Risk of ESRD and Death in Patients with CKD Not Referred to a Nephrologist: A 7-Year Prospective Study

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Abstract

Background and objectives Rising prevalence of CKD requires active involvement of general practitioners to limit ESRD and mortality risk. However, the outcomes of patients with CKD exclusively managed by general practitioners are ill defined.

Design, setting, participants, & measurements We prospectively evaluated 30,326 adult patients with nondialysis CKD stages 1–5 who had never received consultation in tertiary nephrology care recruited from 700 general practitioner offices in Italy during 2002 and 2003. CKD stages were classified as stages 1 and 2 (GFR≥60 ml/min per 1.73 m^2 and either albuminuria or an International Classification of Diseases, Ninth Revision, Clinical Modification code for kidney disease), stage 3a (GFR=59–45), stage 3b (GFR=44–30), stage 4 (GFR=29–15), and stage 5 (GFR<15). Primary outcome was the risk of ESRD (dialysis or transplantation) or all-cause death.

Results Overall 64% of patients were in stage 3a, and 4.5% of patients were in stages 3b–5. Patients with stages 1 and 2 were younger, were predominantly men, more frequently had diabetes, and had lower prevalence of previous cardiovascular disease than patients with stages 3a–5. Hypertension was frequent in all CKD stages (80%–94%), whereas there was a lower prevalence of dyslipidemia, albuminuria, and obesity associated with more advanced CKD. During the follow-up (median=7.2 years; interquartile range=4.7–7.7), 6592 patients died and 295 started ESRD. Compared with stages 1 and 2 (reference), mortality risk (hazard ratio, 95% confidence interval) was higher in stages 3b–5 (1.66, 1.49–1.86, 2.75, 2.41–3.13 and 2.54, 2.01–3.22, respectively) but not stage 3a (1.11, 0.99–1.23). Similarly, ESRD risk (hazard ratio, 95% confidence interval) was not higher at stage 3a (1.44, 0.79–2.64) but was greater in stages 3b–5 (11.0, 6.3–19.5, 91.2, 53.2–156.2 and, 122.8, 67.9–222.0, respectively). Among modifiable risk factors, anemia and albuminuria significantly predicted either outcome, whereas hypertension only predicted mortality.

Conclusions In patients with CKD not referred to nephrology, risks of ESRD and mortality were higher in those with CKD stages 3b–5.

Clin J Am Soc Nephrol 9: 1586–1593, 2014. doi: 10.2215/CJN.10481013

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Introduction

CKD is recognized as a global public health issue because of its rising prevalence worldwide (about 10%) (1) and the burden of adverse outcomes, including mortality (almost doubled in the last two decades) (2,3). Under this view, the implementation of strategies for prevention or treatment of CKD and its complications should require a large involvement of general practitioners (GPs) to not only allow appropriate timing of referral to a specialist but also, optimize management of this illness.

Other than specific indications, such as AKI, persistent hyperkalemia, recurrent nephrolithiasis, and hereditary kidney disease, one indication shared by most guidelines is that patients with a severe stage of CKD (*i.e.*, eGFR<30 ml/min per 1.73 m^2 and/or albuminuria) should be referred to nephrologists, because they are at high risk for progression to ESRD (4). However, this recommendation is opinion based and may engender uncertainty for patients with CKD in stage 3 (eGFR 30–60 ml/min per 1.73 m^2), which represent the vast majority of the CKD population (prevalence 15–20 times higher than that of patients with eGFR<30 ml/min per 1.73 m^2) (5). This point is critical if one considers that the prevalence of CKD in the setting of primary care is high (10%–15%), whereas awareness of CKD among GPs is <20%; consequently, nephrology referral rates are dramatically low and delayed (1,6–9). Overall, these epidemiologic data call for additional studies addressing prognosis in primary care. Others suggest that referral to a nephrologist at least 12 months before initiation of dialysis is sufficient to assess and prepare patients for RRT, but this is a retrospective criterion that cannot be implemented by GPs in clinical practice. Also, the indication of referring when complications ensue is generic, being strictly dependent on the frequency of its assessment by a GP.

