects have given their informed consent.

■ Author Contributions

The authors contributed to this article in the following way: Study design: JS, IF; data collect: JS, AC, SO; data analysis: JS, PO, IF; methodology: JS, PO, AC, LL, IF; manuscript preparation: JS, IF.

Disclosure of potential conflicts of interest: none declared

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APPENDIX 6

Association between severe chronic kidney disease defined by cystatin-C and creatinine and clinical outcomes in an elderly population – an observational study.

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Association between severe chronic kidney disease defined by cystatin-c and creatinine and clinical outcomes in an elderly population – an observational study

Associação entre doença renal crônica grave definida por cistatina-c e creatinina e desfechos clínicos em uma população idosa - um estudo observacional

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Abstract

Introduction: Estimated glomerular filtration rate (eGFR) based on serum cystatin-C (sCys) seems as accurate as when based on serum creatinine (sCr), but sCys seems a better predictor of adverse outcomes. We aimed to study whether sCys could be a reliable tool for the prediction of adverse outcomes in elderly patients with severe chronic kidney disease (CKD). **Methods:** A group of 348 elderly patients with non-end-stage CKD (stages 1-4, according to eGFR-EPI sCr and/or sCys), referred to our consultation unit during 2016, was retrospectively studied and divided into four exclusive categories: CKD_stage4_neither (eGFR-sCr≥30mL/min; eGFR-sCys≥30mL/min), CKD_stage4_sCr_only (eGFR-sCr<30mL/min), CKD_stage4_sCys_only (eGFR-sCys<30mL/min) and CKD_stage4_combined (eGFRsCr<30mL/min; eGFR-sCys<30mL/min). Baseline characteristics, predictors of death, and clinical events (cardiovascular events and admissions for cardiovascular, acute kidney injury or infectious events) were explored until December 2018. **Results:** A 77±7.4 year-old cohort, with a modified Charlson Comorbidty Index (mCCI) of 3 (IQR:1-4), was followed-up during 29 (IQR: 26-33) months. There were no significant differences between the characteristics of the stage 4 groups. Survival analysis was stratified by follow-up at 12 months, and in the first year, survival curves of CKD_stage4_sCys_only and CKD_stage4_combined groups were significantly lower than the other groups (p=0.028). Adjusting for age, sex, and mCCI, CKD_stage4_sCys_only, conversely to CKD_stage4_sCr_only, had higher rates of clinical events (p<0.05) than CKD_stage4_neither group.

Resumo

Introdução: A taxa estimada de filtração glomerular (TFGe) com base na cistatina-C sérica (Cis-C) parece ser tão precisa quanto aquela baseada na creatinina sérica (Cr), mas cis-C parece ser um melhor preditor de resultados adversos. Nosso objetivo foi avaliar se a cis-C poderia ser uma ferramenta confiável para a previsão de desfechos adversos em pacientes idosos com doença renal crônica grave (DRC). **Métodos:** Um grupo de 348 pacientes idosos com DRC em estágio não terminal (estágios 1-4, de acordo com TFGe-EPI Cr e/ou Cis-C), encaminhados para nossa unidade de consulta durante 2016, foi estudado retrospectivamente e dividido em quatro categorias exclusivas: DRC_estágio 4 nenhum (TFGe-Cr≥30mL/min; TFGe -Cis-C≥30mL/min), DRC_estágio 4_Cr apenas (TFGe-Cr <30mL/min), DRC_estágio 4 _Cis-C_apenas (TFGe-Cis-C <30 mL/min), DRC_estágio4_combinado (TFGe-Cis-C <30mL/min. TFGe-Cr <30mL/min). Características basais, preditores de óbito e eventos clínicos (eventos cardiovasculares e internações por doenças cardiovasculares, lesão renal aguda ou eventos infecciosos) foram explorados até dezembro de 2018. **Resultados:** Uma coorte de 77 ± 7,4 anos, com índice de comorbidade de Charlson modificado (mCCI) de 3 (IQR: 1-4), foi acompanhada durante 29 (IQR: 26-33) meses. Não houve diferenças significativas entre as características dos grupos no estágio 4. A análise de sobrevida foi estratificada pelo acompanhamento aos 12 meses, sendo que no primeiro ano, as curvas de sobrevida dos grupos DRC_estágio4_Cis-C_apenas e DRC_estágio4_ combinado foram significativamente inferiores quando comparadas com os restantes grupos (p = 0,028). Ajustando para idade, sexo e mCCI, DRC_estágio4_Cis-C_apenas, ao contrário do grupo DRC_estágio4_Cr_apenas, teve maiores taxas de eventos clínicos (p <0,05) do que o grupo DRC_estágio4_nenhum.

Conclusion: In elderly patients with discordant CKD staging, sCys-based eGFR seems to be a better predictor of adverse outcomes than sCr-based eGFR. Patients with stage 4 CKD defined by sCr alone seem to behave similar to those with less severe CKD.

Keywords: Renal Insufficiency, Chronic; Creatinina; Cystatin C; Aged; Glomerular Filtration Rate; Outcome Assessment, Health Care.

Conclusão: Em pacientes idosos com estadiamento discordante da DRC, a TFGe baseada na Cis-C parece ser um melhor preditor de resultados adversos do que a TFGe baseada na Cr. Pacientes com DRC em estágio 4, definida apenas por Cr, parecem se comportar de forma semelhante àqueles com DRC menos grave.

Descritores: Insuficiência Renal Crônica; Creatinine; Cistatina C; Idosos; Taxa de Filtração Glomerular; Avaliação de Resultados em Cuidados de Saúde.

Introduction

Chronic kidney disease (CKD) is not only a risk factor for end-stage renal disease (ESRD), but it is also associated with hospitalizations, cardiovascular disease (CVD), and death [1].

Glomerular filtration rate (GFR) is the standard renal measure and its estimation (eGFR) accuracy is important to detect and stage CKD, as well as to stratify the patients' risk. It is still unknown if the most accurate GFR estimates correspond to the best clinical risk predictor [2].

Great efforts have been made to determine which is the most suitable method for GFR estimation in the elderly. Flamant et al., in a study comparing Cockcroft-Gault (CG), 4-variable Modification of Diet in Renal Disease (MDRD) Study and CKD Epidemiology Collaboration (CKD-EPI) equations in 786 elderly patients recommended the use of the MDRD Study and CKD-EPI equations rather than the CG equation [3]. Plus, when compared to the MDRD equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations seem to be superior in estimating GFR and in predicting the risk for adverse clinical outcomes, particularly in elderly [4]. On the other hand, despite BIS equations having been designed for older adults, little evidence exists showing that these equations improve patient outcomes prediction [5,6].

Several studies have suggested that the use of serum cystatin C (sCys), a marker less susceptible to metabolic and extra-renal factors than serum creatinine (sCr), for eGFR calculation significantly improves the risk classification for death, cardiovascular disease, and ESRD [7-10]. This observation illustrates the usefulness of cystatin C in the elderly with CKD, in whom important decisions about CKD management and ESRD preparation have to be considered, as it may allow us to better predict CKD progression and appreciate the competitive ESRD versus death risk [11].

The aim of this study was to evaluate, in a cohort of elderly CKD patients, the association of severe CKD (stage 4) defined by either sCr or sCys alone, or by both, with all-cause mortality and progression to ESRD, and secondly, with cardiovascular events and in-hospital admissions (all-cause, and for infection or acute kidney injury (AKI)). We had hypothesized that CKD stage 4 defined by sCys-based equations could identify patients at a higher risk for worse outcomes and events.

Subjects and Methods

Study Population

This longitudinal retrospective study included all patients forwarded to our Nephrology outpatient clinic during the year of 2016 (between the 1st of January and the 31st of December). We studied 348 patients aged over 65 years who had non-ESRD (CKD except stage 5) according to KDIGO 2012 criteria [12].

Our research team, composed of nephrologists only, collected data from electronic medical reports. Besides age and gender, baseline medical history including diabetes, hypertension, dyslipidemia, smoking status, body mass index (BMI), and cardiovascular disease (CVD) was obtained to exclude any potential bias. CVD included coronary artery disease, congestive heart failure, classified by New York Heart Association from stage I to IV, arrhythmia, peripheral artery disease, and cerebrovascular disease. Coronary artery disease was defined as history of myocardial infarction, coronary artery bypass grafting, or coronary stent implantation. Peripheral artery disease was defined as the presence of intermittent claudication or if peripheral revascularization or amputation was performed. Cerebrovascular disease included both previous transient ischemic attacks and stroke.

A modified version of Charlson Comorbidity Index (mCCI) was calculated. This version excludes patients' age and CKD status [13,14].

