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COMPETING-RISK ANALYSIS OF DEATH AND ESKD BY HYPERKALEMIA STATUS IN NON-DIALYSIS CKD PATIENTS RECEIVING STABLE NEPHROLOGY CARE

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RUNNING HEAD: Hyperkalemia Burden in Nephology Clinics

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ABSTRACT

Hyperkalemia burden in non-dialysis CKD under nephrology care is undefined. We prospectively followed 2443 patients with two visits (referral and control with 12-month interval) in 46 nephrology clinics. Patients were stratified in four categories of hyperkalemia (sK≥5.0 mEq/L) by sK at visit 1 and 2: Absent (no-no), Resolving (yes-no), New Onset (no-yes), Persistent (yes-yes). We assessed competing risks of ESKD and death after visit 2. Age was 65±15 y, eGFR 35±17 mL/min/1.73 m^2, proteinuria 0.40 (0.14-1.21) g/24h. In the two visits sK was 4.8±0.6 and levels ≥6 mEq/L were observed in ≤ 4%. Hyperkalemia was absent in 46%, resolving 17%, new onset 15% and persistent 22%. Renin-angiotensin-system inhibitors (RASI) were prescribed in 79% patients. During 3.6-year follow-up, 567 patients reached ESKD and 349 died. Multivariable competing risk analysis [sub-hazard ratio-sHR, 95%Confidence Interval-CI] evidenced that new onset [sHR 1.34, 95%CI 1.05-1.72] and persistent [sHR 1.27, 95%CI 1.02-1.58] hyperkalemia predicted higher ESKD risk versus absent, independently from main determinants of outcome including eGFR change. Conversely, no effect on mortality was observed. Results were confirmed by testing sK as continuous variable. Therefore, in CKD under nephrology care, mild-to-moderate hyperkalemia status is common (37%) and predicts per se higher ESKD risk but not mortality.

KEY WORDS: CKD, ESKD, Death, anti-RAS, hyperkalemia, competing risk

INTRODUCTION

Chronic hyperkalemia is common in non-dialysis chronic kidney disease (ND-CKD). Recent observational studies have reported a greater prevalence of high serum potassium (sK) in this population than in general population, though with rates extremely variable -from 1% to 50%- and mainly dependent on GFR and comorbidities [1-7]. Prevalence of hyperkalemia also increases with the number of measurements, indicating that identification of hyperkalemic patients cannot be based on a single sK test [6].

Hyperkalemia poses a risk excess of mortality that becomes significant for even moderate increases of sK (≥5.0 mEq/L) [7-13]. Conversely, controversial data have been reported on the relationship between hyperkalemia and progression to end-stage kidney disease (ESKD) [1,4,10,13-15]. Gaining insights into this latter association is critical because additional determinant of hyperkalemia is the prescription of inhibitors of renin-angiotensin- system (RASI) [16-17], that are the first-choice antihypertensive agents in CKD due to the nephroprotective efficacy [20]. In this regard, it is interesting that RASI withdrawal driven by hyperkalemia increases mortality of patients seen in the general medicine setting [17,21]. A vicious circle may similarly ensue with hyperkalemia onset and dependent non-use or withdrawal of RASI leading to ESKD. Increased awareness of this phenomenon and adequate management of hyperkalemia through dietary and/or pharmacological intervention may interrupt this circle [22-24].

Noteworthy, the effect of hyperkalemia on ESKD needs to be primarily assessed in tertiary nephrology care, that is, the reference of care of high-risk CKD patients; in this setting, moreover, ESKD overcomes mortality at variance with what observed in unselected CKD population [24-26]. To gain a proper analysis of the effect of sK on kidney survival in referred ND-CKD, two methodological aspects must be considered. First, a competing risk approach should be used to take into account the

potential occurrence of death before ESKD; second, analyses must be adjusted for the severity of CKD progression because GFR decline, that is associated with worse prognosis, also increases *per se* sK levels.