A more pragmatic approach to establish a correct time for referral can be obtained from prognostic models of patients with CKD seen exclusively by GPs to evaluate at which stage of disease the risk for mortality or ESRD significantly increases. Indeed, although it is known that the risk of adverse outcomes increases when GFR declines below 60 ml/min in the population at large (2,10), to our knowledge, only a single study has evaluated outcomes of patients with CKD who were not referred (11). However, this study focused only on mortality risk without adjustment for clinical comorbidities and albuminuria (11).

To fill this critical gap of knowledge, we selected a cohort of >30,000 patients with CKD (stages 1–5) followed by Italian GPs who were characterized by the absence of any nephrology consultation. In this cohort, we assessed the incidence and correlates of ESRD and death over a 7-year follow-up. This study is the prospective phase of the original project; the cross-sectional data have been previously reported by our group (6).

Material and Methods

Data were obtained from the Health Search/Cegedim Strategic Data Longitudinal Patient Database (HS) set up by the Italian College of General Practitioners in 1998. At the time of this study, HS contained information from over 900 Italian GPs, with a total list size of over 1.5 million patients. A description of HS is detailed in the Supplemental Appendix. Each GP undergoes formal training for data entry and uses standard software to record data. Completeness and accuracy of information are assessed by running a set of queries (quality indicators) used to generate a composite score ranging from 0–1. Only physicians (n=700) reaching a composite quality score>0.7 were included in epidemiologic studies (12,13), and the validity of the data has been previously shown (14–16).

Study Design

We selected patients with at least one serum creatinine value in the period from January of 2002 to December of 2003 and age>18 years with CKD stages 1–5 followed in GPs offices by ≥12 months. Exclusion criteria were lack of urinalysis, at least one consultation in tertiary nephrology care, dialysis or transplantation, and acute renal failure in the 6 months before enrollment (to exclude patients who have been seen at least one time by a nephrologist); we also excluded patients with short life expectancy (active neoplasm, chronic liver disease, congestive heart failure [New York Heart Association Class IV], and diseases requiring immunosuppressive therapy). This latter criterion was also chosen to avoid effects of immunosuppressive therapy (mainly corticosteroids) on the prevalence of some modifiable risk factors (hypertension, obesity, and anemia) and renal function.

Baseline data (corresponding to the date of first creatinine measure) included age, sex, body mass index, smoking, eGFR (by means of the four-variable Modification of Diet in Renal Disease [MDRD] Study equation), BP, total cholesterol, hemoglobin, and albuminuria. Presence of diabetes, coronary artery disease (CAD), transient ischemic attack/stroke, congestive heart failure (New York Heart Association Class I–III) or peripheral vascular disease and diagnosis of kidney disease were identified on the basis of International Classification of Diseases, Ninth Revision, Clinical Mofidication (ICD-9-CM) codes (Supplemental Table 1). Hypertension was defined according to the presence of the ICD-9-CM code, antihypertensive treatment, or a recorded BP value in the previous year either >130 mmHg systolic BP or >80 mmHg diastolic BP in patients with CKD and albuminuria or >140 mmHg systolic BP or >90 mmHg diastolic BP in patients without albuminuria (4). Albuminuria was considered present if the patients had a specific ICD-9-CM code, microalbuminuria≥30 mg/d or ≥20 mg/L, proteinuria>200 mg/d or >150 mg/L, or urinary dipstick trace or more. Diagnosis of anemia was made on the basis of either ICD-9-CM codes or hemoglobin values<11 g/dl in the previous year. Dyslipidemia was defined on the basis of an ICD-9-CM code, prescription of lipid-lowering therapy, or a total cholesterol value>190 mg/dl in the previous year. Obesity was defined as body mass index>30 kg/m^2. In patients with two creatinine values, we averaged the two values; when more than two creatinine values were available, we averaged the last creatinine tested with the mean of previous values.