Fasting blood samples were collected at baseline and analyzed in the same laboratory with standardized methods. Serum creatinine was analyzed using a calibrator for automated system (Roche Diagnostics) and serum cystatin C was measured by a particle-enhanced nephelometric assay (DADE-Behring, Siemens Company, European Format)[15].

eGFR was estimated by the equations derived from the CKD-EPI: CKD-EPI creatinine equation (eGFR-sCr) and CKD-EPI cystatin C equation (eGFR-sCys) [16,17].

Patients were divided into four exclusive categories, meaning that no participant of each group could be part of any other:

1. CKD stage 4 neither (eGFR-sCr≥ 30 mL/min/1.73m²; eGFR-sCys ≥30 mL/min/1.73m²) - *the reference group*

2. CKD stage 4 sCr only (eGFR-sCr< 30 mL/min/1.73m²; eGFR-sCys ≥30 mL/min/ 1.73m²)

3. CKD stage 4 sCys only (eGFR-sCr≥30 mL/min 1.73m²; eGFR-sCys <30 mL/min /1.73m²)

4. CKD stage 4 combined (eGFR-sCr < 30 mL/min/1.73 m²; eGFR-sCys < 30 mL/min/1.73 m²

Assessment of Clinical Outcomes

The primary outcomes of the study were all-cause mortality and ESRD defined as the first day of renal replacement therapy initiation. Death was verified by the electronic death certificate.

Secondary outcomes were cardiovascular (CV) events, defined as events secondary to coronary artery disease, congestive heart failure, transient ischemic attack, stroke, and peripheral artery disease; all-cause hospitalization; admissions due AKI, defined by the 2019 ICD-10-CM diagnosis code N17; and infectious events.

Follow-up was calculated from initial evaluation until death or until December 31, 2018.

Statistical Analysis

Baseline characteristics were reported as mean ± standard deviation (SD) and median (inter-quartile range) for continuous variables or as number and percentage for categorical variables. Comparisons of baseline characteristics between stage 4 groups (**stage 4 neither** was excluded) were explored using the Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.

In the following statistical analysis, the **stage 4 neither group** was used as comparison group, as a reference of patients with less severe disease and, for that reason, with an expected lower risk for worse outcomes.

Patient survival curves were analyzed using Kaplan–Meier method, with comparison between patients' groups being done by log-rank test, stratified by follow-up time at 12 months. CKD stage 4 groups were explored as predictors of death by extended Cox regression stratified by follow-up time at 12 months, since proportionality was not met. Age, sex, and mCCI, as potential cofounders, were selected as covariates for the extended Cox model.

Incident rate ratio (IRR) of cardiovascular and admission events was calculated by Poisson regression. A two-sided P-value of <0.05 was considered as statistically significant.

Statistical calculations were performed using SPSS, version 24.0 (SPSS Inc., Chicago, IL, USA), and Stata/MP, version 14.1 (Stata Corp, College Station, TX).

Results

Baseline Characteristics

The cohort had a mean age of 77 ± 7.4 years old, a median mCCI of 3 (IQR: 1-4), and all patients were Caucasian. In 59% of the patients, referral was made by the primary care practitioner, and as for the rest, referral was made from other specialties or after admission in our inward department. The median eGFR defined by sCr was 39 (28 - 50) mL/min/1.73 m² and 33 (25 - 44) mL/min/1.73 m² when defined by sCys. Participants were followed-up during a median time of 29 (IQR: 26 - 33) months.

Comparison of the baseline characteristics of the four groups is shown in Table 1.

After excluding the **CKD stage 4 neither** group, there were no significant differences in age, gender, or co-morbidities defined by either sCr or sCys between the groups. Unsurprisingly, patients in the **CKD stage 4 neither** group were younger, majority was male, had less heart failure, arrhythmia, and cerebrovascular disease, and consequently, presented a lower mCCI score.

Primary Outcomes

By the end of the follow-up period, 54 patients had died and only 4 initiated dialysis. No difference between the groups was observed considering patient death (overall or by cause) and ESRD at the end of the follow-up (Table 2). Cardiovascular and infection were the main causes of death.

As proportionality was not met, survival analysis was stratified by follow-up time at 12 months.

In the first year, survival curves of the **CKD stage 4 combined** and **sCys only** groups were significantly lower (P=0.028) when compared to the **CKD stage 4 neither** and **sCr only** groups. However, this difference was not found after 12 months (P=0.148).

Similarly, **CKD stage 4 combined** and **sCys only** groups were better predictors of early (<12 months) death in both unadjusted and adjusted extended Cox models (Table 3). Importantly, only **CKD stage 4 sCys only** group was an independent predictor of early mortality in the adjusted model. No differences were detected for the risk of late mortality between the groups in any of the models analyzed.

Table 1 Comparison of baseline characteristics of the four CKD stage 4 groups

Baseline Characteristics	1.CKD stage 4 Neither n=158 (45%)	2.CKD stage 4 sCr only n=21 (6%)	3.CKD stage 4 sCys only n=62 (18%)	4.CKD stage 4 combined n=107 (31%)	P excluding group 1
Age, mean ± SD	75.0±6.7	76.4±6.6	78.2±7.8	79.4±7.5	0.197
Female (%)	38	48	56	58	0.683
mCCI (IQR)	2 (1-4)	3 (2-4)	3 (1-5)	3 (2-5)	0.483
EPI_sCr mL/min, median (IQR)	50 (43-67)	27 (25-29)	39 (35-45)	25 (21-28)	**<0.001**
EPI_sCys mL/min, median (IQR)	45 (39-62)	35 (33-40)	27 (24-29)	23 (19-27)	**<0.001**

CKD: chronic kidney disease; mCCI: modified Charlson Comorbidity Index; sCr: serum creatinine; sCys: serum cystatin C; SD: standard deviation; IQR: interquartile range.

Table 2 Primary outcomes compared between the CKD stage 4 groups

Primary Outcomes	1.CKD stage 4 Neither n=158 (45%)	2.CKD stage 4 sCr only n=21 (6%)	3.CKD stage 4 sCys only n=62 (18%)	4.CKD stage 4 combined n=107 (31%)	P excluding group 1
Patient death, n (%)	15 (9)	4 (15)	11 (18)	24 (22)	0.810
Causes of death, n (total n=54)					0.217
Cardiovascular	4	4	5	12	
Infection	5	0	3	10	
Neoplasia	5	0	1	2	
	1	0	2	0	
Others/unknown	(39-62)	(33-40)	(24-29)	(19-27)	
Dialysis initiation, n	0	1	1	2	0.663

CKD: chronic kidney disease; sCr: serum creatinine; sCys: serum cystatin C.

Secondary Outcomes

After excluding group 1 (**CKD stage 4 neither**), in which the occurrence of CV events, all-cause admissions, admissions due to AKI, or infectious events was lower, there were no differences between the rest of the groups for CV events, all-cause admissions, and admissions due to AKI. Differently, infectious events seemed to occur in a higher percentage in **CKD stage 4 combined** group (Table 4).

When calculating incident rate ratio (IRR) for each type of event (Table 5), with an unadjusted model, CV events occurred more often in the **sCys-based only** group and in the **combined** group. However, when using an adjusted model for potential confounders, as age, sex, and mCCI, this difference only remained significant for the **sCys-based only** group.

As for all-cause admissions and admissions due to AKI, there was a higher IRR in the **sCys-based only** group and in the **combined** group for both unadjusted and adjusted models.

The IRR for infectious events in the **combined** group was two times higher than the IRR in **sCys-based only** group and almost four times higher than the IRR of the **sCr-based** only and **stage 4 neither** group.

Table 3 Extended Cox regression exploring predictors of death, considering CKD stage 4 groups at two time-periods

			Unadjusted		Adjusted	
	n per group	n events	HR (95% CI)	P	HR (95% CI)	P
CKD stage 4						
[0-12 months]	158	5	Ref.	Ref.	Ref.	Ref.
Neither	21	0	- (no events)	-	- (no events)	-
sCr only	62	7	3.7 (1.2-11.7)	**0.025**	3.5 (1.1-11)	**0.033**
sCys only	107	11	3.4 (1.2-9.8)	**0.024**	2.252 (0.80-6.6)	0.138
Combined						
CKD stage 4						
[12-36 months]	153	10	Ref.	Ref.	Ref.	Ref.
Neither	21	4	2,7 (0,8-8,5)	0,099	2,2 (0,7-7,1)	0,188
sCr only	55	4	1,1 (0,4-3,6)	0,839	1,1 (0,3-3,4)	0,911
sCys only	96	13	2,2 (1-5)	0,060	1,5 (0,7-3,6)	0,330
Combined						

Adjusted to: Age, Sex, mCCI

CKD: Chronic kidney disease; mCCI: Modified Charlson Comorbidity Index; Ref. : Reference; sCr: Serum Creatinine; sCys: serum cystatin C.