To date, no study has properly evaluated the effect of hyperkalemia on ESKD in outpatient renal clinics. We therefore studied a large prospective cohort of ND-CKD patients under stable nephrology care to verify in outpatient CKD clinics (I) the prevalence of hyperkalemia at referral and after 12 months, (II) the hyperkalemia-related risk of ESKD and all-cause death in the subsequent period of follow up. The effect of exposure was evaluated by competing risk analysis adjusted for main confounders, including the eGFR change in the first year of nephrology care.

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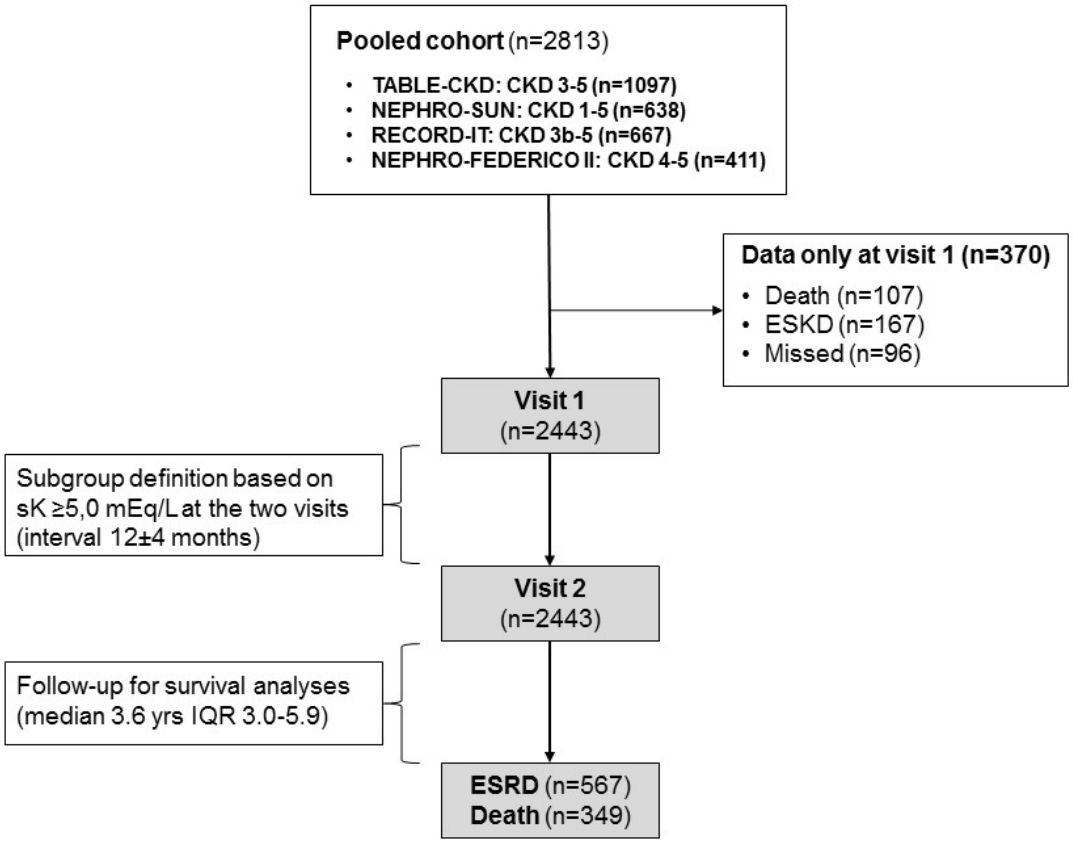
MATERIALS AND METHODS

This is a multicenter prospective study pooling data from four established cohorts (Figure 1).

Figure 1. Study flow chart



Cohorts included ND-CKD patients (eGFR <60 mL/min/1.73m^2 or proteinuria >0.15 g/24h) under stable care in Italian outpatients nephrology clinics to gain information on clinical features and outcome of referred CKD. Methodological details are described in the published papers [25,27-29], and here summarized in Appendix. To the aims of this study, we excluded duplicate patients, those with missing sK level as patients with only referral visit.