We classified enrolled patients into six CKD stages (4). CKD stages 1 and 2 were defined by the presence of either albuminuria or at least one ICD-9-CM code for kidney disease (Supplemental Table 1) and eGFR≥90 ml/min per 1.73 m^2 (stage 1) or eGFR=89–60 ml/min per 1.73 m^2 (stage 2). More advanced stages were defined only on the basis of eGFR values.

Outcome Measures

We considered ESRD (either dialysis or renal transplant) and all-cause death before ESRD as outcome measures. The follow-up expiration date was December 31, 2010. To identify the outcome ESRD and the respective date, we used either specific ICD-9-CM codes for dialysis and renal transplant (Supplemental Table 1) or manual review of the free-text electronic medical charts (dialysis and renal transplant) followed by a validation procedure. Death and respective date were extracted from the specific fields of the database, because in Italy, certificate of death is filled by a GP.

Statistical Analyses

Data are expressed as means±SDs or medians (interquartile range) for continuous variables according to their distribution and percentages for categorical variables. Comparison between groups was performed by ANOVA or chi-squared test. Confidence intervals of rates of ESRD and all-cause death were calculated assuming a Poisson distribution. For descriptive purposes, we compared incidence of ESRD and death in our patients not referred to a nephrologist with that recorded in a cohort of patients with CKD regularly followed by nephrologists in the same geographical area and timeframe (TArget Blood pressure Levels [TABLE] Study) (17).

Because ESRD and death before ESRD are competitive events (*i.e.*, the occurrence of death prevents the occurrence of ESRD), we calculated the cumulative incidence of ESRD or death before ESRD using the competing-risk approach (18), and stages were compared with the Gray test (19). The relationship between CKD stage and outcomes was examined by constructing multivariable Cox

proportional hazards models (using stages 1 and 2 as the reference) by including *a priori* as potential confounders age, sex, obesity, diabetes, CAD, hypertension, dyslipidemia, anemia, albuminuria, and use of renin-angiotensin system inhibitors. Statistical analysis was performed by using Stata 11.2 (Stata Corp, College Station, TX).

Results

Patient Characteristics

Figure 1 shows the flow chart of the study. The majority of enrolled patients were in stage 3a (64.5%), and only 4.5% of patients had more advanced CKD. Patients with early CKD (stages 1 and 2) were younger, were predominantly men, had higher frequency of diabetes, and had lower prevalence of previous cardiovascular disease than patients with stages 3a–5 CKD (Table 1). Hypertension (90.7%) and dyslipidemia (65.3%) were the most frequent modifiable risk factors (Figure 2); however, although hypertension remained highly prevalent in all CKD stages (range 80%–94%), the frequency of dyslipidemia was lower among patients with worse renal function (from 62.8% at stage 1 to 52.5% at stage 5; $P<0.001$), despite similar statin use (Table 2). Albuminuria was more frequent at stages 1 and 2 (63.4% and 52.0%, respectively) than stages 3a–5 (ranging from 3.6% to 13.3%); obesity prevalence was higher in stage 1 (28.5%) than in more advanced CKD. Conversely, anemia was less frequent in early stages of CKD ($P<0.001$).