Table 4 Occurrence (at least 1) of CV events, all-cause admissions, admissions due to AKI, and infectious events in the CKD stage 4 groups

Secondary Outcomes	1.CKD stage 4 Neither n=158 (45%)	2.CKD stage 4 sCr only n=21 (6%)	3.CKD stage 4 sCys only n=62 (18%)	4.CKD stage 4 combined n=107 (31%)	P excluding group 1
With CV events, n (%)	18 (11)	4 (19)	16 (26)	22 (21)	0.717
With admissions, n (%)	28 (18)	5 (24)	23 (37)	45 (42)	0.281
With admissions for AKI, n (%)	18 (11)	3 (14)	15 (24)	39 (36)	0.067
With admissions of infectious events, n (%)	10 (6)	2 (10)	5 (8)	28 (26)	<0.001

AKI: Acute kidney injury; CKD: Chronic kidney disease; CV: Cardiovascular; sCr: Serum Creatinine; sCys: Serum cystatin C.

Table 5 Incident rate ratio of CV events, all-cause admissions, admissions due to AKI, and infectious events in the CKD stage 4 groups

	CV Events	Unadjusted		Adjusted	
	Event rate (100 patients-year)	IRR (95% CI)	P	IRR (95% CI)	P
CKD stage 4					
Neither	5.3	Ref.		Ref.	
sCr only	9.0	1.7 (0.6-4.6)	0.227	1.4 (0.5-3.8)	0.486
sCys only	12.3	2.4 (1.2-4.5)	**0.010**	2.2 (1.1-4.2)	**0.021**
Combined	10.3	2.0 (1.1-3.5)	**0.026**	1.5 (0.8-2.8)	0.214

	All Admissions events	Unadjusted		Adjusted	
	Event rate (100 patients-year)	IRR (95% CI)	P	IRR (95% CI)	P
CKD stage 4					
Neither	11.5	Ref.		Ref.	
sCr only	10.8	0.9 (0.4-2.2)	0.885	0.8(0.3-1.8)	0.543
sCys only	29.0	2.5 (1.6-3.9)	**<0.001**	2.281 (1.477-3.521)	**<0.001**
Combined	35.5	3.1 (2.1-4.4)	**<0.001**	2.213 (1.507-3.251)	**<0.001**

	AKI Events	Unadjusted		Adjusted	
	Event rate (100 patients-year)	IRR (95% CI)	P	IRR (95% CI)	P
CKD stage 4					
Neither	6.0	Ref.		Ref.	
sCr only	5.4	0.9 (0.30-3)	0.861	0.7 (0.2-2.4)	0.597
sCys only	17.4	2.9 (1.6-5.1)	**<0.001**	2.5 (1.4-4.5)	**0.002**
Combined	24.0	3.972 (2.4-6.4)	**<0.001**	2.6 (1.6-4.4)	**<0.001**

	Infectious Events	Unadjusted		Adjusted	
	Event rate (100 patients-year)	IRR (95% CI)	P	IRR (95% CI)	P
CKD stage 4					
Neither	3.7	Ref.		Ref.	
sCr only	3.6	1.0 (0.2-4.3)	0.983	0.8 (0.2-3.4)	0.726
sCys only	8.0	2.2 (1.0-4.8)	0.054	1.8 (0.8-4.1)	0.134
Combined	14.1	3.8 (2.0-7.2)	**<0.001**	2.5 (1.3-4.8)	**0.006**

Adjusted to: age, sex, mCCI

AKI: Acute kidney injury; CKD: Chronic kidney disease; CV: Cardiovascular; mCCI: Modified Charlson Comorbidity Index; Ref.: Reference; sCr: Serum Creatinine; sCys: Serum cystatin C.

Discussion

In our cohort, people with severe CKD defined by cystatin C had a lower early survival rate when compared to severe CKD defined only by creatinine and patients with CKD from stage 1 to 3. After extended cox regression analysis and adjusting for age, sex, and mCCI, just the cystatin C_only group remained as a predictor of early death. This tendency was also verified when analyzing CV event rate, which was the main cause of death. These results could indicate that serum cystatin C, in comparison to serum creatinine, could represent a better tool for risk stratification for adverse outcomes in old people with severe CKD.

These findings seem to be in accordance with prior reports about the role of cystatin C as a biomarker for CV prediction risk. Shlipak et al. in a meta-analysis study, showed a consistent linear association between the reduction of GFR estimated by CKD-EPI cystatin C-derived equations (cystatin C alone and cystatin C plus creatinine) and increased risk of all-cause mortality and CV mortality, even in cases of mildly reduced kidney function (below 85 mL/min/1.73 m^2) [7]. The reason why this biomarker is linked to CVD within CKD, according to experimental data, seems to be related to its association in atherosclerotic physiopathology [18].

However, some studies alerted that this association between cystatin C and all-cause plus CV mortality could be due to other cofounding factors, since the populations studied had variable ages and different characteristics as BMI and comorbidities [19]. In fact, there was a study that showed that this association was not confirmed in an Australian population of 1165 elderly women aged more than 70 years [20].

In order to exclude cofounding factors that could bias our results, we made an extensive characterization of our baseline population, and among the patients with severe CKD (stage 4) no detectable differences were found concerning cardiovascular risk factors as BMI, blood pressure, diabetes, smoking, dyslipidemia, and concerning organ damage as heart disease, cerebrovascular disease, and peripheral arterial disease.

Considering secondary outcomes, all-cause admissions and AKI admissions, when compared with CKD stage 1 to 3, stage 4 cystatin C_only and stage 4_combined groups had significantly higher IRR of these events. These results concur with the already shown role of cystatin C in predicting all-cause AKI [21].

As for infectious events, the IRR was only significantly higher in the stage 4_combined group. Although there was a significantly higher IRR for the cystatin C_only group in the unadjusted model, this disappeared in the adjusted model.

Hence, in elderly patients with severe non-end stage CKD, sCys-based eGFR seemed to be a better predictor of adverse outcomes than sCr-based eGFR in patients with discordant staging. Patients with stage 4 CKD defined by creatinine alone appeared to behave more alike those with less severe CKD (stage 4_neither), while studied outcomes in patients with stage 4 CKD defined by cystatin C alone were similar to the more severe group defined as CKD stage 4 by both cystatin C and creatinine.

Other strengths of this study include a large cohort of elderly patients with CKD with an accurate data collection over a 2-year period, an accurate measurement of serum creatinine and cystatin C using standardized assays, and a rigorous statistical analysis. Moreover, the mean age of our patients was significantly higher than in previous studies, giving more evidence to risk prediction in older people, where CKD is particularly prevalent [22].

Nevertheless, our study strengths should be balanced against its limitations. As all participants were Caucasians, generalizations cannot be made. Plus, the absence of information concerning albuminuria represents a weakness of our project, since albuminuria has been reported as an independent predictor of adverse outcomes [23]. A larger follow-up time would have strengthened our study, especially for the primary outcome of dialysis start, in order to increase the number of incident cases. Even so, we are aware that elderly patients are more likely to die from any cause than to progress to ESRD, as was observed [24]. Differently, for the primary outcome of death, we realize that increasing the follow-up would not change our results, since the differences between the survival rates of the groups vanished after twelve months.

In conclusion, in our cohort, we have demonstrated that the CKD-EPI cystatin C was superior to CKD-EPI creatinine equation in predicting all-cause mortality in the first year, CV events, and all-cause and AKI admissions when used in old patients with severe non-end stage CKD. For that reason, this data cannot be extrapolated to patients with milder stages of CKD. Also, there is a cost-difference between measuring creatinine and cystatin C, therefore clinicians need to understand the usefulness and cost-effectiveness of eGFR based on cystatin C.

Nevertheless, its capacity to better predict the likelihood of adverse events and worse outcomes could help in the clinical decision making: to intervene in the group of patients that will benefit the most and to avoid overtreatment in the ones that will not. Further investigations with prospective studies, albuminuria measurement, and cost-effectiveness data are necessary to validate our hypothesis that cystatin C could be a reliable tool to identify patients at a higher risk of adverse outcomes.

Author's Contribution

All authors contributed to the study conception and design. Material preparation and data collection were performed by Joana Tavares, Josefina Santos, Filipa Silva, João Oliveira, Andreia Campos, and António Cabrita. Data analysis was performed by Jorge Malheiro. The first draft of the manuscript was written by Joana Tavares and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

None declared.

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APPENDIX 7

Use of equations for glomerular filtration rate estimation in the elderly.