We grouped patients according to the presence of hyperkalemia, defined as serum K ≥5.0 mEq/L in the two study visits: no hyperkalemia in either visit (absent), hyperkalemia only at visit 1 (resolving), or only at visit 2 (new onset), or at both visits (persistent). Similar categories were created for RASI prescription: both visits, only visit 1, only visit 2, neither visit.

Endpoints of the study were ESKD, that is, start of chronic dialysis therapy (>30 days) or kidney transplantation, and all-cause death before ESKD, as derived by national registries. For survival analyses, patients were followed from visit 2 up to ESKD, all-cause death, or December 31, 2015, and censored on the date of the last control visit.

Statistics

Continuous variables are reported as either mean±standard deviation (SD) or median and interquartile [IQR] range based on their distribution. Comparison among hyperkalemia categories was assessed by ANOVA or Kruskall-Wallis test, while changes in each category across two visits were performed by paired Student's t-test or paired Wilcoxon test. Categorical variables are reported as percentage and were analyzed using Chi-square test or McNemar test to evaluate changes across two visits.

Follow-up for survival analyses started at visit 2 and median follow-up value was estimated by inverse Kaplan-Meier approach. Incidence rates of ESKD and death before ESKD were reported as number of events/person-time and 95% confidence interval (CI) calculated assuming a Poisson distribution. Risk of ESRD versus death in whole population was compared according to Kochar et al. [30].

Competing risk approach was used in the survival analysis because in ND-CKD, ESKD and death before ESKD are competing events, that is, occurrence of death prevents ESKD. The competing risk

analysis must be considered when the absolute percentage of competing event is >10% [31]; in our population, in fact, death before ESRD occurred in 14.3%.

In the univariate analysis we built and compared cumulative incidence curves among categories by using Gray test [32], while multivariable Fine and Gray model was used to estimate the sub-distribution hazard ratio (sHR) and 95% CI [33].

Models were stratified by cohort to take into account potential differences in the basal risks across the four cohorts and were adjusted for the following potential risk factors of ESKD recorded at visit 2: age, gender, diabetes, body mass index (BMI), systolic blood pressure, cardiovascular (CV) disease history, hemoglobin, eGFR, 24-hour proteinuria, categories of RASI, as well as the eGFR change between baseline (visit 1) and 12-month control (visit 2).

To take into account the non-normal distribution of 24-hour proteinuria and the non-linear association with outcomes, this covariate was log-transformed. Non-linear association of sK as continuous variable with outcomes was tested adding in the model the quadratic value of sK and retained if the coefficient was significant.

A two-tailed P value <0.05 was considered significant. Data were analyzed using STATA version 14 (Stata Corp. College Station, TX, USA) and Cmprsk, CrrSC packages of R software 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline period

The whole cohort was originally composed by 2813 patients referred to 46 outpatient CKD clinics in Italy. According to exclusion criteria, we studied 2443 patients (Figure 1). As compared with included patients, those excluded because of missed visit 2 were older and had more severe disease, while sK and use of RASI did not differ (Table S1).

Included patients still had a high-risk profile, as testified by the high prevalence of diabetes and CV disease, the low eGFR value and the high BMI and blood pressure levels (Table 1).

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Table 1. Demographics of patients at Visit 1.

		Hyperkalemia				P
	Overall	Absent (No-No)	Resolving (Yes-No)	New onset (No-Yes)	Persistent (Yes-Yes)	
Number (%)	2,443 (100)	1,121 (46)	415 (17)	363 (15)	544 (22)	
Age (years)	65.1±14.6	64.4±15.2	66.6±13.6	63.6±15.4	66.4±13.4	0.01
Males (%)	58	57	58	64	59	0.12
BMI (kg/m^2)	27.8±5.1	27.7±5.0	27.8±5.1	27.5±4.8	28.1±5.4	0.35
Diabetes (%)	28	26	28	29	31	0.15
CV disease (%)	36	35	37	36	36	0.86
Smoking (%)	13	13	15	13	12	0.68
eGFR (mL/min/1.73m^2)	35.0±17.3	39.0±19.3	33.1±15.0	34.3±16.7	28.6±12.3	<0.001
Systolic BP (mmHg)	139±20	139±20	139±20	139±21	141±19	0.281
Renal disease (%)						<0.001
HTN	30	33	32	28	24	
DKD	13	10	13	16	17	
GN	17	19	15	15	15	
TIN	9	10	9	10	8	
PKD	5	5	5	5	6	
Other	7	7	6	8	9	
Unknow	19	17	20	19	22	