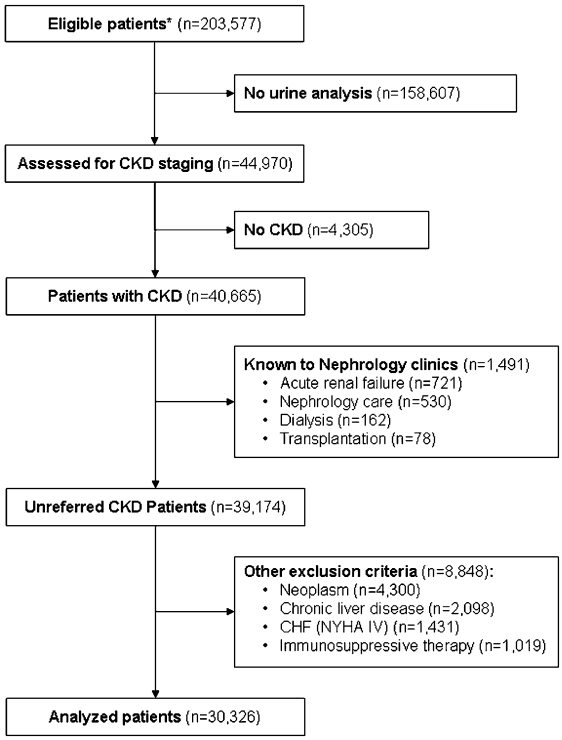

Figure 1. | Flow chart of the study. CHF, congestive heart failure; NYHA IV, New York Heart Association Class IV. *Patients were considered eligible if they were ≥18 years of age, were followed by a general practitioner for ≥12 months, and had at least one serum creatinine in 2002 or 2003.

Table 1. Demographic and clinical characteristics of patients with CKD exclusively followed in primary care stratified for CKD stage

	Overall (n=30,326)	CKD Stage					*P* Value
		1 (n=904)	2 (n=3142)	3a (n=19,561)	3b (n=5341)	4 (n=1083)	5 (n=295)	
Age (yr)	71.0±11.0	57.0±14.5	66.0±12.0	71.7±9.9	76.2±9.7	77.0±11.2	68.9±13.5	<0.001
Women (%)	64.5	35.5	44.7	67.8	68.7	66.1	63.7	<0.001
Smoking (%)	13.8	27.0	18.9	12.7	10.8	13.2	17.8	<0.001
Diabetes (%)	24.5	54.4	46.0	19.2	25.5	27.9	26.1	<0.001
Coronary artery disease (%)	14.7	9.1	13.7	13.8	17.8	22.6	15.3	<0.001
TIA/stroke (%)	8.5	4.8	7.6	7.8	11.6	13.0	7.5	<0.001
CHF (NYHA II and III; %)	1.2	0.6	0.8	0.8	2.5	3.0	1.4	<0.001
Peripheral vascular disease (%)	10.7	9.3	11.8	9.4	13.7	16.7	11.2	<0.001
eGFR (ml/min per 1.73 m^2)	53±16	106±24	73±8	54±4	40±4	25±4	9±3	—
Total cholesterol (mg/dl)[a]	217±34	210±34	212±34	218±34	216±34	211±35	210±34	0.52
Systolic BP (mmHg)[b]	141±17	139±16	140±16	140±17	141±17	141±19	140±18	<0.001
Diastolic BP (mmHg)	82±9	84±9	82±9	81±9	80±9	80±9	82±9	0.04

Values are mean±SD or percentage. TIA, transient ischemic attack; CHF, congestive heart failure; NYHA, New York Heart Association Class.
[a]Missing values=5430.
[b]Missing values=6617.

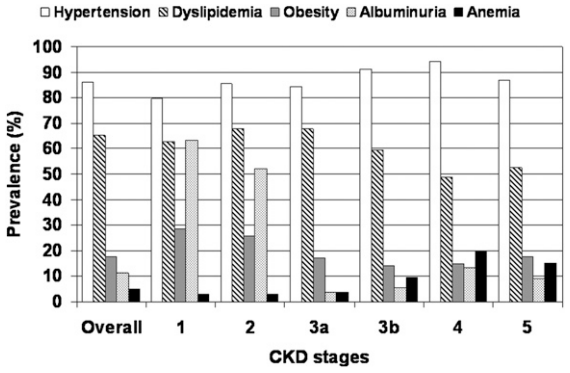

Figure 2. | Prevalence of main modifiable risk factors in the whole cohort and by CKD stage.

Renin-angiotensin system inhibitors were prescribed in more than one half of the cohort, except in patients with stages 1 or 5 (Table 2). Overall, thiazide diuretics were used more frequently than loop diuretics, but this finding was mainly because of the large number of patients with GFR>45 ml/min per 1.73 m^2 (78% of our cohort). Indeed, in stages 4 and 5, the prescription of loop diuretics prevailed over that of thiazides (Table 2). In patients with eGFR<60 ml/min per 1.73 m^2, awareness of CKD by GPs, which was shown by the presence of ICD-9-CM codes for renal disease, was low at stage 3a (4.0%) and reached prevalence of 19.1%, 55.7%, and 36.6% at stages 3b, 4, and 5, respectively.