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Equations for glomerular filtration rate estimation use in the elderly

Utilização de equações para estimar o débito do filtrado glomerular nos idosos

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ABSTRACT

Chronic kidney disease (CKD) has been increasingly diagnosed in the elderly, though its clinical significance is still matter of debate. Serum creatinine and cystatin C are the most used endogenous renal function markers. Several equations, usually adjusted for demographical variables, have been derived from them, in order to estimate glomerular filtration rate. Serum creatinine levels are influenced by muscle mass so, in patients frequently sarcopenic as the elderly, tends to overestimate renal function. Differently, serum cystatin C seems to improve kidney function estimation in the elderly, although the best performance results have been obtained with equations that include both markers. Creatinine is more widely used than cystatin C, with MDRD and EPI being the most common creatinine-based equations. The EPI equation has been shown to improve significantly GFR estimation in subjects with no or mild kidney dysfunction, without jeopardizing eGFR performance in subjects with advanced CKD. Moreover, epidemiological studies have shown that EPI equation may allow a more clinically relevant identification of chronic kidney disease patients. Nevertheless, in the elderly population, one should not overemphasize the issue of GFR accurate estimation, but rather appreciate the probability of kidney dysfunction progression, taking into account the competitive risk between end-stage renal disease and death. Several studies have demonstrated that cystatin C-based (with or without creatinine) equations have considerable better prediction ability than creatinine-only based equations, particularly for death and cardiovascular events. Considering end-stage renal disease, results are more conflicting, although a recent meta-analysis has shown that in the elderly population cystatin C-based equations presented the best predictive behaviour. Thus, we stress the need for an individualized use of glomerular filtration rate equations in the elderly, in whom they should be regarded less as accurate estimators, but more as predictors of clinical outcomes, allowing for their use to be more judicious and clinically relevant.

Key-words: Clinical outcomes; creatinine; cystatin C; renal function.

RESUMO

O diagnóstico de doença renal crónica tem aumentado na população idosa, embora o seu significado clínico seja ainda debatido. A creatinina sérica e cistatina C são os marcadores endógenos de função renal mais utilizados. Várias equações, ajustadas para variáveis demográficas, foram derivadas destes marcadores com o objectivo de estimar o débito do filtrado glomerular. O valor de creatinina sérica é influenciado pela massa muscular pelo que, nos indivíduos com redução da massa muscular como é o caso dos idosos, tende a sobrestimar a função renal. Por outro lado, a cistatina C parece melhorar a estimativa da função renal nos idosos, embora o melhor desempenho tenha sido observado com as equações que incluem ambos os marcadores. A creatinina é mais utilizada do que a cistatina C, sendo as equações MDRD e EPI derivadas da creatinina, as mais usadas. Foi demonstrado que a equação EPI melhora significativamente a estimativa do débito de filtrado glomerular na população sem ou com ligeira disfunção renal, sem comprometer o desempenho em indivíduos com doença renal crónica avançada. Mais ainda, estudos epidemiológicos mostraram que a utilização da equação EPI permitirá uma identificação mais relevante dos doentes com doença renal crónica. Contudo, na população idosa não devemos enfatizar demasiado a necessidade de uma estimativa exata da filtração glomerular, mas sim avaliar a probabilidade de progressão da disfunção renal, tendo em conta o risco competitivo entre doença renal crónica terminal e morte. Vários estudos demonstraram que as equações derivadas da cistatina C (com ou sem creatinina), têm uma melhor capacidade preditiva, relativamente às equações derivadas unicamente da creatinina, no que se refere aos eventos cardiovasculares e à mortalidade. Relativamente à doença renal crónica terminal os resultados são mais controversos, embora uma metanálise recente mostrou que na população idosa as equações derivadas da cistatina C apresentam o melhor valor preditivo. Assim, sublinhamos a necessidade de uma utilização individualizada destas equações na população idosa, na qual estas devem ser valorizadas não tanto como estimadores precisos de função, mas mais como preditores de eventos clínicos, permitindo que a sua utilização seja mais criteriosa e clinicamente relevante.

Palavras-chave: Cistatina C, creatinina, eventos clínicos, função renal.

INTRODUCTION

Chronic kidney disease (CKD) has increasingly been considered a public health problem and a research priority[1] and is associated with an increased risk for all cause and cardiovascular mortality[2].

It is predominantly a disease of the elderly, who are the fastest growing end-stage renal disease (ESRD) group in USA and Europe[3,4], including Portugal, where patients over 65 years correspond to 57.6% of total ESRD incident population (Data from SPN registry 2012).

An accurate assessment of kidney function has several clinical implications, such as timely referral to nephrology, adequate drug dose adjustment, improved decision making in imaging testing and adequate renal replacement therapy consideration. Furthermore, an early detection and treatment of CKD may prevent or delay progression to ESRD.

The glomerular filtration rate (GFR) is considered to be the best indicator of kidney function, but methods to measure GFR using exogenous markers, such as inulin clearance, Cr-EDTA or Tc-DTPA, are laborious as well as expensive, being rarely used in clinical practice. Therefore, endogenous markers, such as serum creatinine or cystatin C, are used to estimate kidney function. Equations using these markers adjusted to other variables (mainly demographical) are an attempt to improve accuracy in estimation of GFR (eGFR). However, none of these eGFR equations have been validated in a large population of elderly patients.

In this article, we aim to review the performance and limitations of these endogenous markers and

their equations as estimators of GFR in the elderly. Additionally, the ability of the different eGFR equations in predicting significant clinical outcomes (ESRD, death) will be sought.

ENDOGENOUS MARKERS

Serum Creatinine

Serum creatinine (SCr), as a marker of renal function, continues to be widely used, in spite of inaccuracies in its measurement and interferences in its turnover, tubular secretion and production rate, which is mainly dependent of the muscle mass[5].

Renal function deteriorates by 8 ml/min per decade in the ageing population, although there is a wide intra-individual variability[6]. The loss of renal parenchyma with ageing accounts for this change, but decreased muscle mass seen in the elderly, resulting in a decrease of creatinine production, also influences renal function measurement[7].

Lower SCr levels have been reported in subjects with vitamin D deficiency, which has a high prevalence in the elderly, and probably increases the rate of loss of muscle mass in this population along with a decrease in muscle strength[8].

In addition, SCr measurement by the most common method (Jaffé) is subject to interferences by chromogens, such as bilirubin, glucose and uric acid. Similarly, the enzymatic method is prone to interference by bilirubin and some antibiotics. Large variations between laboratories in calibration of the SCr assays may also lead to inaccuracies in its determination[9]. Recently, an attempt to standardize measurement has been introduced by adoption of a common calibration to isotope dilution mass spectrophotometry standard with substantial improvement and traceability of SCr measurements[10].

Some authors reported several limitations with SCr as a GFR marker in older patients. Swedko *et al.*[11] reported that an SCr level greater than 1.7 mg/dL had almost perfect specificity but only 12.6% sensitivity for the detection of CKD (GFR ≤ 50 mL/min), in patients 65 years or older. This inability to diagnose CKD in older patients based only in SCr was also found by others[12]. Branten *et al.*[13] reported that hypoalbuminaemia influences the tubular SCr secretion leading to errors in estimation of GFR, highlighting the limitations of SCr as a kidney function marker in patients with nephrotic syndrome.

Creatinine Clearance

Creatinine Clearance (CCr), as measured from 24-h urine collection, is often used in clinical practice to measure GFR, but it overestimates GFR due to creatinine secretion by the renal tubules and the inherent limitations of SCr as a kidney marker. Moreover, CCr is susceptible to urine collection errors, especially in elderly patients[14], thus being a poor screening test for CKD.

Serum Cystatin C

Cystatin C is a 122–amino acid, 13-kDa protein that is a member of a family of competitive inhibitors of lysosomal cysteine proteinases. Its functions include involvement in extracellular proteolysis, immune modulation, and antibacterial and antiviral activities.

Cystatin C has several properties that make it a good candidate as a kidney function marker, including a constant production rate regulated by a gene expressed in all nucleated cells, free filtration at the glomerulus, complete reabsorption and catabolism by the proximal tubules with no reabsorption into the bloodstream, and no renal tubular secretion[15].

Most studies have shown that serum cystatin C levels correlate better with GFR than does SCr alone, especially at higher levels of GFR, and it was also thought to be less influenced by certain demographic factors such as age, race, gender, or muscle mass compared with SCr[16,17]. But, emerging new data have shown that it is, in fact, influenced by some of these factors.

Knight *et al.*[18], in a cross-sectional study, found that older age, male gender, greater weight, greater height, current cigarette smoking, and higher serum C-reactive protein (CRP) levels were independently associated with higher serum cystatin C levels after adjusting for CCr.

A recent study, although not focusing solely on elderly people, concluded that cystatin C was 9% lower in women and 6% higher in blacks for a given GFR[19]. Similarly, another recent study that reported population distributions of cystatin C in the United States using sera samples from the Third National Health and Nutritional Examination Survey noted that abnormal cystatin C was more prevalent with increasing age[20]. Moreover, in certain clinical settings, cystatin C level may be biased as a marker of kidney function, such as in patients with rapid cell turnover, uncontrolled thyroid disease and those under steroid therapy[21].