BMI, body mass index; CV, cardiovascular; BP, blood pressure; HTN, hypertensive nephropathy; DKD, diabetic kidney disease; GN, glomerulonephritis; TIN, tubulo interstitial nephropathy; PKD, polycystic kidney disease. Continuous variables are reported as mean±SD

Mean sK did not differ in the two visits (4.81±0.62 and 4.80±0.59 mEq/L, respectively).

Prevalence of hyperkalemia was similar at visit 1 (39%, 95%CI 37-41) and visit 2 (37%, 95%CI 35%-39%) (p=0.266), and it was dependent on CKD stage (Figure S1). Severe hyperkalemia (sK ≥6

mEq/L) was rare (4% at visit 1 and 3% at visit 2), as hypokalemia (sK<3.5 mEq/L <1% in the two visits).

When considering sK in the two visits, we found that 32% patients changed the hyperkalemia status (Figure S2). New onset and persistent hyperkalemia categories accounted for 37% of population (15% and 22% respectively) while hyperkalemia was never detected in 46% and resolving in 17%.

As shown in Table 2, across hyperkalemia categories, proteinuria and serum phosphate increased from absent to persistent (p<0.001), while hemoglobin and eGFR decreased (p<0.001). At visit 1, the number of antihypertensive drugs was 2.15±1.23 per patient and increased to 2.42±1.34 at visit 2 (P<0.001). RASI prescription in the hyperkalemia categories is reported in Table 2; overall, 79% of patients were prescribed RASI, the vast majority of patients having this therapy at either visit while 11% were treated only at visit 1 and 9% only at visit 2. Use of dual RAS blockade slightly increased overall (from 8% to 10%, P<0.001) from visit 1 to 2. Conversely, anti-aldosterone drugs were prescribed in <1% at either visit. The nephrologist intervention also led to increased prescription of statin (from 32% to 38%) and epoetin (from 13% to 18%) (P <0.001 for both), while intervention aimed at controlling extracellular volume (diuretic administration and/or low salt diet-urinary Na excretion ≤100 mEq/24h), was observed in 71% patients at visit 1 and decreased to 56% at visit 2 (P<0.001), likely due to improved BP control (Table 2).

Table 2. Clinical characteristics of patients by hyperkalemia status (sK+ 5.0 mEq/L) at visit 1 and 2.

	Absent (No-No) (n=1,121)		Resolving (Yes-No) (n=415)		New onset (No-Yes) (n=363)		Persistent (Yes-Yes) (n=544)	
	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2
Systolic BP (mmHg)	139±20	135±19*	139±20	136±19*	139±21	134±19*	141±19	137±18*
Diastolic BP (mmHg)	80±11	78±11*	79±11	77±10*	80±11	77±10*	79±11	77±10*
Potassium (mEq/L)	4.38±0.40	4.40±0.37	5.32±0.35	4.55±0.31	4.57±0.32	5.30±0.30	5.47±0.44	5.46±0.42
Glucose (mg/dL)	104.4±33.4	103.9±32.3	112.6±48.6	110.9±39.6	106.7±36.9	108.6±43.5	108.9±42.9	107.7±37.4
Phosphate (mg/dL)^	3.67±0.78	3.71±1.11	3.84±0.75	3.78±0.77	3.77±0.74	3.84±0.95	3.95±0.79	4.02±0.88*
Hemoglobin (g/dL)^	13.0±1.8	12.9±1.7*	12.7±1.8	12.7±1.7	12.5±1.7	12.5±1.7	12.2±1.7	12.2±1.6
eGFR (mL/min/1.73m^2)^	39.0±19.3	38.3±20.3*	33.1±15.0	33.6±17.1	34.3±16.7	31.4±16.6*	28.6±12.3	25.8±12.3*
eGFR change (mL/min/year)^	-0.55± 10.66		1.13±10.34		-2.93±9.63		-2.90±7.81	
Proteinuria (g/24h)^	0.30 (0.12-1.00)	0.28 (0.11-0.90)*	0.36 (0.12-1.10)	0.40 (0.12-1.06)	0.53 (0.15-1.60)	0.52 (0.14-1.49)	0.60 (0.18-1.50)	0.68 (0.19-1.45)
RASI°								
None (%)	33	34	28	33	33	31	23	30
CEI or ARB (%)	60	55	65	60	58	57	70	60
Dual blockade (%)	7	11	7	7	10	13	7	10