Outcome

During the follow-up (median 7.2 years; interquartile range 4.7–7.7), only 704 patients (2.3% of the whole population) were referred to nephrologists; specifically, nephrology referral occurred in 4.9% of patients at stages 4 and 5, 3.9% of patients at stage 3b, and 1.8% of patients at stages 1–3a. In this period, we registered 6592 deaths and 295 patients with ESRD (95.3% on dialysis). Overall, the absolute risk of death was >20-fold higher than the risk of ESRD. Crude mortality rate was progressively higher among patients with worse renal function, with a peak at stage 4 (Table 3). Incidence rate of ESRD was also greater in advanced stages, whereas in stage 3a, the incidence rate was lower than in stages 1 and 2 (Table 3). However, when these data were analyzed using a competing-risk approach, a progressively higher incidence of either outcome occurred in parallel with the entity of renal impairment (Figure 3).

Multivariable Cox models for ESRD and death are reported in Table 4. Compared with stages 1 and 2, patients with stage 3a were not at higher risk for either ESRD or death. The risk for ESRD was significantly and progressively higher among patients with GFR below 45 ml/min per 1.73 m^2. Indeed, risks for ESRD at stages 3b, 4, and 5 were 11-fold, 91-fold, and 123-fold greater, respectively, than those of patients at stages 1 and 2. This analysis also showed that diabetes, CAD, anemia, and proteinuria were independently associated with the risk of ESRD, whereas elderly patients and women were at lower risk (Table 4). As for ESRD, mortality risk was significantly greater in patients with GFR<45 ml/min per 1.73 m^2 (from 66% in patients at stage 3b to 154% in patients at stage 5 versus stages 1 and 2). Risk factors significantly associated with ESRD (women, diabetes, CAD, hypertension, anemia, and proteinuria) also independently influenced the risk of death. Mortality risk, however, was greater in elderly patients and 33% lower in the presence of dyslipidemia. Estimates of risk for ESRD and death did not change when including the nephrology referral as a covariate during the follow-up.

Table 2. Demographic and clinical characteristics of patients with CKD exclusively followed in primary care stratified for CKD stage

Class of Drugs	Overall (*n*=30,326)	CKD Stage						*P* Value
		1 (*n*=904)	2 (*n*=3142)	3a (*n*=19,561)	3b (*n*=5341)	4 (*n*=1083)	5 (*n*=295)	
Antihypertensive dugs (*N*)	1 (1–2)	1 (0–2)	1 (0–2)	1 (0–2)	2 (1–3)	2 (1–3)	2 (0–3)	<0.001
RAS inhibitors (%)	55.5	45	54.7	52.8	66.2	64.8	44.1	<0.001
Calcium channel blockers (%)	25.8	20.5	25.5	25	29.1	19	13.2	<0.001
β-Blockers (%)	18	12.7	16.8	18.3	18.5	18	17.6	<0.001
Thiazide diuretics (%)	24.6	12.4	20.7	2.5	5.8	8.8	9.8	<0.001
Loop diuretics (%)	14.1	4.8	8	10.8	24.9	43.3	29.5	<0.001
Other (%)	29.8	13.7	22.3	27.9	39.5	48.7	32.2	<0.001
Antithrombotic drugs (%)	36.3	25.4	34.7	34	45.4	48.3	36.3	<0.001
Lipid-lowering drugs (%)	19.1	17.8	20.1	18.8	19.9	19.1	16.9	0.18
Nitrates (%)	11.8	4.8	7.6	24	29.8	39.7	40.3	<0.001
Insulin (%)	3.9	8.8	5.9	11.9	16.1	14.9	11.2	<0.001
Oral hypogycemic agents (%)	15.5	36.5	31.2	10.4	17.7	25.9	17.3	<0.001

Data are percent or median (interquartile range). RAS, renin-angiotensin system.