GFR ESTIMATION FROM SERUM CREATININE BASED EQUATIONS

Cockcroft-Gault (CG) equation

Cockcroft-Gault formula (CG) is one of the most widely used equations to estimate endogenous CCr, even among elderly people, although it was originally derived from mostly younger subjects, with only 24% older than 70 years and 4% female representation[22].

This equation provides an estimate of CCr, which is not equivalent to eGFR due to the effect of creatinine tubular secretion. Moreover, this equation is not adjusted for body surface area, using instead body weight as a surrogate for muscle mass, so it overestimates CCr in oedematous states and in obese patients[23], with bad performance in subjects with extreme weight.

Studies indicate that it actually underestimates GFR in the elderly, especially at higher GFR values. Verhave *et al.*[24] reported that the CG equation underestimates GFR in patients over 65 years old. In addition, Cirrilo *et al.*[25] have found that the CG equation systematically underestimated GFR in the elderly. Nevertheless, most of the estimated values using this equation were within 30% of measured GFR, which is an acceptable performance and superior to SCr alone.

Modification of Diet in Renal Disease (MDRD) Equation

The MDRD study equation[26] was developed using data from 1628 middle-aged patients with a GFR below 60 ml/min, none diabetic, for the estimation of GFR adjusted for 1.73m^{2}. This equation was re-expressed[27] with SCr standardized to the reference methods using isotope dilution mass spectrometry (IDMS). The MDRD equation has been recommended by the KDOQI Study Group for CKD diagnosis and classification[28]. It has several advantages over the CG equation including providing an estimate of GFR rather than CCr.

However, the MDRD equation also has several limitations, namely being less accurate at eGFR levels above 60 ml/min per 1.73 m^2. Consequently, it may lead to misdiagnosis and misclassification of CKD in individuals with mild CKD[29]. Another limitation is the existence of differences between various laboratories regarding the calibration of the SCr assay that leads to differences in GFR estimation[30]. The effect of the calibration of SCr assay was also reported in older patients[31] with the CG formula underestimating eGFR, whereas the MDRD Study equation overestimated it.

Notwithstanding, MDRD equation has been considered as more accurate for the elderly in comparison with the CG formula[32], and is especially advantageous for elderly people compared with the CG formula or CCr, because it only requires serum creatinine, age, gender and race, but not weight or any urine collections. The most widely used form of MDRD in elderly people is the four-variable equation[33].

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

The CKD-EPI equation[34] was developed using data from 16 studies, in an attempt to create a more accurate equation than the one proposed by the MDRD Study. The MDRD Study equation was developed in a study population with CKD and a mean GFR of 40 mL/min per 1.73 m^2, whereas the CKD-EPI equation was developed in a more diverse study population, including participants with and without CKD, with a mean GFR of 68 mL/min per 1.73 m^2.

The estimated prevalence of CKD in the US by using the CKD-EPI equation was 1.6% lower than that obtained by the MDRD equation (11.5% compared to 13.1%)[35], with CKD-EPI equation having

lower bias, especially at eGFR ≥ 60 ml/min/ 1.73m2[34]. Other studies have also reported that the MDRD equation use increased the prevalence of CKD in the general population compared with the CKD-EPI formula[36], and that CKD-EPI equation improved performance in healthier populations, whereas the CKD-MDRD formula provided more reliable results regarding CKD patients[37]. A recent systematic review[38] reported that neither the CKD-EPI nor the MDRD Study equation were optimal for all populations and GFR ranges.

In the development of CKD-EPI equation[34] there were a limited number of participants older than 70 years and also incomplete data on measures of muscle mass and other conditions or medications that may influence SCr. It is important to note that even using CKD-EPI equation, the prevalence of CKD in the elderly remained high. In a meta-analysis of data from 1.1 million adults[39], CKD-EPI equation classified fewer individuals as having CKD and was a better predictor of mortality and ESRD risk than MDRD equation.

However, in a prospective population-based cohort study from France[40], the CKD-EPI and the MDRD equations provided very similar CKD prevalence and long-term risk assessment in the elderly (> 65 years). Recently, in a prospective study[41] the accuracy of these equations was tested in European subjects, 74 years or older, comparing with measured GFR by a reference method. The authors concluded that the CKD-EPI equation appeared less biased and was more accurate than the MDRD Study equation.

GFR ESTIMATION FROM SERUM CYSTATIN C–BASED EQUATIONS WITH OR WITHOUT SERUM CREATININE

Over the last decade, several serum cystatin C-based equations have been developed and proposed to estimate the GFR from serum cystatin C concentration as an alternative filtration marker[42,43] to SCr-based equations.

Overall, serum cystatin appears to be less susceptible to metabolic and extrarenal factors than SCr, namely in the elderly[44]. Therefore, serum cystatin C-based equations seem to be promising for renal function estimation in the elderly. Several studies have confirmed cystatin C as a better estimator of kidney function in the older[45,46] and in the very old[47] subjects.

Stevens et al.[19], reported an equation (CKD-EPI SCr and cystatin formula) incorporating both cystatin C and SCr in addition to age, sex, and race. This study, involving a pooled analysis of individuals with CKD, concluded that this equation provided a better estimation of GFR. In recent years, several studies analyzed the accuracy of this formula in the elderly, without unequivocal results. Bevc *et al.*[48], in a group of 317 Caucasian patients aged > 65 years, compared different equations against 51Cr-EDTA clearance, and found that a higher diagnostic accuracy was achieved with the equation that uses both SCr and cystatin C than with MDRD ($P < 0.013$) or CKD-EPI creatinine formula ($P < 0.01$). Interestingly, the simple cystatin C formula (100/serum cystatin C) presented similar results to the double markers formula, chiefly in patients with mild kidney dysfunction.

In a cross-sectional study[49] designed to evaluate GFR estimating equations in comparison to a measured GFR, investigators from the Berlin Initiative Study (BIS) measured GFR by iohexol clearance in a subset of 610 participants with mean age of 78.5 years. A major finding of this study was that cystatin C had a much stronger association with GFR than SCr. The addition of age and gender greatly improved SCr-based GFR estimation, but the same variables added little value to cystatin C-based eGFR. In this elderly cohort, the best GFR estimation was derived from a combined SCr and cystatin C equation; however, cystatin C-only equation was clearly superior to a creatinine-only equation.

PROGRESSION TRAJECTORY OF GFR IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

Prevalence of CKD in the elderly is, independently from the formula used, high. Published rates vary from 25%[50] to 55%[51] for stage 3-4 CKD using the MDRD formula. Yet, as important as CKD detection, is the understanding of how CKD progresses in the aged population, because it would enable a more

targeted provision of care, particularly for ESRD-related assessments.

The rate of loss of kidney function has been estimated around 7-8 ml/min/decade in subjects over the age of 30[52]. Few studies have addressed this issue specifically in the elderly. In a Canadian cohort of about 10 000 subjects over 65 years, with an eGFR (by MDRD equation) at baseline < 90 ml/min, the age-adjusted eGFR rate of decline varied between 0.8 and 2.7 ml/min/year over a median follow-up of 2 years, with male gender and diabetic status being associated with the highest rates of decline[53]. Furthermore, this study showed that the majority of subjects had a mean eGFR change of 5 ml/min or less, independently from the baseline eGFR. Results from the Cardiovascular Health Study indicated that deterioration in kidney function (increase in serum creatinine > 0.3 mg/dl) was seen in less than 3% of the subjects (mean age 73 years), after a follow-up of at least 3 years[54]. Although these data emphasize the indolent nature of CKD progression in the elderly, we cannot ignore that there is a subset of high-risk patients in whom significant progression is foreseen by the presence of diabetes, substantial proteinuria and lower baseline eGFR (< 30 ml/min)[53,55].

Shlipak *et al.*[56] showed that serum cystatin C-based eGFR detected significantly larger declines in kidney function than creatinine-based formulas in the elderly. In a cohort of 4 380 participants over the age of 65 years, with a maximum follow-up of 7 years, these investigators detected a mean eGFR loss of 0.4 and 1.8 ml/min with creatinine- and cystatin C-based eGFR, respectively ($P < 0.001$). A rapid decline in eGFR (> 3 ml/min/year) was significantly more common with cystatin C- (25%) than with creatinine-based eGFR (16%). The remaining issue is how this higher eGFR decline identified by cystatin C-based formulas eventually correlates with significant clinical outcomes, as ESRD.

CREATININE-BASED EGFR EQUATIONS AS PREDICTORS OF CLINICAL OUTCOMES

Delaying the progression of kidney dysfunction has been one of the clinical targets when managing CKD patients, as it would result in a reduction of the incidence of ESRD. Nonetheless, one should remember that while CKD progresses with time, the chance of death also increases, particularly in the elderly. Hence, when studying the behaviour of eGFR formulas as predictors of ESRD, we have to bear in mind that, inevitably, we also need to consider death as a competitive event.