Data are mean±SD or median (IQR) or percentage of patients. BP, blood pressure; eGFR, estimated glomerular filtration rate by EPI equation; RASI, renin angiotensin system inhibitors; CEI, converting enzyme inhibitor; ARB, angiotensin II receptor blocker. ^ P<0.05 for visit 1 and visit 2 among the groups. * P<0.05 vs Visit 1. ° RASI distribution differs between visit 1 and 2 for Absent and Persistent group.

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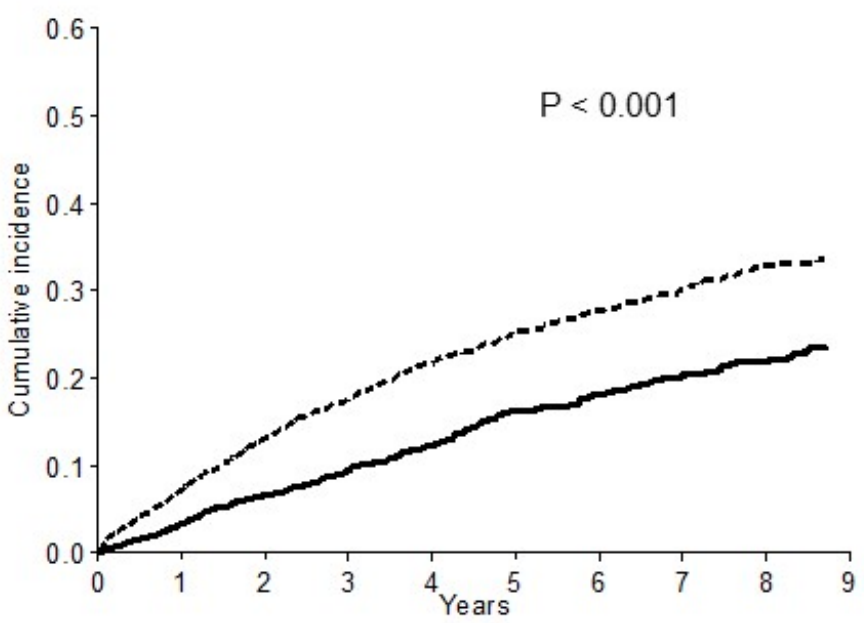
Survival analysis

Survival analyses started after visit 2. During a median follow-up of 3.6 years [IQR 3.0-5.9], we registered 567 ESKD and 349 all-cause death before ESKD, with incidence rate per 100 patient/years being 6.4 (95% CI 5.8-6.9) and 3.9 (95% CI 3.5-4.3), respectively.

The unadjusted competing risk analysis showed that in the overall population the cumulative incidence of ESKD was markedly higher than mortality throughout the entire follow up period (Kochar test p-value <0.001) (Figure 2).

Figure 2. Cumulative incidence of ESKD (dotted line) and death-before-ESKD (solid line) in the whole study population.



Incidence of ESKD was similarly higher in new onset and persistent hyperkalemia categories versus absent and resolving group, while mortality did not differ (Figure 3).