Table 3. Numbers of events and incidence rates of ESRD and all-cause death in CKD stages

CKD Stage	ESRD			Death		
	Events (*n*)	Incidence (×10,000)	95% Confidence Interval	Events (*n*)	Incidence (×10,000)	95% Confidence Interval
1	3	4.8	1.5 to 14.9	98	157.9	129.6 to 192.5
2	14	6.8	4.0 to 11.5	458	222.4	202.9 to 243.7
3a	40	3.2	2.3 to 4.4	3564	284.8	275.6 to 294.3
3b	72	25.3	20.1 to 31.8	1851	650.2	621.2 to 680.4
4	119	295.8	247.3 to 353.7	536	1323.6	1216.2 to 1440.4
5	47	335.3	251.9 to 446.3	85	606.4	490.3 to 750.1

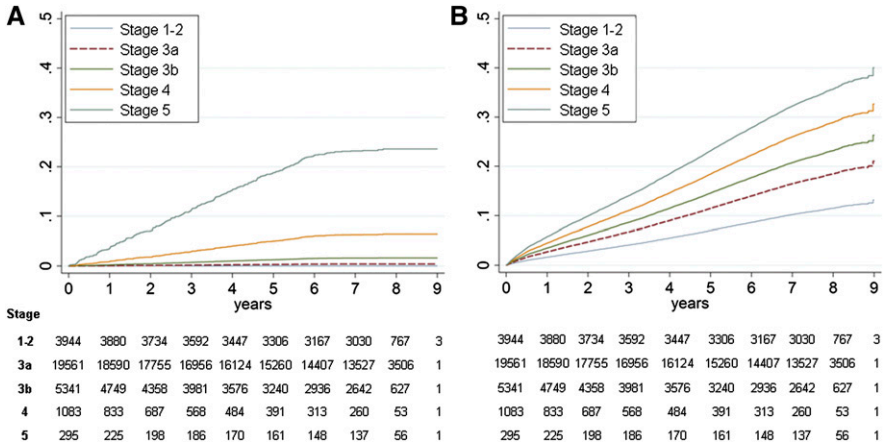

Figure 3. | Incidence of ESRD and death by CKD stage. (Left panel) Competing risk of ESRD (competing event: death before ESRD) and (right panel) death before ESRD (competing event: ESRD) in patients stratified for CKD stages. Tables indicate the numbers of patients at risk (those who did not have ESRD or those who died).

Discussion

In the last two decades, several uncontrolled or retrospective studies have underlined the clinical and economic advantages of timely referral to nephrology (20–23). However, as highlighted by current guidelines (4), the referral recommendations still remain inconsistent. In this study, we evaluated, for the first time, ESRD and mortality risk of patients with CKD not referred to a nephrologist. Patients with CKD without any nephrology consultation have been selected to evaluate the exclusive effect of GPs on hard endpoints to, consequently, derive from this analysis useful information on the timing of nephrology referral.