This point was nicely evaluated within the American Veteran Affairs cohort of about 210 000 subjects with CKD stages 3-5 at baseline (determined by the MDRD equation), predominately male (only 3% women) and old (83% over the age of 65 years), followed for a mean of 3.2 years[57]. This study showed that the level of eGFR below which the risk of ESRD exceeded the risk of death varied with age, ranging from 45 ml/min for 18-44 year-old to 15 ml/min for 65-84 year-old patients. A shift from the uniform stage-based approach in managing CKD to a more individualized one, in which age would be considered a major effect modifier, was called for.

Matsushita *et al.*[39] analyzed simultaneously different hazard outcomes as ESRD and death, comparing reclassification groups resulting from the application of the two main SCr-based eGFR equations: MDRD and EPI. They showed that EPI equation improved eGFR prediction ability for all-cause and cardiovascular mortality, and ESRD in comparison to MDRD equation, although, after stratifying for age, that improvement in subjects older than 65 years remained only for mortality but not for ESRD prediction.

However, we should not forget that SCr close correlation with the muscle mass is a shortcoming when considering its accuracy as kidney function marker, particularly in populations with important sarcopenia, as the elderly. When considering CKD progression by SCr-based eGFR tertiles as a predictor of mortality in a group of around 15 000 subjects with CKD stages 3-5 at baseline (using SCr-only EPI formula) followed for a median of 3.4 years, investigators found that those subjects in the lower (declining) and upper (increasing) eGFR tertiles had a significantly higher risk of death than those in the middle (stable) tertile, if only patients over the age of 60 years were considered[58]. This rather counter-intuitive observation seemed associated with longitudinal changes in nutritional status (as evaluate by body mass index and serum albumin decrease), that

were significantly more severe in the upper (increasing) eGFR tertile.

CYSTATIN C-BASED EGFR EQUATIONS AS PREDICTORS OF CLINICAL OUTCOMES

Chronic kidney disease progression in the elderly seems to be more significant when cystatin C-based formulas are considered[56]. Similarly, cystatin C has been shown to be a better predictor of morbimortality in CKD patients than SCr. In a cohort of close to 5 200 subjects, with a mean age of 72 years, followed for an average 12.2 years, CKD was considered if eGFR below 60 ml/min using EPI SCr- or cystatin C-based formulas[59]. Risk of death (all-cause or cardiovascular) was significantly higher in patients with CKD defined only by cystatin C-based formulas but not in those with CKD defined only by SCr-based equation[59]. CKD status was associated with ESRD prediction, irrespective of the marker used, although the risk of ESRD in patients with CKD defined only by cystatin C-eGFR was more than double the risk of those with CKD defined only by SCr-eGFR[59].

In a meta-analysis of 11 general and 5 CKD-only populations, including almost 94 000 subjects with about 8 years follow-up, it was demonstrated that GFR estimated by cystatin C alone or in combination with SCr was a stronger predictor of death or ESRD than SCr-alone eGFR, particularly in participants over 65 years[60]. It was also shown that, in subjects over the age of 65 years, cystatin C-based eGFR returned a lower GFR estimate than SCr-based eGFR, in contrast with what was seen in the overall population.

CONCLUSIONS

Any endogenous kidney function marker has limitations. Understandably, eGFR formulas derived from them will present similar drawbacks. The close relationship between muscle mass and SCr accounts largely for the inaccuracy of this marker in the elderly, with cystatin C presenting a better performance as GFR estimator. Even so, SCr is a much widely used marker, and the new EPI formula seems to improve significantly GFR estimation in subjects with no or mild kidney dysfunction, without jeopardizing eGFR performance in subjects with advanced CKD. Its use, particularly in the epidemiological setting, has proven to be useful in identifying subjects with a more relevant CKD (i.e., reduction of kidney function but also with high comorbidity and more prone to CKD progression), selecting those that would profit more from specific interventions (as referral to a nephrologist). Nevertheless, growing evidence has shown cystatin C to be a stronger predictor of clinical outcomes, as death and ESRD, than SCr in the elderly. This observation illustrates the usefulness of cystatin C in the elderly with CKD, in whom important decisions about CKD management and ESRD preparation have to be considered, as it may allow us to better predict CKD progression and appreciate the competitive ESRD versus death risk.

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APPENDIX 8

ESRD management in elderly patients: towards an individualized patient-centred approach.

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TOP ARTICLE – A COMMENT

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Brown MA, Collett GK, Josland EA, Foote C, Li Q, Brennan FP. CKD in elderly patients managed without dialysis: survival, symptoms, and quality of life. *Clin J Am Soc Nephrol* 2015; 10 (2):260-268.

ESRD management in elderly patients: towards an individualized patient-centred approach

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Chronic kidney disease (CKD) is a large and growing problem among aging populations. Patients over 65 years of age represent the most rapidly growing segment of the end-stage renal disease (ESRD) population in wealthier countries[1,2], as well as showing a high prevalence of earlier stages of CKD, with relative prevalence equally striking for populations in the USA, Canada and Europe[1,3-5]. One of the major challenges to clinicians caring for older CKD patients expected to progress to ESRD lies in evaluating the overall benefit of offering renal replacement therapy to them. Although survival may have improved over time for older patients initiating dialysis[6], dialysis may be associated with only a limited survival benefit, when comparing to conservative management, as demonstrated by several studies[7,8], with an overall decline in functional status[9],more hospitalization[10], and a poor quality of life. So, among elderly patients with a high burden of comorbidity, conservative management may, therefore, be a therapeutic option, as dialysis is unlikely to prolong or improve quality of life. To offer that option is extremely important to incorporate conservative care pathways into clinical practice, and prioritizes an individualized patient centred model of care.

Brown *et al.*[11] presented data supporting conservative care pathways in an excellent prospective observational study, demonstrated that symptoms can be effectively controlled and that patients experience similar quality of life with or without dialysis. In their programme, patients are seen by both the nephrologist and a palliative care team[11], with specifically but convertible tasks. The palliative care team members manage physical symptoms and psychological issues and help with advance care planning, whereas the nephrology team manages CKD related complications, like anaemia, fluid balance and try to preserve residual renal function.

In this renal supportive care programme, elderly patients with advanced CKD who choose not to do dialysis survived a median of 16 months with a 53% 1-year survival from the time of referral to the programme. Although these patients had a lower survival than younger patients attending the pre-dialysis clinic with a planned future dialysis, there was no significant difference in their adjusted survival compared with a third group of patients who commenced dialysis, during the same period, without attending the pre-dialysis clinic. Moreover, above two thirds of patients in the renal supportive care programme group

achieved improvement in their symptom burden by 6 and 12 months[11].

Conservative management programmes are developing around the world to help care for patients who choose no dialysis therapy. Although the majority of these programmes are still in the beginning are projected to increase over time and may care for an estimated 10% to 20% of the ESRD population[12].

It is essential to increase the training and education of nephrologists in the care of geriatric patients[13], namely in the conservative management of ESRD. They need to be confident in recognizing and managing ESRD related symptoms, to be aware when to refer to palliative care, and they should be comfortable with end-of-life discussions and providing prognostic information to patients, families and caregivers[14].

For evaluating renal replacement therapy benefits and risks and informing patients and their families about ESRD treatment options, there is recently an interest in developing predictive mortality models for incident and prevalent dialysis patients[15-17]. Applying predictive mortality models can be useful, although these models currently fail to address the key question of clinical utility[18], and maybe they are best used to offer information and initiate reflections integrated in a shared decision-making process.

Although these prognostic tools may also help to identify patients at high risk of early death with whom conservative management may be a better option, not all patients starting dialysis with a high score, have a poor prognostic. And it is important to note that a high symptom burden exists in both those patients opting for dialysis and those patients opting for a conservative therapy, as shown by Brown *et al.*[11].

Symptoms, such as chronic pain, fatigue, difficulty sleeping, itchy skin, restless legs, cognitive impairment, and depression are very common in ESRD patients, as evidenced by several studies, often similar to the burden carried by cancer patients[19,20]. Brown *et al.*[11] demonstrated that palliative care teams could reduce the symptom burden in both, dialysis and no dialysis groups.

So, this study draws our attention to the importance to implement an effective collaborative programme with palliative care planning, also for dialysis patients rather than to limit symptom management to those who choose not to do dialysis.

In the management of patients with complex morbidity, as is the case for many ESRD patients, we must incorporate palliative and other supportive interventions to address symptom burden, rehabilitation, and end-of-life care, towards a patient-centred vision of care[21,22].

The nephrology community needs to overcome barriers and move to the implementation and effectiveness of advance care planning programmes, in order to provide the best care for our patients and their families.

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APPENDIX 9

Incorporating Scoring Risk Models for Care Planning of the Elderly with Chronic Kidney Disease.