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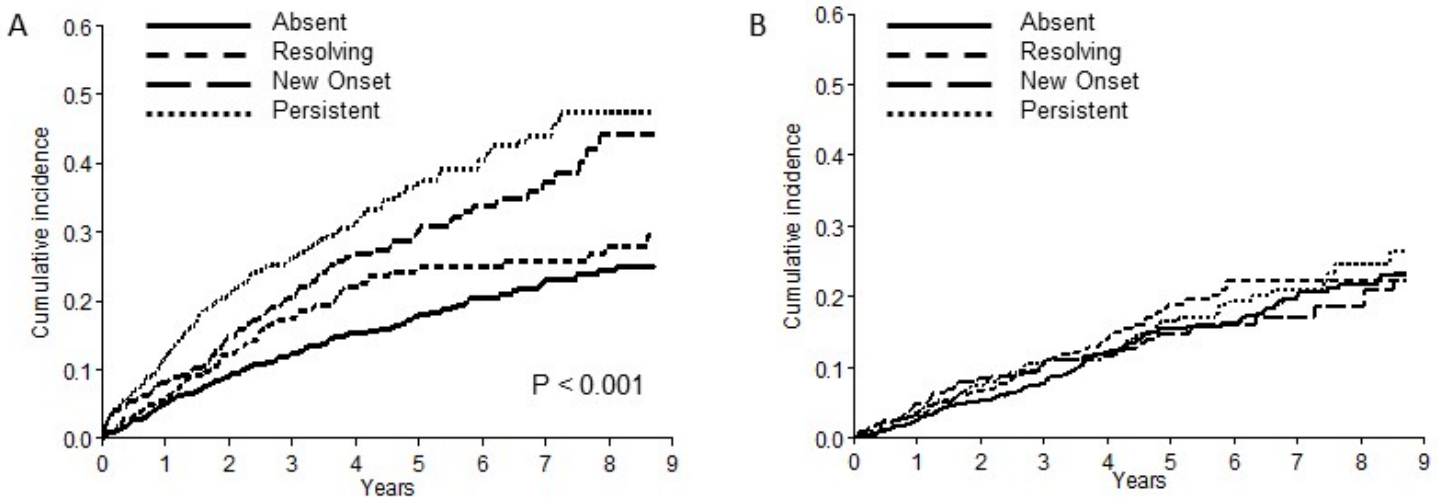
Figure 3. Cumulative incidence after visit 2 of ESKD and all-cause death before ESKD, by competing risk analysis, by hyperkalemia category (panel A-ESKD and panel B-Death).



The multivariable survival analysis examining the independent role of sK as continuous variable showed that 1 mEq/L higher sK at visit 2 was associated with 20% higher risk of ESKD [HR 1.20, 95%CI 1.04-1.39, P=0.014] with no effect on mortality [HR 0.94, 95%CI 0.76-1.17, P=0.57]. The association between sK and outcomes was linear as testified by the non-significant effect of quadratic sK on ESKD (P=0.79) and death (P=0.52). Similarly, the sK change (mEq/L) in the two visits significantly predicted ESKD [HR 1.24, 95%CI 1.05-1.46, P=0.011] with a neutral effect on mortality [HR 0.95, 95%CI 0.75-1.20, P=0.65].

Table 3 illustrates incidence and adjusted risks of ESKD and death in the four hyperkalemia categories. The crude incidence of ESKD progressively increased from absent to persistent hyperkalemia while the association with mortality was less evident. At multivariable analyses, new onset and persistent hyperkalemia were associated with significantly increased risk of ESKD (full multiadjusted models are reported in Table S2). Conversely, no association of hyperkalemia with death emerged.

Table 3. Incidence and multiadjusted risk of ESKD and all-cause death by hyperkalemia status.

	ESKD			All-cause death		
Hyperkalemia	**Incidence** (events/patients)	**Incidence rate** *per 100-pt-y* (95%-CI)	**sHR** (95%-CI)	**Incidence** (events/patients)	**Incidence rate** *per 100-pt-y* (95%-CI)	**sHR** (95%-CI)
Absent	188/1,121	4.32 (3.72-4.98)	Reference	147/1,121	3.38 (2.85-3.97)	Reference
Resolving	93/415	5.98 (4.83-7.33)	0.98 (0.72-1.33)	65/415	4.18 (3.23-5.33)	1.01 (0.73-1.36)
New-onset	105/363	8.23 (6.73-9.96)	**1.34 (1.05-1.72)**	51/363	4.00 (2.98-5.26)	0.94 (0.64-1.38)
Persistent	181/544	10.52 (9.04-12.17)	**1.27 (1.02-1.58)**	86/544	5.00 (3.99-6.17)	0.91 (0.67-1.25)