Our results show that the incidence rate of mortality was progressively higher from stages 1–4, with a subsequent reduction at stage 5 (Table 3). Conversely, the incidence rate for ESRD remained constant in CKD stages 1–3a but exponentially increased among patients with a later CKD stage (Table 3). However, this pattern is influenced by the fact that the two outcomes (ESRD and death before ESRD) are competing events; indeed, by using a competing-risk approach, we found that incidence of mortality was linearly greater across stages, and that the incidence rate of ESRD was noticeably higher than stages 1 and 2 only when eGFR is <30 ml/min per 1.73 m^2 (Figure 3). After adjustment for main risk factors, the risk for both mortality and ESRD was significantly higher in stages 3b–5 than stages 1 and 2 (Table 4). It is interesting to note that patients with CKD stage 3a, representing about 74% of the whole group of patients with eGFR<60 ml/min per 1.73 m^2, were not at higher risk for either ESRD or death with respect to stages 1 and 2. This finding may be, at least in part, because albuminuria and diabetes (of which the effects on faster progression of CKD and mortality are well known) had the lowest prevalence in stage 3a. Other studies reported the increased incidence of adverse outcome with eGFR decline, but the relative weights of ESRD and mortality were quite different. Indeed, the CKD Consortium reported almost the same crude incidence rates of ESRD and death (17.6% and 19.4%, respectively) (24), whereas in the MDRD Study, crude incidence of ESRD markedly prevailed over mortality (25). The same phenomenon can be detected in the TABLE Study, where the incidence rate of ESRD was higher than that of all-cause death (Supplemental Table 2) (17). These differences could be ascribed to the presence of a nephrology referral. Indeed, in the CKD population evaluated by the CKD Consortium, 75% of patients were referred to the nephrology setting, whereas in the TABLE Study and the MDRD Study, all patients had long-lasting nephrology care. In our cohort, the choice of exclusively selecting patients

Table 4. Multivariable Cox model of determinants of ESRD and all-cause death

Variables	ESRD Hazard Ratio (95% Confidence Interval)	All-Cause Death Hazard Ratio (95% Confidence Interval)
Age (1 yr)	0.96 (0.96 to 0.97)[a]	1.10 (1.10 to 1.11)[a]
Women	0.49 (0.39 to 0.63)[a]	0.60 (0.57 to 0.63)[a]
Body mass index≥30 kg/m^2 (yes versus no)	0.71 (0.50 to 1.01)	1.02 (0.94 to 1.11)
Hypertension (yes versus no)	1.60 (0.93 to 2.76)	1.11 (1.02 to 1.21)[a]
Diabetes mellitus (yes versus no)	1.63 (1.26 to 2.11)[a]	1.61 (1.52 to 1.70)[a]
Coronary artery disease (yes versus no)	1.33 (1.03 to 1.71)[a]	1.48 (1.41 to 1.56)[a]
Dyslipidemia (yes versus no)	1.11 (0.86 to 1.44)	0.67 (0.64 to 0.71)[a]
Anemia (yes versus no)	2.08 (1.50 to 2.89)[a]	1.56 (1.44 to 1.69)[a]
Albuminuria (yes versus no)	2.11 (1.57 to 2.84)[a]	1.12 (1.01 to 1.24)[a]
Use of RAS inhibitors (yes versus no)	1.17 (0.89 to 1.53)	1.02 (0.97 to 1.08)
CKD stage		
1 and 2	Reference	Reference
3a	1.44 (0.79 to 2.64)	1.11 (0.99 to 1.23)
3b	11.04 (6.26 to 19.48)[a]	1.66 (1.49 to 1.86)[a]
4	91.2 (53.2 to 156.2)[a]	2.75 (2.41 to 3.13)[a]
5	122.8 (67.9 to 222.0)[a]	2.54 (2.01 to 3.22)[a]

Hazard ratios are adjusted for all variables included into the model. RAS, renin-angiotensin system.
[a]Significant hazard ratio.

with CKD without referral to a nephrologist may likely have influenced the low incidence rate of ESRD, because patients with fast progression, being promptly referred by GPs to nephrologists, were excluded. Conversely, crude incidence of death in this study (23%) is similar to that reported by the CKD Consortium (19%) and the MDRD Study (22%) (24,25), as well as the TABLE Study (20%) (Supplemental Table 2).