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Review Article

Incorporating Scoring Risk Models for Care Planning of the Elderly with Chronic Kidney Disease

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Mortality in chronic kidney disease remains high, particularly among the elderly, who represent the most rapidly growing segment of the end-stage renal disease population in wealthier countries. The management of older adults with chronic kidney disease has become a clinical challenge, and care for those patients expected to progress to end-stage renal disease should focus on evaluating the overall benefit of offering renal replacement therapy to them. Predictive mortality models may help to inform shared decision-making in the trajectory of the elderly with chronic kidney disease. This review discusses current literature on the available predictive models for predicting survival in elderly chronic kidney disease patients and reflects the author's own interpretation and experience.

1. Introduction

The prevalence of chronic kidney disease (CKD) is higher in older people. Patients over 65 years of age represent the most rapidly growing segment of the end-stage renal disease (ESRD) population in wealthier countries [1, 2], as well as showing a high prevalence of earlier stages of CKD, with relative prevalence equally striking for populations in the USA, Canada, and Europe [1, 3–5].

The management of older adults with CKD has become a clinical challenge, and care for those patients expected to progress to ESRD should focus on evaluating the overall benefit of offering renal replacement therapy (RRT) to them. Although survival may have improved over time for older patients initiating dialysis [6], this survival benefit in the elderly is lower as compared to their younger counterparts [7]. Comparing dialysis versus conservative management, dialysis may be associated with a very small survival benefit [8] and associated with a concomitant overall decline in functional and cognitive status [9] and more hospitalizations [10].

In elderly patients with significant comorbidities, conservative management may therefore be a better therapeutic option, as dialysis is unlikely to prolong or improve quality of life [11].

Beyond the usual clinical criteria, the RRT decisions in elderly patients must incorporate assessment of physical and cognition function and other components of geriatric syndrome.

Recently there is a growing interest in developing predictive mortality models to improve patient outcomes through individualized risk prediction. These predictive models may help the nephrologist in their discussions with patients and their families about suitability or otherwise of initiating dialysis.

This review discusses current literature on the available predictive models for predicting survival in elderly CKD patients and reflects the author's own interpretation and experience.

2. Risk Prediction Models

2.1. Definition, Performance, and Validation. Risk prediction models are based on equations designed on the basis of

prognostic factors and clinical outcomes, available at the time the prediction is made, and collected in specific and representative cohorts of individuals followed up for a given period of time [12, 13]. Each prognostic factor or variable is awarded a weight (coefficient) and combined in a mathematical formula, the so-called risk equation, to predict an outcome of interest [12, 13].

The performance of a risk prediction model is commonly assessed by testing its calibration and discrimination. Calibration describes the agreement of observed and predicted event rates [14], and discrimination expresses the ability of prediction model to distinguish individuals who will develop the outcome of interest from those who will not [15].

The most used measure of discrimination is the C-statistic, a measure of concordance between model-based risk estimates and observed events [16–18]. The C-statistic ranges from 0.5 (random concordance) to a theoretical maximum of 1 (perfect concordance), but it has several limitations [18].

First, as a single number, it summarizes the discrimination of a model but does not communicate all the information and lacks direct clinical application. The C-statistic does not effectively balance misclassification errors, and a weighted sum of sensitivity and specificity have more clinical relevance (predicting an individual who ultimately experiences an event to be at low risk; predicting an individual who does not experience an event to be at high risk), according to the principles of decision analysis [19]. Secondly, the value of the C-statistic depends not only on the model being assessed, but also on the distribution of risk factors in the sample to which it is applied.

Calibration, the agreement of observed and predicted outcomes, is most appropriately assessed using a calibration plot [16], which assesses how accurately the model's predictions match overall observed event rates. Unfortunately, in the majority of the studies calibration measures are often omitted [20, 21].

Another important question for physicians to consider is whether the score accurately predicts outcomes in people like their patients. A simple internal validation, that is, a computing performance measures in the same cohort that has been used to develop the model, usually leads to overoptimistic estimates of the performance of a prediction model [13].

Thus, the use of methods such as cross-validation has been proposed for assessing internal validity. With this method, the original cohort is split into a development and a validation sample, to develop the score in one group and test in the other [13, 22].

Another method that can be used if the number of individuals in the cohort is relatively low or to avoid false results caused by one particular random split is the bootstrapping based on many repeated splits of the data [13, 16, 22].

Even with a good performance measures achieved in the same cohort as the one that was used to develop the model, before adopting a risk score into practice, clinicians need to decide whether the score accurately predicts outcomes in people like their patients. Therefore, ideally, the model needs to be tested in a group of people that was not used to develop the model; it needs to be externally validated [23]; that is, the performance of the prediction model is tested in patients with the same disease but belonging to a different source population.

2.2. Clinical Usefulness. Clinical usefulness may be evaluated by utility and usability. The utility reflects the extent to which the risk score actually affects clinical decisions [24]. The usability reflects the availability of a clinical decision aid, such as a nomogram or online calculator, which would allow risk prediction at the bedside [21]. For a risk model to be useful in practice, it needs to include variables that are well defined, measurable, and readily available. Finally, information on outcomes based on these models must be transferred in a way that is understandable for all involved in shared decision-making process.

3. Risk Prediction Scoring Models for Elderly CKD Patients

3.1. Mortality Risk Prediction Models in CKD. In 2013, Tangri et al. [21] conducted a systematic review to identify prediction models for kidney failure, cardiovascular events, and all-cause mortality in CKD patients. They found five studies (6 models) [25–29] that examined either all-cause mortality or the composite outcome of kidney failure or death. More recently, Stryckers et al. [30], in an attempt to construct an algorithm that helps in planning the care of elderly people with advanced CKD, identified 4 risk prediction models that target elderly people with CKD 3–5 [28, 31, 32] and 12 models developed in elderly with ESRD [33–38].

Looking to the risk models that specifically included elderly people with CKD, the study of Johnson et al. [28] used the same variables (age, sex, eGFR, diabetes, hypertension, and anemia) for both outcomes (RRT or death). They found that although the same six variables predicted mortality (C-statistic 0.70) and its composite end of RRT and death (C-statistic 0.71), the overall prediction was markedly less effective than for RRT (C-statistic 0.91). They also found an inverse association between age and hypertension for death and a direct association for kidney failure. They concluded that predicting RRT requires a separate risk score, because predicting the composite endpoint would favor characteristics that predict mortality, since mortality is much more common than RRT in elderly patients. These models [28] were not validated externally, and calibration measures were not reported.

More recently, Bansal et al. [31] developed a prediction equation for 5-year risk of mortality for older people with CKD stages 3–5 not treated with dialysis. The equation included nine readily available clinical variables (age, sex, race, eGFR, urine albumin-to-creatinine ratio, smoking, diabetes mellitus, and history of heart failure and stroke), and it was externally validated in a large cohort of elderly CKD patients. This model has an acceptable calibration and discrimination in both the development (C-statistic = 0.72; 95% confidence interval, 0.68 to 0.74) and validation cohort (C-statistic = 0.69; 95% confidence interval, 0.64 to 0.74). However, one of the limitations pointed is that the validation cohort did not fits the frailty phenotype associated with CKD [39], because the authors enrolled well-functioning

men and women, and it has been well established that frailty is an additional risk factor for mortality in CKD patients [31].

In another model, Weiss et al. [32] developed a risk prediction model in a retrospective cohort of patients aged 65 to 79 and 80 and older with moderate-to-severe CKD (eGFR, <30 mL/min per 1.73 m^2) to predict mortality at 6 months and at 2 years. The model included sixteen comorbidities and measures of health and functional status. Although the C-statistics for each model for both periods (6 months and at 2 years) indicated a moderate discrimination (0.68–0.69), once more, this score risk was not externally validated. In addition, the presence of comorbidities was determined within administrative databases, and in retrospective data, which can considerably reduce the predictive performance of the model.

However, one of the strengths of Weiss et al. score [32] was the incorporation of nondisease specific measures including markers of healthcare use (e.g., hospitalizations) and functional status (e.g., falls, dementia), contrary to the other available risk prediction models for mortality in adults with CKD that mainly focus on traditional risk factors.

3.2. Mortality Risk Prediction Models in ESRD. In 2009, Couchoud et al. [34], using just clinical features, based on the REIN (French Renal Epidemiology and Information Network) cohort data, predicted 6-month mortality in elderly (aged 75 and older) with ESRD patients after initiating dialysis.

Nine risk factors were selected (demographic and baseline clinical variables), and the score showed good calibration, as reflected by the concordance between observed and expected mortality rates in the validation sample, but with only a moderate discrimination (mean C-statistic 0.70). The authors pointed out some limitations, namely, a selection bias due to the imputed missing data, and the fact that no information was available about ESRD patients who were not referred to nephrologists or did not receive dialysis. Therefore, this score cannot be generalizable to the entire population of elderly ESRD patients, particularly to the patients with high comorbidities and poor conditions, in which this score cannot replace the clinical judgment. This score can be used to facilitate discussion with patients and their families, but not to withhold dialysis [34].