sHR, sub-hazard ratio; CI, confidence interval. Bold indicates statistical significance.
Hyperkalemia is defined by sK ≥5.0 mEq/L over the two study visits.
Fine and Gray models are stratified by cohort and adjusted for variables at visit 2 (age, gender, diabetes, CV disease, BMI, hemoglobin, eGFR, 24h proteinuria, systolic BP), RASI therapy over the two visits and for eGFR change between the two study visits.

The full model is shown in the Appendix (Table S2-Appendix).

Since underuse of RASI and persistent/new onset hyperkalemia categories showed higher ESKD risk (Table S2), we did an exploratory analysis evaluating the effect of combing hyperkalemia and RASI categories on patient outcome (Table S3); this analysis suggested that, as compared to reference (absent or resolving hyperkalemia combined with use of RASI), risk of ESKD significantly increases by 57% when new-onset/persistent hyperkalemia associates with non use or discontinuation after visit 1 of RASI. These results were consistent with a multiplicative effect of the two factors on the ESKD risk. Conversely, no effect on mortality risk of combination was found (data not shown).

At variance with sK measured at visit 2, we did not detect any association of sK measured at visit 1 with the subsequent incidence of ESKD [HR 1.04, 95%CI 0.90-1.20, P=0.620]. Also mortality risk related to sK at visit 1 was not significant [0.97, 95%CI 0.79-1.19, P=0.750]. These results persisted when adding the 370 patients initially excluded because of missed visit 2 (Table S4).

DISCUSSION

This study provides novel evidence on the true burden of hyperkalemia in CKD patients under continuous nephrology care. We found that moderate hyperkalemia, as defined over two visits with 12-month interval, is common in ND-CKD patients under nephrology care, with a substantial portion of this population showing new-onset or persistent hyperkalemia over one year of observation. Importantly, these patients showed higher risk of ESKD, with no risk excess of death, in the subsequent 3.6 y-follow up.

Gaining insights into prevalence and prognostic role of hyperkalemia in the setting of tertiary nephrology care is crucial for three major reasons. First, nephrology clinics are the appropriate reference of care for ND-CKD patients, as testified by the more favorable global prognosis in referred patients as compared to those never or inconsistently followed by nephrologist [25,34-38]. In this setting, improving risk stratification is mandatory to optimize practice of nephrology workforce, which is limited today and projected to further shrink in the next future [39]. Second, at variance with unreferred CKD, where death overcomes ESKD, the natural fate of CKD under nephrology care is progression to ESKD [25-28,35-38,40-42]; in this regard, it is important to note that a recent survey among European nephrologists has disclosed that in CKD stage 5 the main driver to start renal substitutive therapy is the clinical picture, as currently recommended by international guidelines [18,43], with refractory hyperkalemia eliciting immediate dialysis start by 100% of interviewed nephrologists [44]. Third, hyperkalemia is expected to be prevalent in this setting because nephrologists manage advanced CKD and, moreover, prescribe anti-RAS agents to prevent CKD progression [1-7,16-21].

We found high prevalence of hyperkalemia in our patient population, with high sK detected in as many as 54% patients in at least one of the two study visits. These figures are higher than previously

reported [1-7,15]. Nevertheless, our study is hardly comparable with early work not only in terms of study setting, but also for two features prevalent in renal clinics, that is, the low level of eGFR (77% had CKD stage 4-5), and the high rate of RASI use (more than two-thirds at either visit). This latter feature confirms the attitude of nephrologists toward maintenance of the only nephroprotective therapy today available in advanced CKD [25,27,45,46]. In particular, analysis of the NephroTest cohort has showed that prevalence of hyperkalemia in ND-CKD was 6.5% [15]; however in that study patients were more healthy (younger age, lower comorbidities and minor renal dysfunction) as compared with our patients, and, in general with referred CKD patients. A likely reason is that additional and burdensome work-up in Physiology Department was required for enrollment into NephroTest.