Overall, these epidemiologic data are useful for better defining the referral criteria to avoid an increased workload for nephrology services. We previously claimed that, because of a low awareness of CKD in primary care, referral of patients with CKD by GPs was unacceptably low (2.7%, 13.6%, 46.7%, and 62.6% in stages 3a–5, respectively), especially in the early stages of CKD, and that this result would have limited implementation of multiple risk factor intervention strategies aimed at decreasing mortality and ESRD (6). On the basis of the results of this study, we temper our earlier statement but support it for patients with GFR<45 ml/min per 1.73 m^2. Indeed, according to this study, GPs can be considered as a reference of care for patients in stage 3a without asking for nephrology consultation, because these patients have the same risk as the reference group (Table 4). The clinical characteristics of our patients with CKD stage 3a, in fact, show low prevalence for the main cardiorenal risk factors (*i.e.*, albuminuria, anemia, diabetes, and CAD) with respect to more advanced stages of CKD (3b–5), and therefore, their profile is compatible with nonprogressive CKD (26–30). However, the suggestion of referring patients with CKD when eGFR is <45 ml/min per 1.73m^2 is in agreement with the timing of onset of CKD-related metabolic complications (31). Obviously, because of the observational nature of this study and the sole inclusion of patients who were not referred to a nephrologist, the indication of starting referral of patients with CKD stage 3b remains a suggestion, because no formal comparison between patients who were and were not referred to a nephrologist could be made in this work. *Ad hoc* randomized trials may provide the answer.

Additional important information is related to clinical conditions acting as independent risk factors for ESRD and mortality (Table 4). Other than unmodifiable risk factors (men, diabetes, and CAD), we found that anemia and albuminuria doubled the risk of ESRD and increased the risk of death by 56% and 12%, respectively, with hypertension playing an independent role on mortality risk. This finding is not surprising but further contributes to better risk stratification and characterization of patients requiring nephrology referral. This information becomes even more relevant if one considers that most elderly patients with multiple comorbidities carry the highest risk of nonreferral to nephrologists (32,33).

It is worth nothing that a proper estimate of CKD prevalence in the general population cannot be obtained because of the selection of patients. Indeed, prevalence of CKD stages 3–5 in primary care (9.3% in Italy and 8.5% in United Kingdom) (6,7) is 3-fold greater than that found in a recent survey of a nationally representative sample of the general Italian population (2.9%) (L. De Nicola, *et al.*, unpublished data). The prevalence of CKD is overestimated in primary care, because GPs are more likely to perform urine and creatinine testing in at-risk patients (elderly patients and patients with diabetes and hypertension) (6).

A strength of this study is that it evaluates the total survival and renal survival in a very large cohort of patients with CKD exclusively followed in primary care. To our knowledge, only one longitudinal study investigated this issue; however, this study focused only on mortality risk assessed during a short follow-up (2.3 years on median), the patients included in the study were older (83 years old on average) with low eGFR (mean value=28 ml/min per 1.73 m^2), and no information on either comorbidities or albuminuria was

available (11). Our study also has some limitations. Serum creatinine was not calibrated because of the spreading of participating GPs throughout Italy; also, in 2002 and 2003, creatinine standardization was not routinely performed. These factors may cause underestimation of risk, mainly for patients in stage 3a. Indeed, this problem is limited mainly to patients with eGFR of 50–60 ml/min per 1.73 m^2, whereas lack of calibration of serum creatinine for eGFR<50 ml/min per 1.73 m^2 does not substantially affect CKD staging (34–36). Furthermore, from cohort selection, we excluded a large number of patients because of lack of urine testing, making this cohort highly selected, which limits the generalizability of our findings. The lack of urine testing was likely caused by the low awareness of prognostic relevance of proteinuria among GPs (6).

In conclusion, this study suggests referral of patients with CKD at stage 3b given that, at this level, we observe a significant rise in ESRD and mortality risks. This indication seems compatible with the workload for nephrology services, because the large majority of patients with CKD seen in primary care are in stage 3a. Finally, our results suggest that GPs should be aware that specific CKD risk factors (hypertension, anemia, and albuminuria) are associated with greater risk of adverse events independent of eGFR level.

Acknowledgments

This work was endorsed by the Italian Society of Nephrology (Gruppo di Studio sul Trattamento Conservativo della Insufficienza Renale Cronica) and supported by an unrestricted grant provided by Amgen (to Italian Society of Nephrology).

The study sponsor did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Disclosures

None.

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Received: October 15, 2013 **Accepted:** May 30, 2014

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.10481013/-/DCSupplemental.