The Couchoud et al. model [34] was further externally validated in an US population [33], although investigators modified the score and they concluded that indices performed poorly with respect to prediction of 6-month mortality in in older patients with ESRD commencing dialysis.

Since mortality may be high in the first few months after initiating dialysis, in 2015, in an attempt to improve their previous prognostic score [34], using the REIN registry, Couchoud et al. [35] chose to focus on very early mortality during the first 3 months of dialysis, in patients aged 75 years and older. They founded that male gender, age over 85 years, congestive heart failure, severe peripheral vascular disease, dysrhythmia, severe behavioral disorders, active malignancy, serum albumin, and impaired mobility were independently associated with 3-month mortality.

Despite a good calibration and discrimination, this model [35] had some limitations. First, this score was built within administrative databases. Second and more important, it was derived from patient population who have initiated RRT and do not include those who refuse, are not selected for, or do not survive to dialysis initiation.

Also, focused in early mortality after dialysis initiation (3 months), Thamer et al. [37], using the US Renal Data System (patients aged ≥ 67 years), validated a score and proposed a simple risk assessment questionnaire, based on ready available information (age, low albumin, assistance with daily living, nursing home residence, cancer, heart failure, and hospitalization).

This model [37] was not externally validated and only used data from administrative databases, with no inclusion of more detailed clinical and psychosocial data, which is much important in elderly ESRD patients. Moreover, this model excluded patients who did not choose dialysis and only included patients with a 2-year previous follow-up.

Floege et al. [40] have published another risk prediction model developed in European hemodialysis cohort with a mean age of 64 years old, using objective measurements only (i.e., no surprise question or dementia). This model was then validated in an external cohort of the Dialysis Outcomes and Practices Patterns Study (DOPPS) and exhibited a moderate discrimination (C-statistic of 0.68 to 0.79).

Nevertheless, the Floege et al. score [40] has not been developed nor validated in a cohort of elderly dialysis patients. In addition, because the development cohort includes only patients who survived the first 3 months, whereas the validation cohort of DOPPS includes mainly prevalent patients, it is still not a perfect risk predictor for frail elderly, in which the risk of short-term mortality is what needs to be predicted.

Considering the impact of comorbidity for predicting survival in elderly dialysis patients, Liu et al. [36] modified the original Charlson Comorbidity Index (CCI) [41] and developed a new comorbidity index (nCI) for mortality analyses for dialysis patients using administrative data, based on the comorbid conditions used by the United States Renal Data System (USRDS). The index was developed using the 2000 US incident dialysis population and validated using the 1999 and 2001 US incident dialysis populations and the 2000 US prevalent dialysis population. Interestingly, the Liu et al. comorbidity index [36] includes 11 comorbid conditions (atherosclerotic heart disease, congestive heart failure, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, dysrhythmia, other cardiac diseases, chronic obstructive pulmonary disease, gastrointestinal bleeding, liver disease, cancer, and diabetes), but not the age factor, one of the components of the original CCI. The authors [36] showed that nCI performance was almost identical to the individual comorbid conditions regarding model fit, predictive ability, and effect on inference, and it its results showed that nCI is a better predictor than the CCI [41]. Actually, age and comorbidities should both be integrated in a risk prediction tool as major drivers for mortality.

Cohen et al. [42] developed a prognostic model to determine the risk of death in dialysis patients by combining selected variables from the modified CCI (age, presence of dementia, and peripheral vascular disease) and serum albumin with the nephrologist's answer to the Surprise Question ("Would I be surprised if this patient died within the next 6 months?"). This simple bedside tool for predicting 6-month mortality had superior prognostic value than either tool independently. Although this prognostic model has not been developed or validated in elderly dialysis patient, it has the advantage of being available as online calculator ("Surprise Question Predictor"at http://nephron.com).

However, we can argue that this model [42] has the limitations of being based on subjective parameters (i.e., dementia), difficult to define in a dialysis patients. In addition, the Surprise Question is highly subjective and variable based on nephrologist training and knowledge of patient.

Recently, Wick et al. [43] developed a risk score (Alberta score) that potentially could be used to estimate mortality risk during the next 6 months for older patient initiating dialysis.

They identify several independent predictors of mortality, which include age of 80 years or older, early dialysis therapy, atrial fibrillation, congestive cardiac failure, lymphoma, metastatic cancer, and hospitalization in the prior 6 months.

They used a large population-based data source (renal registry data from Alberta, Canada) consisting of incident hemodialysis and peritoneal dialysis patients in outpatient settings, which should minimize selection bias.

The incorporation of variables like lymphoma and metastatic malignancy as mortality predictors; it maybe will add clinical utility in contexts in which these conditions appear with reasonable frequency. Moreover, hospitalizations in the 6 months prior to dialysis initiation, like in Thamer score [37], were also a mortality predictor and probably related to comorbidity and disease severity.

Although the Alberta score [43] seems to be a rigorously and useful derived model, it needs to be replicated in an independent population.

Finally, the Study of Heart and Renal Protection (SHARP) CKD-CVD model [44] was developed using data from 9270 patients with moderate-to-severe CKD (including CKD 3B, 4, 5, dialysis, and kidney transplant patients) in the Study of Heart and Renal Protection (SHARP) [45], followed for an average of 5 years. This model projects lifetime cardiovascular event risks, kidney disease progression, and (quality-of-life adjusted) survival. Higher age, previous cardiovascular events, and advanced CKD were the main contributors to increased individual disease risks. The model [44] performs well in categories of patients by CKD stage in SHARP and in external CKD cohorts. A user-friendly web interface (SHARP calculator, available at http://dismod.ndph.ox.ac.uk/kidneymodel/app/) which also includes projection of healthcare costs is freely available which facilitate model use. However, one of the limitations of the SHARP CKD-CVD model was that SHARP cohort [45] excluded patients with major coronary disease, whereas in routine clinical practice coronary heart disease is highly prevalent in CKD patients.

4. The Author's Experience

Portugal has the highest unadjusted incidence and prevalence of ESRD among European countries [46] and 67.7% of the incident dialysis patients, in 2015, were over 65 years with a mean age of prevalent patients of 66.7 years [47].

The Nephrology Department at Hospital de Santo António, Centro Hospitalar do Porto, conducted a retrospective cohort study of patients aged 65 years and over, referred to our Department, who started dialysis as their first RRT. This study aimed to identify elderly ESRD patients who have higher probability of death, early after starting dialysis, and develop a prognostic scoring model of 6-month mortality. This score was developed using data from a cohort of 360 patients who initiated dialysis between 2012 and 2015. Demographics and clinical variables were included as potential predictors. Multivariable adjusted logistic regression was used to determine the independent predictors of 6-month mortality. The β-coefficients from the final model (backward elimination) were used to generate point scores for calculating mortality risk. Then, our score was compared with others previously validated (Couchoud et al. [34] and Cohen et al. scores [42]).

In a univariate logistic analysis, the significant predictors of 6-month mortality were female gender, age > 75 years, ischemic heart disease, congestive heart failure, dysrhythmia, low albumin levels, unplanned dialysis, functional dependence, cognitive impairment, and being institutionalized. These candidate variables were included in a multivariable analysis and the regression β-coefficients from the final model were used to derive point scores to predict a patient's risk of dying in the first 6 months after starting dialysis. The final model for 6-month mortality risk included older age, female gender, ischemic heart disease, and low albumin levels *(articles submitted or in draft)*.

Our model does not seem to be weaker than other published scores (the area under the receiver operating characteristic curve (AUC) in our score, Couchoud et al. [34] and Cohen et al. [42] scores were 0.85, 0.73, and, 0.81, resp.).

This simple prediction score based on readily available clinical and laboratory data can be a practical and useful tool to assess short-term prognosis in elderly ESRD, although further research is needed to confirm and validate the use of this prognostic score.

5. Conclusions

Shared decision-making is a process of communication. It is particularly relevant when counselling elderly patients and their families on different RRT treatment options. This process may enable us to understand the advantages, limitations, and burdens, of the different treatment options, including conservative care.

Reliable, validated risk prediction models that correctly estimate risk of death after starting RRT may provide a more accurate perception of the desirability of starting dialysis and help in shared decision plan. Healthcare workers need to understand the applicability and limitations of these models so that they can be used appropriately.

In addition to the lack of external validation of the majority of the existing mortality scores, another important limitation is their inherent selection bias. Mostly, they were derived from patient populations who have initiated dialysis therapy and do not include those who are not selected for, or not accept, or do not survive to dialysis initiation. A score that evaluates older patients at the point of decision-making, rather than at the point of starting dialysis, would be more helpful.

Determining and communicating information prognosis for individual patients should be a part of clinical practice, and although the scores risk models cannot replace the clinical judgment, they are important instruments because they allow the patient to be aware of the future course of his disease and help physicians to guide clinical decision.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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