The observed high prevalence of hyperkalemia reinforces the need of answering to the critical question that remains unsolved so far, namely, as whether to what extent chronic hyperkalemia increases the risk of dialysis initiation. The previous studies evaluating the renal risk related to hyperkalemia have disclosed any or only weak association [1,4,10,13-15]. However, these earlier data were mostly attained in settings other than outpatient renal clinics, often including patients with preserved renal function, and had short follow up. More important, no study has evaluated the ESKD risk by properly evaluating the competing risk of death and adjusted analyses for the confounding effect of eGFR decline.

The results of current study adds to current knowledge because it evaluates for the first time the effect of sK on ESKD risk by taking into account the competing risk of death before ESKD and the potential confounder of GFR decline. Serum K was consistently identified as independent risk factor of ESKD, when tested as continuous variable at visit 2 as well as sK change over the two visits. The latter finding anticipates the result attained when examining hyperkalemia categories, where new-onset and persistent hyperkalemia did portend a 30% higher risk of ESKD. Noteworthy, renal risk related to hyperkalemia was independent also from the eGFR change between the two visits, thus excluding that

it was merely dictated by the status of progressive CKD. Similarly, hyperkalemia risk was also independent from older age and diabetes, that are main determinants of hyperkalemia besides and beyond a low renal function [24].

Persistent or new-onset hyperkalemia may also associate with lower use of RAASI, that are the key nephroprotective agents today available for ND-CKD, therefore indirectly increasing ESKD risk. Although a cause-effect relationship can only be proven by a trial [46], it is interesting that a post-hoc analysis of RENAAL trial in diabetic CKD patients has shown the nephroprotective efficacy of losartan was in part offset by the hyperkalemic effect of this drug [47]. Furthermore, a 8-week trial testing a new K binder in hyperkalemic ND-CKD patients showed that more patients could continue the nephroprotective therapy with ARB in the K-binder arm (95%) than in the placebo arm (50%) [48]. Our exploratory analysis (Table S3-Appendix) showed that the ESKD risk increases in hyperkalemic patients not taking RASI on regular basis, thus suggesting that that the two factors should be examined jointly to a proper assessment of the hyperkalemia-driven risk in ND-CKD.

Interestingly, patient survival was not influenced by hyperkalemia. Two potential reasons may explain this finding. First, in our referred patients ESKD overcomes mortality, as expected in the tertiary nephrology care setting, and, second, nephrologists start dialysis in the presence of hyperkalemia refractory to therapy to prevent deaths related to potential additional increases of sK.

The study has limitations and strengths. Results cannot be generalized to unreferred patients as those of ethnic group other than Caucasian. Furthermore, we could not evaluate determinants of hyperkalemia because bicarbonate levels/supplementation and dietary K intake were not available in most patients; however, analysis of determinants was not the aim of this outcome study. On the other hand, strengths of the study are the sample size that is relatively large considering the setting of tertiary nephrology care, the evaluation of ESKD risk that took into account the potential confounder of death

before ESKD, and the adjustment for the extent of eGFR change that allows to dissect the role of hyperkalemia from that of GFR decline on ESKD onset.

In conclusion, our study provides novel evidence that in ND-CKD patients under stable nephrology care, true mild-to-moderate hyperkalemia (sK ≥5.0 mEq/L) is (I) common with 37% patients showing new-onset or persistent hyperkalemia over two visits with 12-month interval and (II) portends *per se* a 30% higher risk of ESKD, that is independent from the rate of eGFR decline, while not affecting patient survival.

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CONFLICT OF INTEREST STATEMENT

All Authors declare that there is no conflict of interest relevant to this work.

AUTHORS' CONTRIBUTIONS

Research idea and study design: MP, RM, LDN; data acquisition: VB, FN, DR, SB, CG, CI, TDS; data analysis/interpretation: MP, RM, GC, HJLH, LDN, PC; statistical analysis: MP, RM, PC; supervision or mentorship: GC, HJLH, LDN. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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